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Review

Diagnosis and Surgical Treatment of Gastroenteropancreatic Neuroendocrine Neoplasms: A Literature Review

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Abstract. *This review aimed to highlight the characteristics and surgical treatments of tumours, and answer questions regarding the assessment of gastrointestinal neuroendocrine neoplasms (NENs) and optimal therapy. NENs comprise tumours that can produce hormones and cause a secretory syndrome. The diagnostic method and accuracy differ depending on the site of occurrence; hence, the relevant scientific society has created NEN treatment guidelines for each organ. Gastroenteric pancreatic (GEP) NENs have been unified and classified together according to the 2019 World Health Organization classification. Treatment is based on complete tumour resection, and when metastatic or primary lesions cannot be completely resected, lesions and symptoms are treated. Except for surgery for NENs, chemotherapy, molecularly targeted drugs, transarterial chemoembolization, etc., have also been confirmed as treatments. GEP NEN treatment methods will continue to advance and change because of surgery and other advances in treatment and diagnostic methods.*

Neuroendocrine neoplasms (NENs) are rare heterogeneous tumours that develop from the nervous system and endocrine cells (1-5). NEN refers to neuroendocrine tumours (NETs) in a broad sense; however, NETs include well-differentiated NETs and poorly differentiated invasive neuroendocrine cancer (NEC). NET including NEC, is often expressed as NET and is confusing. NEN occurs in all organs throughout the body but is mainly seen in the digestive system, pancreas, and lungs (5). It presents with hormone production and an array of progressive symptoms in the developing organ. Recently, it has been reported that the incidence of NEN is increasing and that the site of occurrence varies depending on the region (2, 6-8). The incidence of NEN varies because of differences in the survey periods and countries where the national surveys were conducted. The prevalence in the United States (US), which has the largest database, is estimated to be 103,312; cases. The prevalence of gastroenteropancreatic (GEP)-NEN, which has the highest incidence based on site, is reportedly 3.56 cases per 100,000 (6, 8). NEN was first reported by Oberndorfer as a carcinoid in 1907 (9). Progress related to NEN in pathological research, such as immunohistochemical staining and the analysis of genetic information, increased the molecular biological knowledge of NEN (10), consequently advancing its treatment (11). NEN was not uniform at the different sites of occurrence and was evaluated and classified by organ (5). The unified NEN tissue classification for the entire digestive system was developed according to the 2019 World Health Organization (WHO) classification (5, 12-15). Currently, researchers are analysing the entire properties of NEN based on this classification (16). WHO-classified G1 NET is considered to have a high degree of differentiation and slow growth; however, even tumours <1 cm in size metastasize (17). Biological and genomic differences depending on the NEN grade and site of occurrence have been found (4). The 2019 WHO classification also considers the clinicopathological differences between NET and NEC. In studies on NET expression, there are molecular differences between differentiated NETs and NECs (4). Mutations in *DAXX* and *ATRX* have been confirmed for multiple endocrine neoplasia (MEN) type 1 (MEN1), and mutations in *TP53* or *RB1* have been confirmed for NEC (4, 10, 14). Radical treatment requires complete tumour removal,

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and resection is an effective and important part of treatment (18). Regarding the treatment of metastases such as lymph node and liver metastases, treatment aims to prolong prognosis and treat hormone-producing symptoms; surgery, drug therapy, endovascular treatment, *etc*., and novel treatment approaches have been developed, with consistently improving treatment results (1). This study reviews the latest findings on GEP-NEN treated by gastroenterologists, along with the latest trends in organ-specific surgical treatment for the aforementioned tumour.

Epidemiology

The incidence of GEP-NEN is steadily increasing in Asia, Europe, and most notably, North America. It frequently occurs in the small intestine and rectum in North America, the rectum and pancreas in Asia, and the small intestine and pancreas in Europe, and its incidence is biased. The reported worldwide incidence of GEP-NEN per capita is 2.5-8.35% of 100,000 people (6). The differences mentioned above can be attributed to a combination of factors, including country-specific statistics, test accuracy/consultation rates, environmental factors, and biological differences. According to US statistics, the incidence is the highest in individuals aged ≥70 years, while the highest rate of increase (4-5%) is seen between 40 and 74 years of age (6).

Clinical Manifestations

NEN is characterized by its expression as a malignant tumour due to proliferation, metastasis, and symptoms resulting from endocrine function. NENs are often non-functional. However, it is known that the symptoms of functional NENs differ depending on the type of hormone produced and that the frequency of occurrence varies depending on the site of origin of the primary tumour (7). Serotonin is produced in patients with carcinoid syndrome, diarrhoea, flushing of the skin, asthma-like attacks, oedema, and signs of right heart failure development (19). Insulinomas induce hypoglycaemic attacks when insulin is produced from the pancreas, and glucagonomas produced by the pancreas cause necrolytic migratory erythema, weight loss, and diabetes. Gastrinomas cause recurrent peptic ulcers due to Zollinger-Ellison syndrome, which results from gastrin produced by tumours of the stomach, small intestine, pancreas, and papilla of Vater. Somatostatinoma is caused by tumours of the small intestine, pancreas, and papilla of Vater, and somatostatin causes hypochlorhydria, steatorrhea, and diabetes (7, 20). It has been reported that mesenteric fibrosis occurs most often in small bowel (SB) NENs and is observed in approximately half of the cases involving small NENs. NEN-derived fibrosis-promoting factors accelerate the remodelling of the extracellular matrix and contribute to the development of heart valves and/or mesenteric fibrosis (21). In patients with NEN, the severity of progression at the time of discovery differs depending on the site of occurrence; therefore, comparison by organ does not indicate the nature of the tumour by site. However, it has been reported that the disease-specific survival rate for gastrointestinal NENs is the worst for lesions involving the oesophagus and best for lesions involving the appendix (22).

Diagnosis

Immunohistochemistry for neuroendocrine markers is important for the diagnosis and treatment of NENs. The pathological features of NENs are characterized by the expression of general neuroendocrine markers and the production of peptide hormones and/or biogenic amines. Common NEN markers include synaptophysin and chromogranin A, with the former being generally more sensitive and the latter being considered more specific (23, 24). Plasma chromogranin A is the most commonly used biomarker for treatment evaluation and occurs in both functional and non-functional NENs (19, 24). Blood chromogranin A and neuron-specific enolase concentration is also considered effective in determining treatment (25-27). Moreover, the expression of somatostatin receptors is usually used for the diagnosis and treatment of NEN and NETs (24, 28-30). NENs have a common phenotype, but the prognosis, aggressiveness, and response to treatment differ depending on the origin, morphology, function, molecular profile, type, and site (16, 31, 32). Research is progressing in many areas such as the expression of 4F2, which is known as the heavy chain of L-type amino acid transporter 1 (33). The WHO classification has been revised to study the characteristics of NET (14, 15). While interpreting the literature, it is necessary to consider that there is a change in distribution due to changes in tumour grade (32). Ki-67 staining is very important for NET grade classification and has been adopted in the WHO classification. All GEP-NENs were classified into well-differentiated NETs, poorly differentiated neuroendocrine carcinomas, and mixed endocrine/non-endocrine neoplasms. Well-differentiated NETs were classified into grades 1, 2, and 3 (G1, G2, and G3) based on the mitotic rate and Ki-67 index (G1, mitotic rate of <2 per 10 high-power fields and/or Ki67 index of <3%; G2, mitotic rate of 2 to 20 per 10 high-power fields and/or Ki67 index of 3 to 20%; and G3, mitotic rate of >20 per 10 high-power fields and/or Ki67 index of >20%). Neuroendocrine carcinomas were classified as small- or large-cell types. Mixed endocrine/non-endocrine neoplasms consisted of a neuroendocrine component or a non-neuroendocrine component, such as an adenocarcinoma (12, 13). Fluorodeoxyglucose PET/CT and ^{68}Ga- tetraazacyclododecanetetraacetic acid-DPhe1-Tyr3-octeorate (DOTATATE) PET/CT are useful for diagnosing localization and metastasis (34).

