Journal Pre-proof

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PII: S1040-8428(19)30219-7
DOI: <https://doi.org/10.1016/j.critrevonc.2019.102835>
Reference: ONCH 102835

To appear in: *Critical Reviews in Oncology / Hematology*

Received Date: 8 September 2019
Revised Date: 6 November 2019
Accepted Date: 11 November 2019

Please cite this article as: Ishida H, Lam AK-Yin, Pancreatic Neuroendocrine Neoplasms: The Latest Surgical and Medical Treatment Strategies based on the current World Health Organization classification, *Critical Reviews in Oncology / Hematology* (2019), doi: <https://doi.org/10.1016/j.critrevonc.2019.102835>

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Pancreatic Neuroendocrine Neoplasms: The Latest Surgical and Medical Treatment Strategies based on the current World Health Organization classification

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Highlights

- Surgery on PanNENs depends on size, location, and histopathology of the tumour.
- Debulking surgery/resection of the primary PanNENs is beneficial to the patients.
- Systemic medication is for patients with unresectable or metastatic PanNENs.
- Notable antineoplastic agents have been approved for the treatment of PanNENs.

Abstract

There is a recent update in WHO classification of pancreatic neuroendocrine neoplasms (PanNENs). Our aims are to analyse the latest management for patients with PanNENs according to the current classification of these neoplasms. The primary treatment is curative surgery and the surgical procedures depends on size, location, and histopathology of the tumour. Even if tumour has metastases, debulking surgery or resection of the primary lesion could improve the prognosis of these patients. Systemic medication is indicated in patients with unresectable primary and/or distant metastatic lesions. As new antineoplastic agents have been approved in the last decade for the treatment of PanNENs, the clinical outcome is improving. However, the appropriate selection or the effective combination of drugs has not been fully established. To conclude, management of PanNENs depends on various factors and further development of treatment strategies is needed for improvement of survival of patients with PanNENs.

Keywords: pancreas; surgery; drug; pancreatic neuroendocrine neoplasm; pancreatic neuroendocrine tumour; pancreatic neuroendocrine carcinoma.

1. Introduction

Pancreatic neuroendocrine neoplasms (PanNENs) are considered relatively rare neoplasms accounting for only 1 to 2% of all pancreatic malignancies [1, 2]. However, the number of patients with PanNENs has increased according to the surveillance, epidemiology, and end results (SEER) database of United States; 1.09 per 100,000 people in 1973 to 5.25 per 100,000 people in 2004 [3]. Significant increases, particularly in incidence at localized and early stage, were shown. There are some possible reasons; first, PanNENs has become widely known among general clinicians, thus, the number of clinicians who can diagnose PanNENs is increasing. Second, as quality of diagnostic imaging, such as endoscopic ultrasonography (EUS), CT, or MRI have advanced, very small lesions can be detected. Curative surgical resection is the only method to cure PanNENs completely. Patients who underwent surgery had a better prognosis compared to those with the other non-surgical treatment; e.g. chemotherapy, molecular targeted therapy, somatostatin analogue, or peptide receptor radionuclide therapy [2, 4–6]. When tumour shows locoregional infiltration and/or invading adjacent organs, debulking surgery is often indicated in order to control local and endocrine symptoms. Even if complete resection of metastatic lesions is impossible, extensive resection of the primary tumour of the pancreas could improve the prognosis of patients [7].

In the current World Health Organization (WHO) classification of PanNENs, PanNENs comprise pancreatic neuroendocrine tumours (PanNETs), pancreatic neuroendocrine carcinomas (PanNECs) and pancreatic mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs) [8]. PanNETs are well-differentiated PanNENs and categorised into G1, G2, and G3 based on the Ki-67 staining index or mitotic index. PanNECs are poorly-differentiated PanNENs which include large cell NECs and small cell NECs. Pancreatic MiNENs comprise mixed ductal or acinar cell carcinoma with either PanNECs or PanNETs.

The current WHO classification of PanNENs categorised PanNECs in the previous 2010 classification that had not been considered for surgical indication, into well-differentiated PanNETs G3 and poorly-differentiated PanNECs [8]. The cases with PanNETs G3 are considered for surgery as well as conventional PanNETs G1/G2, whereas only very few patients with PanNECs could benefit from surgical resection [9].

If unresectable primary and/or metastatic lesions are detected or the patient has high risk of surgery, systemic medication for improvement of survival would be indicated. The treatment strategies for PanNENs is advancing day by day, and noteworthy agents have been approved in the last decade. In this article, the latest management strategies of surgical and non-surgical therapies for this group of

neoplasms are reviewed.

