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ORIGINAL ARTICLE

Predictors and Outcomes of Minimally Invasive Surgery for Small Bowel Neuroendocrine Tumors

Minimally Invasive Surgery for SBNETs

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Abstract

Background Open surgical resection with regional lymphadenectomy is the standard of care for small bowel neuroendocrine tumors (SBNETs). There is no consensus on the role of minimally invasive surgery (MIS). This study aims to evaluate the current national trends for MIS in treating SBNETs and its association with lymph node (LN) yield.

Methods The National Cancer Database was queried for patients with Stage I-III SBNETs who underwent surgery from 2010–2017. Time trends were examined using the Cochran–Armitage test. Chi-square tests, t test, and multivariable logistic regression assessed associations of surgical approach with patient, clinical, and facility characteristics. Kaplan–Meier curves and propensity score weighted Cox proportional hazards model were used to examine survival.

Results Of the 11,367 patients with Stage I-III SBNETs, 46.5% (N = 5,298) underwent MIS. From 2010–2017, the proportion of MIS increased from 35.6% to 57.7% ($P < 0.001$). Patients of Stage I disease (OR = 1.23), Caucasian race (OR = 1.18), private insurance (OR = 1.29), and higher volume centers (OR = 1.29) were more likely to undergo MIS (all $P < 0.02$). The average number of LN harvested in the MIS cohort was greater than in the open surgery cohort (13.3 vs 11.8 LN, $P < 0.001$). MIS patients had shorter length of stay by 2 days compared to open surgery (5.4 vs 7.6 days, $P < 0.001$). LN yield ≥ 8 was associated with better survival (HR = 0.77, $P < 0.001$).

Conclusion The utilization of a MIS approach to treat Stage I-III SBNETs has increased, especially at higher volume centers. We did not observe an inferior LN harvest with the MIS cohort compared to the open surgery cohort.

Keywords Neuroendocrine tumors · Minimally invasive surgery · Lymph node harvest · NCDB · Outcomes · Surgical access

Meeting Presentations
- Clinical Congress 2021 – American College of Surgeons, Virtual Quick Shot Oral Presentation, October 2021.
- North American Neuroendocrine Tumor Society 2021 Medical Symposium, Virtual Poster Presentation, November 2021.

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Abbreviations

SBNETs	Small bowel neuroendocrine tumors
MIS	Minimally invasive surgery
LN	Lymph node
AJCC	American Joint Committee on Cancer
NCDB	National Cancer Database
ICD	International Classification of Diseases

Introduction

Small bowel neuroendocrine tumors (SBNETs) are the most common small bowel cancer in the USA, and its prevalence and incidence continue to rise.[1,2] The initial treatment for locoregional disease in the jejunum or ileum is segmental small bowel resection of the mass with regional lymphadenectomy, which has been more commonly performed under an open approach.[3–5] A minimally invasive surgery (MIS) approach via laparoscopy continues to be controversial due to concern for inadequate examination for multi-focal and occult sub-centimeter tumors or for lymph node (LN) metastases (which are thought to be more easily detected by manual palpation), and technical difficulties of performing oncologically appropriate and safe resection of masses near the mesenteric root.[4–7] The indolent nature and the rarity of SBNETs (12 cases per 100,000) have been a major barrier in conducting randomized controlled trials on optimal surgical management for this disease.[8] Previous studies have reported positive short-term clinical outcomes with laparoscopic resection of SBNETs (and even occult disease) and concluded that there is a role for laparoscopy.[7,9–13] However, data are limited to small, single institutional studies with small sample sizes and relatively short follow-up times.

With a large national cancer database, the primary aims of this study were to identify factors associated with the MIS approach to SBNET resection and lymphadenectomy and to examine the association between surgical approach and LN yield. The secondary aims were to determine the national trends of the surgical approaches to SBNETs and evaluate clinical outcomes for the two surgical approaches. We hypothesized that the utilization of MIS for SBNET resection and lymphadenectomy has increased over time and LN harvest as well as short-term surgical outcomes would be non-inferior in patients with Stage I-III SBNET undergoing the MIS approach when compared to the open surgery option.

Methods

Data Source

This retrospective cohort study used the National Cancer Database (NCDB), a national collaboration sponsored by the American Cancer Society and the American College of Surgeons. The NCDB captures about 70% of all new cancer diagnoses in the USA.[14] Patient data and data definitions are collected from Commission on Cancer accredited facilities to create this clinical oncology database. The study was exempt from institutional review board approval by the Human Subject Protection Office at the Penn State College of Medicine as all patient information in the NCDB is de-identified.

