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2014 SSAT PLENARY PRESENTATION

# Surgical Resection Provides an Overall Survival Benefit for Patients with Small Pancreatic Neuroendocrine Tumors

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**Abstract**
*Background* The optimal management of small (≤2 cm) pancreatic neuroendocrine tumors (PNETs) remains controversial. We evaluated these tumors in the National Cancer Data Base (NCDB) to determine if resection provides a survival advantage over observation.
*Methods* The NCDB was queried to identify patients with nonmetastatic PNETs ≤2 cm treated between 1998 and 2006. Kaplan-Meier survival estimates, stratified by grade and treatment type, evaluated the difference in 5-year overall survival (OS) between patients who underwent resection and observation. Multivariable Cox regression was used to determine the importance of resection in OS.
*Results* Three hundred eighty patients met inclusion criteria. Eighty-one percent underwent resection; 19 % were observed. Five-year OS was 82.2 % for patients who underwent surgery and 34.3 % for those who were observed ($p<0.0001$). When controlling for age, comorbidities, income, facility type, tumor size and location, grade, margin status, nodal status, surgical management, and nonsurgical therapy in the Cox model, observation [hazard ratio (HR) 2.80], poorly differentiated histology (HR 3.79), lymph node positivity (HR 2.01), and nonsurgical therapies (HR 2.23) were independently associated with an increase in risk of mortality ($p<0.01$).
*Conclusion* Patients with localized PNETs ≤2 cm had an overall survival advantage with resection compared to observation, independent of age, comorbidities, tumor grade, and treatment with nonsurgical therapies.

**Keywords** Pancreas · Neuroendocrine · Tumor · Surgery · Survival

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## Introduction

The biologic variability of pancreatic neuroendocrine tumors (PNETs) has been well documented. There is a generally held belief that larger tumors (>4 cm) have a greater potential for aggressive behavior, but it is also clear that even among large tumors, there is substantial biologic variability, with some tumors being high grade and aggressive and others being low grade and indolent.[1] Predicting which tumor will behave in a malignant manner remains a challenge, and therefore, PNETs that are symptomatic or nonfunctioning and have a size >2 cm are typically resected when found in patients who are otherwise fit for surgery.

There continues to be substantial controversy regarding the best management of PNETs that are smaller than 2 cm. PNETs are rare neoplasms (0.30/100,000 persons in the general population);[2] there are little data to guide the optimal management of incidentally discovered small PNETs, and surgical management remains controversial. The evidence that does

exist to currently guide management comes from underpowered, single institutional, retrospective series. Examined together, these studies offer results that often conflict. Comparing resection of small, nonfunctional tumors with a nonoperative approach in a prospective controlled trial is impractical given the rare incidence of these tumors and has not been done.

In the current study, we sought to use data from the National Cancer Data Base (NCDB) to determine the prognostic significance of demographic, clinical, and pathologic factors in patients with localized, nonfunctioning small PNETs (≤2 cm) in an effort to better understand which, if any, of these small tumors may be safely observed rather than treated with surgical resection. Our hypothesis was that PNETs ≤2 cm and of low pathologic grade would demonstrate better overall survival than high-grade tumors of the same size and might be safely observed.

## Materials and Methods

### Data Source

The NCDB is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The NCDB captures information from approximately 1,500 CoC-accredited hospitals and >70 % of all newly diagnosed malignancies in the USA. It contains specific details about patient demographics (age, sex, race, payer), facility type and location, tumor characteristics (size, grade, stage, histology), treatment course (type of surgery, receipt of chemotherapy, and radiation therapy), and outcomes (margin and lymph node status and vital status). All data within the NCDB are de-identified of specific patient and hospital factors and are thus in compliance with the Health Insurance Portability and Accountability Act (HIPAA).

### Study Population

The NCDB was queried to identify all patients ≥18 years old diagnosed with small (≤2 cm) nonfunctioning pancreatic neuroendocrine carcinomas between 1998 and 2006 and who had all or most of their treatment at the recording facility. Tumor histology at the time of diagnosis was classified according to the International Classification of Disease for Oncology, Third Edition (ICD-O-3). Patients were excluded if they had metastatic disease or other concomitant cancer diagnoses or if resection status was unknown.