2. Current Treatment Strategies

2.1. Neo-Adjuvant Therapy

Neo-adjuvant therapy (therapy before surgery) could be used in the treatment of PanNENs. There are only a few case reports or small case series regarding the neo-adjuvant therapy for PanNENs. No randomized trial has been conducted comparing neo-adjuvant therapy in combination with surgery versus surgical treatment only for the patients with PanNENs. The reported treatment options of neo-adjuvant therapy were cytotoxic agents, molecular targeted drugs, radiotherapy, peptide receptor radionuclide therapy, or various combinations of them [10, 11]. The aim of neo-adjuvant therapy is to reduce the tumour volume, make the curative resection possible and improve the survival [11]. Dumont et al. reported a retrospective study, including 28 patients with locally advanced PanNETs G1/G2 who were treated with cytotoxic agents and underwent subsequent surgery [10]. Forty-six per cent (13 of 28) achieved complete resection and their 5-year overall survival was better than that of patients with incomplete resection (77.9% versus 55.4%). Neo-adjuvant therapy could help in the achievement of complete resection. Considering low feasibility of a randomized prospective study because of the limited number of cases of PanNENs, it is needed to

assess experts experience and evidence from case reports or small case series in order to find out the appropriate candidates who could benefit from neo-adjuvant therapy [11, 12].

2.2. Surgery

As patients with PanNENs without distant organ or lymph node metastases could be cured completely by surgery alone, surgical resection should be performed in these patients. However, curative surgery is possible in only less than 30% of patients with malignant PanNENs and recurrence occurs in >75% of the patients within 15 years [13]. Thus, the careful monitoring after surgery are required even if the complete resection is achieved macroscopically [14]. The management strategies of surgery depend on grading, differentiation, and histopathology of PanNENs.

2.2.1. Well-differentiated PanNET (PanNET G1/G2)

2.2.1.1. Functional PanNET without multiple neuroendocrine neoplasia type 1 (MEN1)

2.2.1.1.1. Insulinoma

More than 90% of insulinoma have benign features and localized in the pancreas, thus it could be resected completely by surgery alone [15–17]. If tumour is

smaller than 2 cm, the enucleation could be performed without damaging its capsule [18–20]. When the distance between the tumour and main pancreatic duct is less than 3mm, distal pancreatectomy or partial pancreatectomy might be indicated to prevent the damage to main pancreatic duct [20]. If lymph node metastases or locoregional invasion are confirmed, pancreaticoduodenectomy or distal pancreatectomy with lymph node dissection would be considered [17–20]. Distal pancreatectomy with splenic artery and vein preservation might be indicated in case of no malignant findings. Furthermore, there is widespread use of laparoscopic pancreatectomy [16, 21, 22], and laparoscopic ultrasonography could detect approximately 90% of insulinomas [23]. Drymoussis et al. analysed 543 patients with insulinoma treated by laparoscopic procedure (n=160) or open surgery (n=383) [24]. Blood loss and hospital length of stay were significantly better in laparoscopic group, while overall complication rates and operation duration did not differ significantly between two groups. Thus, if insulinoma is small and solitary, minimally invasive (laparoscopic/robot-assisted) pancreatic surgery (enucleation or distal pancreatectomy) could be considered in high volume centres specializing in this laparoscopic procedure [20, 21, 23–25]. Real-time subcutaneous continuous glucose monitoring during surgery would be useful to determine if insulinoma is resected completely and hyperinsulinemia disappear [26].

2.2.1.1.2. Gastrinoma

60–90% of sporadic gastrinoma have malignant features [20, 27, 28].

Gastrinoma is known to occur from both pancreas and duodenum, and very rarely

occurs from the other organs, such as stomach, jejunum, biliary tract, and so on [29].

As lymph node metastasis was present in 30–82% of cases [30, 31], the only curative

treatment method is surgical resection with lymph node dissection [20, 27, 32]. It is

vital to assess and identify pancreatic lesions by intraoperative ultrasonography and

palpation for accurate localization diagnosis [30, 33]. Generally, tumours of the head

are treated with pancreaticoduodenectomy or pylorus-preserving

pancreaticoduodenectomy and lymph node dissection whereas tumours located in the

body or tail are treated with distal pancreatectomy and lymphadenectomy [20, 31].

