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Contents

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Contents

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Contents

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MINIREVIEWS

Role of surgical treatments in high-grade or advanced gastroenteropancreatic neuroendocrine neoplasms

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Abstract

Over the last 40 years, the incidence and prevalence of gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) have continued to increase. Compared to other epithelial neoplasms in the same organ, GEP-NENs exhibit indolent biological behavior, resulting in more chances to undergo surgery. However, the role of surgery in high-grade or advanced GEP-NENs is still controversial. Surgery is associated with survival improvement of well-differentiated high-grade GEP-NENs, whereas poorly differentiated GEP-NENs that may benefit from resection require careful selection based on Ki67 and other tissue bio-markers. Additionally, surgery also plays an important role in locally advanced and metastatic disease. For locally advanced GEP-NENs, isolated major vascular involvement is no longer an absolute contraindication. In the setting of metastatic GEP-NENs, radical intended surgery is recommended for patients with low-grade and resectable metastases. For unresectable metastatic disease, a variety of surgical approaches, including cytoreduction of liver metastasis, liver transplantation, and surgery after neoadjuvant treatment, show survival benefits. Primary tumor resection in GEP-NENs with unresectable metastatic disease is associated with symptom control, prolonged survival, and improved sensitivity toward systemic therapies. Although there is no established neoadjuvant or adjuvant strategy, increasing attention has been given to this emerging research area. Some studies have reported that neoadjuvant therapy effectively reduces tumor burden, improves the effectiveness of subsequent surgery, and decreases surgical complications.

Key Words: Gastroenteropancreatic neuroendocrine neoplasms; Neuroendocrine carcinomas; Surgery; Hepatic debulking; Liver transplant; Transplant oncology

Core Tip: Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) encompass a heterogeneous group of tumors with unique indolent biological behavior. The role of surgery in high-grade or advanced GEP-NENs is still controversial. There are several highlights of this review. First, we address the surgical benefits of selected high-grade GEP-NENs and summarize the tumor biological markers correlated with a prognosis. Second, we review various surgical strategies, including curative resection, debulking, resection after neoadjuvant therapy for metastatic GEP-NENs, and the latest clinical evidence. Finally, liver transplantation presents a curative therapeutic option for GEP-NEN patients with liver metastasis. We summarize the new findings and propose directions for future development.

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INTRODUCTION

Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are rare lesions arising from neuroendocrine cells scattered throughout the body. Although GEP-NENs are still regarded as uncommon neoplasms, both their incidence and prevalence have continued to increase over the last 40 years[1,2]. As GEP-NENs are morphologically and biologically heterogeneous[3,4], the World Health Organization has classified them into three grades based on the proliferation index (Ki67) and differentiation level[5]. G3 NENs, showing a Ki67 value (> 20%) and/or mitotic index (> 20 mitoses/10 high-power field), are further subdivided into two subgroups as follows: Well-differentiated neuroendocrine tumors (G3 NET) and poorly differentiated neuroendocrine carcinomas (G3 NEC) (Table 1)[6]. The incidence of liver metastasis (LM) in GEP-NENs is high, and the median overall survival (OS) for patients with metastatic GEP-NENs is 2-4 years[7].

Given the associated high risk of developing distant metastases, the role of surgery in the treatment regimen for high-grade GEP-NEN (hgGEP-NEN) remains controversial. Since treatment strategies for hgGEP-NEN have generally been extrapolated from the findings for small-cell lung cancer[8,9], surgery is not included in the primary therapeutic regimen[10,11]. Given the differences in prognoses and therapeutic responses between pulmonary and digestive neuroendocrine carcinomas, it is necessary to evaluate the role of surgery in GEP-NENs. Moreover, surgery is generally considered nonbeneficial for patients with metastatic diseases. However, as a large proportion of GEP-NEN patients exhibit relatively indolent biology, some studies also report the survival benefits of surgery[12,13]. Therefore, the purpose of this review is to summarize and discuss surgical management strategies for high-grade or advanced GEP-NENs.