Patient age at diagnosis was analyzed as younger than 45, between ages 45 and 64, and 65 years or older. The race of each patient was categorized into White and non-White, and insurance status was examined as private, Medicaid, Medicare, and uninsured/unknown.

Facility type included community cancer program, comprehensive community cancer program, and academic/research/National Cancer Institute (NCI) program and is distinguished according to the number of newly diagnosed cancer patients treated and if postgraduate medical education is offered. Specifically, community cancer programs treat between 100 and 500 newly diagnosed cancer patients each year; comprehensive community cancer programs treat more than 500 cases a year. Academic/research facilities treat more than 500 new cancer cases and offer postgraduate medical education and are grouped with NCI-designated cancer centers that provide clinical care and health professional specialized training and conduct research and public outreach.

### Statistical Analysis

Statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC). $p$ values ≤0.05 were considered statistically significant. Age, demographic factors, comorbid condition (Charlson score), and pathologic features for patients who underwent surgical resection were compared to those for patients undergoing observation to assess bias. Comparisons among groups were performed using Student's $t$ test for continuous variables or chi-square or Fisher's exact test for categorical variables as appropriate. Kaplan-Meier survival estimates were used to evaluate 5-year overall survival (OS) between the patients who received surgery and those who did not; the log-rank test was used to evaluate for statistical significance. Patient, tumor, and facility factors were analyzed in a multivariate Cox logistic regression model using stepwise backward elimination selection ($p$=0.2) to evaluate variables associated with mortality; hazard ratio values >1 represented an increased risk of death.

## Results

### Patient Demographics

Three hundred eighty patients met selection criteria, 309 (81.3 %) underwent a pancreatic resection, and 71 (18.7 %) were observed. Most patients were between 45 and 64 years old (49.5 %); were women (57.4 %), White (76.1 %), healthy [Charlson score 0 (51.1 %)]; and had insurance (75 %). Most patients were treated in a comprehensive community cancer center or academic/research/NCI institution (93.9 %) and did not receive additional nonsurgical therapy (i.e., chemotherapy, chemoradiation, or radiation) (87.1 %). Tumors were generally 1–2 cm (80.8 %), located in the body/tail (67.6 %), and with unknown grade status (49.7 %).

Table 1 shows the patient and demographic characteristics of patients who did and did not undergo surgical resection.