Currently, in terms of minimally invasive procedures, enucleation or partial resection

with/without lymphadenectomy might be also indicated if no locoregional invasion or

distant metastases are identified [30, 33–35]. However, average time to recurrence

was shorter in patients treated by enucleation without lymphadenectomy compared to in

those treated by radical resection with lymph node dissection [36]. Systematic

lymphadenectomy also reduced the risk of recurrence and improve survival outcome

after surgery than no or selective lymph node dissection [37]. Thus, an aggressive treatment with systematic lymphadenectomy is justified in patients with sporadic gastrinomas if they do not have multiple hepatic metastases and/or the other distant metastases [30, 33, 36]. In contrast, considering the invasive procedure and possible long-term complications, enucleation or partial resection could be the option of surgical procedure [20]. The appropriate procedure of surgery has been controversial, and further investigation should be needed in the future. There were a few reports of laparoscopic surgery in a patient with sporadic and small gastrinomas. As intraoperative ultrasonography and palpation are needed, laparoscopic resection might be indicated in only selected cases, and it has been still a technically challenging procedure [30, 38–40].

2.2.1.1.3. *Glucagonoma*

The curative treatment for glucagonoma is surgical resection. More than 70% of glucagonomas are located in the body and/or tail of the pancreas, and the average diameter of glucagonoma was 5.8 to 6cm which is larger than the other PanNENs [41–43]. Overall, 49 to 90% of patients had metastases at the time of diagnosis; the most common site of metastases was liver (80.5%), and followed by lymph nodes (33.1%),

bone (7.8%), and mesentery/omentum/peritoneum (3.4%) [41, 43–45]. Although the standard surgical procedure is distal pancreatectomy or pancreaticoduodenectomy with lymphadenectomy [20], it should be modified depending on the localization of the primary site. Even if the distant metastases and/or locoregional invasion are detected, a more aggressive surgical resection should be considered if the primary tumour and metastases lesion could be resected simultaneously [42, 44]. Even in the patients with locally advanced unresectable tumour, if the patients have clinical symptoms due to hormone excessive amount, such as diabetes mellitus, necrolytic migratory erythema, weight loss, or anaemia, the debulking procedures might be indicated for rapid relief of the symptoms [46, 47].

2.2.1.2. Non-functional PanNET

Non-functional PanNETs account for 43 to 90% of all PanNETs [2, 33, 48]. More than 90% of the non-functional PanNET cases have malignant features, and locoregional infiltration is found in many cases upon diagnosis. Approximately 49 to 70% of non-functional PanNETs are larger than 2cm. It indicates that the tumour would be detected at more advanced stages due to the symptoms of locoregional infiltration because non-functional PanNETs show no hormone-related symptoms [48,

49]. If the lesion is localized in the pancreas, surgical resection of primary tumour improved survival of the patients across all disease stages [50]. Surgical resection was carried out in 83% of non-functional PanNET cases [48], and the operative procedures should be decided depending on the size, location of the tumour, and the predicted pancreatic function after surgery [20]. The basic procedure is pancreatectomy with lymphadenectomy. Enucleation should be considered if the tumour is less than 1 to 2cm without risk factors, such as lymph node metastasis [51, 52]. Then, enough care must be taken with enucleation not to damage the main pancreatic duct. In the current National Comprehensive Cancer Network (NCCN) guideline from United States of America, lymphadenectomy could be omitted if tumour size is less than 1cm [20]. In contrast, even if tumour is less than 1cm, the rate of nodal metastasis reported to be 12–23% [53, 54]. Thus, lymph node sampling may be needed regardless of extent of resection. Decision for appropriate and enough area for lymphadenectomy should be done in the future. Minimally invasive (laparoscopic/robot-assisted) enucleation/partial resection/spleen-preserving distal pancreatectomy would be indicated in patients with small non-functional PanNETs (<2cm) [20]. Zhang et al. investigated 214 patients with PanNETs who had undergone laparoscopic/robot-assisted surgery [55]. Approximately 80% of the patients presented with non-functional

PanNETs, and minimally invasive procedure was associated with less blood loss, a lower incidence of postoperative morbidity, a shorter hospital stay, and longer overall survival compared with open procedure. As the number of lymph node retrieved were also equivalent between the two group, minimally invasive procedure for patients with small non-functional PanNETs is currently supported [25, 55].

Observation might be done in selected cases if tumour is less than 1cm, low-grade, and incidentally discovered [20]. Kishi et al. found that 5-year progression-free survival of the patients with small non-functional PanNETs (range, 6–38mm) was 83%, and none of them developed distant metastases. Furthermore, none of patients with non-functional PanNETs ≤ 1.5 cm in size who underwent surgery did not develop lymph node or distant metastases, and 5-year recurrence-free survival of them (100%) was significantly better compared with those with size more than 16 mm [56]. Thus, a wait and see approach has been proposed for those patients with tumours less than 1.5cm. Partelli et al. evaluated five studies systematically regarding the active surveillance of asymptomatic, sporadic, small non-functional PanNETs, and revealed that there was wide variation of threshold (2cm to any size) for surgery and 14.1% (n=46) of these patients underwent surgery after initial surveillance [57]. There was no difference in terms of survival outcome between conservative management and surgical approach

group, and no disease-related deaths happened in the active surveillance group. In contrast, there was a significant relationship between the size ($>2\text{cm}$) and distant metastasis in cases with non-functional PanNETs via multivariate analysis [48]. Lymph node metastasis also occurred in small non-functional PanNETs ($<1\text{ cm}$) as mentioned above. Thus, the criteria and threshold of size for observation remains controversial.