Treatment

Generally, surgery is the basis of treatment for localized NENs (18, 35), but systemic treatment should be considered for metastatic lesions (4, 36). In patients with GEP-NEN, lymph node metastasis is known to affect the survival curve, and extensive lymph node metastases are considered to require aggressive treatment in addition to surgery (37, 38). Surgical resection of the primary lesion reduces the risk of tumour-specific mortality, but surgical resection of metastatic sites has been reported to have no survival benefit (22). Treatment of G3 NET has not been clarified, but is considered to be between that of G1/G2 NET and NEC (18, 39). The European and US guidelines recommend surgical resection for localized NETs without distant metastases (18, 36). Chemotherapy is performed as a multidisciplinary treatment combined with surgery and radiation therapy in unresectable cases (4), and is generally performed using a combination of drugs such as carboplatin, etoposide, folic acid, 5-fluorouracil, and oxaliplatin (40). Studies have developed various drugs and administration methods that prolong survival and are being compared and examined (41). Intra-arterial therapy (IAT) includes transarterial embolization, transarterial chemoembolization, and radioembolization. IAT is mainly used to treat liver metastases and can be performed on unresectable metastatic liver lesions with proven efficacy (42, 43). There is no randomized control study comparing IAT and hepatectomy, but a study has reported that there is no difference in treatment results for asymptomatic liver metastasis being treated as an NEN liver metastasis compared to surgical resection (44). In patients with G3 NET and those with NEC, the European Neuroendocrine Tumor Society (ENETS) recommends the multidisciplinary treatment of radical surgery combined with systemic chemotherapy and radiotherapy when there is a possibility of complete resection due to localized lesions (18). Most patients with G3 NET and NEC have been reported to present with metastatic disease and overall poor survival, and chemotherapy has been demonstrated to improve survival (39, 45, 46). Treatment for metastatic lesions includes surgical intervention by chemoembolization, radiofrequency ablation, and biological therapy, in addition to somatostatin analogues, peptide receptor radionuclide therapy (47-49), and immunotherapy (11, 34, 50). ^{177}Lu-DOTATATE is effective for peptide receptor radionuclide therapy, with particularly enhanced effectiveness against well-differentiated NETs (47). Immunosuppressive mammalian targets of rapamycin (mTOR) inhibitors have been shown to be effective against advanced NENs; however, everolimus is associated with resistance, and a third-generation mTOR inhibitor is being developed (51). Regarding symptomatic NET syndrome, the treatment method is selected based on the hormone produced, site, metastasis, *etc*. (14). Especially in this field, new drugs and administration methods have been developed and are effective (40).

Endoscopic Resection

Increased use of gastrointestinal fiberscopy has increased the detection rate of NENs in the upper gastrointestinal tract (52). NETs <1 cm in the stomach, duodenum, pancreas, appendix, and rectum are considered to be early stage, and intramucosal ly0 and v0 tumours <1 cm in size in the stomach, duodenum, and rectum are considered indications for endoscopic treatment. However, small intestinal NETs are not early stage, even if they are <1 cm in size, and lymph node dissection is required (53). Indications for endoscopic tumour resection were defined for each organ. In many cases, NETs cannot be completely excised by conventional snare polypectomy, and endoscopic membrane dissection using a cap or ligation device or endoscopic submucosal resection is recommended depending on the endoscopist's skill (53, 54).

Surgical Therapy

Localized lesions that can be completely resected are indicated for surgical treatment (11, 18, 55). According to the Surveillance, Epidemiology, and End Results database, which collects statistical data on cancer in the US, 52.4% of patients with NEN had a localized stage, 20.1% had a regional stage, and 27.4% had a distant stage (56). Localized GEP-NEN is indicated for surgery, and in cases where lymph node metastasis is possible, it is indicated for lesion resection with lymph node dissection (57). Among patients with metastatic NEN, excision of the primary lesion has been reported to improve prognosis in the group with low-grade NET (15). Treatment for G3 NET and NEC is unclear. The National comprehensive cancer network (NCCN) recommended that radical surgery + adjuvant chemotherapy for resectable lesions, locoregional radiation therapy + chemotherapy for locoregional unresectable, and radiotherapy for chemotherapy and radiotherapy for selected sites of distant metastases (18, 38). Regarding liver metastasis, there are cases in which it is localized and can be completely resected, and there are surgeries aimed at tumour de-bulking. The indications for hepatectomy are described below. Prophylactic cholecystectomy is not indicated as a concomitant surgical treatment because the incidence of cholelithiasis due to the administration of octreotide after NET is high, but the frequency of symptomatic cholelithiasis is low (58, 59).

Surgical Procedures for GEP-NEN

Oesophagus. Oesophageal NEN is the rarest and reportedly accounts for 0.05% of all GEP-NENs (60). This tumour is often diagnosed at an advanced stage with nausea being the

most common symptom, followed by weight loss and loss of appetite (60, 61). Because there are few cases, there is no clear treatment algorithm (61). In patients with NEC, there is a report that survival was improved by surgery depending on the stage (61-64). A previous study reported that the prognosis was significantly improved by the combined administration of chemotherapy (65). Chemotherapy, radiation therapy, and surgical therapy alone do not produce good results; therefore, in any case, multidisciplinary treatment is appropriate. Complete resection may be possible for well-differentiated and localized lesions, and endoscopic resection or surgery should be considered (63). Unlike other sites, endoscopic resection has no indication criteria. Surgical treatment may include transthoracic esophagectomy without minimally invasive radical lymph node dissection in the middle and lower oesophagus and transthoracic oesophagectomy in the upper oesophagus (61). Lymph node dissection needs to be examined in each case from the viewpoint of the magnitude and effect of surgical invasion. A study reported good results after oesophagectomy alone for small-cell NEC (63); however, another study (66) obtained good results with chemoradiotherapy and chemotherapy depending on the case. Surgical treatment should be considered in the localized stage (12, 62, 67).

Stomach. The algorithm for treating gastric NEN was selected based on whether the tumour was NEC or NET. If it was NET, it was further classified according to the Rindi classification (68) and subdivided according to the size and depth of invasion by type. According to Rindi's classification of gastric NET, type I is caused by hypergastrinemia associated with atrophic gastritis, type II is caused by hypergastrinemia associated with MEN1 and Zollinger-Ellison syndrome, and type III is caused by sporadic and non-gastrin-independent tumours (69). Type I comprises 70-80% of gastric NETs and is reported to occur frequently in the body of the stomach and comprise a large proportion of G1 NETs (69, 70). In patients with this type, a tumour diameter <1 cm, no infiltration of the muscularis propria, and no lymph node metastasis are indicated for endoscopic resection or follow-up. Gastrectomy and lymph node dissection are required if the tumour diameter is ≥1 cm or if infiltration of the muscularis propria is observed. For large numbers of tumours (≥5), local, partial, or total gastrectomy is recommended (19, 70, 71). No evaluation has been made regarding pyloric resection to reduce gastrin (18). Type II accounts for 5-6% of the gastric corpus, has many small NETG1/G2 lesions in the body of the stomach, and has a 10-20% chance of lymph node metastasis (69). The surgical policy is the same as for type I, but treatment for coexisting gastrinoma and MEN1-related diseases is added (19, 71). Type III tumours include NET and NEC, accounting for 14-25% of all gastric NETs, and are generally sporadic and often infiltrate the muscular layer (70). Surgery for type III tumours involves extensive gastrectomy and lymph node dissection if there is no distant metastasis (19). NEC-related surgical indications do not exist in cases in which locally advanced resection is impossible, and multidisciplinary treatment is recommended.

Duodenum. Most duodenal NENs are non-functional. NEC is reported to comprise 1.8% of NENs (72). It has been reported that the lymph node metastasis of duodenal NEN is determined by tumour diameter, and prognosis is affected by grade (73). Endoscopic resection was indicated for groups without lymph node metastasis (52, 70, 72). Duodenal G1 NETs with a maximum endoscopic diameter of ≤10 mm that are confined to the mucosal and submucosal layers can be resected endoscopically. If the tumour diameter is 10-20 mm, the treatment method, *i.e.*, endoscopic resection or resection with lymph node dissection, will be decided by individual consultation. Well-differentiated duodenal NETs >20 mm in diameter, those with lymph node metastasis, and those with vascular infiltration, localized sporadic gastrinomas, localized poorly differentiated NETs, and NEC are indications for surgery with lymph node dissection (52, 72, 74, 75). Approximately 25% of duodenal gastrinomas are MEN1, which cannot be cured by surgery alone. MEN1 is a disease that causes multiple adenomas or hyperplasia, mainly parathyroid tumours, pancreatic gastrointestinal endocrine tumours, and pituitary adenomas. Gastrinoma is common among pancreatic gastrointestinal endocrine tumours with the occurrence of Zollinger-Ellison syndrome (gastric acid hypersecretion, refractory/recurrent gastroduodenal ulcers). Therefore, Zollinger-Ellison syndrome in patients with MEN1 can be effectively treated with the administration of long-term proton pump inhibitors (75, 76). Moreover, duodenal NENs with hyperparathyroidism require appropriate treatment and surgical resection. NETs located in the papilla of Vater cause obstructive jaundice if they are large or remain asymptomatic if they are small. Although there is no control study on early papilla NET, those over 2 cm in diameter are subjected to pancreaticoduodenectomy or pylorus-preserving pancreaticoduodenectomy. It has been reported that well-differentiated NETs <2 cm in diameter without lymph node metastasis can be resected endoscopically (72), and, depending on the case, removal by local resection with lymph node dissection or lymph node picking is recommended (70).