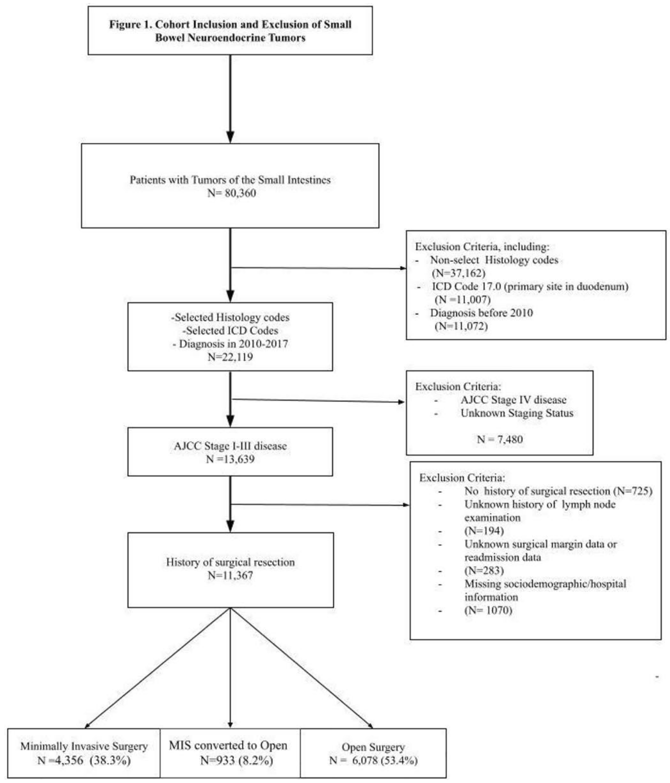
Case Selection Criteria

The NCDB was queried for non-duodenal SBNETs from 2010 to 2017 using the PUF 2017 data dictionary. International Classification of Disease site [ICD] topography codes analyzed included: C17.1, C17.2, C17.3, C17.8, C17.9. Histology codes analyzed included: 8240–8242, 8246, 8249. Duodenal tumors (C17.0) were excluded secondary to having more complex and different presentation and treatment strategies than jejunoileal SBNETs. Additional inclusion criteria involved patients diagnosed with pathological Stage I (T1N0M0), Stage II (T2-3N0M0), and Stage III (T4N0M0 or TxN1-2M0) SBNETs who underwent surgical resection of the primary tumor site. Staging was determined based on the American Joint Committee on Cancer (AJCC) Staging Manual, seventh edition. Patients with unknown staging status, and missing sociodemographic status (age, insurance status, facility type, facility location, distance traveled to hospital, and urban–rural status) were excluded. Stage IV disease, which may require more extensive resection and surgical cytoreduction of metastatic lesions, was excluded to avoid potential palliative cases. The cohort was divided between patients who underwent minimally invasive surgery (laparoscopic and robotic assisted) and patients who underwent open surgery (Fig. 1). Cases that reported conversion from MIS to open surgery were included in the MIS cohort for intention to treat trend analysis but converted cases were included in the open cohort in the other statistical analyses on associations and perioperative outcomes.

Factors Considered

Patient demographics and characteristics analyzed included age, sex, race, insurance status, median household income status, percentage with no high school degree within area of residence, Charlson–Deyo Comorbidity Index (CDCI),[15] and metropolitan/rural status. Facility-related characteristics included distance traveled to treatment facility from home zip code, facility type (academic, comprehensive community, and community), and facility case volume ($<50^{th}$ percentile vs $\geq 50^{th}$ percentile). Tumor characteristics included primary tumor site location, histologic grade (well, moderately, poorly differentiated, unknown), tumor size (< 1 cm, 1–2 cm, > 2 cm), AJCC staging category, and surgical margin status. Surgical outcomes included number of LNs resected, length of hospital stay after surgery, unplanned 30-day readmission from initial operation, and 90-day mortality after initial operation. A binary variable for optimal lymph node yield (≥ 8 lymph nodes) was based on previous

Fig. 1 Small Bowel Neuroendocrine Tumor Study Cohort Inclusion and Exclusion Criteria



Histology Code	Pathology Type
8240	Carcinoid Tumor
8241	Enterochromaffin cell carcinoid
8242	Enterochromaffin-like cell carcinoid
8246	Neuroendocrine carcinoma
8249	Atypical carcinoid tumor

ICD Code	Location
C17.1	Jejunum
C17.2	Ileum
C17.3	Meckel's Diverticulum
C17.8	Overlapping lesion of small intestines
C17.9	Small Intestines

literature on the minimum of lymph nodes needed to identify node positive patients.[16]

Statistical Analysis

Patient characteristics, treatment facility features, and tumor characteristics were stratified by surgical approach. A Chi-square test was performed to examine the subgroup differences. Cochran–Armitage test was used to analyze trends of both surgical approaches over time. The trend in cases requiring conversion from MIS to open surgery over the same study period was evaluated separately. Multivariable logistic regression analysis was used to evaluate the likelihood of undergoing MIS based on factors mentioned above. Additional logistic regression analysis on surgical outcomes after propensity score weighting was performed. Propensity score, adjusting for age, sex, race, insurance status, median household income, high school education, facility cancer program type, facility surgical case volume, distance traveled to hospital, urban–rural status, CDCI, stage group, was estimated from prior multivariable logistic regression. Overall survival (OS) rates were estimated using Kaplan–Meier method using log-rank test. Multivariable survival analysis was performed using Cox proportional hazard model with inverse probability of treatment weight based on propensity score. Sensitivity analysis for logistic regression and Cox proportional hazard model excluded patients who required readmission within 30 days from initial operation or who died within 90 days of initial operation. All statistical tests were two-sided and alpha was set at a significance level of 0.05. All analyses were conducted using SAS statistical software (version 9.4).

Results

Univariate Analysis

A total of 11,367 patients with Stage I-III non-duodenal SBNETs who underwent surgical intervention from 2010 to 2017 were captured in the NCDB. Of these patients, 38.3% (N = 4,356) underwent MIS only, 53.4% (N = 6,078) underwent open surgery only, and 8.2% (N = 933) had a conversion from MIS to open surgery. The total case volume increased by 17.0% between 2010 and 2017. Attempted minimally invasive cases increased by 90.0% over the same study period ($p < 0.001$). When compared to an open surgical approach, the proportion of MIS significantly increased from 35.6% in 2010 to 57.7% in 2017, and became the larger annual proportion of total cases by 2016 (51.2% vs. 48.8%, $P < 0.001$). From 2010–2017, 8.2% (N = 933) reported a surgery requiring conversion from MIS to open. Under an intention to treat analysis, the conversion rate was calculated to be 17.7% (N = 933/5,289). The percentage of cases requiring conversion remained stable from 2010 to 2017 ($p = 0.491$). (Fig. 2).

