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SHORT COMMUNICATION

Sequence of therapy and survival in patients with advanced pancreatic neuroendocrine tumours

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ABSTRACT

Background Pancreatic neuroendocrine tumours (pNETs) often present as advanced disease. The optimal sequence of therapy is unknown.

Methods Sequential patients with advanced pNETs referred to BC Cancer between 2000 and 2013 who received 1 or more treatment modalities were reviewed, and treatment patterns, progression-free survival (PFS), and overall survival (OS) were characterized. Systemic treatments included chemotherapy, small-molecule therapy, and peptide receptor radionuclide therapy.

Results In 66 cases of advanced pNETs, median patient age was 61.2 years (25%–75% interquartile range: 50.8–66.2 years), and men constituted 47% of the group. First-line therapies were surgery (36%), chemotherapy (33%), and somatostatin analogues (32%). Compared with first-line systemic therapy, surgery in the first line was associated with increased PFS and OS (20.6 months vs. 6.3 months and 100.3 months vs. 30.5 months respectively, $p < 0.05$). In 42 patients (64%) who received more than 1 line of therapy, no difference in OS or PFS between second-line therapies was observed.

Conclusions Our results confirm the primary role of surgery for advanced pNETs. New systemic treatments will further increase options.

Key Words Pancreas, neuroendocrine tumours, treatment sequencing

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INTRODUCTION

Pancreatic neuroendocrine tumours (pNETs) are rare malignancies, with an age-adjusted annual incidence rate of 0.48 per 100,000 population, and 64% of patients present with metastatic disease[1–3]. Available treatments include surgical resection, chemotherapy, targeted agents, liver-directed therapy, and peptide receptor radionuclide therapy (PRRT)[4–6]. First-line therapies are often selected based on clinical presentation, and upfront surgical resection is considered when possible. However, in the second-line setting, evidence-based recommendations are limited, and choice of therapy and treatment sequence have largely been based on clinician judgment[7].

To date, the literature detailing sequential treatment after disease progression is limited. The objectives of the present study were to characterize the sequence of therapy for advanced pNETs in a population-based setting and to explore differences in survival between treatment cohorts.

METHODS

Patient Population

In British Columbia, BC Cancer is a provincial institution that oversees all cancer therapy for approximately 4.4 million residents. BC Cancer is responsible for maintenance of cancer therapy guidelines, provision of radiation therapy, and funding oversight for all systemic therapies. The BC Cancer Gastrointestinal Cancer Outcomes Unit database maintains demographic, clinical, pathology, staging, treatment, and outcomes data for all patients referred to BC Cancer with gastrointestinal and neuroendocrine malignancies. Patients are consented to be included in the database.

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For the present study, we identified all patients with advanced pNETs who were referred to BC Cancer during 2000–2013. Histologically, tumours had to be well or moderately differentiated; poorly differentiated neuroendocrine carcinomas were excluded. Advanced pNETs included both locally advanced and metastatic disease. The TNM classification was assigned using the 7th edition of the American Joint Committee on Cancer TNM staging system. Baseline clinicopathologic data were extracted by retrospective chart review, including demographics, TNM stage, therapies, and treatment outcomes. The study was approved by the BC Cancer Research Ethics Board.

Statistical Analyses

Descriptive statistics were calculated to characterize our cohort of patients with advanced pNETs, and categorical variables were compared using the Pearson chi-square test. Therapies were divided into surgical and nonsurgical options. Surgical therapy included any resection of the primary tumour or distant disease. Systemic therapy included chemotherapy, small-molecule therapy, and PRRT. Liver-directed therapies included ^{90}Y radioembolization and radiofrequency ablation. First-line treatment was defined as upfront treatment after diagnosis of locally advanced or metastatic disease, and second-line treatment was defined as subsequent therapy after first-line treatment, including surgical resection. Outcomes were compared based on initial therapeutic modality, and survival estimates were calculated from the date of diagnosis of advanced disease. Second-line progression-free survival (PFS) was calculated from the date of initiation of second-line therapy to the date of progression. Overall survival (OS) was calculated from the date of diagnosis of advanced disease to the date of death or last follow-up. Kaplan–Meier survival analyses were performed to estimate PFS and OS. The PFS and OS estimates were compared using the log-rank test. All tests were 2-sided, with $p \leq 0.05$ as the cut-off for statistical significance. The IBM SPSS Statistics software application (version 22.0: IBM, Armonk, NY, U.S.A.) was used for all statistical analyses.

