Duodenal neuroendocrine tumors (d-NETs): challenges in diagnosis and treatment

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Abstract
Duodenal neuroendocrine tumors (d-NETs) represent 2% of all gastroenteropancreatic neuroendocrine neoplasms. Approximately 40 to 60% of patients at the time of diagnosis have metastases to regional lymph nodes and 10% have liver metastases. D-NETs are mostly incidentally discovered during upper gastrointestinal endoscopy as solitary lesions confined to the mucosa and submucosa. The majority of d-NETs are non-functional, but 10% are gastrinomas and less than 4% present with typical carcinoid syndrome. Measurement of serum gastrin and chromogranin A and screening for the MEN-1 syndrome is mandatory in all patients, while 5-HIAA should be measured only in case of typical symptoms. Magnetic resonance imaging (MRI) may be used to assess tumor spread and to detect primary tumor. Endoscopic ultrasound should be routinely used only for patients who are candidates for endoscopic treatment. Approximately 50% of patients have positive findings on somatostatin receptor scintigraphy (SRS), which should be used only in patients with metastatic disease. Treatment of d-NETs is controversial. Further studies are mandatory in order to detect patients who would benefit from radical surgery, which is associated with high mortality and morbidity rates. Current knowledge suggests that all tumors larger than 20 mm in diameter, sporadic gastrinomas and all periampulary dNETs must undergo radical surgery. Endoscopic mucosal resection is treatment of choice for G1 d-NETs smaller than 20 mm confined to submucosa. Transduodenal surgical resection may be used for patients with d-NETs invading muscularis propria. Additional surgical interventions are recommended after endoscopic treatment in case of G1 or G2 d-NETs with positive margins, G2 or G3 histological grading, invasion into muscular layer or in case of lymphovascular invasion. In case of metastatic disease, cytoreductive surgery should be considered as it improves overall 5-year survival rates. Somatostatin analogs may be used for G1 and G2 tumors, while cisplatin and etoposide should be used for G3 d-NETs. Everolimus may be effective for patients with G2 d-NETs. Peptide receptor radionuclide therapy may be used for patients with positive SRS and progressive disease.

Keywords: duodenal neuroendocrine tumors, classification, endoscopic resection, surgical treatment, liver transplantation.
1. Introduction

Neuroendocrine tumors (NETs) of the gastroenteropancreatic (GEP) system are defined as epithelial neoplasms with predominant neuroendocrine differentiation.

Most GEP-NETs are slow-growing neoplasms with significantly increased incidence rates in the last 40 year due to rapid advance in diagnostic procedures. The age-adjusted incidence of GEP-NETs has increased over the past four decades [1]. Small intestine NETs (SI-NETs) have been the most common GEP-NETs for many years [2], until recently, when they were surpassed by rectal NETs [3]. On the basis of gene expression profiles, NETs of the duodenum are considered a distinct entity from tumors of jejunum and ileum [4,5]. D-NETs are mostly non-functional and often discovered incidentally during a routine upper gastrointestinal endoscopy for other indications [5]. Although primary d-NETs are rare, slow growing neoplasms with indolent clinical behavior, they can be potentially malignant [6]. These tumors tend to spread to the submucosal layer even during the early stages of the disease, so the treatment of choice for localized disease is still debated. Moreover, prospective trials analyzing the efficacy of systemic treatment options are still lacking.

In this review, we will focus on the overall knowledge of d-NETs with regard to their clinical characteristics, diagnosis and endoscopic and surgical treatment.

2. Characteristics of d-NETs

Neuroendocrine tumors of the duodenum (d-NETs) present 2% of GEP-NETs and 1 to 3% of all duodenal tumors [7]. They most commonly occur in the 6th decade of life with male predominance [8]. According to the secretory activity, they can be functional or non-functional. In 90% of cases these tumors are non-functional and are often discovered incidentally during upper endoscopy that is being carried out for other indications [5]. Although primary d-NETs are rare, slow growing neoplasms with indolent clinical behavior, they can be potentially malignant [6]. These tumors tend to spread to the submucosal layer even during the early stages of the disease, so the treatment of choice for localized disease is still debated. Moreover, prospective trials analyzing the efficacy of systemic treatment options are still lacking.

In this review, we will focus on the overall knowledge of d-NETs with regard to their clinical characteristics, diagnosis and endoscopic and surgical treatment.

3. Clinical features

D-NETs include duodenal gastrinoma, duodenal somatostatinoma, non-functional duodenal NET, duodenal gangliocytic paraganglioma and poorly differentiated neuroendocrine duodenal carcinoma. [7,8]. These tumors usually present with symptoms of abdominal pain, nausea, vomiting, diarrhea, jaundice and mechanical ileus.

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D-NETs are usually non-functional, sporadic and well-differentiated slow-growing tumors [13]. Non-functional d-NETs are mostly incidentally discovered during an upper gastrointestinal endoscopy. The most common symptoms that lead to diagnostic work-up are abdominal pain (37%), upper gastrointestinal bleeding (21%), anemia (21%) and jaundice (18%) [14]. Functioning NETs are characterized by the presence of clinical symptoms due to excess hormone secretion by the tumor. The most common functional d-NET is gastrinoma. Although gastrinomas can occur at any age, the initial clinical manifestation usually appears in people aged 30-50 years [15]. These tumors over-secrete gastrin, which stimulates the acid-secreting cells leading to hyperacidity. Hyperacidity promotes chronic gastritis and gastrointestinal mucosal ulceration, all which are called Zollinger-Ellison syndrome (ZES). ZES usually presents with abdominal pain, diarrhea and reflux esophagitis. One fourth of gastrinomas are related to MEN 1 syndrome [16]. While sporadic usually result from single lesion, in MEN 1 represent like multiple lesions [16].

Over 50% of gastrinomas metastasize to regional lymph nodes and the liver [15]. The diagnosis of gastrinoma
can be established if the fasting serum gastrin is 1000 ng/L or greater and gastric pH is less than 2.5 [17]. It should be stressed out that the diagnosis of gastrinoma cannot be established solely by positive immunostaining for gastrin, although this is mandatory to confirm the diagnosis in patients that fulfill previously mentioned criteria.

