Risk of Cancer-Specific Death for Patients Diagnosed With Neuroendocrine Tumors: A Population-Based Analysis

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ABSTRACT

Background: Although patients with neuroendocrine tumors (NETs) are known to have prolonged overall survival, the contribution of cancer-specific and noncancer deaths is undefined. This study examined cancer-specific and noncancer death after NET diagnosis.

Methods: We conducted a population-based retrospective cohort study of adult patients with NETs from 2001 through 2015. Using competing risks methods, we estimated the cumulative incidence of cancer-specific and noncancer death and stratified by primary NET site and metastatic status. Subdistribution hazard models examined prognostic factors. **Results:** Among 8,607 included patients, median follow-up was 42 months (interquartile range, 17–82). Risk of cancer-specific death was higher than that of noncancer death, at 27.3% (95% CI, 26.3%–28.4%) and 5.6% (95% CI, 5.1%–6.1%), respectively, at 5 years. Cancer-specific deaths largely exceeded noncancer deaths in synchronous and metachronous metastatic NETs. Patterns varied by primary tumor site, with highest risks of cancer-specific death in bronchopulmonary and pancreatic NETs. For nonmetastatic gastric, small intestine, colonic, and rectal NETs, the risk of noncancer death exceeded that of cancer-specific deaths. Advancing age, higher material deprivation, and metastases were independently associated with higher hazards, and female sex and high comorbidity burden with lower hazards of cancer-specific death. **Conclusions:** Among all NETs, the risk of dying of cancer was higher than that of dying of other causes. Heterogeneity exists by primary NET site. Some patients with nonmetastatic NETs are more likely to die of noncancer causes than of cancer causes. This information is important for counseling, decision-making, and design of future trials. Cancer-specific mortality should be included in outcomes when assessing treatment strategies.

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Background

With increasing incidence worldwide and prolonged survival in the presence of active cancer because of unique tumor biology, neuroendocrine tumors (NETs) are now more prevalent than pancreatic, esophageal, and gastric cancers combined.^{1–5} There have been more clinical trials, new drug development studies, and epidemiology and healthcare delivery analyses that have improved the knowledge of and therapeutic options for NETs.^{4–9} However, information on the burden of cancer on mortality for patients with NETs remains scarce.

NETs are a heterogeneous malignancy with variable biologic, clinical, and prognostic characteristics. There is an evolving need to adapt treatment plans to their unique biology and chronic behavior, which is generally atypical for malignancies. With prolonged survival and more frequent incidental findings, patients with NETs may not die of their disease.^{4,5} Understanding the cancer and noncancer prognosis of NETs is critical in guiding decisions regarding care, monitoring strategies, aggressiveness of therapy, and patient counseling to enable shared decision-making.¹⁰ Yet, although overall survival, recurrence-free survival, and associated prognostic factors have been described in several studies, few have reported cancer-specific survival.^{4,5,11–15} Existing studies are limited to a single NET primary tumor site, consider a specific treatment modality, and do not address competing risks.^{11,13–15}

Thus, we conducted a population-based study of patients diagnosed with NETs to examine cancer and noncancer deaths after diagnosis and identify prognostic factors associated with cause-specific death.

Methods

Study Design

We conducted a population-based retrospective cohort study using prospectively collected administrative datasets

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linked to administrative health databases stored at ICES in Toronto, Canada. The study was approved by Sunnybrook Health Sciences Centre Research Ethics Board, and was conducted and reported following the RECORD statement¹⁶ and the PROgnosis REsearch Strategy (PROGRESS).¹⁰

Data Sources

Datasets used included the Ontario Cancer Registry (OCR), Registered Persons Database (RPDB), Ontario Health Insurance Plan (OHIP), and Ontario Registrar General Death database (ORGD).^{17–19} Detailed information on all the databases used are provided in supplemental eTable 1 (available with this article at JNCCN.org). Datasets were linked using unique encoded identifiers at ICES.

Study Population and Cohort

Under the Canada Health Act, Ontario's 13.5 million residents benefit from universally accessible and publicly funded healthcare through OHIP.²⁰ Adult patients (aged ≥ 18 years) diagnosed with NETs from January 1, 2001, through December 31, 2015, were identified in the OCR with ICD-O-3 codes using a previously reported strategy (supplemental eTable 2).^{4,21}

Outcomes

Our primary outcome was death after NET diagnosis, classified as cancer-specific death or noncancer death. Time to death was calculated from date of diagnosis to date of death. Cancer-specific death was defined as ICD-9 codes 140 through 239 (topography codes for any cancer death whether from NET or other histology) and noncancer death as other codes in the ORGD. The primary cause of death was defined as the antecedent cause of death when available or the immediate cause of death when antecedent causes were not captured. High agreement in cause of death has been reported between ORGD and clinical follow-up in a prospective cohort of patients with cancer.²² Noncancer cause of death was further described using a previously described strategy (supplemental eTable 3).²³ The category "other cause of death" included stomach and duodenal ulcers; complications of pregnancy, childbirth, and the perinatal period; congenital anomalies; homicide and legal intervention; and other causes of death. Proportion of patients for each cause of death was reported for 2 time periods: ≤ 5 and > 5 years from date of NET diagnosis. Participants were observed until date of death, date of last clinical contact, or December 31, 2016, allowing for a minimum of 12 months of follow-up for each patient.

Covariates

Baseline characteristics were measured at the time of diagnosis. Rural living was determined using the rurality index of Ontario based on the postal code of the patients' primary

residence, with index ≥ 40 representing rural residence.²⁴ Material deprivation is a composite index of the inability for individuals or households to afford consumption goods and activities typical in a society at a given point in time.^{25,26} Baseline comorbidity burden was measured using the Johns Hopkins Adjusted Clinical Group system score based on health services use with a 24-month look-back window before the date of NET diagnosis.^{27,28} The 32 aggregated diagnosis groups (ADGs) were summed and dichotomized, with a cutoff of 10 for high comorbidity burden.^{28,29}

NETs were subdivided according to primary tumor site into bronchopulmonary, gastroenteric, pancreatic, and others using ICD-O-3 topography codes. Gastroenteric NETs were further subdivided as gastric, small intestinal, colonic, and rectal. Metastatic disease was defined using ICD-9 and ICD-10 codes and divided into synchronous metastases (metastasis code ≤ 6 months from the date of NET diagnosis) and metachronous metastases (metastasis code > 6 months after the date of NET diagnosis) (supplemental eTable 4).