**Table 1** Demographic, clinical, and pathologic characteristics for patients with PNETs ≤2 cm, $n=380$

| Characteristic | Observation, $n$ (%) $n=71$ (18.7) | Resection, $n$ (%) $n=309$ (81.3) | $p$ value |
|---|---|---|---|
| Age (years) | | | 0.0003 |
| <45 | 9 (12.7) | 81 (26.2) | |
| 45–64 | 30 (42.3) | 158 (51.1) | |
| ≥65 | 32 (45.1) | 70 (22.7) | |
| Sex | | | 0.691 |
| Male | 32 (45.1) | 130 (42.1) | |
| Female | 39 (54.9) | 179 (57.9) | |
| Race | | | 0.878 |
| White | 55 (77.5) | 234 (75.7) | |
| Black | 16 (22.5) | 75 (24.3) | |
| Charlson score | | | 0.480 |
| 0 | 38 (53.5) | 156 (50.5) | |
| 1 | 6 (8.5) | 42 (13.6) | |
| 2 | 1 (1.4) | 11 (3.6) | |
| Unknown | 26 (36.6) | 100 (32.4) | |
| Income status (annual median, $) | | | 0.973 |
| <35,000 | 17 (23.9) | 65 (21) | |
| 35,000–44,999 | 21 (29.6) | 92 (29.8) | |
| 45,000–59,999 | 17 (23.9) | 72 (23.3) | |
| ≥60,000 | 12 (16.9) | 59 (19.1) | |
| Unknown | 4 (5.6) | 21 (6.8) | |
| Insurance status | | | 0.0013 |
| Private | 22 (31) | 143 (46.3) | |
| Medicaid | 5 (7) | 17 (5.5) | |
| Medicare | 31 (43.7) | 67 (21.7) | |
| Uninsured/others | 13 (18.3) | 82 (26.5) | |
| Facility type | | | 0.0151 |
| Community cancer program | 0 (0) | 8 (2.1) | |
| Comprehensive community cancer program | 29 (40.8) | 81 (26.2) | |
| Academic/research/NCI program | 37 (52.1) | 210 (68) | |
| Others | 5 (7) | 10 (3.2) | |
| Tumor size (cm) | | | 0.409 |
| 0–1 | 16 (22.5) | 57 (18.5) | |
| 1.1–2 | 55 (77.5) | 252 (81.6) | |
| Tumor location | | | 0.264 |
| Body/tail | 44 (62) | 213 (68.9) | |
| Head | 27 (38) | 96 (31.1) | |
| Grade | | | 0.003 |
| Well differentiated | 13 (18.3) | 116 (37.5) | |
| Moderately differentiated | 4 (5.6) | 28 (9.1) | |
| Poorly differentiated/ undifferentiated | 10 (14.1) | 20 (6.5) | |
| Unknown | 44 (62) | 145 (46.9) | |
| Nonsurgical therapy | | | 0.0016 |
| No | 53 (74.7) | 278 (90) | |
| Yes | 15 (21.1) | 23 (7.4) | |
| Unknown | 3 (4.2) | 8 (3) | |

Patients who underwent resection were more likely to have private insurance, be treated in an academic/research/NCI center, and to have well-differentiated tumors where grade status was known. Patients who were observed were more likely to have tumors with an unknown grade status and to receive additional nonsurgical therapy. There was no difference between patients who did and did not undergo surgical resection with regard to race, Charlson score, or tumor size. Patients who underwent resection had a 29 % lymph node positivity rate, and 9 % of patients had positive margins.

## Survival

The 5-year overall survival rate for the whole cohort was 73.6 % with a median follow-up of 5 years. For patients who underwent resection, the median survival was >5 years, with a 5-year OS rate of 82.2 %; for those who were observed, the median survival was 2 years, with a 5-year OS rate 34.3 %. Figure 1 shows the Kaplan-Meier survival curves and the significant survival advantage of patients with PNETs ≤2 cm who underwent surgical resection over patients who were observed ($p<0.0001$).

In the multivariate Cox regression model, adjusting for age, Charlson score, income, facility type, tumor size, tumor location, grade, margin status, lymph node status, surgical status (observation or resection), and nonsurgical therapies, surgical resection continued to be a significant predictor of survival, with nearly three times the risk of mortality when surgery was not performed compared to surgical resection [hazard ratio (HR) 2.80, $p=0.0103$] (Table 2). Poorly differentiated/undifferentiated tumors were associated with almost four times the risk of mortality when compared to well-differentiated/moderately differentiated tumors (HR 3.79, $p<0.0001$). Other factors found to be significantly associated with mortality were age ≥65 years compared to <45 years (HR=3.26), income (HR=0.26–0.53), facility type (HR=0.19–0.28), tumor location in the head (HR=1.75), lymph node positivity (HR=2.01), and nonsurgical therapy (HR=2.23). The size of these small tumors did not affect survival, and margin status also did not affect survival.

