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Role of Resection of the Primary in Metastatic Well-Differentiated Neuroendocrine Tumor

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Abstract

Objectives: Resection of the primary (RP) in metastatic neuroendocrine tumor (NET) is controversial. The aim is to evaluate survival outcomes for RP in metastatic NET patients.

Methods: Data were obtained from United States (US) hospitals at the National Cancer Database between 2004 and 2014. Chi-square, analysis of variance tests, univariate and multivariate cox

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Statements

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Statement of Ethics

Ethical approval was not required for the study since patient information in the database is completely de-identified and the database is legally accessible to the public.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

proportional hazards models were evaluated. Kaplan-Meier curves and log-rank tests conducted to compare the survival difference of patient characteristics.

Results: A total of 2361 patients identified. The mean age was 62.1 years (standard deviation, 13), male to female ratio 1:1; 33% were small intestine, 26.3% pancreas, and 24.4% lung; 69.6% were well differentiated grade and 42.5% underwent RP. The 5-year overall survival (OS) was significantly improved for patients who underwent RP in small intestine (5-year OS, 63.9% vs 44.2%), lung (5-year OS, 65.4% vs 20.2%), and pancreas tumors (5-year OS, 75.6% vs 30.6%). On multivariate analysis, RP (hazard ratio, 0.46; 95% confidence interval, 0.29–0.73; $P < 0.001$), female, year of diagnosis 2010–2014, margin, Charlson-Deyo score <2, and age <51 years, were associated with better OS.

Conclusions: Resection of the primary in metastatic well/intermediate-differentiated NET is associated with improved OS compared to no RP.

Keywords

resection; metastatic; well/intermediate-differentiated; neuroendocrine tumor

Introduction

The annual incidence of neuroendocrine tumor (NET) is increasing, due to a true increase in incidence, increased use of improved diagnostic tools, or a combination.[1,2] The clinical course of NET is highly variable and is manly determined by the pathologic grade and clinical stage. NET vary from well-differentiated, slow growing tumors to aggressive, highly proliferative poorly differentiated tumors.[3] Within the well/moderately differentiated group of tumors, the functional NET pose a therapeutic challenge compared to the non-functional NET because of the impact of hormonal production on organ function and quality of life.[4,5] The majority of NET are diagnosed at advanced stages with around 60–80% presenting with distant metastasis at diagnosis.[6] The 5-year overall survival of patients with NET ranges from 35 to 82% in well/moderately differentiated NET.[7,8]

There are no prospective studies to show survival benefit of the resection of the primary tumor in patients with metastatic NET. Many retrospective studies advocate the resection of the primary pancreatic and small bowel tumors in the setting of metastatic disease.[9–13] The most recent European Neuroendocrine Tumor Society (ENETS) and North American Neuroendocrine Tumor Society (NANETS) guidelines have adopted removing the primary tumor in patients with G1-G2 NET carrying distant metastases only if limited complication risks and intent-to-cure in offering treatments are provided.[14,15] The utility of primary tumor resection is even more questionable for functional NET because of the minimal benefit in the palliative setting of symptom control[11,16–18] and for pancreatic NET, considering the risk of postoperative complications.[19, 20] The management of lung NET is similar to that of gastroenteropancreatic NET taking into consideration pathological features (mitotic count, Ki-67), somatostatin receptor expression, growth rate and disease extent[21].

Stage IV well/intermediate differentiated NET treated with surgical resection of the primary site is frequently associated with improved overall survival (OS) compared to non-surgical

therapy in small retrospective analyses. The aim of this study is to evaluate the impact of surgical resection of the primary tumor in patients with unresected distant metastases from NET as well as identify variables associated with prolonged survival in this patient population using the National Cancer Database (NCDB).

MATERIALS AND METHODS

Data was obtained from the NCDB between the years 2004 and 2014. With more than 1500 Commission-on-Cancer-accredited cancer programs participating, the database contains clinical and demographic information on the majority of US cancer patients. Selection criteria for the study included well/intermediate differentiated stage IV NET. Exclusion criteria were patients with missing follow up data and patients who received surgery for metastatic sites. The primary outcome was overall survival in stage IV NET patients who received surgical resection of the primary site. Patient-specific covariates included age at diagnosis, sex, race, insurance status, year of diagnosis, primary site, histology, treatment received (including surgical resection of primary site, chemotherapy and radiation), surgical margins, and Charlson-Deyo score. Ethical approval was not required for the study since patient information in the database is completely de-identified and the database is legally accessible to the public.

Statistical Analysis

The clinical and demographic characteristics of the patients were summarized using descriptive statistics as appropriate for variable type and distribution. All clinically meaningful variables were included and subsequently eliminated based on the level of significance. Chi-square and ANOVA tests were done to identify factors associated with surgical modality. Univariate and multivariate analyses were conducted to identify factors associated with patient outcome. To assess the association between patient characteristics and survival, Cox proportional hazards models were fitted with a backward elimination method (removal criteria $P = 0.05$). Likelihood ratio test (LRT) was used to compare the model with the covariate being assessed; both added with the model and with the assessed covariate dropped. An alpha level of 0.05 was used, and any covariate with LRT P value >0.05 was removed from the final multivariate model. We used backward elimination to automate the LRTs, and determine the final model with the covariates presented. In addition, sensitivity analysis was added to force the covariates with concerns back to the multivariate model to ascertain significant association with overall survival (OS). Kaplan-Meier curves were generated for overall survival. All analyses were done using SAS 9.4 (SAS Institute, Inc., Cary, NC) with a significant level of 0.05.