RESULTS

We identified 115 patients from the Gastrointestinal Cancers Outcomes Unit, but excluded 49 because of poorly differentiated histology ($n = 20$), no therapy received ($n = 24$), or insufficient records available ($n = 5$). Reasons for no treatment included either poor performance status or patient choice.

Of the 66 patients included, 42 received more than 1 line of treatment (Figure 1). Median age was 61.2 years (25%–75% interquartile range: 50.8–66.2 years), and 31 (47%) were men. Table I describes baseline patient and tumour characteristics.

Initial sites of metastases at diagnosis of advanced disease included liver ($n = 47$, 71%), lymph nodes ($n = 8$, 12%), lung ($n = 2$, 3%), peritoneum ($n = 3$, 5%), and bone ($n = 5$, 8%). First-line therapy included surgical resection ($n = 24$, 36%), chemotherapy ($n = 11$, 17%), targeted therapy ($n = 7$, 11%), PRRT ($n = 3$, 5%), and somatostatin analogues ($n = 21$,

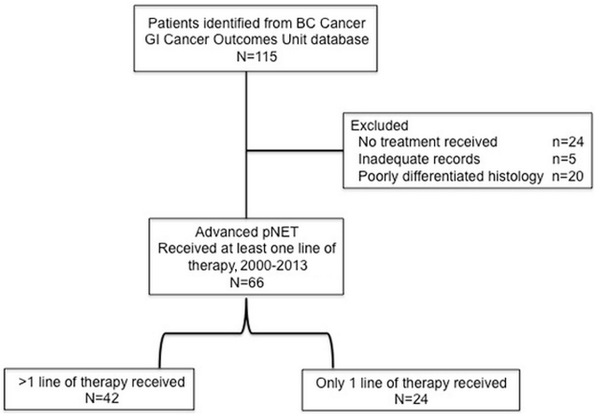

FIGURE 1 CONSORT diagram showing all advanced cases of pancreatic neuroendocrine tumour (pNET) identified. GI = gastrointestinal.

TABLE I Baseline characteristics of 66 patients with advanced pancreatic neuroendocrine tumours, by lines-of-therapy group

Characteristic	Lines-of-treatment group			*p* Value[a]
	Overall	>1 Line	Only 1 line	
Patients	66	42	24	
Age (years)				
Median	61.2	56.2	63.9	0.44
Range	32.9–80.8	32.9–72.8	49.0–80.8	
Sex [*n* (%)]				
Men	31 (47)	22 (53)	9 (38)	0.24
Women	35 (53)	20 (48)	15 (63)	
T Stage [*n* (%)]				
2	12 (18)	10 (24)	2 (8)	**0.03**
3	13 (20)	12 (29)	1 (4)	
4	1 (2)	0	1 (4)	
Unknown	40 (61)	20 (48)	20 (83)	
N Stage [*n* (%)]				
0	9 (14)	7 (17)	2 (8)	0.17
1	13 (20)	11 (26)	2 (8)	
Unknown	44 (67)	24 (57)	20 (83)	
Metastases [*n* (%)]				
Initial location				
Lymph node	8 (12)	6 (14)	2 (9)	0.48
Liver	47 (71)	29 (69)	18 (82)	0.61
Lung	2 (3)	1 (2)	1 (5)	0.68
Peritoneum	3 (5)	2 (5)	1 (5)	0.91
Bone	5 (8)	5 (12)	0	0.08
Synchronous				
Yes	51 (77)	32 (76)	19 (79)	0.78
No	15 (23)	10 (24)	5 (21)	
Hepatic				
Bilobar	38 (81)	24 (83)	14 (78)	0.67
One lobe only	9 (19)	5 (17)	4 (22)	
Tumour histology [*n* (%)]				
Well differentiated	39 (59)	24 (57)	15 (63)	0.15
Moderately differentiated	20 (30)	16 (38)	4 (17)	
Unknown[b]	7 (11)	2 (5)	5 (21)	

