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ORIGINAL ARTICLE

Non-functional Neuroendocrine Carcinoma of the Pancreas: Incidence, Tumor Biology, and Outcomes in 2,158 Patients

Jan Franko · Wentao Feng · Linwah Yip · Elizabeth Genovese · A. James Moser

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Abstract
Objective Pancreatic neuroendocrine cancer is a rare, indolent malignancy with no effective systemic therapy currently available. This population-based analysis evaluated the hypothesis that long-term survival benefit is greater with aggressive, rather than limited, surgical therapy.
Methods Non-functional pancreatic neuroendocrine carcinoma (NF-pNEC) cases diagnosed from 1973 to 2004 were retrieved from the SEER database.
Results A total of 2,158 patients with NF-pNEC were identified, representing 2% of all pancreatic malignancies. The annual incidence increased from 1.4 to 3.0 per million during the study period. On average, tumors measured 59±35 mm (median 50), and age at diagnosis was 59±15 years; 29% of patients were younger than 50. Nodal (44%) and systemic metastases (60%) were common. Overall the 5-, 10-, and 20-year survival rates were 33%, 17%, and 10%, respectively. Removal of the primary tumor significantly prolonged survival in the entire cohort (median 1.2 vs. 8.4 years; $p<0.001$) and among those with metastases (median 1.0 vs. 4.8 years; $p<0.001$). No survival difference was seen between enucleation and resection of the primary tumor (median 10.2 versus 9.2 years, $p=0.456$).
Conclusion This study suggests that surgical therapy improves survival among patients with localized, as well as metastatic, NF-pNEC. Enucleation may be oncologically equivalent to resection.

Keywords Pancreatic endocrine tumor · Islet cell carcinoma · Carcinoid · Incidence · Metastasectomy · Enucleation

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J. Franko · L. Yip · E. Genovese · A. J. Moser
Division of Surgical Oncology,
University of Pittsburgh Medical Center,
Pittsburgh, PA, USA

W. Feng
Department of Biostatistics, University of Pittsburgh,
Pittsburgh, PA, USA

A. J. Moser (✉)
Department of Surgery, University of Pittsburgh Medical Center,
497 Scaife Hall,
Pittsburgh, PA 15261, USA
e-mail: moseraj@upmc.edu

Introduction

The clinical manifestations and survival outcomes of neuroendocrine tumors vary significantly by their site of origin,[1–3] with pancreatic lesions being the most aggressive.[4] The heterogeneous morphology of neuroendocrine tumors, and the varying degrees of their clinical endocrine function, have prevented the adoption of a uniform pathologic classification. Although the 2000 World Health Organization (WHO) classification is recommended by most,[3,5] a prognostically superior staging and grading system was recently suggested by others.[6]

Lately, the use of the term *pancreatic endocrine tumor* has been recommended, whereas the use of older terms, such as *neuroendocrine* or *islet cell tumor* or *carcinoid*, have been discouraged.[5] The 2000 WHO classification provided a much needed framework for the integration of biologic behavior and histological features of pancreatic endocrine tumors.[3,5] In comparison, the use of the term *neuroendocrine carcinoma* is supported by the International Classification of

Diseases for Oncology[7] and is currently used in clinical practice. Therefore, for the purpose of this report, we adopted the term *neuroendocrine carcinoma* to describe pancreatic endocrine tumors with malignant and/or biologically unclear potential.

The natural history of pancreatic neuroendocrine tumors has been elucidated mostly by longitudinal studies on functional tumors,[8] however, there are multiple characteristics that differ between functional and non-functional tumors.[6,9–11] For example, insulinomas have approximately a 10% malignancy rate whereas non-functional tumors have a 92% malignancy rate.[12] A recent audit of 9,281 pancreatic neuroendocrine tumors, from the National Cancer Data Base, demonstrates that 85% were non-functional.[13] Most institutional studies[6,14] and database analyses[13,15] have combined functional and non-functional tumors. These data have contributed to the prognostic assessment of individual patients with pancreatic neuroendocrine carcinoma; however, their heterogeneity does not permit the establishment of good, evidence-based treatment algorithms.

