Original Study

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Benefit of Primary Tumor Resection in Stage IV, Grade 1 and 2, Pancreatic Neuroendocrine Tumors

A Propensity-Score Matched Cohort Study

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Objective: To determine the association of primary tumor resection in stage IV pancreatic neuroendocrine tumors (Pan-NET) and survival in a propensity-score matched study.

Background: Pan-NET are often diagnosed with stage IV disease. The oncologic benefit from primary tumor resection in this scenario is debated and previous studies show contradictory results.

Methods: Patients from 3 tertiary referral centers from January 1, 1985, through December 31, 2019: Uppsala University Hospital (Uppsala, Sweden), Sahlgrenska University Hospital (Gothenburg, Sweden), and Brigham and Women's Hospital/Dana-Farber Cancer Institute (Boston, USA) were assessed for eligibility. Patients with sporadic, grade 1 and 2, stage IV pan-NET, with baseline 2000–2019 were divided between those undergoing primary tumor resection combined with oncologic treatment (surgery group [SG]), and those who received oncologic treatment without primary tumor resection (non-SG). A propensity-score matching was performed to account for the variability in the extent of metastatic disease and comorbidity. Primary outcome was overall survival.

Results: Patients with stage IV Pan-NET (n = 733) were assessed for eligibility, 194 were included. Patients were divided into a SG (n = 65) and a non-SG (n = 129). Two isonumerical groups with 50 patients in each group remained after propensity-score matching. The 5-year survival was 65.4% (95% CI, 51.5-79.3) in the matched SG and 47.8% (95% CI, 30.6-65.0) in the matched non-SG (log-rank, $P = 0.043$).

Conclusions: Resection of the primary tumor in patients with stage IV Pan-NET and G1/G2 grade was associated with prolonged overall survival compared to nonoperative management. A surgically aggressive regime should be considered where resection is not contraindicated.

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INTRODUCTION

Pancreatic neuroendocrine tumors (Pan-NET) are a heterogeneous group of tumors, presenting either as incidental tumors with no symptoms or with symptoms due to hormone secretion or local growth. As over 70% of the tumors are nonfunctioning and present in a delayed manner, many patients with Pan-NET present with metastatic disease (40%–95%).[1,2]

Whether resection of the primary tumor in patients with stage IV Pan-NET offers oncologic benefit is controversial, and management strategies vary between various centers.[3–8] Meta-analyses as well as studies from local registries suggest prolonged survival in patients who undergo primary tumor resection,[6,9–14] but other studies have not demonstrated any association with primary tumor resection and improved survival.[4,15] No randomized controlled trials address the benefit of primary tumor resection in stage IV Pan-NET, and only 2 studies with data from Surveillance, Epidemiology and End Results (SEER) database with matched groups exist, both suggesting a survival benefit with primary tumor resection.[16,17] For patients with unresectable hepatic metastases, European Neuroendocrine Tumor Society (ENETS) guidelines recommend consideration of resection of the primary tumor to prevent life-threatening or obstructive complications, whereas North American Neuroendocrine Tumor Society guidelines favor a resection of the primary tumor in select cases.[8,18] The aim of this study is to evaluate outcomes in patients with stage IV Pan-NET who underwent resection of the primary tumor compared with those managed nonoperatively, while also accounting for the variability in the extent of metastatic disease and comorbidity.

METHODS

Patients diagnosed with stage IV Pan-NET who were evaluated at 3 centers, Uppsala University Hospital (Uppsala, Sweden), Sahlgrenska University Hospital (Gothenburg, Sweden), and Brigham and Women´s Hospital/Dana-Farber Cancer Institute (Boston, USA) from 1985 to 2019 were assessed for eligibility. Because of changes in treatments and radiologic advances over time, patients diagnosed before 2000 were excluded. Patients who underwent primary tumor resection before diagnosis of stage IV disease were excluded, as were patients deemed inoperable due to advanced comorbidity or an unresectable primary tumor. Patients with grade 3 NET, poorly differentiated neuroendocrine carcinoma, unknown tumor grade, and genetically confirmed or clinically suspected MEN-1 and VHL were excluded. The final analysis included patients who were diagnosed with sporadic, grade 1–2, stage IV Pan-NET between 2000 and 2019. Patients with simultaneous liver metastases from another malignancy and those who underwent liver transplantation were excluded. Patients for whom, no follow-up data were retrievable were also excluded. To ensure the quality of data reporting, the STROBE statement was followed.[19]