TABLE I Continued

Characteristic	Lines-of-treatment group			*p* Value[a]
	Overall	>1 Line	Only 1 line	
Ki-67 index [*n* (%)]				
≤2%	6 (9)	4 (10)	2 (8)	0.33
3%–20%	18 (27)	16 (38)	2 (8)	
>20%	6 (9)	4 (10)	2 (8)	
Unknown	36 (55)	18 (43)	18 (75)	
Mitotic count [*n* (%)]				
≤2	17 (26)	11 (26)	6 (25)	**0.04**
3–20	9 (14)	9 (21)	0	
>20	0	0	0	
Unknown	40 (61)	22 (52)	18 (75)	
Chromogranin A (ng/L)				
Median	131.5	149	59	0.40
Range	5–16000	5–16000	14–2100	
Baseline ALP				
Median (IU/L)	114	120	90	
Range (IU/L)	42–552	42–470	50–552	
Elevated above ULN [*n* (%)]	22 (33)	17 (41)	5 (21)	0.17
Unknown [*n* (%)]	4 (6)	1 (2)	3 (13)	
Baseline LDH				
Median (U/L)	204	194	211	
Range (U/L)	102–2053	112–676	102–2053	
Elevated above ULN [*n* (%)]	13 (20)	7 (17)	6 (25)	0.23
Unknown [*n* (%)]	14 (21)	7 (17)	7 (29)	
First-line therapy [*n* (%)]				
Surgical resection	24 (36)	18 (43)	6 (25)	0.38
Chemotherapy	11 (17)	8 (19)	3 (13)	
Targeted therapy	7 (11)	4 (10)	3 (13)	
PRRT	3 (5)	2 (5)	1 (4)	
Somatostatin analog	21 (32)	10 (24)	11 (46)	
Primary tumour resected [*n* (%)][b]				
Yes	25 (38)	20 (48)	5 (21)	0.62
No	41 (62)	22 (52)	19 (79)	

[a] Significant values shown in boldface type.
[b] Does not include poorly differentiated histologies.
[c] At initial diagnosis or relapse.
ALP = alkaline phosphatase; ULN = upper limit of normal; LDH = lactate dehydrogenase; PRRT = peptide receptor radionuclide therapy.

32%). Median OS measured 77.6 months (95% confidence interval: 44.7 months to 110.6 months) for all patients.

For the 42 patients (64%) who went on to receive second-line therapy, therapies (Table II) consisted of surgical resection ($n = 5$), chemotherapy ($n = 11$), targeted agents ($n = 6$), liver-directed therapies ($n = 6$), PRRT ($n = 3$), and somatostatin analogues ($n = 11$). Systemic regimens included streptozocin–doxorubicin ($n = 1$), streptomycin–doxorubicin ($n = 3$), streptozocin–5-fluorouracil ($n = 1$), cisplatin–etoposide ($n = 3$), and capecitabine–temozolomide ($n = 3$). Of the patients who did not receive upfront surgery, 8% underwent surgical resection in a later line of treatment, and 13% subsequently received liver-directed therapy.

Univariable analysis demonstrated that T stage and mitotic count were associated with receipt of more than 1 line of therapy ($p < 0.05$, Table I). Other baseline characteristics, including N stage, location of metastases, extent of hepatic metastases, grade, Ki-67 index, chromogranin A, alkaline phosphatase, and lactate dehydrogenase were not associated with receipt of more than 1 line of therapy. For the 42 patients who received more than 1 line of therapy, median PFS and OS measured, respectively, 5.7 months (95% confidence interval: 2.1 months to 9.2 months) and 67.3 months (95% confidence interval: 29.2 months to 105.5 months). No differences in OS or PFS between any second-line therapies were evident. Multivariable analysis was not performed secondary to insufficient sample size.

When outcomes were compared according to initial therapeutic modality, first-line surgery, compared with nonsurgical modalities, was associated with increased PFS [20.6 months vs. 6.3 months, $p = 0.03$, Figure 2(A)] and OS [100.3 months vs. 30.5 months, $p < 0.01$, Figure 2(B)]. For patients who did not receive upfront surgery, a first-line somatostatin analogue was not associated with increased PFS, but OS trended toward significance in a comparison with first-line systemic therapy [PFS: 8.6 months vs. 4.5 months, $p = 0.11$, Figure 2(C); OS: 44.4 months vs. 21.0 months, $p = 0.05$, Figure 2(D)].