A specific focus on pancreatic neuroendocrine tumors is warranted because (1) nationwide incidence data are not available, (2) characteristics differ depending on functional status[6,9–11] and site of origin,[1,2], and (3) surgical outcomes are associated with functional status.[16] In the current literature, there are only three institutional studies limited to non-functional pancreatic neuroendocrine tumors, which include at least 100 patients each.[14,17,18] In the absence of prospective trials, treatment effectiveness should be analyzed by large retrospective studies. Our objective was to evaluate the incidence of non-functional pancreatic neuroendocrine carcinomas (NF-pNEC) in the US population by collecting data from the Surveillance, Epidemiology and End Results (SEER) Program and to analyze outcome variables correlating with surgical treatment. We hypothesized that aggressive surgical intervention, including formal pancreatic resection and/or resection of metastases, is associated with improved survival compared to limited interventions, such as enucleation and/or no surgical treatment.

Methods

Identification of Pancreatic Neuroendocrine Carcinomas in the SEER Database

Diagnosis codes from the 3rd edition of the International Classification of Diseases for Oncology (ICD-O-3) are used to classify neuroendocrine tumors in the SEER database, which collects detailed information on the incidents of all malignant tumors within its respective populations.[7] The SEER registrars assign codes after review of the original pathology reports. Methods to differentiate between the benign, borderline, and malignant subtypes of neuroendocrine tumor are not fully validated and remain controversial.[3,5,10] Since it is recognized that over 85% of non-functional pancreatic neuroendocrine tumors have borderline or malignant biology,[10,12,14] the SEER program collects available data on clinical and pathological information for each case of pancreatic neuroendocrine tumors.[7]

A total of 2,531 pancreatic neuroendocrine tumors were identified, of which 2,158 (85%) were non-functional. Non-functional lesions included large cell neuroendocrine carcinoma (8013/3, n=7), islet cell carcinoma (8150/3, n=1,066), and neuroendocrine carcinoma (8246/3, n=1,085). All functional, atypical, and mixed tumors were excluded, as well as those designated carcinoid or enterochromaffin-like tumors (n=373). *Extent of disease* data was used to reconstruct the nodal and systemic metastatic status. Survival data is current as of November 2006.[7]

We analyzed the following outcome variables: year of diagnosis, patient gender and age at diagnosis, primary tumor size and grade, presence of lymph nodes and distant metastases, and type of surgical intervention. We did not include the Alaskan Native and Native Indian registries in our analysis of annual incidence because valid estimated annual censuses of these populations were not available.

Data Analysis

Values are expressed as mean±standard deviation (median). The 95% confidence intervals for annual incidence were calculated using the Poisson distribution. Categorical variables were analyzed with χ^2 test. Dichotomous outcomes were analyzed using multivariable logistic regression, and models were built with clinically significant variables identified in the SEER dataset. Continuous variables were compared using independent sample t test. Variance equality assumptions were validated using Bartlett's test. The Mantel–Haenszel trend test was used for evaluation of ordinal data. Kaplan–Meier estimates of survival were plotted, and survival differences were analyzed using the log-rank test. Proportional-hazards assumptions were tested using Schoenfeld's residuals. Multivariable survival analysis was performed using a stepwise forward inclusion algorithm of Cox proportional hazard model with inclusion and exclusion probabilities of 0.05 and 0.10, respectively. Statistical significance was assumed at $p \leq 0.05$.

