



Malignant gastrointestinal neuroectodermal tumor: A rare differential diagnosis of neuroendocrine neoplasm of the Small Intestine - Case reports and Review of the literature

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Abstract

The malignant gastrointestinal neuroectodermal tumor (GNET) is a rare and very aggressive neoplasm. Due to its rarity, the tumor is often misdiagnosed. We report on two female patients who were operated on under the suspected diagnosis of a neuroendocrine tumor of the small intestine (SI-NET). The patients, aged 37 and 57 years, presented with symptoms of bowel obstruction. In a 37-year-old patient with a chronic bowel obstruction, MRI enterography revealed a tumor in the jejunum with lymph node metastases as well as liver metastases. Laparotomy confirmed the presence of a tumor in the jejunum with lymph node and liver metastases. Segmental resection of the small bowel with lymphadenectomy was performed. The remaining hepatic metastases in the right liver lobe were removed 8 weeks later by right hemihepatectomy. Four months later, the Ga68-FAPI-PET/CT showed significant disease progression. Unfortunately, the patient died 22 months later after initial diagnosis. In the second case, a 57-year-old female presented to our clinic with progressive bowel obstruction for 2 years. The MRI examination revealed a small bowel obstruction due to a tumor mass in the ileum with lymph node metastases suspicious for a SI-NET. Exploratory laparotomy revealed a tumor in the jejunum with peritoneal metastases. A vessel-sparing small bowel resection with lymphadenectomy and partial peritonectomy was performed. The follow-up examinations using MRI and CT six months postoperatively showed no evidence of tumor progression. The final pathology confirmed the diagnosis of a GNET in both cases. Molecular analysis revealed EWSR1 translocations in the tumors of both patients.

Keywords: Malignant gastrointestinal neuroectodermal tumor; GNET; Small intestine; SI-NEN; EWSR1 translocation

Introduction

Malignant gastrointestinal neuroectodermal tumor (GNET) is an extremely rare primary neoplasm [1]. This entity is also referred to as clear cell sarcoma-like tumor of the gastrointestinal tract (GCS-like tumor of the gastrointestinal tract) [2]. The most common tumor location is the small intestine (58%), followed by the stomach (16%), colon (11%), ileocecal junction (5%), lower esophagus (5%) and anal canal (5%) [3]. Already in 1985, Alpers and Beckstead described a malignant neuroendocrine tumor of the jejunum with osteoclast-like giant cells [4]. In 2003 Zambrano et al. first defined clear cell sarcoma of the gastrointestinal tract as a distinct entity. They reported six cases of osteoclast-rich tumors of the gastrointestinal tract

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that resembled clear cell sarcoma of soft tissues and could be clearly distinguished from gastrointestinal stromal tumors (GIST) [5]. In 2012 the term GNET was introduced based on histomorphological and immunohistochemical criteria of 16 cases [6]. The median age at diagnosis for GNET is around 45 years (range: 13–85 years) with an equal gender distribution [7]. At the time of diagnosis, 30% of patients already present with distant metastases and the prognosis is poor with a median survival time of only 18 months [3,8]. To date, approximately 80 cases of small bowel GNETs have been documented in the English literature. The clinical symptoms and imaging findings might mimic those of a small intestine neuroendocrine tumor (SI-NET), a neoplasm with a significantly better prognosis.

Here we report two cases of small bowel GNETs that were operated on under the suspicion of a SI-NET and provide a brief overview of the literature regarding GNET of the small intestine as a differential diagnosis to SI-NET.

Case presentations

Case 1: A 37-year-old woman presented to our hospital with recurrent abdominal pain of variable localization for 2 years. Physical examination revealed abdominal tenderness without signs of peritonitis. Standard blood analysis showed iron-deficiency anemia with a normal count of white blood cells and platelets. Chromogranin A was within the normal range at 35 ng/ml (normal < 108 ng/ml). The 5-hydroxyindoleacetic acid (5-HIAA) in the urine was also within the normal range at 26.3 μ mol/d (normal 10.4 - 47.1 μ mol/d). No lesions were found during the upper and lower endoscopies. Magnetic resonance enterography showed a rounded wall thickening of a small intestine loop in the left abdomen with intense contrast enhancement of pathological lymph nodes up to 2 cm in size, extending from the small bowel to the superior mesenteric artery [level 2 according to the Marburg classification, 9], as well as at least 3 liver metastases in the right liver lobe (figure 1A and 1B). No mesenteric desmoplasia was visible.

