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Research Article

Peritoneal Carcinomatosis in Well-Differentiated Small-Intestinal Neuroendocrine Tumors with Mesenteric Tumor Deposits

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ABSTRACT

Objective: Well-differentiated small-intestinal neuroendocrine tumors (SI-NETs) tend to be biologically indolent. Despite this tendency, they have a predilection for metastasis. Peritoneal involvement is quite common as is unfortunately peritoneal carcinomatosis (PC). PC is a dreaded metastatic complication due to the significant morbidity it creates for patients as well as well as increasing their mortality risk. The risk factors for PC development in SI-NETs remain understudied; however, one such factor may be the presence of mesenteric tumor deposits (MTDs).

Methods: We performed a retrospective analysis on 208 well-differentiated SI-NET patient samples, the majority with mesenteric masses, from the pathology archives of Vanderbilt University Medical Center. We sought to explore whether MTD presence was associated with PC, what other patient determinants were associated with PC and prognostic implication of these determinants.

Results: Patients with MTDs had an OR of 3.9 (CI 1.6, 10.9) for PC compared to patients without MTDs in the analysis. Patients who developed PC fared more poorly than those who did not (p=0.044).

Conclusion: Our analysis, to the best of our knowledge, is the first to demonstrate an association between MTD presence and PC in this patient subgroup. We believe this finding warrants prospective evaluation given the possible therapeutic implications of being able to stratify SI-NET patients by their risk for developing PC based upon MTD presence.

Keywords: Peritoneal carcinomatosis; Mesenteric tumor deposits; Small intestinal neuroendocrine tumors

Introduction

Small-intestinal neuroendocrine tumors (SI-NETs) represent the fastest growing cohort of gastroenteropancreatic NETs [1]. The small bowel is the most common primary location for gastrointestinal NETs, and tumors from this location behave heterogeneously depending on determinants such as grade, defined by Ki-67% and mitoses/10 high-power field (HPF). Well-

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differentiated SI-NETs are typically G1 (Ki-67<3% and <2 mitoses) or G2 (Ki-67 3%-20% or 2-20 mitoses) and behave more indolently than G3 tumors with Ki-67>55% or poorly differentiated variants [2].

Despite their generally indolent growth patterns, these tumors tend to metastasize. Common sites of metastasis include the liver, distant lymph nodes, peritoneum, lung and bone, in descending order of frequency [3]. From existing reports in the literature, rates of peritoneal carcinomatosis (PC) in well-differentiated SI-NET patients range from 5%-33%; more recently, this rate has been estimated as closer to 14% [4,5]. PC is a source of significant morbidity in patients because it causes abdominal pain, early satiety, severe nausea, and bowel obstructions. Furthermore, across studies, SI-NET patients with PC have poorer OS than those patients who do not develop PC [5].

SI-NETs are one of several tumor types that form mesenteric tumor deposits (MTDs). MTDs are a specific subtype of mesenteric mass (MM) with discrete irregularly contoured tumor nodules, frequent location adjacent to neurovascular bundles and limited lymphoid tissue [6]. MTDs are thought to represent local rather than distant hematogenous spread and can lead to complications such as small bowel obstruction from mesenteric tethering, abdominal pain from compression of visceral nerves, ischemic bowel from mesenteric fibrosis around the superior mesenteric artery and ascites, small bowel varices and bowel edema from superior mesenteric venous involvement [7,8]. Given the location of MTDs in the mesentery, a parietal peritoneal reflection, intuitively it seems that patients possessing them should have higher rates of PC. This association has yet to be explored in existing literature.

Our pathology group previously published data on the poorer prognostic implications of patients with MTDs and perhaps, higher rates of PC in this population contributed to this finding [9]. We sought to estimate rates of PC among well-differentiated SI-NET patients at Vanderbilt University Medical Center (VUMC) with MMs, and specifically within the MTD cohort of these patients. Our primary research question was whether patients with MTDs experienced greater rates of PC compared to patients without MTDs. We also were interested in what other patient determinants were associated with PC.

METHODS

We searched the VUMC pathology archives for SI-NETs with H&E slides available for review and documented MM presence from the original pathology report or relevant abdominal imaging study (CT scans or MRI), after garnering institutional IRB approval. In the absence of pathologic confirmation, MMs were identified radiographically by the presence of a well-defined enhancing peri-intestinal mass with surrounding desmoplasia or internal calcifications; adjacent small bowel tethering was a less frequent identifying characteristic [7]. We identified 208 SI-NET samples from patients diagnosed between 01/01/1994 and 12/31/2015. Pathology slides were reviewed by our neuroendocrine pathologists who used Ki-67% and mitoses to classify tumors as G1-G3 by 2017 WHO NET criteria.

