Royal Australasian College of Surgeons

Survival of patients with small bowel neuroendocrine neoplasms in Auckland, Aotearoa New Zealand

Matthew J. McGuinness,*† Braden Woodhouse,* Christopher Harmston,*† Kate Parker,‡ Nicole Kramer,§ Michael Findlay,* Cristin Print,* Arend Merrie*¶ and Ben Lawrence*¶

*Faculty of Medical and Health Sciences and Maurice Wilkins Centre, University of Auckland, Auckland, New Zealand
†Whangārei Hospital, Northland District Health Board, Whangārei, New Zealand
‡Planning, Funding and Outcomes, Waitematā District Health Board, Waitakere, New Zealand
§Department of Pathology, North Shore Hospital, Waitematā District Health Board, Waitakere, New Zealand and
¶Auckland City Hospital, Auckland District Health Board, Auckland, New Zealand

Key words
general surgery, neuroendocrine, NET, SI-NET, SB-NET, surgical oncology.

Correspondence
Dr Ben Lawrence, Faculty of Medical and Health Sciences and Maurice Wilkins Centre, University of Auckland, Auckland, New Zealand.
Email: b.lawrence@auckland.ac.nz

M. J. McGuinness MBChB; **B. Woodhouse** BSc (Hons); **C. Harmston** MB ChB; **K. Parker** PhD; **N. Kramer** MBChB; **M. Findlay** MD; **C. Print** PhD; **A. Merrie**; **B. Lawrence** MBChB MSc.

Arend Merrie and Ben Lawrence are joint senior authors.

Accepted for publication 31 May 2022.

doi: 10.1111/ans.17851

Abstract

Background: Small intestinal Neuroendocrine Neoplasms (SI-NENs) are the most common primary malignancy of the small bowel. The aim of this study is to define the survival of patients with an SI-NEN in Auckland, Aotearoa New Zealand (AoNZ).

Methods: A retrospective study of all patients diagnosed with a jejunal or ileal SI-NEN in the Auckland region between 2000 and 2012 was performed. The New Zealand NETwork! Registry was searched to identify the study cohort. Retrospective data collection was performed to collect stage, survival and follow up data.

Results: One hundred and seven patients were included in the study. The mean age of patients was 62.8 years (SD 11.9). The 5 and 10-year disease-specific survival for all patients was 66.1% (95% CI 56.5–75.7%) and 61.8% (95% CI 51.8–71.8%), respectively. Ten-year disease-specific survival was 100% for stage I and II, 74% (95%CI 61.7–84.4%) for stage III and 33.9% (95%CI 16.9–35.6%) for stage IV SI-NEN. Eleven of 40 (27.5%) patients with stage III disease had recurrence and 3 of 7 (42.8%) patients with stage IV disease had recurrence. In patients with stage IV disease, neither primary resection (HR 2.25, 95% CI 0.92–5.5) nor distant resection (HR 1.72, 95% CI 0.63–4.7) were significantly associated with a disease-specific or overall survival benefit.

Conclusion: This study demonstrates that stage at SI-NEN diagnosis is associated with survival, but resection of the primary or distant metastases in patients with stage IV disease is not. There was no recurrence in patients with stage I or II disease after complete resection.

Introduction

Neuroendocrine neoplasms (NENs) are rare and are thought to arise from neuroendocrine cells throughout the body.[1] The majority of NENS arise in the gastrointestinal tract. Gastrointestinal tract NENs are classified in two broad groups: neuroendocrine tumours (NETs) and neuroendocrine carcinomas (NECs).[2] The majority of NENs arise within the gastrointestinal tract and can be grouped based on location.[3,4] Small intestinal NENs (SI-NENs) are the most common primary malignancy of the small bowel.[1] The small bowel is the third most common site for NENs behind the lung and rectum however the most common site for NENs that develop metastatic disease.[4]

The incidence of NENs is increasing worldwide.[5,6] The Surveillance, Epidemiology, and End Results program has shown a 6.4-fold increase in NENs in the USA since its inception in 1973.[7] This increase is likely multifactorial with factors including a true increase in incidence, an increase in detection, and a change over time in histological classification.[5] Incidence of SI-NENs has increased in Queensland, Australia by 222% from 0.36 cases per 100 000 between 1986 and 1995 to 1.16 cases per 100,00 between 2006 and 2015.[8]