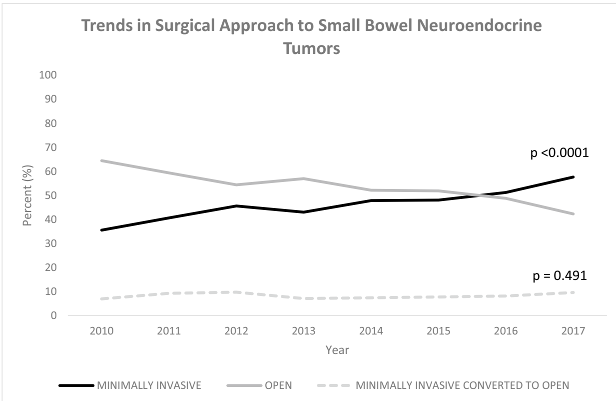


Fig. 2 Trends in Surgical Approach to Stage I-III Small Bowel Neuroendocrine Tumors

Table 1 summarizes all patient demographics and disease characteristics stratified by surgical procedure. Regardless of surgical approach utilized, the majority of patients were white non-Hispanic, received care in facilities with case volume ≥ 50th percentile, traveled < 50 miles to the hospital, resided in metropolitan areas, and had one or no comorbidities. Facilities with SBNET case volumes ≥ 50th percentile performed a median of 27 cases (IQR: 17–47) from 2010–2017, while facilities with case volumes < 50th percentile performed a median of 5 cases (IQR: 4–7) cases from 2010–2017 (p < 0.001). The majority of SBNET cases for both techniques had well-differentiated histology, Stage III disease, and negative surgical margin status. The majority of the final cohort had lymph nodes examined but the open surgery subgroup had more cases with no LN harvested compared to the MIS subgroup (12.8% vs. 10.3%, p < 0.001). The median number of LNs examined was greater in the MIS cohort (13 LNs [IQR 5, 19]) than in the open surgery cohort (10 LNs [IQR 3, 17]) (p < 0.001). The median length of hospital stay was 2 days shorter for the MIS cohort (4 days [IQR 3, 6]) compared to the open surgery cohort (6 days [IQR 4, 8]) (p < 0.001). Unplanned 30-day re-admission (5.5% for open vs 4.2% for MIS, p = 0.002) and 90-day mortality (4.6% for open vs 1.6% for MIS, p < 0.001) were low for both subgroups.

Multivariable Logistic Regression Analysis

Patients were more likely to undergo a MIS approach for SBNET resection and lymphadenectomy if they were < 56 years old (OR 1.20, 95% CI 1.080–1.34), female (OR 1.27, 95% CI 1.18–1.37), have private insurance (OR 1.29, 95% CI 1.14–1.45) when compared to patients ≥ 56 years old, male, and have government-issued insurance. Black patients (OR 0.84, 95% CI 0.74–0.95), uninsured patients (OR 0.56, 95% CI 0.41–0.77), and patients receiving care at community cancer programs (OR 0.71, 95% 0.59–0.84) were less likely to receive MIS when compared to white non-Hispanic patients, patients on a government-issued insurance, and patients at academic centers (all P < 0.05). Patients receiving care at facilities with SBNET surgical case volume ≥ 50th percentile (OR 1.29, 95% CI 1.11–1.49) and facilities < 50 miles away (OR 1.31, 95% CI 1.12–1.53) were more likely to receive MIS when compared to patients at facilities with case volume < 50th percentile and facilities ≥ 50 miles away (all P < 0.001). Patients with ≤ 1 comorbidity (OR 1.17, 95% CI 1.01–1.36) and Stage I disease (OR 1.23, 95% CI 1.07–1.41) were more likely to receive MIS when compared to patients with multiple comorbidities or Stage III disease (all P < 0.05). (Table 2).

Patients who underwent MIS were more likely to have had ≥ 8 LNs examined when compared to patients in the open surgery cohort (OR 1.34, 95% CI 1.22–1.48). Patients treated at facilities of higher case volume ≥ 50th percentile were more likely to have ≥ 8 lymph nodes examined when compared to patients in the open surgery cohort (OR 1.30, 95% CI 1.13–1.49). Finally, patients with Stage III SBNETs were also more likely to have had ≥ 8 lymph nodes examined when compared to patients with Stage II disease (OR 3.86, 95% CI 3.42–4.31) (Table 3).

Kaplan–Meier Analysis of Overall Survival

In both the open surgery cohort and MIS cohort, overall survival was noted to be significantly better for patients with LN yield ≥ 8 LNs compare to patients with < 8 LNs (all p < 0.001) (Fig. 3A, Fig. 3B). In the open surgery cohort, five-year OS rates for LN yield ≥ 8 and LN yield < 8 in the open surgery cohort were 81.0% and 74.0%, respectively. In the MIS cohort, five-year OS rates were 89.7% with LN yield ≥ 8 and 82.2% with LN yield < 8.

Multivariable Cox Proportion Hazards Model Analysis

Patients with Stage I-III SBNETs who had LN yield ≥ 8 were associated with better overall survival than patients with LN yield < 8 (HR 0.77, 95% CI 0.68–0.87). Additional factors associated with better overall survival in patients undergoing surgery for SBNETs included younger age (< 56 years old), female gender, white non-Hispanic race, private insurance, metropolitan setting, existence of ≤ 1 comorbidity, and negative surgical margin status (all P < 0.05). (Table 4).