SURGERY FOR LOCALIZED HGGEP-NEN

Platinum-based chemotherapy is considered the standard treatment for hgGEP-NEN, whereas the role of surgery has not been fully assessed. In this setting, Merola *et al*[14] investigated survival outcomes in 60 patients with localized hgGEP-NEN who underwent radical surgical procedures. The 2-year OS rate was 64.5%, and the 2-year recurrence-free survival (RFS) rate was 44.9%[14]. Moreover, in a Nordic multicenter retrospective cohort study, the median OS in 201-G3 GEP-NEN patients upon surgical resection was 32 mo[15]. In a large retrospective study consisting of 1517 G3 GEP-NEC patients, surgery was significantly associated with improved OS [hazard ratio (HR): 0.41][16]. Despite the lack of high-quality long-term prospective trials, there is sufficient evidence to suggest that careful patient selection for surgical resection can increase clinical benefits in G3 GEP-NENs. Many factors can predict the

Table 1 Classification for gastroenteropancreatic neuroendocrine neoplasms by World Health Organization

Terminology	Differentiation	Grade	Ki67 index, %	Mitotic count, 2 mm^2
NET, G1	Well differentiated	Low	< 3	< 2
NET, G2	Well differentiated	Intermediate	3–20	2–20
NET, G3	Well differentiated	High	> 20	> 20
NEC, G3	Poorly differentiated	High	> 20	> 20

NET: Neuroendocrine tumor; NEC: Neuroendocrine carcinoma.

prognosis of GEP-NENs and may aid in the selection of suitable patients for surgery; among them, differentiation and the Ki67 value are the two most important prognostic factors[17-19].

Since hgGEP-NENs are highly heterogeneous, comprising both G3 NETs and G3 NECs, G3 NENs cannot be considered a single entity[20]. In contrast to well-differentiated NENs, G3 NEC is highly aggressive and metastasizes early, resulting in a poor prognosis[4]. Tumor differentiation is associated with surgical prognosis. In a retrospective study consisting of 67 patients, including 21 with pancreatic G3 NETs and 46 with pancreatic G3 NECs, those with G3 NETs were found to benefit from surgical resection, unlike those with G3 NENs who did not show any significant improvements[21]. Consistently, Merola *et al*[14] drew a similar conclusion from their study involving 60 hgGEP-NEN patients [14]. The OS of patients with G3 NET was significantly better than that in G3 NEC patients; G3 NEC was a marker of a poor prognosis (NEC G3 *vs* NET G3: HR 4.24, P = 0.05). However, in another study, no significant difference was observed in postsurgical survival between G3 NETs and G3 NECs in patients with pancreatic hgGEP-NENs[22]. In a large-scale retrospective study consisting of 2245 patients with GEP NECs, the median survival after surgery was 31 mo (n = 1549) *vs* 9 mo after nonoperative therapy (n = 696, P < 0.001)[23]. The 5-year OS rates were 39% and 10%, respectively. Abdel-Rahman *et al*[16] performed propensity score matching between 233 G3 GEP NEC patients who did not undergo surgery and 233 G3 GEP NEC surgical patients. They reported that radical surgery was significantly associated with improved survival (P < 0.001)[16]. GEP G3 NECs were further distinguished based on poorly differentiated histology and undifferentiated histology; poorly differentiated histology was significantly associated with improved OS compared with undifferentiated histology (HR: 0.83), which could explain the discrepancy in the results of the abovementioned studies. Additionally, heterogeneity within hgGEP-NENs could lead to differences in surgical outcomes, which may be observed in a small sample size. Moreover, the heterogeneity is not only derived from hgGEP-NENs themselves but also the difficulty associated with the morphological diagnoses by pathologists[9,24]. A high percentage of inconclusive diagnoses have been reported (61%), which may be attributed to limited pathological resources, a lack of well-defined histological criteria, and the complexity underlying GEP-NEN origins [25].