Statistical Analysis

Treating time to death as a time-to-event variable, we estimated the cumulative incidence of death after NET diagnosis using the cumulative incidence function for cancer death, treating noncancer death as a competing risk.^{30,31} We reported estimates for probability of death as percentages with 95% confidence intervals at 5 and 10 years. Because use of ICD-9 codes to define cancer-specific death relies on topography and not histology, it is possible that cancer-specific deaths would have been related to non-NET cancer. To explore the potential contribution of non-NET cancer-specific death to the results, we conducted a sensitivity analysis that excluded patients with a non-NET cancer diagnosis after NET diagnosis.

To explore the independent association of potential prognostic factors on the probability of noncancer death, we constructed multivariable subdistribution hazard models.^{32,33} We selected potential prognostic factors a priori based on clinical relevance and literature review, including age, sex, primary tumor site, material deprivation quintile, rural residence, year of diagnosis (dichotomous), and metastatic status.^{4,5,32} We reported the subdistribution hazard ratios (sHRs) with 95% confidence interval.

We examined missing data for key variables. Data were missing for rural residency in 1.2% and material deprivation in 1.1% 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 $P \leq .05$. All analyses were conducted using SAS Enterprise Guide 7.1 (SAS Institute Inc.).

Results

Of 8,707 identified patients with NET diagnosis, 91 were excluded for being aged < 18 or > 105 years and 9 for

having a date of death recorded before the date of NET diagnosis. The final cohort comprised 8,607 patients diagnosed with NETs (Table 1 and supplemental eTable 5). Median follow-up was 42 months (interquartile range [IQR], 17–82 months) and there were 3,121 (36.3%) death events during follow-up, of which 2,487 were because of cancer. The most common primary tumor site was bronchopulmonary (22.8%), followed by small intestine (19.3%) and rectum (14.4%). A total of 42.2% of patients had metastases, including 32.0% synchronous metastases. This varied by primary tumor sites. For rectal and pancreatic NET, 90.8% and 70.7% of patients, respectively, did not have metastases. A non-NET cancer was diagnosed after NET diagnosis in 765 patients.

Overall survival for the entire cohort was 67.1% (95% CI, 66.0%–68.1%) at 5 years and 55.1% (95% CI, 53.6%–56.6%) at 10 years. The cumulative incidences of cancer-specific deaths along with the competing risk of noncancer death for the entire cohort are presented in Figure 1. The risk of cancer-specific death for all patients was higher than that of noncancer death, with 27.3% (95% CI, 26.3%–28.4%) and 5.6% (95% CI, 5.1%–6.1%), respectively, at 5 years, and 34.5% (95% CI, 33.2%–35.8%) and 10.3% (95% CI, 9.4%–11.3%), respectively, at 10 years. In patients with metastatic disease, both synchronous and metachronous, the risk of cancer-specific death largely exceeded that of noncancer death immediately after diagnosis. In patients without metastases, the risk of cancer-specific and noncancer deaths paralleled each other. Cancer-specific death was initially slightly higher than noncancer death with 7.7% (95% CI, 7.0%–8.6%) and 6.2% (95% CI, 5.4%–6.9%) at 5 years, respectively. Only after 8 years from diagnosis did the risk of noncancer death (11.7%; 95% CI, 10.4%–13.2%, at 10 years) become slightly higher than that of cancer-specific death (10.2%; 95% CI, 9.1%–11.3%, at 10 years). Sensitivity analysis excluding patients with non-NET cancer diagnosis after NET diagnosis did not substantially alter the results (supplemental eFigure 1).

Different patterns of cancer and noncancer deaths were observed depending on the primary NET site. When considering all patients, regardless of metastatic status, the risk of cancer-specific death was consistently higher than that of noncancer death; however, the magnitude of the cancer-specific death varied (Figures 2 and 3, and supplemental eFigure 2). The highest risks of cancer-specific death were observed for bronchopulmonary NETs, with 36.4% (95% CI, 34.2%–38.7%) at 5 years and 42.7% (95% CI, 0.1%–45.3%) at 10 years (Figure 3). This was followed by pancreatic NETs (34.8% [95% CI, 31.5%–38.2%] at 5 years and 48.4% [95% CI, 43.5%–53.0%] at 10 years)

Table 1. Characteristics of Patient Cohort

Characteristic	n (%)
Patients, N	8,607
Age at diagnosis, y	
<50	1,862 (21.6)
50–59	2,004 (23.3)
60–69	2,226 (25.9)
≥70	2,515 (29.2)
Sex	
Female	4,323 (50.2)
Male	4,284 (49.8)
Year of diagnosis	
2001–2008	2,961 (34.4)
2009–2015	5,646 (65.6)
Location of residence	
Missing	102 (1.2)
Rural	824 (9.6)
Urban	7,681 (89.2)
Material deprivation quintile	
Missing	93 (1.1)
1st (least deprived)	1,648 (19.1)
2nd	1,704 (19.8)
3rd	1,660 (19.3)
4th	1,724 (20.0)
5th (most deprived)	1,778 (20.7)
Comorbidity burden	
Low (ADG <10)	6,210 (72.2)
High (ADG ≥10)	2,397 (27.8)
Metastatic status	
None	4,978 (57.8)
Synchronous ^a	2,754 (32.0)
Metachronous ^b	875 (10.2)
Median duration of follow-up (IQR), mo	42 (17–82)
Death of any cause during follow-up	3,121 (36.3)

Abbreviations: ADG, aggregated diagnosis group; IQR, interquartile range.

^aSynchronous: <6 months from diagnosis.

^bMetachronous: ≥6 months from diagnosis.

(Figure 2) and colonic NETs (21.4% [95% CI, 18.9%–24.0%] at 5 years and 26.6% [95% CI, 23.4%–29.9%] at 10 years) (Figure 4). When stratifying by metastatic status, the risk of cancer-specific death largely exceeded that of noncancer death across all primary NET sites, with most of the increase in cancer-specific death occurring in the first 2 years after diagnosis.