RESULTS

Patient Demographics and Tumor Characteristics

A total of 2361 patients with advanced stage well to intermediate-differentiated NET older than 18 years were identified (Table 1). The mean age at diagnosis was 62.1 years (standard deviation [SD], 13), with an equal male to female ratio [1:1] (Table 2). About 83% (n = 1958) were White and the majority of NET primaries were in the small intestine (n =780,

33.0%), pancreas (n = 620, 26.3%), lung (n = 576, 24.4%), and colon/rectum (n =278, 11.8%). Majority of the tumors were well differentiated tumors (n = 1643, 69.6%) followed by moderately differentiated (n = 718, 30.4%). Histology codes included neuroendocrine carcinoma (n = 1690, 71.6%), carcinoid tumor (n = 595, 25.2%), and atypical carcinoid tumor (n = 76, 3.2%). The most common metastatic site was the liver (n = 1179, 49.9%), followed by lung (n = 176, 7.5%), bone (n = 152, 6.4%), and brain (n = 44, 1.9%). Most patients had a Charlson-Deyo score of 0 (n = 1784, 75.6%), 18.0% (n = 425) had a score of 1, and 6.4% (n = 152) had a score of 2. A higher number of patients were diagnosed between 2010 and 2014 compared to 2004–2009 (% of patients,70.6% vs 29.4%). About 44.5% (n = 1051) of the patients were treated at community practices, while 40.1% (n = 946) were treated at academic or research cancer centers.

Treatment

Surgery—Patients who underwent surgery at the primary site constituted 42.5% (n =1003), while 57.5% (n = 1358) did not have surgery (Table 3). About 67.3% (n = 675) of the patients who underwent resection had negative margins ($P < 0.001$) (Table 4). Surgery for primary site occurred more often in patients with private insurance (% of patients, 53.6%), year of diagnosis 2010–2014 (78.0%), small bowel primary site (% of patients, 58.2%), and 0–3 positive regional nodes (% of patients, 47.1%) compared to uninsured/Medicaid/Medicare (4.3%/5.3%/36.8%), year of diagnosis 2004–2009 (% of patients, 22.0%), pancreas/lung/colon and rectum primary site (11.1%/10.3%/17.5%), 4–86 positive regional nodes (% of patients, 34.3%) respectively ($P < 0.001$) (Table 4).

Chemotherapy and Radiation Therapy—Chemotherapy was given in 31.9% of patients (11.5% single agent, 18.3% multi-agent) and 10.8% received radiation (Table 3). In patients who underwent surgery for primary site, 18.6% received chemotherapy, compared to non-surgical candidates that received chemotherapy more often (41.8%) (Table 4). In patients who underwent surgery for primary site, 5.1% received radiation, compared to 15.1% in the non-surgery group ($P < 0.001$).

Overall Survival

On univariate and multivariate analyses resection of the primary (hazard ratio [HR], 0.46; 95% confidence interval [CI], 0.29–0.73; $P < 0.001$) was associated with improved overall survival (OS) compared to no surgery. Other covariates associated with improved survival included female sex (HR, 0.88; 95% CI, 0.78–0.99; $P = 0.030$), year of diagnosis 2010–2014 (HR, 0.82; 95% CI, 0.73–0.94; $P = 0.003$), neuroendocrine tumor histology (HR, 0.67; 95% CI, 0.57–0.78; $P < 0.001$), negative surgical margin (HR, 0.73; 95% CI, 0.57–0.94; $P = 0.014$), Charlson-Deyo score <2, and age <51 years at diagnosis (HR, 0.62; 95% CI, 0.51–0.75; $P < 0.001$) compared to male sex, year of diagnosis 2004–2009, other histologies, positive surgical margin, Charlson-Deyo score = 2 (HR, 1.78; 95% CI, 1.44–2.21; $P < 0.001$), and age >52 years at diagnosis respectively (Table 5). Chemotherapy and radiation were not associated with improved OS (Table 5). Five-year OS for resection of the primary site (5-year OS, 60.6%) was higher than for no surgical treatment (5-year OS, 28.1%) (Fig. 1). A similar pattern is seen when stratified for comorbidity score, age, and histology. Resection of the primary in stage IV well/intermediate-differentiated NET is associated with

improved 5-year OS compared to patients with no surgery in small intestine (5-year OS, 63.9% vs 44.2%) (Fig. 2), lung (5-year OS, 65.4% vs 20.2%) (Fig. 3), pancreas tumors (5-year OS, 75.6% vs 30.6%) (Fig. 4), and rectum/colon tumors (5-year OS, 39.6% vs 19.7%) (Fig. 5).

Subtype Analysis

For the pancreas subset, 17.9% (n =111/620) underwent resection. On univariate (HR, 0.29; 0.19–0.43; P <0.001) and multivariate (HR 0.33; 95% CI, 0.22–0.49; P < 0.001) analyses, resection of the primary was associated with improved OS compared to no surgery (Supplemental Table 1). Five-year OS for resection of the primary site (% of patients, 75.6%) was higher than for no surgical treatment (% of patients, 30.6%) (P < 0.001) (Fig. 4).

For the small bowel subset, 74.9% (n = 584/780) underwent resection. On univariate analysis, resection of the primary was associated with improved OS compared to no surgery (HR, 0.47; 95% CI, 0.36–0.61; P < 0.001). On multivariate analysis, resection of the primary leaned towards improved OS compared to no surgery, but did not reach statistical significance (HR, 0.76; 95% CI, 0.50–1.16; P = 0.210) (Supplemental Table 1). Five-year OS for resection of the primary site (% of patients, 63.9%) was higher than for no surgical treatment (% of patients, 44.2%) (P < 0.001) (Fig. 2).