The Ki67 value is easier to examine and provides a more objective basis for evaluation. Ki67 can reflect the heterogeneity of hgGEP-NENs and predict responsiveness to treatment[4,26]. Sorbye *et al*[27] evaluated 305 hgGEP-NEN cases and obtained a cutoff value (55% Ki67) by ROC analysis[27]. Patients with Ki67 < 55% showed a better OS than those with Ki67 ≥ 55% but a lower response rate to platinum-based chemotherapy. Differences in treatment responses were also observed for surgical resection. Merola *et al*[14] reported that the median OS for Ki67 ≤ 55% was not achieved *vs* 26 mo in patients with Ki67 > 55% after surgery[14]. Similarly, in a study from Tokyo, 63 hgGEP-NEN patients who underwent surgical resections between 2005 and 2018 were reviewed[28]. Patients were divided into low-Ki67 (Ki67 < 52%) and high-Ki67 (Ki67 ≥ 52%) groups according to the median Ki67 value (52%). In the low Ki67 group, the median survival times were 82.7, 16.3, and 27.7 mo for patients in the R0/1, R2, and chemotherapy groups, respectively. Surgery (P = 0.013, HR = 0.46) and low Ki67 (P = 0.007, HR = 0.43) were independent prognostic factors related to improved OS.

Recently, the National Comprehensive Cancer Network guidelines have recommended hgGEP-NENs with Ki67 < 55%, slow growth, and positivity for somatostatin receptor as the criteria for surgery, although caution for heterogeneity remains[29]. In addition to the Ki67 value, other tissue biomarkers are also correlated with differentiation, including the neuroendocrine markers synaptophysin, chromogranin-A (CgA), death domain-associated protein (DAXX), p53, and Rb1. At present, a conclusive decision for the prognostic value remains lacking for all these biomarkers. Therefore, there is a need for large, long-term studies using GEP-NEN cohorts and assessing the effects of tissue and blood biomarkers.

SURGERY FOR LOCALLY ADVANCED GEP-NEN

Recently, experts from the European Neuroendocrine Tumor Society acknowledged that the surgical strategy for locally advanced pancreatic NENs (pNENs) is an important unanswered query[30]. Birnbaum *et al*[13] evaluated 43 cases of advanced pNENs and 91 cases of isolated pNENs[13]. In the advanced pNEN group, the median survival time for 16 patients who underwent resections of adjacent organs was 90 mo, and the 5-year OS (84%) was not significantly different from that in the isolated pNEN group (P = 0.175), which indicated that nonmetastatic locally advanced pNENs showed a favorable prognosis after surgery. A case series study reviewed 99 locally advanced pNEN patients who underwent surgical resection between 2003 and 2018, including 84 G1/G2, 1 G3, and 14 'tumor grade not available' patients[31]. The 5-year disease-free survival (DFS) was 61%, and the 5-year OS was 91%. Although there was no control group in this study, the excellent prognosis suggested that surgery could be beneficial in patients with locally advanced pNEN. In another study, 25% of patients showed major vascular involvement on preoperative imaging; however, only 17% required resection and reconstruction. Similar to previous studies, major vascular invasion implicated by preoperative imaging might not be fully consistent with intraoperative situations, as the tumors were only abutting or distorting the vein rather than invading in most cases[32,33]. Even though 17% of patients underwent venous resection/reconstruction, none of them died postoperatively. Based on these impressive results, the latest guidelines from the North American Neuroendocrine Tumor Society (NANETS) also recommend that isolated major vascular involvement should not be an absolute contraindication to surgery for patients with advanced pNEN[34]. However, it should be noted that these conclusions were drawn for advanced pNEN only. The outcomes for patients with different primary tumor sites may vary correspondingly. Future studies should examine the role of surgery in GEP-NENs for different primary tumor sites.

Retrospective studies suggest that neoadjuvant peptide receptor radionuclide therapy (PRRT) can effectively reduce the tumor burden and improve surgical safety[35,36]. Parghane *et al*[36] evaluated 57 patients with locally advanced GEP-NENs who had received PRRT[36]. They found that 48 (84%) patients exhibited symptomatic responses, and 15 patients were eligible for resection according to the National Comprehensive Cancer Network criteria for pancreatic ductal adenocarcinoma. Although long-term survival following surgery has not been reported, regression of primary tumors following PRRT was observed, and no hematological or renal side effects were encountered. Therefore, neoadjuvant PRRT may be a potential therapeutic option for locally advanced GEP-NETs.