In general NETs are slow growing tumours with 5-year overall survival of 70–80%.[5] This is despite 20–45% of patients having metastatic disease at the time of diagnosis.[5,9–12] The high frequency of metastases at diagnosis is a result of early stage tumours often not causing symptoms or causing non-specific symptoms, meaning patients frequently do not present until the NET causes a degree of obstruction or becomes metastatic leading to carcinoid syndrome in some cases.[4] The indolent nature of SI-NENs complicates treatment decisions as aggressive management that would not be considered in other comparably staged gastrointestinal malignancies is often considered in SI-NENs.[4] NEC are poorly differentiated fast growing tumours. Patients typically present with metastatic disease and have a median survival measured in months.[13]

An important component guiding treatment decisions by clinicians is an understanding of the expected survival of patients. Although survival has been described in patients with SI-NENs internationally it has not been described in an Aotearoa New Zealand (AoNZ) population. The aim of this study is to describe the survival of patients with jejunal or ileal SI-NENs in Auckland, AoNZ.

Methods

Design

A retrospective study of all patients diagnosed with a jejunal or ileal SI-NEN in the Auckland region between 2000 and 2012 was performed. The New Zealand NETwork! Registry (NETR) was searched to identify the study cohort.

New Zealand NETwork! Registry

NETR is a retrospective database that includes all NEN in AoNZ diagnosed 2008–2012, and all NEN in the Auckland Region (Auckland, Waitematā, and Counties Manukau District Health Boards) diagnosed from 1995 to 2012.[14] The NETR identified cases by searching the New Zealand Cancer Registry using ICD-O morphology codes and searching public and private histology records in all 20 AoNZ District Health Boards to ensure complete patient capture. Classification of NEN was defined as per WHO 2010 nomenclature and included gastroenteropancreatic (GEP) NENs, bronchopulmonary carcinoids and neuroendocrine carcinoma, extrapulmonary small cell carcinoma, large cell carcinoma, medullary thyroid carcinoma, Merkel cell carcinoma, paraganglioma, phaechromocytoma and NENs of other primary sites such as gynaecological and genitourinary. Pulmonary small cell carcinoma were excluded.

Clinical data, including detailed histopathology, was collected from individual electronic and paper medical records according to a centralised protocol and data dictionary. Data was entered via a remote desktop directly into a SQL-based database (MS Access), secured using a double-password system (University of Auckland network and separate password-protected database access).

The NETR was searched by identifying patients coded as 'Small bowel', 'Jejunal/Ileal', 'Duodenal' in the 'PrimaryLocation' field, and 'Small bowel', 'Jejunum and Ileum', 'Duodenum' in the histology 'SiteOrgan' field. The histology 'Diagnosis' field was also searched for key terms ('*small bowel*', '*jeju*', '*ileal*', '*ileum*', '*duoden*') as a secondary check for complete patient capture. Small intestine was coded as small bowel during data entry. For the purposes of this paper, the search was limited to patients who were treated in one of Auckland's three District Health Boards. Ethnicity was retrospectively collected from central hospital records.

Cohort inclusion and exclusion criteria

All SI-NENs were histologically diagnosed from a biopsy of a liver metastasis or a surgical specimen. Patients were excluded if the tumour was located in the duodenum, the location was indeterminate, there was no histological diagnosis or there was insufficient available documentation to identify stage at time of diagnosis. Duodenal NENs were excluded *(n=21)(n=21)* due to the different embryological origin and management strategies. A patient was deemed to have a functional NEN if on retrospective review the patient had an elevated urine 5-HIAA >50 (upper limit of normal) and documented flushing or diarrhoea.

The search of the NETR found 131 patients with SI-NENs of which 24 were excluded . Two had no histological diagnosis, one patient was diagnosed on post-mortem and 21 patients had inadequate documentation to determine the stage at diagnosis. A total of 107 patients were included in this study.