2.2.1.3. PanNET with multiple neuroendocrine neoplasia type 1 (MEN1)

Ten per cent of patients with PanNETs had MEN1 [48]. The treatment strategy for PanNETs with MEN1 should be decided taking synchronous/metachronous occurrence of PanNETs into account [58]. Nearly 80% of the patients with MEN1 had multiple NETs in the pancreas and/or the duodenum; non-functional NETs account for 80 to 100% of NETs associated with MEN1, followed by gastrinomas (54%) and insulinomas (18%) [59, 60]. The most frequent functional NET with MEN1 is duodenal gastrinoma, and 25 to 33% of all gastrinomas are also associated with MEN1 [29, 61, 62]. Thus, the search for MEN1, e.g. the examination of parathyroid and pituitary gland function, would be essential when gastrinoma is diagnosed. It is well-known that 50–100% of gastrinomas with MEN1 are localized in the duodenum,

therefore, pancreas-preserving total duodenectomy might be indicated for MEN1 patients without tumours in the pancreas [63]. The other NETs in MEN1 are almost primary located in the pancreas. Selective arterial secretagogue injection test with secretin or calcium solution was performed as well as somatostatin receptor scintigraphy and other diagnostic imaging methods, such as EUS, CT and MRI, for accurate localization of the tumour. Kann et al. reported that EUS seemed to be more sensitive than MRI in case of localizing PanNETs (EUS 80% versus MRI 66%) [64]. Furthermore, intraoperative ultrasonography and palpation are needed for more accurate localization diagnosis, especially in case of gastrinoma.

Decision of surgical procedure for NETs associated with MEN1 is often challenging, especially due to the presence of multifocal pancreatic neoplasms. The presence of hormone secretion, the size, the number, the site, and synchronous/metachronous occurrence of neoplasms should be considered, and the operative procedure for the improvement of hormone-related symptoms, the preservation of pancreatic function, and the better survival of patients with MEN1 must be decided for each case. Pancreaticoduodenectomy/pylorus-preserving pancreaticoduodenectomy, distal pancreatectomy, partial excision, or enucleation would be performed [20, 63]. Some researchers reported that minimally invasive

(laparoscopic/robot-assisted) distal pancreatectomy and enucleation were feasible and safe in MEN1 patients with insulinoma or non-functional PanNETs [55, 65–67].

However, this method might not be indicated so far in case of gastrinoma since there is a need for intraoperative ultrasonography and palpation, and duodenotomy or duodenectomy might be needed if these tumours arise in the duodenum [65, 66].

It was reported that the absolute indication of surgical management for PanNETs with MEN1 would be as follows; “functional PanNETs”, “with resectable lymph node metastases”, “size more than 2 cm”, “non-functional PanNETs with symptoms (e.g. abdominal pain)”, and “rapid growth (>5mm per year)” [20, 59, 68]. As lymph node metastases occur in 70% of the patients with MEN1-gastrinomas, lymphadenectomy should be performed in any surgical procedures in cases with gastrinomas [59, 69]. The patients who were treated conservatively have a higher risk of liver metastases (23–29%) compared to those who underwent radical surgery (3–5%). Thus, aggressive surgery is recommended in patients with MEN1-gastrinomas [59, 69–71]. As no one can predict the metachronous occurrence of neoplasm in the future at the first treatment, total pancreatectomy should not be performed. The most appropriate procedure that preserves pancreatic function as much as possible needs to be selected. Even in the case of multiple PanNETs, it is recommended to avoid total

pancreatectomy considering a postoperative severe pancreatic diabetes mellitus. As patients with MEN1-non-functional PanNETs of size <2 cm are associated with a very low risk of metastases and patients' mortality, they could be managed by careful observation [20]. The treatment strategies for PanNET with MEN1 were summarized in Figure 1.

Figure 1. Treatment strategies for PanNET with MEN1.

PanNET: pancreatic neuroendocrine tumour; MEN1: multiple neuroendocrine neoplasia type 1; NET: neuroendocrine tumour; CT: computed tomography; MRI: magnetic resonance imaging; EUS: endoscopic ultrasonography; SRS: somatostatin receptor scintigraphy; SASI: selective arterial secretagogue injection test; LD: lymph node dissection.