SURGERY FOR METASTATIC GEP-NEN

Metastasis is the main feature of GEP-NENs, and its most common location is the liver. The incidence of LM is 40%-95%[37-39], which varies based on the origin of primary NEN, with extremely low rates in gastric, appendiceal, and rectal NENs, an incidence rate of 28%-78% in pNENs, and 67%-91% in small intestinal NENs. LM represents a major risk factor for cancer-related death in GEP-NENs, and the only potentially curative option is surgery. However, strategies for surgery and selection of the appropriate patients remain controversial.

Surgery for primary GEP-NEN

According to NANETS guidelines, primary tumor resection (PTR) is recommended for small bowel NEN in unresectable disease, but for pNEN in unresectable disease, there is no consensus[34,40]. Possible benefits for PTR include the reduction of tumor burden, which controls functional symptoms or prevents obstructive complications, and improvement in survival by decreasing the likelihood of distant metastasis and increasing sensitivity toward systemic therapies. A substantial number of studies based on the Surveillance, Epidemiology, and End Results database have demonstrated that PTR is significantly associated with prolonged survival in metastatic GEP-NEN patients[41-43]. Zheng *et al*[42] evaluated a large cohort of 1547 GEP-NEN cases with unresectable LM, including 897 cases with PTR and 650 nonresection patients, using the Surveillance, Epidemiology, and End Results database[42]. They found that the 5-year OS rate for PTR patients was 57% *vs* 15.4% in those who did not undergo PTR; a significant difference in median OS between the groups was observed (not reached *vs* 14 mo, P < 0.001). When the two groups were further stratified into four groups according to their primary tumor locations (gastric, small intestinal, colorectal, and pancreatic NENs), the 5-year OS rates were significantly prolonged in all groups compared with non-PTR patients. However, some differences were observed among the groups, as PTR groups patients were younger, had many small tumors, and presented well-differentiated and a few poorly differentiated neoplasms. All these factors were significantly associated with survival in both the univariate and multivariate analyses.

Another large study evaluating PTR in a total of 854 IV stage GEP-NEN cases with unresectable or resectable LM from the California Cancer Registry showed similar results[44]. To reduce selection bias, Hüttner *et al*[43] used propensity matching to 442 stage IV pNEN patients who did not receive surgery for metastasis[43]. After propensity score adjustment, significant differences in 5-year OS rates were found between the two groups (52.5% of the PTR group *vs* 20.6% of the non-PTR group). Daskalakis *et al*[45] performed a similar study with 363 asymptomatic stage IV SBNEN cases, including 161 patients undergoing PTR[45]. After propensity matching, no substantial differences were found in the median OS and cancer-specific survival between the surgical and nonsurgical groups. This study suggested that surgery for asymptomatic patients is a topic of further discussion. The survival benefits in the overall GEP-NEN cases may arise from the survival improvement in functional GEP-NENs. Some studies have shown that systemic agents can effectively improve the prognosis of GEP-NENs[46,47]. The use of systemic agents as an adjuvant treatment cannot be controlled in retrospective studies, which leads to an inevitable bias. A lower tumor burden further increases the responsiveness of GEP-NENs to PRRT[7,48]. A retrospective study reviewed 889 GEP-NEN cases; among them, 483 patients who underwent PTR before PRRT and 403 patients who did not undergo PTR before PRRT[49]. In this study, 56 of the 617 patients showed G3 tumors (based on the available grading data). In the prior PTR group, the median OS was 134 mo, and the 5-year OS rate was 70.8%, while in the nonresected group, the median OS was 67 mo, and the 5-year OS rate was 41.7% ($P < 0.001$). Additionally, in patients with pNENs or SBNENs, accounting for 70% of the total patients, these remarkable differences were detected.