The median survival for patients with well-differentiated/moderately differentiated tumors who underwent resection was >5 years; for those who had poorly differentiated/undifferentiated tumors and who underwent surgery, the

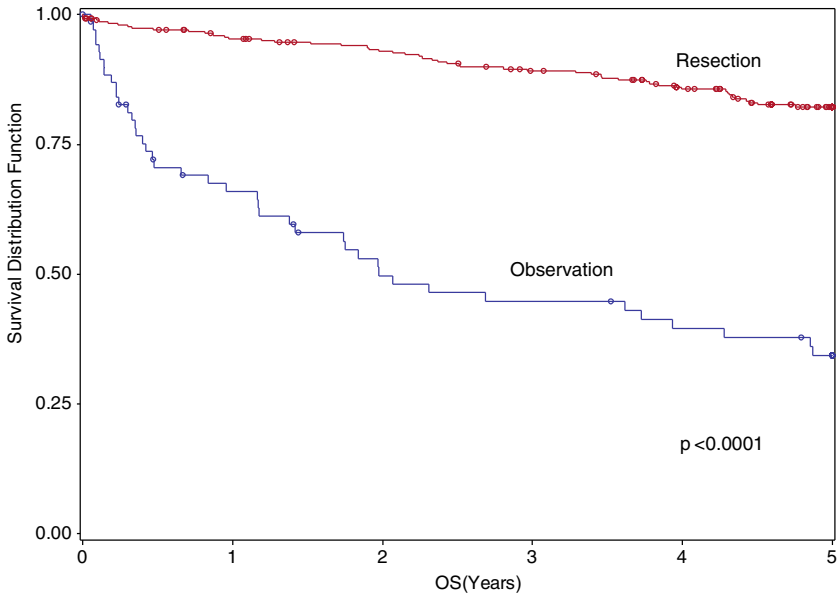


**Fig. 1** Kaplan-Meier survival estimates comparing patients with PNETs ≤2 cm who underwent surgical resection or observation

median survival was 2.3 years. To examine the interaction between surgery and the degree of tumor grade, separate Kaplan-Meier survival estimates were created for patients stratified by surgery and grade and compared with the log-rank test (Fig. 2). Patients who had well-differentiated/moderately differentiated tumors and underwent resection had the best 5-year overall survival, while patients with poorly differentiated/undifferentiated tumors who were observed had the worst survival. In patients with well-differentiated/moderately differentiated tumors, the median survival for patients who received surgery was >5 years, while for patients who did not, the median survival was 4.9 years ($p<0.0001$). In patients with poorly differentiated/undifferentiated tumors, the median survival for patients who underwent resection was 2.37 years, while patients who were observed had a median survival of 0.4 years ($p=0.64$).

## Discussion

The biologic behavior of PNETs is variable. Prior efforts to determine factors predictive of tumor growth, nodal or distant metastases, or survival have not yielded consistent data. Surgical resection is the typical management for these tumors but has been challenged for PNETs <2 cm for which there is a lack of demonstrable benefit on survival. Currently, the National Comprehensive Cancer Network acknowledges *careful observation* as an appropriate management course in patients with nonfunctioning, incidentally discovered tumors <1 cm, specifically for tumors in the pancreatic head, patients with significant comorbid diseases, and patients perceived to be at high surgical risks. However, the data for this exclusion of surgical management are sparse.

Our current study is the largest to date of nonfunctioning PNETs exclusively ≤2 cm and has several important findings. We have shown that patients who are managed with observation have nearly three times the risk of mortality as those who undergo resection. Our data suggest that surgical resection provides a survival benefit independent of patient age, Charlson score, facility type, grade, margin and lymph node status, and additional nonsurgical therapy, even in patients with well-differentiated/moderately differentiated histology. This observation is based on the best available data and provides evidence supporting aggressive surgical resection in a subpopulation of PNETs frequently observed.

Consistent with other studies,[3,4] we demonstrated grade in general to be a significant predictor of mortality, with high-grade tumors exhibiting the worst overall survival. In our study, surgical resection seemed to provide a benefit regardless of tumor grade. Patients with poorly differentiated/undifferentiated tumors who underwent resection had a median overall survival longer than 2 years, while those who were observed had a median survival of only 4.8 months. This difference did not reach statistical significance; however, the number of patients who had poorly differentiated/undifferentiated tumors was small (30 of the 380) and our dataset may simply not have been powered to detect a difference between those that were and were not resected in the subgroup of poorly differentiated/undifferentiated tumors. It is our opinion that resection results in improved survival for patients with poorly differentiated/undifferentiated tumors, but our study lacks statistical power to demonstrate this, and no conclusive recommendations can be made. We also hypothesized that patients with low-grade PNETs ≤2 cm would