Patient Baseline Data

Information regarding patient sex and age at the time of diagnosis of stage IV Pan-NET was obtained from the medical record. Charlson Comorbidity Index was chosen to categorize comorbidity due to its validated prognostic indicator for mortality.[20,21] Primary tumor size and presence of liver metastases and extrahepatic spread were extracted from pathology or radiology reports. Grade according to WHO 2017 criteria was obtained from pathology reports: among well differentiated tumors, NET G1 is defined as Ki67 <3% or mitotic index <2/10 high power field (HPF), NET G2 as Ki67 3% to 20% or mitotic index 2–20/10 HPF, NET G3 as Ki67 >20% or mitotic rate >20/10 HPF; poorly differentiated neuroendocrine carcinoma, NEC G3 as Ki67 >20% or >20/10 HPF. Hormonal syndromes were determined by a combination of clinical symptoms and hormonal levels. Patients´ records were scrutinized for the above-mentioned variables as well as dates of primary tumor and liver surgery, other forms of liver-directed therapy such as tumor ablation and transhepatic embolizations, peptide receptor radionuclide therapy, chemotherapy, and other systemic medical treatments.

Definition of Treatment Groups

Patients who underwent surgery for the primary tumor with or without resection of liver metastases were included in the primary tumor surgery group (SG), whereas the remaining patients were defined as the non-SG. To compare survival in time and to avoid immortal time bias, a time zero (baseline) was defined.[22] In the SG, baseline was set at the time of surgery for the primary tumor and in the nonoperative management group at the time of stage IV diagnosis.

Follow-up and Study Endpoints

All patients were followed until death or last clinical appointment before the cutoff date of December 31, 2019. The primary outcome measure was overall survival (OS), which was measured from baseline to death or last follow-up. Secondary outcome measures were progression free survival (PFS) measured from baseline to first clinical progression. Clinical progression was determined by a change in oncological or surgical treatment for each patient, suggesting evidence of progressive disease. Date of first clinical progression was noted, and was used to determine PFS. Postoperative complication rates were categorized according to the Clavien Dindo classification.[23] In addition, 90-day mortality after baseline was calculated.

Statistics

For baseline and follow-up data, median (interquartile range [IQR]) or mean (SD) were used as appropriate. The 2 groups baseline variables were analyzed for significant differences with Chi-square or Fisher's exact as appropriate, before matching.

A propensity score was calculated based on baseline characteristics and used as a balancing score to match the 2 groups 1:1. The variables chosen to match the groups at baseline were age, sex, functioning/nonfunctioning tumor, calendar year, Charlson Comorbidity Index, size of the primary tumor, number of liver metastases, extrahepatic metastases, and WHO tumor grade. A caliper width of maximum 0.1 was chosen to increase the likelihood of 2 equally balanced groups. Standardized mean difference was used to examine covariate balance between the 2 groups and a standardized mean difference <10% was considered to equal an insignificant difference between groups.[24] Kaplan-Meier analysis were used to compute OS and log-rank tests were performed to compare OS and PFS between the groups. SPSS (IBM, Armonk, USA) was used for the statistical analysis. A P value of <0.05 was considered significant for all statistical tests.

A power calculation was performed. Choosing a power of 80% and an alpha of 0.05 while accounting for a relative hazard ratio between the 2 groups of 0.5, some 65 events would be needed. With a 10-year follow-up and a 10-year survival of 35%, a total sample size of 100 for the matched groups was calculated.