The second most common functional tumors are duodenal somatostatinomas which are rare NETs. The pancreas is the most common site of somatostatinoma (68%), followed by the duodenum (19%), ampulla of Vater (3%), and small intestine (3%) [18]. Duodenal somatostatinomas are more often associated with non-specific symptoms and neurofibromatosis, but less often with somatostatinoma syndrome or metastasis. The classic somatostatin syndrome presenting with diarrhea, diabetes and biliary lithiasis is rare. This syndrome may occur only with pancreatic somatostatinomas or extrapancreatic tumors larger than 4 cm [19]. Although typical somatostatinomas are large, solitary, malignant tumors that are often discovered with lymph node or liver metastases at the time of diagnosis, duodenal somatostatinomas are mostly well-differentiated tumours [20].

Gangliocytic paragangliomas are rare and mostly have indolent course of the disease [21]. Their typical histology appearance consists of 3 cell types-epithelioid, spindle and ganglion cells. These tumours occur most frequently in the second portion of the duodenum, near the ampulla of Vater [21]. The clinical features vary from an incidental finding at endoscopy to upper gastrointestinal bleeding and abdominal pain. The most common presentation is gastrointestinal hemorrhage, which occurs in 44% of patients and is caused by submucosal erosion and ulceration at the site of the tumor [21].

Poorly differentiated neuroendocrine carcinomas of the duodenum (d-NEC) are very aggressive tumors, diagnosed in advanced stage of the disease with lymph node or liver metastases. Their clinical behavior is similar to that of small cell carcinoma of the lung [22]. D-NEC represent 6 - 8% of all d-NETs and are primarily located in periampullary region [22]. These tumors are mostly non-functional and may not cause any signs or symptoms in early stage of the disease. Symptoms appear once the tumour grows into surrounding tissues. Early symptoms may be non-specific, which makes NEC hard to diagnose. Symptoms of NEC can include: persistent pain in a specific area, changes in bowel habits, unexplained weight gain or loss, jaundice, gastrointestinal bleeding etc.

Periampullary tumors are more aggressive tumors regardless of their histology and grade. Tumor size doesn’t correlate with the depth of invasion, the presence of metastases and overall survival [23]. These tumors present with jaundice, progressive weight loss, dull abdominal pain, dyspepsia and vomiting in case of duodenal stenosis. Other symptoms include gastrointestinal bleeding and acute pancreatitis. Periampullary d-NETs are often associated with Recklinghausen’s disease [24].

Carcinoid syndrome is generally rare in patients with d-NETs. Even in patients with serotonin-producing d-NETs, carcinoid syndrome becomes clinically evident in patients with liver metastasis, when secreted serotonin enters the systemic circulation escaping hepatic degradation [25]. Patients can present with flushing, diarrhea, cough due to bronchoconstriction and secondary restrictive cardiomyopathy which is caused by serotonin-induced fibrosis of the valvular endocardium, notably the tricuspid and pulmonary valves.

4. Classification and prognosis of NETs

In 2010, the World Health Organization (WHO) updated its classification of NETs based on the histopathology of the tumor and the assessment of proliferation fraction and/or mitotic count.

Classical histological features and positive immunostaining for two neuroendocrine markers, usually chromogranin A and synaptophysin, are mandatory to establish the diagnosis of NET regardless of the primary tumor site.

The proliferative rate of the neoplasm is the most important feature used for grading (G) [26]. It is assessed as the percentage of neoplastic cells showing
positive immunostaining for the proliferation marker Ki-67 (the Ki-67 index) and by counting mitotic figures. At least 500 tumor cells are needed and it is evaluated in areas of highest mitotic density. Mitoses are counted on 50 high-power microscopic fields (HPFs) and are assigned as count per 10 HPF. Tumors with higher Ki-67 expression are associated with worse prognosis. Childs et al. concluded that response to chemotherapy increases with Ki-67 index but Ki-67 alone is not reliable parameter to select patients for this form of treatment [27].

Table 1. Classification of neuroendocrine tumors.

<table>
<thead>
<tr>
<th>Histological classification</th>
<th>Well differentiated (low grade, G1)</th>
<th>Moderately differentiated (intermediate grade, G2)</th>
<th>Poorly differentiated (high grade, G3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prognosis</td>
<td>prolonged survival</td>
<td>intermediate</td>
<td>poor</td>
</tr>
<tr>
<td>Mitotic rate (per 10HPF)</td>
<td>&lt;2</td>
<td>2-20</td>
<td>&gt;20</td>
</tr>
<tr>
<td>Ki-67 index</td>
<td>&lt;3%</td>
<td>3-20%</td>
<td>&gt;20%</td>
</tr>
</tbody>
</table>

Van Velthuysen et al. investigated which of the two indexes (Ki-67 index or mitoses) is most informative to predict survival. They assessed 362 patients with GEP-NETs, NETs of lung and unknown primary site. Results showed discordances in these indexes in one third of cases; survival for the most part was associated with a higher index level, mostly Ki-67 [26].

The World Health Organization (WHO) classification places NETs into three main categories, which emphasize the tumor grade rather than the anatomical origin (Table 1).

The classification categorizes NETs as either well-differentiated (grade 1 and 2) neuroendocrine tumors and poorly differentiated neuroendocrine carcinomas (grade 3).

Grading system correlates well with the pathological classification. For instance, approximately 85% of patients with G1 and G2 tumors are well-differentiated [28]. Most recently, G3 NETs presenting with a well-differentiated morphology have been suggested to be classified separately as well-differentiated grade 3 NETs [29].

The European Neuroendocrine Tumor Society (ENETS) and the American Joint Committee on Cancer (AJCC) stage NET by using the tumor-node-metastasis (TNM) system, similar to other types of carcinomas [28]. The 2010 WHO classification guidelines also incorporate TNM staging.

Patients with well-differentiated d-NETs (G1) have a 5-year survival rate of 80 to 85% while patients with well-differentiated NEC (G2) have a 5-year survival rate of 72% [30].

Survival rates vary between 65 and 75% in case of lymph node involvement and 20 - 40% in patients with liver metastases [31]. D-NETs metastasize to the liver or distant sites in less than 10% of cases [32]. Patients with gastrinomas have lymph node metastases 11 - 50%, while distant metastases are present in less than 6%-10% of cases [15]. There is an ongoing debate regarding new classification of NETs. It has been suggested that a Ki67 cut-off value of 5% should separate G1 and G2 NETs, since it has better prognostic accuracy. Moreover, G3 NETs should also be divided into two groups according to Ki67: G3a (Ki67 21 – 55%) and G3b (Ki67 > 55%) [29]. All of these changes would imply the change of classification of d-NETs.