Taken together, although several retrospective studies have reported a potential benefit of PTR in metastatic GEP-NENs, the selection bias may be inadvertent. Some factors may aid in the identification and distinction of GEP-NENs from PTR, including functional metastatic GEP-NENs, young age, a small tumor size, and well-differentiated tumor characteristics. The excellent clinical benefits of postoperative PRRT have been previously reported. Based on these encouraging results, a large-scale multicenter prospective study is warranted to confirm and obtain further novel definitive prognostic factors.

Surgery for liver metastasis

Current guidelines propose that G1/G2 NEN LM patients without extrahepatic disease should undergo surgical interventions, while for those with G3 NET LM, resection is not recommended[34,50], as the prognoses and survival outcomes in G3 NEN LM are suboptimal (median OS range: 4.6-29 mo)[51-54]. However, several studies in G3 GEP-NEN patients with resectable LMs have yielded encouraging results in recent years. Galleberg *et al*[55] reviewed the central Nordic GEP-NEC database and reported an OS and RFS in 32 G3 NEN LM cases (8 NETs and 24 NECs) after resection/radiofrequency ablation of 35.9 mo and 8.4 mo, respectively[55]. Ki67 < 55% along with adjuvant chemotherapy were independent significant prognostic factors for favorable outcomes. Consistently, in a retrospective study of a stage IV G3 GEP-NEN cohort, Merola *et al*[56] analyzed 15 patients who underwent radical resection (R0/R1); among them, 7 had G3 NETs, 6 had G3 NECs, and 2 had MiNENs[56]. The median OS was 59 mo, and the median RFS was 8 mo. Unfortunately, there were no comparison groups in these two trials. A direct comparison of different results from the literature is unreliable, especially due to the heterogeneity in G3 GEP-NENs as discussed above, varying range of metastases, and selection biases. However, these findings suggest that highly advanced G3 GEP-NEN cases might benefit from radical resection procedures. Thus far, the lack of studies and small sample sizes limit the identification of subgroups suitable for surgical interventions.

As NEN LMs are seldom isolated or few and most cannot be removed completely, debulking, also referred to as “cytoreductive resection” or “R2 resection”, is used to treat unresectable NEN LMs. Several retrospective studies have suggested that cytoreduction of NEN LMs improves both symptoms and survival[57,58]. Forty years ago, Foster *et al*[59,60] reported good symptom control in 44 cases with at least 95% surgical cytoreduction[59,60]. Likewise, three subsequent studies from the Mayo Clinic reported that at least 90% hepatic cytoreduction provides effective symptomatic palliation and prolongs survival[61,62] However, 90% as the debulking threshold was not carefully calculated using an algorithm but was chosen with the intent to select a suitable threshold, which may result in a loss of potential operative and curative opportunities for numerous patients.

Additionally, the development of new adjuvant therapies (such as the availability of somatostatin analog) may further enhance the efficacy of cytoreduction and expand the beneficiary population. Recently, studies have attempted to propose a lower threshold, and some have demonstrated that cytoreduction > 70% provides survival benefits. Maxwell *et al*[63] estimated the threshold level by dividing 28 pNEN LM cases and 80 SB NEN LM cases into < 50%, ≥ 50%, ≥ 70%, and ≥ 90% categories [63]. The 5-year PFS of all patients was 30.2%, and the 5-year OS was 76.1%. Patients with cytoreduction ≥ 70% showed better OS and PFS than those with cytoreduction < 50%. In this study, only 38.9% of patients showed debulking ≥ 90%, while 63.9% of patients exhibited cytoreduction with a lower threshold of > 70%.