Survival and follow up

Overall survival (OS) was defined as the number of patients who had not died from any cause. Disease-specific survival (DSS) was defined as the number of patient who had not died from a cause relating to their NEN diagnosis. Recurrence was defined as a patient who underwent a curative intent R0 resection and subsequently had local or distant cancer recurrence. OS, DSS and follow up was retrospectively collected. Using the unique National Hospital Index number of each patient, routinely collected data from the AoNZ Ministry of Health was used to provide updated follow-up data. This included cause of death from death certificate information, publicly funded hospital discharge information (via the National Minimum Dataset) and pharmaceutical dispensing (Pharmaceutical Collection) data.

Stage

The TNM stage published by the European Neuroendocrine Tumour Society (ENETS) was used to stage patients.[15] Where stage was not reported in a clinical letter, multidisciplinary meeting letter or histology report, a retrospectively inferred stage was given by author MJM and BL based on histology reports, radiology reports, clinical letters and multidisciplinary letters. Due to low numbers TNM stage was grouped into stage I, II (including IIa and IIb), III (including IIIa and IIIb) and IV. Stage I and II are described separately but grouped as stage I/II for statistical analysis due to low numbers.

Ethical approval

Ethical approval was granted by the Northern A Health and Disability Ethics Committee (ref 12/NTA/60).

Statistical analysis

Data was entered into SPSS (Version 25.0. Armonk, NY) for statistical analysis. Categorical data was described as number,

percentage, with normally distributed data described as mean, standard deviation (SD) and non-parametrically distributed data was described as median and interquartile range (IQR). Kaplan–Meier graphs were created using R (Version 3.2.5. Vienna, Austria) with survival measured from the time of diagnosis to date of death. Log rank tests were run to determine a difference in distribution in survival, and when significant, a pairwise log rank comparison was performed with Bonferroni correction. Cox proportional hazard regression models were used to calculate unadjusted hazard ratios (HR) in patients with primary and distant resections.

Results

Demographics

One hundred and seven patients were included in the study. The mean age of patients was 62.8 years (SD 11.9) at time of diagnosis with 44% female and 56% male. About 72% of patients were European, 15% AoNZ Māori, 10% Pasifika and 3% other. An over-representation of European patients and under-representation of Asian patients was found when the study population's ethnicity is compared with the 2018 New Zealand census population distribution.[16] Table 1 outlines patients' demographics overall and by stage. At presentation two (2%) patients had stage I disease, seven (7%) patients had stage II disease, 58 (54%) patients had stage III disease and 40 (37%) patients had stage IV disease.

Stage and survival

Across all stages the 5 and 10 year OS was 59% (95% CI 49.2–68.8%) and 43.7% (95% CI 32.1–55.3%), respectively, during an average follow up of 72.5 months and 646.74 person years of observation. As seen in Figure 1(a) a significant difference in OS was found between TNM stages ($p < 0.001$). 10-year OS was 100% for stage I/II, 55.6% (95% CI 40.3–70.9%) for stage III and 13.4% (95% CI -1.69–28.5%) for stage IV. The median OS for patients with stage IV disease was 56.2 months (95% CI 42.1–70.3). Post-hoc testing revealed a statistically significant incremental decrease in OS between stage I/II and IV ($p < 0.001$), stage III and IV ($p < 0.001$) and between stage I/II and III (p 0.0468).

The 5 and 10 year DSS for all patients was 66.1% (95% CI 56.5–75.7%) and 61.8% (95% CI 51.8–71.8%), respectively. 10-year DSS varied significantly across stages, as seen in Figure 1 (b) ($p < 0.001$). 10-year DSS was 100% for stage I/II, 74% (95%CI 61.7–84.4%) for stage III and 33.9% (95%CI 16.9–35.6%) for stage IV. The median DSS for patients with stage IV disease was 64.5 months (95% CI,48.9–80). Post-hoc testing revealed a statistically significant incremental decrease in DSS between stage I/II and IV (p 0.004) and stage III and IV ($p < 0.001$) but not between stage I/II and III (p 0.1196).