Tumors were staged by tumor, node and metastasis (TNM) SI-NET staging from the AJCC 8th edition. Nodal status was defined in the following manner: N0 for no involved lymph nodes, N1 for <12 involved regional lymph nodes and N2 by the presence of either a MM>2 cm or by >12 involved regional lymph nodes. T stages, for the purpose of our analysis, were categorized into the following groups: T3 or T4 primary lesions (T3/T4) and T1 or T2 primary lesions (T1/T2). Resection status was classified as follows: R0 (complete resections with negative microscopic margins) or R1 (complete macroscopic resections with positive microscopic margins)/R2 (incomplete macroscopic resections).

Of 191 samples that included MMs, 138 were identified as having suspected MTDs; 79 were considered definitive after careful review by our neuroendocrine pathologists while the other 59 were considered likely based on descriptions from gross surgical pathology reports. MTDs were defined as discrete mesenteric tumor nodules>1 mm and a specific effort were made to distinguish these deposits from completely replaced mesenteric lymph nodes. Mesenteric lymph nodes tend to have a rounded contour, prominent peripheral lymphoid aggregates and absence of neurovascular bundles microscopically; MTDs, as noted above, tend to have the opposite characteristics. In the event of dissent between pathologists regarding MTD classification of a sample, consensus opinion was reached *via* intra-department review.

Patient characteristics were compared between those with and without PC (Tables 1.1-1.4) using Pearson chi-squared test (categorical) and Wilcoxon rank sum test (continuous). Kaplan-Meier method was used to estimate progression free survival and overall survival. To assess the impact of the pre-specified factors on progression free survival (PFS) and overall survival (OS), log-rank test was used. Association between PC (yes/no) and the baseline factors was summarized using odds ratios (OR), and we used Fisher's exact test to assess their association. All statistical analyses were conducted using R version 3.4.

RESULTS

Demographics and baseline characteristics

Complete patient data are summarized in Table 1 Median age of the study population was 56.7 y with 52% males and 48% females. Of 208 patients, 204 had complete pathologic data (Ki-67% and mitotic rate) available to determine grade. There were one-hundred forty-seven (72%) G1, 50 (25%) G2 and 7 (3%) G3 patients in the cohort. Among patients with N2 disease, 106 of the 109 met criteria by MM>2 cm whereas the remainder met criteria by number of involved lymph nodes.

Table 1: Baseline characteristics between patients who did and did not develop PC. N refers to number of patients.

Patient characteristic (N)	Developed PC (N=64)	No PC (N=144)	P value
Gender (208)			0.66
Male (109)	54.7% (35)	51.4% (74)	
Female (99)	45.3% (29)	48.6% (70)	
Age (208)	58.1 ± 9.94 y	56 ± 12.48 y	0.2
WHO Grade (204)			0.29
G1 (147)	69.4% (43)	73.2% (104)	
G2 (50)	24.2% (15)	25% (35)	
G3 (7)	6.5% (4)	2.1% (3)	
Nodal involvement (201)			0.02
N0 (21)	1.61% (1)	14.39% (20)	
N1 (66)	32.3% (20)	33.1% (46)	
N2 (114)	66.1% (41)	52.5% (73)	
Mesenteric mass size (191)	2.92 ± 1.63 cm	2.38 ± 1.99 cm	0.02
Octreotide (205)			<0.001
Yes (105)	84.1% (53)	36.6% (52)	
No (100)	15.9% (10)	63.4% (90)	
Resection status (206)			<0.001
R0 (109)	30.6% (19)	62.5% (90)	
R1 (4)	1.6% (1)	2.1% (3)	
R2 (93)	67.7% (42)	35.4% (51)	
Original stage (207)			<0.001
I (6)	0% (0)	4.17% (6)	
II (10)	1.59% (1)	6.25% (9)	
III (95)	31.75% (20)	52.08% (75)	
IV (96)	66.67% (42)	37.5% (54)	
T stage of primary at diagnosis (192)			<0.002
T1 (8)	0% (0)	5.93% (8)	
T2 (35)	8.77% (5)	22.2% (30)	
T3 (96)	47.37% (27)	51.11% (69)	
T4 (53)	43.86% (25)	20.74% (28)	