Ethics

The study was approved by the regional ethics review boards in Uppsala, Gothenburg and Institutional Review Board at Boston.

RESULTS

In total, 733 patients with stage IV pan-NET were assessed for eligibility from the 3 centers; Uppsala University Hospital (n = 335), Sahlgrenska University Hospital (n = 63), and Brigham and Women's Hospital/Dana-Farber Cancer Institute (n = 335) (Fig. 1). A total of 194 patients remained after exclusion (Fig. 1). The mean (SD) age was 57.6 (±11.9) years, and 76 were women (39.2%). Median follow-up time was 3.9 years (IQR 1.5–6.4) and 115 patients died.

Unmatched Groups

Patients that underwent primary tumor resection were defined as the unmatched SG (unmatched SG, n = 65) and patients undergoing nonoperative management were defined as the unmatched non-SG (unmatched non-SG, n = 129) (Fig. 1). Baseline variables of the unmatched SG and unmatched non-SG are presented in Table 1. The unmatched SG had younger patients and less intrahepatic and extrahepatic spread than the unmatched non-SG (Table 1).

In the unmatched SG, median time from stage IV diagnosis to primary surgery was 0.2 years (IQR 0.0–0.6). One patient underwent a central pancreatectomy, 1 underwent enucleation, 15 patients underwent pancreaticoduodenectomy (Whipple's procedure), and 48 underwent a pancreatic tail resection. Nineteen patients (29.2%) in the unmatched SG experienced a complication after surgery classified as Clavien Dindo grade 2 or higher. Of these, 14 patients (21.5%) suffered a complication classified as Clavien Dindo ≥3. The 90-day mortality after primary tumor surgery was 4.6% (n = 3). Of the 19 patients that suffered a complication, 5 patients underwent a pancreaticoduodenectomy and 14 underwent a pancreatic tail resection, a complication rate of 33.3% of the pancreaticoduodenectomys and 29,2% of the pancreatic tail resections.

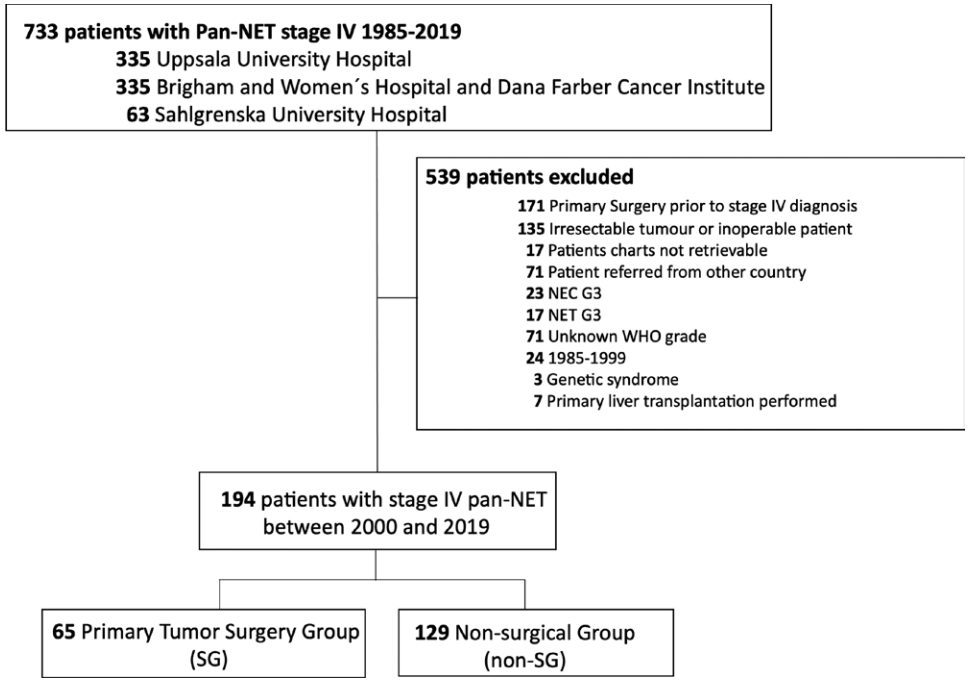

FIGURE 1. Consort diagram of patients enrolled in the study.