Complete resection and recurrence

Complete macroscopic and microscopic resection was achieved in 57 patients (53.3%) and was associated with increased OS and DSS ($p < 0.001$). Complete resection was achieved in 2 (100%) patients with stage I disease, 7 (100%) patients with stage II disease, 41 (70.7%) patients with stage III disease and 7 (17.5%) patients stage IV disease. In patients with complete resection there was no recurrence in patients with stage I or II disease. Eleven of 40 (27.5%) patients with stage III disease had recurrence and 3 of 7 (42.8%) patients with stage IV disease had recurrence. Of the 4 patients who

Table 1 Demographic and clinical characteristics by stage at time of diagnosis

	Stage I	Stage II	Stage III	Stage IV	Total
Total number	2	7	58	40	107
Age, *mean* (SD)	66.7 (4.4)	60.7 (12)	62.6 (12.4)	63.3 (11.7)	62.8 (11.9)
Female gender, *n* (%)	0 (0%)	5 (71%)	25 (43%)	17 (43%)	47 (44%)
Ethnicity, *n* (%)					
European	2 (100%)	5 (71%)	44 (76%)	26 (65%)	77 (72%)
Māori	0 (0%)	1 (14%)	10 (17%)	5 (13%)	16 (15%)
Pasifika	0 (0%)	0 (0%)	4 (7%)	7 (18%)	11 (10%)
Other	0 (0%)	1 (14%)	0 (0%)	2 (5%)	3 (3%)
Presentation, *n* (%)					
Acute symptoms	0 (0%)	5 (71%)	27 (47%)	16 (40%)	48 (45%)
Asymptomatic	2 (100%)	1 (14%)	11 (19%)	4 (10%)	18 (17%)
Chronic symptoms	0 (0%)	1 (14%)	11 (19%)	13 (33%)	25 (23%)
Unknown	0 (0%)	0 (0%)	9 (16%)	7 (18%)	16 (15%)
Grade, *n* (%)					
NET G1	0 (0%)	5 (71%)	33 (57%)	18 (45%)	56 (52%)
NET G2	0 (0%)	0 (0%)	9 (16%)	8 (20%)	17 (16%)
NEC	0 (0%)	0 (0%)	1 (2%)	1 (3%)	2 (2%)
Other	0 (0%)	0 (0%)	4 (7%)	5 (13%)	9 (8%)
Unknown	2 (100%)	2 (29%)	11 (19%)	8 (20%)	23 (21%)
Primary site, *n* (%)					
Ileum	1 (50%)	1 (14%)	37 (64%)	17 (43%)	56 (52%)
Jejunum	0 (0%)	0 (0%)	4 (7%)	5 (13%)	9 (8%)
Not further specified	1 (50%)	6 (86%)	17 (29%)	18 (45%)	42 (39%)
Primary resection, *n* (%)	2 (100%)	7 (100%)	58 (100%)	31 (78%)	98 (92%)
Distant resection, *n* (%)	0 (0%)	0 (0%)	0 (0%)	11 (28%)	11 (10%)
Functional tumour, *n* (%)	0 (0%)	0 (0%)	8 (14%)	14 (35%)	22 (21%)