An additional surgical outcomes analysis demonstrated that patients who underwent MIS were less likely to have an unplanned readmission within 30 days of surgical discharge than patients who underwent an open procedure (OR 0.48, 95% CI 0.34–0.68, P < 0.001). In addition, cases that reported positive surgical margin status after the initial procedure were less likely associated with the MIS approach than cases that involved open approach (OR 0.65, 95% CI 0.57–0.74, P < 0.001).

Table 1 Description and Univariate Analysis for Stage I-III Small Bowel Neuroendocrine Tumor Study Cohort, Years 2010–2017, N = 11,367

	Open (N = 7011)	Minimally invasive (N = 4356)	P value
Age			< 0.001
< 56	1580 (22.5%)	1311 (30.1%)	
56–64	1709 (24.4%)	1168 (26.8%)	
65–72	1659 (23.7%)	961 (22.1%)	
73 +	2063 (29.4%)	916 (21%)	
Sex			< 0.001
Male	3792 (54.1%)	2107 (48.4%)	
Female	3219 (45.9%)	2249 (51.6%)	
Race			0.001
White Non-Hispanic	5427 (77.4%)	3471 (79.7%)	
Black	1029 (14.7%)	538 (12.4%)	
Other (Asian, Hispanic)	555 (7.9%)	347 (8%)	
Insurance Status			< 0.001
Not Insured	197 (2.8%)	64 (1.5%)	
Private	2792 (39.8%)	2278 (52.3%)	
Medicaid	331 (4.7%)	188 (4.3%)	
Medicare	3691 (52.6%)	1826 (41.9%)	
Median Household Income			< 0.001
< $40,227	1189 (17%)	507 (11.6%)	
$40,227—$50,353	1403 (20%)	692 (15.9%)	
$50,354—$63,332	1466 (20.9%)	854 (19.6%)	
> = $63,333	2161 (30.8%)	1739 (39.9%)	
Unknown	792 (11.3%)	564 (12.9%)	
Percent with No High School Degree			< 0.001
> 21%	1237 (17.6%)	576 (13.2%)	
13–20.9%	1585 (22.6%)	861 (19.8%)	
7–12.9%	1792 (25.6%)	1073 (24.6%)	
< 7%	1613 (23%)	1286 (29.5%)	
Unknown	784 (11.2%)	560 (12.9%)	
Facility Location			< 0.001
Northeast and Atlantic	1189 (17%)	1011 (23.2%)	
South Atlantic and South East	2129 (30.4%)	1190 (27.3%)	
Midwest	2695 (38.4%)	1449 (33.3%)	
West and Pacific	998 (14.2%)	706 (16.2%)	
Facility Cancer Program Type			< 0.001
Community	707 (10.1%)	268 (6.2%)	
Comprehensive Community	2983 (42.5%)	1899 (43.6%)	
Academic/Research	3321 (47.4%)	2189 (50.3%)	
Facility Volume of Surgical Operation			< 0.001
0-49th	1189 (17%)	543 (12.5%)	
50th-100th	5822 (83%)	3813 (87.5%)	
Distance Traveled to Hospital			< 0.001
1–49 Miles	6329 (90.3%)	4050 (93%)	
50 + Miles	682 (9.7%)	306 (7%)	
Urban/Rural Status			< 0.001
Metropolitan	5918 (84.4%)	3861 (88.6%)	
Rural	1093 (15.6%)	495 (11.4%)	
Charlson–Deyo Comorbidity Index			< 0.001
None/Few Comorbidities	6409 (91.4%)	4074 (93.5%)	
Multiple Comorbidities	602 (8.6%)	282 (6.5%)	

Table 1 (continued)

	Open (N = 7011)	Minimally invasive (N = 4356)	P value
Primary Site of Tumor			< 0.001
Jejunum	471 (6.7%)	216 (5%)	
Ileum	3548 (50.6%)	2944 (67.6%)	
Not Otherwise Specified	2992 (42.7%)	1196 (27.5%)	
Histograde			0.002
Well-differentiated	4969 (70.9%)	3132 (71.9%)	
Moderately differentiated	1028 (14.7%)	689 (15.8%)	
Poorly differentiated	85 (1.2%)	33 (0.8%)	
Unknown	929 (13.3%)	502 (11.5%)	
Tumor Size			< 0.001
< 1 cm	1475 (21%)	1130 (25.9%)	
1–2 cm	2988 (42.6%)	1824 (41.9%)	
> 2 cm	2548 (36.3%)	1402 (32.2%)	
AJCC Stage Group*			< 0.001
Stage I	534 (7.6%)	409 (9.4%)	
Stage II	1318 (18.8%)	758 (17.4%)	
Stage III	5159 (73.6%)	3189 (73.2%)	
Surgical Margin Status			< 0.001
Negative	6051 (86.3%)	3973 (91.2%)	
Positive	960 (13.7%)	383 (8.8%)	
Lymph Nodes Examined			< 0.001
Yes	6111 (87.2%)	3908 (89.7%)	
None	900 (12.8%)	448 (10.3%)	
Average Lymph Nodes Yield			< 0.001
Mean (SD)	11.8 (10.87)	13.3 (10.80)	
Median (IQR)	10.0 (3.0, 17.0)	13.0 (5.0, 19.0)	
Length of Stay after Surgery			< 0.001
Mean (SD)	7.6 (7.53)	5.4 (5.19)	
Median (IQR)	6.0 (4.0, 8.0)	4.0 (3.0, 6.0)	
Unplanned 30-Day Readmission			0.002
None	6624 (94.5%)	4174 (95.8%)	
Yes	387 (5.5%)	182 (4.2%)	
90-Day Mortality			< 0.001
Alive	5838 (83.3%)	3534 (81.1%)	
Dead	323 (4.6%)	70 (1.6%)	
Unknown	850 (12.1%)	752 (17.3%)	