In conclusion, the diagnosis of d-NET is based on the presence of positive immunostaining for chromogranin A and synaptophysin. Ki67 immunostaining is mandatory for all NET findings, in order to make proper classification, which is important for making decisions regarding diagnostic procedures, treatment and follow-up.

5. Biochemical monitoring

Due to NETs ability to synthesize and release peptide hormones and the monoamine neurotransmitters, sensitive assays for the measurement of these substances have been developed. Biochemical markers may have important diagnostic, predictive and prognostic role [33].
5.1. Chromogranin A (CgA)

Chromogranin A (CgA) is a protein contained in the neurosecretory vesicles of neuroendocrine tumor cells no matter of tumor secretory activity and localization of the primary tumor. Serum CgA is elevated in 56-100% of d-NETs and positively correlates with metastatic disease and overall tumor burden [34]. Excessive secretion of CgA is mediated by IGF-1 receptor activation of the Arf 1 protein from the Golgy apparatus [35]. Sensitivity and specificity of CgA for the detection of NETs is 68% and 86%, respectively [36]. However, falsely elevated CgA levels are associated with several clinical conditions: liver, heart and renal failure, chronic inflammatory diseases, arterial hypertension and the use of proton pumps inhibitors. The presence of these conditions has substantial impact of the diagnostic accuracy of serum CgA, although studies in real-life setting have not been performed. Therefore, CgA is not recommended as a diagnostic marker for NETs [34]. However, baseline CgA levels may be used as independent prognostic factor, the decrease in CgA levels right after the treatment may predict long-term treatment efficacy and the increase of CgA in patients who achieved remission may be indicative for tumor recurrence of dissemination [34]. Patients with poorly differentiated NEC may have normal CgA levels [37]. Serum CgA is a more sensitive tumor marker than urinary 5-hydroxyindoleacetic acid (5-HIAA) as its secretion doesn’t depend on serotonin secretion. But consequently, urinary 5-HIAA has higher specificity in diagnosing NETs.

5.2. Urinary 5-HIAA

5-HIAA is an important tumor marker and is mandatory to make the diagnosis of carcinoid syndrome. A 24-hour urine sample is preferred for the 5-HIAA test because the level of the metabolite can vary during the day. Recent studies have showed that plasma fasting 5-HIAA values are proportional to urinary 5-HIAA values [38], but this assay is not routinely used in everyday clinical practice. Measurement of 5-HIAA has a sensitivity of 64% and a specificity of 98% in diagnosis of NETs [39]. There is a good correlation between tumor mass and urinary 5-HIAA levels, both in functional and non-functional tumors [39]. Expectedly, patients with carcinoid syndrome have substantially higher 5-HIAA levels, but 5-HIAA may have diagnostic role in non-functional tumors as well. The consumption of tryptophan-serotonin-rich foods may lead to falsely increased urinary 5-HIAA. The normal rate of 5-HIAA excretion ranges from 2 to 8 mg (10 to 42 micromol) per day [41]. Most patients with advanced functional NETs have values above 100 mg (523 micromol) per day [41]. 5-HIAA does not correlate with treatment response and therefore has no prognostic value in patients with advanced NETs [42]. Routine measurement of 5-HIAA in patients with d-NETs is not recommended and should be performed only in patients with symptoms and signs of carcinoid syndrome.

5.3. Neuron - specific enolase (NSE)

NSE is an enzyme that is present in the cytoplasm of most neuroendocrine cells and just like CgA is not associated with tumor secretory activity. This marker is useful for the follow-up and monitoring of patients with NETs. NSE is not specific marker due to its presence in other tumors such as fibroadenomas of the breast, carcinomas, and lymphomas. The sensitivity and specificity of NSE in diagnosis of NETs ranges from 33% to 100% [43]. Patients with G3 NECs have the highest diagnostic accuracy of serum NSE. Therefore, serum NSE should be measured in all patients with G3 NETs and NECs. This marker is indicative for diagnosis of NETs but it is not used as prognostic indicator or determination of disease progression [44].

5.4. Other markers

Serum markers, such as alfa-fetoprotein (AFP) and human chorionic gonadotropin (hCG) are elevated in some patients with NETs but their clinical utility has not been demonstrated.

Pancreatic neuroendocrine tumors (p-NET) can be revealed determining variety of peptide hormones: insulin, gastrin, glucagon, and vasoactive intestinal peptide (VIP) although they are in 75% of cases non-functioning tumors. Pancreatic polypeptide is another nonspecific biochemical marker for non-functioning p-NETs, but it has a relatively low sensitivity when used alone [45,46]. However, these markers should not be used routinely in patients with d-NETs.
A National Cancer Institute Neuroendocrine Tumor summit conference held in 2007 on NETs noted biomarker limitations to be a crucial unmet need in the management of these tumors as broad spectrum markers such as CgA have limitations in sensitivity, specificity and reproducibility [47]. There are studies aimed to investigate novel potential biomarkers to guide management of NETs as well as determine disease aggressiveness and predict treatment response. Recent studies investigate multiple molecular markers like gene transcripts, miRNA and circulating tumor cells that will more accurately monitor the efficacy of therapy and provide prognostic assessment [47].

Miller et al. represented the largest global miRNA profiling of small bowel NETs which have the potential to act as biomarkers but further studies to define molecular mechanisms and validate these miRNA are needed [48]. Andersson et al. have defined specific gene expression patterns associated with tumor grade and chromosomal alteration transcriptome of small bowel NETs as novel prognostic biomarkers [49]. Darmanis et al. proposed a new potential protein biomarker for classifying well-differentiated small intestinal NETs but further investigations of these proteins in larger sample sets are needed [50].

