Upfront Small Bowel Resection for Small Bowel Neuroendocrine Tumors With Synchronous Metastases

A Propensity-score Matched Comparative Population-based Analysis

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Objective: We examined the impact of upfront small bowel resection (USBR) for metastatic small bowel neuroendocrine (SB-NET) compared to nonoperative management (NOM) on long-term healthcare utilization and survival outcomes.

Summary of Background Data: The role of early resection of the primary tumor in metastatic SB-NET remains controversial. Conflicting data exist regarding its clinical and survival benefits.

Methods: This is a population-based retrospective matched comparative cohort study of adults diagnosed with synchronous metastatic SB-NET between 2001 and 2017 in Ontario. USBR was defined as resection within 6 months of diagnosis. Primary outcomes were subsequent unplanned acute care admissions and small bowel-related surgery. Secondary outcome was overall survival. USBR and NOM patients were matched 2:1 using a propensity-score. We used time-to-event analyses with cumulative incidence functions and univariate Andersen-Gill regression for primary outcomes. *E*value methods assessed the potential for residual confounding.

Results: Of 1000 patients identified, 785 had USBR. The matched cohort included 348 patients with USBR and 174 with NOM. Patients with USBR had lower 3-year risk of subsequent admissions (72.6% vs 86.4%, $P < 0.001$) than those with NOM, with hazard ratio 0.72 (95% confidence interval 0.570.91). USBR was associated with lower risk of subsequent small bowel-related surgery (15.4% vs 40.3%, $P < 0.001$), with hazard ratio 0.44 (95% confidence interval 0.29–0.67). *E*-values indicated it was unlikely that the observed risk estimates could be explained by an unmeasured confounder. Sensitivity analysis excluding emergent resections to define USBR did not alter the results.

Conclusions: USBR for SB-NETs in the presence of metastatic disease was associated with better patient-oriented outcomes of decreased subsequent admissions and interventions, compared to NOM. USBR should be considered for metastatic SB-NETs.

Keywords: metastatic, neuroendocrine, small bowel, surgery

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Small bowel neuroendocrine tumors (SB-NETs) are heterogeneous tumors that are typically slow-growing, and often present at an advanced stage with over 30% of patients found to have synchronous metastases at diagnosis.[1,2] Although the incidence of SB-NETs is similar to that of small bowel adenocarcinoma, their indolent nature results in a prevalence that exceeds many other gastrointestinal malignancies such as esophageal, gastric, and pancreatic adenocarcinoma.[3,4] Furthermore, systemic and liver-directed therapies have become standard of care over the past decade, allowing patients to live longer with persistent disease.[5–9]

Systemic and local hormonal repercussions of NETs further complicate care; patients with NETs report a high rate of moderate to severe chronic symptoms after diagnosis.[10] In 50% of patients, mesenteric and retroperitoneal fibrosis result from fibroblastic reaction surrounding the tumor.[10,11] Although survival is not reduced by this manifestation, it can have lasting impact on symptom burden and quality of life. Fibrosis can lead to mesenteric angina and ischemia, venous congestion, intestinal obstruction, and ureteral obstruction, even with small primary tumors.[12] Once such clinical manifestations develop, resection is rarely possible and patients may be subjected to repeat hospital stays and procedures for palliative purposes.

Resection of primary SB-NETs in patients with metastatic disease has been suggested to prevent life-altering and lasting locoregional complications, regardless of the resectability of metastases. However, this is controversial, with previous studies yielding conflicting results. Most analyses have examined the effect of primary tumor resection on overall survival, but those results are tinted by selection bias.[13,14] In 2018, a single-center retrospective cohort study of asymptomatic patients with metastatic SB-NETs found no difference in overall survival, cancer-specific survival, or total hospital length of stay for patients either undergoing upfront local resection within 6 months of diagnosis, or not.[15] Despite the importance of chronic symptoms and their repercussions on patient care and life, long-term patient-oriented outcomes of primary tumor resection have yet to be investigated.

This study sought to evaluate the impact of upfront small bowel resection (USBR) compared to initial nonoperative management (NOM) for metastatic SB-NETs on unplanned acute care admissions and repeated small bowel-related surgical interventions, as patient-centered measures of small bowel-related complications.

METHODS

Study Design

Through ICES (formerly known as the Institute for Clinical Evaluative Sciences), linked administrative healthcare datasets from the province of Ontario, Canada, were used to conduct a retrospective propensity-matched comparative cohort study. The study was approved by the Research Ethics Board at Sunnybrook Health Sciences Center and reported following the Reporting of studies Conducted using Observational Routinely collected health Data statement.[16]

Study Population

This study was conducted on patients with valid Ontario Health Insurance Plan (OHIP) insurance from 2001 to 2017. Under the Canada Health Act, Ontario's 13.5 million residents benefit from universally accessible and publicly funded healthcare through OHIP.[17]

Patients ≥ 18 years old with a new NET diagnosis from January 2001 and December 2017 were identified with International Classification of Diseases for Oncology version 3 (ICD-0.3 codes) using a strategy previously reported by our team (Supplemental Table 1, http://links.lww.com/SLA/C788).[1,18,19] Patients with primary jejunum and ileum NET (ICD-O.3 C17*) and presenting with synchronous metastatic disease (≤6 months from date of diagnosis) were retained. Metastatic disease was identified with ICD-10 codes using a previously published algorithm.[20] Patients were excluded if they were over the age of 105 years old, had a prior diagnosis of cancer, had a subsequent cancer diagnosis within 1 year of their SB-NET diagnosis, or had a date of death recorded before date of diagnosis.