For the remaining subset in the total cohort, 32.0% (n = 308/961) underwent resection. On univariate (HR, 0.39; 95% CI, 0.32–0.48; P < 0.001) and multivariate (HR, 0.44; 95% CI, 0.32–0.61; P < 0.001) analyses, resection of the primary was associated with improved OS compared to no surgery (Supplemental Table 1). Five-year OS for resection of the primary site (49.3%) was higher than for no surgical treatment (21.7%) (P < 0.001) (Supplemental Fig. 1).

DISCUSSION

Surgical resection of the primary tumor in patients with metastatic well/intermediate differentiated NET is a controversial practice.[22] The majority of patients with NET have diffuse metastatic disease at presentation.[23] In these patients, curative metastatectomy is challenging. There remains uncertainty whether removal of the primary tumor leads to a survival benefit.[10,11,14,21,24–30] This study suggests that primary tumor resection is associated with prolonged survival for patients with well or intermediate differentiated metastatic NET of the small bowel, pancreas, lung, colon and rectum, even without metastatectomy. Similarly, a study from the United States reported a progression-free survival of 56 months after primary tumor resection in patients with non-resectable liver metastases from NET compared with 25 months observed when the primary tumor was not resected, with median survivals of 159 vs 47 months, respectively.[18] In the UK and Ireland Neuroendocrine Tumor Society (UKINETS) study, resection of the primary tumor was one of the independent predictors of prolonged survival in midgut tumors with liver metastases.[17] A positive impact on prognosis after resection of the primary tumor has also been reported for pancreatic NET.[10,31] In addition, a study conducted using the California Cancer Registry between the years 2005 and 2011 found that primary tumor resection

in gastrointestinal NET is associated with better OS, with or without liver treatment, irrespective of grade.[32]

Interestingly, in a study conducted by Citterio et al, the gain in survival obtained by surgical resection of the primary tumor was significant and independent from primary tumor site in the selected unfavorable population of metastatic NET.[22] The observed median survival of the patients treated with somatostatin analogue and other medical therapies was 37 months,[8,33] whereas patients in whom medical treatment was complemented with resection of the primary NET tumor, a median survival of 138 months was observed,[22] Similarly, our study reached the conclusion that resection of the primary in stage IV well/intermediate-differentiated NET is associated with improved 5-year OS compared to patients with no surgery in small intestine, lung, and pancreas tumors.

The 2016 ENETS consensus guidelines, in the setting of unresectable metastatic disease recommend palliative resection of primary jejunal and ileal tumors, but did not comment on the role of palliative primary tumor resection in pancreatic NET.[14,21,26] These recommendations are based on early data suggesting the potential for improved survival following resection of intestinal primaries, with the intention of avoiding intestinal obstruction and ischemic complications.[23] The NANETS recommendation for localized pancreatic NET patients who have functional disease is to undergo surgery irrespective of size[34] but no consensus guideline reached in 2020 NANETS update regarding the resection of the non-pancreatic primary in the metastatic disease setting[34] except for locally symptomatic patients. In some reports, resection of the primary NET has a trend towards improved survival for patients who received peptide receptor radionuclide therapy (PRRT) after the resection[35–37] with higher stabilization and objective responses after PRRT leading to better survival outcomes.[35,37] This deserves future retrospective and prospective studies.

Earlier single-center studies, a series of reports using the Surveillance, Epidemiology, and End Results (SEER) database, a review from the California Cancer registry, and an NCDB study for gastroenteropancreatic NET previously established similar findings in more limited patient populations.[18,27,32,36,38–40] To date, this is the largest study examining resection of the primary tumor in stage IV well/intermediate differentiated NET with different anatomical primaries (small bowel, pancreas, lung, colon, rectum) published in the literature and the first report to demonstrate in such selected subgroups of NET a clear positive impact of primary tumor resection on survival.

There are no randomized controlled trials evaluating the outcomes of palliative primary NET resection in stage IV disease.[23] The majority of included studies were retrospective cohort series, which may have therefore been subject to publication bias.[23] In addition, several studies made no attempt to control for confounding variables, leading to a likely bias towards patient who underwent resection.[23] The limitations of this study are related to the retrospective database analysis design. Even though fairly complete and recognized to capture the largest number of cancer patients in the US, disease-specific mortality, recurrence indices, response to treatment and prior history of malignancies are not captured by the NCDB.[41] Information on the specific agents of chemotherapy are not available, however, octreotide analogs are part of the systemic therapy defined

by the NCDB as chemotherapy. Octreotide was not amongst the chemotherapy agents that changed their category to immunotherapy in 2013 (six drugs previously classified as chemotherapy are now classified as biological response modifier therapy (BRM)/ Immunotherapy: Alemtuzumab/Campath, Bevacizumab/Avastin, Rituximab, Trastuzumab/ Herceptin, Pertuzumab/Perjeta, and Cetuximab/Erbitux), so if octreotide was used as first line treatment among the year range which our cohort was diagnosed, then it should be considered in the chemotherapy category. The chemotherapy category group reported here is likely related to the 5FU based treatments like 5FU and streptozocin combinations that were common before year 2010. The chemotherapy category excludes oral therapies which are standard of care now. The oral therapies include tyrosine kinase inhibitors, like sunitinib, and mTOR inhibitors, like everolimus and temsirolimus. In addition, capecitabine and temozolomide combination treatment is not captured by this database. The radiation data included in this analysis is likely to be palliative radiation for symptom management. Additionally, indications for surgery is not available. Patients had surgery for symptomatic or asymptomatic disease. Also, burden of disease, peritoneal, liver and bone disease which usually determine prognosis, is not available. Furthermore, the selection criteria of the patients undergoing surgery is not defined. Missing data on immunohistochemistry, Ki-67 index, mitotic rate, grade and differentiation affect survival and limit the conclusion. Subsequent therapies and exposure to PRRT affect survival and these data are missing. Another limitation of the NCDB is that we do not know if the primary tumor was ‘symptomatic’. Furthermore, the obvious contribution of good patient selection, performance status, and the ability to do the resection with minimal morbidity/mortality to the improved outcomes observed with resection of the primary cannot be overstated. This analysis included different NET primaries with separate sub-group analyses performed. Furthermore, only four distant sites of metastases were assessed and the information on involvement of other organs was unavailable. We excluded patients that received metastatectomies, therefore we were unable to study the benefit of distant site resection in addition to primary site resection. Despite these limitations, our findings have important implications.