In conclusion, chromogranin A and gastrin should be measured in all patients with d-NETs. Serum NSE should be measured in all patients with d-NEC and G3 d-NETs should. 5-HIAA should be measured only in patients with signs and symptoms of carcinoid syndrome. Patients with serum gastrin >1000 ng/L should undergo ph-metry and the status of parietal cell antibodies should be obtained. This is important in order to classify the functional status of d-NETs. Measurement of serum calcium, parathyroid hormone, prolactin, IGF-I, ACTH, urinary-free cortisol should be made in all patients as screening for MEN-1 syndrome.

6. Diagnosis of d-NETs

Upper gastrointestinal endoscopy with biopsies represents the gold standard in the diagnosis of d-NETs. The pathologic diagnosis is therefore established according to histological morphology and architectural pattern of NETs, as well as immunohistochemical staining, as described previously in the text.

Endoscopic ultrasonography (EUS) has an important role in assessing the depth of tumor invasion and lymph node assessment. EUS can detect tumors located in the submucosa that can not be seen during upper endoscopy. The ability to perform ultrasound guided fine-needle aspiration (FNA) for d-NETs in deeper layers is another advantage of EUS. The majority of d-NETs have a well-defined hypoechoic and relatively homogeneous pattern on EUS [51,52]. Computed tomography (CT) and magnetic resonance imaging (MRI) have an important role in monitoring patients with advanced GEP-NETs. However, their ability to locate the primary tumor is limited. These methods can detect tumors less than 1 cm in diameter in 15% of cases, 1 to 3 cm in diameter in 20-50% of cases and larger than 3 cm in 95% of cases [53].

CT scans are often the initial imaging study for a patient presenting with signs or symptoms suggestive of a NET. There are no studies comparing the effectiveness of CT and MRI in detecting primary d-NETs and liver metastases. However, according to European Neuroendocrine Tumor Society (ENETS) guidelines, MRI is considered superior for the detection and follow-up of both primary tumors and liver metastases when compared to CT [54]. The main advantage of MRI is the use of diffusion-weighted sequences, which have very high sensitivity and low specificity. Therefore, MRI with diffusion-weighted sequences should be used in patients with d-NETs.

Conventional imaging and functional imaging methods are often unable to detect d-NETs due to small lesion size. Therefore, functional imaging plays a crucial role in management of d-NETs. The majority of GEP-NETs express high concentrations of somatostatin receptors and can be visualised using a somatostatin receptor scintigraphy (SRS) with 111-Indium pentetreotide or 99-Tecnethium tectrotide. SRS is widely used for NETs staging, follow- and for selection of patients for peptide receptor radionuclide therapy (PRRT) [55].

Positron emission tomography/computed tomography (PET/CT) with 68Gallium (68Ga)-labeled somatostatin analogues has shown excellent results for imaging
of NETs and superiority over conventional SRS [56]. 68Ga-labeled somatostatin analogues are peptide analogues of somatostatin which are linked to the positron emitter 68Ga by a bifunctional chelate, usually 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA). Three major 68Ga-DOTA-peptides are currently available for imaging: 68Ga-DOTA-Phe1-Tyr3-Octreotide (TOC), 68Ga-DOTA-NaI3-Octreotide (NOC), and 68Ga-DOTA-Tyr3-Octreotate (TATE). The main difference among these three tracers is their high affinity to somatostatin receptors. For instance, 68Ga-DOTA peptides have about ten-fold higher affinity for somatostatin receptors when compared to 111In-Octreotide, meaning that the tumors with decreased expression of somatostatin receptors would also have positive findings. Moreover, the use of positron emission tomography increases the resolution of the image, which consequently leads to higher diagnostic accuracy [57]. 68Ga-DOTA peptide PET/CT has significantly higher detection rates for small lymph nodes and bone metastasis in comparison with single-photon emission computed tomography (SPECT) and CT [57]. This nuclear method has an important role in localizing primary tumors, metastases and in patients’ follow-up.

18F-deoxyglucose (FDG)-PET has significant uptake only in poorly differentiated tumors [58] and it should be performed only if SRS is negative [58]. However, some centers perform both 18F-FDG and 68Ga-DOTANOC PET/CT in patients with metastatic NETs in order to obtain more information about therapeutic strategy and prognosis, since patients with FDG positive tumors have low efficacy of treatment with somatostatin analogues [59].

In conclusion, MRI should be used for assessing the presence of metastatic disease in patients with established diagnosis of d-NET, but also to find primary tumors in patients with biochemical criteria for gastrinoma. SRS or 68Ga-DOTA peptide PET/CT should be used in all patients with positive or inconclusive MRI and G1 and G2 dNETs. The use of 18F-deoxyglucose (FDG) PET is mandatory in all patients with G3 d-NETs and is optional for patients with G1 and G2 tumors. EUS is of limited value in detection of the primary tumor, but should be used in all patients with visible tumors before making treatment decisions.

7. Treatment of d-NETs

Clinical course of d-NETs varies from benign tumors with low metastatic capacity to high metastatic capacity but indolent clinical course and very aggressive tumors with poor prognosis. Tumor size, morphology, Ki67 and functional status failed as reliable predictive and prognostic factors. Due to unpredictable behaviour and low incidence of d-NETs, treatment strategies remain uncertain.

7.1. Endoscopic treatment

D-NETs are mostly presented as solitary lesions confined to the mucosa and submucosa and therefore are available for endoscopic treatment. Initial biopsy is needed to provide the diagnosis of these tumors before starting with treatment. According to current recommendations, endoscopic resection is used for treatment of well differentiated non-functional dNETs (G1) smaller than 10 mm in diameter, which are confined to mucosa or submucosa [51].

