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ORIGINAL ARTICLE

Impact of surgical approach on short- and long-term outcomes in gastroenteropancreatic neuroendocrine carcinomas

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Abstract

Background: Literature is lacking on the impact of advancements in minimally invasive surgery (MIS) on outcomes for patients with gastroenteropancreatic neuroendocrine carcinomas (GEP-NECs). Herein, we compared perioperative and oncologic outcomes among patients with GEP-NECs undergoing open, laparoscopic, and robotic resection.

Methods: Patients with GEP-NECs diagnosed 2010-2019 were identified from the National Cancer Database (NCDB). We used the inverse probability of treatment weighting method to account for selection bias. Patients were stratified by surgical approach; and pairwise comparisons were conducted by analyzing short- and long-term outcomes.

Results: Receipt of MIS increased from 34.2% in 2010 to 67.5 % in 2019. Altogether, 6560 patients met study criteria: 3444 (52.5%) underwent open resection, 2783 (42.4%) underwent laparoscopic resection and 333 (5.1%) underwent robotic resection. Compared with open resection, laparoscopic or robotic resection were associated with shorter post-operative length of stay, reduced 30-day and 90-day post-operative mortality, and prolonged overall survival (OS). Compared with laparoscopic resection, robotic resection was associated with reduced 90-day post-operative mortality, however, there was no significant difference in OS.

Conclusion: This NCDB analysis demonstrates that MIS approaches for treating GEP-NECs have become more common, with improved perioperative mortality, shorter post-operative length of stay and favorable OS, compared with open resection.

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Introduction

Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are a heterogeneous class of tumors arising from neuroendocrine cells within the gastrointestinal tract and pancreas with variable disease biology.[1] One particular class of GEP-NENs, gastroenteropancreatic neuroendocrine carcinomas (GEP-NECs), are a poorly differentiated type with unfavorable median survival of only 5–37 months.[1,2] With an increasing incidence of GEP-NECs,[1,3] optimizing their management has become an important research focus.

Complete surgical resection, as recommended by many national guidelines (e.g., European Neuroendocrine Tumor Society, National Comprehensive Cancer Network), is the primary treatment strategy for GEP-NECs without distant metastases, which can lead to a favorable survival.[4,5] Modern surgical technologies have enabled a shift towards minimally invasive surgery (MIS), such as laparoscopy, and more recently, robotics. MIS for patients with gastroenteropancreatic tumors have been shown to be safe and feasible, and these techniques have beneficial outcomes with lower rates of perioperative complications, faster recovery times and comparable survival, compared with open resection.[6−11] Particular advantages of robotic techniques include improved precision in manipulation, stabilization of tremors, improved 3D visualization and ergonomics for surgeons, which have led to its increased use across surgical disciplines.[12,13] However, the impact of MIS techniques (laparoscopic and robotic resection) on short- and long-term outcomes among GEP-NEC patients undergoing curative-intent resection remains unknown. Therefore, we aimed to investigate the impact of surgical approaches on GEP-NEC outcomes in a large national dataset.

Methods

Patient population and variables of interest

The National Cancer Database (NCDB) is a national cancer registry sponsored by the American College of Surgeons and American Cancer Society. The NCDB contains 34 million historical records and accounts for 70% of new cancer diagnoses in the United States.[14] GEP-NEC patients without distant metastases were identified from the NCDB between 2010 and 2019. All data are de-identified and this study was deemed exempt by the Duke University Institutional Review Board.

Primary tumor sites consisted of stomach (C16.0-C16.9), small intestine (C17.0 - C17.9), colon (C18.0 - C18.9), rectum (C20.9) and pancreas (C25.0 - C25.9). We used available histology codes to identify patients with NECs (8013, 8041–8045 and 8246). Exclusion criteria consisted of 1) distant metastases; 2) age less than 18 years old; 3) no resection or missing resection status; 4) robotic resection converting to open resection or laparoscopic resection converting to open resection; 5) resection for palliative intent; 6) missing margin status; 7) missing pathology; 8) incomplete survival data; 9) missing 30- or 90-day post-operative mortality; 10) incomplete post-operative length of stay data; 11) lack of 30-day post-operative unplanned readmission information and 12) undergoing treatment outside of the reporting facility. The current study included two cohorts: a temporal-trend cohort and a primary-analysis cohort. Based on exclusion criteria (No.1–4), patients were included in the temporal-trend cohort to assess the trends in surgical approach. Based on exclusion criteria (No.1–12), patients were included in the primary-analysis cohort for perioperative outcome and survival analyses (Fig. 1).

The clinicopathologic variables of interest for primary analyses were age, sex, ethnicity, year of diagnosis, insurance status, facility type, insurance type, median household income, high school degree, location of residence, Charlson-Deyo Score, primary tumor site, tumor grade, tumor stage, tumor size, regional nodal examination, number of regional nodes, number of positive regional nodes, radiotherapy, and chemotherapy. Surgical approaches consisted of open, laparoscopic, and robotic resection. MIS included laparoscopic and robotic resection. The patients were stratified by the surgical approaches, and pairwise comparisons were conducted: laparoscopic vs. open resection, robotic vs. open resection, and robotic vs. laparoscopic resection, respectively.

Statistical analysis

The clinicopathologic factors had various levels of missingness: facility type (10.2%), ethnicity (1.0%), insurance (1.2%), median income (12.6%), tumor grade (7.5%), tumor stage (6.9%), high school degree (12.5%), tumor size (4.2%), location of residence (3.9%), radiotherapy (0.8%) and chemotherapy (0.8%). Multiple imputations by chained equations were performed to impute missing data under the missing at random assumption. There were factors associated with the "missingness" of certain variables, so a wide range of variables (e.g., patient demographics, tumor characteristics, and treatment) were used to generate missing data on a variable-by -variable basis.