Data Sources

The Ontario Cancer Registry (OCR) is a provincial database comprised of all patients with a cancer diagnosis (excluding non-melanoma skin cancers) since 1964.[21,22] The Registered Persons Database contains vital status and demographic data on all individuals covered under the OHIP. Information regarding health services provided is included in the Canadian Institute of Health Information Discharge Abstract Database (CIHI-DAD), the National Ambulatory Care Reporting System, the cancer Activity Level Reporting, the OHIP Claims Database, and the Ontario Drug Database covering patients ≥65 years old.[23] The Ontario Laboratories Information System database contains information on tests performed in community, hospital, and public health laboratories. Datasets are detailed in Supplemental Table 2, http://links.lww.com/SLA/C788.

Exposure

The exposure of interest was USBR following diagnosis, defined as small bowel resection within ≤6 months from date of diagnosis using physicians claims (Supplemental Table 3, http://link-s.lww.com/SLA/C788). To have a pragmatic approach to the effect of resecting the primary tumor in the setting of metastatic disease, both emergency and elective resections were included in this definition.

Outcomes

The primary outcomes of interest were unplanned acute care admissions and subsequent small bowel-related surgery (Supplemental Table 3, http://links.lww.com/SLA/C788). Unplanned acute care admission was defined as an inpatient hospital admission with an emergency department visit immediately preceding admission, to avoid capturing planned elective admissions related to ongoing therapy for metastatic NETs, such as liver embolization. A subsequent small bowel-related surgery was defined as receipt of surgery related to intestinal complications, either from primary tumor or as morbidity from USBR (eg, obstruction, ischemia, perforation, or bleeding), such as resection, stoma, enteric bypass, and lysis of adhesions. Both outcomes were treated as recurrent dichotomous outcomes. The index date was defined as day after discharge from the surgery defining the exposure for the USBR group, and as the date of diagnosis for the group without initial small bowel resection.

Median overall survival from the date of diagnosis to death from any cause was examined as secondary outcome.

Patients were followed until date of death, date of last clinical contact with the healthcare system, or end of study date on December 31, 2018, thereby allowing a minimum of 12 months to contribute data for all patients.

Covariates

Baseline characteristics were measured at the time of NET diagnosis. Age and sex were abstracted from the Registered Persons Database. Rural residence was defined according to the Rurality Index of Ontario.[24] Material deprivation quintile, a multi-dimensional, ecologic measure incorporating socioeconomic factors such as education and income, assessed socioeconomic status.[25] Baseline comorbidity burden was measured using the Johns Hopkins Adjusted Clinical Groups system score based on health services use with a 24-month look-back window before the date of NET diagnosis.[26] The 32 aggregated diagnosis groups were summed to create a total score, then dichotomized with a cut-off of 10 for high comorbidity bur-den.[26,27] Treatment institution status was divided into academic or community as defined by the Ministry of Health and Long-Term Care.[28] Diagnosis year was determined using the Ontario Cancer Registry and categorized into 2 time periods (2001–2009 vs 20102017) for reporting of characteristics to avoid reporting small cells (≤6 patients) as per ICES privacy and confidentiality regulations. Finally, elevated 24-hour urinary 5-hydroxyindoleacetic acid (u5HIAA) at diagnosis (first value ≤6 months from date of diagnosis) was determined using Ontario Laboratories Information System as a measure of functional status of NET.

Considering variations in units and normal range values between laboratories, 24-hour u5HIAA was categorized as elevated or not based on each laboratory normal range, and as unmeasured if no value was available over the time window. Finally, use of long-acting somatostatin analogs was reported for the sub-group of patients ≥65 years old for which this information is available in the Ontario Drug Database. Covariates definitions are further detailed in Supplemental Table 4, http://links.lww.com/SLA/C788.

Propensity Score Matched Cohort

Each patient's propensity to receive USBR was calculated using a multivariable logistic regression including baseline characteristics determined a priori as potentially associated with the decision to proceed with USBR based on clinical relevance and the existing literature. Those covariates were: age (continuous), sex, year of diagnosis (ordinal), material deprivation quintile, comorbidity burden, treatment institution type, and elevated u5HIAA at diagnosis. Patients were matched 2:1 (USBR:NOM) using a nearest neighbor algorithm with a caliper width of 0.2 standard deviation of the logit of the propensity score.[29,30] We used balanced diagnostics to assess the propensity-score matching. The standardized difference between the matched groups was calculated, with a difference greater than 10% considered significant. Cumulative density plots and quantile-quantile plots were used to examine the distribution of continuous variable (age) in the entire and the matched cohorts.[29,31]

Statistical Analysis

Primary outcomes were described and compared between USBR and NOM groups in the entire and the matched cohorts. We computed the overall, 1-year, and 5-year cumulative incidence and compared them with Gray test. Cumulative incidence accounted for competing risk of death or loss of OHIP eligibility. Median overall survival was computed using Kaplan-Meier methods and compared with the log-rank test for the entire cohort and the stratified log-rank test for the matched cohort. We modeled the risk of the unplanned acute care admission and small bowel-related surgery associated with USBR compared to NOM using Andersen-Gill models.[32] In the entire cohort, main effect multivariable models were constructed to adjust for baseline characteristics potentially associated with the exposure (and included in the propensity score for matching). For the propensity-matched cohort, univariable models including the exposure variable were created. Results are reported as hazard ratios (HR) with 95% confidence interval (CI).