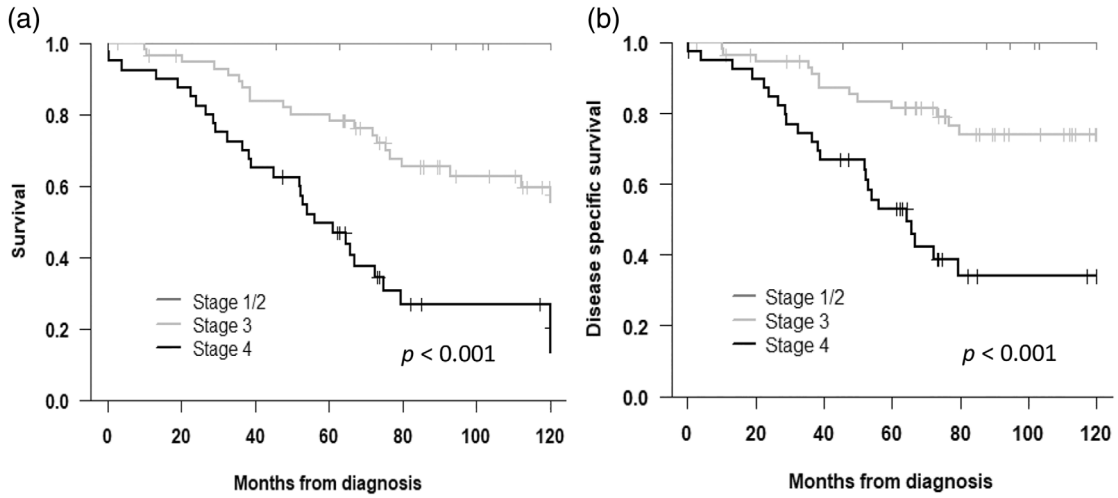

Fig. 1. 10 year overall survival (a, left) and 10 year disease-specific survival (b, right) by stage at time of diagnosis.

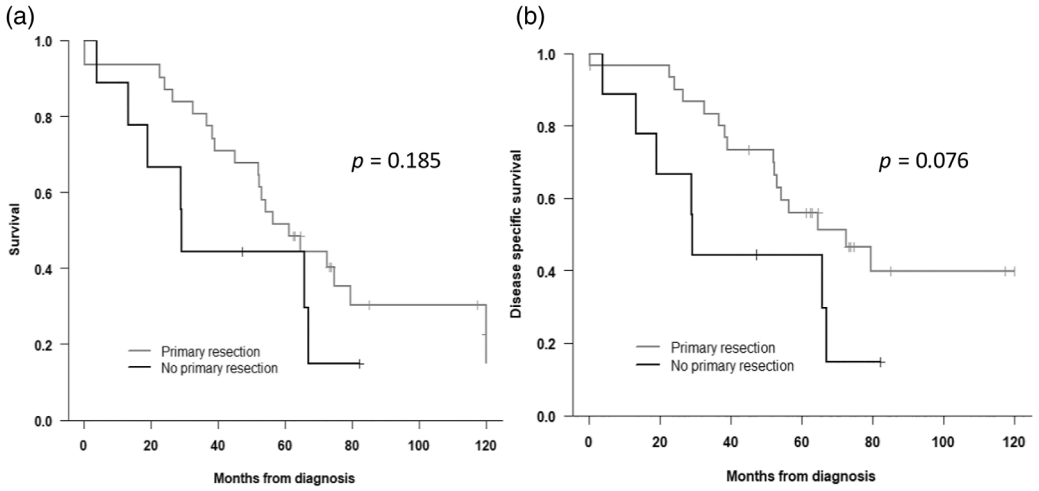

Fig. 2. 10 year overall survival (a, left) and 10 year disease-specific survival (b, right) comparing primary resection with no primary resection in patients with stage IV disease.

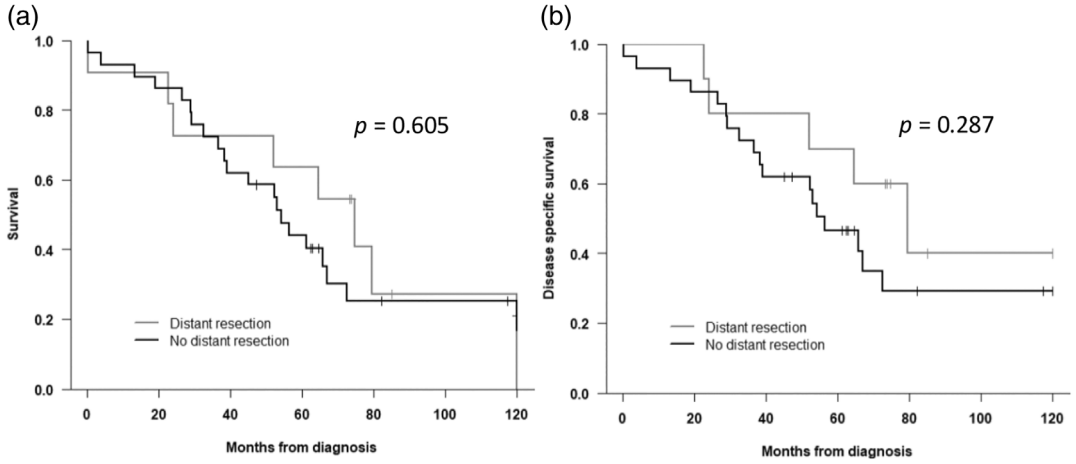

Fig. 3. 10 year survival (a, left) and disease-specific survival (b, right) comparing distant resection with no distant resection in patients with stage IV disease.