Due to the nonspecific abdominal pain and the radiologically detected small bowel tumor with liver metastases, the suspicion of a metastatic SI-NET was raised. To complement the diagnostic workup for SI-NET, a preoperative DOTATOC-PET/CT was also performed. The Ga68-DOTATOC-PET/CT examination showed only weak somatostatin receptor expression in the tumor and the enlarged lymph nodes, raising some doubts in the diagnosis.

To confirm the dignity of the hepatic mass, a sonographically guided biopsy was performed. Histology revealed liver tissue infiltrated by a nest-forming tumor. Immunohistochemically weak synaptophysin expression, and negativity for cytokeratins (CKMNF 116, CK 18, CK 19) was noted. Chromogranin A also tested negative. Given the

positivity for S100, the metastasis of a malignant melanoma was among the possible diagnoses.

The patient subsequently underwent an exploratory laparotomy. Intraoperatively, a small bowel tumor was found in the jejunum, 120 cm distal of the Treitz ligament, without mesenteric shrinkage, but with mesenteric lymph node metastases extending to the inferior border of the pancreatic neck [level 2 according to the Marburg classification, 9], as well as multiple liver metastases. A segmental resection of the jejunum with retrograde vessel-sparing lymphadenectomy, as well as resection of the liver metastases in segments III and IVb, was performed (figure 2). The liver metastases in the right liver lobe (segments VI, VII, VIII) were left behind to perform a second stage right hemihepatectomy.

Frozen section described a malignant tumor most likely of epithelial origin, but without precise differentiation. The final histological examination after paraffin embedding revealed a 3 cm small bowel tumor with areas of solid, pseudopapillary, and isolated alveolar growth. The tumor cells exhibited areas of clear cell cytoplasm. Of the 18 resected mesenteric lymph nodes, 10 were found to be tumor infiltrated. The immunohistochemical analysis showed strong positivity for S-100 protein. However, HMB-45, Melan-A, and PanCK were consistently negative. Synaptophysin showed partial and weak expression (figure 3). The Ki-67 proliferation index was approximately 40%. The fusion analysis performed using Next-Generation Sequencing (NGS) identified an EWSR1-CREB1 translocation. In conclusion, the diagnosis of a lymphatic and hepatic metastasized malignant gastrointestinal neuroectodermal tumor (GNET) of the jejunum pT2a, pN1(10/18), pM1, R0 was established.

The postoperative course was uneventful and the patient was discharged at postoperative day 10. The remaining hepatic metastases in the right liver lobe were removed 8 weeks later by right hemihepatectomy. Two months later, new liver metastases were detected in the Ga68-FAPI-PET/CT, which were still progressive one month later in the MRI. Two months later, the Ga68-FAPI-PET/CT showed significant disease progression with numerous liver metastases, as well as mesenteric and peritoneal manifestations. Despite four courses radiopeptide therapies with 7,0 GBq Y-90 FAP, 7,5 GBq Lu-177 plus 10MBq Ac-225 FAP, 7,3 MBq Ac-225 FAP/ 7,0 GBq Y-90, 9,0 MBq Ac-225 FAP, as well as 4 transarterial embolizations of the liver, the tumor continued to progress. The patient died 22 months after initial diagnosis.

Case 2: A 57-year-old female patient complained of progressively worsening, intermittent abdominal pain over 2 years. Within the last 3 weeks prior to admission, she also experienced episodes of bowel obstruction and recurrent vomiting. At initial presentation physical examination revealed a massively distended and tender abdomen without signs of peritonitis. Standard blood analysis showed no

anemia with a hemoglobin level of 13.3 g/l. Chromogranin A was within the normal range at 48.0 µg/l (normal < 102 µg/l). The 5-hydroxyindoleacetic acid (5-HIAA) in the urine was also within the normal range at 5.6 mg/g Krea (normal 1.3-6.9 mg/g Krea). CEA and CA 19-9 were also within the normal range. Magnetic resonance enterography had already been performed on an outpatient basis. The imaging showed signs of a small bowel obstruction due to a rounded small bowel lesion in the middle part of the ileum. The enlarged lymph nodes, up to 1 cm in size, extended to the segmental branches of the mesenteric vessels [level 1 according to the Marburg classification, 9]. No mesenteric shrinkage was visible, but peritoneal carcinomatosis was suggested because of multiple peritoneal nodes up to 5mm in size. Liver metastases were not visible. The MRI diagnosis was small bowel tumor with manifest bowel obstruction, lymph node and peritoneal metastases, possibly a SI-NET (figure 1C and 1D).