2.2.1.4. Surgery for distant metastases

21 to 80% of patients with PanNENs have metastatic lesions at diagnosis, and

the most frequent site is the liver (40–93%), followed by the bone (12–20%) and the lung (8–10%) [48, 72]. Liver metastasis is one of the most important factors that determine prognosis of the patients. Resection of the liver metastasis is associated with long-term survival advantages and disease control [72–74]. It is indicated in patients with resectable lesion in whom having no other distant organ and/or lymph node metastases or peritoneal dissemination. Patients also need to have tolerance to surgery and enough residual liver volume.

In general, surgery for resectable liver metastatic lesions in patients with low grades PanNETs (G1/G2) is recommended. Recently, it was reported that some cases with PanNENs G3 having liver metastases could benefit from resection of the metastatic lesions [75]. However, this report included all high grade PanNENs with Ki-67 index higher than 20% without differentiation of grading. Surgery would not be indicated in patients with metastatic PanNECs (according to the current WHO classification) due to the highly aggressive clinical behaviour.

Unfortunately, potential curative surgery is possible in only 10 to 25% of patients with liver metastases [72, 76]. Tumour recurrence occurs in the first 2 years after surgery and the rate of recurrence reaches up to 80% at 5 years [72]. In contrast, despite the high rate of recurrence, 5-year survival rate could reach 85%, and the 10-

year survival could reach up to 90.4% after complete resection of the hepatic metastases [77]. Thus, the aggressive surgical resection of liver synchronous/metachronous metastatic lesions is currently supported [6, 72, 77–84].

In patients with distant metastases, surgical resection of only primary tumours also showed a significant better survival, with a 5-year survival of up to 90% compared to non-surgical treatment, such as 50% for peptide receptor radionuclide therapy, 29% for somatostatin analogue and 14% for no therapy [6]. The surgical procedure for the primary PanNENs with metastatic lesion is pancreatectomy with lymph node dissection along that of pancreatic ductal carcinoma. Thus, pancreaticoduodenectomy, pylorus-preserving pancreaticoduodenectomy, or distal pancreatectomy with lymphadenectomy would be performed depending on the site of tumour [20]. In contrast, it was reported that there was no significant difference in terms of survival rate between patients with resection of the primary non-functional PanNETs and those without resection, especially in tumour with Ki-67 index $\geq 10\%$ [85, 86]. Thus, the role of resection of primary non-functional PanNETs in patients with unresectable distant metastasis has been controversial due to lack of prospective trial data.

The protocol of hepatectomy were established [20, 31, 87]. In patients with solitary/simple lesion, partial resection or systematic segmentectomy is indicated. If

deemed medically unfit for surgery, patients should be considered for non-surgical therapy, such as radiofrequency ablation (RFA), laser-induced thermotherapy (LITT), trans-catheter arterial embolization (TAE), or trans-catheter arterial chemoembolization (TACE). If patients have bilobular metastases and they are resectable lesions, major and/or minor hepatectomy would be undergone. The decision to perform concurrent or staged resection depends on the number and location of the metastatic tumours. Radiofrequency ablation (RFA), right portal vein embolization (RPVE), or right portal vein ligation (RPVL) would be performed additionally if needed. If the lesions are multiple and unresectable, systemic treatments (such as cytotoxic agents or molecular targeted drugs), trans-catheter arterial embolization (TAE), or trans-catheter arterial chemoembolization (TACE) are generally performed instead of the surgical resection.

Liver transplantation were used in selected cases. The overall survival rates at 1-, 3-, and 5-year after transplantation were reported to be 89%, 69%, and 63%, respectively in a systematic review [88]. Recurrence rate after liver transplantation ranged from 31.3% to 56.8%. PanNENs with >50% liver tumour involvement and with high Ki-67 index >10% are associated with poorer survival after transplantation as compared with other gastrointestinal NENs [88]. Mazzaferro et al. suggested that indications for liver transplantation in patients with PanNENs having liver metastases

are as follows; age <60, histological grading (G1/G2), hepatic involvement (<50% of the total liver volume), metachronous metastasis (no extrahepatic lesions), and stable disease for at least 6 months [89].

The concurrent resection of the primary PanNENs and the metastatic lesions, especially in the liver, could be performed. The complication rate of concurrent resection ranged from 18 to 25% whereas the 5-year overall survival rates reached up to 71% [72, 82, 83, 90]. If the patient could not stand the extent of the concurrent surgery, staged surgery should be considered. A combination of pancreaticoduodenectomy and hepatectomy was associated with considerable morbidity, such as hepatic abscess or pancreatic fistula, no matter in operated synchronously or staged surgeries [91]. In contrast, Chawla et al. reported that pancreaticoduodenectomy with metastasectomy might result in improvement of overall survival for patients with metastatic PanNENs [92]. Thus, the indication of this combination has been unclear. However, the procedure should be considered carefully due to high rates of complications after surgery [33, 91, 92]. Trans-catheter arterial embolization (TAE) or trans-catheter arterial chemoembolization (TACE) should be avoided after pancreaticoduodenectomy in patients with PanNENs having liver metastasis because hepatic abscess or severe cholangitis could happen.