DISCUSSION

Sequential treatments and standardized second-line therapies are not well delineated for patients with advanced pNETs. Based on American Joint Committee on Cancer staging, the reported 5-year OS rates are 92% for stage I, 84% for stage II, 81% for stage III, and 57% for stage IV[8]. We present a population-based cohort of consecutive cases spanning 13 years and characterize their treatments and associated outcomes. Compared with other treatments, upfront surgical resection in eligible patients was associated with improved PFS and OS.

The consensus guidelines from the European Neuroendocrine Tumor Society recommend surgical resection for metastatic pNETs, because resection has been associated with better survival rates, and our results are consistent with that recommendation[6]. Similarly, Partelli *et al.*[9] reported increased OS with curative and palliative resection, compared with conservative management, in patients with advanced pNETs and liver metastases. For patients who did not undergo first-line surgery, initial use of a somatostatin analogue, compared with initial systemic therapy, trended toward improved outcomes. That observation is in keeping with recent phase III trials that have shown the efficacy of somatostatin analogues[10,11]. In the CLARINET trial, lanreotide, compared with placebo, was associated with improved PFS, but not OS[11].

In our cohort, no survival differences between second-line therapies were evident. In recent years, the number of treatment options has increased, including targeted agents and PRRT[12,13]. Given that there is no level I evidence for a particular treatment sequence or timing of initiation, clinical judgment based on tumour, patient, and treatment factors has been recommended[7,14,15]. For instance, a symptomatic patient might benefit from a somatostatin analogue, but

TABLE II Second-line therapies in 42 patients who received more than 1 line of therapy

First-line therapy	Pts *(n)*	Second-line therapy [*n* (%)]					
		Surgical resection	Chemotherapy agents	Targeted therapy	Liver-directed	PRRT	Somatostatin analogue
Surgical resection	18	3 (17)	4 (22)	4 (22)	3 (17)	0	4 (22)
Chemotherapy	8	0	2 (25)	1 (13)	0	2 (25)	3 (38)
Targeted agents	4	1 (25)	1 (25)	0	0	0	2 (50)
PRRT	2	0	0	0	0	0	2 (100)
Somatostatin analogue	10	1 (10)	4 (40)	1 (10)	3 (30)	1 (10)	0

Pts = patients; PRRT = peptide receptor radionuclide therapy.