**Table 2** Cox multivariate regression analysis predicting risk of all-cause mortality for patients with PNETs ≤2 cm, $n$=380

| Characteristic | Hazard ratio | 95 % CI | $p$ value |
|---|---|---|---|
| Age (years) | | | |
| <45 | Ref | Ref | Ref |
| 45–64 | 1.59 | 0.922, 2.753 | 0.0949 |
| ≥65 | 3.26 | 1.814, 5.864 | <0.0001 |
| Charlson score | | | |
| 0 | Ref | Ref | Ref |
| 1 | 0.98 | 0.514, 1.880 | 0.958 |
| 2 | 0.93 | 0.219, 3.959 | 0.924 |
| Unknown | 1.86 | 1.210, 2.844 | 0.0046 |
| Income status (annual median, $) | | | |
| <35,000 | Ref | Ref | Ref |
| 35,000–44,999 | 0.53 | 0.321, 0.863 | 0.0109 |
| 45,000–59,999 | 0.50 | 0.298, 0.851 | 0.0104 |
| ≥60,000 | 0.26 | 0.131, 0.523 | 0.0001 |
| Unknown | 0.83 | 0.370, 1.844 | 0.641 |
| Facility type | | | |
| Community cancer program | Ref | Ref | Ref |
| Comprehensive community cancer program | 0.28 | 0.101, 0.772 | 0.014 |
| Academic/research/NCI program | 0.19 | 0.070, 0.515 | 0.0011 |
| Others | 0.40 | 0.115, 1.404 | 0.153 |
| Tumor size (cm) | | | |
| 0–1 | Ref | Ref | Ref |
| 1.1–2 | 1.24 | 0.728, 2.109 | 0.429 |
| Tumor location | | | |
| Body/tail | Ref | Ref | Ref |
| Head | 1.75 | 1.178, 2.607 | 0.0056 |
| Grade | | | |
| Well differentiated | Ref | Ref | Ref |
| Moderately differentiated | 0.99 | 0.465, 2.109 | 0.979 |
| Poorly differentiated/ undifferentiated | 3.79 | 2.104, 6.838 | <0.0001 |
| Unknown | 0.92 | 0.581, 1.460 | 0.726 |
| Margin status | | | |
| Negative | Ref | Ref | Ref |
| Positive | 1.43 | 0.702, 2.928 | 0.323 |
| Unknown | 1.32 | 0.649, 2.675 | 0.446 |
| Lymph nodes status | | | |
| Negative | Ref | Ref | Ref |
| Positive | 2.01 | 1.199, 3.369 | 0.0081 |
| Not examined | 1.59 | 0.922, 2.758 | 0.0952 |
| Surgical management | | | |
| Yes | Ref | Ref | Ref |
| No | 2.80 | 1.275, 6.159 | 0.0103 |
| Nonsurgical therapy | | | |
| Yes | Ref | Ref | Ref |
| No | 2.23 | 1.347, 3.676 | 0.0018 |
| Unknown | 0.98 | 0.231, 4.193 | 0.982 |

not only have a better overall survival than those with high-grade tumors but also that they may be safely observed. Our data demonstrate, however, that even patients with low-grade tumors have a better overall survival with surgical resection. This is an important finding since this is the group of patients who are often considered for nonoperative management.

Our study suggests that small size alone is not a reliable indicator of aggressive behavior. In a prior study from our group[3] using multi-institutional data from resected PNETs, we demonstrated that of the 56 patients who had tumors ≤2 cm, three (5.4 %) developed distant metastases over a median follow-up of 33 months. Likewise, the retrospective series by Haynes et al.[5] from Massachusetts General Hospital reviewed 139 patients with incidental nonfunctioning PNETs and found a 7.7 % rate of distant metastases in resected PNETs <2 cm with a median follow-up of 34 months. In contrast, other studies have shown no change in tumor size, evidence of local invasion, nodal or distant metastases, or deaths from disease over 4 years of follow-up in PNETs <2 cm.[6,7] These latter studies, however, were single institutional series and were limited by small numbers of patients.