The relatively indolent behavior of well/intermediate differentiated NET promotes a strategy of aggressive surgical intervention, even in the setting of metastatic disease. This is particularly true in symptomatic patients with good functional status.[42–44] The findings of the present analysis endorse a role for primary tumor resection in small intestinal, pancreatic, lung, and colorectal tumors, provided surgery can be performed with low morbidity and mortality. Further work is necessary to evaluate any additional benefit of debulking surgery, simultaneous metastatic hepatic and/or peritoneal debulking, cytoreductive surgery with hyperthermic intra-peritoneal chemotherapy and non-surgical targeted liver therapies in extensive hepatic involvement.[23]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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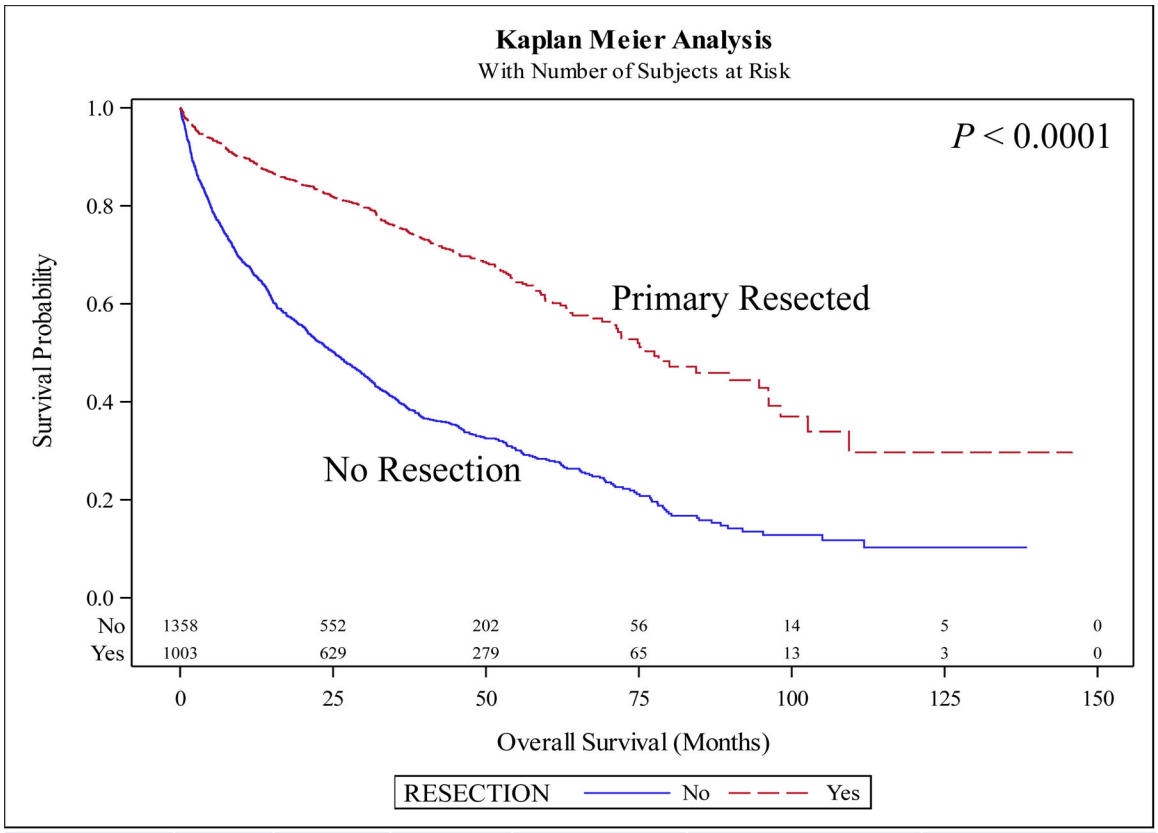
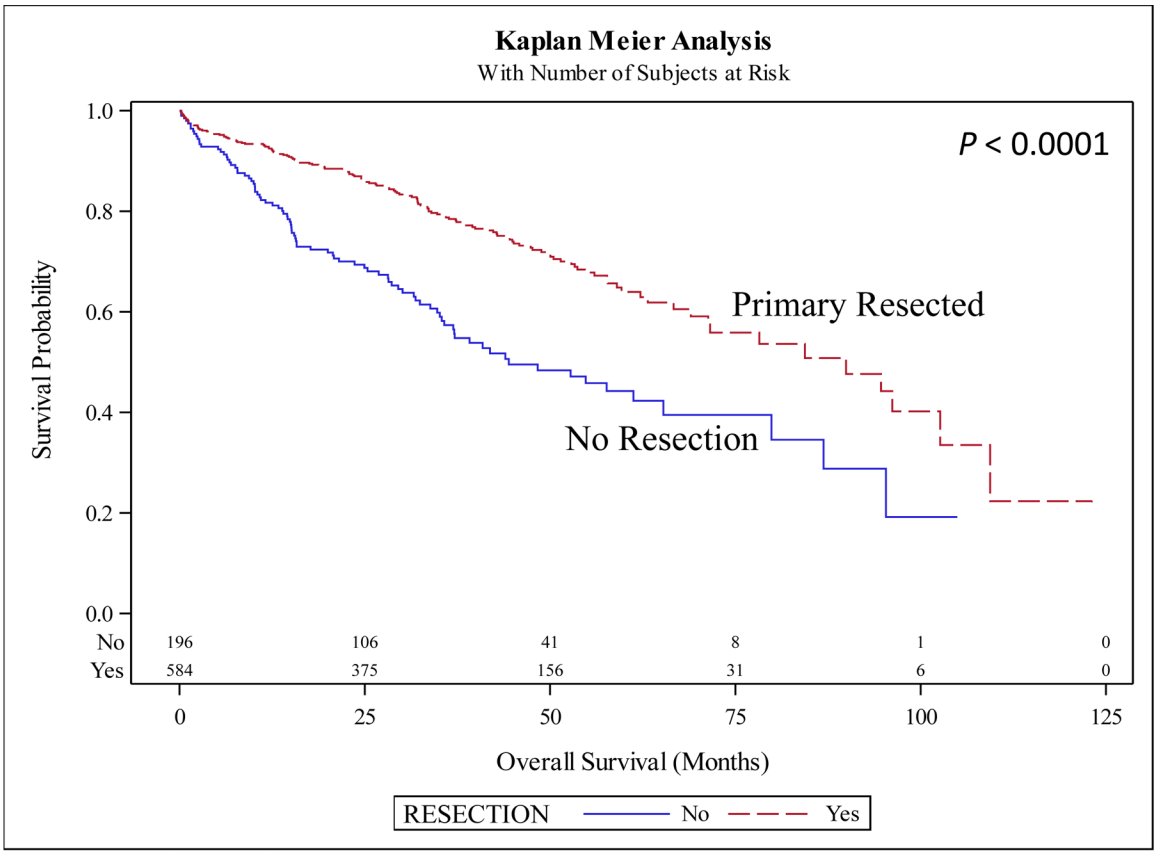