M1 disease at diagnosis (207)			<0.001
Yes (96)	66.7% (42)	37.5% (54)	
No (111)	33.3% (21)	62.5% (90)	
MTD present (208)			0.017
Suspected (138)	78.1% (50)	61.1% (88)	
No (70)	21.9% (14)	38.9% (56)	

Local and systemic treatment

Of 202 patients who underwent surgery, 106, 4, and 92 underwent R0, R1 and R2 resections, respectively. Systemic therapy-wise, 105 patients received octreotide, 9 received everolimus, 5 received capecitabine plus temozolomide, 3 received peptide receptor radionuclide therapy (PRRT) and 1 received pertuzumab plus bevacizumab.

Peritoneal carcinomatosis (PC)

Rates of PC was 36% in patients with suspected MTDs compared to 20% in patients without MTDs (p=0.017). Other patient determinants associated with statistically significant difference in rates of PC included MM size, original stage at diagnosis, other metastatic sites of involvement and original resection status (Table 1). Patients with PC had a median mesenteric mass size of 2.5 (Quartiles: 1.8, 4.0) cm compared to 2.0 (1.0 cm and 3.12 cm) in patients without PC (p=0.016). PC rates did not differ by tumor grade (p=0.292).

Statistically significant increases in PC rates were seen in patients with suspected MTDs (OR: 3.9 (95% CI: 1.6, 10.9)), patients with metastases at diagnosis (OR: 3.3 (1.7, 6.6)), patients with R1/R2 resections (OR: 3.8 (1.9, 7.6)) and patients with T3/T4 primary tumors (OR: 4.1 (1.5, 14.0)). No significant association in PC rates were found by MTD size (>2 cm *vs.* <2 cm) (OR: 1.6 (0.7, 3.8)) or by confirmed/likely MTD status (OR: 1.1 (0.5 and 2.3)) (Table 1).

Table 2: Odds ratio (OR) of PC by specific patient determinants.

Variable name	Comparator groups	Odds ratio	Confidence interval	P-value
WHO grade	G2 and G3/G1	1.2	(0.6, 2.4)	0.61
MTD size	>2 cm/<2 cm	1.6	(0.7, 3.8)	0.33
Resection	R1 and R2/R0	3.8	(1.9, 7.6)	0
T-stage	T3 and T4/T1 and T2	4.1	(1.5, 14.0)	0.002
Metastatic disease at diagnosis	Yes/No	3.3	(1.7, 6.6)	0
Diagnosis age	<65 y/>65 y	1	(0.5, 2.2)	1
Octreotide	Yes/no	9.1	(4.1, 21.8)	0
Suspected MTD	Yes/no	3.9	(1.6, 10.9)	0.001
Suspected MTD	Confirmed/likely	1.1	(0.5, 2.3)	1
Nodal disease	N2/N1	1.3	(0.7, 2.6)	0.51

Overall survival

There were statistically significant OS differences in patients by presence of PC, age at diagnosis and WHO grade. OS differences were not statistically significant between patients who were metastatic at diagnosis and those with local disease (p=0.051) and based on T stage (p=0.06). No OS difference was seen between patients based on MTD presence (p=0.83) (Table 3)

(Figure 1.1). Patients with confirmed MTDs however, had trend toward poorer OS compared to patients with likely MTDs (p=0.05) (Figure 2). There was no difference in OS between patients by N2 *vs.* N1 nodal status (p=0.67).

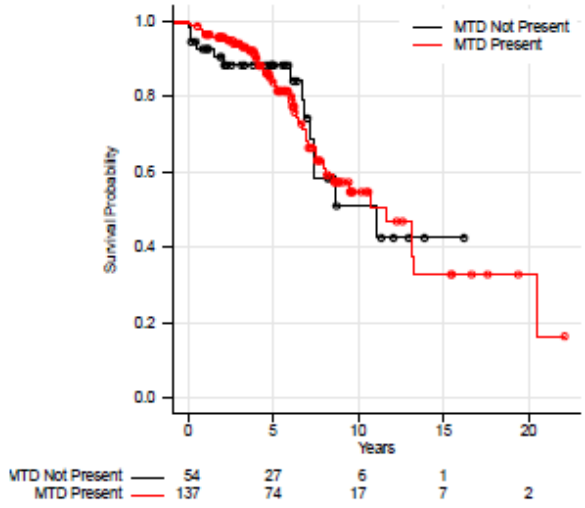

Figure 1: Univariate analysis of OS in patients by the presence or absence of suspected MTDs. P value of log-rank test is 0.97.