Results

Demographics, Tumor Characteristics, and Incidence Rates

NF-pNEC accounted for 2% of 109,811 pancreatic malignancies registered between 1973 and 2004. The annual

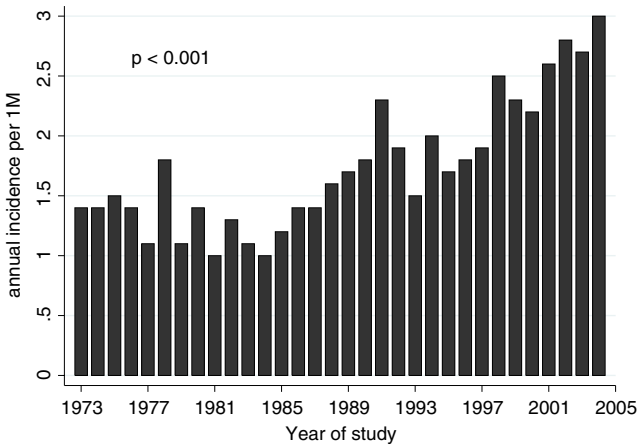

Figure 1 Annual incidence of non-functioning pancreatic endocrine carcinomas.

incidence increased from 1.4 per million in 1973 to 3.0 per million in 2004 (Mantel–Haenszel trend test χ^2 20.9, $p<$ 0.001, Fig. 1). The annual incidence over the first 5 years of the study was 1.34 cases per million (95% CI, 1.12–1.59). In the last 5 years of this study there were 1,087 cases in 415,088,938 person-years, resulting in an average incidence of 2.62 cases per million (95% CI, 2.47–2.78). Trend showed a significant change over the last 5 years of the study (Mantel–Haenszel trend test χ^2 4.2, p=0.040, Fig. 1).

The majority of patients were men (1,206/2,158; 55.9%). The mean age at diagnosis was 59±15 years (median 60 years) with 29% of cases younger than 50 years. Tumors measured 59±35 mm (median 50 mm) in diameter and were either located in the pancreatic head (42%), body (11%), tail (27%), or were diffuse (20%). There was no significant difference in tumor size between surgical and non-surgical treatments (58±36 mm vs. 59±34, p=0.394). Nodal metastases were present in 43.5% of patients (270 patients among 620 cases with known nodal status). Distant metastases were documented in 60% of patients (944 patients) with available data during their initial evaluation (n=1,573). Within the entire cohort, prior malignancy was reported in 15.1% of cases (326/2,158). Tumor grade was determined in 614 patients, with 34.2% grade I, 27.2% grade II, and 38.6% grade III and IV. Resection was performed in 46.2% of patients (735 out of 1,590 with available detailed information).

Is the Presence of Nodal and Systemic Metastases Predictable?

Using preoperative clinical variables only, we predicted the presence of nodal and distant metastases (Table 1). Interestingly, tumor size was predictive of nodal involvement, but not of systemic metastases. Conversely, age was not predictive of nodal involvement, but was predictive of systemic metastases. Discrimination ability of both models was poor (area under receiver operator curve 0.61 and 0.59, respectively), and thus they are of limited clinical utility.

Survival Analysis: Tumor and Patient Characteristics

At the censor date, 746 of 2,158 patients were alive. Of the 1,412 who died, 958 patients (67.8%) succumbed to NF-pNEC, and 454 died of other causes. Median survival was 2.2 years. Overall 5-, 10-, and 20-year survival rates were 33%, 17%, and 10%, respectively. Increasing age was associated with reduced survival. Patients with distant metastases at the time of diagnosis experienced significantly shorter overall survival than those without metastases (median 7.1 years vs. 1.4 years; p<0.001; Table 2 and Fig. 2). The presence of nodal metastases had no significant impact on the duration of survival in univariate analysis (median 6.0 years for node negative vs. 6.3 years for node positive; p=0.139). Higher tumor grade correlated with dismal overall survival (median 7 months for pooled grades III and IV) compared to low grade lesions (5 and 4.4 years for grades I and II, respectively; p<0.001; Fig. 3).