We looked at missing data for key variables. Data were missing for rural residency in 1.3% and material deprivation in 0.9% of the cohort. We performed a complete case analysis whereby patients with missing data were excluded for analyses using these variables.

Statistical significance was set at $P \leq 0.05$. All analyses were conducted using SAS Enterprise Guide 7.1 (SAS Institute, Cary, NC).

Sensitivity Analysis and Unmeasured Confounding

First, we conducted a sensitivity analysis excluding emergency small bowel resection from the definition of USBR to

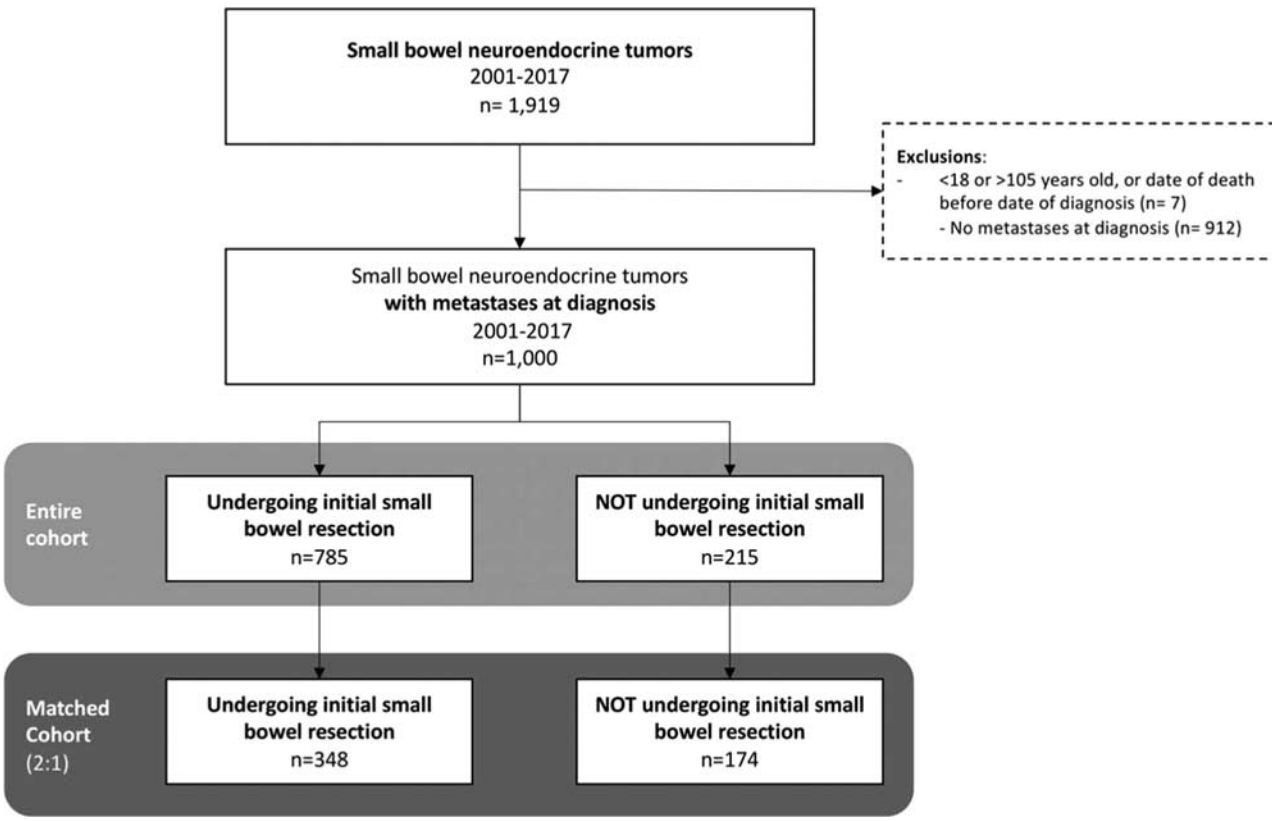


FIGURE 1. Flow chart of entire and propensity-matched cohorts.

TABLE 1. Characteristics of Patients Stratified by Receipt of Upfront Small Bowel Resection, for the Entire Cohort

Characteristic	Nonoperative Management (n = 215)	Upfront Small Bowel Resection (n = 785)	*P*-value
Age at diagnosis (years old)–median (IQR)	65 (54–73)	63 (54–72)	0.484
Female sex	98 (45.6%)	363 (46.2%)	0.863
Rural residence	27 (12.6%)	90 (11.5%)	0.896
High comorbidity burden (ADG ≥10)	67 (31.2%)	231 (29.4%)	0.622
Deprivation Quintile			0.75
First–least deprived	48 (22.3%)	179 (22.8%)	
Second	42 (19.5%)	166 (21.1%)	
Third	39 (18.1%)	149 (19.0%)	
Fourth	51 (23.7%)	148 (18.9%)	
Fifth–most deprived	35 (16.3%)	143 (18.2%)	
Diagnosis year			0.518
200–2009	81 (37.7%)	277 (35.3%)	
2010–2017	134 (62.3%)	508 (64.7%)	
Treatment institution			< 0.001
Academic	110 (51.2%)	357 (45.5%)	
Community	105 (48.9%)	428 (54.5%)	
Elevated 24-h urinary 5HIAA at diagnosis			< 0.001
Yes	49 (22.8%)	128 (16.3%)	
No	8 (3.7%)	91 (11.6%)	
Unknown	158 (73.5%)	566 (72.1%)	