Surgical resection of liver metastases could be a debulking surgery for improving the patients' prognosis, control of symptoms as well as improvement of quality of life of this group of patients. Cusati et al. reported that patients undergoing complete resection (both in non-functional PanNETs and synchronous liver metastases) did not show significantly longer survival rate compared to those undergoing debulking of $\geq 90\%$ tumour burden [93]. These data might indicate that complete resection of primary non-functional PanNETs plus synchronous liver metastases is not routinely recommended, considering the complication by aggressive surgery. Although liver debulking threshold had been regarded as 90% [94, 95], a recent study found that there were no significant differences in survival outcome among 100%, $\geq 90\%$, and $\geq 70\%$ liver debulking groups [96]. Thus, a new threshold of $\geq 70\%$ liver debulking has been suggested. A debulking surgery of more than 90% tumour burden can relieve hormonal symptoms in nearly 90% of patients even if the symptoms have developed resistance to medical treatment [97–99].

Scharf et al. reported that 12.6% of patients with gastroenteropancreatic (GEP)-NENs presented with bone metastases. Small intestine (37.6%) and pancreas (30.6%) were the most common primaries giving rise to bone metastases [100]. 83.5% of the pancreatic NENs having bone metastases were well- and moderately-differentiated

(G1/G2). Nearly half of these patients had symptomatic pain or fractures. The overall survival was significantly worse in patients with bone metastases than in those with other distant metastases (49 months versus 101 months) [100]. Though bisphosphonate, RANK inhibitors, or radiation therapy were performed for improvement of symptoms [31, 100], there has been no prospective study that investigates the benefit of these treatment strategies for the patients with bone metastases.

There have been few reports studying the results of resection of lung metastases and prognosis. However, surgical resection of pulmonary metastases could occur only in patients with enough respiratory function after surgery.

Peritoneal dissemination was diagnosed in 3% of patients with PanNENs. There was no significant difference in terms of survival rate compared to patients with other metastases [101].

2.2.2. *Well-Differentiated PanNET (PanNET G3)/Poorly-Differentiated PanNEC (PanNEC)*

The current European Neuroendocrine Tumor Society (ENETS) consensus guideline and NCCN guideline do not separate the surgical treatment strategy for

PanNETs G3 and PanNECs [20, 31]. As there is lack of reports that compared the outcome after surgery between patients with PanNETs G3 and PanNECs according to the current WHO classification of PanNENs, the role of surgery for PanNENs G3 is still unclear. Yoshida et al. reported the clinical outcome after surgery in a large multicentre study on PanNENs G3. This study included data from 21 patients with PanNETs G3 and 46 patients with PanNECs [9], in which 11 patients (52%) having PanNETs G3 and 13 patients (28%) having PanNECs underwent surgery. Curative surgical resection was achieved in all patients with PanNETs G3 and PanNECs without distant metastases, and in two of the five patients in each of PanNETs G3 and PanNECs with distant metastases. Overall survival was significantly longer for patients with PanNETs G3 than patients with PanNECs (median overall survival, 41.8 months versus 11.3 months). Overall survival of patients with PanNETs G3 was also significantly longer after surgery than with non-surgical procedures. In contrast, overall survival did not significantly differ between patients with tumour-targeted surgery and those with non-surgical procedures among patients with PanNECs. These results indicated that surgical resection was effective for PanNETs G3 and the role of surgery for PanNETs G3 might be like PanNETs G1/G2, whereas the indication of surgery for PanNECs should be considered carefully and be limited to selected patients. Although

curative resections were performed in most of patients with PanNECs, the overall survival of these patients was short (median overall survival, 16 months; 3-year survival rate, 20%). They also warned that preoperative diagnosis of PanNETs G3 and PanNECs should be obtained correctly before surgery. However, it is very difficult to distinguish PanNETs G3 from PanNECs before surgery because of small amounts of specimens obtained by EUS-guided fine-needle aspiration. Genetic differences, such as *KRAS* mutation or abnormal immunoreactivity of p53/Retinoblastoma (Rb) between PanNETs G3 and PanNECs can be detected using preoperative small specimen. These tests may have potential to distinguish these two entities and may play a pivotal role to decide appropriate surgical indications [9, 102].