We generated 25 complete datasets for subsequent analyses. The number of imputations was selected according to the guidelines that the number of imputations should be similar to the percentage of missing cases.[15]

To account for selection bias, the observed differences in baseline characteristics were adjusted by using the inverse probability of treatment weighting (IPTW) method. Specifically, we first estimated, in each of the imputed dataset, the propensity score which reflecting the conditional probability of receiving each treatment category (open, laparoscopic, or robotic resection), using a multinomial logistic regression.[16] The following patient characteristics and clinical risk factors were included in the models: age, sex, ethnicity, year of diagnosis, insurance status,

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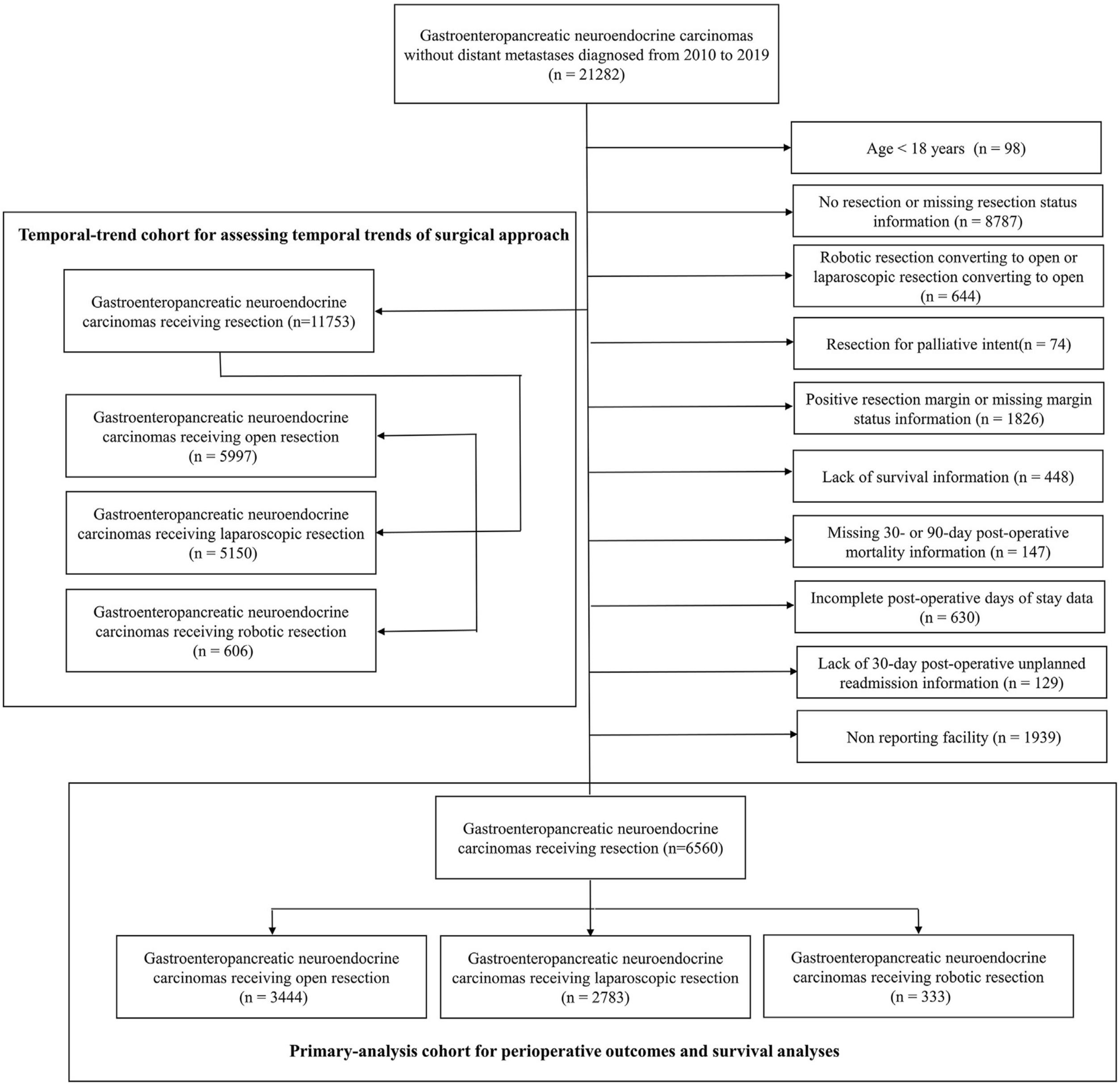

Figure 1 Flow diagram for the selection of gastroenteropancreatic neuroendocrine carcinomas receiving resection

facility type, insurance type, median household income, high school degree, location of residence, Charlson-Deyo Score, primary tumor site, tumor grade, tumor stage, tumor size, radiotherapy and chemotherapy. According to the Rubin's rules,[17] the estimated propensity scores from 25 imputed datasets were combined by using mean of the individual estimates in each dataset. The propensity scores were then used to weight each patient with the aim of balancing the characteristics between groups (laparoscopic vs. open resection, robotic vs. open resection, and robotic vs. laparoscopic resection). The imbalance of baseline characteristics between groups were assessed using standardized differences (SD)[18] in the original (unweighted) study population and the weighted population, respectively. A SD less than 0.1 was considered indicative of a negligible imbalance between groups.

The short-term outcomes included regional nodal examination (yes/no), number of regional nodes (count variable), number of positive regional nodes (count variable), post-operative length of stay (count variable), 30-day post-operative mortality (yes/no), 90-day post-operative mortality

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(yes/no), and unplanned 30-day post-operative readmission (yes/no). A weighted logistic regression model (for binary variables) or a weighted Poisson regression model (for count variables) with treatment group as the sole predictor were used to estimate the odds ratio (OR) or relative risk (RR) of patient experiencing each of the short-term outcomes between groups. OS was defined as the long-term outcome. The adjusted Kaplan−Meier curves and log-rank tests based on IPTW were computed to compare OS between treatment groups. In addition, an inverse probability weighted Cox proportional hazards regression model with treatment group as the sole predictor was used to determine the relative change in hazards (i.e., the IPTW-adjusted hazards ratio [HR]) associated with receiving open resection or laparoscopic resection or robotic resection. A nominal $P < 0.05$ (two-sided) was considered statistically significant, and all statistical analyses were performed with R version 4.1.1.