Values are n (%) unless otherwise specified.
5HIAA indicates 5-Hydroxyindoleacetic acid; ADG, aggregated diagnosis group; IQR, interquartile range.

examine the robustness of the results to our analytic choices. Patients in the USBR group whose exposure defining surgery was performed as emergency surgery (performed during an admission starting with an emergency department visit) were excluded. Second, we conducted an analysis of unplanned admissions restricted to those related to small bowel complications, including obstruction, mesenteric angina or ischemia, and perforation (Supplemental Table 3, http://link-s.lww.com/SLA/C788). Finally, we assessed the potential effect of unmeasured confounding on the results using the E-value methodology, which is an alternative approach to sensitivity analyses which avoid making assumptions.[33,34] This method estimates the minimum strength of the association an unmeasured confounder would need to have with both the exposure (USBR) and each outcome, while controlling for other confounders, to explain away the observed association between the exposure and outcome. We computed the *E*value for each outcome using an online platform.[33–35]

RESULTS

Study Cohort

Of 1000 patients diagnosed with SB-NETs and synchronous metastases, 785 (78.5%) underwent USBR (Fig. 1). In the entire cohort, 92.9% of patients had consultation with a surgeon,

TABLE 2. Characteristics of Patients in the Propensity-matched Cohort, Stratified by Receipt of Upfront Small Bowel Resection

Characteristic	Nonoperative Management (n = 174)	Upfront Small Bowel Resection (n = 348)	*P*-value
Age at diagnosis (years old)–median (IQR)	66 (55–74)	65 (54–73)	0.606
Female sex	79 (45.4%)	158 (45.4%)	1.0
Rural residence	19 (10.9%)	29 (8.3%)	0.611
High comorbidity burden (ADG ≥ 10)	53 (30.5%)	98 (28.2%)	0.585
Deprivation quintile			0.974
First–least deprived	41 (23.6%)	87 (25.0%)	
Second	34 (19.5%)	65 (18.7%)	
Third	32 (18.4%)	57 (16.4%)	
Fourth	36 (20.7%)	76 (21.8%)	
Fifth–most deprived	31 (17.8%)	63 (18.1%)	
Diagnosis year			0.894
2001–2009	55 (31.6%)	112 (32.2%)	
2010–2017	119 (68.4%)	236 (67.8%)	
Treatment institution			0.534
Academic	92 (52.9%)	194 (55.7%)	
Community	82 (47.1%)	154 (44.3%)	
Elevated 24-h urinary 5HIAA at diagnosis			0.976
Yes	41 (23.6%)	79 (22.7%)	
No	7 (4.0%)	14 (4.0%)	
Unknown	126 (72.4%)	255 (73.3%)	

Values are n (%) unless otherwise specified.
5HIAA indicates 5-Hydroxyindoleacetic acid; ADG, aggregated diagnosis group; IQR, interquartile range.