In certain scenarios of nonmetastatic NET, the cumulative incidence of cancer-specific death was lower than that of noncancer death (Figure 4). For nonmetastatic gastric NETs, incidence of noncancer

Figure 1. Cancer-specific death and noncancer death cumulative incidence after neuroendocrine tumor diagnosis for (A) all patients and (B) stratified by metastatic status.

death became higher than cancer-specific death starting at 1 year after diagnosis, with 10.4% (95% CI, 7.1%–14.4%) at 5 years and 18.9% (95% CI, 13.4%–25.2%) at 10 years versus 5.8% (95% CI, 3.5%–8.9%) at 5 years and 9.0% (95% CI, 5.1%–14.3%) at 10 years, respectively (Figure 4). The same was observed for nonmetastatic small intestine NETs from the time of diagnosis, with 13.0% (95% CI, 10.2%–16.0%) at 5 years and 22.4% (95% CI, 17.7%–27.4%) at 10 years for noncancer death versus 4.7% (95% CI, 3.1%–6.7%) at 5 years and 8.6% (95% CI, 5.7%–12.3%) at 10 years for cancer-specific death, as well as for colonic NETs starting at 3 years after diagnosis, with noncancer death of 6.4% (95% CI, 4.5%–8.8%) at 5 years and 11.4%

(95% CI, 7.9%–15.6%) at 10 years, and cancer-specific death of 4.1% (95% CI, 2.7%–5.9%) at 5 years and 5.9% (95% CI, 3.8%–8.6%) at 10 years, and finally rectal NETs starting at 2 years after diagnosis, with noncancer death of 2.7% (95% CI, 1.8%–3.9%) at 5 years and 6.6% (95% CI, 4.7%–9.0%) at 10 years, and cancer-specific death of 7.4% (95% CI, 5.9%–8.9%) at 5 years and 9.3% (95% CI, 7.4%–11.4%) at 10 years. This was not observed for nonmetastatic pancreatic and bronchopulmonary NETs, for which cancer-specific death exceeded noncancer death from the time of diagnosis (Figures 2 and 3).

We performed multivariable analyses to identify factors associated with the risk of cancer-specific death,

Figure 2. Cancer-specific death and noncancer death cumulative incidence after pancreatic neuroendocrine tumor diagnosis for (A) all patients and (B) stratified by metastatic status.

Figure 3. Cancer-specific death and noncancer death cumulative incidence after bronchopulmonary neuroendocrine tumor diagnosis for (A) all patients and (B) stratified by metastatic status.

accounting for the competing risk of noncancer death (Table 2 and supplemental eTable 6). Advancing age was consistently associated with increased hazards of cancer-specific death in all NETs and when stratifying by NET group of bronchopulmonary, pancreatic, and gastroenteric. Female sex was associated with lower hazards of cancer-specific death compared with male sex for all NETs and stratified by NET group, although the association was not significant for pancreatic NETs. Higher material deprivation, indicating lower socioeconomic status, was independently associated with increased hazards of cancer-specific death. Higher comorbidity burden was associated with lower hazards of cancer-specific death, likely because of the observed higher hazards of noncancer death (sHR, 1.73; 95% CI, 1.46–2.04), compared with patients with lower comorbidity burden. Both synchronous and metachronous metastases were independently associated with increased hazards of cancer-specific death in all NETs (sHR, 9.19 [95% CI, 8.16–10.36] vs 6.55 [95% CI, 5.84–7.60], respectively). This was also observed in stratified categories of NETs for bronchopulmonary, pancreatic, and gastroenteric NETs. Among all NETs, gastroenteric (sHR, 0.33; 95% CI, 0.29–0.36) and pancreatic NETs (sHR, 0.74; 95% CI, 0.65–0.85) presented independently lower hazards of cancer-specific death compared with bronchopulmonary NETs.

Factors associated with noncancer death were also examined (supplemental eTable 7). Advancing age, higher comorbidity burden, and increased material deprivation were associated with increased hazards of noncancer death. Both synchronous (sHR, 0.64; 95% CI, 0.53–0.77) and metachronous (sHR, 0.68; 95% CI, 0.52–0.89)

metastatic disease was associated with lower hazards of noncancer death, compared with no metastases.

Finally, looking at noncancer cause of death by time period, 420 deaths (16.0% of deaths over the time period) were caused by cancer in ≤ 5 years and 214 deaths (8.2% of deaths over the time period) in >5 years from NET diagnosis. The breakdown of noncancer cause of death is presented in Figure 5. The most common causes of noncancer death were diseases of the heart and non-cardiac vascular diseases.

Discussion

This population-based cohort study is the first to describe patterns of and factors associated with cancer-specific death after a NET diagnosis. We showed that patients with NETs experienced prolonged survival, and quantified how the risk of cancer-specific and noncancer death contributed to this. Patients with metastatic disease consistently had a largely higher risk of cancer-specific versus noncancer deaths. On the other hand, the risk of noncancer death exceeded that of cancer-specific death in some nonmetastatic NETs, namely gastric, small intestine, colonic, and rectal.

Data on cancer-specific mortality for NETs are scarce.^{11,13–15} Two studies developed nomograms to predict cancer-specific survival in all pancreatic NETs and in metastatic pancreatic NETs, but there was no specific information regarding risk estimates for cancer-specific survival or noncancer death.^{14,15} Two studies reported on cancer-specific survival for pancreatic NETs using Kaplan-Meier methods, which do not account for the competing risk of noncancer death.¹³ Competing-risk methods and assessment of noncancer death along with cancer-specific death are recommended to improve the

Figure 4. Cancer-specific death and noncancer death cumulative incidence after gastroenteric NET diagnosis stratified by metastatic status for (A) gastric, (B) small intestine, (C) colonic, and (D) rectal NETs. Abbreviation: NET, neuroendocrine tumor.