Pancreas. In patients with pancreatic NENs, the possibility of radical cure exists only through surgical resection (77). Moreover, 60-90% of NEN cases are non-functional (57). Most hormone-producing tumours are insulinomas, gastrinomas, and, rarely, glucagonomas, VIPomas, somatostatinomas, and growth hormone-releasing hormone tumours (78, 79). Pancreatic NETs are classified according to their functionality or function, and each NET has a

recommended surgical procedure. For insulinomas, enucleation or local resection, such as partial resection, is recommended. In cases of multiple tumours, infiltration into surrounding tissues, or lymph node metastasis, pancreaticoduodenectomy or distal pancreatectomy with lymph node dissection is recommended (36, 80). Gastrinoma is a tumour that can be cured only by resection and has a high metastasis rate (78). To treat pancreatic and duodenal gastrinomas, pancreaticoduodenectomy or distal pancreatectomy accompanied by lymph node dissection is recommended (78, 80-82). In the treatment of insulinomas and gastrinomas, there is also a guideline that allows selection of enucleation or partial resection as reduction surgery in cases where the tumour is located peripherally (36). Tumour resection is thought to be effective, but as minimally invasive techniques are widely applied, enucleation is becoming more common in some areas. Pancreaticoduodenectomy or distal pancreatectomy is recommended when partial resection is impossible, such as when the lesion is in close proximity to the main pancreatic duct. The purpose of therapy for functional pancreatic NETs other than insulinoma and gastrinoma is to improve prognosis and alleviate hormonal symptoms. Surgical resection is the only curative treatment, but pancreaticoduodenectomy or distal pancreatectomy with lymph node dissection is recommended because of the high likelihood of lymph node metastasis (78, 80, 83). Regarding the treatment of non-functional pancreatic NETs, locally advanced unresectable lesions and metastatic lesions are not indicated for resection surgery for tumour volume reduction but rather for multidisciplinary treatment (84). Only surgical indications for symptom relief are applied for complications such as intestinal obstruction. In patients with localized non-functional well-differentiated NET, the possibility of lymph node metastasis is low in lesions <1 cm, but widespread metastasis has been reported, and whether lymph node dissection is needed is unclear (85, 86). Guidelines such as those of the ENETS conditionally indicate that non-functional pancreatic NETs <2 cm can be selectively followed up (78, 84, 87). Moreover, it is reported that tumours <1.5 cm can be followed up (88). However, there is no consensus on follow-up as a treatment for non-functional NETs <2 cm. The North American Neuroendocrine Tumor Society (NANETS) recommends follow-up for lesions <1 cm, resection for lesions 1-2 cm depending on the case, and resection for lesions ≥2 cm (79). According to the NCCN guidelines, nucleation, pancreaticoduodenectomy, and pancreatoduodenectomy ± lymph node dissection are indicated for localized NETs with a major axis of 2 cm or less, and follow-up is indicated in the selected case (34), although pancreatic NEC has unclear indications for surgical treatment (57, 89), There are also reports that surgical resection is effective for some localized NEC (89).

Ileum and Jejunum. SB-NENs are commonly detected at advanced stages without specific symptoms; therefore, metastases are very often already present at the time of surgery (90). It has been reported that emergency surgery often leads to a postoperative diagnosis and that the emergency surgery group has a worse prognosis than the elective surgery group (91, 92). Surgical treatment is not standardized for SB-NENs. SB-NEN often occurs in the ileum, and even tumours with a diameter of ≤1 cm have a high rate of lymph node metastasis (93). If resection is possible, resection of the main lesion and lymph node dissection are thought to improve prognosis (23, 59, 94). The surgical procedure for the primary lesion based on the extent of resection and the extent of lymph node dissection has been discussed (90, 94). Since one tumour induces the development of other tumours, it is necessary to consider malnutrition due to extensive resection, but complete resection of NEN and optimal lymph node dissections are thought to help improve prognosis (95, 96). Therefore, intraoperative palpation is important for the complete resection of multiple lesions, and laparotomy has been reported to be more effective than laparoscopic surgery (96). Regarding liver metastasis, hepatectomy, if possible, is expected to improve prognosis (97). There are advantages and disadvantages for the resection of lesions in the presence of unresectable liver or distant metastases in patients with SB-NEN (59, 98). In patients with SB-NEN, mesenteric tumour deposits are considered to affect prognosis along with liver metastasis, and treatment methods are being investigated (99). Bioamines and peptides in patients with SB-NEN can cause mesenteric fibrosis, and corresponding treatment research is ongoing (21, 95). Treatments other than surgical treatment for metastatic lesions have been developed and others are currently under development (49).

Appendix. Most appendiceal NENs are found incidentally after appendectomy (100), and characteristically, tumours develop at the tip of the appendix (15). Goblet cell adenocarcinoma, which was previously classified as a mixed adenoneurocrine carcinoma, is no longer classified as an NEN in the new 2019 WHO classification and is now treated as an adenocarcinoma (15). This must be kept in mind when considering a suitable treatment (101). Appendiceal NEN develops in relatively young people, and most appendiceal NENs are G1 or G2 NET (57, 102). It has been reported that surgery will improve prognosis only if lymph node metastasis is localized. G2 NET or higher, positive vascular invasion, and a large tumour diameter increase the possibility of lymph node metastasis. It has been reported that additional resection surgery improves prognosis (100, 101). Some studies have suggested that the cut-off value for tumour diameter that is an indication for additional surgery is 1 or 2 cm for G1 and G2 NET (100, 101, 103, 104). As

additional resections, right hemicolectomy and lymph node dissection are performed; however, in some cases, they are excessively invasive (104). NEC is not indicated for surgery only, but if it is resectable and has a local lesion, surgery should be performed, followed by chemotherapy and radiation therapy (11).

Colon/rectum. The diagnosis of colorectal NENs is rapidly increasing in the US and Asia (6, 105, 106). This is partly due to the increasing number of endoscopy cases in this area. Colon and rectal NENs are more likely to be small lesions in areas where endoscopy is progressing. Treatment for patients with a lymph node metastasis <1 cm in size is selected based on the results of histopathological findings (17). Indications for the endoscopic resection of colorectal NENs are a tumour size <1 cm, no infiltration into the muscularis propria, and no vascular infiltration (107-110). For cases where there is infiltration into the muscularis propria, even if it is <1 cm, when vascular infiltration is observed, when a positive margin is confirmed after endoscopic resection, or when the tumour diameter is ≥1 cm, depending on the possibility of lymph node metastasis, it is recommended to perform colon or rectal resection with lymph node dissection (36, 84, 108, 110). Recent ENETS consensus guidelines indicate that tumours <2 cm with no intrinsic muscular layer infiltration and vascular infiltration should be endoscopically resected (52, 105, 106, 111, 112). There are no surgical indications for locally advanced unresectable lesions or metastatic lesions of the colorectal NEN, and these tumours are indicated for multidisciplinary treatment (113).

Liver metastasis. For NET liver metastasis, it is necessary to consider hormone production and residual lesions after treatment. There are three treatments for liver metastasis. The first is hepatectomy and cytoreduction surgery, the second is nonsurgical liver direct therapy, and the third is systemic therapy. Combined therapy and not monotherapy is expected to improve prognosis (114). Hepatectomy or cytoreduction, if feasible, is the first-line treatment for NET liver metastasis and is reported to be effective in improving survival and hormone production symptoms. According to NANETS, hepatectomies were recommended for R0 (without residual tumour) and R1 (possibly without residual tumour) lesions and were controversial for R2 (with residual tumour) lesions (59). Cytoreduction has been effective in more than 90% of lesion resections (59), but a 2018 NANETS consensus conference reported that it was effective in 70% of lesion resections cases (79). A parenchymal sparing procedure is recommended for resection based on NANETS. Enucleation or wedge resection is recommended if the tumour is present on the surface, and microwave ablation or radiofrequency ablation is recommended if the tumour is deep (115). Liver transplantation may have a life-prolonging effect on patients with diffuse metastases of NENs to the liver. However, owing to the high recurrence rate, indications are limited (44,116).