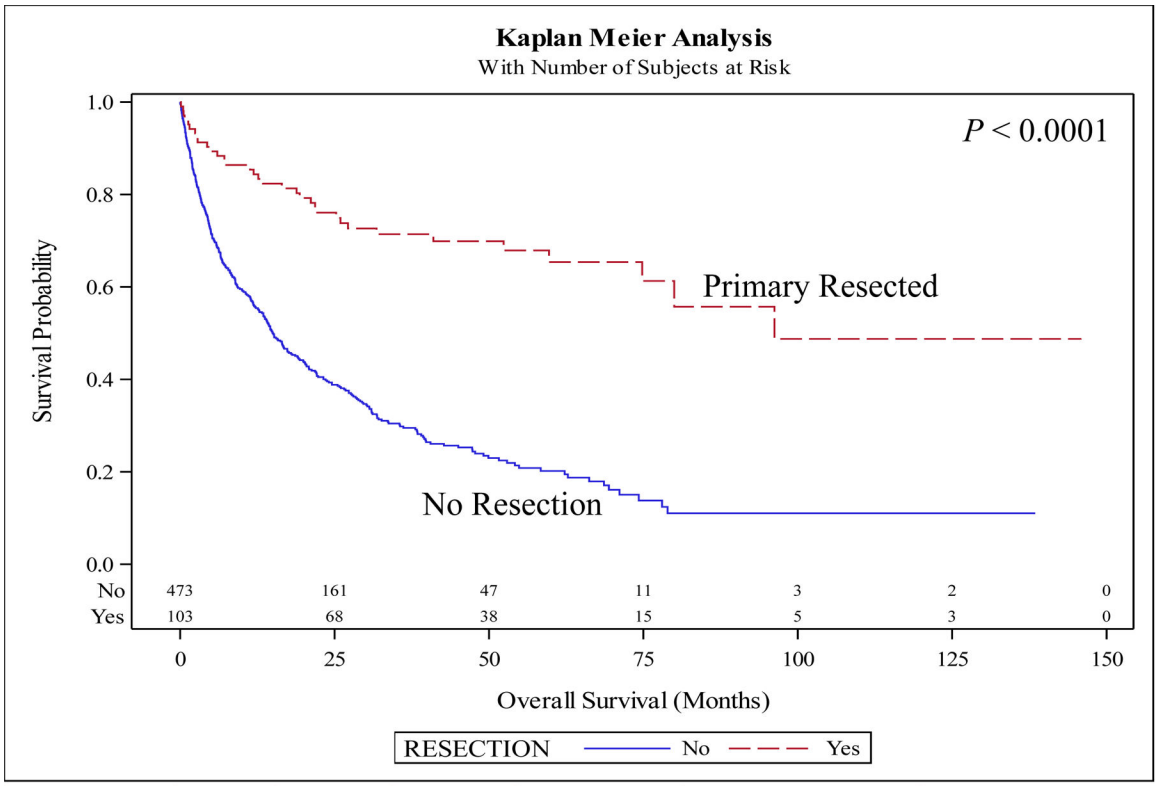
Resection	No. of Subject	Event	Censored	Median Survival (95% CI)	12 mo Survival (95% CI)	60 mo Survival (95% CI)
No	1358	873 (64%)	485 (36%)	25.3 (22.1–28.1)	66.1% (63.5%–68.6%)	28.1% (25.2%–31.2%)
Yes	1003	301 (30%)	702 (70%)	77.5 (71.3–96.2)	89.0% (86.9%–90.8%)	60.6% (56.2%–64.7%)

FIGURE 1.
Kaplan-Meier plot for resection in all patients.



