Surgical management for non-functional pancreatic neuroendocrine neoplasms with synchronous liver metastasis: A consensus from the Chinese Study Group for Neuroendocrine Tumors (CSNET)

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Abstract. Pancreatic neuroendocrine neoplasms (p-NENs) are slowly growing tumors with frequent liver metastasis. There is a variety of approaches to treat non-functional p-NENs with synchronous liver metastasis (LM) which complicates the determination of optimal treatment. Based on updated literature review, we discussed the treatment strategy determinants for p-NEN with LM. According to the resectability of primary tumor, the WHO 2010 grade classification and the radiological type of liver metastasis, the CSNET group reached agreements on a number of issues, including the following. Prior to treatment, biopsy is required to confirm pathology. Liver biopsy is important for more accurate grading of tumor and percutaneous core needle biopsy is more available than EUS-FNA. In patients with unresectable primary, surgical resection for liver-metastatic lesions should be avoided. Curative surgery is recommended for G1/G2 p-NET with type I LM and R1 resection also seems to improve overall survival rate. Cytoreductive surgery is recommended for G1/G2 p-NET with type II LM in select patients, and should meet stated requirements. Surgical resection for G1/G2 p-NET with type III LM and p-NEC with LM should be avoided, and insufficient evidence exists to guide the surgical treatment of G3 p-NET with LM. Liver transplantation may be an option in highly select patients. In addition, the optimal time for surgical approach is still required for more evidence.

Introduction

The incidence of pancreatic neuroendocrine neoplasms (p-NENs), which originate from pancreatic neuroendocrine cells, has been increasing over the last 20 years (1,2). The vast majority of p-NENs are non-functioning, with symptoms stemming from distant metastases or mass effects (3,4). In metastatic p-NENs, liver is the most important location for metastatic disease and LM is frequently observed in p-NEN patients (5-7).

Having low mortality and complication rates, surgery for local p-NENs has long been the standard treatment strategy (8). In recent decades, technological improvements have also improved surgical success for liver-metastatic p-NENs, which has an overall mortality rate of <5% (9,10).

To allow for more specific and individualized treatment of liver-metastatic p-NENs, Frilling *et al* (11) classified them into three radiological types. Type I is defined as a single metastasis regardless of size. Type II is defined as an isolated metastatic bulk accompanied by smaller deposits. Type III is defined as a disseminated metastatic spread. These three groups differ significantly in terms of treatment strategies and clinical outcomes (12).

Pathological classification is another key prognostic factor in p-NENs (13). In 2010, the WHO updated their grading system for the pathological classification of p-NEN based on the Ki-67 index and mitotic counts (14). A pancreatic carcinoid is now defined as G1/G2 p-NET, while small-cell or large-cell neuroendocrine carcinoma is defined as G3 p-NEC. Tumors with a Ki-67 index of ≤2%, 3-20% or >20% are classified as G1, G2 and G3, respectively. While a group of well-to-moderately differentiated G3 p-NETs respond more poorly to chemotherapy than poorly differentiated G3 p-NEC, they are nevertheless associated with longer median survival (15). This group of G3 p-NETs may be considered separate from p-NEC (16). In 2013, 15 Chinese pathology experts reached the consensus for NET G3 and defined it as NET with high proliferative activity.

Despite the existence of various guidelines and comprehensive reviews addressing surgical management for non-functional p-NENs with synchronous LM, the best strategy is still poorly defined. In the present study, we report the findings of a panel of multidisciplinary experts from CSNET who assessed available evidence with the aim of developing recommendations for the surgical management of patients with liver-metastatic p-NENs. Consensus statements were developed that take into consideration the radiological

type of liver metastasis, the WHO 2010 grade classification and the resectability of the primary tumor.

Materials and methods

The PubMed database was searched for studies relating to the treatment of p-NENs with LM by entering the terms including (pancreatic neuroendocrine tumor OR neuroendocrine tumor OR carcinoma), (operative OR surgical, operative surgical OR pancreatectomies OR pancreaticoduodenectomy OR pancreaticoduodenectomies OR duodenopancreatectomy OR duodenopancreatectomies OR primary resection), (metastatic OR metastasis OR metastases), (neoplasm OR neoplasms), and (liver OR hepatic). Randomized trials, reviews and observational studies were included. Studies published in English were reviewed and selected for further screening analyses and for subsequent consensus studies. Data extraction was carried out by all experts in CSNET.