The importance of lymph node status in small PNETs has not been definitively delineated. We found that patients with positive lymph nodes had an increased risk of mortality and that 29 % of patients who underwent resection had positive nodes. In another study using the SEER database, Franko et al.[2] evaluated 2,158 patients with a median tumor size of 5 cm and demonstrated that surgical resection, distant metastases, and high-grade tumors, but not tumor size or nodal status, were predictors of overall survival. Our study, however, focused on patients with PNETs ≤2 cm and suggests that even for these small tumors, positive lymph nodes are associated with an increased risk of death. Consistent with other studies,[6] our series showed that margin status was not associated with an effect on overall survival.

Our current study also demonstrated that higher income status was associated with improved overall survival in patients with PNETs ≤2 cm. This association with income and overall survival has previously been shown in an analysis of the NCDB of patients who are resected for pancreatic adenocarcinoma.[8] This may be due to increased access to general health care or the ability to travel to academic/research institutions for treatment in high-volume centers for pancreatic disease, including high-volume surgeons and multidisciplinary care.

There has been one prior study from the National Cancer Data Base on PNETs. This study[4] developed a prognostic model predicting malignancy for PNETs of all sizes and found no correlation between tumor size and survival. This study, however, has limited implications in our understanding of small PNETs, since the majority of tumors were >2 cm and the conclusions from the analyses will be driven by these larger tumors. Our analysis is unique in the number of patients

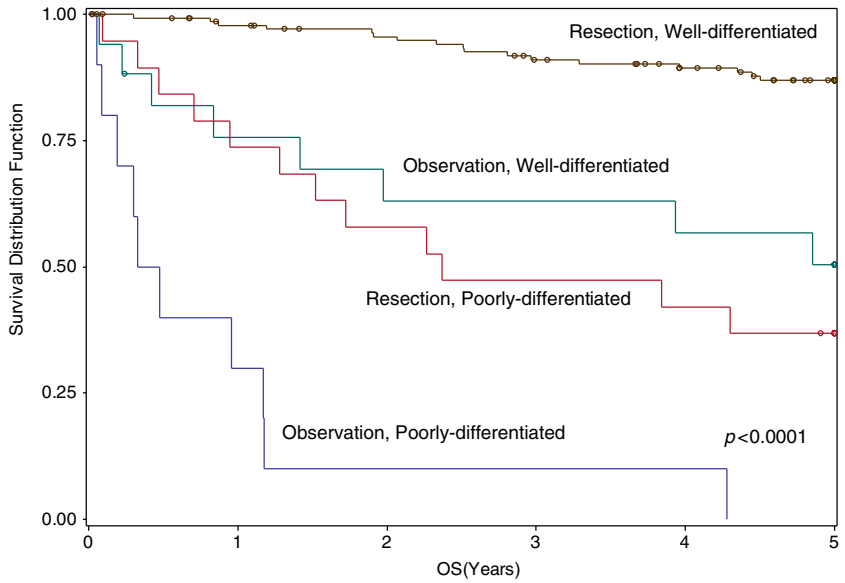


**Fig. 2** Kaplan-Meier survival estimates comparing patients with PNETs ≤2 cm who underwent surgical resection or observation, by histologic grade. Well-differentiated/moderately differentiated tumors that were resected had a significantly greater overall survival compared to all other groups ($p<0.0001$). There was no statistical difference in the survival between well-differentiated/moderately differentiated tumors that were observed compared to poorly differentiated/undifferentiated tumors that were resected ($p=0.167$). Within the subgroup of poorly differentiated/undifferentiated tumors, there was no statistical difference in overall survival based on surgical management ($p=0.640$)

and its focus on tumors specifically ≤2 cm. Within this small subset of PNETs, we also demonstrated no effect on survival of patients with tumors ≤1 cm or between 1 and 2 cm.