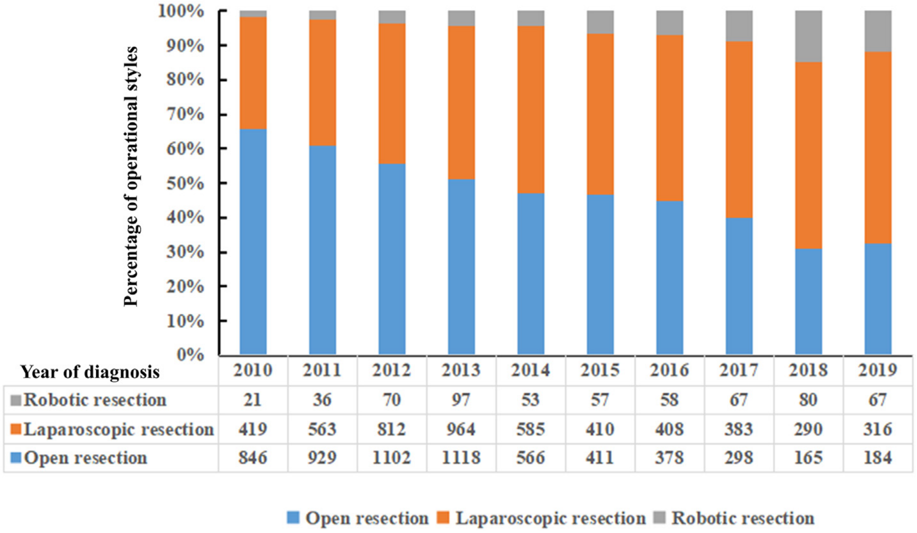
Results

Temporal trend in surgical approach and population demographics

The temporal-trend cohort included a total of 11,753 GEP-NEC patients receiving resection from 2010 to 2019. The temporal trend in surgical approach is shown in Fig. 2. Receipt of laparoscopic resection increased from 32.6% in 2010 to 55.7% in 2019 and receipt of robotic resection increased over time from 1.6% in 2010 to 11.8% in 2019. Altogether, receipt of MIS (including both laparoscopic and robotic resections) notably increased over time from 34.2% in 2010 to 67.5% in 2019.

There were 6560 GEP-NEC patients included in the primary-analysis cohort. Clinicopathologic characteristics of the primary-analysis cohort are presented in Table 1. Among all patients, 3444 (52.5%) underwent open resection, 2783 (42.4%) underwent laparoscopic resection and 333 (5.1%) underwent robotic resection. The mean age of all participants was 59.4 years and 51.2% of the cohort were female. Primary tumor sites included: stomach (5.7%), small intestine (32.0%), colon (20.5%), rectum (9.3%) and pancreas (32.5%). Compared with patients managed with open resection, patients undergoing laparoscopic resection were more likely to be younger (57.2 years vs. 61.2 years), have primary tumors located in the colon (26.9% vs. 14.3%) and rectum (17.5% vs. 4.0%), tumor size <2 cm (63.0% vs. 45.3%) and AJCC stage I disease (49.2% vs. 35.1%). Compared with patients managed with open resection, patients undergoing robotic resection were more likely to be younger (59.5 years vs. 61.2 years), diagnosed in 2016−2018 (38.1% vs. 15.9%), have a primary tumor located in the pancreas (53.2% vs. 39.4%) and AJCC stageIdisease (49.8% vs. 35.1%). Compared with patients managed with laparoscopic resection, patients receiving robotic resection were more likely to be older (59.5 years vs. 57.2 years), diagnosed in 2016−2018 (38.1% vs. 22.1%), have a primary tumor located in the pancreas (53.2% vs. 21.5%) and tumor size 2−4 cm (34.2% vs. 22.7%). The SDs, evaluating the balance in covariates between each of the two groups before and after the IPTW adjustment, are shown in Table 1. The imbalances shown between groups in the unweighted study population were well mitigated after adjustment, with SDs for most characteristics being <0.1 in each pair of comparison. The weighted population in the three groups were generally comparable.

Multivariable logistic regression analysis was performed to identify factors that predicted an MIS approach (Table 2). Patients who were white (compared to black), younger, diagnosed in 2013−2015 and 2016−2018 (compared to 2010−2012), had primary tumors located in the small intestine, colon and rectum (compared to pancreas), had AJCC stage I disease (compared to stage III), had well differentiated and moderately differentiated tumors (compared to undifferentiated), or had tumor size <2 cm



Year of diagnosis	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
■Robotic resection	21	36	70	97	53	57	58	67	80	67
■Laparoscopic resection	419	563	812	964	585	410	408	383	290	316
■Open resection	846	929	1102	1118	566	411	378	298	165	184

Figure 2 Temporal trends for robotic resection, laparoscopic resection and open resection from 2010 to 2019

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Table 1 Clinicopathologic characteristics of patients receiving resection and standardized difference in unweighted and weighted study populations