EUS is used to assess the depth of tumor invasion and the involvement of surrounding structures. Endoscopic methods available in treatment of d-NETs are: endoscopic polypectomy, endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). Depending on the technique applied, EMR can be subdivided into EMR with ligation, EMR with circumferential precutting and EMR with a cap [51]. EMR is more often applied than ESD, because it is easier to perform with lower complication rates [51]. Endoscopic mucosal resection with circumferential mucosal incision (EMR-CMI) using SB knife with an additional submucosal injection of hyaluronic acid solution given beneath the lesions is also an effective method for treatment of d-NETs less than 10 mm in the absence of local or distant metastases [60]. Endoscopic resection with polypectomy or strip biopsy can be associated with crush injury of the resected specimens [60]. EMR with band ligation has a risk of muscular involvement [60]. EMR technique is successful and safe for most small d-NETs measuring less than 1 cm in diameter that are superficial, reaching only up to the submucosal layer [61]. Complete resection may not always be easy to achieve by using EMR because most d-NETs are not confined to the mucosa.
Table 2. An overview of studies that report outcomes of endoscopic treatment of d-NETs

<table>
<thead>
<tr>
<th>Authors</th>
<th>No. of patients</th>
<th>Treatment</th>
<th>Tumor size (mm)</th>
<th>Follow-up (months)</th>
<th>Remission rates (%)</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yokoyama S (67)</td>
<td>4</td>
<td>EMR</td>
<td>12 ± 1</td>
<td>49</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Otaki Y (60)</td>
<td>5</td>
<td>EMR-CMI</td>
<td>4.6 ± 1.8</td>
<td>NA</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Matsumoto (63)</td>
<td>13</td>
<td>ESD</td>
<td>12.7 ± 14.8</td>
<td>NA</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Min BH (65)</td>
<td>11</td>
<td>EMR, APC</td>
<td>≤10</td>
<td>37</td>
<td>91</td>
<td>100</td>
</tr>
<tr>
<td>Kim GH (61)</td>
<td>41</td>
<td>EMR, EMR-L, EMR-CMI, ESD</td>
<td>≤10</td>
<td>17</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Matsumoto (64)</td>
<td>9</td>
<td>ESD 7, EMR 2</td>
<td>NA</td>
<td>10</td>
<td>98</td>
<td>100</td>
</tr>
<tr>
<td>Kim SH (51)</td>
<td>14</td>
<td>EMR, ESD, surgical treatment</td>
<td>8.4±1.7</td>
<td>16</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Zyromski NJ (66)</td>
<td>19</td>
<td>Endoscopic or transduodenal resection</td>
<td>&lt; 20</td>
<td>24 -108</td>
<td>95</td>
<td>100</td>
</tr>
</tbody>
</table>

EMR-c - endoscopic mucosal resection + using a cap-fitted endoscope; ESD - endoscopic submucosal dissection; APC - argon plasma coagulation; EMR-CMI - endoscopic mucosal resection with circumferential mucosal incision; EMR-L: endoscopic mucosal resection with a ligation device; NA – not analyzed

However, pathological complete resection may not correlate with endoscopic complete resection. In a study by Kim et al. which included patients with non-periampullary dNETs smaller than 10 mm, complete pathological resection was achieved in 41% of patients, while 98% of patients achieved endoscopic resection. Interestingly, complete pathological resection did not correlate very well, since neither one patient had endoscopic signs of local tumor recurrence or metastases during a median of 17 months of follow-up.

ESD involves circumferential cutting of the mucosa surrounding the tumor followed by dissection of the submucosa under the lesion. ESD can achieve complete en bloc resection, which refers to a resection in one piece, and consequently no need for additional surgery [62].

Li et al. retrospectively evaluated the feasibility and efficacy of ESD for d-NETs.

Their study included 24 patients who were treated with ESD. None had regional lymph node enlargement or distant metastases. Mean diameter of the lesions was 9.4 mm and all tumors were confined to the submucosa. Their study confirmed that ESD showed a high histologically complete resection rate and provided accurate histopathological evaluation [62]. However, the majority of patients with tumors >10 mm, required additional surgery.
EDS is technically difficult and it is associated with a higher risk of bleeding and perforation.

Matsumoto et al. retrospectively compared EMR and ESD for treatment of d-NETs [63]. They reported that ESD may be indicated for well-differentiated intramucosal NETs measuring less than 1 cm in diameter and not invading deeper than the submucosal layer [63]. ESD may be preferable for endoscopic treatment of NETs if en block resection is required as the studies showed that en bloc resection by EMR is difficult [63].

Ligation-assisted endoscopic submucosal resection (ESMR-L) with circumferential mucosal incision (CMI) may be effective in cases with substantial fibrosis of the submucosa. This technique has minimal burning effect on the cutting margin, because the tumor is cut by snare beneath the rubber band. Further investigations are warranted to compare these procedures [64]. Min et al. showed that conservative management with close follow-up may represent an alternative to endoscopic treatment in patients with multiple comorbidities who have tumors less than 10 mm in diameter outside the periampullary region [65]. In the previously mentioned study, 13 patients with d-NETs <10 mm were only followed for a median of 37 months. Neither one patient experienced tumor enlargement nor metastases, while d-NETs disappeared in 5 patients.

There is an ongoing debate for treatment of patients with d-NETs measuring 10-20 mm [51]. Zyromski et al. suggested open transduodenal excision for tumors between 10 and 20 mm will ensure complete resection with low complication rates [66]. Yokoama et al. reported that patients with d-NETs larger than 10 mm in diameter could be treated endoscopically if the tumor is confined to the submucosal layer confirmed by EUS and with no signs of lymph node involvement [67]. However, it should be noted that there is no evidence-based data confirming the most suitable treatment option for this group of tumors.

Most reports have shown that a tumor diameter greater than 2 cm is associates with metastatic risk [67]. However, evidence exists that d-NETs less than 10 mm can also develop metastases [60]. Burke et al. showed that the features associated with increased risk of metastasis are tumor size larger than 20 mm, involvement of muscularis propria and presence of mitotic figures [68].

Endoscopic resection for non-ampullary d-NETs has a risk of delayed perforation, especially if lesions are located distal from the ampulla and if ESD or piecemeal EMR methods are used [69]. It is recommended that patients must undergo follow-up endoscopy and/ or EUS at 1, 3, 6 and 12 months after ESD and annually thereafter to evaluate for any residual tumor or recurrence [69]. Other imaging methods in monitoring of these patients are abdominal ultrasound, chest radiography, computerized tomography (CT) or magnetic resonance imaging (MRI).

There is a consensus that tumors larger than 20 mm in diameter and all sporadic gastrinomas must be treated surgically [51]. Additional surgical interventions are recommended after endoscopic methods in the case of G1 or G2 d-NETs with positive margins, G2-G3 histological grading and invasion into muscular layer or vessel infiltration of tumor cells [62].

An overview of endoscopic treatment in patients with d-NETs are presented in table 2. Overall, studies that analyzed the outcomes of patients with dNETs are very heterogenous. They included relatively small number of patients, who were treated with different endoscopic procedures. Majority of studies did not report Ki67 or mitotic index. Therefore, comparisons between studies are impossible and conclusions are limited.