Patients with PC had a median OS of 8 y compared to 12 y in patients without PC (p=0.044) (Figure 3). Patients older than 65 with PC had no difference in median OS compared to patients younger than 65 with PC (p=0.4) (Figure 4). Patients older than 65 had a median OS of 8 y compared to 13 y in patients younger than 65 (p<0.001) (Figure 5). Patients with T3/T4 tumors had a median OS of 13 y compared to 7 y in patients with T1/T2 tumors (p=0.044) (Figure 6). One-hundred forty-five patients were alive at the time of final analysis.

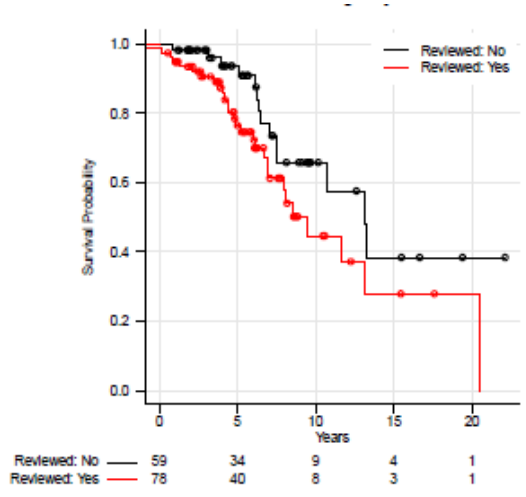

Figure 2: Univariate analysis of OS in patients by confirmed versus likely MTD status. P value of log-rank test is 0.05.

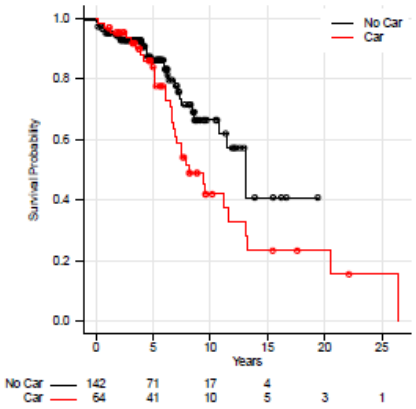

Figure 3: Univariate analysis of OS in patients by the presence or absence of PC. No car refers to any carcinomatosis while car refers to presence of carcinomatosis. P value of log-rank test is 0.044.

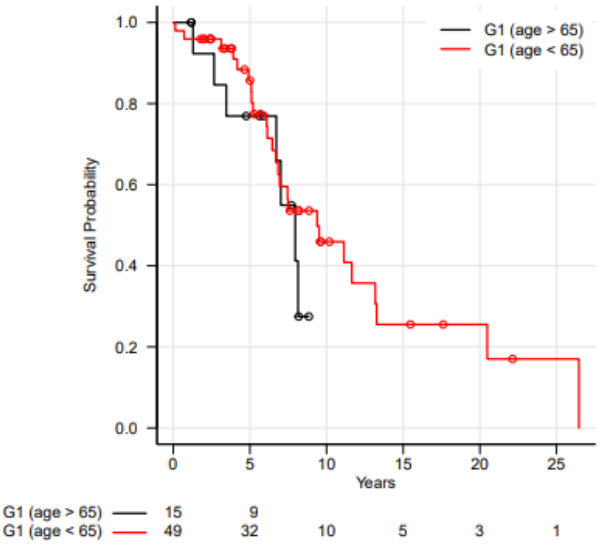

Figure 4: Univariate analysis of OS in patients with PC by age>65 y or <65 y. P value of log-rank test<0.001.