reporting of cancer-specific mortality.³³ A SEER study reported on NET recurrence patterns in the Medicare population (aged ≥ 65 years), but although it indicated that patients with localized NETs at diagnosis have low risk of recurrence and therefore low likelihood of dying from NETs, it did not examine cancer-specific death.³⁴ Our study provided long-term cancer and noncancer mortality outcomes for a contemporary cohort of NETs, further stratified by primary NET site and metastatic status, accounted for competing risks to avoid overestimation of the risk of cancer death, and offered a detailed analysis of prognostic factors for cancer-specific and noncancer death.^{30,31,35}

Because of the unique biology of NETs, most patients experience prolonged survival. This potentially comes with associated longitudinal risk for noncancer death, which can complicate decisions regarding goals, modality, and sequencing of therapy, as well as individual patient counseling and supportive care. Thus, it is important to have data-driven insights for estimates of

cancer-specific death across all patients and NET sites, which we have provided herein using population-based data representative of the full spectrum of patients encountered in contemporary clinical practice. Our results indicate that the probability of dying of cancer was greater than that of dying of noncancer causes overall. Those findings are modulated by NET type and metastatic status.

Patients with metastatic NETs had a much higher risk of dying from cancer than from other causes, consistent with the more aggressive nature of their disease. Accordingly, metastatic status was a strong independent prognostic factor of cancer death, but not of noncancer death. The curves for all NETs and those stratified by primary NET site showed an initial steep increase in cancer death in the first 2 years after diagnosis, indicating potentially more-aggressive NETs, consistent with known biology of advanced gastric, pancreatic, colonic, rectal, and bronchopulmonary

Table 2. Multivariable Fine-Gray Model Showing Factors Associated With Cancer-Specific Death

Variable	sHR (95% CI)
Age at diagnosis, y	
<50	Ref
50–59	1.60 (1.38–1.87)
60–69	2.11 (1.82–2.44)
≥70	3.33 (2.89–3.84)
Sex	
Female	0.82 (0.75–0.89)
Male	Ref
Comorbidity burden	
Low (ADG 0–9)	Ref
High (ADG ≥10)	0.90 (0.82–0.99)
Deprivation quintile	
1st (least deprived)	Ref
2nd	1.07 (0.94–1.23)
3rd	1.03 (0.90–1.18)
4th	1.09 (0.96–1.24)
5th (most deprived)	1.24 (1.09–1.41)
Location of residence	
Rural	0.99 (0.70–1.13)
Urban	Ref
Year of diagnosis	
2001–2008	Ref
2009–2015	0.93 (0.85–1.02)
Primary NET site	
Bronchopulmonary	Ref
Gastroenteric	0.33 (0.29–0.36)
Pancreatic	0.74 (0.65–0.85)
Others	1.04 (0.92–1.18)
Metastatic status	
None	Ref
Synchronous ^a	9.19 (8.16–10.36)
Metachronous ^b	6.66 (5.84–7.60)

Abbreviations: ADG, aggregated diagnosis group; NET, neuroendocrine tumor; sHR, subhazard ratio.

^aSynchronous: <6 months from diagnosis.

^bMetachronous: ≥6 months from diagnosis.

NETs. Metastatic small intestine NETs presented a unique pattern of risk of cancer-specific death, with a gradual increase over 10 years, along with more favorable risk estimates than other primary NET sites. This can indicate a different and more chronic disease behavior, the availability of more treatment options, or higher levels of comfort among providers in treating those tumors. Nevertheless, the slow pace and lower incidence of cancer death in small intestine NETs

should be taken into consideration. It supports longitudinal sequencing of therapy for metastatic small bowel NETs over years, as well as treatment strategies that consider long-term sequelae and quality of life, such as early resection of primary small intestinal NETs to prevent abdominal complications.^{36,37}

In certain circumstances, cancer-specific death did not exceed noncancer death. The increase in incidence of NETs has previously been hypothesized as being related to diagnosis at an earlier stage and even possible overdiagnosis.^{4,5} There is ongoing debate regarding the best management of incidental NETs; although some support monitoring and nonoperative management, others propose a more aggressive surgical approach capitalizing on the opportunity to achieve cure and avoid subsequent NET spread and its associated mortality. In this setting, patterns of cancer-specific and noncancer death can provide important information to avoid overtreatment. Patients with nonmetastatic gastric, small intestine, colonic, and rectal NETs are less likely to die of cancer-specific versus other causes. However, the current analysis could not ascertain the contribution of therapy patterns to the risk of cancer-specific death. It is important that data on cancer-specific mortality be used along with specific patient and tumor information, such as age, comorbidity, endocrinopathy, tumor grade and size, and individual preferences, to optimize the design of personalized treatment strategies. It is acknowledged that various types of NETs do not have the same opportunity for therapy, ranging from potentially curative resection for localized small bowel NETs to multiple lines of systemic therapy for metastatic pancreatic NETs. Our observations warrant further investigation into cancer-specific mortality according to therapy and management patterns. The unique patterns observed also suggest that cancer-specific mortality should be used as an outcome when assessing treatment approaches for those types of NETs.

Finally, examination of factors associated with cancer-specific and noncancer-related death showed that efforts to address cancer-specific death in NETs should include special considerations for older adults and socioeconomically deprived patients to ensure they can access and receive care throughout their cancer journey. The association of advancing age with an increased risk of cancer death may be related to underlying increased vulnerability and frailty, but also risks of de-escalating cancer care in older adults who are underrepresented in clinical studies.^{38,39} Patients with a higher level of deprivation are known to exhibit different health-seeking behaviors and experience delayed diagnosis and access to care, which impact outcomes.^{32,40,41}

Despite the inherent challenges associated with retrospective population-based studies, this examination

Figure 5. Causes of noncancer death after NET diagnosis.
Abbreviation: NET, neuroendocrine tumor.

provides a long-term detailed and robust appraisal of cancer-specific mortality among patients with NETs. However, the administrative data used was not collected specifically to address the current research question. We lacked some information regarding tumor characteristics, including stage and grade. We used metastases as a surrogate for advanced disease due to the unique biology of NETs and previous observations of metastatic status being the most significant prognostic factor.³ Using grade classification for the multivariable analysis and to stratify the results could have provided even more detailed information for clinical use, as could further stratification of primary NET site in models to examine factors associated with cancer-specific death. However, despite the overall large cohort, this resulted in too many levels for the covariates, with loss of levels of freedom and appropriateness of the regression model, such that primary NET sites were grouped into gastroenteric, pancreatic, bronchopulmonary, and others for the main model. Nevertheless, the population-based design of this study is a strength that allowed for a novel real-world assessment of the prognosis of patients diagnosed with NETs. These data also represent outcomes within a universal healthcare system, avoiding bias by insurance status–limited access.