Variables	All patients	Open resection	Laparoscopic resection	Robotic resection	Laparoscopic resection vs. Open resection		Robotic resection vs. Open resection		Robotic resection vs. Laparoscopic resection	
					Standardized Difference		Standardized Difference		Standardized Difference	
	(n = 6560)	(n = 3444)	(n = 2783)	(n = 333)	Unweighted Study Population	weighted Study Population	Unweighted Study Population	weighted Study Population	Unweighted Study Population	weighted Study Population
Age, mean (SD), years	59.4 (14.9)	61.2 (14.2)	57.2 (15.5)	59.5 (13.5)	0.272	0.015	0.116	0.026	0.156	0.041
Female (%)	3356 (51.2)	1726 (50.1)	1459 (52.4)	171 (51.4)	0.023	0.002	0.012	0.033	0.011	0.034
Ethnicity (%)										
White	5239 (79.9)	2749 (79.8)	2218 (79.7)	272 (81.7)	0.001	0.002	0.015	0.029	0.016	0.027
Black	992 (15.1)	543 (15.8)	410 (14.7)	39 (11.7)	0.010	0.001	0.041	0.027	0.031	0.025
Others	265 (4.0)	119 (3.5)	126 (4.5)	20 (6.0)	0.011	0.001	0.025	0.002	0.015	0.002
Facility type (%)										
Community Cancer Program	289 (4.4)	159 (4.6)	122 (4.4)	8 (2.4)	0.005	0.003	0.022	0.006	0.027	0.007
Comprehensive Community Cancer Program	1887 (28.8)	963 (28.0)	841 (30.2)	83 (24.9)	0.049	0.006	0.025	0.009	0.074	0.008
Academic Program	2467 (37.6)	1393 (40.4)	935 (33.6)	139 (41.7)	0.057	0.008	0.015	0.016	0.072	0.009
Integrated Network Cancer Program	1248 (19.0)	668 (19.4)	505 (18.1)	75 (22.5)	0.004	0.003	0.032	0.018	0.030	0.018
Location of residence (%)										
Metro	5435 (82.9)	2815 (81.7)	2335 (83.9)	285 (85.6)	0.016	0.002	0.034	0.033	0.018	0.034
Urban	759 (11.6)	414 (12.0)	311 (11.2)	34 (10.2)	0.010	0.002	0.017	0.023	0.007	0.025
Rural	110 (1.7)	70 (2.0)	39 (1.4)	1 (0.3)	0.006	0.001	0.017	0.010	0.011	0.009
High school degree (%)										
<79.0%	947 (14.4)	499 (14.5)	396 (14.2)	52 (15.6)	0.003	0.002	0.010	0.013	0.012	0.013
79.0%–87.0%	1450 (22.1)	804 (23.3)	584 (21.0)	62 (18.6)	0.023	0.006	0.053	0.009	0.030	0.011
87.1%–93.0%	1871 (28.5)	979 (28.4)	778 (28.0)	114 (34.2)	0.007	0.004	0.054	0.022	0.060	0.024
>93.0%	1471 (22.4)	728 (21.1)	675 (24.3)	68 (20.4)	0.031	0.004	0.012	0.028	0.042	0.026
Insurance status (%)										
No insurance	187 (2.9)	98 (2.8)	79 (2.8)	10 (3.0)	0.000	0.001	0.002	0.004	0.002	0.004
Private insurance	3219 (49.1)	1577 (45.8)	1481 (53.2)	161 (48.3)	0.074	0.004	0.029	0.022	0.045	0.026
Medicaid and other government	546 (8.3)	262 (7.6)	257 (9.2)	27 (8.1)	0.017	0.003	0.005	0.012	0.012	0.014
Medicare	2531 (38.6)	1467 (42.6)	933 (33.5)	131 (39.3)	0.091	0.002	0.035	0.006	0.055	0.008
Median income (%)										
< $38,000	972 (14.8)	529 (15.4)	394 (14.2)	49 (14.7)	0.010	0.005	0.012	0.019	0.006	0.024
$38,000 - $47,999	1283 (19.6)	690 (20.0)	536 (19.3)	57 (17.1)	0.007	0.004	0.032	0.011	0.025	0.012
$48,000 - $62,999	1529 (23.3)	808 (23.5)	630 (22.6)	91 (27.3)	0.011	0.008	0.034	0.009	0.045	0.014
≥ $63,000	1950 (29.7)	980 (28.5)	871 (31.3)	99 (29.7)	0.028	0.004	0.012	0.023	0.018	0.021

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Table 1 (*continued*)

Variables	All patients	Open resection	Laparoscopic resection	Robotic resection	Laparoscopic resection vs. Open resection		Robotic resection vs. Open resection		Robotic resection vs. Laparoscopic resection	
					Standardized Difference		Standardized Difference		Standardized Difference	
	(n = 6560)	(n = 3444)	(n = 2783)	(n = 333)	Un weighted Study Population	weighted Study Population	Un weighted Study Population	weighted Study Population	Un weighted Study Population	weighted Study Population
Diagnosis year (%)										
2010–2012	2675 (40.8)	1600 (46.5)	1003 (36.0)	72 (21.6)	0.104	0.003	0.248	0.020	0.144	0.017
2013–2015	2596 (39.6)	1297 (37.7)	1165 (41.9)	134 (40.2)	0.042	0.002	0.026	0.013	0.016	0.011
2016–2018	1289 (19.6)	547 (15.9)	615 (22.1)	127 (38.1)	0.062	0.001	0.223	0.007	0.160	0.006
Charlson-Deyo Score (%)										
0	4722 (72.0)	2411 (70.0)	2059 (74.0)	252 (75.7)	0.040	0.002	0.057	0.016	0.017	0.014
1	1352 (20.6)	756 (22.0)	537 (19.3)	59 (17.7)	0.027	0.002	0.042	0.016	0.016	0.014
2 and 3	486 (7.4)	277 (8.0)	187 (6.7)	22 (6.6)	0.013	0.000	0.014	0.000	0.001	0.000
Tumor site (%)										
Stomach and small intestine	2477 (37.8)	1458 (42.3)	948 (34.1)	71 (21.3)	0.083	0.007	0.210	0.030	0.127	0.037
Colon	1301 (19.8)	492 (14.3)	750 (26.9)	59 (17.7)	0.127	0.002	0.034	0.003	0.092	0.005
Rectum	649 (9.9)	137 (4.0)	486 (17.5)	26 (7.8)	0.135	0.002	0.038	0.022	0.097	0.021
Pancreas	2133 (32.5)	1357 (39.4)	599 (21.5)	177 (53.2)	0.179	0.011	0.138	0.010	0.316	0.021
AJCC stage (%)										
I	2744 (41.8)	1209 (35.1)	1369 (49.2)	166 (49.8)	0.186	0.006	0.174	0.038	0.012	0.032
II	1480 (22.6)	945 (27.4)	466 (16.7)	69 (20.7)	0.095	0.013	0.064	0.051	0.031	0.038
III	1886 (28.7)	1151 (33.4)	661 (23.8)	74 (22.2)	0.091	0.007	0.110	0.013	0.019	0.009
Grade (%)										
Well differentiation	4583 (69.9)	2354 (68.4)	2014 (72.4)	215 (64.6)	0.044	0.008	0.042	0.006	0.086	0.013
Moderate differentiation	881 (13.4)	460 (13.4)	370 (13.3)	51 (15.3)	0.002	0.002	0.017	0.005	0.019	0.005
Poor differentiation	447 (6.8)	271 (7.9)	140 (5.0)	36 (10.8)	0.029	0.007	0.027	0.006	0.056	0.013
Undifferentiation	157 (2.4)	102 (3.0)	46 (1.7)	9 (2.7)	0.013	0.002	0.003	0.003	0.011	0.001
Tumor size (%)										
<2 cm	3476 (53.0)	1560 (45.3)	1753 (63.0)	163 (48.9)	0.206	0.007	0.032	0.010	0.174	0.007
2–4 cm	1905 (29.0)	1160 (33.7)	631 (22.7)	114 (34.2)	0.110	0.003	0.010	0.010	0.120	0.008
>4 cm	901 (13.7)	620 (18.0)	237 (8.5)	44 (13.2)	0.096	0.005	0.042	0.002	0.054	0.007
Radiotherapy (%)	71 (1.1)	48 (1.4)	14 (0.5)	9 (2.7)	0.009	0.006	0.013	0.002	0.022	0.008
Chemotherapy (%)	268 (4.1)	173 (5.0)	78 (2.8)	17 (5.1)	0.022	0.004	0.001	0.010	0.023	0.006

and 2–4 cm (compared to tumor size >4 cm) were more likely to undergo resection with MIS approaches.