Survival Analysis: Effect of Surgical Treatment

Surgical removal of the primary tumor was performed in 46% of cases and was associated with prolonged survival (median 1.1 vs. 8.4 years; p<0.001). Analysis of survival between those who did and did not receive surgical resection after stratifying by distant metastases status demonstrated that, within both groups, patients treated with

Table 1 Multivariable Logistic Regression Models Predicting Lymph Node and Distant Metastatic Involvement from pNECs

	Lymph node metastasis			Distant metastasis		
	Odds ratio	p	95% confidence interval	Odds ratio	p	95% confidence interval
Gender (referent: male)	0.795	0.207	0.558–1.135	0.793	0.072	0.616–1.020
Age	1.000	0.961	0.988–1.012	1.018	0.001	1.009–1.027
Tumor size (mm)	0.986	0.001	0.980–0.992	1.002	0.245	0.998–1.005

Adjusted effects of preoperative variables (age, gender and tumor size) are indicated. Overall p values for both models is less than 0.001

Table 2 Proportions of Actual 5, 10, 15, and 20-Year Survivors

		Overall survival		Cancer-specific survival	
	n	M_0	M_1	M_0	M_1
5-year	1,573	0.58	0.22	0.70	0.39
10-year	228	0.43	0.08	0.55	0.20
15-year	65	0.30	0.06	0.39	0.17
20-year	8	0.21	0.06	0.39	0.17

Overall and pancreatic cancer specific survival rates are listed separately for cases initially presenting as metastatic and non-metastatic

surgical resection had a longer median survival. There was a significant increase in median survival for patients with resection without distant metastases (1.6 versus 11.3 years, $p<0.001$) and patients with distant metastases (1.0 versus 4.8 years, $p<0.001$). Enucleation compared to resection of the primary tumor was not a significant predictor of survival (median 10.2 versus 9.2 years, $p=0.456$) in the univariate analysis. Based on a multivariable Cox proportional hazard model, the most influential predictors of survival in the order of significance were resection of the primary tumor, low tumor grade, absence of distant metastases, and younger age (Table 3).

We also evaluated the survival benefit of surgical treatment for the subset of patients who presented with distant metastases ($n=614$). The likelihood of resection of the primary tumor was highly dependent on tumor grade: 79% of grade I and II primary tumors were resected compared to 25% of grade III and IV tumors ($p<0.001$). This strong association between tumor grade and surgical resection introduced substantial collinearity into the comprehensive Cox models for patients presenting with metastatic disease, thus a limited model using age and surgical therapy was used. Resection of either the primary tumor or distant metastatic site was associated with increased survival compared to no resection; the greatest survival benefit was seen in patients with the resection of both the primary tumor and metastases ($p<0.001$, Fig. 4, Table 4).

Discussion

Non-functional pancreatic neuroendocrine carcinomas represent about 2% of all pancreatic malignant tumors. In general, patients with pNECs manifest a prolonged survival;[14,16,19] however, there is a substantial variability in their clinical outcomes.[11,14] Despite a considerable amount of research, our understanding of natural history,[2,8,20] predictors of survival,[3,14,19] efficacy of multimodality therapy,[9,13,21,22] and prognosis[6,10,14,18] remains incomplete.

The SEER program is an excellent tool for population analysis of rare malignancies because of its data collection for over 30 years, extraordinary accuracy, and close approximation to the general US population.[7] Therefore, we conducted this study to elucidate some aspects of incidence trends, tumor characteristics, prognostic factors, and effectiveness of surgical therapy in patients with non-functional pNECs.