Because of the bowel obstruction the patient underwent an exploratory laparotomy without further imaging such as Ga68-DOTATOC-PET/CT. Intraoperatively, extensive peritoneal metastases were observed with multiple tumor deposits up to 3 mm in size in the whole peritoneum and intestinal mesentery summing up to a peritoneal carcinomatosis index (PCI) according to Sugarbaker [10] of 18. The highly obstructive tumor was located in the jejunum, 160 cm distal to the Treitz ligament. Enlarged, mesenteric lymph nodes

were found up to the origin of the superior mesenteric artery, but without mesenteric desmoplasia. A segmental small bowel resection with vessel-sparing lymphadenectomy and partial peritonectomy was performed, which resulted in a R2 resection.

On frozen section analysis, the peritoneal deposits were classified as a malignant, the potential diagnoses included a diffusely growing carcinoma, a neuroendocrine tumor or a mesenchymal neoplasm, respectively.

After paraffin embedding, a malignant tumor was observed in the small intestine and peritoneum, consisting of a predominantly monomorphic cell population with small, hyperchromatic, oval nuclei and a narrow eosinophilic cytoplasmic rim. The primary tumor exhibited a spindle-shaped growth pattern with clear cell cytoplasm, while the tumor tissue in the peritoneum displayed a diffuse infiltrative cell pattern that differed from the primary tumor. The mitotic activity of the neoplasm was overall low, with a maximum of 6 mitoses per 10 high power fields (HPF). Of the 16 examined locoregional lymph nodes, 5 showed capsular-invasive metastases.

Immunohistochemically the tumor cells exhibited strong positivity for SOX10 and S-100. Melan-A and HMB-45 were negative, as were the stains for broad-spectrum cytokeratins (CK18, CKpan), Calretinin, Inhibin, Hormone receptors, E-cadherin and GATA 3. Synaptophysin exhibited a heterogeneous, partially strong expression (figure 3). Chromogranin A was negative. The Ki-67 proliferation index was up to 20%. Using Next-Generation Sequencing (NGS) an EWSR1-ATF1 fusion was detected. Thus, finally the diagnosis of a malignant gastrointestinal neuroectodermal tumor (GNET) pT2b, pN1(5/16), pM1(PER), R0 (local) was made.

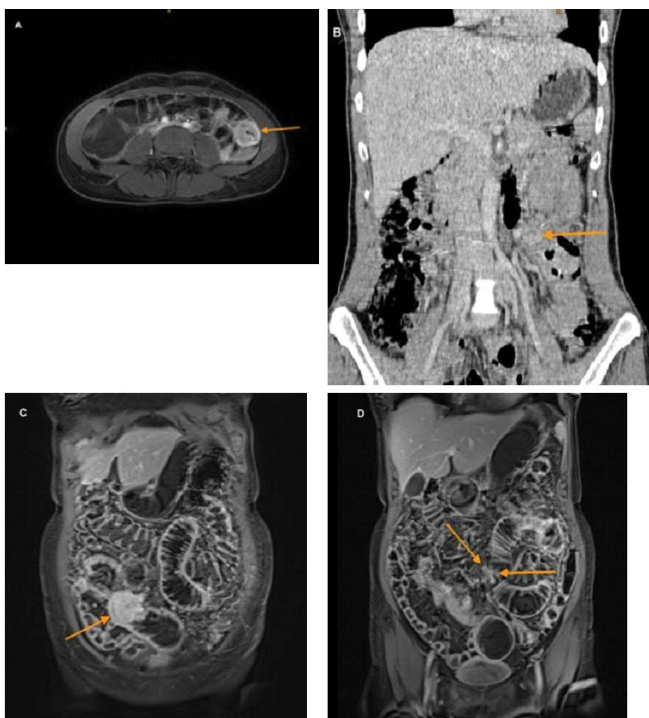


Figure 1: A: Case 1, MRI shows the primary tumor in the small intestine, B: Case 1, the CT shows the enlarged lymph node (arrows) C: Case 2, MRI reveals the primary tumor in the small intestine and D: Case 2, the enlarged lymph nodes (arrows)