Resection	No. of Subject	Event	Censored	Median Survival (95% CI)	12 mo Survival (95% CI)	60 mo Survival (95% CI)
No	196	90 (46%)	106 (54%)	44.4 (35.7–65.3)	81.7% (75.4%–86.5%)	44.2% (35.1%–52.9%)
Yes	584	147 (25%)	437 (75%)	89.9 (71.3–102.6)	92.8% (90.4%–94.7%)	63.9% (57.8%–69.5%)

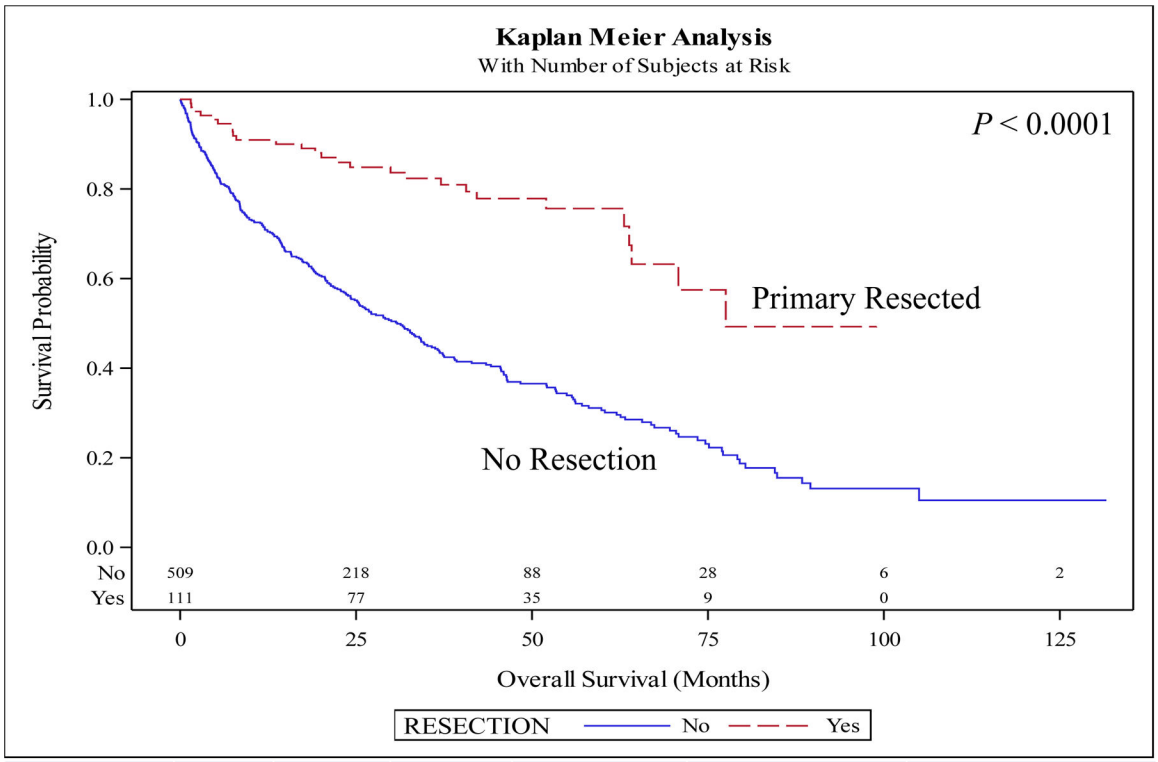
FIGURE 2.
Kaplan-Meier plot for resection stratified by primary site (small bowel).



Resection	No. of Subject	Event	Censored	Median Survival (95% CI)	12 mo Survival (95% CI)	60 mo Survival (95% CI)
No	473	348 (74%)	125 (26%)	15 (12.9–17.9)	55.9% (51.2%–60.2%)	20.2% (15.9%–24.9%)
Yes	103	34 (33%)	69 (67%)	96.2 (74.8–NA)	84.4% (75.8%–90.1%)	65.4% (53.6%–74.8%)

FIGURE 3.

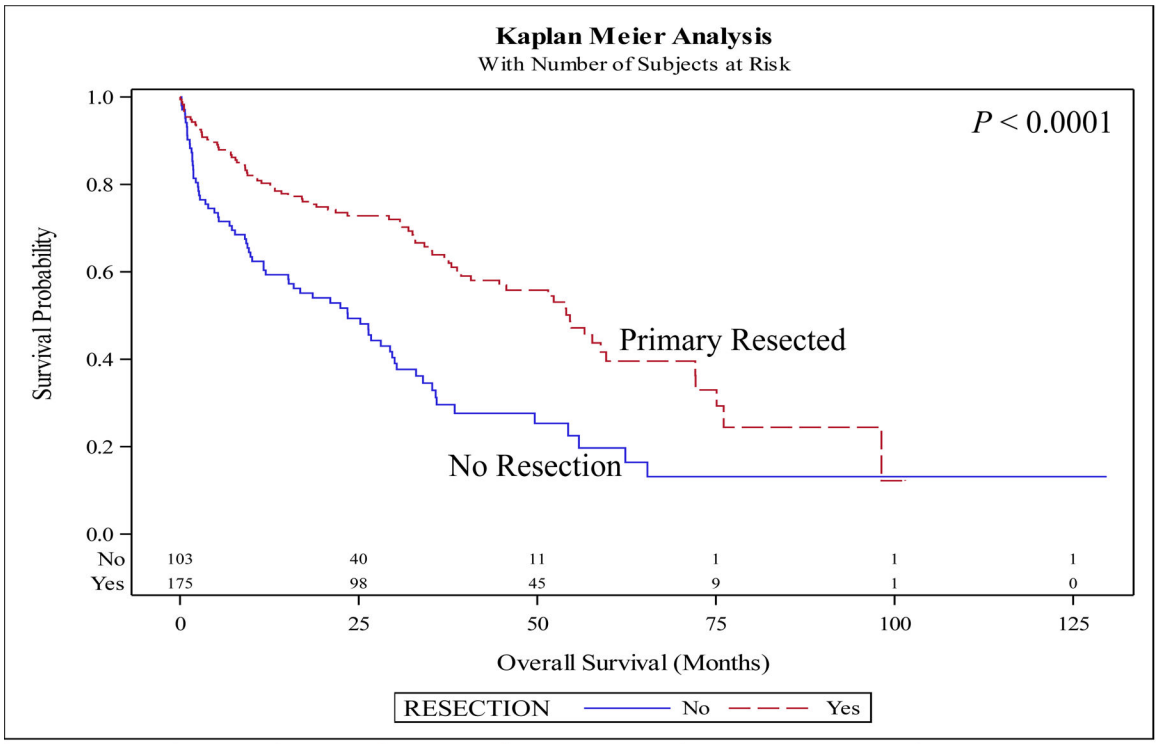
Kaplan-Meier plot for resection stratified by primary site (lung). NA, not applicable or not reached at the time of the analysis.