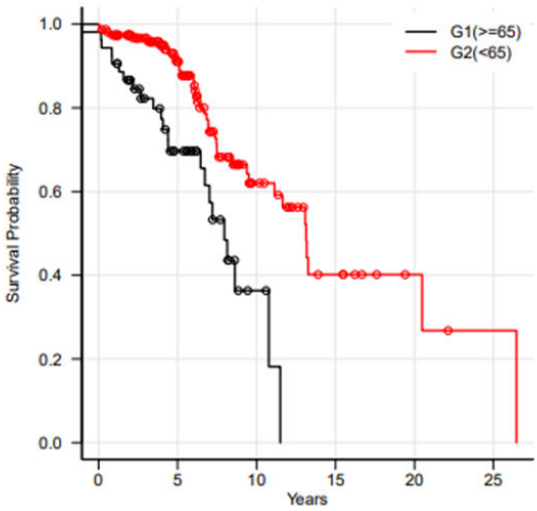

Figure 5: Univariate analysis of OS in patients by age>65 y or <65 y. P value of log-rank test<0.001.

Progression-free survival

There were statistically significant differences in PFS in our patients by age, WHO grade, gender and octreotide use (Table 4). Patients with WHO G1 *vs.* G2/G3 tumors demonstrated significant PFS difference; median PFS of patients with G1 tumors was 4.8 y compared to 4.0 y in patients with G2/G3 tumors (p=0.02). No differences in PFS were seen in patients by suspected MTD presence (p=0.37) or when comparing PFS of patients with confirmed MTDs and those with likely MTDs (p=0.40).

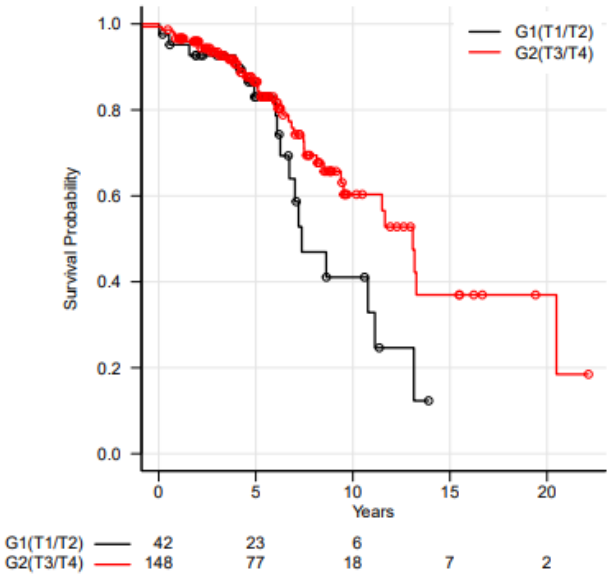

Figure 6: Univariate analysis of OS in patients by T stage category, T3/T4 or T1/T2. P value of long-rank test=0.044.

Table 3: Baseline characteristics between patients who survived or died in the analysis. N refers to number of patients.

Patient characteristic (N)	Alive (145)	Deceased (62)	P-value
Gender (208)			0.92
Male (109)	52.4% (76)	53.2% (33)	
Female (99)	47.6% (69)	46.8% (29)	
Age (208)	55.1 y ± 11.8 y	60.3 y ± 11.0 y	0.002
WHO grade (204)			0.026
G1 (147)	71.33% (102)	73.33% (44)	
G2 (50)	27.27% (39)	18.33% (11)	
G3 (7)	2.3% (2)	4% (1)	
Nodal involvement (201)			0.67
N0 (21)	11.5% (16)	8.2% (5)	
N1 (66)	33.8% (47)	31.1% (19)	
N2 (113)	54.7% (76)	60.7% (37)	
Mesenteric mass size (191)	2.41 ± 1.41 cm	2.83 ± 2.04 cm	0.175
Octreotide (205)			0.06
Yes (105)	47.2% (68)	61.7% (37)	
No (100)	52.8% (76)	38.3% (23)	
Resection status (206)			0.2
R0 (109)	56.94% (82)	44.26% (27)	
R1 (4)	1.39% (2)	3.28% (2)	
R2 (93)	41.67% (60)	52.46% (32)	
Original stage (207)			0.14
I (6)	2.78% (4)	3.23% (2)	
II (10)	4.17% (6)	6.45% (4)	
III (95)	51.39% (74)	33.87% (21)	
IV (96)	41.67% (60)	56.45% (35)	
T Stage of primary at diagnosis (192)			0.06
T1 (8)	5.15% (7)	1.82% (1)	
T2 (35)	13.23% (18)	29.09% (16)	
T3 (96)	52.21% (71)	45.45% (25)	
T4 (53)	29.41% (40)	23.64% (13)	
M1 disease at diagnosis (207)			0.051
Yes (96)	41.7% (60)	56.5% (35)	
No (111)	58.3% (84)	43.5% (111)	
MTD present (208)			0.83
Yes (138)	66.2% (96)	67.7% (42)	
No (70)	33.8% (49)	32.3% (20)	

Table 4: Baseline characteristics between patients who did or did not recur in the analysis. N refers to number of patients.