Outcomes analyses

The short-term outcomes are shown in Table 3. Among all patients, 4485 (68.4%) received regional nodal examination. The mean number of regional nodes and positive regional nodes was 9.6 and 1.4, respectively. The mean post-operative length of stay was 6.2 days. Postoperative mortality was observed in 145 (2.2%) patients within 30 days and in 223 (3.4%) patients within 90 days, and 387 (5.9%) patients required unplanned 30-day post-operative readmission. The median follow-up time was 79.9 months [interquartile range (IQR), 78.9–81.0], and 21.9% (1438/6560) of the study population were deceased at the time of analysis, with 1-, 3-, 5- and 10-year OS of 93.6%, 87.8%, 82.3% and 63.8%, respectively.

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Table 2 Multivariable logistic regression model predicting receipt of minimally invasive surgery in the unweighted study population

Variables	OR	95% CI	*P*
Age (per year)	0.991	0.983–0.998	0.015
Female	1.034	0.905–1.181	0.625
Ethnicity			
Black	1.000	Reference	
White	1.240	1.013–1.516	0.037
Others	1.385	0.940–2.041	0.100
Facility type			
Community Cancer Program	1.000	Reference	
Comprehensive Community Cancer Program	1.627	1.167–2.270	0.004
Academic Program	1.539	1.100–2.154	0.012
Integrated Network Cancer Program	1.618	1.145–2.285	0.006
Location of residence			
Metro	1.000	Reference	
Urban	0.903	0.727–1.121	0.356
Rural	0.849	0.521–1.385	0.513
High school degree			
<79.0%	1.000	Reference	
79.0%–87.0%	0.849	0.677–1.063	0.154
87.1%–93.0%	0.985	0.772–1.258	0.905
>93.0%	1.048	0.791–1.388	0.745
Insurance status			
No insurance	1	Reference	
Private insurance	1.027	0.652–1.618	0.907
Medicaid and other government	1.079	0.650–1.790	0.769
Medicare	0.913	0.571–1.458	0.703
Median income			
< $38,000	1.000	Reference	
$38,000 - $47,999	1.125	0.890–1.422	0.325
$48,000 - $62,999	1.028	0.800–1.321	0.827
≥ $63,000	1.144	0.865–1.513	0.345
Diagnosis year			
2010–2012	1.000	Reference	
2013–2015	1.294	1.116–1.501	0.001
2016–2018	1.800	1.490–2.174	<0.001
Charlson-Deyo Score			
0	1.000	Reference	
1	0.928	0.787–1.094	0.375
2 and 3	1.018	0.800–1.296	0.882
Tumor site			
Pancreas	1.000	Reference	
Stomach and small intestine	1.401	1.142–1.718	0.001
Colon	2.873	2.271–3.635	<0.001
Rectum	5.766	4.232–7.856	<0.001
AJCC stage			

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Table 2 (*continued*)

Variables	OR	95% CI	*P*
III	1.000	Reference	
I	1.574	1.282–1.933	<0.001
II	1.046	0.861–1.269	0.652
Grade			
Undifferentiation	1.000	Reference	
Well differentiation	1.632	1.041–2.558	0.033
Moderate differentiation	1.760	1.100–2.814	0.018
Poor differentiation	1.133	0.703–1.826	0.607
Tumor size			
>4 cm	1.000	Reference	
<2 cm	1.741	1.377–2.203	<0.001
2–4 cm	1.428	1.140–1.788	0.002

Laparoscopic vs. open resection

For short-term outcomes (Table 4), compared with open resection, laparoscopic resection was associated with a decreased likelihood of regional nodal examination (IPTW-adjusted OR = 0.742, 95% CI: 0.689–0.799; *P* < 0.001), less regional nodes examined (IPTW-adjusted RR = 0.908, 95% CI: 0.898–0.918; *P* < 0.001), less positive regional nodes (IPTW-adjusted RR = 0.899, 95% CI: 0.872–0.926; *P* < 0.001), shorter post-operative length of stay (IPTW-adjusted RR = 0.693, 95% CI: 0.684–0.703; *P* < 0.001), reduced 30-day post-operative mortality (IPTW-adjusted OR = 0.447, 95% CI: 0.344–0.576; *P* < 0.001) and reduced 90-day post-operative mortality (IPTW-adjusted OR = 0.501, 95% CI: 0.409–0.612; *P* < 0.001). The above-mentioned results were consistent with the unweighted populations (Table S1). Regarding survival, patients receiving laparoscopic resection had a favorable OS both before (5-year rate of OS: 87.1% vs. 78.1%, 10-year rate of OS: 69.4% vs. 59.1%, *P* < 0.001) and after IPTW adjustment (5-year rate of OS: 84.4% vs. 79.6%, 10-year rate of OS: 64.9% vs. 61.8%, *P* < 0.001 in IPTW-adjusted log-rank test) (Fig. 3a and b). This survival advantage for laparoscopic resection was preserved in the adjusted analysis (IPTW-adjusted HR = 0.767, 95% CI: 0.676–0.870; *P* < 0.001).