Future Aspects

Currently, NEN treatments are being prospectively investigated. Although it is difficult to select and assign cases, it is important to proceed with research in order to obtain strong recommendations in the guidelines (11). Because the development of new therapeutic agents and treatment methods has also progressed with good results, further improvements in treatment outcomes are expected through basic and clinical studies.

Conclusion

NEN is a rare and heterogeneous tumour, and most previous analyses of its treatment were retrospective; moreover, randomized controlled studies are limited. Because of the variety of lesions among GEP-NENs, even for the same site, the indications for surgery differ among lesions. It is thought that advances and changes in GEP treatment methods will continue because of advances in treatment and diagnostic methods other than surgery. Therefore, our knowledge should be updated.

Conflicts of Interest

The Author declares no conflicts of interest relevant to this article.

References

1 Walter MA, Nesti C, Spanjol M, Kollár A, Bütikofer L, Gloy VL, Dumont RA, Seiler CA, Christ ER, Radojewski P, Briel M and Kaderli RM: Treatment for gastrointestinal and pancreatic neuroendocrine tumours: a network meta-analysis. Cochrane Database Syst Rev *11*: CD013700, 2021. PMID: 34822169. DOI: 10.1002/14651858.CD013700.pub2

2 Basuroy R, Srirajaskanthan R and Ramage JK: Neuroendocrine tumors. Gastroenterol Clin North Am *45(3)*: 487-507, 2016. PMID: 27546845. DOI: 10.1016/j.gtc.2016.04.007

3 Gonzalez RS: Diagnosis and management of gastrointestinal neuroendocrine neoplasms. Surg Pathol Clin *13(3)*: 377-397, 2020. PMID: 32773190. DOI: 10.1016/j.path.2020.04.002

4 Cives M and Strosberg JR: Gastroenteropancreatic neuroendocrine tumors. CA Cancer J Clin *68(6)*: 471-487, 2018. PMID: 30295930. DOI: 10.3322/caac.21493

5 La Rosa S and Uccella S: Classification of neuroendocrine neoplasms: lights and shadows. Rev Endocr Metab Disord *22(3)*: 527-538, 2021. PMID: 33169199. DOI: 10.1007/s11154-020-09612-2

6 Das S and Dasari A: Epidemiology, incidence, and prevalence of neuroendocrine neoplasms: are there global differences? Curr Oncol Rep *23(4)*: 43, 2021. PMID: 33719003. DOI: 10.1007/s11912-021-01029-7

7 Bonds M and Rocha FG: Neuroendocrine tumors of the pancreatobiliary and gastrointestinal tracts. Surg Clin North Am *100(3)*: 635-648, 2020. PMID: 32402306. DOI: 10.1016/j.suc.2020.02.010

8 Oronsky B, Ma PC, Morgensztern D and Carter CA: Nothing but NET: a review of neuroendocrine tumors and carcinomas. Neoplasia *19(12)*: 991-1002, 2017. PMID: 29091800. DOI: 10.1016/j.neo.2017.09.002

9 Oberndorfer S: Karzinoide Tumorgen des Dunndarms. Frankf Z für Pathol *1*: 425-432, 1907.

10 Rindi G and Wiedenmann B: Neuroendocrine neoplasia of the gastrointestinal tract revisited: towards precision medicine. Nat Rev Endocrinol *16(10)*: 590-607, 2020. PMID: 32839579. DOI: 10.1038/s41574-020-0391-3

11 Zandee WT and de Herder WW: The evolution of neuroendocrine tumor treatment reflected by ENETS guidelines. Neuroendocrinology *106(4)*: 357-365, 2018. PMID: 29320780. DOI: 10.1159/000486096

12 WHO Classification of Tumors Editorial Board: WHO Classification of Tumors. Digestive System Tumors, 5th ed. Lyon, France, International Agency for Research on Cancer (LARC), 2019.

13 Klimstra DS, Kloppell G, La Rosa S and Rindi G: Classification of neuroendocrine neoplasms of the digestive system. In: WHO Classification of Tumours: Digestive System Tumours, 5th ed. Lyon, France, International Agency for Research on Cancer IARC, pp. 16-19, 2019.

14 Nagtegaal ID, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, Washington KM, Carneiro F, Cree IA and WHO Classification of Tumours Editorial Board: The 2019 WHO classification of tumours of the digestive system. Histopathology *76(2)*: 182-188, 2020. PMID: 31433515. DOI: 10.1111/his.13975

15 Assarzadegan N and Montgomery E: What is new in the 2019 World Health Organization (WHO) Classification of tumors of the digestive system: Review of selected updates on neuroendocrine neoplasms, appendiceal tumors, and molecular testing. Arch Pathol Lab Med *145(6)*: 664-677, 2021. PMID: 32233993. DOI: 10.5858/arpa.2019-0665-RA

16 Rindi G and Inzani F: Neuroendocrine neoplasm update: toward universal nomenclature. Endocr Relat Cancer *27(6)*: R211-R218, 2020. PMID: 32276263. DOI: 10.1530/ERC-20-0036

17 Soga J: Early-stage carcinoids of the gastrointestinal tract: an analysis of 1914 reported cases. Cancer *103(8)*: 1587-1595, 2005. PMID: 15742328. DOI: 10.1002/cncr.20939

18 Shah MH, Goldner WS, Benson AB, Bergsland E, Blaszkowsky LS, Brock P, Chan J, Das S, Dickson PV, Fanta P, Giordano T, Halfdanarson TR, Halperin D, He J, Heaney A, Heslin MJ, Kandeel F, Kardan A, Khan SA, Kuvshinoff BW, Lieu C, Miller K, Pillarisetty VG, Reidy D, Salgado SA, Shaheen S, Soares HP, Soulen MC, Strosberg JR, Sussman CR, Trikalinos NA, Uboha NA, Vijayvergia N, Wong T, Lynn B and Hochstetler C: Neuroendocrine and adrenal tumors, version 2.2021, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw *19(7)*: 839-868, 2021. PMID: 34340212. DOI: 10.6004/jnccn.2021.0032

19 Ahmed M: Gastrointestinal neuroendocrine tumors in 2020. World J Gastrointest Oncol *12(8)*: 791-807, 2020. PMID: 32879660. DOI: 10.4251/wjgo.v12.i8.791

20 Ito T, Lee L and Jensen RT: Treatment of symptomatic neuroendocrine tumor syndromes: recent advances and controversies. Expert Opin Pharmacother *17(16)*: 2191-2205, 2016. PMID: 27635672. DOI: 10.1080/14656566.2016.1236916

21 Cives M, Pelle' E, Quaresmini D, Rizzo FM, Tucci M and Silvestris F: The tumor microenvironment in neuroendocrine tumors: biology and therapeutic implications. Neuroendocrinology *109(2)*: 83-99, 2019. PMID: 30699437. DOI: 10.1159/000497355

22 Cai W, Tan Y, Ge W, Ding K and Hu H: Pattern and risk factors for distant metastases in gastrointestinal neuroendocrine neoplasms: a population-based study. Cancer Med *7(6)*: 2699-2709, 2018. PMID: 29733523. DOI: 10.1002/cam4.1507

23 Modlin IM, Bodei L and Kidd M: Neuroendocrine tumor biomarkers: From monoanalytes to transcripts and algorithms. Best Pract Res Clin Endocrinol Metab *30(1)*: 59-77, 2016. PMID: 26971844. DOI: 10.1016/j.beem.2016.01.002

24 Bellizzi AM: Immunohistochemistry in the diagnosis and classification of neuroendocrine neoplasms: what can brown do for you? Hum Pathol *96*: 8-33, 2020. PMID: 31857137. DOI: 10.1016/j.humpath.2019.12.002

25 Nikou GC, Marinou K, Thomakos P, Papageorgiou D, Sanzanidis V, Nikolaou P, Kosmidis C, Moulakakis A and Mallas E: Chromogranin A levels in diagnosis, treatment and follow-up of 42 patients with non-functioning pancreatic endocrine tumours. Pancreatology *8(4-5)*: 510-519, 2008. PMID: 18765956. DOI: 10.1159/000152000

26 Jensen KH, Hilsted L, Jensen C, Mynster T, Rehfeld JF and Knigge U: Chromogranin A is a sensitive marker of progression or regression in ileo-cecal neuroendocrine tumors. Scand J Gastroenterol *48(1)*: 70-77, 2013. PMID: 23094948. DOI: 10.3109/00365521.2012.733953