We used high-quality linked administrative databases and definitions with known accuracy and reliability, which included comprehensive availability of cause of death and had limited missing data and measurement error.

Conclusions

In this population-based analysis, we reported cancer-specific mortality for patients diagnosed with NETs. Among all patients diagnosed with NETs, the risk of dying of cancer is higher than that of dying of other causes, especially in those with metastatic disease. Heterogeneity exists by primary NET site in patterns of cancer and noncancer death. This initial description of cancer-specific mortality for NETs can support patient counseling, clinical decision-making, discussion regarding clinical practice guidelines, and future trial designs.

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Risk of Cancer-Specific Death for Patients Diagnosed With Neuroendocrine Tumors: A Population-Based Analysis

Julie Hallet, MD, MSc; Calvin Law, MD, MPH; Simron Singh, MD, MPH; Alyson Mahar, PhD; Sten Myrehaug, MD; Victoria Zuk, MSc; Haoyu Zhao, MPH; Wing Chan, MPH; Angela Assal, MD, MSc; and Natalie Coburn, MD, MPH

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eFigure 1: Cancer-Specific Death After NET Diagnosis

eFigure 2: Cancer-Specific Death After Gastroenteric NET Diagnosis

eTable 1: Data Sources

eTable 2: Coding Strategy Used to Identify Patients Diagnosed With NETs and Determine Tumor Characteristics

eTable 3: Definition of Noncancer Cause of Death Categories

eTable 4: Covariate Definitions

eTable 5: Characteristics of Included Patients Stratified by Primary NET Site

eTable 6: Multivariable Fine-Gray Model Showing Factors Associated With Cancer-Specific Death Stratified by Primary NET Site

eTable 7: Multivariable Fine-Gray Model Showing Factors Associated With Noncancer Death

eFigure 1. Cancer-specific death after NET diagnosis in sensitivity analysis excluding patients with non-NET cancer diagnosis after NET diagnosis (n=7,942).
Abbreviation: NET, neuroendocrine tumor.

eFigure 2. Cancer-specific death after gastroenteric NET diagnosis for (A) gastric, (B) small intestine, (C) colonic, and (D) rectal NETs. Abbreviation: NET, neuroendocrine tumor.

eTable 1. Data Sources

Database	Description
OCR	A passive, provincial registry all incident cancer diagnoses in Ontario. It includes 96% of cancer diagnoses in the province. Information included in the registry: cancer topography and morphology/histology, and details on diagnosis (eg, types of contributing information to the diagnosis, dates).
ALR of CCO	CCO maintains a database of cancer-specific services, including consultations, chemotherapy, and radiotherapy provided by regional cancer centers in the province. Because all radiotherapy is delivered at RCCs, it is a complete source of information. However, because not all patients with cancer who receive surgery or chemotherapy visit an RCC, it cannot be used as a population data sources for those treatments.
RPDB	An ICES database derived from all administrative data sources and provides demographic data including age, patient residence, vital status, date of last contact with the healthcare system, and OHIP eligibility.
ORG	Contains gold standard vital status data for all Ontarians. According to the Vital Statistics Act, it is mandatory to register all deaths occurring in the province.
ON-Marg	A specialized database using Census data to profile relative area-level marginalization dependency, deprivation, ethnic concentration, and instability at various geographic levels in Ontario.
OHIP database	Contains all physician billing data including information on diagnoses as well as services provided, such as receipt of surgery, chemotherapy, and radiotherapy.
ODB database	Contains all information for prescription drug claims for individuals covered by the provincial plan (all individuals aged ≥ 65 years), including type of medication, dose, date of prescription filling, and duration of treatment.
CIHI-DAD and CIHI-SDS	Mandatory reporting systems that provide information on hospital admissions and same-day surgeries, including diagnoses, procedures, and length of stay.

Abbreviations: ALR, Activity Level Report; CCO, Cancer Care Ontario; CIHI-DAD, Canadian Institute of Health Information Discharge Abstract Database; CIHI-SDS, Canadian Institute of Health Information Same-Day Surgery; OCR, Ontario Cancer Registry; ODB, Ontario Drug Benefit; OHIP, Ontario Health Insurance Plan; ON-Marg, Ontario Marginalization Index; ORG, Ontario Registrar General; RCC, regional cancer center; RPDB, Registered Patient Database.

eTable 2. Coding Strategy Used to Identify Patients Diagnosed With NETs and Determine Tumor Characteristics

Identify NETs (ICD-O-3)	
81503	Islet cell carcinoma
81501	Islet cell tumor, NOS
81510	Insulinoma, NOS
81513	Insulinoma, malignant
81521	Glucagonoma
81523	Glucagonoma, malignant
81531	Gastrinoma
81533	Gastrinoma, malignant
81543	Mixed islet-cell/exocrine adenocarcinoma
81551	VIPoma
81553	VIPoma, malignant
81561	Somatostatinoma
81563	Somatostatinoma, malignant
81571	Enteroglucagonoma
81573	Enteroglucagonoma, malignant
82401	Carcinoid tumor of uncertain malignant potential
82403	Carcinoid tumor, NOS
82413	Enterochromaffin-like cell carcinoid
82421	Enterochromaffin-like cell tumors, NOS
82423	Enterochromaffin-like cell tumors, malignant
82443	Composite carcinoid
82453	Adenocarcinoid
82451	Tubular carcinoid
8463	Neuroendocrine carcinoma
82493	Atypical carcinoid
Exclusions (ICD-O-3)	
80023	Malignant tumor, small cell type
80400	Tumorlet
80413	Small cell carcinoma, NOS
80423	Oat cell carcinoma
80433	Small cell carcinoma, NOS, fusiform cell type
80443	Small cell carcinoma, intermediate cell
80453	Combined small cell carcinoma
80133	Large cell neuroendocrine carcinoma of the lung
87000	Pheochromocytoma, NOS
87003	Pheochromocytoma, malignant
86801	Paraganglioma
86803	Paraganglioma, malignant
86931	Extra-adrenal paraganglioma
86933	Extra-adrenal paraganglioma, malignant
85103	Medullary carcinoma of the thyroid

(continued)

eTable 2. Coding Strategy Used to Identify Patients Diagnosed With NETs and Determine Tumor Characteristics (cont.)