Median and 5-year survival for the unmatched SG patients was higher, 7.8 years (IQR 4.1–10.6) and 67.0% (95% CI, 79.0), respectively, compared with 5.0 years (IQR 2.8–8.4) and 51.6% (95% CI, 42.2-61.0) in the patients managed nonoperatively (log-rank, $P = 0.018$). The median PFS in the unmatched SG was 1.4 years (IQR 0.6–3.4) compared to 1.6 years (IQR 0.6–2.9) (log-rank, $P = 0.218$) in unmatched non-SG.

Propensity Score–matched Groups

The 1:1 propensity score match produced a cohort of 100 patients (50 patients in each group). Median follow up in matched groups was 4.3 years (IQR 2.8–6.0) and 52 patients died. After propensity score matching, the differences in most baseline variables were minimal between the groups (Table 1).

The matched SG median and 5-year survival was 7.4 years (IQR 4.1–10.5) and 65.4% (95% CI, 51.5-79.3), respectively, compared with 4.6 years (IQR 3.5–6.5, log-rank $P = 0.043$) and 47.8% (95% CI, 30.6-65.0) in the matched non-SG (log-rank, $P = 0.043$) (Fig. 2). The 3-year PFS in the matched SG was 27.7% (95% CI, 15.5-40.2) versus 24.8% (95% CI, 11.5-38.1) in the matched non-SG (log-rank, $P = 0.458$). The 90-day mortality calculated from baseline in the matched SG and matched non-SG was 6.0% (95% CI, 0-12.6) and 10.0% (95% CI, 1.7-18.3), respectively ($P = 0.459$).

Multimodal Treatment Between Matched Groups

Patients in both matched SG and matched non-SG received systemic treatments including interferon alpha, somatostatin analogue therapy, peptide receptor radionuclide therapy, and chemotherapy as well as surgical and ablative treatment (Table 2). No difference in the number of lines of systemic therapy and types of systemic therapy received between the groups was found. However, more liver resection and thermal ablative treatment was performed in the matched SG. In the matched groups, there were 19 patients who underwent liver resection during the study period, 15 patients in the matched SG and 4 patients in the matched non-SG. In a sensitivity analysis excluding these 19 patients and respective matches, there were still a difference of the OS between the matched groups; median and 5-year survival in the matched SG 8.3 years (95% CI, 5.2-11.4) and 67.8% (95% CI, 50.4-85.2), respectively, versus in the matched non-SG 4.4 years (95% CI, 3.3-5.5) and 42.3% (95% CI, 21.1-63.5) ($P = 0.028$).

DISCUSSION

Surgical resection is the sole potentially curative treatment modality for patients with Pan-NET. Whether primary tumor resection is beneficial in patients with stage IV Pan-NET, however, is under debate. This study assessed outcomes of patients with stage IV Pan-NETs with grade 1–2 disease who underwent primary tumor resection versus nonoperative management, using prospectively collected data from 3 large neuroendocrine tumor referral centers in the United States and Sweden. Primary tumor resection was associated with improved OS, both before and after propensity score matching.

As Pan-NET commonly presents as stage IV disease, various systemic treatments are used to control symptoms and to prolong survival.[25] In patients with unresectable hepatic disease and resectable primary tumors, some studies with inconsistent or contradictory results have addressed the question of whether patients benefit from primary tumor resection. In this analysis, resection of the primary tumor was associated with a survival benefit despite the fact that most patients did not undergo resection of liver metastases. Nonetheless, more patients in the matched SG than in the matched non-SG received local treatment of liver metastases, such as liver resection and thermal hepatic ablation. The interpretation of this is somewhat enigmatic, of course, these treatments may impact the survival, however, prolonged survival also increases the time each patient is eligible for such treatment. In summary, it seems clear that primary tumor resection, at times in conjunction with active local treatment of liver metastases, is associated with prolonged survival. No randomized controlled trials are available, though several retrospective studies have reported a potential survival benefit for patients undergoing primary tumor resection in stage IV Pan-NET.[3–5,9,10,22] The interpretation of available retrospective studies is limited by immortal time bias[22] as well as significant

TABLE 1.