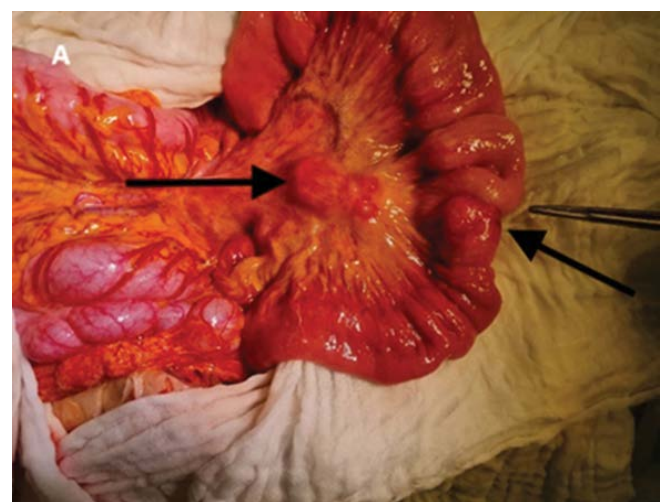


Figure 2: Intraoperative situs of case 1 with the primary tumor in the jejunum and pathological lymph nodes in the mesentery (arrows).

The postoperative course was uneventful and the patient was discharged after 10 days. The interdisciplinary tumor conference recommended palliative chemotherapy only in the event of tumor progression. The follow-up examinations using MRI of the abdomen and CT of the thorax six months and 12 months postoperatively showed no definitive tumor formations, indicating no evidence of tumor progression.

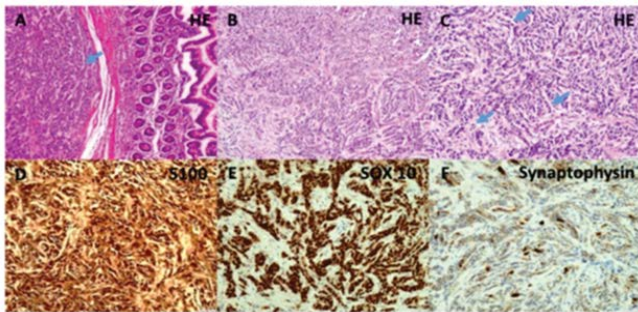


Figure 3: A: Histologic appearance of a primary GNET presenting as a submucosal mass beneath non-dysplastic small intestinal mucosa. The tumor shows solid growth with sheets and nests of oval to spindle mesenchymal cells featuring clear or eosinophilic cytoplasm, prominent nucleoli, and rare mitotic figures (HE, magnification $\times 10$)

B-C: Peritoneal metastases from the same neoplasm demonstrating an alternating growth pattern, including dissociative tumor architecture with trabecular arrangements and infiltrating single tumor cells. Despite the invasive pattern, the cytomorphological features remain low-grade. (B magnification $\times 10$, C magnification $\times 20$)

D-F: Immunohistochemistry of the peritoneal metastases reveals strong nuclear expression of S100 (D magnification $\times 20$) and SOX10 (E magnification $\times 20$), along with heterogeneous cytoplasmic expression of Synaptophysin (F magnification $\times 20$).

Discussion

Between 1998 and 2024, 81 cases of small bowel GNETs with relevant clinical data have been reported in the English literature (table 1). More than 60% of patients were younger than 45 years at the time of diagnosis, as was one of our patients [3]. Genders are equally affected in the literature, although both our patients were female [8].

The clinical symptoms include abdominal pain, nausea, obstruction, abdominal distension, bloating, ascites and abdominal mass [3,6,11]. Other nonspecific symptoms include anorexia, weight loss, weakness, anemia and fever [6]. Our two patients were diagnosed because of progressive symptoms of bowel obstruction.

The CT and/or MRI morphological signs of GNETs include irregular masses, thickening of the intestinal wall often associated with bowel obstruction, enlarged lymph nodes and liver metastases as in our two patients [11-14]. These radiological signs are quite similar to those of SI-NET, although these tumors are frequently associated with mesenteric desmoplasia and shrinkage of the mesentery [9].