PanNECs, both large cell and small cell NECs, should be assessed for the possible of surgical excision before the use of non-surgical therapy. However, the criteria of proper indication of surgical resection in patients with PanNECs is still controversial. Surgical resection followed by adjuvant therapy was noted to have improved survival in non-metastatic PanNENs G3 [75], however, this study included PanNETs G3 which may bias comparison. Ivanics et al. assessed 514 cases of pancreatic small cell NECs and noted that patients with anatomically resectable tumours benefited from aggressive surgical intervention [103]. In contrast, Basturk et al.

investigated 44 patients with PanNECs who underwent surgery and revealed that 33 patients (75%) had died of disease with a median survival of 11 months [104]. There was also no significant difference between the survival of large cell and small cell NECs. Thus, appropriate candidates with PanNECs (according to the current WHO classification) for indication of surgical excision need to be found out in the future.

2.2.3. *Mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN)*

In the current WHO classification of PanNENs, mixed epithelial neoplasms (a neuroendocrine and a non-neuroendocrine component) are classified as MiNENs. Each of them is morphologically and immunohistochemically recognizable as a discrete component and constitutes $\geq 30\%$ of the neoplasm. In MiNENs of gastrointestinal tract and hepatopancreatobiliary system, both components are usually carcinomas, such as ductal adenocarcinomas or acinar cell carcinomas and NECs [8]. Although there are some case reports of successful treatment of MiNENs, the management strategies have not been established due to the limit number of cases. Basically, the only method to cure MiNENs completely is surgical resection. Surgical procedures for MiNENs need to be considered in each case because of the difficulty of implementation of a prospective trial. Pokrzywa et al. investigated 515 cases with mixed acinar-

neuroendocrine carcinomas treated with surgery [105]. Approximately 75% of patients with MiNENs achieved complete resection and 5-year overall survival of them was 37%, which was better than that of patients with ductal adenocarcinomas (22%) or poorly-differentiated NECs (20%). However, the survival of these patients was worse than survival of patients with acinar cell carcinomas (51%). It is very difficult to diagnose MiNENs before surgery via small amounts of specimens obtained by EUS-guided fine-needle aspiration because the tiny specimens could not satisfy the definition of MiNENs as mentioned above. Strait et al. revealed that only 5 out of 46 cases (11%) of MiNENs of the pancreas were diagnosed on cytopathology specimens before surgical resection in a retrospective study [106]. Even if PanNENs is diagnosed via preoperative specimens, there is a potential possibility that the neoplasm includes other component(s). Thus, it is pivotal to diagnose MiNENs correctly and thoroughly via resected specimens, and adjuvant therapy may be indicated in high risk group of recurrence.

2.3. Medical Treatment

2.3.1. Well-Differentiated PanNET (PanNET G1/G2)

2.3.1.1. Drug treatment for hormonal symptoms

Medical treatment is performed in order to relieve symptoms caused by excessive amounts of hormones in patients with functional PanNETs. These may include use of proton pump inhibitors (inhibitors of acid secretion) for Zollinger-Ellison Syndrome of gastrinoma, glucose infusions with frequent small feedings and the use of diazoxide (a potassium channel activator which inhibits the secretion of insulin) for hypoglycaemia of insulinoma, infusion of a large volume of fluids for severe diarrhea due to VIPoma, and amino acid solution infusion to replace the amino acid depletion in necrotizing migratory erythema of glucagonoma [30, 41, 46, 107].

Somatostatin analogues are also recommended for management of hormone excess state in patients with functional PanNETs through direct binding with somatostatin receptors and effectively reducing the release of peptides and neuroamines [46, 107, 108]. Approximately 70 to 80% of PanNETs express somatostatin receptors on their cell surface, and the symptoms can be controlled in up to 60% of cases. However, insulinoma-related hypoglycaemia may be worsened by somatostatin analogues in half of the patients because glucagon secretion is also inhibited by this drug. Thus, somatostatin analogues should be prescribed only in patients with positive somatostatin receptor scintigraphy (octreotide scan). Octreotide scan is a radionuclide scan in which radioactive octreotide, a drug similar to somatostatin, is injected into the

vein and attaches to tumour cells that have receptors for somatostatin.

2.3.1.2. Antineoplastic Drug

Systemic medication is indicated in patients with unresectable primary and/or distant metastatic lesions for improvement of survival outcome. The antineoplastic drugs include cytotoxic agent, molecular targeted drug, somatostatin analogue, and peptide receptor radionuclide therapy. Basically, antineoplastic option could be selected depending on tumour volume and proliferative activity (the Ki-67 proliferation index). Somatostatin analogues might be a better option in patients with relatively low volume and/or slowly progressive PanNETs (e.g. G1/G2), while cytotoxic agents would be indicated for patients with high volume and/or high proliferative PanNETs (e.g. G2/G3) [31]. Molecular targeted drugs or peptide receptor radionuclide therapy tend to be applied to cases with low to intermediate tumour volume and/or proliferative activity [31]. There are no evidence of concrete cut-off values of the Ki-67 proliferation index or tumour volume at the present for the choice of these therapies.