*Abbreviations: AJCC = American Joint Committee on Cancer, 7th edition

Sensitivity Analysis

A sensitivity analysis was conducted that excluded patients who had unplanned 30-day readmission and died within 90 days of discharge (N = 683 in open cohorts excluded, N = 245 in MIS cohort excluded) as a proxy for non-elective, acute care surgery cases. This analysis demonstrated that the MIS cohort was still more likely to obtain at least 8 LNs for examination when compared to the open surgery cohort (OR 1.45, 95% CI 1.30–1.60, P < 0.001).

Discussion

This study provides the first large database analysis on the utilization of minimally invasive surgery (MIS) in the management of Stage I-III SBNETs. Our study identified a rising utilization of a minimally invasive approach for SBNET resection with regional lymphadenectomy. In addition, our study demonstrated that a MIS approach is associated with greater LN harvest compared to an open approach. The results of our study demonstrate that the

Table 2 Multivariable Logistic Regression: Predictors of Undergoing Minimally Invasive Surgery Technique for Small Bowel Neuroendocrine Tumors

	Adjusted Odds Ratio	95% Confidence Interval		p value
Age				
56–64	Reference			
< 56	1.202	1.080	1.338	< 0.001
65–72	0.981	0.855	1.127	0.8451
73 +	0.761	0.660	0.878	< 0.001
Sex				
Male	Reference			
Female	1.271	1.176	1.374	< 0.001
Race				
White Non-Hispanic	Reference			
Black	0.842	0.745	0.950	0.0174
Other (Asian, Hispanic)	0.976	0.843	1.129	0.4192
Insurance Status				
Medicare	Reference			
Not Insured	0.563	0.414	0.767	< 0.001
Private	1.285	1.137	1.452	< 0.001
Medicaid	1.010	0.818	1.248	0.2690
Median Household Income				
> = $63,333	Reference			
< $40,227	0.723	0.630	0.829	0.5543
$40,227—$50,353	0.795	0.707	0.894	0.8870
$50,354—$63,332	0.645	0.545	0.764	0.1580
Unknown	0.783	0.231	2.646	0.9961
Percent with No High School Degree				
< 7%	Reference			
> 21%	0.919	0.802	1.054	0.8251
13–20.9%	0.868	0.775	0.973	0.5106
7–12.9%	0.886	0.750	1.047	0.6257
Unknown	1.072	0.316	3.639	0.8016
Facility Cancer Program Type				
Academic/Research	Reference			
Community	0.706	0.594	0.840	< 0.001
Comprehensive Community	1.003	0.924	1.089	0.0007
Facility Volume of Surgical Operation				
0-49th	Reference			
50th-100th	1.286	1.111	1.488	0.001
Distance Traveled to Hospital				
50 + Miles	Reference			
1–49 Miles	1.313	1.123	1.534	0.0006
Urban/Rural Status				
Metropolitan	Reference			
Rural	0.923	0.811	1.051	0.2270
Charlson–Deyo Comorbidity Index				
Multiple Comorbidities	Reference			
None/Few Comorbidities	1.170	1.006	1.360	0.0410
AJCC Stage Group*				
Stage III	Reference			
Stage I	1.229	1.070	1.413	0.0053
Stage II	1.011	0.912	1.119	0.1148

*Abbreviations: AJCC = American Joint Committee on Cancer, 7th edition

Table 3 Multivariable Logistic Regression: Predictors of Obtaining ≥ 8 lymph nodes for Stage I-III Small Bowel Neuroendocrine Tumors

	Adjusted Odds Ratio	95% Confidence Interval		p value
Surgical Technique				
Open	Reference			
Minimally Invasive	1.348	1.225	1.483	< 0.001
Age				
56–64	Reference			
< 56	1.223	1.074	1.393	< 0.001
65–72	0.953	0.811	1.120	0.8977
73 +	0.691	0.587	0.813	< 0.001
Sex				
Male	Reference			
Female	1.189	1.086	1.302	0.0002
Race				
White Non-Hispanic	Reference			
Black	0.711	0.620	0.815	0.0070
Other (Asian, Hispanic)	0.760	0.644	0.897	0.2256
Insurance Status				
Medicare	Reference			
Not Insured	0.873	0.636	1.200	0.1212
Private	1.110	0.962	1.280	0.2839
Medicaid	1.230	0.960	1.575	0.0760
Median Household Income				
> = $63,333	Reference			
< $40,227	0.816	0.675	0.987	0.4443
$40,227—$50,353	0.856	0.731	1.002	0.6459
$50,354—$63,332	1.009	0.878	1.158	0.5102
Unknown	0.914	0.234	3.580	0.9979
Percent with No High School Degree				
< 7%	Reference			
> 21%	0.935	0.773	1.131	0.7794
13–20.9%	0.930	0.793	1.091	0.7469
7–12.9%	0.948	0.828	1.085	0.8421
Unknown	1.073	0.273	4.216	0.8655
Facility Cancer Program Type				
Academic/Research	Reference			
Community	0.936	0.776	1.129	0.6560
Comprehensive Community	0.950	0.863	1.046	0.7507
Facility Volume of Surgical Operation				
0-49th	Reference			
50th-100th	1.299	1.130	1.493	0.0002
Distance Traveled to Hospital				
1–49 Miles	Reference			
50 + Miles	1.147	0.962	1.368	0.1261
Urban/Rural Status				
Metropolitan	Reference			
Rural	1.023	0.885	1.183	0.7592
Charlson–Deyo Comorbidity Index				
None/Few Comorbidities	Reference			
Multiple Comorbidities	0.862	0.731	1.015	0.0746
AJCC Stage Group*				
Stage II	Reference			