did not have a recurrence with stage IV disease, two had resection of ovarian metastatic deposits and two had resection of liver deposits with one of these patients dying day 7 post-operatively. Of the three patients who had recurrence, two had liver resections and one had metastatic deposits resected from the omentum.

Primary and distant resection and survival

All patients with stage I, II or III disease underwent a primary resection. Of patients with stage IV disease 31 (77.5%) underwent a primary resection and 11 (28%) underwent a primary and distant resection. All patients that underwent a distant resection also underwent a primary resection. In patients with stage IV disease who underwent a primary resection, no significant OS (HR 0.56, 95% CI 0.23–1.32) or DSS (HR 0.44, 95% CI 0.18–1.10) benefit was found as seen in Figure 2. Similarly, in these patients distant resection was not found to have an OS (HR 0.81, 95% CI 0.35–1.83) or DSS (HR 0.58, 95% CI 0.21–1.58) benefit as seen in Figure 3.

Discussion

This study defines the survival of patients with NENs in Auckland, AoNZ. It demonstrates that stage at diagnosis is associated with survival, a low risk of recurrence in patients with stage I or II disease, and no association between primary or distant resection and survival in patients with stage IV disease.

The overall 10-year disease-specific survival of 61.8% was lower than the 85.3% recently reported in Australia, however within the wide internationally reported range of 48.5–85.3%.[5,9,12,17–19] This lower survival is likely multifactorial and influenced by the difficulties of direct comparison which include the different time periods data was collected and variation in tumour grade, noting the significant number of patients in this study whose grade was unclear. Recent advance in treatment of NENs, including radio-labelled somatostatin analogues and molecular therapy, have led to improved survival which are not reflected in this study. The grading and nomenclature of NENs has changed significantly since this cohort of patients were diagnosed. Prior to the publication of the *2019 WHO classification of tumours of the digestive system* all NENs of the gastrointestinal tract with a Ki-67 > 20% or a mitotic rate > 20/mm^2 were categorized as NECs.[20,21]The new classification system allows for a high grade but well differentiated NET, that is, grade 3 NET, in recognition of the understanding that NETs and NECs are biologically unrelated, despite sharing neuroendocrine differentiation. Data suggests they differ in the degree of biological aggressiveness and response to medical therapy and therefore patient survival.[21]

This study shows that survival is highly dependent on stage at presentation with patients presenting with metastatic disease having significantly worse outcomes compared to patients with local or locoregional disease. Over a third of patients in this study presented with metastatic disease, a finding consistent with the literature which suggests 20–45% present with metastatic disease.[5,9–12] In these patients there has been debate regarding the upfront resection of the primary tumour without curative intent. This study found no survival benefit of primary resection in these patients, albeit with a separation in the curves for disease specific survival. The evidence suggests a benefit from primary resection to relieve existing symptoms however the evidence is controversial when it comes to primary resection prophylactically to avoid future symptoms and complications or with the aim of improving survival.[22] Evidence on this topic is restricted to retrospective studies which limits the interpretability.

Two systematic reviews and meta-analyses have reported a survival benefit with primary resection in the setting of metastatic disease.[23,24] Primary resection is included in recommendations by both ENETS and the North American Neuroendocrine Tumour Society (NANETS) in patients with stage IV disease without curative intent or emergent symptoms.[4,15] A recent study of asymptomatic patients with stage IV SI-NETs has challenged this assertion as after propensity score matching no difference in survival was found (HR, 0.98; 95% CI, 0.70–1.37).[25] The current study adds to this literature and makes it clear further high quality prospective clinical trials are required.