Resection	No. of Subject	Event	Censored	Median Survival (95% CI)	12 mo Survival (95% CI)	60 mo Survival (95% CI)
No	509	312 (61%)	197 (39%)	30.9 (25.3–34.7)	71.5% (67.3%–75.2%)	30.6% (25.6%–35.7%)
Yes	111	27 (24%)	84 (76%)	77.5 (64.2–NA)	90.9% (83.8%–95.0%)	75.6% (64.6%–83.6%)

FIGURE 4.

Kaplan-Meier plot for resection stratified by primary site (pancreas). NA, not applicable or not reached at the time of the analysis.



Resection	No. of Subject	Event	Censored	Median Survival (95% CI)	12 mo Survival (95% CI)	60 mo Survival (95% CI)
No	103	70 (68%)	33 (32%)	23.5 (12–30)	59.3% (49.1%–68.2%)	19.7% (10.4%–31.1%)
Yes	175	79 (45%)	96 (55%)	54.6 (40.7–59.6)	80.3% (73.5%–85.5%)	39.6% (28.9%–50.0%)

FIGURE 5.
Kaplan-Meier plot for resection stratified by primary site (rectum/colon).

TABLE 1.

Selection/Exclusion Criteria

Selection and Exclusion Criteria	Sample Size	Excluded
NCDB NET cancer cases	130,234	—
Include stage IV patients	24,028	106,206
Well/intermediate differentiated	5376	18,652
Exclude in situ	5376	0
Exclude patients with unknown surgical status for primary site	5358	18
Exclude patients who did not have pathologic confirmation	5341	17
Exclude CLASS OF CASE = 0 *	4831	510
Include SEQUENCE_NUMBER in (0 1) †	4027	804
Exclude patients without follow up data	3342	685
Exclude patients who received surgery for the metastatic sites	2361	981

*Classifies cases recorded in the database.

†Indicates the sequence of malignant and non-malignant neoplasms over the lifetime of the patient.

TABLE 2.

Descriptive Statistics for all Variables of Interest

	N = 2361, n (%)
Age at Diagnosis	
18–34	60 (2.5)
35–50	375 (15.9)
51+	1926 (81.6)
Sex	
Male	1181 (50.0)
Female	1180 (50.0)
Race	
White	1958 (82.9)
Black	316 (13.4)
Other/unknown	87 (3.7)
Primary payor	
Not insured/unknown	121 (5.1)
Private	1103 (46.7)
Medicaid	142 (6.0)
Medicare/other government	995 (42.1)
Year of diagnosis	
2004–2009	694 (29.4)
2010–2014	1667 (70.6)
Histology	
Carcinoid tumor, NOS	595 (25.2)
Neuroendocrine carcinoma, NOS	1690 (71.6)
Atypical carcinoid tumor	76 (3.2)
Primary Site	
Small bowel (ileum, duodenum, jejunum)	780 (33.0)
Pancreas	620 (26.3)
Gastric and stomach	81 (3.4)
Liver	14 (0.6)
Lung	576 (24.4)
Kidney	9 (0.4)
Prostate	3 (0.1)
Rectum and colon	278 (11.8)
Charlson-Deyo score	
0	1784 (75.6)
1	425 (18.0)
2+	152 (6.4)

TABLE 3.

Treatment Received by Study Participants

	N = 2361, n (%)
Resection	
No surgery for primary site	1358 (57.5)
Local tumor destruction	56 (2.4)
Partial resection	681 (28.8)
Total resection	231 (9.8)
Total or partial unknown	35 (1.5)
Regional nodes examined	
0	1415 (59.9)
1–90	842 (35.7)
Not available	104 (4.4)
Regional nodes positive	
0–3	510 (21.6)
4–86	348 (14.7)
Not available	1503 (63.7)
Surgical margins	
Yes	276 (11.7)
No	675 (28.6)
Not available	1410 (59.7)
Radiation therapy at any CoC facility	
No	2084 (88.3)
Yes	256 (10.8)
Not available	21 (0.9)
Chemotherapy at any CoC facility	
No	1518 (64.3)
Chemotherapy administered, type and number of agents not documented	50 (2.1)
Single-agent chemotherapy	272 (11.5)
Multi-agent chemotherapy	431 (18.3)
Not available	90 (3.8)

CoC indicates Commission on cancer coding

TABLE 4.