Results and Consensus statements

Pathological confirmation. Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) and percutaneous core needle biopsy are two common methods for obtaining tissue samples in p-NENs (17).

EUS-FNA has become a successful approach in establishing a definitive tissue diagnosis of p-NENs for more than 20 years (18). Several retrospective studies have shown advantages of EUS-FNA, including generation of high-resolution images enabling detection of small lesions (19-21). However, EUS-FNA has an accuracy fluctuation dependent upon the tumor type. Diagnostic accuracy is lower for p-NENs (46.7%) than for adenocarcinomas (81.4%) (22). The accuracy in the grading of p-NENs (the concordance rate between EUS-FNA samples and surgical specimens) is also unsatisfactory (23), especially without adequate cellularity (24). Only when more than 2000 tumor cells obtained by EUS-FNA may increase the accuracy of tumor grading (24). Therefore, due to the small amount of tissue obtained from EUS-FNA, it remains unclear if EUS-FNA samples truly reflect the entire tumor.

In comparison, percutaneous core needle biopsy has relatively greater availability, lower cost, a higher success rate, enables access to sufficient material and allows access to lesions in any part of the pancreas (17,25-27). Sufficient material can be extracted to determine cell type and origin via histologic and immunohistochemical analyses, thus, allowing for reliable differentiation of p-NENs (28). Moreover, collecting sufficient tissue may also decrease the difference between percutaneous core needle biopsy and surgical specimens.

There is no guideline as to whether liver-metastatic lesions should be biopsied for tumor grading in cases of liver-metastatic p-NENs and several studies have considered the homogeneity of the Ki-67 staining expression between primaries and metastases (29,30). Nevertheless, Zen *et al* (31) reported that biopsy of liver metastasis may yield a higher Ki-67 index than that in primary tumor; moreover, increased Ki-67 index in liver metastases is associated with a poorer prognosis. Similar results were also reported in another

two retrospective studies (32,33). Therefore, liver biopsy is required for an accurate evaluation and biopsies of both primary tumors and metastatic tumors was recommended by a Canadian National Expert Group (34).

According to the ENETS 2012 guidelines, pathological classification (either primary tumor or metastatic lesions) should be confirmed before treatment, as only G1/G2 are recommended for operation in liver-metastatic p-NENs (35). The updated NCCN guidelines (8), NANETS guidelines (36), and the European Society for Medical Oncology (ESMO) (37) guidelines all suggest that Ki-67 assessment is required in liver-metastatic p-NENs, no matter which method is used.

Consensus statements. Biopsy for Ki-67 assessment is required in liver-metastatic p-NENs before a treatment decision is made. Liver biopsy is important for more accurate grading of tumors in patients with LM. Percutaneous core needle biopsy is more available than EUS-FNA.

Liver-metastatic p-NENs with unresectable primary tumor. The aim of the surgery for non-functional p-NENs with LM is to prolong overall survival through potential curative resection or cytoreduction. Previous reports showed that survival benefits were observed for R0/R1 resection (38). Nevertheless, for liver-metastatic p-NENs with an unresectable primary, surgical resection of the metastases is always considered as less effective.

No guideline from ENETS (39), NANETS (40), or NCCN (8) reports any survival benefit associated with cytoreductive resection only for liver metastases per se. In the 2010 UICC/AJCC/WHO TNM staging system (41), stage T4 was defined as unresectable tumor with the involvement of the celiac axis or the superior mesenteric artery. Tumor-invading adjacent organs (stomach, spleen, colon and adrenal gland) were also grouped in T4 in the ENETS staging system; surgery should not be performed in patients with a T4 primary tumor (42). Multiphasic CT or MRI are recommended to preoperative evaluation (8).