27 Kečkéš Š, Palaj J, Waczulíková I, Dyttert D, Mojtová E, Kováč G and Durdík Š: Pretreatment levels of chromogranin A and neuron-specific enolase in patients with gastroenteropancreatic neuroendocrine neoplasia. In Vivo *35(5)*: 2863-2868, 2021. PMID: 34410979. DOI: 10.21873/invivo.12574

28 Barrio M, Czernin J, Fanti S, Ambrosini V, Binse I, Du L, Eiber M, Herrmann K and Fendler WP: The impact of somatostatin receptor-directed PET/CT on the management of patients with neuroendocrine tumor: a systematic review and meta-analysis. J Nucl Med *58(5)*: 756-761, 2017. PMID: 28082438. DOI: 10.2967/jnumed.116.185587

29 Desai H, Borges-Neto S and Wong TZ: Molecular imaging and therapy for neuroendocrine tumors. Curr Treat Options Oncol *20(10)*: 78, 2019. PMID: 31468190. DOI: 10.1007/s11864-019-0678-6

30 Mittra ES: Neuroendocrine Tumor Therapy: ^{177}Lu-DOTATATE. AJR Am J Roentgenol *211(2)*: 278-285, 2018. PMID: 29949416. DOI: 10.2214/AJR.18.19953

31 Klöppel G: Neuroendocrine neoplasms: Dichotomy, origin and classifications. Visc Med *33(5)*: 324-330, 2017. PMID: 29177160. DOI: 10.1159/000481390

32 Rindi G, Klimstra DS, Abedi-Ardekani B, Asa SL, Bosman FT, Brambilla E, Busam KJ, de Krijger RR, Dietel M, El-Naggar AK, Fernandez-Cuesta L, Klöppel G, McCluggage WG, Moch H, Ohgaki H, Rakha EA, Reed NS, Rous BA, Sasano H, Scarpa A, Scoazec JY, Travis WD, Tallini G, Trouillas J, van Krieken JH and Cree IA: A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. Mod Pathol *31(12)*: 1770-1786, 2018. PMID: 30140036. DOI: 10.1038/s41379-018-0110-y

33 Horita Y, Kaira K, Kawasaki T, Mihara Y, Sakuramoto S, Yamaguchi S, Okamoto K, Ryozawa S, Kanai Y, Yasuda M and Hamaguchi T: Expression of LAT1 and 4F2hc in gastroenteropancreatic neuroendocrine neoplasms. In Vivo *35(4)*: 2425-2432, 2021. PMID: 34182526. DOI: 10.21873/invivo.12520

34 Sanli Y, Garg I, Kandathil A, Kendi T, Zanetti MJB, Kuyumcu S and Subramaniam RM: Neuroendocrine tumor diagnosis and management: ^{68}Ga-DOTATATE PET/CT. AJR Am J Roentgenol *211(2)*: 267-277, 2018. PMID: 29975116. DOI: 10.2214/AJR.18.19881

35 Eto K, Yoshida N, Iwagami S, Iwatsuki M and Baba H: Surgical treatment for gastrointestinal neuroendocrine tumors. Ann Gastroenterol Surg *4(6)*: 652-659, 2020. PMID: 33319155. DOI: 10.1002/ags3.12396

36 Kulke MH, Shah MH, Benson AB 3rd, Bergsland E, Berlin JD, Blaszkowsky LS, Emerson L, Engstrom PF, Fanta P, Giordano T, Goldner WS, Halfdanarson TR, Heslin MJ, Kandeel F, Kunz PL, Kuvshinoff BW 2nd, Lieu C, Moley JF, Munene G, Pillarisetty VG, Saltz L, Sosa JA, Strosberg JR, Vauthey JN, Wolfgang C, Yao JC, Burns J, Freedman-Cass D and National comprehensive cancer network: Neuroendocrine tumors, version 1.2015. J Natl Compr Canc Netw *13(1)*: 78-108, 2015. PMID: 25583772. DOI: 10.6004/jnccn.2015.0011

37 Martin JA, Warner RRP, Aronson A, Wisnivesky JP and Kim MK: Lymph node metastasis in the prognosis of gastroenteropancreatic neuroendocrine tumors. Pancreas *46(9)*: 1214-1218, 2017. PMID: 28902794. DOI: 10.1097/MPA.0000000000000921

38 Garcia-Carbonero R, Sorbye H, Baudin E, Raymond E, Wiedenmann B, Niederle B, Sedlackova E, Toumpanakis C, Anlauf M, Cwikla JB, Caplin M, O'Toole D, Perren A and Vienna Consensus Conference participants: ENETS Consensus guidelines for high-grade gastroenteropancreatic neuroendocrine tumors and neuroendocrine carcinomas. Neuroendocrinology *103(2)*: 186-194, 2016. PMID: 26731334. DOI: 10.1159/000443172

39 Coriat R, Walter T, Terris B, Couvelard A and Ruszniewski P: Gastroenteropancreatic well-differentiated grade 3 neuroendocrine tumors: review and position statement. Oncologist *21(10)*: 1191-1199, 2016. PMID: 27401895. DOI: 10.1634/theoncologist.2015-0476

40 Kaderli RM, Spanjol M, Kollár A, Bütikofer L, Gloy V, Dumont RA, Seiler CA, Christ ER, Radojewski P, Briel M and Walter MA: Therapeutic options for neuroendocrine tumors: a systematic review and network meta-analysis. JAMA Oncol *5(4)*: 480-489, 2019. PMID: 30763436. DOI: 10.1001/jamaoncol.2018.6720

41 Maire F, Lombard-Bohas C, O'Toole D, Vullierme MP, Rebours V, Couvelard A, Pelletier AL, Zappa M, Pilleul F, Hentic O, Hammel P and Ruszniewski P: Hepatic arterial embolization versus chemoembolization in the treatment of liver metastases from well-differentiated midgut endocrine tumors: a prospective randomized study. Neuroendocrinology *96(4)*: 294-300, 2012. PMID: 22507901. DOI: 10.1159/000336941

42 Grozinsky-Glasberg S, Kaltsas G, Kaltsatou M, Lev-Cohain N, Klimov A, Vergadis V, Uri I, Bloom AI and Gross DJ: Hepatic intra-arterial therapies in metastatic neuroendocrine tumors: lessons from clinical practice. Endocrine *60(3)*: 499-509, 2018. PMID: 29383678. DOI: 10.1007/s12020-018-1537-0

43 Gupta S, Yao JC, Ahrar K, Wallace MJ, Morello FA, Madoff DC, Murthy R, Hicks ME and Ajani JA: Hepatic artery embolization and chemoembolization for treatment of patients with metastatic carcinoid tumors: the M.D. Anderson experience. Cancer J *9(4)*: 261-267, 2003. PMID: 12967136. DOI: 10.1097/00130404-200307000-00008

44 Mayo SC, de Jong MC, Bloomston M, Pulitano C, Clary BM, Reddy SK, Clark Gamblin T, Celinski SA, Kooby DA, Staley CA, Stokes JB, Chu CK, Arrese D, Ferrero A, Schulick RD, Choti MA, Geschwind JF, Strub J, Bauer TW, Adams RB, Aldrighetti L, Mentha G, Capussotti L and Pawlik TM: Surgery versus intra-arterial therapy for neuroendocrine liver metastasis: a multicenter international analysis. Ann Surg Oncol *18(13)*: 3657-3665, 2011. PMID: 21681380. DOI: 10.1245/s10434-011-1832-y

45 Alese OB, Jiang R, Shaib W, Wu C, Akce M, Behera M and El-Rayes BF: High-grade gastrointestinal neuroendocrine carcinoma management and outcomes: a National Cancer Database study. Oncologist *24(7)*: 911-920, 2019. PMID: 30482824. DOI: 10.1634/theoncologist.2018-0382

46 Strosberg J, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, Mittra E, Kunz PL, Kulke MH, Jacene H, Bushnell D, O'Dorisio TM, Baum RP, Kulkarni HR, Caplin M, Lebtahi R, Hobday T, Delpassand E, Van Cutsem E, Benson A, Srirajaskanthan R, Pavel M, Mora J, Berlin J, Grande E, Reed N, Seregni E, Öberg K, Lopera Sierra M, Santoro P, Thevenet T, Erion JL, Ruszniewski P, Kwekkeboom D, Krenning E and NETTER-1 Trial Investigators: Phase 3 trial of ^{177}Lu-Dotatate for midgut neuroendocrine tumors. N Engl J Med *376(2)*: 125-135, 2017. PMID: 28076709. DOI: 10.1056/NEJMoa1607427