Exclusions (ICD-O-3) - cont.	
80000	Neoplasm, benign
80001	Neoplasm, uncertain whether benign or malignant
80003	Neoplasm, malignant
80100	Epithelial tumor, benign
80702	Squamous cell carcinoma, in situ, NOS
80703	Squamous, cell carcinoma, NOS
80706	Squamous cell carcinoma, metastatic, NOS
81400	Adenoma, NOS
81401	Atypical adenoma
83413	Papillary microcarcinoma
84813	Mucinous producing adenocarcinoma
85002	Intraductal carcinoma, noninfiltrating, NOS
85003	Infiltrating duct carcinoma, NOS
93643	Peripheral neuroectodermal tumor
93703	Chordoma
82433	Goblet cell carcinoid
Define primary tumor type (ICD-O-3 topography codes)	
C16*	Stomach
C17*	Small intestine
C18*, C19*	Large intestine
C20*	Rectum
C25*	Pancreas
C34*	Bronchus
All others	Others

Abbreviations: NET, neuroendocrine tumor; NOS, not otherwise specified; VIPoma, vasoactive intestinal peptide tumor.

eTable 3. Definition of Noncancer Cause of Death Categories

Category	Noncancer Causes of Death	ICD-10 Corresponding Codes	Cause of Death Definition
Benign tumors	In situ, benign or unknown behavior neoplasms	D00–D09	In situ neoplasms
		D10–D36	Benign neoplasms
		D37–D48	Neoplasms of uncertain or unknown behavior
Diabetes	Diabetes mellitus	E10–E14	Diabetes mellitus
Infectious diseases	Septicemia	A40–A41	Sepsis
	Other infectious diseases	A00–A14, A20–A39, A42–A49, A54–A99, B00–B99	Tuberculosis, syphilis, and other bacterial, viral, and parasitic disease
Noncardiac vascular diseases	Hypertension without heart disease	I10	Essential (primary) hypertension
		I12	Hypertensive renal disease
	Cerebrovascular disease	I60–I62	Nontraumatic intracranial hemorrhage
		I63	Cerebral infarction
		I64	Stroke, not specified as hemorrhage or infarction
		I65–I66	Occlusion and stenosis of precerebral/cerebral arteries, not resulting in cerebral infarction
		I67–I69	Other cerebrovascular diseases or sequelae of cerebrovascular disease
	Atherosclerosis	I70	Atherosclerosis
	Aortic aneurysm and dissection	I71	Aortic aneurysm and dissection
	Other diseases of arteries, arterioles, capillaries	I72–I73	Other aneurysm and dissection or other peripheral vascular diseases
		I74	Arterial embolism and thrombosis
		I77	Other disorders of arteries and arterioles
		I78	Diseases of capillaries
Respiratory diseases	Pneumonia and influenza	J09–J18	Influenza and pneumonia
	Chronic obstructive pulmonary disease	J40–J42	Bronchitis
		J43	Emphysema
		J44	Other chronic obstructive pulmonary disease
		J45–J46	Asthma or status asthmaticus
		J47	Bronchiectasis
Liver and kidney diseases	Chronic liver disease and cirrhosis	K70	Alcoholic liver disease
		K73	Chronic hepatitis
		K74	Fibrosis and cirrhosis of liver
	Nephritis, nephrotic syndrome, and nephrosis	N00–N07	Glomerular diseases
		N17–N19	Renal failure
		N25	Disorders resulting from impaired renal tubular function
		N26	Unspecified contracted kidney
		N27	Small kidney of unknown cause
Accidents and self-harm	Accidents and adverse effects	V01–V99	Transport accidents
		W00–X59	Other external causes of accidental injury
		Y85–Y86	Sequelae of transport accidents or other accidents
	Suicide and self-inflicted injury	X60–X84	Intentional self-harm
		Y87	Sequelae of intentional self-harm, assault, and events of undetermined intent

(continued on next page)

eTable 3. Definition of Noncancer Cause of Death Categories (cont.)

Category	Noncancer Causes of Death	ICD-10 Corresponding Codes	Cause of Death Definition
Alzheimer	Alzheimer	G30	Alzheimer disease
Diseases of the heart		I00–I02	Acute rheumatic fever
		I05–I09	Chronic rheumatic heart diseases
		I11	Hypertensive heart disease
		I13	Hypertensive heart and renal disease
		I20–I25	Ischemic heart diseases
		I26–I28	Pulmonary heart disease and diseases of pulmonary circulation
		I30–I32	Diseases of pericardium
		I33	Acute and subacute endocarditis
		I34–I39	Nonrheumatic valve disorders
		I40–I41	Myocarditis
		I42–I43	Cardiomyopathy
		I44–I45	Conduction disorders
		I46	Cardiac arrest
		I47–I49	Arrhythmias
		I50	Heart failure
		I51	Complications and ill-defined descriptions of heart disease
Other noncancer	Symptoms, signs, and ill-defined conditions	R00–R99	Symptoms, signs, abnormal results of clinical or other investigative procedures, and ill-defined conditions regarding which no diagnosis classifiable elsewhere is recorded
	Other cause of death	All others not included in any of the above	