Univariate Association With Surgical Modality

Covariates	Resection		*P*
	Yes, n = 1003, n (%)	No, n = 1358, n (%)	
Primary payor			**<0.001**
Not insured/unknown	43 (4.29)	78 (5.74)	
Private	538 (53.64)	565 (41.61)	
Medicaid	53 (5.28)	89 (6.55)	
Medicare/other government	369 (36.79)	626 (46.1)	
Year of diagnosis			**<0.001**
2004–2009	221 (22.03)	473 (34.83)	
2010–2014	782 (77.97)	885 (65.17)	
Histology			**<0.001**
Carcinoid tumor, NOS	350 (34.9)	245 (18.04)	
Neuroendocrine carcinoma, NOS	634 (63.21)	1056 (77.76)	
Atypical carcinoid tumor	19 (1.89)	57 (4.2)	
Primary site			**<0.001**
Small bowel (ileum, duodenum, jejunum)	584 (58.23)	196 (14.43)	
Pancreas	111 (11.07)	509 (37.48)	
Gastric and stomach	26 (2.59)	55 (4.05)	
Liver	0 (0)	14 (1.03)	
Lung	103 (10.27)	473 (34.83)	
Kidney	4 (0.4)	5 (0.37)	
Prostate	0 (0)	3 (0.22)	
Rectum and colon	175 (17.45)	103 (7.58)	
Regional nodes examined			**<0.001**
0	166 (16.55)	1249 (91.97)	
1–90	810 (80.76)	32 (2.36)	
Not available	27 (2.69)	77 (5.67)	
Regional nodes positive			**<0.001**
0–3	472 (47.06)	38 (2.8)	
4–86	344 (34.3)	4 (0.29)	
Not available	187 (18.64)	1316 (96.91)	
Surgical margins			**<0.001**
Yes	276 (27.52)	0 (0)	
No	675 (67.3)	0 (0)	
Not available	52 (5.18)	1358 (100)	
Radiation therapy at any CoC facility			**<0.001**
No	938 (93.52)	1146 (84.39)	
Yes	51 (5.08)	205 (15.1)	
Not available	14 (1.4)	7 (0.52)	
Chemotherapy at any CoC facility			**<0.001**

	Resection		
Covariates	**Yes, n = 1003, n (%)**	**No, n = 1358, n (%)**	***P***
No	766 (76.37)	752 (55.38)	
Chemotherapy administered, type and number of agents not documented	14 (1.4)	36 (2.65)	
Single-agent chemotherapy	95 (9.47)	177 (13.03)	
Multi-agent chemotherapy	77 (7.68)	354 (26.07)	
Not available	51 (5.08)	39 (2.87)	
Charlson-Deyo score			0.070
0	776 (77.37)	1008 (74.23)	
1	175 (17.45)	250 (18.41)	
2+	52 (5.18)	100 (7.36)	

$P < 0.05$ is the significant cutoff difference shown in bold font.

TABLE 5.

Multivariable Survival Analysis of OS

	Overall Survival, mo*		
Covariates	**Hazard Ratio (95% CI)**	**HR *P***	**Type3 $P^{\dagger}$**
Resection			**<0.001**
Yes	0.46 (0.29–0.73)	**<0.0001**	
No	REF	—	
Age at diagnosis			**<0.001**
18–34	0.55 (0.34–0.90)	**0.018**	
35–50	0.62 (0.51–0.76)	**<0.001**	
51+	REF	—	
Sex			**0.030**
Female	0.88 (0.78–0.99)	**0.030**	
Male	REF	—	
Year of diagnosis			**0.003**
2010–2014	0.82 (0.73–0.94)	**0.003**	
2004–2009	REF	—	
Histology			**<0.001**
Carcinoid tumor, NOS	0.67 (0.57–0.78)	**<0.001**	
Atypical carcinoid tumor	1.16 (0.86–1.57)	0.331	
Neuroendocrine carcinoma, NOS	REF	—	
Primary Site			**<0.001**
Rectum and colon	1.81 (1.47–2.24)	**<0.001**	
Prostate	2.15 (0.67–6.87)	0.195	
Kidney	2.06 (0.84–5.05)	0.115	
Lung	1.50 (1.24–1.81)	**<0.001**	
Liver	1.09 (0.60–1.98)	0.777	
Gastric and stomach	1.86 (1.34–2.57)	**<0.001**	
Pancreas	1.17 (0.97–1.41)	0.106	
Small bowel (ileum, duodenum, jejunum)	REF	—	
Surgical margins			**0.048**
Not available	0.79 (0.48–1.31)	0.366	
No	0.73 (0.57–0.94)	**0.014**	
Yes	REF	—	
Radiation therapy at any CoC facility			**0.001**
Not available	0.37 (0.11–1.17)	0.090	
Yes	1.33 (1.12–1.58)	**0.001**	
No	REF	—	
Chemotherapy at any CoC Facility			**<0.001**
Not Available	0.83 (0.56–1.22)	0.340	
Multi–agent chemotherapy	1.34 (1.15–1.56)	**<0.001**	

	Overall Survival, mo*		
Covariates	**Hazard Ratio (95% CI)**	**HR *P***	**Type3 *P*†**
Single–agent chemotherapy	1.03 (0.85–1.25)	0.741	
Chemotherapy administered, type and number of agents not documented	1.39 (0.99–1.96)	0.057	
No	REF	—	
Charlson–Deyo Score			**<0.001**
2+	1.78 (1.44–2.21)	**<0.001**	
1	1.03 (0.88–1.20)	0.692	
0	REF	—	

Bold values are statistically significant.

*Number of observations in the original data set = 2361. Number of observations used = 2361.

†Backward selection with an alpha level of removal of .20 was used. The following variables were removed from the model: Regional Nodes Examined, Regional Nodes Positive, Pathologic Stage Group, Race, Spanish Hispanic Origin, and Urban/Rural 2013.

REF indicates reference