Consensus statements. If the primary tumor is T4, surgical resection for liver-metastatic lesions should be avoided, and this should be carefully assessed preoperatively. Whether R2 resection to the primary improves prognosis is not yet clear.

G1/G2 p-NET with type I LM. Unlike pancreatic adenocarcinoma, when the R0 resection is possible, surgery may also be considered in part of patients with G1/G2 liver-metastatic p-NET. Type I metastasis is defined as one metastatic lesion regardless of size (11). Generally, for type I metastasis, surgical treatment should be undertaken with the goal of an R0 resection (12).

An early study of 16 patients recommended aggressive surgery as the first choice for G1/G2 liver-metastatic p-NET (43). If the metastasis is unilobar, LM can be resected at the same time as the primary tumor with little additional risk (44).

When an R0 resection can be achieved (all macroscopic disease is removed and surgical margins are negative for microscopic disease), G1/G2 liver-metastatic p-NET patients can benefit from improved long-term survival compared to patients with unresected disease, as confirmed by several

retrospective studies (45,46). Furthermore, another relatively large-scale study prospectively reported there were no differences in survival found between R0 and R1 resection. Both R0 and R1 resection can be beneficial (38).

In recent years, ENETS issued general guidelines for patients with hepatic involvement of type I, with surgical resection being the first therapeutic option (39). Despite the lack of randomized data, the ENETS consensus statement emphasized that a curative resection for type I liver metastasis should be the first-line treatment option (39,47). Since then, curative surgery in G1/G2 p-NET with type I LM has been accepted in clinical practice.

Additional studies published in last decade have demonstrated the advantage of surgery in type I liver-metastatic p-NET. Patients can have 3- and 5-year overall survival rates of up to 100% if R0/R1 resection is performed (11,45). However, the 5- and 10-year recurrence rate was 84 and 94%, respectively, even if an R0 resection was performed (48). This high postoperative recurrence should be noted.

Also, laparoscopic surgery, which has a similar surgical complication rate and short-term prognosis as compared to open surgery, is also a practical option for the treatment of p-NET with type I LM (49).

Consensus statements. Curative surgery is recommended for resectable G1/G2 p-NET with type I LM. While R0 resection is the aim of the operation, R1 resection also seems to improve the overall survival rate.

G1/G2 p-NET with type II LM. Compared to type I metastasis, curative surgery may not always be performed in patients with type II LM. Only for unilobar metastatic lesions, curative surgery is the goal just like that in type I liver-metastatic p-NETs. Therefore, regarding type II liver-metastatic p-NETs, whether cytoreductive surgery can be of benefit needs to be determined.

In early 1996, liver resection in patients with a metastatic neuroendocrine tumor was recommended to provide good long-term symptom palliation (50). In general, cytoreductive surgery for liver-metastatic p-NET is indicated to reduce hormone levels and improve clinical symptoms (51,52). The effects on the prognosis are still debatable (51,53,54).

Furthermore, hepatic resection, used in cytoreductive surgery, may come at the cost of high morbidity and mortality (55), especially when combined with the pancreaticoduodenectomy (56). A study of 120 p-NET patients reported that cytoreductive surgery carried significant perioperative mortality (6%) and complication rates (43%) without long-term survival benefits, and should be discouraged (53).

Nevertheless, with the development of surgical technology, improved long-term survival of patients with type II liver-metastatic p-NET after cytoreductive surgery has also been recently reported. In a prospective, multicenter study from Zerbi *et al* (57), the 2-year prognosis of patients undergoing cytoreductive surgery was satisfactory and cytoreductive surgery for patients with low Ki-67 staining may achieve a statistically improved OS. In another relatively larger retrospective study of 72 patients with metastatic non-functional p-NETs from the Mayo Clinic, there was no difference in overall survival in patients undergoing cytoreductive surgery vs. those undergoing R0 resections, despite a higher incidence

of tumor recurrence in the cytoreductive surgery group (58). Therefore, some researchers believe cytoreductive surgery should be pursued whenever possible, even if curative resection may not be achievable.