### 7.2. Surgical treatment of d-NETs

Although there is a lack of randomised trials about the role of laparoscopy for d-NETs, there is some evidence to show that laparoscopy provides certain advantages; for example reduced risk of external contamination compared with open surgery, reduced risk of post-operative infection and shorter length of hospital stay. Moreover, laparoscopy is a safe and beneficial method for exact localizing the tumor which earlier imaging methods failed to detect [70].

Tsujimoto et al. described endoscopic full-thickness
resection of the duodenum under laparoscopic observation as a safe surgical procedure for small d-NETs, which may be complementary to endoscopic resection [71]. Recent case study showed that laparoscopy-assisted endoscopic full-thickness resection with lymphadenectomy (LAEFR) may be a minimally invasive and effective treatment for non-periampullary duodenal lesions [72]. Tsushimi et al. reported a case of d-NET G1 resected by laparoscopic and endoscopic cooperative surgery (LECS) technique. They concluded that this method is appropriate for early duodenal G1 NETs in cases when previous endoscopic methods did not achieve success [73].

Sentinel node navigation surgery (SNNS) has been developed as a promising surgical option to avoid unnecessary lymphadenectomy in patients with gastro-duodenal NETs [74]. This method can detect the clinical undetectable lymph node metastasis, which may lead to individualized, less invasive surgical approach [74]. For detecting the sentinel node, Arigami et al. used radioisotope tracer- technetium-tin colloid including indocyanine green, which was injected around the primary tumor the day before surgery. Sentinel nodes were then identified by Navigator GPS and infrared fluorescence imaging during laparoscopic surgery [74].

A radical resection should be considered for tumors > 2 cm [70]. Most commonly used surgical approaches include duodenopancreatectomy or Whipple procedure, pylorus-preserving duodenopancreatectomy and segmental distal duodenectomy. Recent studies showed that specialised centers can perform a duodenopancreatectomy laparoscopically with low surgical mortality (5%) and acceptable morbidity (20-30%) [70]. However, even after the complete surgical resection, tumors larger than 2 cm in diameter often recur [66].

Non-ampullary dNETs and ampullary dNETs differ in clinical features and consequently in treatment approach. For non-ampullary dNETs smaller than 1 cm in diameter, transduodenal resection is favorable to endoscopic resection. Ampullary dNETs are more aggressive tumors and their tumor size doesn’t

### Table 3. An overview of studies that report outcomes of surgical treatment of d-NETs

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of patients</th>
<th>Type</th>
<th>Tumorsize (mm)</th>
<th>Surgical method</th>
<th>Follow-up (months)</th>
<th>Remission rates (%)</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hwang S (24)</td>
<td>10</td>
<td>aNETs</td>
<td>20.1 ± 13.0</td>
<td>PD, PPPD</td>
<td>36</td>
<td>NA</td>
<td>64</td>
</tr>
<tr>
<td>Witzigmann H (75)</td>
<td>6, 6</td>
<td>NaNETs, aNET</td>
<td>&lt; 6, 15 - 40</td>
<td>PD, AM</td>
<td>NA</td>
<td>NA, NA</td>
<td>50, 67</td>
</tr>
<tr>
<td>Hamy A (18)</td>
<td>12</td>
<td>Somatostatinoma</td>
<td>27 (4 – 60)</td>
<td>PD, SBR, IG, GJ</td>
<td>84</td>
<td>75</td>
<td>67</td>
</tr>
<tr>
<td>Atema JJ (76)</td>
<td>11</td>
<td>Gastrinoma</td>
<td>NA</td>
<td>PPPD, DT, CP</td>
<td>36</td>
<td>64</td>
<td>90</td>
</tr>
<tr>
<td>Zyromski NJ (66)</td>
<td>4</td>
<td>NaNETs</td>
<td>&gt; 20</td>
<td>PD, DT</td>
<td>24 -108</td>
<td>0</td>
<td>100</td>
</tr>
</tbody>
</table>

PD - pancreaticoduodenectomy; PPPD - pylorus-preserving pancreaticoduodenectomy; AM – ampulectomy; SBR - small bowel resection; IG - inferior gastrectomy; GJ - gastrojejunostomy; DT- duodenectomy; CP- central pancreatectomy; NaNTs- non-ampullary NETs; aNTs-ampullary NETs
correlate with the depth of invasion, the presence of metastatic disease and overall survival [75]. It is considered that the Kausch-Whipple procedure or pylorus-preserving pancreaticoduodenectomy is the treatment of choice for all ampullary dNETs [75]. Although surgical resection is the mainstay of treatment, to date no studies have been done to establish optimal management of these tumors.

Gastrinomas are the most common functional d-NETs. These tumors are frequently small and multiple. More than 80% of gastrinomas are found in the gastrinoma triangle which includes the duodenum, the pancreatic head and hepatoduodenal ligament. Approximately 50 to 70% of gastrinomas in pancreas have lymph node metastases at the time of diagnosis [76]. Some studies suggest that SRS is more sensitive than conventional imaging methods for localizing these tumors [76]. All patients with gastrinomas and localized disease (absence of liver metastases) should be treated by radical surgery. Recurrence rates go up to 30% [67]. Patients with biochemical evidence of primary hypergastrinemia in whom imaging techniques failed to localize primary tumor, should undergo explorative duodenectomy [76].

An overview of surgical procedures used for d-NETs is presented in table 3. Studies reporting outcomes of surgical treatment of d-NETs are scarce, small and heterogeneous. Studies included patients with functional, non-functional, ampullary and non-ampullary d-NETs. Therefore, it is hard to make any comparisons and draw valid conclusions. However, there are some indices that radical surgery should be used only in selected patients, because it is associated with high rates of perioperative complications and long-term morbidity. For instance, overall survival in 6 patients with non-periampullary d-NETs smaller than 6 mm was only 50%. On the other hand, patients with d-NETs > 10 mm who treated endoscopically, had an overall survival of 100%. Therefore, further studies are mandatory in order to detect patients who would benefit from radical surgery, which is associated with high mortality and morbidity rates.