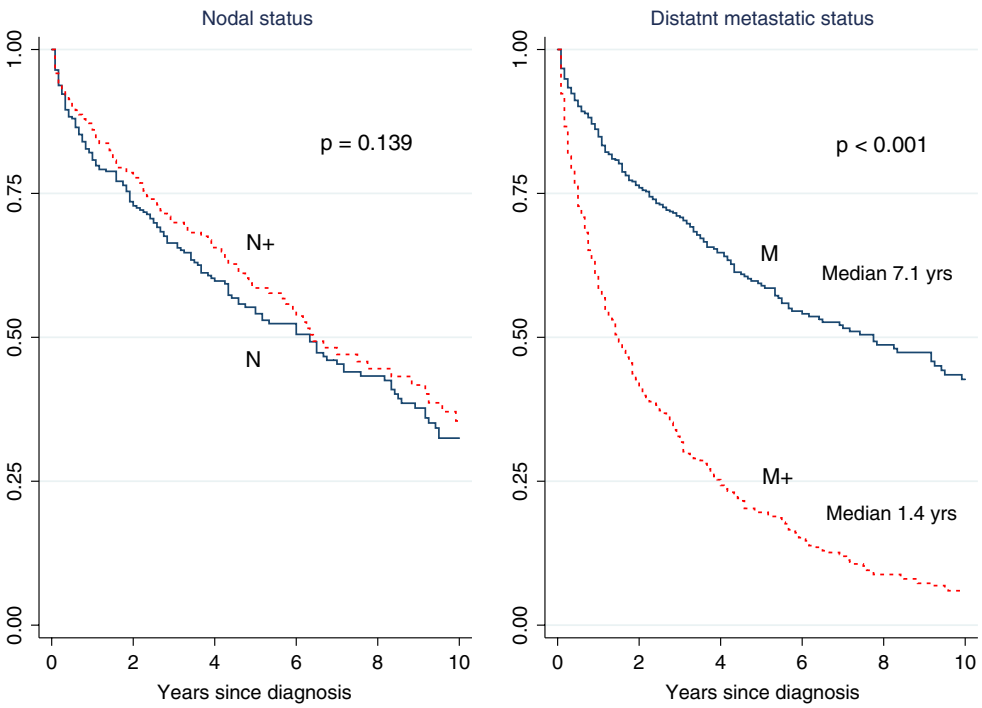

Figure 2 Survival estimates for patients by nodal status (*left panel*; median survival 6 and 6.3 years, $p=0.139$) and distant metastatic status at the time of diagnosis (*right panel*; $p<0.001$).

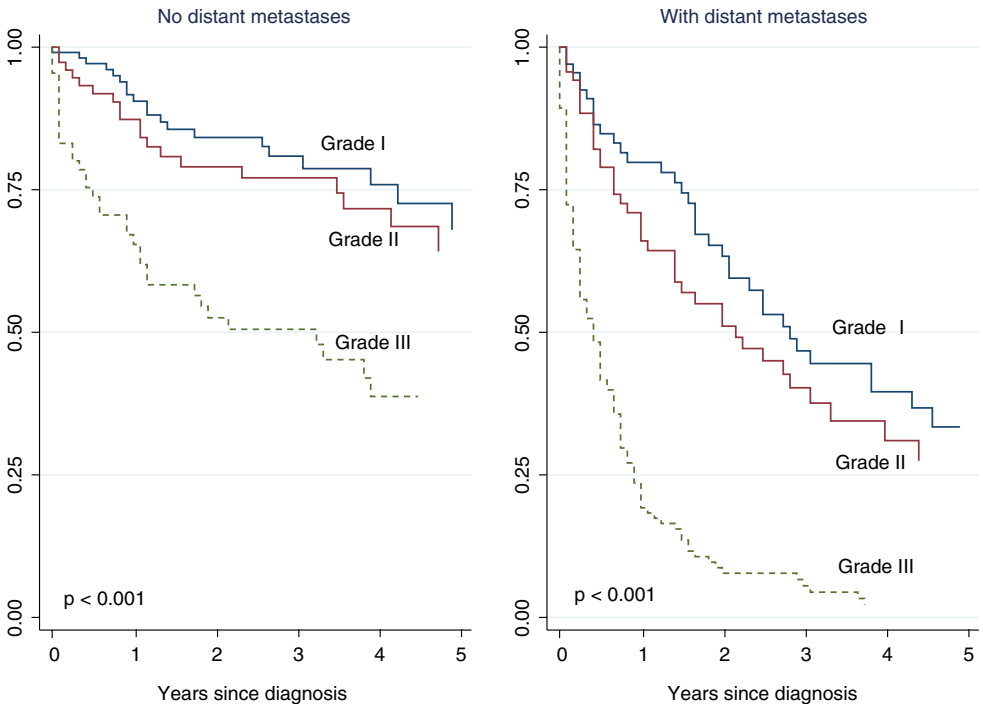

Figure 3 Survival estimates by tumor grade for patients without and with distant metastatic disease ($p<0.001$ for both).