To identify the population that may benefit from the operation, Mayo *et al* (59) compared patients who underwent liver resection (n=339) with those who underwent intra-arterial therapy (IAT) (n=414). Their data indicated that non-functional p-NET patients with low (<25%) liver involvement benefited most from surgery, while patients with a large (>25%) burden of liver metastases benefited the least from surgery. Tumor volume with <25% liver involvement was identified as a useful selection criterion for patients who may benefit from cytoreductive surgery (55,60). Other researchers also considered the tumor volume as one of key prognostic factors (5).

In order for treatment to be successful, cytoreductive surgery is required to remove at least 90% of the tumor, including not only liver metastases, but the primary tumor and lymph nodes (46,52,61). ENETS, NCCN and NANETS guidelines have recommended 90% reduction of all visible tumors (8,35,36). However, securing a 90% reduction is relatively difficult, and such a reduction may only be practical for less than 10% of patients (5,35,36,48).

Nevertheless, a recent study of 108 pancreatic and small bowel NET patients showed that where 70% cytoreduction was achieved (in nearly two-thirds of p-NET cases), patients enjoyed improved progression-free survival (median 3.0 years). Also, it is worth noting that there was no perioperative mortality (55). Similar results also suggested that a 70% or greater reduction of the tumor burden was enough to prolong survival and should be considered in the surgical strategy (55,62-64). According to ESMO guidelines, excision of >70% of the tumor load is recommended to improve combined treatment (37).

Liver surgery can be performed as either a one-step or a two-step procedure. For unilobar metastases and during a low-risk operation, resection for LM can be performed at the same time as the primary. If major or complex liver resection is required, a two-stage surgery may be preferable in order to reduce the operative risk, especially in patients with type II metastases (65). The two-step surgery may include a resection of the primary tumor, lymph nodes and metastases of one lobe. Then, contralateral liver volume, enhanced by right portal venous embolization hypertrophy, after that, right hepatectomy or lobectomy may be performed as a second step (66). Such an approach can benefit patients with bilobar metastases and avoid or delay indications for LT (67).

In an effort to achieve loco-regional control, cytoreductive surgery in combination with liver-directed therapies may also be considered. Combination approaches to cytoreduction are very effective and are associated with similar survival rates as those that use R0 resection only. Recent reports of cytoreduction that use resection and ablation or resection combined with other liver-directed therapy demonstrated a 5-year survival rate of ~75% (62,68,69), which was comparable to those undergoing R0 resection (46).

An estimate of the remnant liver parenchyma volume is another factor in surgical decision making. Studies have reported that up to 70% of the whole liver volume can be safely removed by specialized liver surgeons (63,64). A

Table I. Selection criteria and requirements for cytoreduction in p-NETs with type II LM.

Selection criteria
G1/G2 p-NET with LM;
The primary is resectable;
No unresectable extrahepatic disease;
Younger patients with an acceptable morbidity and low mortality;
Tumor volume <25% liver involvement;
Up to 90% when possible or >70% of tumor load is thought resectable preoperatively;
Treatment decision making requires a multidisciplinary approach.

Requirements
Up to 90% when possible or >70% tumor volume is required to be excised;
One-stage or two-stage surgery may be recommended;
Liver-directed therapies are complements to cytoreduction;
A remnant functional liver parenchyma volume should be at least 30% of the entire liver.

remnant functional liver parenchyma volume should be at least 30% of the entire liver volume to ensure the safety of operation. Therefore, more remnant functional liver parenchyma volume is required for the patient with impaired hepatic function.

ENETS guidelines have established and updated the essential criteria for patient selection. NCCN guidelines also recommend non-curative debulking surgery in select cases of type II liver-metastatic p-NET. According to guidelines and related studies (8,47,54,70-72), the minimum criteria for cytoreductive surgery of liver-metastatic p-NETs are as follows (Table I): i) G1/G2 liver-metastatic p-NET; ii) the primary is resectable; iii) no unresectable extrahepatic disease; iv) younger patients with an acceptable morbidity and low mortality; v) tumor volume with <25% liver involvement; vi) up to 90% or at least >70% of tumor load is thought to be resectable preoperatively; and vii) treatment decision making requires a multidisciplinary approach.