Patient characteristic (N)	Recurrence (177)	No recurrence (30)	P-value
Gender (208)			0.04
Male (109)	50.3% (89)	30% (9)	
Female (99)	49.7% (88)	70% (21)	
Age (208)	55.4 y ± 11.72 y	63.8 y ± 9.48 y	<.001
WHO grade (204)			0.04
G1 (147)	71.1% (123)	76.67% (23)	
G2 (50)	26.59% (46)	13.33% (4)	
G3 (7)	2.94% (3)	0% (0)	
Nodal involvement (201)			0.68
N0 (21)	10% (17)	13.3% (4)	
N1 (66)	34.1% (58)	26.7% (8)	
N2 (113)	55.9% (95)	60% (18)	
Mesenteric mass size (191)	2.53 cm ± 1.91 cm	2.56 cm ± 1.75 cm	0.68
Octreotide (205)			0.05
Yes (105)	54.3% (95)	34.5% (10)	
No (100)	45.7% (80)	65.5% (19)	
Resection status (206)			0.55
R0 (109)	54.55% (96)	44.83% (13)	
R1 (4)	1.71% (3)	3.45% (1)	
R2 (93)	43.75% (77)	51.72% (15)	
Original stage (207)			0.06
I (6)	2.84% (5)	3.33% (1)	
II (10)	3.41% (6)	13.33% (4)	
III (95)	48.86% (860	30% (9)	
IV (96)	44.89% (79)	53.33% (16)	
T stage of primary at diagnosis (192)			0.11
T1 (8)	4.88% (8)	0% (0)	
T2 (35)	15.24% (25)	33.33% (9)	
T3 (96)	51.22% (84)	44.44% (12)	
T4 (53)	28.66% (47)	22.22% (6)	

M1 disease at diagnosis (207)			0.39
Yes (96)	44.9% (79)	53.3% (16)	
No (111)	55.1% (97)	46.7% (14)	
MTD presence (208)			0.675
Yes (119)	67.2% (119)	63.3% (19)	
No (58)	32.8% (58)	36.7% (11)	

DISCUSSION

MTDs remain an understudied phenomenon in SI-NETs. Although they fall within the category of MMs, not all MMs are MTDs, which are defined by strict pathologic criteria. To our knowledge, no existing study has examined the association between MTD presence and PC in this population. Our analysis found that SI-NET patients with suspected MTDs had an OR of 3.9 for PC compared to patients without MTDs. Although only 78 of the suspected 138 patients had confirmed MTDs, there was no difference in rates of PC between those with suspected and likely MTDs, suggesting the magnitude of the association we observed is real. We saw a non-statistically significant association between MTD size (>2 cm compared to <2 cm) and rates of PC (OR 1.6, p=0.33). One reason for this finding could be that larger MTDs have greater peritoneal extension, and thus perhaps carry a greater risk of tumor cell shedding and peritoneal seeding.

In contrast to other analyses, we did not see MTD presence influence PFS or OS negatively. SI-NET patients with MTDs from Gonzalez et al. had a HR of 4.0 for PFS compared to patient without MTDs [9]. From Fata et al. SI-NET patients with MTDs had a HR of 11.9 for disease-free survival compared to patients without MTD [6]. The primary reason we may not have seen PFS or OS differences between patients with and without MTDs is our grouping system. We combined patients with confirmed and likely MTDs into the suspected MTDs group, and by doing so may have diluted the negative prognostic influence of MTD presence. This was suggested by our subsequent analysis in which we compared OS between patients with confirmed and likely MTDs and found the former group had a trend toward poorer OS (p=0.05). The difference in OS seen between these two groups is because some lesions categorized as likely MTDs were actually enlarged metastatic lymph nodes. Lymph node metastasis carries a weaker negative prognostic impact than true MTDs and therefore, it is important to differentiate true MTDs from lymph node replacement by tumor microscopically if possible [6]. A secondary reason could have been patient selection. We had fewer patients in our series without MTDs (28%) compared with the previously cited series. The reason for this likely is because of the tertiary referral nature of our center; we tend to see patients with more advanced and aggressive disease. Thus, our non-MTD patient group may have had more aggressive disease than typical non-MTD possessing populations.