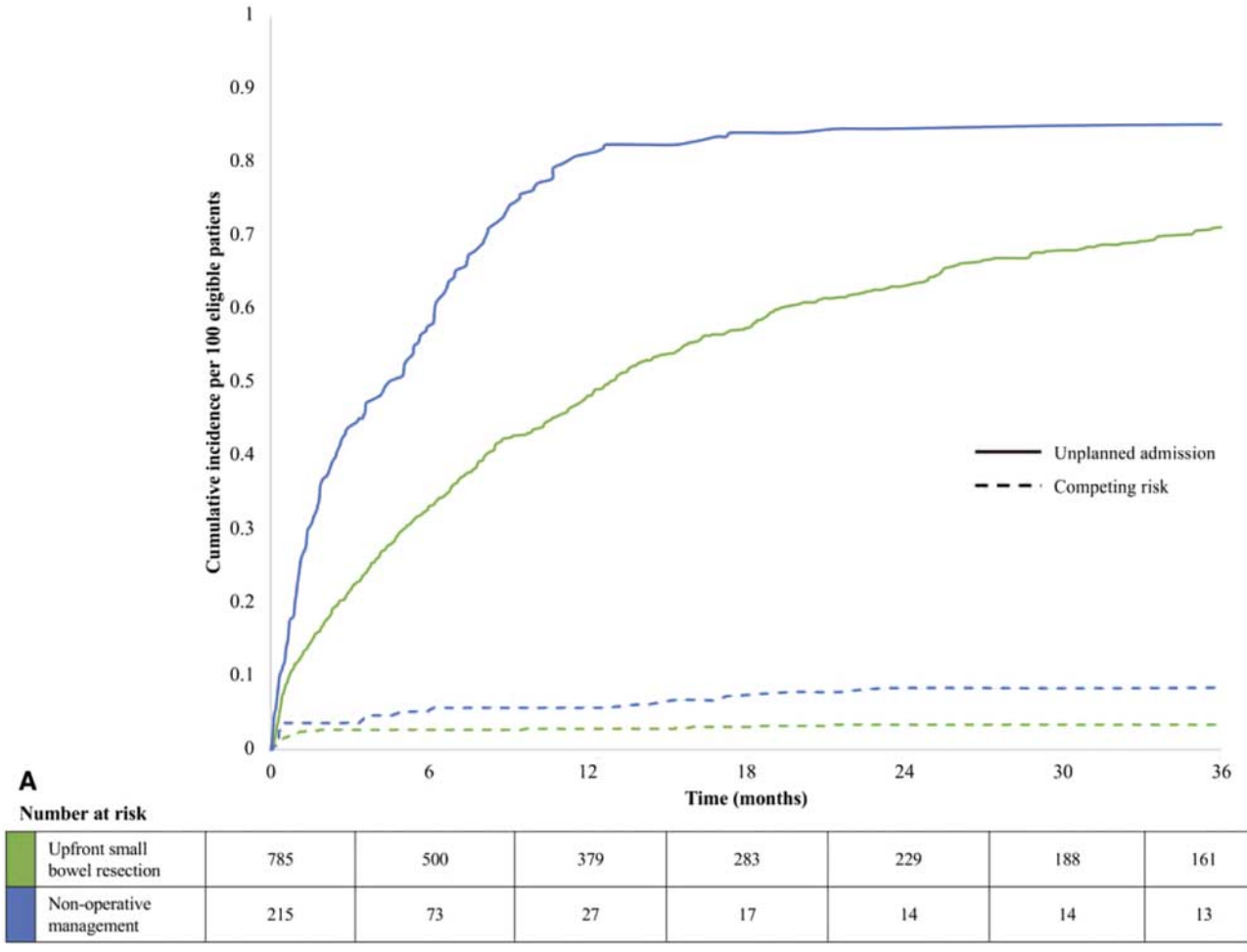


FIGURE 2. Cumulative incidence function of unplanned acute care admissions following diagnosis, stratified by receipt of upfront small bowel resection, in the entire cohort (A) and the propensity-matched cohort (B).

12.2% of patients underwent a liver resection, and 18.9% underwent liver embolization. Median follow-up for was 4.6 years (interquartile range, 2.1–7.4). Characteristics of patients in the entire cohort stratified by receipt of USBR are presented in Table 1. The propensity-matched cohort was composed of 558 patients, including 384 with USBR. Their characteristics are detailed in Table 2. There was adequate balance between groups in the matched cohort for the variables included in the propensity score (Supplemental Figures 1-3, http://links.lww.com/SLA/C788 and Table 5, http://links.lww.com/SLA/C788). Of note, long-acting somatostatin analogs were received by 37.7% of patients with USBR and 56.5% with NOM in those ≥65 years old, in the propensity-matched cohort.

Unplanned Acute Care Admissions

In the entire cohort, patients with USBR had a lower cumulative incidence of unplanned acute care admissions compared to those withNOM, with48.1% (95% CI,44.6%–51.6%) versus 81.3% (95% CI, 75.0%–86.2%) at 1-year, and 71.1% (95% CI, 67.7%–74.3%) versus 84.6% (95% CI, 78.5%–89.0%) at 3-year ($P < 0.001$) (Fig. 2A). USBR was independently associated with lower hazards of unplanned acute care admissions with HR 0.71 (95% CI, 0.58–0.87) adjusted for age, sex, year of diagnosis, material deprivation, comorbidity burden, treatment institution type, and elevated u5HIAA at diagnosis.

In the propensity-score matched cohort, patients with USBR remained less likely to have unplanned acute care admissions than those with NOM, with 49.1% (95% CI, 43.7%–54.3%) versus 82.2% (95% CI, 75.6%–87.2%) at 1-year, and 72.6% (95% CI, 67.3%– 77.2%) versus 86.4% (95% CI, 80.2%–90.7%) at 3-year ($P < 0.001$) (Fig. 2B). The hazards of unplanned acute care admissions were lower for USBR (HR 0.72; 95% CI, 0.57–0.91).

Subsequent Small Bowel-related Surgery

In the entire cohort, patients undergoing USBR had lower cumulative incidence of subsequent small bowel-related surgery compared to those with NOM, with 14.6% (95% CI, 12.2%–17.2%) versus 31.1% (95% CI, 24.7%–37.7%) at 1-year, and 18.5% (95% CI, 15.8%–21.4%) versus 38.9% (95% CI, 78.5%–89.0%) at 3-year ($P < 0.001$) (Fig. 3A). USBR was associated with lower hazards of subsequent small bowel-related surgery, with HR 0.47 (95% CI, 0.36–0.61) adjusted for previously mentioned baseline characteristics.

In the propensity-score matched cohort, cumulative incidence of subsequent small bowel surgery was 11.8% (95% CI,