Scott *et al*[64] reviewed 188 NEN LM patients who underwent cytoreductive procedures and stratified them into three groups according to the number of treated metastases (1-5, 6-10, and > 10)[64]. The median OS was 89 mo, and the PFS was 23 mo; there were no significant differences in OS or PFS among the three groups. In both univariate and multivariate analyses, age, grade, Ki67 index, percent liver replacement, and debulking > 70% were significantly associated with OS. When the study population was grouped by percent cytoreduction, the debulking > 70% group showed an improved OS compared with the debulking < 70% group (median 134.3 mo *vs* 37.6 mo, $P < 0.01$); debulking > 90% was not significantly associated with a better outcome compared to the 70%-90% or < 90% groups. This study provided further evidence for adopting a debulking threshold > 70% and indicated that NEN LM patients who underwent cytoreduction for > 10 lesions had acceptable OS. Moreover, the grade was associated with a poor OS and PFS, with HRs of 2.12 for the G2 (97 cases) and 11.69 for the G3 (15 cases) groups. The 23-mo median OS and absence of 5-year OS of G3 did not improve after debulking, unlike previously reported results[65]. However, whether G3 GEP-NEN LM patients may benefit from cytoreduction remains difficult to address based on the current data, and evidence of heterogeneity between primary tumors and LMs is scarce. NANETS recommends that G2 primary or LM is not a contraindication for hepatic cytoreduction[34].

Neoadjuvant therapy may convert unresectable GEP-NEN LMs to resectable forms, reduce the difficulty of surgery, and decrease postoperative complications. To date, various systemic treatments demonstrated their efficacy in controlling tumor progression and reducing tumor burden[66,67]. However, whether neoadjuvant treatments can improve the surgical prognoses in GEP-NEN LM remains unclear. Murase *et al*[68] analyzed 106 pNEN cases with LM or locally advanced tumors[68]. All patients received sunitinib, among which 31 underwent surgery after sunitinib treatment. The median OS was not achieved in the surgical group *vs* 36.7 mo in the nonsurgical group. Poor predictive factors included the absence of surgical resection (HR: 13.1, P = 0.001), poor differentiation, and bilateral liver metastases. Thus, surgery after sunitinib treatment could improve OS for distant metastases or in locally advanced pNEN.

Liver transplantation for hepatic metastases

Compared with debulking, liver transplantation (LT) offers a long-term curative solution to expand the conventional margin in surgical oncology and LT for LMs, an important component of transplant oncology. The world-renowned LT expert Makowka *et al*[69] and Mazzaferro *et al*[70] proposed the Milan NEN criteria in 1995 (Table 2)[69,70]. In their recent report, Mazzaferro *et al*[71] prospectively analyzed 280 GEP-NEN LM cases during a 15-year follow-up[71]. Ultimately, 88 unresectable GEP-NEN LM patients who met the predetermined criteria were included, 42 of whom underwent LT. The 5- and 10-year OS rates for LT patients were 97.2% and 88.8%, respectively, *vs* 50.9% and 22.4% in the non-LT group, with eligibility according to Milan-NEN criteria (n = 46). Moreover, the researchers estimated that the 5- and 10-year survival benefits associated with LT were 12.79 mo and 48.62 mo, respectively, which suggested that the survival benefits increased over time. However, there was an inherent selection bias between the LT and non-LT groups, including a more advanced T-stage and older patients with less locoregional treatments included in the non-LT group. Considering the shortage of donated organs, it is necessary to weight carefully the benefits against the risks.

Kim *et al*[72] performed a systematic review of GEP-NEN LM patients who underwent LT and reported that the 5-year DFS rate ranged from 20% to 32%, which was worse than that of hepatocellular carcinoma (HCC) patients who underwent LT[72]. Due to these high rates of recurrence, Sposito *et al*[73] focused on the postrecurrence survival of GEP-NEN LT patients and observed excellent long-term survival (5-year survival rate of 76.5%, 10-year survival rate of 45.5%)[73]. In conclusion, despite the high recurrence rate, GEP-NEN LT patients still have promising long-term outcomes, which may be attributable to the indolent biological behaviors of GEP-NENs.

For resectable GEP-NEN LM patients who are consistent with the Milan criteria, surgical resection may still be the first option. Ruzzenente *et al*[74] investigated the long-term survival of a multi-institutional cohort of GEP-NEN LM patients undergoing surgical resection and found that 28 of 238 patients met Milan criteria with a 5-year OS of 83%, which was comparable to that reported in GEP-NEN LM patients undergoing LT within Milan criteria[74].