Table 3 (continued)

	Adjusted Odds Ratio	95% Confidence Interval		p value
Stage I	2.161	1.760	2.655	0.3103
Stage III	3.864	3.416	4.371	<0.001

*Abbreviations: AJCC = American Joint Committee on Cancer, 7th edition

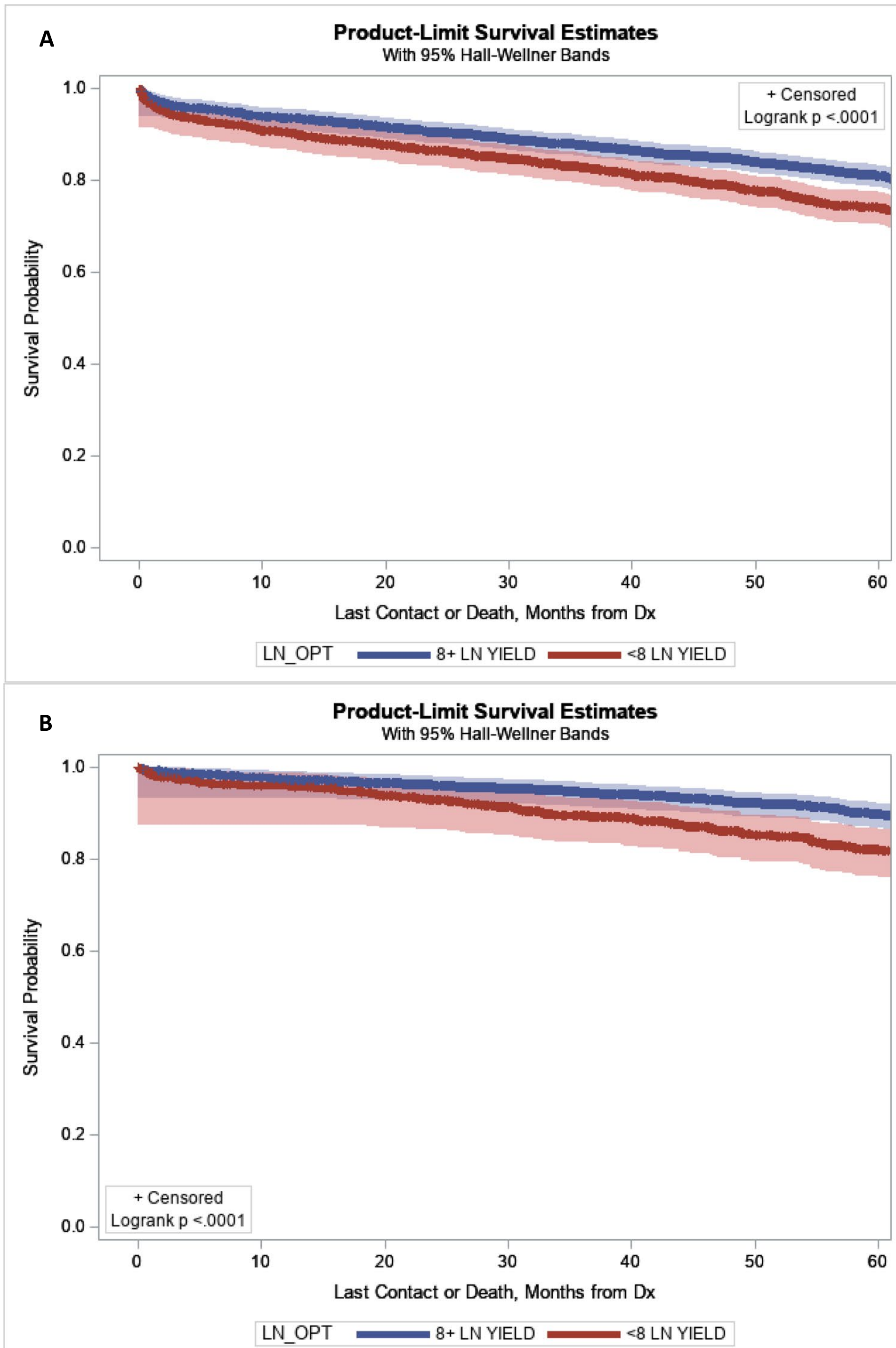


Fig. 3 Kaplan–Meier Analysis of overall survival (OS) for Stage I-III small bowel neuroendocrine tumors. **A** In the open surgery cohort, five-year OS for LN yield ≥ 8 and LN yield < 8 (81.0% and 74.0%, respectively). **B** In the minimally invasive surgery cohort, five-year OS for LN yield ≥ 8 and LN yield < 8 (89.7% and 82.2%, respectively)

Table 4 Weighted Cox Proportional Hazard Model for Patients with Stage I-III Small Bowel Neuroendocrine Tumors