Robotic vs. open resection

In the adjusted multivariable analyses for short-term outcomes, compared with open resection, robotic resection was associated with decreased regional nodal examination (IPTW-adjusted OR = 0.763, 95% CI: 0.708–0.822; *P* < 0.001), less regional nodes examined (IPTW-adjusted RR = 0.929, 95% CI: 0.919–0.940; *P* < 0.001), less positive regional nodes (IPTW-adjusted RR = 0.937, 95% CI: 0.910–0.965; *P* < 0.001), shorter post-operative length of stay (IPTW-adjusted RR = 0.692, 95% CI: 0.682–0.701; *P* < 0.001), reduced 30-day post-operative mortality (IPTW-adjusted OR = 0.345, 95% CI: 0.258–0.455; *P* < 0.001) and reduced 90-day post-operative mortality (IPTW-adjusted OR = 0.239, 95% CI: 0.183–0.308; *P* < 0.001), and had no differences in odds of unplanned 30-day post-operative readmission (IPTW-adjusted OR = 0.878, 95% CI: 0.756–1.019; *P* = 0.086) (Table 4). The above-mentioned results were consistent in the unweighted populations (Table S1). In the survival analysis, robotic resection was associated with prolonged OS both before (5-year rate of OS: 84.7% vs. 78.1%, 10-year rate of OS: 65.4% vs. 59.1%, *P* < 0.011) and after (5-year rate of OS: 87.6% vs. 79.6%, 10-year rate of OS: 69.7% vs. 61.8%, *P* = 0.027 in IPTW-adjusted log-rank test) the IPTW adjustment (Fig. 4a and b). This prolonged survival for robotic resection was also

Table 3 Short-term outcomes of patients receiving open resection, laparoscopic resection and robotic resection

Variables	All patients	Open resection	Laparoscopic resection	Robotic resection
	(n = 6560)	(n = 3444)	(n = 2783)	(n = 333)
Regional nodal examination (%)	4485 (68.4)	238 (71.5)	1487 (53.4)	2760 (80.1)
Number of regional nodes, mean (SD)	9.6 (10.6)	10.0 (10.5)	7.6 (10.4)	11.1 (10.6)
Number of positive regional nodes, mean (SD)	1.4 (2.8)	1.2 (2.9)	1.0 (2.2)	1.7 (3.2)
Post-operative length of stay, mean (SD), days	6.2 (7.9)	8.0 (8.3)	4.2 (7.0)	5.2 (4.6)
30-day post-operative mortality (%)	145 (2.2)	111 (3.2)	30 (1.1)	4 (1.2)
90-day post-operative mortality (%)	223 (3.4)	168 (4.9)	50 (1.8)	5 (1.5)
Unplanned 30-day post-operative readmission (%)	387 (5.9)	236 (6.9)	130 (4.7)	21 (6.3)

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Table 4 Multivariable analyses for short-term outcomes in weighted study populations

Variables	Laparoscopic resection vs. Open resection		Robotic resection vs. Open resection		Robotic resection vs. Laparoscopic resection	
	OR/RR (95% CI)	*P*	OR/RR (95% CI)	*P*	OR/RR (95% CI)	*P*
Regional nodal examination	0.742 (0.689−0.799)	<0.001	0.763 (0.708−0.822)	<0.001	1.028 (0.957−1.106)	0.450
Number of regional nodes	0.908 (0.898−0.918)	<0.001	0.929 (0.919−0.940)	<0.001	1.024 (1.013−1.035)	<0.001
Number of positive regional nodes	0.899 (0.872−0.926)	<0.001	0.937 (0.910−0.965)	<0.001	1.043 (1.012−1.074)	0.007
Post-operative length of stay (days)	0.693 (0.684−0.703)	<0.001	0.692 (0.682−0.701)	<0.001	0.998 (0.983−1.013)	0.758
30-day post-operative mortality	0.447 (0.344−0.576)	<0.001	0.345 (0.258−0.455)	<0.001	0.771 (0.557−1.062)	0.113
90-day post-operative mortality	0.501 (0.409−0.612)	<0.001	0.239 (0.183−0.308)	<0.001	0.476 (0.357−0.631)	<0.001
Unplanned 30-day post-operative readmission	0.985 (0.852−1.138)	0.839	0.878 (0.756−1.019)	0.086	0.891 (0.767−1.034)	0.129

OR: Odds ratio; RR: Relative risk.

preserved in the adjusted analysis (IPTW-adjusted HR = 0.637, 95% CI: 0.454−0.894; $P = 0.009$).

Robotic vs. laparoscopic resection

In the adjusted multivariable analyses for short-term outcomes, compared with laparoscopic resection, robotic resection was associated with more regional nodes examined (IPTW-adjusted RR = 1.024, 95% CI: 1.013−1.035; $P < 0.001$), more positive regional nodes (IPTW-adjusted RR = 1.043, 95% CI: 1.012−1.074; $P = 0.007$), and reduced 90-day post-operative mortality (IPTW-adjusted OR = 0.476, 95% CI: 0.357−0.631; $P < 0.001$) (Table 4). However, there was no significant difference in OS for patients receiving robotic vs. laparoscopic resection before (5-year rate of OS: 84.7% vs. 87.1%, 10-year rate of OS: 65.4% vs. 69.4%, $P = 0.121$) and after (5-year rate of OS: 84.4% vs. 87.6%, 10-year rate of OS: 69.7% vs. 64.9%, $P = 0.332$ in IPTW-adjusted log-rank test) the IPTW adjustment (Fig. 5a and b). Accordingly, in the IPTW-adjusted Cox proportional hazards regression analysis, OS after robotic resection was similar to that of laparoscopic resection (IPTW-adjusted HR = 0.834, 95% CI: 0.587−1.186; $P = 0.313$).

Discussion

To our knowledge, this is the first study to characterize MIS utilization and compare outcomes by surgical approach among GEP-NEC patients undergoing resection. As expected, rates of MIS utilization notably increased during the last decade, especially for laparoscopic resection. Compared with open resection, we found that MIS approaches had several outcome advantages, including shorter post-operative length of stay, reduced 30- and 90-day post-operative mortality, as well as more favorable OS. Although robotic resection was associated with more regional nodes examined, more positive regional nodes and reduced 90-day post-operative mortality compared with laparoscopic resection, other short-term outcomes and OS were comparable.