Consensus statements. Curative surgery is the goal and cytoreduction should also be performed in select patients (Table I). For cytoreduction, the following requirements should also be met (Table I): i) up to 90% or at least >70% of the tumor volume needs to be excised; ii) either one-stage or two-stage surgery may be recommended; iii) liver-directed therapies are complements to cytoreduction in surgical effectiveness; and iv) a remnant functional liver parenchyma volume should be at least 30% of the entire liver.

G1/G2 p-NET with type III LM. Type III liver-metastatic p-NET is defined as p-NET with disseminated metastatic spread in the liver. It is generally believed that there is limited potential for palliative hepatic resection due to excessive loss of functional liver parenchyma volume.

Both the guidelines of ENETS and NANETS currently do not make any recommendations on whether the primary tumor should be removed in this clinical scenario (36,39). They also currently do not recommend routine resection in patients with type III liver-metastatic p-NET (resection of the primary alone fails to improve survival). Furthermore, standard resection in the presence of unresectable metastatic disease is also not suggested in the NCCN 2015 guidelines (8).

However, recent retrospective data suggest that resection of the pancreatic primary is associated with improved survival rate in p-NET patients with disseminated and unresected liver-metastases (73,74). Patients undergoing surgical resection of the primary tumor had a better 5-year survival rate than patients with no resection (55-82 vs. 30-50%) (73). These studies suggest that resection of the primary tumor may be beneficial even in the case of globally unresectable liver-metastatic lesions.

Consensus statements. Available evidence does not support standard resection for type III liver-metastatic p-NET. Whether these patients benefit from removal of their primary tumor remains to be demonstrated.

G3 p-NET with LM. p-NET G3 is characterized by a Ki-67 index in the G3 range (Ki-67 index always <55%) and a mitotic rate suggestive of G2. p-NET G3 is significantly less aggressive than poorly differentiated NECs and is not defined in the WHO 2010 classification (54,75). Prognostic outcomes associated with cases of p-NET G3 are much better than that of p-NEC (16). A multicenter study that included 37 NETs G3 and 167 NECs found that the median Ki-67 index was significantly different (30% in NET G3 vs. 80% in NEC), and that overall survival was also significantly higher in NET G3 (99 months in NET G3 vs. 17 months in NEC) (76).

Further details on the management of G3 p-NET have been summarized in a recently published comprehensive review (77), albeit without any definite recommendations related to surgical treatment. In the 2016 ENETS guidelines, chemotherapy and radiotherapy, rather than surgery, were suggested in cases of p-NET G3 with distant metastases (16).