In contrast to SI-NET, mesenteric desmoplasia associated with GNET is not yet described. This was also the case in the presented two patients, although both had advanced GNET disease. The Ga68-DOTATOC-PET/CT in GNET seems to show heterogeneous expression, but mainly negative or weak somatostatin receptor positivity as in one of our patients, whereas the vast majority of SI-NET show strong positive results [15]. Thus, if a patient with a small bowel tumor and mesenteric lymph node metastases has a normal serum chromogranin A, no radiological signs of a mesenteric desmoplasia and none or only weak somatostatin receptor expression on the Ga68-DOTATOC-PET/CT, then a GNET has to be kept in mind. In addition, as in our two patients about 30% of small bowel GNETs are located in the jejunum. This is in contrast to SI-NENs, which are located in over 90% in the ileum [16-18].

Our systematic review of the literature revealed that 38% (30/78) of patients already had distant metastases at the time of diagnosis (table 1), which is lower than for SI-NEN with around 60% [19,20]. These were present in either the liver or the peritoneum, as in our patients. Bone or lung metastases seem to be rare in GNET in contrast to SI-NET (table 1).

The only chance for cure for small bowel GNET is the resection of the primary tumor with an oncologic, organ-sparing lymphadenectomy as also proposed for SI-NEN [16]. Since the majority of these tumors are located in the jejunum or proximal ileum, this means a segmental small bowel resection, as reported in the literature (table 1) and performed in our two patients. The extent of lymphadenectomy is not defined for GNET. Since these tumors are intraoperatively difficult to distinguish from SI-NET by frozen section, as in our two patients, we propose a systematic bowel-sparing lymphadenectomy up to the inferior border of the pancreas with the dissection of at least 8 lymph nodes as recommended for SI-NEN [9,15]. If ever possible R0 resection of the primary tumor and all metastases should be accomplished, even with two-stage hepatectomy, to prolong survival. This strategy was followed by one of the presented patients, but she died 22 months after diagnosis due to diffuse liver metastases.

The rarity and histological similarities of GNET with other neoplasms can easily lead to a misdiagnosis. The histological appearance of a GNET is heterogeneous, making intraoperative frozen section analysis very challenging for diagnosis. The diagnosis GNET could not be made on frozen section in the presented two patients, the diagnosis remained quite vague. In the vast majority of patients, the diagnosis GNET can only be established postoperatively after immunohistochemical analysis. The typical immunohistochemical markers of a GNET are positivity for S100 and SOX10 proteins, along with negativity for melanocytic markers. Neuroendocrine markers are variable positive. Around 50% of cases exhibit positive staining for synaptophysin and neuron-specific

enolase [21]. Of the 25 cases in the literature that included the evaluation of the expression of at least one neuroendocrine marker (including chromogranin A, synaptophysin, neuron-specific enolase and CD56) immunohistochemically, 19 (76%) were found to express at least one of these markers [8]. The molecular hallmark of the GNET is the gene fusion translocations involving EWSR1, usually EWSR1-CREB1 or EWSR1-ATF1 [6,22], as in our two patients.

Several differential diagnoses can be considered, including NET, GIST, clear cell sarcoma and primary or metastatic melanoma [6,8]. A SI-NET was primarily considered as a differential diagnosis in both of our cases. Although GNET might express neuroendocrine markers, especially synaptophysin and neuron-specific enolase, the EWSR1 rearrangement clearly differentiates it from a neuroendocrine tumor [1]. Metastatic clear cell sarcoma of tendons and aponeuroses is the most important differential diagnosis of GNET [13]. Clear cell sarcoma (CCS) is a rare soft tissue sarcoma and was first described in 1965. The main characteristic of clear cell sarcoma (CCS) is the expression of melanin pigments and melanocytic markers. Both tumors share positivity for S100 protein and SOX10 and exhibit similar genetic abnormalities, including EWSR1 fusions. Lack of melanocytic-associated markers expression is helpful for differentiating GNET [3]. GIST can be also a differential diagnosis, as it may also exhibit epithelioid and spindle cell morphology. The negativity for CD34, CD117 and DOG1, however, supports the diagnosis of GNET [3]. Melanomas, another differential diagnosis, typically occur in older patients, who may have a synchronous or a history of primary cutaneous or acral melanoma, are usually positive for MB-45 or Melan-A and do not have EWSR1 rearrangements [8].