In patients with stage III and IV disease, disease specific survival from SI-NENs was more favourable than overall survival, particularly at 10 years of follow up. This suggests that previous estimates of survival, based on overall survival, may have overestimated the impact of SI-NENs. This highlights the indolent nature of many SI-NENs with some patients succumbing to other medical conditions rather than the SI-NEN. This has ramifications for clinicians when discussing prognosis with patients, planning for care of non-NEN co-morbidities, and leads to NENs being treated more aggressively than other comparably staged other gastrointestinal malignancies.[4]

This study is limited by its retrospective design and small sample size likely obscuring clinically meaningful differences between groups. Comparison of primary and distant resection in patients with metastatic disease is limited by the likelihood of significant selection and immortal time bias, the small sample size and the lack of data on targeted therapies other than surgery. The need for a patient to have a histological diagnosis to be included in this study may have led to ascertainment bias, predominantly in patients presenting with stage IV disease. This cohort lacked standardized, up-to-date grading and classification. It is therefore not possible to meaningfully interpret the impact of grade in this study or compare it to other studies. Restricting the study cohort to the Auckland region allows prolonged follow up to detect late relapse, but reduces the sample size, which reduces confidence in estimates of survival in smaller subsets e.g., early-stage NENs.

This is the first AoNZ study to investigate the survival of patients with NENs in AoNZ. This is essential information for clinicians and patients as it guides therapeutic decisions and patient expectations. It demonstrates stage at diagnosis is associated with survival, a low risk of recurrence in patients with stage I or II disease, and no association between primary or distant resection and survival in patients with stage IV disease.

Acknowledgement

Open access publishing facilitated by The University of Auckland, as part of the Wiley - The University of Auckland agreement via the Council of Australian University Librarians.

Conflict of interest

None declared.

Funding information

This study was funded by Translational Medicine Trust, University of Auckland.

Author contributions

Matthew J. McGuinness: Data curation; formal analysis; visualization; writing – original draft; writing – review and editing. **Braden Woodhouse:** Data curation; formal analysis; methodology; project administration; resources; supervision; writing – original draft; writing – review and editing. **Christopher Harmston:** Writing – original draft; writing – review and editing. **Kate Parker:** Conceptualization; data curation; formal analysis; methodology; project administration; supervision; writing – review and editing. **Nicole Kramer:** Methodology; supervision; writing – review and editing. **Michael Findlay:** Conceptualization; supervision; writing – review and editing. **Cristin Gregor Print:** Conceptualization; supervision; writing – review and editing. **Arend Merrie:** Conceptualization; methodology; supervision; writing – review and editing. **Ben Lawrence:** Conceptualization; formal analysis; methodology; resources; supervision; writing – original draft; writing – review and editing.