Consensus statements. There is insufficient data relating to the value of surgery in the treatment of G3 p-NET; therefore,
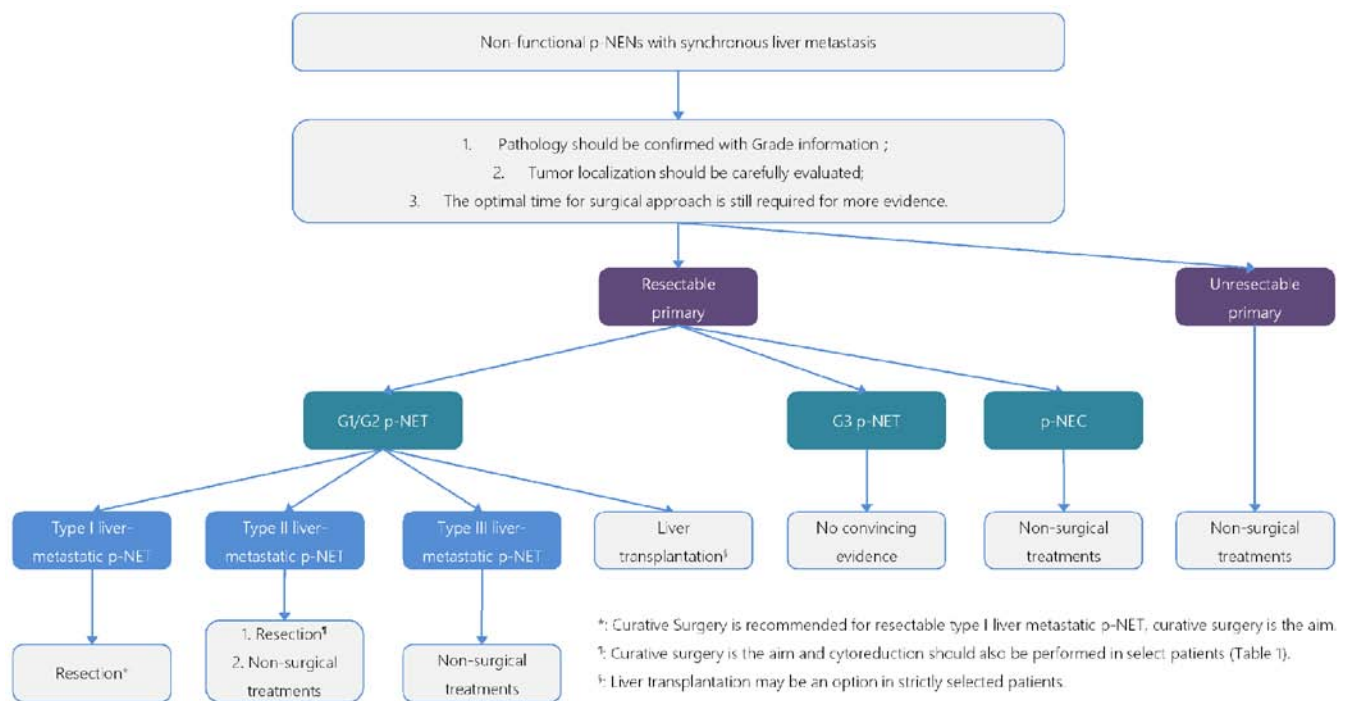
Figure 1. Treatment approach to non-functional p-NENs with synchronous liver metastasis.

studies are needed that investigate the effect of surgery patient survival in cases of liver-metastatic G3 p-NET.

G3 p-NEC with LM. Compared to G3 p-NET, p-NEC is highly malignant and has a poor prognosis and this results in there being distinct treatment strategies for p-NET vs. p-NEC. Therefore, an accurate grade classification is also required before making a treatment decision for liver-metastatic p-NENs (1).

p-NECs are highly malignant neoplasms that typically invade adjacent structures or have frequently metastasized at diagnosis (78).

Surgery is recommended, along with postoperative chemotherapy, for p-NEC with local disease (40). Generally, p-NEC with LM is considered not amenable for resection due to high recurrence rates and no overall survival benefit (79-81).

ENETS guidelines (81) for the surgical treatment of p-NEC refer to only two early studies (82,83), and state that 'curative surgery should be attempted only in localized disease'. NANETS and NCCN guidelines do not mention surgical options for the treatment of liver metastatic p-NEC (8,80). Moreover, the ESMO guidelines also agree that 'it is a general agreement not to operate on G3 p-NEC' (37).

Other recent studies report that multifocal and even diffuse disseminated hepatic lesions are common for p-NEC, which leads to a low rate of surgical intervention (84). Systemic therapy is recommended as the primary course of therapy in the majority of studies (79-81).

Nevertheless, in 2015, a Chinese retrospective study of 36 GEP-NEC with liver metastases patients suggested that aggressive cytoreductive surgery, as well as radiofrequency ablation and liver-directed intra-arterial intervention, may improve clinical outcomes (84).

A study of the largest cohort of patients with advanced p-NEC to date was recently published. The authors demonstrated that resection of the primary tumor was an independent prognostic factor in improved survival for patients with p-NEC at different disease stages (85). These results suggest that resection of localized p-NEC and p-NEC with LM should both be considered.

However, it is worth noting that these two retrospective studies did not distinguish p-NET G3 from p-NEC. Not separating p-NET G3 from all G3 patients may lead to bias in the results.

Consensus statements. Surgical strategy is not mentioned in guidelines for the treatment of p-NEC with LM. Large randomized studies are required to fully justify the role of surgery in liver-metastatic p-NEC.