	Adjusted Hazard ratio	95% Confidence interval		p value
Surgical technique				
Open	Reference			
Minimally invasive	0.657	0.581	0.742	< 0.001
Age				
56–64	Reference			
< 56	0.501	0.397	0.632	< 0.001
65–72	1.127	0.878	1.447	0.3488
73 +	2.700	2.124	3.434	< 0.001
Sex				
Male	Reference			
Female	0.855	0.763	0.958	0.0071
Race				
White Non-Hispanic	Reference			
Black	1.213	1.004	1.467	0.0458
Other (Asian, Hispanic)	0.868	0.694	1.085	0.2127
Insurance Status				
Medicare	Reference			
Not Insured	1.177	0.735	1.884	0.4984
Private	0.548	0.434	0.691	< 0.001
Medicaid	1.211	0.872	1.681	0.2531
Median Household Income				
> = $63,333	Reference			
< $40,227	1.064	0.841	1.345	0.6061
$40,227—$50,353	0.998	0.823	1.210	0.9852
$50,354—$63,332	1.103	0.934	1.303	0.2466
Unknown	1.603	0.352	7.298	0.5417
Percent with No High School Degree				
< 7%	Reference			
> 21%	1.227	0.971	1.550	0.0861
13–20.9%	1.168	0.965	1.415	0.1104
7–12.9%	1.148	0.973	1.355	0.1029
Unknown	0.299	0.065	1.387	0.1231
Facility Cancer Program Type				
Academic/Research	Reference			
Community	1.086	0.851	1.385	0.5072
Comprehensive Community	1.007	0.891	1.138	0.9120
Facility Volume of Surgical Operation				
50th-100th	Reference			
0-49th	0.939	0.783	1.127	0.5004
Distance Traveled to Hospital				
1–49 Miles	Reference			
50 + Miles	1.053	0.835	1.329	0.6628
Urban/Rural Status				
Metropolitan	Reference			
Rural	1.215	1.018	1.450	0.0307
Charlson–Deyo Comorbidity Index				
None/Few Comorbidities	Reference			
Multiple Comorbidities	1.920	1.622	2.274	< 0.001
AJCC Stage Group*				
Stage III	Reference			

Table 4 (continued)

	Adjusted Hazard ratio	95% Confidence interval		p value
Stage I	1.568	1.260	1.951	< 0.001
Stage II	1.374	1.170	1.613	0.0001
Histograde				
Well-differentiated	Reference			
Moderately differentiated	1.005	0.852	1.185	0.9517
Poorly Differentiated	2.931	1.944	4.417	< 0.001
Unknown	1.113	0.950	1.304	0.1862
8 + Lymph Nodes Examined				
No	Reference			
Yes	0.773	0.684	0.874	< 0.001
Margins				
Negative	Reference			
Positive	1.315	1.117	1.549	< 0.001

*Abbreviations: AJCC = American Joint Committee on Cancer, 7th edition

preference of a surgical approach is multifactorial, with differences in patient characteristics, socioeconomic status, and hospital characteristics, which may highlight targets in quality improvement for patients with resectable SBNETs, especially as a MIS approach is associated with improved short-term outcomes without compromising lymph node harvest.

The standard surgical approach for SBNET resection and lymphadenectomy is an open surgical approach. Current North American and European SBNET guidelines acknowledge the controversial role of MIS for SBNETs and question whether MIS can adhere to the universal principles of surgical oncology including complete resection of the primary tumor, mesenteric masses, and nodal disease to complete staging as well as an adequate evaluation of abdominal organs and peritoneum.[4,5] This is particularly essential for a disease that typically presents with a high rate (> 80%) of regional lymph node metastasis[4] and a high 5-year recurrence rate (33%)[17] after open surgery. In addition, with high rates of multifocal disease and sub-centimeter tumor sizes, it is recommended to conduct an exploratory laparotomy and digital palpation of the entire jejunum and ileum.[4]

The primary concern of a MIS approach is a reliance on visualization of occult lesions without accurate tactile feedback, as well as the technical difficulties of safely removing masses near the mesenteric root. One solution is to use a hand-assisted laparoscopic device or enlarge an incision to exteriorize the small bowel for digital palpation of bowel.[7,9,11,12] It is possible that variations of the hand-assisted technique were included in this study's MIS only cohort. Another adjunct involves careful patient selection prior to consideration of a MIS approach to resection and lymphadenectomy. Kasai et al. developed an objective system for predicting cases when an MIS only approach is likely to fail based on the proximal location and size of mesenteric masses identified on preoperative imaging.[9] Although there is inconclusive evidence to define the role of MIS for SBNETs, its short-term clinical benefits (i.e., shorter length of hospital stay, less postoperative pain, and decrease surgical morbidity) make the option of MIS worth considering, which seems to be the case based on the significantly increased use of MIS observed in this study.

The ability for clinicians to detect SBNETs, especially at early stages, is important in deciding on the clinical management and surgical approach for patients. Diagnostic imaging with injection of a somatostatin analogue labeled with positron emitting gallium 68 (^{68}Ga) dota peptides is highly accurate for guiding preoperative and intraoperative surgical management of patients.[18] Lakis et al. conducted a clinical trial illustrating the benefit of radioguided surgery for a curative resection of NETs.[19] However, the majority of patients in this clinical trial underwent open laparotomy. If a minimally invasive approach is being considered, one study did suggest using ^{68}Ga DOTATATE as an adjunct imaging study when all other studies are negative.[20] Future prospective studies are needed to assess appropriate oncologic resection with radioguided minimally invasive surgery. Within the current years of our study sample, the imaging modality is not routinely covered by some insurance companies,[18] which may also be a reason why patients with no insurance or government issued insurance were less likely associated with a MIS approach in this study.