Similar to findings for LT in HCC, patients conforming to the Milan criteria show excellent prognoses from LT; however, this does not imply that the Milan criteria cover all patients who may potentially benefit from LT[75,76]. In a retrospective study, 15 NEN LMs who were up to 64 years of age with 12 of the 15 exceeding 50% hepatic involvement were included; the 5-year OS rate was 90%[77]. Downstaging in HCC has been extensively discussed[75], while in GEP-NEN LMs, high-quality studies are lacking.

Taken together, the survival benefits for resectable GEP-NEN LMs are limited, but for unresectable GEP-NEN LM patients who meet the Milan-NEN criteria, LT is recommended. Several outstanding questions remain to be addressed, including the following: (1) Can the Milan-NEN criteria be safely expanded, and what is the exact threshold? (2) What are the appropriate prognostic factors of GEP-NEN LMs? and (3) How can neoadjuvant be used as downstaging/bridging therapy before LT?

NEOADJUVANT PRRT FOR GEP-NEN

Recently, neoadjuvant therapy has become a critical treatment for various tumors, which may potentially reduce the tumor load, increase the likelihood that patients undergo surgical resection, enhance the safety of surgery, monitor the tumor response, and guide subsequent treatment based on the response to neoadjuvant therapy. Neoadjuvant therapy for NENs primarily includes chemotherapy small molecule drugs and PRRT. At present, the effectiveness of chemotherapy for NENs is not clear [78]. However, neoadjuvant PRRT, particularly ^{90}Y-DOTATATE and ^{177}Lu-DOTATATE, has been used in NENs with good prospects. In a randomized phase III trial (NETTER-1 Clinical Trial), PRRT for well-

Table 2 Milan neuroendocrine neoplasms criteria

	Milan selection criteria of GEP-NEN LM
1	Low grade NEN
2	Portal drainage of the primary tumor with complete resection of extrahepatic disease
3	Liver involvement < 50%
4	Duration of stable disease over 6 mo
5	Age < 60 yr (relative criteria)

GEP-NEN: Gastroenteropancreatic neuroendocrine neoplasms; LM: Liver metastasis.

differentiated, metastatic GEP-NEN effectively reduced the tumor burden, suppressed tumor progression, and prolonged survival[79]. In a study reported by van Vliet *et al*[35], PRRT was used as neoadjuvant therapy in 29 borderline or unresectable nonfunctional pNEN[35]. Thirty-one percent of these patients underwent successful surgery and achieved a better median PFS than those who were not resected (69 mo *vs* 49 mo). In addition to PTR, neoadjuvant PRRT has been evaluated in unresectable NEN LMs and successfully aids downstaging[80]. Several clinical studies are currently underway, including a phase II trial aimed at assessing the safety and efficacy of neoadjuvant PRRT for resectable pNENs with a high recurrence risk (NCT04385992), indicating that neoadjuvant PRRT for GEP-NEN is a promising field.

CONCLUSION

In conclusion, surgery plays a crucial role in the management of GEP-NENs and comprises curative resection, debulking, resection after neoadjuvant therapy, and LT for LMs. Compared with epithelial neoplasms of the same organs, GEP-NENs exhibit indolent biology and better outcomes, which increases the possibility of surgery for patients with hgGEP-NENs or advanced GEP-NENs. HgGEP-NEN is correlated with a poor prognosis. However, its heterogeneity is the major feature, and after careful selection for tumor biology, hgGEP-NENs with low Ki67 show greater benefits from resection. In metastatic GEP-NENs, radical surgery represents a favorable outcome but is limited to only a few patients. For unresectable LMs, cytoreduction improves the prognoses of patients, and the threshold for cytoreduction is reduced from 90% to 70%. LT for hgGEP-NEN LMs shows therapeutic advantages, but several problems need to be addressed. Additionally, neoadjuvant and adjuvant therapies have been investigated in the setting of advanced GEP-NENs, which may further control tumor recurrence. However, in cases of low prevalence and incidence, most of the evidence comes from retrospective studies that include less than 100 cases, and the administration of systemic therapy is not well controlled. The heterogeneity in GEP-NENs further influences the accuracy of the conclusions. Therefore, further multicenter collaborative prospective studies are needed to assess the effects of surgery and determine the prognostic factors.

FOOTNOTES

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