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Neuroendocrine tumors of the small intestine causing a desmoplastic reaction of the mesentery are a more aggressive cohort

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ABSTRACT

Background: Desmoplastic reaction of the mesentery is commonly seen in patients with neuroendocrine tumors of the small intestine. However, it is not clear whether desmoplastic reaction is associated with tumor-specific characteristics and diminished prognosis. Therefore, the aim of this study was to investigate whether the presence of a desmoplastic reaction correlates with prognostic and molecular markers of neuroendocrine tumors of the small intestine.

Methods: Patients with neuroendocrine tumors of the small intestine operated at our department from 2000 to 2016 were analyzed. Patient and tumor characteristics were evaluated. Kaplan-Meier and multivariate analyses were performed.

Results: In total, 148 patients underwent surgery, and preoperative imaging was available in 113 patients. A total of 45 patients showed desmoplastic reaction of the mesentery and progression-free survival was significantly impaired (26 months versus 65.4 months) compared with patients without desmoplastic reaction. These patients had significantly more often distant metastases (84.4% vs 39.7%), lymphatic vessel (68.9% vs 44.1%), and perineural tissue infiltration (57.8% vs 17.6%) compared with patients without desmoplastic reaction. However, proliferation index (positive desmoplastic reaction 4.1% versus negative desmoplastic reaction 3.3%) and tumor size (positive desmoplastic reaction 2 cm versus negative desmoplastic reaction 1.9 cm) were not diverging significantly.

Conclusion: This study revealed that tumors leading to desmoplastic reaction are more aggressive, despite similar Ki67 indices.

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Introduction

Neuroendocrine tumors of the small intestine (si-NET) represent a rare disease; however, the incidence is continuously increasing and varies around 0.67–2/100,000/year. Si-NETs are the most widely recognized gastrointestinal neuroendocrine tumors and account for nearly 50% of all small intestine neoplasms.¹ At the time of diagnosis, the primary tumors of si-NETs are regularly small but can cause symptoms. Most tumors are diagnosed by chance, attributable to symptoms induced by hormonal secretion or recognized by metastatic lesions.^{2,3}

The primary tumor size relates to the probability to develop lymphatic or distant metastases. In this regard, the rate of lymphatic metastases has been reported to be 20%–30% in patients with primary tumors < 1 cm and increases to 80% when the primary tumor exceeds 2 cm.^{4,5} Many patients with lymphatic metastases from neuroendocrine tumors present with a typical desmoplastic reaction (DR) of the tumor masses in the intestinal mesentery.

Remarkably, those metastatic masses frequently exceed the size of the primary tumor. Computed tomography (CT) scans reveal typical signs of the desmoplastic mesentery like spoke-wheel appearance with radiating strands of soft tissue.⁶ The desmoplastic mesentery may prompt a venous stasis, intestine kinking, and hypoxia, resulting in abdominal pain. Patients with DR frequently get symptomatic because of bowel obstruction and therefore emergency operation may be indicated.⁷ However, sparse information is

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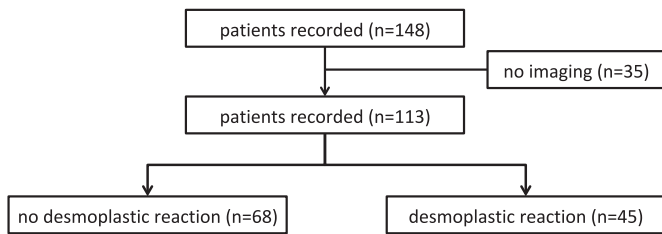


Fig. 1. Enclosed patients.



Fig. 2. Computed tomography scan of a patient with a desmoplastic reaction of the mesentery (arrows) shows a mesenteric mass with a stellate configuration detached from the primary tumor.

available on the value of DR of the mesentery with respect to prognosis. The aim of the present study was to investigate the impact of DR, as radiologically and histopathologically recognized, on the clinical course and survival prognosis of the patient.