7.3. Surgical treatment of liver metastases in patients with NETs

d-NETs have a low rate of distant metastases (9-15%) and therefore a high postoperative survival rate (83.3%) [70]. Although complete surgical resection is the optimal therapy for patients with metastatic hepatic NETs, other alternative treatment options include: thermal ablative techniques [radiofrequency ablation (RFA), microwave ablation, cryotherapy], embolisation using transcatheter embolisation, transarterial chemoembolisation (TACE) and transarterial radioembolisation (TARE).

Laparoscopic RFA is suggested when other treatment options failed. It offers effective local tumor destruction in appropriately selected lesions and reduces morbidity and mortality of an open resection [77]. Akyildiz et al. proposed criteria for selection of candidates for laparoscopic RFA: maximum tumor size 10 cm or less, maximum number of metastases 15 or less and less than 20% liver involvement [77].

Singla et al. reported that Ki-67 score is a potential predictor in selection of liver-directed therapies (TACE and TARE) for patients with metastatic NETs. In their study, patients with Ki-67 ≥ 3% had greater benefit with TARE, while patients with Ki-67 < 3% had greater benefit with TACE [78].

Aggressive surgical management of primary tumor and liver metastases improve overall 5-year survival rates [79]. Debulking surgery should be considered if more than 90% of the tumor mass can be removed. Laparoscopic liver resection has lower recurrence rate and peri/postoperative complications compered to open liver resection [80]. Previous studies have shown that long-term results of laparoscopy are equivalent to those of open surgery [81].

Due to exceedingly high tumor recurrence rate, liver transplantation should not be performed in these patients [82]. Grat et al. reported that Ki67 > 2% is associated with significantly worse disease free survival, while the extent of liver involvement, primary tumor site and recipient age were not significantly associated with the progression–free survival after liver transplantation [83].

The primary tumor resection with lymphadenectomy must be conducted before liver transplant [84]. Patients selection criteria for liver transplantation include younger patients (< 50 years old), low grade tumor, Ki-67
Figure 1. Diagnostic and treatment algorithm for patients with duodenal neuroendocrine tumor (dNETs). CgA – chromogranin A; EUS – endoscopic ultrasound; MRI – magnetic resonance imaging; FDG PET – fluorodeoxyglucose positron emission tomography; SRS – somatostatin receptor scintigraphy; SSA – somatostatin analogues; EMR – endoscopic mucosal resection; ESD – endoscopic submucosal dissection.
index < 10% and 2 or less mitoses per high-power field and absence of extrahepatic disease [84, 85].

7.4. Systemic treatment

Due to the rarity of this disease, data on systemic therapy options that deal specifically with d-NETs are scarce or non-existent. However, since this is a type of gastrointestinal neuroendocrine tumor, data from studies dealing with different kinds of GI-NETs can be extrapolated to d-NETs, with reasonable assumption that the therapeutic effects are going to be the same or at least, similar.

Patients with well differentiated metastatic d-NETs that exhibit expression of somatostatine analogs on somatostatin-receptor-scintigraphy (SRS), especially if they have significant tumor burden or progressive disease, should receive therapy with somatostatin analogs (SSA) for control of carcinoid syndrome [86], and possibly, for antiproliferative effect on tumor growth [87]. Available SSAs are octreotide and lanreotide. Octreotide is a long-acting release (LAR) formulation that is often used in the chronic management of symptoms of carcinoid syndrome of various origins [88]. Standard dose of octreotide LAR is 20 or 30 mg intramuscularly every four weeks. The 30 mg dose has potentially antiproliferative tumor effect, based on the results of the PROMID study [87]. Dosage and treatment frequency may be further increased to optimize symptom control as required. Until therapeutic serum levels of octreotide LAR formulation are achieved, rapid symptom relief can be achieved in the first 10 – 14 days after LAR injection with short-acting subcutaneous form of octreotide, usually given in dosage of 150 – 250 μg three times daily [89]. PROMID study, a placebo-controlled phase III trial of octreotide use in metastatic midgut neuroendocrine tumors, showed median time to tumor progression of 14.3 and 6 months in the octreotide LAR and placebo groups, respectively (P=.000072) [87]. Stable disease was observed in 66.7% of patients in the octreotide LAR group after 6 months of treatment, versus 37.2% of patients in the placebo group. Long-term survival results of the PROMID study showed that median OS was not significantly different at 84 months in the placebo arm, and not reached in the octreotide arm (HR, 0.85; 95% CI 0.46 – 1.56, P=.59) [90]. However, crossover was allowed, and post-study treatment with octreotide was included in 38 of 43 patients from the placebo arm, possibly interfering with long-term survival results.

Another SSA, lanreotide, has a similar mechanism of action as octreotide, however, it is administered subcutaneously. It is effective in control of symptoms in carcinoid syndrome, as well as in gastrinomas, and VIPomas [91-94]. Phase III ELECT trial randomized 115 patients with carcinoid syndrome who were either naive or non-responsive to octreotide to receive either 120 mg of lanreotide or placebo, resulting in certain percentage of patients achieving symptom control in lanreotide arm [95]. CLARINET study, a placebo-controlled phase III trial of lanreotide use in patients with clinically significant tumor burden or progressive locally advanced or metastatic nonfunctioning pancreatic or intestinal neuroendocrine tumors, showed that treatment with lanreotide for 2 years resulted in an improvement in progression free survival (PFS) over placebo (PFS not reached vs. 18 months; HR 0.47; CI 0.30 – 0.73; P<.001) [96].

In patients with asymptomatic metastatic neuroendocrine tumors and low tumor burden, SSA therapy can be postponed until evidence of tumor progression or appearance of symptomatic disease.