Beyond suspected MTD presence, the most significant patient factors in our series associated with PC were T3/T4 primary tumors, presence of other metastases at diagnosis and R1/R2 resections. Patients with T3/T4 primary lesions in our series had an OR of 4.1 for developing PC compared to patients with T1/T2 primary lesions. This is not surprising given that penetrating primary lesions are more likely to involve the serosa and visceral peritoneum [10]. Somewhat surprisingly, patients with T3/T4 lesions had improved OS compared to patients with T1/T2 lesions. This was likely also a by-product of patient selection as we had many fewer patients with T1/T2 disease (42) compared to those with T3/T4 disease (148). Thus, patients in our cohort with T1/T2 disease performed worse than expected compared to their same-stage counterparts from other studies. Finally, it was not surprising that patients with other sites of metastatic disease at diagnosis and incomplete resections had higher rates of PC than those who presented with local disease and had R0 resections. Biologically, patients with hematogenous dissemination leading to distant metastatic involvement are more likely to have same process occurring more proximally in the peritoneum, leading to PC [11].

PC carries a poor prognosis in SI-NET patients, much as it does in patients with other abdominopelvic malignancies [12-14]. In our series, SI-NET patients with PC had reduced OS (8 y) compared to those without (12 y). This same trend was seen in the series from Norlen et al. and Madani et al. [15,16]. In the former, patients with and without PC had a median OS of 5.1 y and 11 y, respectively. In the latter, patients with PC from SI-NET origin had a 5-year survival of 67% compared to 78% in those without PC. We did not observe higher rates of PC in older patients compared to younger patients as seen in the series from Norlen et al. and Madani et al. [15,16]. In the former, mean age of patients with PC was 65 ± 10 compared to 61 ± 11 in those without PC. In the latter, the authors noted 73% of patients with PC *vs.* 49% without PC were older than 60 y. Norlen et al. [15] did observe differential rates of PC in patients based on tumor grade however the series from Madani et al. [16] along with ours did not.

PC causes significant morbidity and mortality in SI-NET patients and as such, identifying associated factors such as MTDs, could potentially prompt earlier more aggressive interventions to prevent its onset. Cytoreductive therapies such as radionuclide therapy with 177 lutetium-dotatate and capecitabine plus temozolomide are now available for SI-NET patients; treating physicians would perhaps be more inclined to

utilize these therapies rather than cytostatic options (somatostatin analogs, everolimus) for patients with MTDs in the setting of unresectable disease [17,18]. We realize this is purely speculative and that the association between MTD presence and PC needs to first be established prospectively. However, the potential promise of being able to risk-stratify SI-NET patients more optimally, particularly with regards to PC development, would be tremendously valuable.

The primary limitations of our analysis stem from its retrospective nature, patient selection and potential patient misclassification. The retrospective nature of our study makes it difficult to draw definitive conclusions about the associations we observed between patient determinants and PC. We had imbalanced patient selection among our cohort with regards to specific patient characteristics (MTD presence, T-stage). This imbalance certainly could have contributed to some of the findings from our study which is inconsistent with findings from other published literature, such as patients with suspected MTDs having no difference in prognosis from patients without MTDs and patients with T3/T4 primary lesions having a much better prognosis than patients with T1/T2 primary lesions. Additionally, all patients in our suspected MTDs group did not have confirmed MTDs. Given that only 79/138 were definitively confirmed, we could have overestimated the association between MTD presence and PC and underestimated the OS difference between patients with and without MTDs. Reassuringly in our analysis, we saw no difference in rates of PC when comparing between patients with confirmed and likely MTDs. We did see however that there was trend toward poorer OS in the confirmed compared to the likely MTD group which informs us that we underestimated the negative prognostic influence of MTD presence by our grouping method.

CONCLUSION

We believe our analysis is the first to suggest an association between MTD presence and PC in well-differentiated SI-NETs. If this association is demonstrated prospectively, MTD presence in the setting of unresectable disease could change the way we approach treatment for patients with these tumors. SI-NET patients with MTDs would potentially warrant more aggressive treatment with cytoreductive therapies to prevent development of PC compared to those without MTDs. At this point, until definitive confirmation, this remains purely hypothetical. We still have much to learn about the biology of MTDs, how to monitor patients with them and when to intervene to prevent peritoneal complications.

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