References

1. Scott AT, Howe JR. Management of Small Bowel Neuroendocrine Tumors. *J. Oncol. Pract.* 2018; **14**: 471–82.
2. Fléjou JF. WHO classification of digestive tumors: the fourth edition. *Ann. Pathol.* 2011; **31**(5 Suppl): S27–31.
3. Boudreaux JP, Wang YZ, Diebold AE *et al*. A single institution's experience with surgical cytoreduction of stage IV, well-differentiated, small bowel neuroendocrine tumors. *J. Am. Coll. Surg.* 2014; **218**: 837–44.
4. Howe JR, Cardona K, Fraker DL *et al*. The surgical management of small bowel neuroendocrine tumors: consensus guidelines of the north American Neuroendocrine Tumor Society. *Pancreas* 2017; **46**: 715–31.
5. Wyld D, Moore J, Tran N, Youl P. Incidence, survival and stage at diagnosis of small intestinal neuroendocrine tumours in Queensland, Australia, 2001-2015. *Asia Pac. J. Clin. Oncol.* 2021; **17**: 350–8.
6. Lawrence B, Gustafsson BI, Chan A, Svejda B, Kidd M, Modlin IM. The epidemiology of gastroenteropancreatic neuroendocrine tumors. *Endocrinol. Metab. Clin. North Am.* 2011; **40**: 1–18 vii.
7. Dasari A, Shen C, Halperin D *et al*. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncol.* 2017; **3**: 1335–42.
8. Wyld D, Wan MH, Moore J, Dunn N, Youl P. Epidemiological trends of neuroendocrine tumours over three decades in Queensland, Australia. *Cancer Epidemiol.* 2019; **63**: 101598.
9. Hallet J, Law CH, Cukier M, Saskin R, Liu N, Singh S. Exploring the rising incidence of neuroendocrine tumors: a population-based analysis of epidemiology, metastatic presentation, and outcomes. *Cancer* 2015; **121**: 589–97.
10. Boyar Cetinkaya R, Aagnes B, Myklebust T, Thiis-Evensen E. Survival in neuroendocrine neoplasms; a report from a large Norwegian population-based study. *Int. J. Cancer* 2018; **142**: 1139–47.
11. Landerholm K, Falkmer S, Järhult J. Epidemiology of small bowel carcinoids in a defined population. *World J. Surg.* 2010; **34**: 1500–5.
12. Jann H, Roll S, Couvelard A *et al*. Neuroendocrine tumors of midgut and hindgut origin: tumor-node-metastasis classification determines clinical outcome. *Cancer* 2011; **117**: 3332–41.
13. Smith J, Reidy-Lagunes D. The management of extrapulmonary poorly differentiated (high-grade) neuroendocrine carcinomas. *Semin. Oncol.* 2013; **40**: 100–8.
14. Parker KCE, Woodhouse B, Knowlton N, Print C, Findlay M, Lawrence B. T he NETwork! Registry: preliminary data suggests increasing incidence in a national study of neuroendocrine cancer in New Zealand. *Neuroendocrinology* 2018; **106**: 1–301.
15. Niederle B, Pape UF, Costa F *et al*. ENETS consensus guidelines update for neuroendocrine neoplasms of the jejunum and ileum. *Neuroendocrinology* 2016; **103**: 125–38.
16. Zealand SN. New Zealand population statistics 2020. Available from URL: www.stats.govt.nz/topics/population.
17. Quaedvlieg PF, Visser O, Lamers CB, Janssen-Heijen ML, Taal BG. Epidemiology and survival in patients with carcinoid disease in The Netherlands. An epidemiological study with 2391 patients. *Ann. Oncol.* 2001; **12**: 1295–300.
18. Luke C, Price T, Townsend A *et al*. Epidemiology of neuroendocrine cancers in an Australian population. *Cancer Causes Control* 2010; **21**: 931–8.
19. Srirajaskanthan R, Ahmed A, Prachialias A *et al*. ENETS TNM staging predicts prognosis in small bowel neuroendocrine tumours. *ISRN Oncol.* 2013; **2013**: 420795.
20. Nagtegaal ID, Odze RD, Klimstra D *et al*. The 2019 WHO classification of tumours of the digestive system. *Histopathology* 2020; **76**: 182–8.
21. Rindi G, Klimstra DS, Abedi-Ardekani B *et al*. A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. *Mod. Pathol.* 2018; **31**: 1770–86.
22. Capurso G, Rinzivillo M, Bettini R, Boninsegna L, Delle Fave G, Falconi M. Systematic review of resection of primary midgut carcinoid tumour in patients with unresectable liver metastases. *Br. J. Surg.* 2012; **99**: 1480–6.
23. Tsilimigras DI, Ntanasis-Stathopoulos I, Kostakis ID *et al*. Is resection of primary midgut neuroendocrine tumors in patients with unresectable metastatic liver disease justified? A systematic review and meta-analysis. *J. Gastrointest. Surg.* 2019; **23**: 1044–54.
24. Almond LM, Hodson J, Ford SJ *et al*. Role of palliative resection of the primary tumour in advanced pancreatic and small intestinal neuroendocrine tumours: a systematic review and meta-analysis. *Eur. J. Surg. Oncol.* 2017; **43**: 1808–15.
25. Daskalakis K, Karakatsanis A, Hessman O *et al*. Association of a prophylactic surgical approach to stage IV small intestinal neuroendocrine tumors with survival. *JAMA Oncol.* 2018; **4**: 183–9.