Methods

From this study's prospective database 148 patients undergoing surgery for si-NET at the University Hospital of Munich Großhadern, Germany, between September 2000 and December 2016 were identified. For inclusion in the present study, interpretation of preoperative cross-sectional imaging was mandatory. Because of the lack of preoperative imaging, 35 patients had to be excluded. Thus, a total of 113 patients were analyzed about the presence of DR (Fig. 1). More than 40 variables were collected. Patients with missing variables were not excluded from the entire assessment but rather were excluded from specific calculations. Because of this process, included cases and reported percentages differ between different variables in this report. The assessed variables refer to demographic data, the primary tumor characteristics, histopathology and grading of tumors, surgical resection type, postoperative complications, and overall and progression-free survival.

From a clinical standpoint it is most valuable to detect DR in preoperative imaging. Therefore, patients with si-NET were divided into two groups, depending on the presence or the absence of DR. A lymph node was considered positive when it exceeded 10 mm.⁸ The presence of DR was defined by radiologic criteria and confirmed on histopathologic sections. Nonetheless, if DR is detected radiologically, this pathologic finding is regularly evident intraoperatively. The radiologic criteria of DR were a mesenteric mass with a stellate configuration detached from the primary tumor (Fig. 2).^{6,9} Patients with these radiologic findings were classified as DR positive. In line with the literature, we define DR as a yes or no phenomenon and do not grade DR. One independent and blinded radi-

ologist (M.D.) and one independent and blinded nuclear medicine physician (H.I.) evaluated the preoperative CT, dotatate positron emission tomography (PET)/CT, and/or magnetic resonance imaging scans. A blinded pathologist (T.K.) reviewed hematoxylin and eosin-stained slides for the presence or absence of a desmoplastic mesentery. The aim of this report was to investigate whether the presence of DR correlates with prognostic and molecular markers of si-NET. In this respect, we speculated that the presence of DR is associated with higher tumor aggressiveness irrespective of the size of DR. Therefore, in this report, a classification system for grading DR was not introduced.

Postoperative complications were graded according to the classification of Dindo et al.¹⁰

For survival data, mean survival times, along with their 95% confidence intervals (CI95%) and Kaplan-Meier survival statistics, were calculated for the entire sample stratified by DR, using log-rank tests. Overall and progression-free survival were obtained by examining patient records. Postoperative imaging reports were used to categorize patients into progressive or stable disease. Every patient received a sectional imaging modality every 6 months within the first 2 years and annual imaging thereafter.

Bivariate analysis was carried out by using χ^2 test for categorical parameters (eg, grading, presence of distant metastases); *P* values lower than .05 were considered significant.

For the identification of specific risk factors of survival and time to progression, a Cox proportional hazards model was used, including the variables DR, T stage, angioinvasion, lymphatic vessel infiltration, grading, and perineural tissue infiltration, which were entered into the mathematic model using the backward stepwise Wald method.¹¹ SPSS v 20.0 for Mac (IBM Corp., Armonk, NY) and Prism 6.0 for Mac (GraphPad Software, Inc., La Jolla, CA) were used for data analysis.

Results

Within the analyzed cohort of 113 patients, DR was present in 45 patients (39.8%). The 113 patients include 44 (38.9%) female and 69 (61.1%) male. Specific sex differences in the appearance of DR, as well as a correlation with patient's age to DR, were not evident (Table 1).

Histopathologic findings

The histopathologic parameters of the operative specimen of patients with DR were analyzed in the primary tumor. Tumors leading to DR in the mesenteric lymph nodes showed a highly significant increased rate of perineural tissue infiltration (DR+ 57.8% versus DR- 17.6%; *P* < .001) and significantly more often an invasion into lymphatic vessels (DR+ 68.9% versus DR- 44.1%; *P* < .05). We found no significant difference in the rate of angioinvasion (DR+ 22.2% versus DR- 14.7%; *P* > .05).

Another finding was that tumor grading, defined by the proliferation index (Ki-67 index) of the primary tumor, was not diverging between patients, with or without DR (*P* > .05). The mean Ki-67 index of patients with DR was 4.1%, and tumors that did not induce DR had a Ki-67 index of 3.3% (*P* > .05; Table 1).

Examination of desmoplastic lymph nodes revealed a distinctive histopathologic pattern (Fig. 3). These lymph nodes showed an irregular contour and consistently an infiltration of neurovascular bundles. Fibrotic strands of conjunctive tissue replaced the architecture of the desmoplastic lymph nodes. The desmoplastic lymph nodes were detached from the primary tumor, as seen in CT scans.

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