47 Das S, Al-Toubah T, El-Haddad G and Strosberg J: ^{177}Lu-DOTATATE for the treatment of gastroenteropancreatic neuroendocrine tumors. Expert Rev Gastroenterol Hepatol *13(11)*: 1023-1031, 2019. PMID: 31652074. DOI: 10.1080/17474124.2019.1685381

48 Sorbye H, Kong G and Grozinsky-Glasberg S: PRRT in high-grade gastroenteropancreatic neuroendocrine neoplasms (WHO G3). Endocr Relat Cancer *27(3)*: R67-R77, 2020. PMID: 31846429. DOI: 10.1530/ERC-19-0400

49 Strosberg JR, Halfdanarson TR, Bellizzi AM, Chan JA, Dillon JS, Heaney AP, Kunz PL, O'Dorisio TM, Salem R, Segelov E, Howe JR, Pommier RF, Brendtro K, Bashir MA, Singh S, Soulen MC, Tang L, Zacks JS, Yao JC and Bergsland EK: The North American Neuroendocrine Tumor Society Consensus guidelines for surveillance and medical management of midgut neuroendocrine tumors. Pancreas *46(6)*: 707-714, 2017. PMID: 28609356. DOI: 10.1097/MPA.0000000000000850

50 Cives M and Strosberg J: Treatment strategies for metastatic neuroendocrine tumors of the gastrointestinal tract. Curr Treat Options Oncol *18(3)*: 14, 2017. PMID: 28286921. DOI: 10.1007/s11864-017-0461-5

51 Zanini S, Renzi S, Giovinazzo F and Bermano G: mTOR pathway in gastroenteropancreatic neuroendocrine tumor (GEP-NETs). Front Endocrinol (Lausanne) *11*: 562505, 2020. PMID: 33304317. DOI: 10.3389/fendo.2020.562505

52 Delle Fave G, O'Toole D, Sundin A, Taal B, Ferolla P, Ramage JK, Ferone D, Ito T, Weber W, Zheng-Pei Z, De Herder WW, Pascher A, Ruszniewski P and Vienna Consensus Conference participants: ENETS Consensus guidelines update for gastroduodenal neuroendocrine neoplasms. Neuroendocrinology *103(2)*: 119-124, 2016. PMID: 26784901. DOI: 10.1159/000443168

53 Scherübl H and Cadiot G: Early gastroenteropancreatic neuroendocrine tumors: endoscopic therapy and surveillance.

Visc Med *33(5)*: 332-338, 2017. PMID: 29177161. DOI: 10.1159/000459404

54 de Mestier L, Brixi H, Gincul R, Ponchon T and Cadiot G: Updating the management of patients with rectal neuroendocrine tumors. Endoscopy *45(12)*: 1039-1046, 2013. PMID: 24163193. DOI: 10.1055/s-0033-1344794

55 Shah MH, Goldner WS, Halfdanarson TR, Bergsland E, Berlin JD, Halperin D, Chan J, Kulke MH, Benson AB, Blaszkowsky LS, Eads J, Engstrom PF, Fanta P, Giordano T, He J, Heslin MJ, Kalemkerian GP, Kandeel F, Khan SA, Kidwai WZ, Kunz PL, Kuvshinoff BW, Lieu C, Pillarisetty VG, Saltz L, Sosa JA, Strosberg JR, Sussman CA, Trikalinos NA, Uboha NA, Whisenant J, Wong T, Yao JC, Burns JL, Ogba N and Zuccarino-Catania G: NCCN Guidelines insights: neuroendocrine and adrenal tumors, version 2.2018. J Natl Compr Canc Netw *16(6)*: 693-702, 2018. PMID: 29891520. DOI: 10.6004/jnccn.2018.0056

56 Sackstein PE, O'Neil DS, Neugut AI, Chabot J and Fojo T: Epidemiologic trends in neuroendocrine tumors: An examination of incidence rates and survival of specific patient subgroups over the past 20 years. Semin Oncol *45(4)*: 249-258, 2018. PMID: 30348533. DOI: 10.1053/j.seminoncol.2018.07.001

57 Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, Shih T and Yao JC: Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. JAMA Oncol *3(10)*: 1335-1342, 2017. PMID: 28448665. DOI: 10.1001/jamaoncol.2017.0589

58 Trendle MC, Moertel CG and Kvols LK: Incidence and morbidity of cholelithiasis in patients receiving chronic octreotide for metastatic carcinoid and malignant islet cell tumors. Cancer *79(4)*: 830-834, 1997. PMID: 9024721. DOI: 10.1002/(sici)1097-0142(19970215)79:4<830::aid-cncr20>3.0.co;2-#

59 Howe JR, Cardona K, Fraker DL, Kebebew E, Untch BR, Wang YZ, Law CH, Liu EH, Kim MK, Menda Y, Morse BG, Bergsland EK, Strosberg JR, Nakakura EK and Pommier RF: The surgical management of small bowel neuroendocrine tumors: Consensus guidelines of the North American Neuroendocrine Tumor Society. Pancreas *46(6)*: 715-731, 2017. PMID: 28609357. DOI: 10.1097/MPA.0000000000000846

60 Ramezani M and Sadeghi M: Carcinoid tumour of the oesophagus: a systematic review. Prz Gastroenterol *13(3)*: 196-199, 2018. PMID: 30302162. DOI: 10.5114/pg.2018.78285

61 Giannetta E, Guarnotta V, Rota F, de Cicco F, Grillo F, Colao A, Faggiano A and NIKE: A rare rarity: Neuroendocrine tumor of the esophagus. Crit Rev Oncol Hematol *137*: 92-107, 2019. PMID: 31014519. DOI: 10.1016/j.critrevonc.2019.02.012

62 Wong AT, Shao M, Rineer J, Osborn V, Schwartz D and Schreiber D: Treatment and survival outcomes of small cell carcinoma of the esophagus: an analysis of the National Cancer Data Base. Dis Esophagus *30(2)*: 1-5, 2017. PMID: 27860114. DOI: 10.1111/dote.12487

63 Gray KD, Moore MD, Panjwani S, Elmously A, Afaneh C, Fahey TJ 3rd and Zarnegar R: Predicting survival and response to treatment in gastroesophageal neuroendocrine tumors: an analysis of the National Cancer Database. Ann Surg Oncol *25(5)*: 1418-1424, 2018. PMID: 29476295. DOI: 10.1245/s10434-018-6389-6

64 Morita M, Taguchi K, Kagawa M, Nakanoko T, Uehara H, Sugiyama M, Ota M, Ikebe M, Sugimachi K, Esaki T and Toh Y: Treatment strategies for neuroendocrine carcinoma of the upper digestive tract. Int J Clin Oncol *25(5)*: 842-850, 2020. PMID: 32036480. DOI: 10.1007/s10147-020-01631-y

65 Deng HY, Li G, Luo J, Li XR, Alai G and Lin YD: The role of surgery in treating resectable limited disease of esophageal neuroendocrine carcinoma. World J Surg *42(8)*: 2428-2436, 2018. PMID: 29340724. DOI: 10.1007/s00268-018-4475-3

66 Murakami R, Nishimura R, Baba Y, Yumoto E, Oya N and Yamashita Y: Concurrent chemoradiation therapy with low-dose CDDP and UFT for glottic carcinomas: evaluation using the sixth edition of the UICC TNM staging system. Acta Oncol *45(2)*: 162-167, 2006. PMID: 16546861. DOI: 10.1080/02841860500490269

67 Xu L, Li Y, Liu X, Sun H, Zhang R, Zhang J, Zheng Y, Wang Z, Liu S and Chen X: Treatment strategies and prognostic factors of limited-stage primary small cell carcinoma of the esophagus. J Thorac Oncol *12(12)*: 1834-1844, 2017. PMID: 29024756. DOI: 10.1016/j.jtho.2017.09.1966

68 Rindi G, Luinetti O, Cornaggia M, Capella C and Solcia E: Three subtypes of gastric argyrophil carcinoid and the gastric neuroendocrine carcinoma: a clinicopathologic study. Gastroenterology *104(4)*: 994-1006, 1993. PMID: 7681798. DOI: 10.1016/0016-5085(93)90266-f

69 Rindi G, Arnord R, Bosman FT, Capella C, Klimstra DS, Kloppel G, Komminoth P and Solcia E: Nomenclature and classification of Neuroendocrine Neoplasms of the Digestive System. In: F.T. Bosman, F. Carneiro, R.H. Hruban and N.D. Theise (eds.). WHO classification of tumours of the digestive system, 13-14, Lyon, France, International Agency for Research on Cancer, 2010.