Besides the observed short-term clinical benefits in the MIS only cohort, our study demonstrated a significantly greater (but clinically similar) number of LN harvested in the MIS cohort (13.3 in the MIS cohort vs 11.8 in the open cohort). This is also greater than the optimal cutoff of 8–9 LN needed to accurately identify nodal positivity in patients with SBNET as demonstrated by Motz et al. and Tran et al.[16,21]. Our study is the first to show that patients who underwent the MIS approach were more likely to obtain at least 8 lymph nodes than patients who underwent the open approach. Although the average number of nodes obtained (12 LNs) was similar, results from recent literature showed no statistical difference in LN yield between the two surgical groups, which is likely due to their small sample sizes (N = 61 and N = 93, respectively).[10,13] Obtaining a larger LN harvest from a MIS approach (including hand-assisted techniques) has been demonstrated in the surgical management of other cancer types such as colorectal cancer because of better visualization and better access to more proximal areas of mesentery with laparoscopy for more complete mesenteric resection.[22,23]

Greater LN harvest is associated with improved prognosis regardless of nodal positivity in SBNETs, which is consistent with previous literature.[16,24] This may be due to the high prevalence of occult nodal metastases with SBNETs regardless of pathologic stage. The results of our study confirm that examination of at least 8 LNs is associated with an improved overall survival, and, therefore, we agree with previous literature that harvesting at least 8 LNs is a desirable target goal for surgeons when performing regional lymphadenectomy for locoregional SBNETs.[16,24]

The MIS cohort's likelihood to obtain at least 8 LN for both staging and removal of nodal micro-metastases may be due to the appropriate perioperative care at higher case volume centers received. Because of the greater learning curve to complete complex surgical oncology cases laparoscopically, higher case volume centers and academic centers have higher rates of laparoscopy experience in surgical oncology.[8,16,25–27] This association is consistent with our findings for SBNETs, as we observed that patients treated at higher volume facilities were more likely to undergo minimally invasive surgery.

Our study highlights that insurance status and race are independent predictors of the utilization of MIS and survival. Insured and white non-Hispanic patients were more likely to be treated under MIS over uninsured and black patients. Private insurance and white non-Hispanic patients were associated with better survival than patients on Medicare and black patients. This racial and socioeconomic disparity is well established in laparoscopic surgeries including appendectomies, colectomies, and hysterectomies.[28–30] Minority and lower socioeconomic groups may present with more advanced disease or present within hospital systems that provide lower quality of care for managing SBNETs.[28] Therefore, further investigation is warranted to identify solutions to more equitable surgical access across race and insurance status.

This study should be interpreted with the following limitations. Utilizing a large registry such as the NCDB for a retrospective study may lead to selection bias. However, potential bias is mitigated by using a large sample size and using propensity score weighting to control for patient, socioeconomic, facility, and pathologic factors in our logistic regression and Cox proportional hazards models. Molecular biomarkers, such as Ki-67 index, which can be important for prognostication, are not collected in the NCDB to ensure it is equally distributed or controlled between the two surgical groups.[31] In addition, the NCDB does not collect data on whether each case involved multifocal disease, on disease-free survival, and on recurrence of disease, which are common in SBNETs.[17,32] Ethun et al.[10] found that MIS cases for SBNETs were less likely to report multiple tumors resected, and recurrence rates were similar between both surgical approaches.

Another limitation especially for assessing overall survival between the MIS and open surgical approach is that the NCDB does not collect data on the urgency of the operation as patients may have been more likely to undergo open surgery and less likely to perform adequate regional lymphadenectomy if the initial presentation (such as complete intestinal obstruction or ischemic bowel) required emergent or urgent surgery. This may also explain the difference in survival between the two approaches in our Cox proportional hazards model. There may still be other unobserved factors (such as type of diagnostic imaging used) driving the decision to choose MIS or an open approach. To mitigate the limitation of identifying the urgency of surgery, patients who were readmitted within 30 days from initial operation and who died within 90 days of initial operation were excluded as a proxy for emergent surgeries in our sensitivity analysis. Significant results of MIS utilization and LN harvest were unchanged.

It is also important to note that cases identified as MIS only could have included a variation of hand-assisted techniques,[7,9,11,12] which are not mentioned in the NCDB. However, cases that required a conversion to open surgery were captured as a separate variable and incorporated into the MIS cohort for this study's trend analysis similar to an intention to treat analyses. The significant uptrend of MIS cases with the unchanged proportion of converted cases over the study period highlights the potential of attempting MIS initially for oncologic resection of SBNETs. It was assumed that postoperative outcomes such as LN harvest in converted cases would be similar to that of open surgery only. Therefore, the multivariable regression models as well as the weighted Cox proportional hazard models included the converted cases into the Open surgery subgroup.

Conclusion

To date, this is the only multicenter study highlighting the increasing prevalence of MIS for surgical resection of Stage I-III SBNETs and regional lymphadenectomy in the USA. We established that the utility of MIS should be recognized, considering its short-term clinical benefits such as shorter length of stay and lower unplanned readmissions. After careful preoperative planning with select patients, obtaining oncological outcomes including optimal LN harvest (≥ 8 LN) for adequate staging and treatment may be possible. Future randomized prospective studies will be needed to confirm non-inferiority with overall survival with a MIS approach when compared to an open surgery. As new advancements in minimally invasive techniques, new diagnostic modalities for detecting occult disease, and new systematic therapies arise, we predict that the role of MIS will be more clearly defined and may be the preferred initial approach to surgically managing SBNETs.

Declarations

Author Disclosures The authors have no relevant financial disclosures.

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