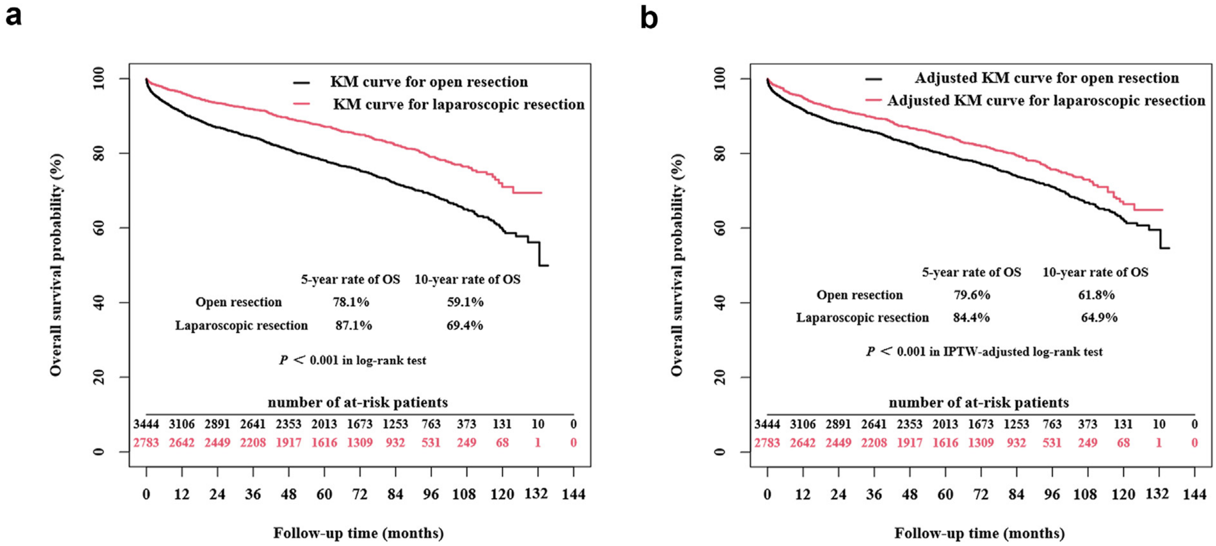

Figure 3 Survival analysis of laparoscopic resection vs. open resection before IPTW **(a)** and after IPTW **(b)**

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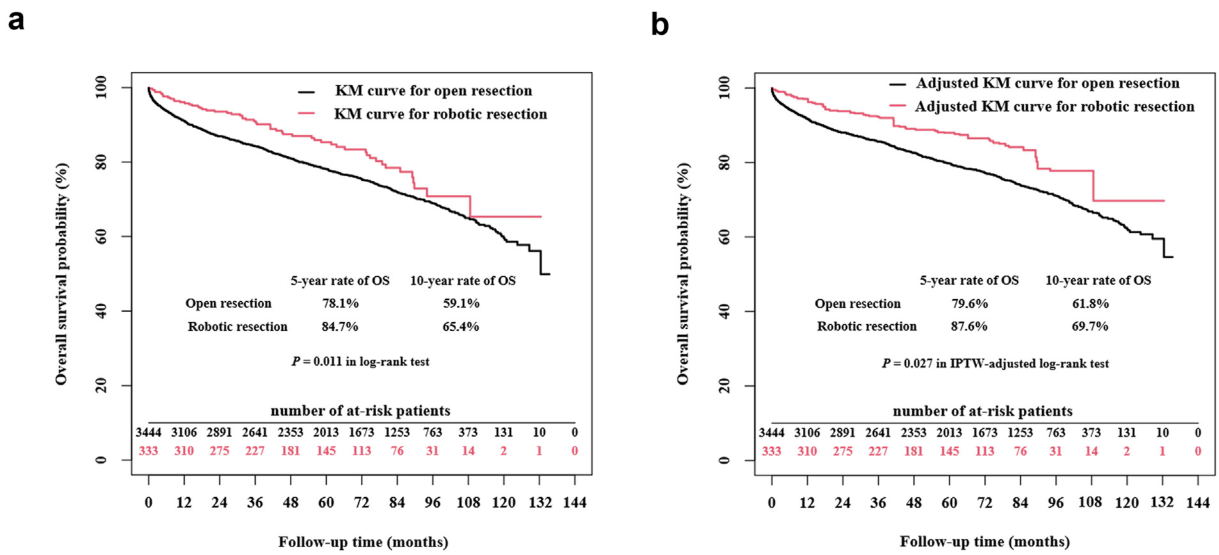

Figure 4 Survival analysis of robotic resection vs. open resection before IPTW **(a)** and after IPTW **(b)**

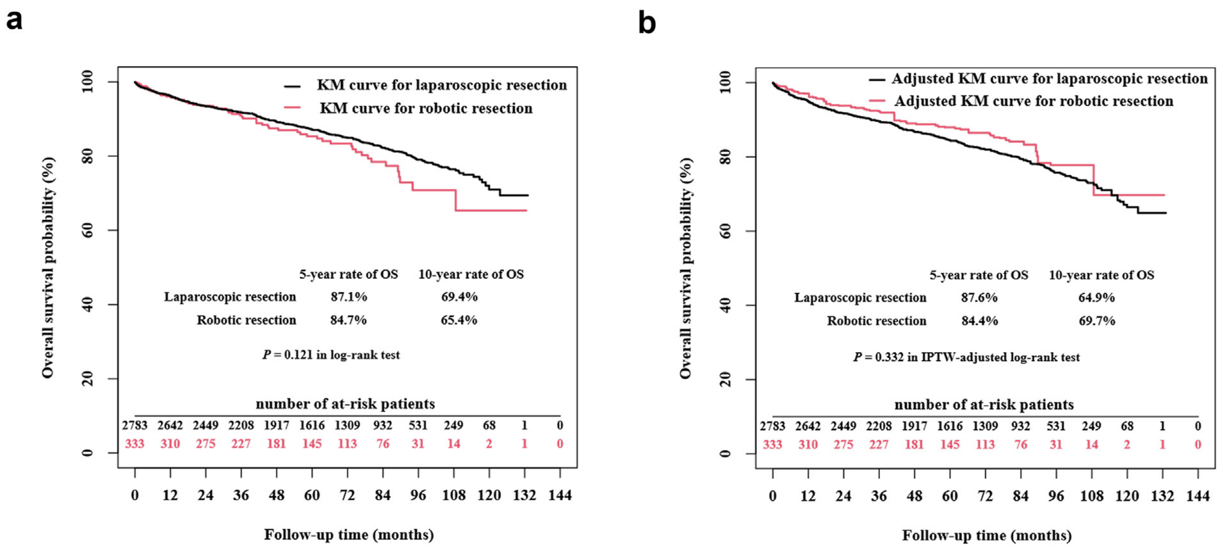

Figure 5 Survival analysis of robotic resection vs. laparoscopic resection before IPTW **(a)** and after IPTW **(b)**

Altogether, these findings demonstrate the feasibility of MIS approaches for resection of GEP-NECs with favorable short- and long-term outcomes.