The current study has several limitations. It is a retrospective review of a National Cancer Data Base and, as such, is subject to omitted variable bias. It also only captures information on tumors classified as malignant by NCDB coders; those that are benign are not reported, and our population subset may consequently represent a selection of tumors that is more aggressive than the average PNET. Patients with tumors that appear to have benign features on imaging or biopsy or lack significant growth change may be under observation and perhaps are underreported to the NCDB. Because tumor grade has only in the last decade become recognized as an important prognostic factor of survival in patients with PNETs, the NCDB had not consistently captured tumor grade prior to the most recent version of the AJCC grading system. Further, it is not possible within the NCDB to determine symptoms at presentation; therefore, of the tumors that were resected, the percentage that was asymptomatic is not known. Whether these tumors were incidentally discovered is also unknown. Additionally, the use of octreotide is not captured by the database. The NCDB also only records overall survival; disease-specific survival is not described. The reason for nonoperative management, despite a small tumor size, is not delineated. It is not known if these tumors increased in size or displayed malignant characteristics prompting surgical resection. The NCDB does record some information on the reason as to why patients do not receive surgery, including if the patient had comorbidities that precluded an operation. A very small percentage of patients (1.6 %) were reported to have forgone surgery as a result of comorbid disease. The majority of patients under observation have listed that surgery was not part of the planned treatment course, but the reason itself is not given. It is therefore possible that these patients were encouraged to pursue observation for reasons related to debilitating comorbid cardiopulmonary disease but that those data were simply not captured. Given this, the low 5-year OS of patients who underwent observation for nonmetastatic small PNETs may be secondary to mortality from comorbid diseases. However, >50 % of patients who underwent observation or surgical resection had a Charlson score of 0 and the substantial difference in survival may not be wholly explained by a burden of comorbid conditions. Despite the limitations, this is the largest study of nonfunctional PNETs ≤2 cm utilizing a large national database with the best available data and supports the contention that resection of small PNETs is associated with an overall survival advantage.

## Conclusion

In conclusion, we have demonstrated that surgical resection provides a survival benefit in nonfunctional pancreatic neuroendocrine tumors ≤2 cm, even in patients with favorable well-differentiated and moderately differentiated histology. Tumor size and margin status were not predictors of survival; however, lymph node positivity was associated with a decreased 5-year overall survival. These data may provide additional

guidance for clinicians' decision-making regarding observation versus resection for these small pancreatic tumors.

## References


1. Bettini R, Partelli S, Boninsegna L, Capelli P, Crippa S, Pederzoli P, Scarpa A, Falconi M. Tumor size correlates with malignancy in nonfunctioning pancreatic endocrine tumor. Surgery 2011;150:75–82.
2. Franko J, Feng W, Yip L, Genovese E, Moser AJ. Non-functional neuroendocrine carcinoma of the pancreas: incidence, tumor biology, and outcomes in 2,158 patients. Journal of Gastrointestinal Surgery 2010;14:541–548.
3. Cherenfant J, Stocker SJ, Gage MK, Du H, Thurow TA, Odeleye M, Schimpke SW, Kaul KL, Hall CR, Lamzabi I, Gattuso P, Winchester DJ, Marsh RW, Roggin KK, Bentrem DJ, Baker MS, Prinz RA, Talamonti MS. Predicting aggressive behavior in nonfunctioning pancreatic neuroendocrine tumors. Surgery 2013;154:785–791.
4. Bilimoria KY, Talamonti MS, Tomlinson JS, Stewart AK, Winchester DP, Ko CY, Bentrem DJ. Prognostic score predicting survival after resection of pancreatic neuroendocrine tumors: Analysis of 3851 patients. Annals of Surgery 2008;247:490–500.
5. Haynes AB, Deshpande V, Ingkakul T, Vagefi PA, Szymonifka J, Thayer SP, Ferrone CR, Wargo JA, Warshaw AL, Fernandez-del Castillo C. Implications of incidentally discovered, nonfunctioning pancreatic endocrine tumors: Short-term and long-term patient outcomes. Archives of Surgery 2011;146:534–538.
6. Lee LC, Grant CS, Salomao DR, Fletcher JG, Takahashi N, Fidler JL, Levy MJ, Huebner M. Small, nonfunctioning, asymptomatic pancreatic neuroendocrine tumors (PNETs): Role for nonoperative management. Surgery 2012;152:965–974.
7. Gaujoux S, Partelli S, Maire F, D'Onofrio M, Larroque B, Tamburrino D, Sauvanet A, Falconi M, Ruszniewski P. Observational study of natural history of small sporadic nonfunctioning pancreatic neuroendocrine tumors. Journal of Clinical Endocrinology and Metabolism 2013;98:4784–4789.
8. Kooby DA, Gillespie TW, Liu Y, Byrd-Sellers J, Landry J, Bian J, Lipscomb J. Impact of adjuvant radiotherapy on survival after pancreatic cancer resection: An appraisal of data from the National Cancer Data Base. Annals of Surgical Oncology 2013;20:3634–3642.