eTable 4. Covariate Definitions

Variable	Definition	Source	Type	Analysis Format
Sociodemographic characteristics				
Age	Age at diagnosis	OCR	Categorical	<50 50–59 60–69 ≥70
			Continuous	Years
Sex	Sex	OCR	Dichotomous	Male/Female
Material deprivation	Measure of the inability for individuals or households to afford goods or activities typical in a society at a given time ^{1,2}	Canadian Census RPDB ON-Marg	Categorical	1st (least deprived) 2nd 3rd 4th 5th (most deprived)
Rural residence	Determined with postal code of residence as per national census definition of a community <10,000 people ³	RPDB	Dichotomous	Urban/Rural
Clinical characteristics				
Time period of diagnosis	Year of cancer diagnosis date	OCR	Categorical	2001–2008 2009–2015
Comorbidity burden	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 cancer diagnosis whereby the 32 ADGs are summed to create a total score ^{4,5}	CIHI-DAD CIHI-SDS OHIP	Dichotomous	<10 ≥10
Primary NET site	Type of primary NET on ICD-O-3 codes (supplemental eTable 2)	OCR	Categorical	Gastric Small intestinal Colonic Rectal Pancreatic Bronchopulmonary Others
Metastatic status	Presence of metastases using ICD-O-3 codes	OCR CIHI-DAD CIHI-SDS NACRS	Categorical	No metastases Synchronous Metachronous

Abbreviations: ADG, aggregated diagnosis group; CIHI-DAD, Canadian Institute of Health Information Discharge Abstract Database; CIHI-SDS, Canadian Institute of Health Information Same-Day Surgery; NACRS, national ambulatory care reporting system; NET, neuroendocrine tumor; OCR, Ontario Cancer Registry; OHIP, Ontario Health Insurance Plan; ON-Marg, Ontario Marginalization Index; RPDB, Registered Patient Database.

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eTable 5. Characteristics of Included Patients Stratified by Primary NET Site

Variable	Bronchopulmonary n (%)	Pancreatic n (%)	Gastric n (%)	Small Intestinal n (%)	Colonic n (%)	Rectal n (%)	Others n (%)
Total, N	1,960	1,001	501	1,662	1,175	1,240	1,068
Age at diagnosis, y							
<50	236 (23.6)	96 (19.2)	328 (16.7)	426 (36.3)	236 (14.2)	348 (28.1)	192 (18.0)
50–59	252 (25.2)	94 (18.8)	381 (19.4)	249 (21.2)	396 (23.8)	453 (36.5)	179 (16.8)
60–69	288 (28.8)	123 (24.6)	559 (28.5)	229 (19.5)	485 (29.2)	278 (22.4)	264 (24.7)
≥70	225 (22.5)	188 (37.5)	692 (35.3)	271 (23.1)	545 (32.8)	161 (13.0)	433 (40.5)
Sex							
Female	448 (44.8)	251 (50.1)	1,148 (58.6)	617 (52.5)	748 (45.0)	589 (47.5)	522 (48.9)
Male	553 (55.2)	250 (49.9)	812 (41.4)	558 (47.5)	914 (55.0)	651 (52.5)	546 (51.1)
Year of diagnosis							
2001–2008	284 (28.4)	170 (33.9)	747 (38.1)	357 (30.4)	578 (34.8)	383 (30.9)	442 (41.4)
2009–2015	717 (71.6)	331 (66.1)	1,213 (61.9)	818 (69.6)	1,084 (65.2)	857 (69.1)	626 (58.6)
Location of residence							
Missing	10 (1.0)	11 (2.2)	22 (1.1)	11 (0.9)	22 (1.3)	12 (1.0)	14 (1.3)
Rural	76 (7.6)	35 (7.0)	223 (11.4)	102 (8.7)	186 (11.2)	83 (6.7)	119 (11.1)
Urban	915 (91.4)	455 (90.8)	1,715 (87.5)	1,062 (90.4)	1,454 (87.5)	1,145 (92.3)	935 (87.5)
Material deprivation quintile							
Missing	7 (0.7)	11 (2.2)	22 (1.1)	11 (0.9)	20 (1.2)	11 (0.9)	11 (1.0)
1st (least deprived)	204 (20.4)	81 (16.2)	352 (18.0)	261 (22.2)	328 (19.7)	226 (18.2)	196 (18.4)
2nd	211 (21.1)	90 (18.0)	386 (19.7)	228 (19.4)	338 (20.3)	252 (20.3)	199 (18.6)
3rd	183 (18.3)	102 (20.4)	388 (19.8)	212 (18.0)	323 (19.4)	261 (21.0)	191 (17.9)
4th	193 (19.3)	90 (18.0)	394 (20.1)	223 (19.0)	320 (19.3)	275 (22.2)	229 (21.4)
5th (most deprived)	203 (20.3)	127 (25.3)	418 (21.3)	240 (20.4)	333 (20.0)	215 (17.3)	242 (22.7)
Comorbidity burden							
Low (ADG <10)	709 (70.8)	326 (65.1)	1,355 (69.1)	930 (79.1)	1,119 (67.3)	1,014 (81.8)	757 (70.9)
High (ADG ≥10)	292 (29.2)	175 (34.9)	605 (30.9)	245 (20.9)	543 (32.7)	226 (18.2)	311 (29.1)
Metastatic status							
None	486 (48.6)	354 (70.7)	1,182 (60.3)	768 (65.4)	666 (40.1)	1,126 (90.8)	396 (37.1)
Synchronous ^a	348 (34.8)	104 (20.8)	609 (31.1)	326 (27.7)	791 (47.6)	71 (5.7)	505 (47.3)
Metachronous ^b	167 (16.7)	43 (8.6)	169 (8.6)	81 (6.9)	205 (12.3)	43 (3.5)	167 (15.6)
Median duration of follow-up (IQR), mo	36 (11–85)	36 (17–64)	45 (18–77)	51 (27–87)	41 (19–77)	61 (29–97)	19 (5–58)
Death of any cause during follow-up	869 (44.3)	413 (41.3)	167 (33.3)	500 (30.1)	332 (28.3)	153 (12.3)	687 (64.3)

Abbreviations: ADG, aggregated diagnosis group; IQR, interquartile range; NET, neuroendocrine tumor.