Due to its extreme rarity, prognostic information for GNET is very limited, standardized staging protocols are lacking and there is no consensus on treatment, despite the attempt for curative resection, if ever possible [3]. The presented two patients and 38% (30/78) of reported patients with GNET had stage IV disease at the time of diagnosis, which could not be completely resected (table 1). Because of the rarity of the disease, there are as yet no standardized palliative treatment regimens. Su et al. showed the therapeutic effect of apatinib against this malignancy [23]. Su et al. presented a case with a tumor stage of IV and poor prognosis. The young patient was initially treated with traditional chemotherapy, including gemcitabine plus paclitaxel/gemcitabine plus vinorelbine, which showed progressive disease. Apatinib was administered as a fifth-line therapy. It was given with temozolomide. The overall survival of the young patient from the initiation of treatment with apatinib was 33 months [23]. Apatinib mesylate (hereafter referred to as Apatinib) is a tyrosine kinase inhibitor (TKI), that selectively targets the vascular endothelial growth factor receptor 2 (VEGFR-2) and has shown promising effects in prolonging progression-

free survival (PFS) for a variety of advanced sarcomas after failure of standard multimodal therapy [24].

Subbiah et al. presented a case of a metastatic GNET, which showed a near-complete response to crizotinib and pazopanib for 1.5 years [25]. EWSR1-ATF and EWSR1-CREB1 are both believed to upregulate the mesenchymal-epithelial-transition pathway through the melanocyte transcription factor (MITF), and thus, may create a vulnerability to MET inhibitors [26].

The GNET is highly prone to local recurrence and has a poor prognosis [8]. The time to distant recurrence varied between 2 weeks and 109 months [1]. The median survival was 32 months in one patient series [6]. In another patient series by Chang et al. 5 (33%) patients were alive with tumor recurrence or metastasis, whereas 8 (53%) were alive with no evidence of disease after a median follow-up of 25 months [3]. Our literature review showed that follow-up information was available for 61 patients. The median disease-free survival was 15 months (range 1-161 months).

In conclusion, GNET is an extremely rare tumor of the small bowel which might mimic the clinical symptoms, the radiological appearance and the histological frozen section features of SI-NEN. However, GNET has unique clinical and histopathological features, including absence of mesenteric desmoplasia and presence of EWSR1-ATF1/CREB1 fusions, which establish the diagnosis. Since the prognosis is otherwise dismal, an oncologic organ-sparing small bowel resection with systematic lymphadenectomy and metastasectomy with the goal of a R0 resection should be performed, whenever possible.

Table 1: Characteristics of malignant gastrointestinal neuroectodermal tumor in the small bowel – summary of 81 cases (including the present 2 cases) reported in the world literature [1,3,5,7,11,13,14,22,23,25,27-69].

Parameter	
Age years, median (range)	39 (12-70)
Female gender	37/81 (46%)
Localisation jejunum	22/81 (27%)
Localisation ileum	28/81 (35%)
Unknown (small Intestine)	31/81 (38%)
Distant metastases at diagnosis	30/78 (38%)
EWSR1 Gen Fusions	65/ 81 (80%)
EWSR1- ATF1	25/81 (31%)
EWSR1-CREB1	9/81 (11%)
EWSR1 rearrangements	31/81(38%)
Unknown	16/81 (20%)
Curative treatment intention	53/67 (79%)
Palliative treatment intention	14 /67 (21%)
Operation	78/78 (100%)

SB-resection plus systematic LAD	51/ 78 (65%)
SB resection	18/78 (23%)
Right hemicolectomy	5/78(6%)
Resection of distant metastases	4/78 (5%)
Median follow-up (range), months	21 (1-161)
Median survival (range), months	15 (1-161)
Disease status	
NED	28/81 (35%)
AWD	13/81 (16%)
DOD	19/81 (23%)
DFS	1/81 (1%)
Unknown	20/81 (25%)

SB - small bowel, LAD - lymphadenectomy, NED - no evidence of disease, AWD - alive with disease, DOD - dead of disease, DFS - disease-free survival

Conflicts of interest

The authors declare no conflict of interest.

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