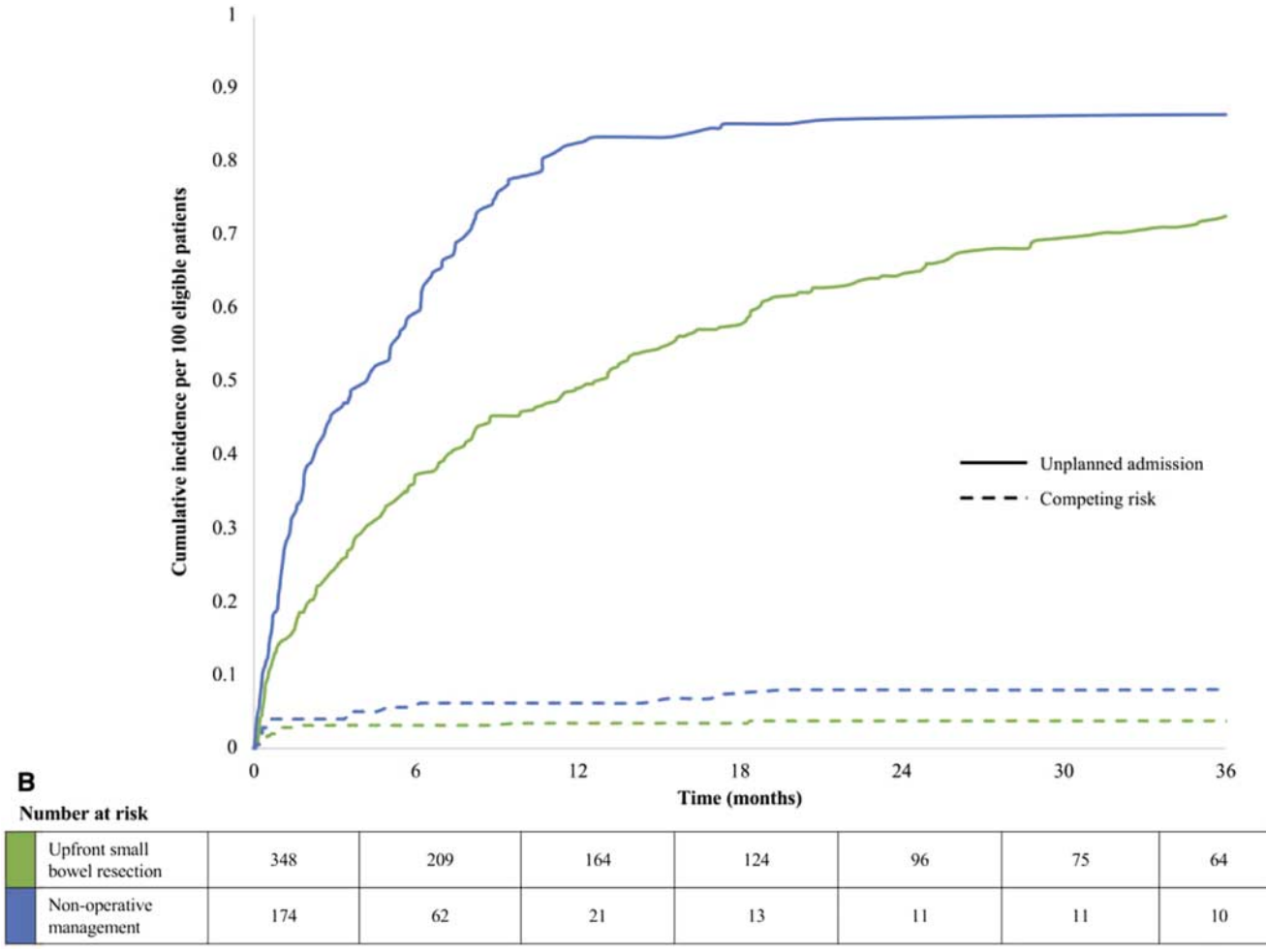


Figure 2 (Continued).

8.7%–15.4%) for the USBR and 31.6% (95% CI, 24.8%–38.6%) for the NOM at 1-year, and 15.4% (95% CI, 11.7–19.4) and 40.3% (95% CI, 32.8–47.6) at 3-year ($P < 0.001$) (Fig. 3B). The hazards of subsequent small bowel-related surgery were lower for USBR with HR 0.44 (95% CI, 0.29–0.67).

Median Survival

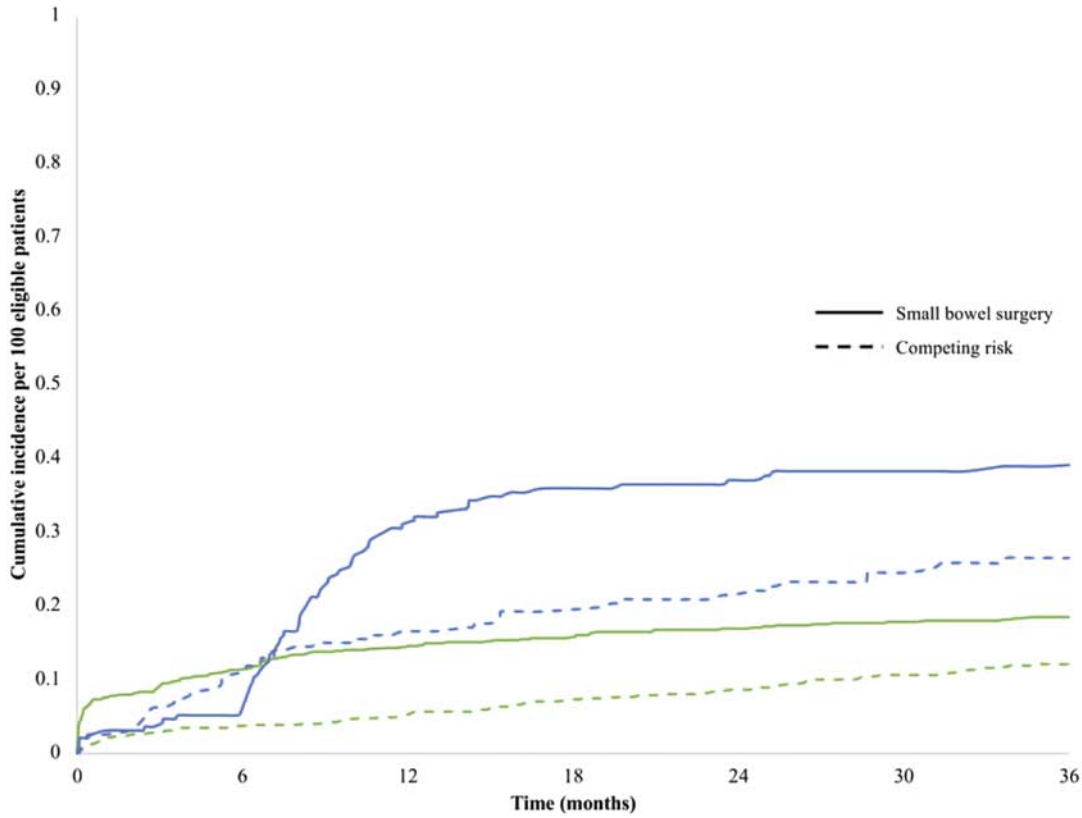
The median overall survival in the entire cohort was 13.2 years (95% CI, 11.72–14.78) for the USBR compared to 7.1 years (95% CI, 4.7–10.6) for the NOM ($P < 0.001$). In the propensity-score matched cohort, median overall survival was 11.6 years (95% CI, 9.3–13.9) for USBR and 6.2 years (95% CI, 4.6–10.6) for NOM ($P < 0.001$).