^aSynchronous: <6 months from diagnosis.^bMetachronous: ≥6 months from diagnosis.

eTable 6. Multivariable Fine-Gray Model Showing Factors Associated With Cancer-Specific Death Stratified by Primary NET Site

Variable	Bronchopulmonary sHR (95% CI)	Pancreatic sHR (95% CI)	Gastroenteric ^a sHR (95% CI)
Age at diagnosis, y			
<50	Ref	Ref	Ref
50–59	2.13 (1.54–2.94)	1.98 (1.44–2.72)	1.53 (1.13–2.08)
60–69	2.60 (1.92–3.53)	1.94 (1.40–2.68)	2.60 (1.96–3.46)
≥70	3.91 (2.91–5.27)	3.82 (2.72–5.37)	4.25 (3.22–5.61)
Sex			
Female	0.72 (0.61–0.84)	0.84 (0.67–1.06)	0.79 (0.68–0.91)
Male	Ref	Ref	Ref
Comorbidity burden			
Low (ADG 0–9)	Ref	Ref	Ref
High (ADG ≥10)	1.09 (0.92–1.29)	0.87 (0.68–1.12)	0.86 (0.73–1.03)
Deprivation quintile			
1st (least deprived)	Ref	Ref	Ref
2nd	1.01 (0.79–1.29)	1.13 (0.79–1.61)	0.97 (0.76–1.23)
3rd	0.93 (0.73–1.19)	1.20 (0.85–1.71)	1.03 (0.81–1.30)
4th	1.22 (0.97–1.55)	1.05 (0.74–1.50)	0.98 (0.78–1.24)
5th (most deprived)	1.35 (1.06–1.71)	1.16 (0.82–1.65)	1.23 (0.97–1.55)
Location of residence			
Rural	1.07 (0.84–1.36)	1.06 (0.73–1.53)	0.76 (0.60–0.97)
Urban	Ref	Ref	Ref
Year of diagnosis			
2001–2008	Ref	Ref	Ref
2009–2015	0.99 (0.84–1.16)	0.93 (0.73–1.18)	0.89 (0.76–1.05)
Primary NET site			
Gastric	—	—	1.21 (0.90–1.63)
Small intestinal	—	—	0.41 (0.31–0.54)
Colonic	—	—	1.06 (0.81–1.38)
Rectal	—	—	Ref
Metastatic status			
None	Ref	Ref	Ref
Synchronous ^b	11.23 (9.15–13.77)	9.74 (6.86–13.83)	15.64 (11.95–20.47)
Metachronous ^c	6.68 (5.36–8.32)	5.67 (3.93–8.16)	15.36 (11.71–20.16)

Abbreviations: ADG, aggregated diagnosis group; NET, neuroendocrine tumor; sHR, subhazard ratio.

^aGastroenteric: stomach, small intestine, colon, rectum.^bSynchronous: <6 months from diagnosis.^cMetachronous: ≥6 months from diagnosis.

eTable 7. Multivariable Fine-Gray Model Showing Factors Associated With Noncancer Death

Variable	All Patients sHR (95% CI)	Bronchopulmonary sHR (95% CI)	Pancreatic sHR (95% CI)	Gastroenteric ^a sHR (95% CI)
Age at diagnosis, y				
<50	Ref	Ref	Ref	Ref
50–59	1.97 (1.40–2.98)	1.90 (0.75–4.80)	0.47 (0.16–1.40)	2.58 (1.42–4.70)
60–69	3.63 (2.48–5.31)	3.69 (1.60–8.49)	1.50 (0.66–3.41)	4.57 (2.60–8.05)
≥70	8.38 (5.83–12.0)	4.39 (1.94–9.94)	2.04 (0.96–4.31)	13.39 (7.76–23.1)
Sex				
Female	0.73 (0.62–0.87)	0.48 (0.33–0.71)	0.52 (0.28–0.95)	0.94 (0.76–1.16)
Male	Ref	Ref	Ref	Ref
Comorbidity burden				
Low (ADG 0–9)	Ref	Ref	Ref	Ref
High (ADG ≥10)	1.73 (1.46–2.04)	1.29 (0.87–1.92)	2.68 (1.47–4.89)	1.66 (1.34–2.07)
Deprivation quintile				
1st (least deprived)	Ref	Ref	Ref	Ref
2nd	0.99 (0.75–1.31)	1.19 (0.59–2.40)	1.30 (0.46–3.63)	0.92 (0.64–1.31)
3rd	1.18 (0.90–1.56)	1.32 (0.66–2.64)	1.85 (0.65–5.26)	0.95 (0.67–1.37)
4th	1.34 (1.03–1.76)	1.97 (1.03–3.74)	0.71 (0.20–2.50)	1.19 (0.85–1.67)
5th (most deprived)	1.68 (1.30–2.16)	1.84 (0.98–3.47)	3.94 (1.57–9.89)	1.54 (1.12–2.12)
Location of residence				
Rural	1.16 (0.90–1.50)	0.77 (0.38–1.56)	0.71 (0.17–2.94)	1.35 (0.98–1.85)
Urban	Ref	Ref	Ref	Ref
Year of diagnosis				
2001–2008	Ref	Ref	Ref	Ref
2009–2015	0.85 (0.72–0.99)	0.94 (0.65–1.38)	1.39 (0.74–2.61)	0.80 (0.65–1.00)
Primary NET site				
Bronchopulmonary	Ref	—	—	—
Gastroenteric	1.81 (0.45–2.28)	—	—	—
Pancreatic	1.31 (0.93–1.85)	—	—	—
Others	1.38 (1.02–1.86)	—	—	—
Gastric	—	—	—	1.89 (1.27–2.81)
Small intestinal	—	—	—	2.15 (1.54–3.00)
Colonic	—	—	—	1.64 (1.14–2.36)
Rectal	—	—	—	Ref
Metastatic status				
None	Ref	Ref	Ref	Ref
Synchronous ^b	0.64 (0.53–0.77)	0.52 (0.33–0.82)	1.08 (0.53–2.22)	0.50 (0.39–0.65)
Metachronous ^c	0.68 (0.52–0.89)	0.26 (0.10–0.72)	2.72 (1.34–5.54)	0.56 (0.38–0.81)

Abbreviations: ADG, aggregated diagnosis group; NET, neuroendocrine tumor; sHR, subhazard ratio.

^aGastroenteric: stomach, small intestine, colon, rectum.^bSynchronous: <6 months from diagnosis.^cMetachronous: ≥6 months from diagnosis.