In the SEER database, we identified 85% of pNECs as non-functional, which is similar to some previous findings.[13] An increasing incidence of all neuroendocrine tumors has been suggested over the last 50 years;[2] data from the Michigan registry[15] and Mayo clinic[11] demonstrate an increasing incidence of NF-pNEC. We also identified an increased incidence of clinically detectable NF-pNECs, with the annual incidence rate increasing from 1.4 to 3.0 new cases per million from 1973 to 2004.

There are substantial differences in the natural history and clinical behavior of neuroendocrine tumors arising in different anatomic sites.[2,3] Currently, pancreatic neuroendocrine tumors do not have a commonly accepted staging system, although a specific scheme was suggested.[3] While the American Joint Committee on Cancer staging excludes pNEC histology, it has good discrimination prognostic ability.[19] Tumor size was not predictive of survival in a large report from the MD Anderson Cancer Center,[18] but univariate analysis in two other large studies, suggested that small tumors (<2–3 cm) are associated with better survival.[14,17] Conversely, and in agreement with our data, tumor size and nodal status were not predictive of survival in the analysis of nearly 10,000 cases from the National Cancer Data Base.[13] Therefore, we, and others, believe that other factors, such as systemic metastases, local, vascular and lymphatic invasion, and grade,[5,10,18] are more powerful indicators of outcome. Additionally, in our study, tumor grade influence on survival was larger than the presence of distant metastases. Despite presumed variability in grading methodology among institutions, this variable retained its pivotal prognostic value.

A recent validation study of the WHO classification assessed 180 patients with non-functional pancreatic neuroendocrine tumors[14] and confirmed that distant metastatic spread and poor differentiation as negative prognostic markers. Conversely to our report, these authors identified nodal metastases as a negative predictor of survival among patients with malignant non-functional pancreatic neuroendocrine tumors. A proposed expert consensus-based TNM staging classification for pancreatic neuroendocrine tumors[3] utilizes tumor size and nodal metastases as predictors. On the contrary, we and others[6,16,18] found no survival predictive value of nodal metastases and tumor size.

Table 3 Multivariable Cox Regression Model for All Patients with NF-pNEC (n=2,158)

	HR	95% CI for HR		p
		Lower	Upper	
Age	1.022	0.999	1.043	0.051
T size (mm)	1.005	0.999	1.010	0.073
N status	1.382	0.809	2.361	0.236
M status	1.895	1.092	3.289	0.023
Grade				
I	1.000	Referent		
II	2.268	1.215	4.232	0.010
III	3.422	1.751	6.687	0.001
Resection of the primary site	0.237	0.132	0.424	0.001

Adjusted effect of age, primary tumor resection, nodal status, distant metastatic status, tumor grade, and size on survival. Overall model $p<0.001$