70 Sato Y, Hashimoto S, Mizuno K, Takeuchi M and Terai S: Management of gastric and duodenal neuroendocrine tumors. World J Gastroenterol *22(30)*: 6817-6828, 2016. PMID: 27570419. DOI: 10.3748/wjg.v22.i30.6817

71 Gluckman CR and Metz DC: Gastric neuroendocrine tumors (carcinoids). Curr Gastroenterol Rep *21(4)*: 13, 2019. PMID: 30868284. DOI: 10.1007/s11894-019-0684-7

72 Scherübl H, Jensen RT, Cadiot G, Stölzel U and Klöppel G: Neuroendocrine tumors of the small bowels are on the rise: Early aspects and management. World J Gastrointest Endosc *2(10)*: 325-334, 2010. PMID: 21160582. DOI: 10.4253/wjge.v2.i10.325

73 Zhang XF, Wu XN, Tsilimigras DI, Poultsides G, Rocha F, Abbott DE, Fields R, Idrees K, Cho C, Maithel SK, Pawlik TM and other members of the US Neuroendocrine Tumor Study Group: Duodenal neuroendocrine tumors: Impact of tumor size and total number of lymph nodes examined. J Surg Oncol *120(8)*: 1302-1310, 2019. PMID: 31680243. DOI: 10.1002/jso.25753

74 Scherübl H, Schwertner C, Steinberg J, Stölzel U, Pohl J, Dralle H and Klöppel G: Neuroendocrine tumors of the small bowels are on the rise: early tumors and their management. Z Gastroenterol *48(3)*: 406-413, 2010. PMID: 20183784. DOI: 10.1055/s-0028-1109862

75 Norton JA, Alexander HR, Fraker DL, Venzon DJ, Gibril F and Jensen RT: Does the use of routine duodenotomy (DUODX) affect rate of cure, development of liver metastases, or survival in patients with Zollinger-Ellison syndrome? Ann Surg *239(5)*: 617-25; discussion 626, 2004. PMID: 15082965. DOI: 10.1097/01.sla.0000124290.05524.5e

76 Hoffmann KM, Furukawa M and Jensen RT: Duodenal neuroendocrine tumors: Classification, functional syndromes, diagnosis and medical treatment. Best Pract Res Clin Gastroenterol *19(5)*: 675-697, 2005. PMID: 16253893. DOI: 10.1016/j.bpg.2005.05.009

77 Ma ZY, Gong YF, Zhuang HK, Zhou ZX, Huang SZ, Zou YP, Huang BW, Sun ZH, Zhang CZ, Tang YQ and Hou BH: Pancreatic neuroendocrine tumors: A review of serum biomarkers, staging, and management. World J Gastroenterol *26(19)*: 2305-2322, 2020. PMID: 32476795. DOI: 10.3748/wjg.v26.i19.2305

78 Falconi M, Eriksson B, Kaltsas G, Bartsch DK, Capdevila J, Caplin M, Kos-Kudla B, Kwekkeboom D, Rindi G, Klöppel G, Reed N, Kianmanesh R, Jensen RT and Vienna Consensus Conference participants: ENETS Consensus guidelines update for the management of patients with functional pancreatic neuroendocrine tumors and non-functional pancreatic neuroendocrine tumors. Neuroendocrinology *103(2)*: 153-171, 2016. PMID: 26742109. DOI: 10.1159/000443171

79 Howe JR, Merchant NB, Conrad C, Keutgen XM, Hallet J, Drebin JA, Minter RM, Lairmore TC, Tseng JF, Zeh HJ, Libutti SK, Singh G, Lee JE, Hope TA, Kim MK, Menda Y, Halfdanarson TR, Chan JA and Pommier RF: The North American Neuroendocrine Tumor Society Consensus paper on the surgical management of pancreatic neuroendocrine tumors. Pancreas *49(1)*: 1-33, 2020. PMID: 31856076. DOI: 10.1097/MPA.0000000000001454

80 Kulke MH, Anthony LB, Bushnell DL, de Herder WW, Goldsmith SJ, Klimstra DS, Marx SJ, Pasieka JL, Pommier RF, Yao JC, Jensen RT and North American Neuroendocrine Tumor Society (NANETS): NANETS treatment guidelines: well-differentiated neuroendocrine tumors of the stomach and pancreas. Pancreas *39(6)*: 735-752, 2010. PMID: 20664472. DOI: 10.1097/MPA.0b013e3181ebb168

81 Norton JA, Fraker DL, Alexander HR and Jensen RT: Value of surgery in patients with negative imaging and sporadic Zollinger-Ellison syndrome. Ann Surg *256(3)*: 509-517, 2012. PMID: 22868363. DOI: 10.1097/SLA.0b013e318265f08d

82 Doi R: Determinants of surgical resection for pancreatic neuroendocrine tumors. J Hepatobiliary Pancreat Sci *22(8)*: 610-617, 2015. PMID: 25773163. DOI: 10.1002/jhbp.224

83 Oberg K: Pancreatic endocrine tumors. Semin Oncol *37(6)*: 594-618, 2010. PMID: 21167379. DOI: 10.1053/j.seminoncol.2010.10.014

84 Falconi M, Bartsch DK, Eriksson B, Klöppel G, Lopes JM, O'Connor JM, Salazar R, Taal BG, Vullierme MP, O'Toole D and Barcelona Consensus Conference participants: ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms of the digestive system: well-differentiated pancreatic non-functioning tumors. Neuroendocrinology *95(2)*: 120-134, 2012. PMID: 22261872. DOI: 10.1159/000335587

85 Ausania F and Senra Del Rio P: Lymphadenectomy in pancreatic neuroendocrine neoplasms: Why are we still debating? Pancreatology *18(8)*: 855-861, 2018. PMID: 30253923. DOI: 10.1016/j.pan.2018.09.005

86 Hashim YM, Trinkaus KM, Linehan DC, Strasberg SS, Fields RC, Cao D and Hawkins WG: Regional lymphadenectomy is indicated in the surgical treatment of pancreatic neuroendocrine tumors (PNETs). Ann Surg *259(2)*: 197-203, 2014. PMID: 24253141. DOI: 10.1097/SLA.0000000000000348

87 Bettini R, Partelli S, Boninsegna L, Capelli P, Crippa S, Pederzoli P, Scarpa A and Falconi M: Tumor size correlates with malignancy in nonfunctioning pancreatic endocrine tumor. Surgery *150(1)*: 75-82, 2011. PMID: 21683859. DOI: 10.1016/j.surg.2011.02.022

88 Dong DH, Zhang XF, Poultsides G, Rocha F, Weber S, Fields R, Idrees K, Cho C, Maithel SK, Pawlik TM and other members of the US Neuroendocrine Tumor Study Group: Impact of tumor size and nodal status on recurrence of nonfunctional pancreatic neuroendocrine tumors ≤2 cm after curative resection: A multi-institutional study of 392 cases. J Surg Oncol *120(7)*: 1071-1079, 2019. PMID: 31571225. DOI: 10.1002/jso.25716

89 Haugvik SP, Janson ET, Österlund P, Langer SW, Falk RS, Labori KJ, Vestermark LW, Grønbæk H, Gladhaug IP and Sorbye H: Surgical treatment as a principle for patients with high-grade pancreatic neuroendocrine carcinoma: a Nordic multicenter comparative study. Ann Surg Oncol *23(5)*: 1721-1728, 2016. PMID: 26678407. DOI: 10.1245/s10434-015-5013-2

90 Pasquer A, Walter T, Rousset P, Hervieu V, Forestier J, Lombard-Bohas C and Poncet G: Lymphadenectomy during small bowel neuroendocrine tumor surgery: the concept of skip metastases. Ann Surg Oncol *23(Suppl 5)*: 804-808, 2016. PMID: 27613554. DOI: 10.1245/s10434-016-5574-8

91 Folkestad O, Wasmuth HH, Mjønes P, Fougner R, Hauso Ø and Fossmark R: Survival and disease recurrence in patients operated for small intestinal neuroendocrine tumors at a referral hospital. Surg Oncol *35*: 336-343, 2020. PMID: 32979699. DOI: 10.1016/j.suronc.2020.09.015

92 Le Roux C, Lombard-Bohas C, Delmas C, Dominguez-Tinajero S, Ruszniewski P, Samalin E, Raoul JL, Renard P, Baudin E, Robaskiewicz M, Mitry E, Cadiot G and Groupe d'étude des Tumeurs Endocrines (GTE): Relapse factors for ileal neuroendocrine tumours after curative surgery: a retrospective French multicentre study. Dig Liver Dis *43(10)*: 828-833, 2011. PMID: 21641888. DOI: 10.1016/j.dld.2011.04.021