LT for p-NET with LM. LT for patients with metastatic neuro-endocrine tumors was first reported in 1993 (86). Later, in 1998, Lehnert (87) reported a 2- and a 5-year survival rate of 44 and 30% in a series of 48 patients transplanted for p-NET with LM; however, recurrence rate was found to be high. For unresectable liver-metastatic lesions, whether LT is an option in patients with type II or III liver metastases is still unclear.

Several retrospective and prospective studies have shown encouraging results with a 5-year overall survival between 67 and 90% and a low 5-year recurrence-free survival rate between 20 and 48% (88-91). Recently, a relatively large-sample study reviewed 94 patients who had undergone LT for liver-metastatic p-NET in 35 centers between 1982 and 2009. The overall three-month postoperative mortality was 10%. At 5 years after LT, overall survival was 52%, while disease-free survival was only 30% (92).

Due to the scarcity and heterogeneity of reported cases of LT and the lack of randomized trials, controversy continues

surrounding patient selection for LT. NCCN guidelines recommend that LT should not be included amongst routine treatment strategies (8). In the ENETS and NANETS guidelines, LT is also generally not recommended as a routine treatment option in p-NEN with LM; rather, it may only be an option in highly selected patients (36,39).

The minimal selection criteria are as follows: i) well-differentiated p-NETs with Ki-67 <10%; ii) age <55 years; iii) absence of extrahepatic disease; iv) primary tumor removed before transplantation; v) stable disease for at least six months before LT; vi) <50% liver involvement (39,93). Unfortunately, these selection criteria have not been validated in large prospective studies.

Consensus statements. LT is generally not recommended as a routine treatment option in liver-metastatic p-NENs; it may be an option in strictly select patients.

Appropriate timing for aurgical approach. It is still controversial how to determine the best timing of a surgical approach, and we still do not have enough data nor research regarding this topic.

In ENETS guidelines, debulking surgery may be considered if the disease is not progressive over a 6-month period and the patients are suffering from symptoms related to tumor burden (55). However, the evidence is still insufficient. In some cases the surgical approach could be carried out first, while other patients may benefit from pre-operative medical treatments or observations of tumor biologic behavior. Therefore, multidisciplinary discussion is required to determine the best choice of treatment (8) and re-evaluating for the treatment's effectiveness of a surgical approach is also required.

Consensus statements. Due to insufficient evidence, the appropriate time for surgical approach is still unclear.

Conclusions

Surgical management of liver-metastatic p-NENs still lacks consensus recomendations. Slow growth of the tumor and the availability of numerous effective treatment strategies make determination complicated of the optimal treatment. Different combinations of liver metastases types, localization, and pathological classification have different outcomes and require different treatment strategies. Surgical resection may be an optimal treatment option for some patients with liver-metastatic p-NENs. Based on the existing evidence, experts in CSNET have reached an agreement regarding the following treatment aspects (Fig. 1):

Biopsy in p-NEN with LM: i) biopsy is essential prior to treatment to confirm pathology; ii) liver biopsy is important for the accuracy of tumor grading; iii) percutaneous core needle biopsy procedure maybe more available in comparison to EUS-FNA.

Liver-metastatic p-NEN with unresectable primary: i) surgical resection for liver-metastatic lesions should be avoided.

G1/G2 p-NET with type I LM: i) curative surgery is recommended; ii) curative resection (R0 resection) is the aim of the operation; iii) R1 resection seems to contribute to the overall survival rate.

G1/G2 p-NET with type II LM: i) curative surgery is also the goal; ii) cytoreductive surgery is recommended in select patients and should meet requirements (Table I).

G1/G2 p-NET with type III LM: Surgical resection should be avoided.

G3 p-NET with LM: There is insufficient data to guide recommendations on surgical treatment.

p-NEC with LM: Surgical resection is not currently recommended.

LT in liver-metastatic p-NEN: LT may be an option in strictly selected patients for liver-metastatic p-NET.

Appropriate timing for surgical approach: The optimal time for surgery still requires more evidence.

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