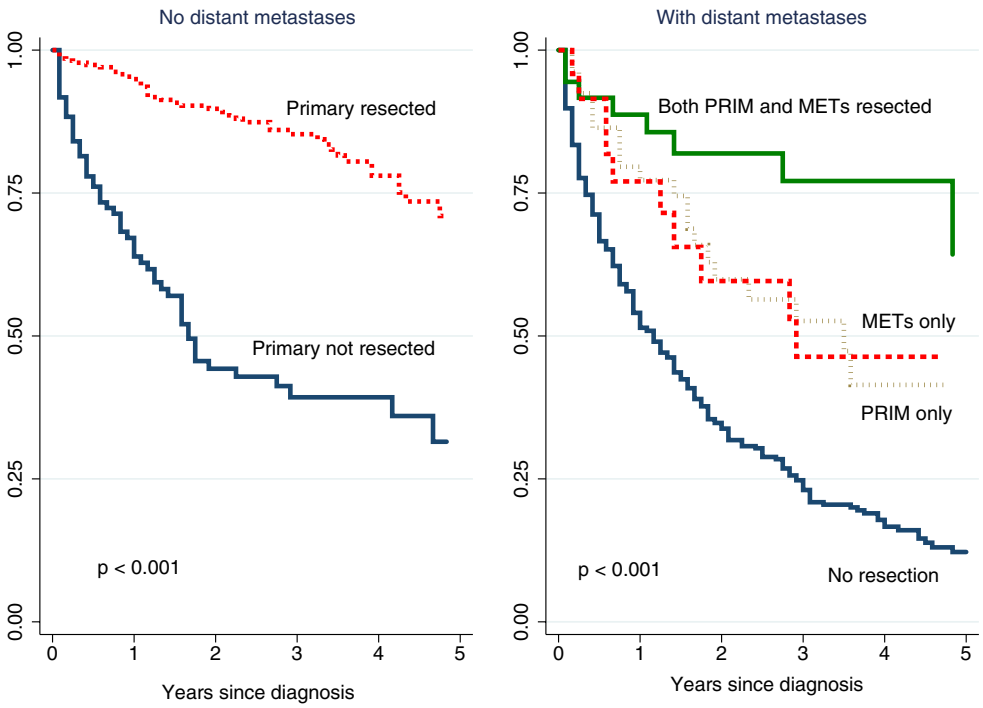

Figure 4 Survival estimates for patients according to metastatic status and resection of the primary tumor ($p<0.001$). Median survival times are listed in years.

Aggressive resection of both the primary tumor and metastasectomy is associated with improved survival in the present series. As expected, the largest benefit in this study was seen among patients undergoing the removal of both primary and metastatic sites. Patients with distant metastases undergoing resection of primary tumor only or metastases only, had similar survival rates of 3.5 and 2.9 years, respectively. Nevertheless, this was significantly longer than the median survival for those without any surgical treatment (1.0 year, $p<0.001$ for each). Other studies have specifically noted that a cytoreductive approach to hepatic metastatic disease[22–25] and nodal clearance[20] are associated with prolonged survival. Additionally, patients with liver metastases benefit from removal of primary neuroendocrine tumor alone.[26]

There are striking similarities between data presented here and those reported on 163 NF-pNEC treated at MD Anderson Cancer Center.[18] Both studies demonstrate a 60% distant metastatic involvement at presentation, beneficial effect of primary tumor resection, a lack of tumor size as a survival predictor, and similar overall survivals rates. It should be noted that despite the prolonged survival[9,18,21] this tumor can be fatal, and is cause of death in 67% of patients diagnosed with pancreatic neuroendocrine carcinoma.

We had hypothesized that enucleation is less effective in prolonging survival compared to formal pancreatic resection for treatment of pNEC, despite being associated with better functional outcomes.[27] Therefore, we evaluated enucleation versus formal resection for pNECs and found no survival difference between the two operations. It must be assumed that proper patient selection influenced this finding.

The present study is not prospective and all patients underwent individualized treatment, therefore, these results

Table 4 Multivariable Cox Regression Model for Patients with Metastatic NF-pNEC and Detailed Data on Resection of Primary and Distant Sites ($n=614$)

	HR	95% CI for HR		P
		Lower	Upper	
Age (per year)	1.030	1.023	1.038	<0.001
Resection of the primary site	0.457	0.306	0.683	<0.001
Resection of the metastatic site	0.404	0.245	0.668	<0.001

Adjusted effect of primary tumor resection and metastatic site resection on the survival are noted. Overall model $p<0.001$

cannot be viewed as a proof for the efficacy of surgical therapy. Nevertheless, we have demonstrated that surgical resection, including removal of metastases, is associated with improved survival. Multiple additional factors could influence these results including evolving terminology, changing registry protocols, and our inability to review histological material. Tumor grading for pNEC is in evolution and in the past has not been consistently reported. Determination of the malignant potential remains controversial in neuroendocrine tumors; however, most non-functional pancreatic neuroendocrine tumors are considered malignant.[10,12,14] Although these aspects may lower the reliability of our study, population characteristics remain important.

Conclusion

In summary, non-functional pancreatic NECs are uncommon, but their incidence is rising. Tumor size and nodal metastases do not predict survival, whereas grading and systemic metastases have a significant impact on survival. There is a clear association between survival and surgical therapy among select patients with both localized and metastatic disease. Moreover, resection and enucleation result in similar survival rates.

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