Baseline Characteristics, Before and After Propensity-Score Match

	Before Matching				After Propensity Score Matching		
Baseline Characteristics	**Primary Tumor Resection Group (SG)**	**Nonsurgery Group (non-SG)**	***P***	**SMD***	**Primary Tumor Resection Group (SG)**	**Nonsurgery Group (non-SG)**	**SMD***
Age							
<50	18 (27.7)	32 (24.8)		32.8	14 (28.0)	12 (24.0)	5.9
50–59	21 (32.3)	39 (30.2)	0.272†	25.9	16 (32.0)	19 (38.0)	7.9
60–69	20 (30.8)	32 (24.8)		18.2	15 (30.0)	14 (28.0)	2.8
>70	6 (9.2)	26 (20.2)		38.2	5 (10.0)	5 (10.0)	0
Sex							
Female	26 (40.0)	50 (38.8)	0.867†	51.0	21 (42.0)	20 (40.0)	2.5
Male	39 (60.0)	79 (61.2)		46.0	29 (58.0)	30 (60.0)	2.2
Hormonal expression							
Functioning	13 (20.0)	30 (23.3)	0.606†	42.3	10 (20.0)	8 (16.0)	7.0
Nonfunctioning	52 (80.0)	99 (76.7)		51.3	40 (80.0)	42 (84.0)	4.1
Calendar year							
2000–2009	19 (29.2)	14 (10.9)	0.001†	13.5	10 (20.0)	6 (12.0)	14.8
2010–2019	46 (70.8)	115 (89.1)		77.4	40 (80.0)	44 (88.0)	8.1
Charlson CI							
0–1	53 (81.5)	108 (83.7)		192.8	42 (84.0)	46 (92.0)	8.1
2–3	9 (13.8)	13 (10.1)	0.627†	8.9	6 (12.0)	3 (6.0)	14.5
≥4	3 (4.6)	8 (6.2)		15.6	2 (4.0)	1 (2.0)	8.2
Size primary tumor (cm)							
<2	6 (9.2)	18 (14.0)		37.6	4 (8.0)	6 (12.0)	9.2
2–5	34 (52.3)	72 (55.8)	0.100†	45.1	27 (54.0)	28 (56.0)	2.2
>5	24 (36.9)	30 (23.3)		8.9	18 (36.0)	15 (30.0)	8.1
N/A	1 (1.5)	9 (7.0)		26.2	1 (2.0)	1 (2.0)	0
No liver met							
1–3	21 (32.3)	12 (9.3)		24.4	11 (22.0)	10 (20.0)	3.3
4–9	20 (30.8)	40 (31.0)	<0.001†	28.8	17 (34.0)	23 (46.0)	15.0
≥10	17 (26.2)	68 (52.7)		67.0	15 (30.0)	12 (24.0)	8.8
N/A	7 (10.8)	9 (7.0)		5.2	7 (14.0)	5 (10.0)	8.4
Extraabdominal metastases							
Yes	3 (4.6)	12 (9.3)	0.393‡	34.7	47 (94.0)	47 (94.0)	0
No	62 (95.4)	117 (90.7)		59.3	3 (6.0)	3 (6.0)	0
WHO grade§							
NET G1	25 (38.5)	38 (29.5)		28.3	18 (36.0)	21 (42.0)	7.6
NET G2	40 (61.5)	91 (70.5)	0.206†	57.9	32 (64.0)	29 (58.0)	6.5
Total number of patients	65	129			50	50	

*Standardized means difference in absolute number; values in parentheses are percentages.

†Chi-Square test.

‡Fisher's exact test

§Tumor grade according to WHO 2017.