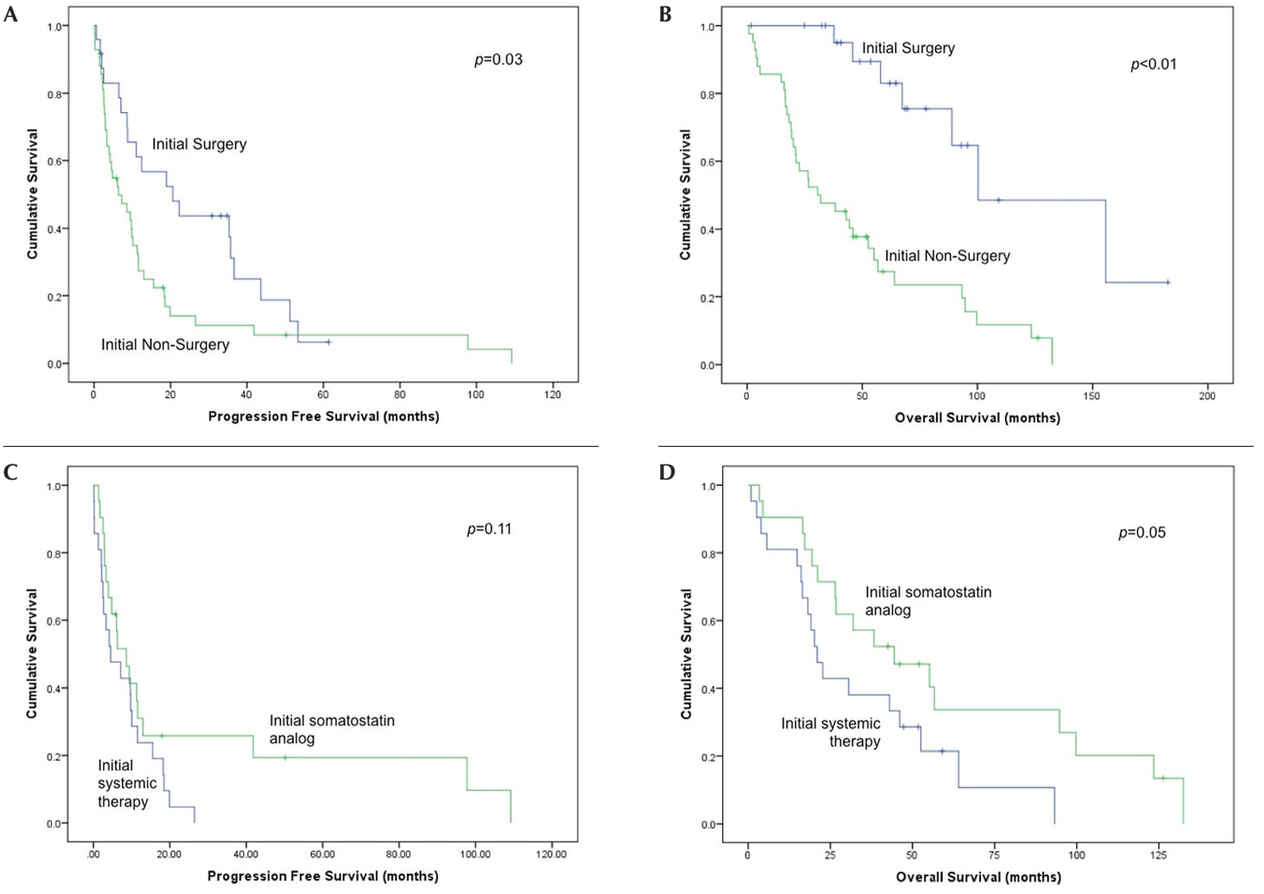

FIGURE 2 Kaplan–Meier curves. (A) Progression-free survival and (B) overall survival, comparing patients who initially received surgical resection with those who initially received nonsurgical modalities. (C) Progression-free survival and (D) overall survival, comparing patients who initially received a somatostatin analog with those who initially received systemic therapy.

a patient with a significant tumour burden could derive greater benefit from earlier chemotherapy.

In the present analysis, we found that factors associated with receipt of more than 1 line of treatment included T stage and mitotic count, but not N stage, location of metastases, grade, Ki-67 index, or chromogranin A. Tumour grade has been reported to be prognostic, as reflected in the protocol from the College of American Pathologists for reporting pNETs[8,16]. However, we note that our study specifically excluded high-grade, poorly differentiated histology, which might affect the prognostic value of grade in our cohort. TNM staging has been shown to be a useful predictor of survival, and certainly our results were consistent in that T stage was associated with more than 1 line of therapy[17]. Other reported prognostic factors for worse survival include worse Eastern Cooperative Oncology

Group performance status, synchronous metastases, 10% or greater Ki-67 index, and high serum alkaline phosphatase[18,19]. Although those factors were included in our analysis, they were not significantly associated with more than 1 line of therapy, and our cohort might have been too small to demonstrate such associations. Prognostic nomograms have also included the pathologic markers T stage and Ki-67, although those nomograms are not specific for pNETs[20]. With the advent of novel technologies, further prospective studies using whole-genome sequencing, circulating tumour cells, and biomarkers might be helpful in the delineation of useful prognostic factors for pNETs[21].

Limitations of our study include a small sample size, likely related to the rarity of this tumour type and the select number of patients who receive more than 1 line of therapy. We collected consecutive cases over 13 years, acquiring a total of 66 cases of metastatic disease. A larger sample size would allow for multivariable analyses and further delineation of optimal treatment sequencing and potential prognostic factors.

CONCLUSIONS

We outlined the treatment sequence and outcomes in a population-based cohort of patients with advanced pNETs. Our results seem to confirm the primary role of surgical resection, reserving systemic therapies for the second-line setting. Upon progression, choice of second-line therapy is not prognostic; the decision can be based on patient and disease characteristics, highlighting the need for a multidisciplinary approach in treating affected patients. Larger prospective studies might help to elucidate prognostic factors and optimize sequencing and timing of therapies.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

AUTHOR AFFILIATIONS

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