For patients with advanced NETs usually after failure of SSA treatment, as a second line therapy due to its less-favorable toxic profile, use of interferon-alpha can be considered. In several large, though non-randomized analyses it was associated with an antitumor effect in this group of patients. However, potential side effects are numerous, and the therapeutic experience limited [97-99]. In patients with clinical syndromes that are not controlled with somatostatin analogs, it can be used as an add-on therapy. For patients with unresectable hepatic-predominant progressive disease, hepatic-directed therapies may be considered as the palliative therapeutic option for the relief of hormonal symptoms, and possible life prolongation. Those therapies include cytoreductive surgery, radiofrequency ablation (RFA), cryoablation, and various hepatic regional therapies – arterial embolization, chemoembolization, or radioembolization [100-103].
For patients with advanced unresectable or metastatic disease, that show presence of somatostatine receptors on SRS, peptide receptor radionuclide therapy (PRRT) should be considered. Although there is extensive experience with this therapy with other GI-NENs, especially with lutetium-177 or yttrium-90 labeled SSAs [104-106], there is minimal experience with d-NETs specifically. PRRT has been reported to result in tumor responses in patients with advanced carcinoid tumors of various origins [107,108]. There are number of large, though non-randomized cohort analyses that have reported encouraging survival rates with this therapeutic approach [109-111]. However, patients included are often highly selected. A prospective phase II study of PRRT in 90 patients with metastatic carcinoid tumors refractory to octreotide showed that PRRT led to relief in symptoms, however, objective radiographic regression on imaging studies was relatively uncommon [112]. Randomized trials to further evaluate the relative benefits and potential toxicities of PRRT in advanced carcinoid tumors are needed [113] and in progress.

For patients with G3, i.e. neuroendocrine carcinoma (NEC), either with progressive advanced (inoperable), or progressive metastatic disease, or symptomatic metastatic disease in need of quick relief of the symptoms, combination chemotherapy using cisplatine and etoposide is recommended first line therapeutic option regardless of the origin of the primary tumor [114].

For patients with well or moderately differentiated NETs (G1/G2) with progressive, advanced or metastatic disease, various combinations of streptozotocin, 5-fluoro-uracil, and doxorubicin are recommended chemotherapy options [115]. However, in many countries there are difficulties in providing streptozotocin, limiting these protocol combinations. For patients with well differentiated (G1) classical carcinoid tumors, chemotherapy plays little role, with poor response rates (<15%). No established second-line therapy for NET/NEC of either origin exists, although recent studies in pancreatic NETs demonstrate efficacy of several therapeutic options - temozolomide, alone or in combination with capcitabine [116-119]. Protocols that are studied, primarily in pancreatic NETs, are also capcitabine combined with oxaliplatin or irinotecan.

For patients with progressive metastatic NETs, everolimus, the mTOR inhibitor, can be considered as a therapeutic option, although it is registered only in G1/G2 NETs of pancreatic origin. In phase II trial [120], evidence of antitumor effect of everolimus was noticed in patients with advanced carcinoid tumors in combination with octreotide LAR. In the RADIANT-2, randomized phase III trial, everolimus demonstrated a significant antitumor effect compared with placebo by local review but not by central review [121]. Clinically beneficial effects have been reported in carcinoid patients. In RADIANT-3 trial, focusing on patients with pancreatic NETs, patients were randomized to either everolimus-octreotide or placebo-octreotide, significantly prolonged PFS, 11 versus 4.6 months, was noticed in everolimus arm [122]. Recent report focused on the outcomes of 169 pre-treated patients with advanced neuroendocrine tumors of various origin, who received everolimus through a compassionate use program [123]. An increased risk of adverse events in patients pretreated with radiolabeled peptide therapy and chemotherapy was noticed. Another targeted therapies, tyrosine kinase inhibitors, sunitinib and pazopanib, have demonstrated significant antitumor efficacy in pancreatic NETs, leading to the registration of sunitinib in the same therapeutic indication in pancreatic NETs as everolimus. However, no data exists for these therapies in patients with d-NETs [124].

8. Conclusion

We propose the diagnostic algorithm as presented in figure 1. The majority of d-NETs are non-functional tumors. The diagnosis of d-NET is based on the pathological findings, positive immunostaining for two neuroendocrine markers is mandatory, as well as Ki67 immunostaining, in order to make proper classification, which is important for making decisions regarding diagnostic procedures, treatment and follow-up. Chromogranin A and gastrin should be measured in all patients with d-NETs. Serum NSE should be measured in all patients with d-NEC (G3 tumors). 5-HIAA should be measured only in patients with signs and symptoms of carcinoid syndrome. Patients with serum gastrin > 1000 ng/L should undergo ph-metry and the status of parietal cell antibodies should be obtained. This is important in order to classify the functional status od d-NETs. Measurement of serum calcium, parathyroid hormone, prolactin, IGF-I, ACTH,
urinary-free cortisol should be made in all patients as screening for MEN-1 syndrome. MRI should be used for assessing the presence of metastatic disease in patients with established diagnosis of d-NET, but also to find primary tumors in patients with biochemical criteria for gastrinoma. SRS or 68Ga-DOTA peptide PET/CT should be used in all patients with positive or inconclusive MRI and G1 and G2 dNETs. The use of 18F-deoxyglucose (FDG) PET is mandatory in all patients with G3 d-NETs and is optional for patients with G1 and G2 tumors. EUS is of limited value in detection of the primary tumor, but should be used in all patients with visible tumors before making treatment decisions. Treatment of dNETs is controversial. Further studies are mandatory in order to detect patients who would benefit from radical surgery, which is associated with high mortality and morbidity rates. Current knowledge suggest that all tumors larger than 20 mm in diameter, sporadic gastrinomas and all periampullary dNETs should undergo radical surgery. Endoscopic mucosal resection is treatment of choice for G1 d-NETs smaller than 20 mm confined to submucosa. Transduodenal surgical resection may be used for patients with dNETs invading muscularis propria. Additional surgical interventions are recommended after endoscopic methods in the case of G1 or G2 d-NETs with positive margins, G2-G3 histological grading, invasion into muscular layer or in case of lymphovascular invasion. In case of metastatic disease, cytoreductive surgery should be considered as it improves overall 5-year survival rates. Somatostatin analogs should be used for G1 and G2 tumors, while cisplatin and etopoide should be used for G3 dNETs. Everolimus may be effective for patients with G2 dNETs. Peptide receptor radionuclide therapy should be used for patients with positive SRI and progressive disease.

Author contributions

MS and ND participated in literature review, paper writing and gave their final approval. IK gave the idea for the article, participated in paper writing and gave the final approval. AM performed literature review and gave the final approval. MN, NLj, JFČ, LjV, JMB, PPO, VGN, DM, MU, AD and MV are members of the team for diagnostics and treatment of neuroendocrine tumors, they critically revised the paper, gave their suggestions and gave their final approval.

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