SMD indicates suboptimal matching.

selection bias, as a decision to surgically resect a primary tumor also depend on the patients comorbidity, age or performance status, primary tumor characteristics, tumor grade, and the extent of metastatic disease. The propensity score matching in this analysis overcomes many of these limitations.

Several retrospective studies have utilized the SEER database,[3,5] which lacks data on comorbidity, allowing a selection bias for healthier patients for surgery. In the 2 studies using matched groups,[16,17] the SEER database was also utilized. While a correlation was suggested between primary tumor resection and survival, limitations of the data still include absence of information on comorbidities, information on tumor grade, and information on therapies in addition to tumor resection.[16]

A recent meta-analysis of studies examining primary tumor resection in stage IV Pan-NET suggests a possible survival benefit of primary tumor resection, particularly with low-volume liver tumor burden.[9] However, the potential for selection bias was noted in all studies in the meta-analysis, including those using propensity score matching. Moreover, morbidity following primary tumor resection was as high as 27% and was not reported in all studies.

In the present study, baseline covariates and outcomes of the unmatched groups highlight the fact that patients subjected to primary tumor resection may differ in baseline characteristics from non-surgical patients, and that these differences could explain much of the divergence in survival seen between such groups. However, after a propensity score match, removing most of the disparity in baseline covariates, the association of primary tumor resection with improved survival was still evident. Of note, baseline covariates with suboptimal matching >10% conferred to more liver metastases and more severe comorbidity in the matched SG (Table 1). Also, primary tumor resection was more common during 2000 to 2009 than in the latter period in the matched SG (Table 1). All in all, these results support the notion that removal of the primary tumor may result in improved OS despite remaining metastatic disease.[4,5,9,10]

In occasional patients with stage IV Pan-NET, surgery may be necessary to manage local complications such as bleeding, splenomegaly, or symptoms of obstruction. However, in patients with Pan-NET the primary tumor often must be quite large before causing complications due to mass effect or invasion by the primary tumor present, especially in the absence of hormonal symptoms. Surgery for palliation of symptoms from local tumor growth is likely an uncommon indication for surgery in the setting of metastases. Primary tumor surgery may also alleviate hormonal symptoms by debulking of the overall tumor load. However hormonal symptoms are often adequately controlled by antitumoral agents and antihormonal therapies.