## Discussant

**Dr. Nabil Wasif (Scottsdale, AZ):** Management of incidentally found small pancreatic neuroendocrine tumors can be clinically quite vexing, and I commend the authors for carrying out this study. The difficulty of studying this "orphan" tumor is highlighted by the fact that even in the largest cancer registry in the world, only 380 patients met inclusion criteria. I have the following questions and comments.

1. The difference in overall survival between patients undergoing surgery versus observation (82 and 34 %) is so stark that I cannot shake the possibility of selection bias explaining your findings. Patients who are judged unfit for surgery are observed and, hence, may be dying of the comorbid diseases that precluded surgical resection in the first place, and not from the neuroendocrine tumor under observation. Are you satisfied with the risk adjustment methodology, i.e., Charlson score and age, used for this study?
2. As a corollary to the first question why did you choose to use overall survival and not disease-specific survival as an endpoint? Do you agree that disease-specific survival would be a more appropriate endpoint in order to account for competing risks from comorbidity?
3. You examine the interaction between surgery and tumor grade in your manuscript. In your experience, how often do patients with a classic PNET on imaging undergo FNA? If they do, how accurate is the assessment of tumor grade based on cytology and can that be reliably used to inform decision making?

## Closing Discussant

**Dr. Sharpe:** Thank you for your comments and questions. I agree that the overall survival difference between patients who undergo resection and those who are observed is quite impressive. There is no doubt that there is selection bias in the database. The cases within the NCDB are all malignant tumors and likely represent the more aggressive versions of pancreatic neuroendocrine tumors being seen nationally each year. There may also be reporting bias. Patients who are observed may not necessarily get captured in the NCDB. We did attempt to ensure that the survival advantage observed was related to treatment type as best as possible within the limits of the database by controlling for age and Charlson score in our multivariate model. Moreover, this is the largest series specifically addressing the effect of resection on overall survival in PNETs 2 cm or less and demonstrates a survival benefit with resection that is quite large. Given the magnitude of this difference, it would be hard to imagine that the whole difference is due to some omitted variable(s). Certainly, surgical resection has associated morbidity, but I think we should carefully consider future recommendations for observation in patients with tumors between 1 and 2 cm.

I do agree that disease-specific survival would be a more appropriate endpoint than overall survival to account for comorbidities, but at this time, the National Cancer Data Base reports only overall survival and not disease-specific survival.

In our experience, almost all patients with a classic PNET on imaging undergo FNA and many are referred to us having already had the procedure. Several papers have looked at EUS-FNA sensitivity and specificity for tumor diagnosis and in assessment of grade. For tumor diagnosis, the sensitivity and specificity is 80–95 %; for assessment of grade, it is 80 % sensitive and 100 % specific. In our institution, the EUS-FNA is about 80 % sensitive, so I think with a skilled endosonographer and cytopathologist, EUS-FNA is highly accurate. Data for the accuracy of EUS-FNA in the NCDB are not available and could not be determined for this current review.