Sensitivity Analyses and Residual Confounding

After excluding patients who underwent emergency surgery as their index operation, 534 patients and 240 patients remained in the USBR groups for the entire and propensity-matched cohorts, respectively. The cumulative incidence of unplanned acute care admissions remained significantly lower for USBR compared to NOM, with 45.2% (95% CI, 38.8%–51.4%) at 1-year and 70.0% (95% CI, 63.3%–75.7%) at 3-year in the propensity-matched cohort. The cumulative incidence of subsequent small bowel-related surgery also remained significantly lower for USBR ($P < 0.001$), with 15.0% (95% CI, 10.8–19.9) at 1-year and 18.3% (95% CI, 13.6–23.5) at 3-year in the propensity-matched cohort.

When restricting unplanned acute care admissions to those related to small bowel complications, the cumulative incidence remained significantly lower for USBR compared to NOM, with 18.1% (95% CI 14.1%–22.5%) compared to 39.7% (95% CI 32.3%– 47.0%) at 3-year in the propensity-matched cohort.

In the propensity-matched cohort, the E-value for the association between USBR and outcomes was 1.85 for unplanned acute care admissions and 2.75 for subsequent small bowel-related surgery. This determines the strength of the unmeasured confounding necessary to invalidate the observed association between USBR and outcomes. An unmeasured confounder would need to be associated with a 1.85-fold increased probability of being in the USBR group, and a 1.85-fold increased risk of unplanned acute care admission, while adjusting for other covariates outlined. This increase in risk would have to be 2.75-fold for the outcome of subsequent small bowel-related surgery. None of the risk estimates between covariates and exposure of USBR, or between covariates and outcomes, presented such a magnitude (Supplemental Tables 6, http://links.lww.com/SLA/C788 and 7, http://links.lww.com/SLA/C788).



A

Number at risk

Upfront small bowel resection	785	657	613	546	495	453	422
Non-operative management	215	162	102	83	71	58	49

FIGURE 3. Cumulative incidence function of small bowel-related surgery following diagnosis, stratified by receipt of upfront small bowel resection, in the entire cohort (A) and the propensity-matched cohort (B).

DISCUSSION

In this population-based study, we demonstrated that USBR for metastatic SB-NETs was associated with a reduction in unplanned acute care admissions and receipt of subsequent small bowel-related surgeries. With USBR, the hazards of unplanned acute care admissions were 28% lower than with NOM, and those of subsequent small bowel-related surgery were 56% lower than with NOM. This supports a benefit of USBR by potentially preventing loco-regional complications for SB-NETs over a chronic course of disease.

Previous studies addressing resection of the primary tumor for metastatic NETs have focused mostly on survival outcomes.[13,14,36–38] Meta-analyses have reported improved overall and progressionfree survival with primary tumor resection for patients with metastatic SB-NETs.[13,14] Survival is not necessarily the most appropriate outcome for this question, as it is heavily confounded by the extent of tumor, especially metastases. We focused on healthcare utilization outcomes instead. It is acknowledged that unplanned admissions may not all have been directly related to the unresected primary tumor. Subsequent surgical procedures were carefully selected to be plausibly related to either repercussions of the USBR or the unresected primary tumor but could also have been attributable to peritoneal disease. Both outcomes represent pragmatic patient-oriented outcomes that reflect the impact of the intervention on the burden of care and the patient experience comprehensively. Such outcomes can also appreciate the impact of the intervention on health systems and resources, which could be further assessed in costing analyses, though this fell beyond the scope of the present study.

The 2017 ENETS and NANETS consensus statements suggest resection of the primary tumor in the setting of unresectable metastases to avoid local complications and possibly improve prognosis.[39,40] However, a retrospective cohort study from Sweden challenged those recommendations by reporting no benefit in overall survival, cancer-specific survival, or total hospital length of stay with early small bowel resection (within 6 months of presentation).[15] That study also described a higher rate of reoperation for bowel obstruction in those who underwent early small bowel resection, but no details were provided regarding other intestinal or abdominal complications. Generalizability in that study was hampered by a single center sample of patients treated between 1985 and 2005. The noncontemporary cohort bridged the introduction of effective therapies for NETs that have resulted in improved control of metastatic disease, and therefore the potential for increased risk

of primary tumor complications over time. The study also included only patients deemed asymptomatic at diagnosis upon retrospective data collection, whereas our study did not differentiate on the basis symptoms. It can be argued that most patients are not truly asymptomatic.[39] With up to 7 years delay in diagnosis and non-specific signs and symptoms, the symptomatic status SB-NETs is difficult to ascertain accurately.[41] Indeed, patients tend to cope with abdominal symptoms for years before clinical assessment and the fact that they had investigations leading to diagnosis of metastatic SB-NETs suggests that they had some symptoms.[42,43] Finally, it should be noted that 58% of their initial non-operative cohort eventually required surgery during follow-up, highlighting that most patients will eventually progress over time and challenging their interpretation that USBR is not helpful. Overall, our study provides new insight into USBR with a pragmatic examination of all patients presenting with metastatic SB-NETs in clinical practice in a contemporary, multi-institutional, population-based cohort focusing on healthcare utilization outcomes rather than more heavily biased survival outcomes.