93 Walsh JC, Schaeffer DF, Kirsch R, Pollett A, Manzoni M, Riddell RH and Albarello L: Ileal "carcinoid" tumors-small size belies deadly intent: high rate of nodal metastasis in tumors ≤1 cm in size. Hum Pathol *56*: 123-127, 2016. PMID: 27327193. DOI: 10.1016/j.humpath.2016.05.023

94 Landry CS, Lin HY, Phan A, Charnsangavej C, Abdalla EK, Aloia T, Nicolas Vauthey J, Katz MH, Yao JC and Fleming JB: Resection of at-risk mesenteric lymph nodes is associated with improved survival in patients with small bowel neuroendocrine tumors. World J Surg *37(7)*: 1695-1700, 2013. PMID: 23657749. DOI: 10.1007/s00268-013-1918-8

95 Blažević A, Hofland J, Hofland LJ, Feelders RA and de Herder WW: Small intestinal neuroendocrine tumours and fibrosis: an entangled conundrum. Endocr Relat Cancer *25(3)*: R115-R130, 2018. PMID: 29233841. DOI: 10.1530/ERC-17-0380

96 Niederle B, Pape UF, Costa F, Gross D, Kelestimur F, Knigge U, Öberg K, Pavel M, Perren A, Toumpanakis C, O'Connor J, O'Toole D, Krenning E, Reed N, Kianmanesh R and Vienna Consensus Conference participants: ENETS Consensus guidelines update for neuroendocrine neoplasms of the Jejunum and Ileum. Neuroendocrinology *103(2)*: 125-138, 2016. PMID: 26758972. DOI: 10.1159/000443170

97 Ahmed A, Turner G, King B, Jones L, Culliford D, McCance D, Ardill J, Johnston BT, Poston G, Rees M, Buxton-Thomas M, Caplin M and Ramage JK: Midgut neuroendocrine tumours with liver metastases: results of the UKINETS study. Endocr Relat Cancer *16(3)*: 885-894, 2009. PMID: 19458024. DOI: 10.1677/ERC-09-0042

98 Bennett S, Coburn N, Law C, Mahar A, Zhao H, Singh S, Zuk V, Myrehaug S, Gupta V, Levy J and Hallet J: Upfront small

bowel resection for small bowel neuroendocrine tumors with synchronous metastases: a propensity-score matched comparative population-based analysis. Ann Surg, 2020. PMID: 33214481. DOI: 10.1097/SLA.0000000000004647

99 Fata CR, Gonzalez RS, Liu E, Cates JM and Shi C: Mesenteric tumor deposits in midgut small intestinal neuroendocrine tumors are a stronger indicator than lymph node metastasis for liver metastasis and poor prognosis. Am J Surg Pathol *41(1)*: 128-133, 2017. PMID: 27684993. DOI: 10.1097/PAS.0000000000000751

100 Mehrvarz Sarshekeh A, Advani S, Halperin DM, Conrad C, Shen C, Yao JC and Dasari A: Regional lymph node involvement and outcomes in appendiceal neuroendocrine tumors: a SEER database analysis. Oncotarget *8(59)*: 99541-99551, 2017. PMID: 29245922. DOI: 10.18632/oncotarget.20362

101 Pawa N, Clift AK, Osmani H, Drymousis P, Cichocki A, Flora R, Goldin R, Patsouras D, Baird A, Malczewska A, Kinross J, Faiz O, Antoniou A, Wasan H, Kaltsas GA, Darzi A, Cwikla JB and Frilling A: Surgical management of patients with neuroendocrine neoplasms of the appendix: appendectomy or more. Neuroendocrinology *106(3)*: 242-251, 2018. PMID: 28641291. DOI: 10.1159/000478742

102 Pape UF, Niederle B, Costa F, Gross D, Kelestimur F, Kianmanesh R, Knigge U, Öberg K, Pavel M, Perren A, Toumpanakis C, O'Connor J, Krenning E, Reed N, O'Toole D and Vienna Consensus Conference participants: ENETS Consensus Guidelines for neuroendocrine neoplasms of the appendix (excluding goblet cell carcinomas). Neuroendocrinology *103(2)*: 144-152, 2016. PMID: 26730583. DOI: 10.1159/000443165

103 Moris D, Tsilimigras DI, Vagios S, Ntanasis-Stathopoulos I, Karachaliou GS, Papalampros A, Alexandrou A, Blazer DG 3RD and Felekouras E: Neuroendocrine neoplasms of the appendix: a review of the literature. Anticancer Res *38(2)*: 601-611, 2018. PMID: 29374682. DOI: 10.21873/anticanres.12264

104 Grozinsky-Glasberg S, Alexandraki KI, Barak D, Doviner V, Reissman P, Kaltsas GA and Gross DJ: Current size criteria for the management of neuroendocrine tumors of the appendix: are they valid? Clinical experience and review of the literature. Neuroendocrinology *98(1)*: 31-37, 2013. PMID: 23051855. DOI: 10.1159/000343801

105 Basuroy R, Haji A, Ramage JK, Quaglia A and Srirajaskanthan R: Review article: the investigation and management of rectal neuroendocrine tumours. Aliment Pharmacol Ther *44(4)*: 332-345, 2016. PMID: 27302838. DOI: 10.1111/apt.13697

106 Bertani E, Ravizza D, Milione M, Massironi S, Grana CM, Zerini D, Piccioli AN, Spinoglio G and Fazio N: Neuroendocrine neoplasms of rectum: A management update. Cancer Treat Rev *66*: 45-55, 2018. PMID: 29684743. DOI: 10.1016/j.ctrv.2018.04.003

107 Zhou X, Xie H, Xie L, Li J and Fu W: Factors associated with lymph node metastasis in radically resected rectal carcinoids: a systematic review and meta-analysis. J Gastrointest Surg *17(9)*: 1689-1697, 2013. PMID: 23818123. DOI: 10.1007/s11605-013-2249-7

108 Konishi T, Watanabe T, Kishimoto J, Kotake K, Muto T, Nagawa H and Japanese Society for Cancer of the Colon and Rectum: Prognosis and risk factors of metastasis in colorectal carcinoids: results of a nationwide registry over 15 years. Gut *56(6)*: 863-868, 2007. PMID: 17213340. DOI: 10.1136/gut.2006.109157

109 Soga J: Carcinoids of the rectum: an evaluation of 1271 reported cases. Surg Today *27(2)*: 112-119, 1997. PMID: 9017986. DOI: 10.1007/BF02385898

110 Shields CJ, Tiret E, Winter DC and International Rectal Carcinoid Study Group: Carcinoid tumors of the rectum: a multi-institutional international collaboration. Ann Surg *252(5)*: 750-755, 2010. PMID: 21037430. DOI: 10.1097/SLA.0b013e3181fb8df6

111 Kim J, Kim JH, Lee JY, Chun J, Im JP and Kim JS: Clinical outcomes of endoscopic mucosal resection for rectal neuroendocrine tumor. BMC Gastroenterol *18(1)*: 77, 2018. PMID: 29866049. DOI: 10.1186/s12876-018-0806-y

112 Sohn B, Kwon Y, Ryoo SB, Song I, Kwon YH, Lee DW, Moon SH, Park JW, Jeong SY and Park KJ: Predictive factors for lymph node metastasis and prognostic factors for survival in rectal neuroendocrine tumors. J Gastrointest Surg *21(12)*: 2066-2074, 2017. PMID: 29047070. DOI: 10.1007/s11605-017-3603-y

113 Hrabe J: Neuroendocrine tumors of the appendix, colon, and rectum. Surg Oncol Clin N Am *29(2)*: 267-279, 2020. PMID: 32151360. DOI: 10.1016/j.soc.2019.11.010

114 Tran CG, Sherman SK, Chandrasekharan C and Howe JR: Surgical management of neuroendocrine tumor liver metastases. Surg Oncol Clin N Am *30(1)*: 39-55, 2021. PMID: 33220808. DOI: 10.1016/j.soc.2020.08.001

115 Gangi A and Howe JR: The landmark series: neuroendocrine tumor liver metastases. Ann Surg Oncol *27(9)*: 3270-3280, 2020. PMID: 32632880. DOI: 10.1245/s10434-020-08787-x

116 Moris D, Tsilimigras DI, Ntanasis-Stathopoulos I, Beal EW, Felekouras E, Vernadakis S, Fung JJ and Pawlik TM: Liver transplantation in patients with liver metastases from neuroendocrine tumors: A systematic review. Surgery *162(3)*: 525-536, 2017. PMID: 28624178. DOI: 10.1016/j.surg.2017.05.006

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