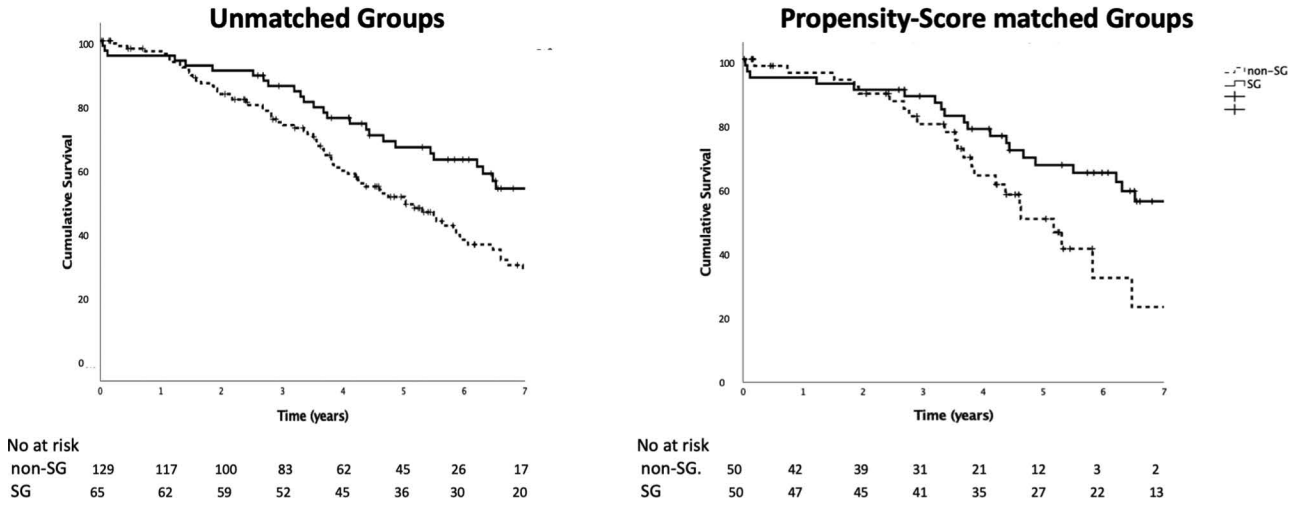

FIGURE 2. Kaplan-Meier curves for overall survival (log-rank in unmatched groups, $P = 0.018$; Propensity Score–matched groups, $P = 0.043$).

The indications for the primary tumor surgery may differ in various gastro-entero-pancreatic neuroendocrine tumors (GEP-NET) and in conflict with the results of a recent study of patients with stage IV SI-NET (small intestinal neuroendocrine tumors), this study favors primary tumor resection in stage IV disease.[26] The underlying reasons for this disparity may be multifactorial; for example, Pan-NET, in comparison a more aggressive disease, may be more likely to die from the metastatic disease. Moreover, the higher response rate to chemotherapy in Pan-NET in comparison to SI-NET may offer a different potential to eradicate remaining disease after resection and thus support aggressive surgical debulking.[27,28]

Limitations

Several potential limitations of the study may be noted. Even though a propensity score match for possible confounders was performed, important variables may have been overlooked and occult differences in baseline variables may thus exist between the groups. For example, differences in radiological methods and varying available data between centers may contribute to difference in baseline variables. Moreover, incomplete matching excluded more than 40% of the included patients from the final analysis, but was required to achieve balance in baseline variables between the 2 groups. Incomplete matching may limit the generalizability of the results, and the results of this study may thus not apply for patients with extreme propensity scores whom were not matched (i.e., very young and healthy patients in the SG or very old patients with extensive tumor burden and comorbidity in the non-SG group).

Of course, a randomized controlled trial would be needed to definitively address the question at hand. However, such a trial would be challenging to complete due to the low incidence of the disease and the relatively long survival of patients with Pan-NET. Ideally, disease-specific survival would be available to assess treatment effect, although based on the retrospective nature of this study only OS data are available and PFS may be inferred. As all patients in the study had metastatic disease, it is likely that this metastatic disease was a primary or contributing cause of death, and therefore disease-specific survival would likely not differ from OS.

TABLE 2.

PRRT with ^{177}[Lu]

Treatment for Systemic Disease	Primary Tumor Resection Group n = 50	Nonsurgery Group n = 50	*P*
First-line chemotherapy	35 (70.0)	31 (62.0)	0.405*
Second-line chemotherapy	20 (40.0)	16 (32.0)	0.405*
Third-line chemotherapy	10 (20.0)	12 (24.0)	0.629*
Interferon alpha	11 (22.0)	4 (8.0)	0.091†
Somatostatin analogue	34 (68.0)	35 (70.0)	0.829*
Liver resection	14 (28.0)	5 (10.0)	0.04†
Thermal hepatic ablation	11 (22.0)	0 (0.0)	<0.001*
Hepatic artery embolization	21 (42.0)	14 (28.0)	0.142*
PRRT	2 (4.0)	3 (6.0)	0.646†

Values in parentheses are percentages.
*Chi-Square test.
†Fischer's exact test.
PRRT indicates peptide receptor radionuclide therapy.

CONCLUSION

This study is the largest to date investigating primary tumor resection in stage IV Pan-NETs that both extensively controls for confounding variables and has a relatively long follow-up period. The results from this study favor resection of the primary tumor in stage IV Pan-NET with low- to intermediate-grade disease and hence, a surgically aggressive regime should be considered in all patients where resection is not contraindicated. Only a prospective randomized controlled trial could further clarify the role of primary tumor resection in stage IV pan-NET with distant metastases.

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