In addition to including all types of primary tumors, we included patients with all types of metastases. A small proportion underwent hepatectomy, consistent with other reports on similar cohorts.[14] It could be argued that patients undergoing hepatectomy had a different intent of therapy. However, resectability of NET metastases, hepatic or extra-hepatic, is highly dependent on the surgical assessment as there is no standardized definitions of criteria or goals of resectability.[39,43,44] Moreover, R0 or curative resection for NET metastases may not truly exist.[45]

Both USBR and NOM groups had prolonged survival for patients presenting with metastatic disease, such that both have potential for increased need of interventions or hospitalizations related to the primary tumor. This outlines the importance of planning interventions aimed at minimizing NET morbidity and its impact on patients' lives. Although not all patients in the NOM group may have been amenable to USBR for medical or technical reasons, their median survival of 7 years suggests that there might have been an opportunity to prevent hospitalizations and unplanned surgical interventions. In addition, the comorbidity burden was accounted for in propensity-score matching, such that medical status that may have influenced surgical decision-making was balanced between groups. With regards to technical considerations, it is important to note that the ability to resect primary SB-NETs and potentially associated extensive mesenteric nodal disease depends on the surgeon's expertise and the use of techniques tailored to NETs. Mesenteric sparing resection of nodal masses adherent to the superior mesenteric arterial or venous axes is feasible with lifting of the root of the mesentery and sharp dissection along the major mesenteric vessels to dissect the tumor capsule away from those vessels.[39,46,47] It can be accomplished with low perioperative morbidity and mortality.[14,42] Though USBR may not be feasible in or aligned with the wishes of all patients, those diagnosed with meta-static SB-NETs should be assessed and counseled for USBR by surgeons experienced in managing NETs. Discussion of USBR should be part of routine assessment for those patients.

Like all retrospective analyses, our study is subjected to inherent selection bias. For instance, a higher proportion of patients in the NOM group had elevated urinary 5-HIAA levels at diagnosis and in patients ≥65 years old, long-acting somatostatin analogs were more commonly used in the NOM group, both are potential surrogates for extent of metastatic disease. Although data on long-acting somatostatin analogs were not available reliably for the entire population and therefore could not be used to matching or adjustment, the status of urinary 5-HIAA was accounted for in the propensity score. Propensity-matching for the likelihood of receiving USBR was used to address the selection bias. We also conducted sensitivity analyses excluding emergency surgery from the definition of USBR. Finally, we examined the effect of potential unmeasured confounders on the results. Propensity-matched and sensitivity analyses showed a significant reduction in unplanned acute care admission and subsequent small bowel-related surgery with USBR. Examining the E-value indicated that it is unlikely that unmeasured confounding would negate the observed results, above and beyond the measured confounders.[33,34]

There are other study limitations. The data used was not specifically collected for the purpose of answering the research question. We lacked information on some tumor characteristics. Symptoms and metastases information were addressed above. Information on grade was not available. However, very few SB-NETs are aggressive grade 3 tumors, with 99% being grade 1 and 2 tumors.[48] Therefore it can be assumed that the majority of included patients had low grade NETs with typical indolent growth, which is further supported by the prolonged survival observed in both groups. There could have been more patients with grade 2 compared to grade 1 NETs in the NOM group due to surgeon selection bias. This would have mostly biased the survival comparison which was not the focus of this study. Moreover, acknowledging the potential differences in survival, we limited the analysis to 3 years following diagnosis to avoid analyzing outcomes beyond median follow-up, and used competing-risks methods. A randomized clinical trial of primary tumor resection compared to no resection in asymptomatic metastatic SB-NETs is currently enrolling, although it is powered for NET-specific death with a small sample size of 50 patients.[49] Pending such results, future work should address cost-utility and health system benefits for USBR and explore patients' perceptions and priorities with primary tumor management to further support counseling and shared decision-making.

The true population-based design of this study is a strength that allowed for a pragmatic real-world assessment of USBR in metastatic SB-NETs with data available across the entire continuum of care. We used high quality data to create the cohort, define the exposure, and measure outcomes. This is the only study on this topic to report on patient-centered healthcare utilization outcomes, and to provide a detailed and robust assessment of potential confounding and its impact on the observed results.

CONCLUSIONS

Patients diagnosed with metastatic SB-NETs had prolonged median overall survival beyond 5 years, which comes with increased likelihood of requiring interventions or hospitalizations related to an unresected primary tumor. USBR offered benefits over NOM by reducing unplanned acute care admissions and subsequent small bowel-related surgery. Therefore, USBR can potentially prevent loco-regional complications from SB-NETs. Examination of unmeasured confounding indicated that the observed risk estimates were unlikely to be explained by unmeasured confounders. This information is important as it highlights the need for patients diagnosed with metastatic SB-NETs to be assessed for USBR by surgeons experienced in the care of NETs and for USBR to be routinely discussed as part of multi-disciplinary discussions.

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