MIS approaches are increasingly being utilized in major abdominal surgeries.[8,19–23] Accordingly, we identified an increased use of MIS among GEP-NEC patients from 2010 to 2019. Many studies have examined utilization of MIS approaches in colorectal and hepatobiliary surgery.[19–22] In our study focusing on localized GEP-NECs, we found that MIS approaches were more prevalent in younger patients with well differentiated tumors, those outside the pancreas, and those with an early AJCC stage. These factors demonstrate that although MIS is becoming more prevalent in GEP-NECs, it remains most common in cases traditionally viewed as "safer" and "less difficult", and those with less aggressive disease biology.

The technical benefits of MIS have been well described, including an enhanced visual magnification, a better exposure, and a more delicate manipulation of organs, vessels, and nerves. However, certain MIS approaches may have a greater utility for particular disease sites and resections. In the current study, a robotic approach was most commonly utilized for pancreatic tumors, perhaps due to the superior precision, articulation of movement, and optics. Similarly, many studies have reported advantages of laparoscopic and robotic resection in the short-term outcomes (e.g., decreased intra-operative blood loss, intra-operative time, post-operative complications) among

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gastroenteropancreatic tumors.[7,9,11,23] Similar to studies in other disease sites, our study reports shorter post-operative length of stay, and reduced 30- and 90-day post-operative mortality in GEP-NEC patients undergoing resection with MIS approaches than open resection. Together, these may contribute to short-term oncologic improvements conferred by MIS.

While the safety of MIS has been broadly established, its impact on the long-term survival has remained controversial. Some suggest the manipulation of MIS instruments and pneumoperitoneum may increase the risk of cancer cell dissemination to nearby organs, particularly for tumors with serosal invasion, potentially increasing the risk of recurrence.[8,24,25] However, the current study demonstrated that MIS achieved a favorable OS, compared with open resection. As such, we cannot discount the possibility of clinical or biological explanations that may contribute to the favorable survival associated with MIS. Potentially plausible explanations may include: (1) patients undergoing MIS resection may initiate adjuvant therapies, a key component in the treatment of poorly differentiated GEP-NECs or GEP-NECs with distant metastases,[4,26] more promptly than their counterparts receiving open resection due to shorter post-operative length of stay and reduced post-operative complications.[27,28] Indeed, it has been described that timely adjuvant chemotherapy can significantly improve survival.[27,28] (2) High post-operative mortality with open resection may weaken the long-term survival, and conversely, MIS has been demonstrated to be associated with lower 30- and 90-day mortality rates than open resection in the current study. (3) Immune-mediated mechanisms should also be considered, as open resection was found to induce increased levels of pro-inflammatory molecules, such as IL-6, IL-8, and CCL-2.[29,30] Indeed, recent studies have demonstrated that the change of inflammatory molecules after open resection may trigger the promotion of tumor growth,[29–32] and this biological phenomenon may account for the sharp rise in distant recurrence after surgery.[33,34] (4) Anti-cancer immunity has been found to be diminished by serious surgical trauma; therefore, the more traumatic nature of open resection may render patients more susceptible to cancer recurrence than patients receiving MIS.[35–37]

The current study further compared the outcomes between laparoscopic resection and robotic resection and found that robotic resection was associated with lower post-operative 90-day mortality and comparable survival in GEP-NEC patients. The robotic platform has the added benefit of reducing surgical trauma due to further intrinsic advantages, such as the accurate 3D view, tremor filtration, and extremely accurate lymph node dissection.[12,13,38] Indeed, the endowristed instruments allow easier vessel ligation, clamping and suturing than with laparoscopic resection.[12,13,38] The above-mentioned advantages may contribute to the reduced post-operative mortality. For other outcomes, some studies have shown robotic resection to be associated with reduced intra-operative blood loss and lower rate of surgical complications, especially for Dindo-Clavien ≥ 3 classifications in gastroenteropancreatic cancer.[11,12,38] However, some concerns regarding the high costs of robotic resection continue to exist. Previous cost analyses of robotic and laparoscopic resection showed that the average total cost for robotic surgery was considerably higher than laparoscopy (gastrectomy for gastric adenocarcinoma: $13,432 vs. $8090; low anterior resection for rectal cancer: $ 17,314 vs $ 14,093).[39–41] Therefore, the choice of robotic or laparoscopic resection should comprehensively consider the aforementioned factors. Further, cost discrepancies may contribute to the widening of health disparities.

There are several limitations in the current study. First, this was a retrospective study, and there was a lack of randomization of patients into each surgical approach potentially introducing surgeon and selection bias. Second, operation-related variables such as volume of operations performed by individual surgeons and surgeon-specific data, such as years of training, present further confounding in the results of the analysis. Further, due to the learning curve and heterogeneity in reasons for conversion of MIS to open, such cases were excluded and warrant more granular study of their own. Third, the NCDB lacks granularity on numerous intraoperative (e.g., operative time, operative blood loss) and postoperative outcomes (e.g., post-operative complication rate, post-operative complication variables) of interest. Notable oncologic outcomes, such as disease-free and disease-specific survival are not captured in the NCDB. To mitigate these limitations, we applied rigorous statistical methods to a large national dataset and describe contemporary practices of MIS approaches in GEP-NECs.

In conclusion, this NCDB analysis suggests that MIS approaches are feasible options for surgical resection of GEP-NECs. Further, both laparoscopic and robotic approaches portend better short-term outcomes and favorable OS compared to open resection. Surgical oncologists should weigh their operative skillsets and consider MIS approaches for patients with GEP-NECs. As MIS approaches become more prevalent, prospective investigations of its impact on and drivers of OS are warranted.

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Submission declaration

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Conflict of Interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2023.06.008.

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