In addition to development of new therapeutic options, the predictive factors, such as Ki-67 index and clinicopathological parameters, may be useful to predict the optimal agents for personalized treatment that could improve the prognosis of this group of patients [108, 109].

2.3.1.2.1. Cytotoxic agent

Cytotoxic agents might be the best option of the cytoreductive systemic therapy in advanced well-differentiated PanNETs when tumour is bulky and unresectable [110].

Streptozotocin is a naturally occurring alkylating antineoplastic agent that is selectively toxic to the beta cells of the pancreas [111]. Moertel et al. reported that the combination of streptozotocin and doxorubicin had a significant advantage in terms of response rate and survival than streptozotocin plus fluorouracil or chlorozotocin alone in a randomized trial [112]. However, as this result was not reproducible later [108], thus, there is no panel consensus on which chemotherapy regimen is the best for patients with PanNETs (G1/G2). Recently, the clinical outcome regarding streptozotocin-based chemotherapy for 110 patients with metastatic PanNENs (nearly 90% of patients had G1/G2) were reported [113]. In this study, response rate of streptozotocin-based chemotherapy was 21.8%, and progression-free survival was 9.8 months. There was not significantly difference between response rate of weekly (21.6%) and daily regimens (22.0%) of streptozotocin. In addition, there was no difference in response rate between monotherapy of streptozotocin (21.1%) when compared with combination therapy with 5-fluorouracil or combination drug containing

oral tegafur/gimeracil/oteracil (S-1) (25.0%). It is worth noting that Ki-67 labelling index of >5%, not 3%, can be a predictive marker of response rate to streptozotocin, thus, patients with Ki-67 index >5% might benefit from weekly streptozotocin monotherapy.

Temozolomide is an oral chemotherapy drug which is an alkylating agent most commonly used to treat brain cancers [114]. Temozolomide-based regimens have been reported with more than 70% of response rate in patients with PanNENs [115, 116]. In randomized phase II trial comparing the combination of temozolomide and capecitabine (CAPTEM) and temozolomide alone in patients with advanced PanNETs, the survival rates of patients with combination therapies are significantly better than temozolomide alone [117]. In addition, CAPTEM could show more cytoreductive impact than the other treatment strategies (e.g. everolimus or sunitinib) in patients with advanced well-differentiated PanNETs [110].

2.3.1.2.2. *Molecular targeted drug*

Everolimus is an oral inhibitor of mammalian target of rapamycin (mTOR). This drug shows the reduced antiproliferative activity and antiangiogenesis via mTOR activity inhibition. Yao et al. reported that everolimus showed significantly prolonged

progression-free survival among patients with advanced PanNETs compared to placebo in a randomized phase III study (RADIANT-3 trial) (median progression-free survival, 11.0 months versus 4.6 months) [118].

Sunitinib is an oral small-molecule multi-target tyrosine kinase inhibitor that blocks vascular endothelial growth factor receptor (VEGFR)-1,2, 3, platelet-derived growth factor receptor (PDGFR) β , c-KIT, Fms-like tyrosine kinase3 (FLT3), colony stimulating factor 1 receptor (CSF-1R), and RET. A randomized, placebo-controlled phase III trial of sunitinib in patients with advanced well-differentiated PanNETs was reported. In this study, continuous intake of sunitinib significantly improved progression-free survival as compared to placebo group (median progression-free survival, 11.4 months versus 5.5 months) [119, 120].

On the basis of these two phase III studies, everolimus and sunitinib were approved for management of unresectable or metastasizing PanNETs. The treatment strategies are included in the current ENETS consensus guideline and NCCN guideline for management of this group of patients [20, 31]. However, there has been no directly comparative study between everolimus and sunitinib so far, thus, the drug should be selected carefully considering the side effects that these drugs might cause.

Representative severe side effects of everolimus are pneumonitis and hyperglycaemia,

whereas those of sunitinib are hypertension, hand-foot syndrome, and hypothyroidism.

A randomized phase II study of everolimus in combination with pasireotide (multi-receptor ligand somatostatin analogue) long-acting release (LAR) versus everolimus alone (COOPERATE-2 trial) was performed which include 160 patients with well-differentiated, progressive PanNETs were randomly assigned to everolimus plus pasireotide LAR (79 patients) or everolimus alone (81 patients) [121]. There was no significant difference in progression-free survival between the group of patients. Thus, therapy combining molecular targeted drugs with somatostatin analogues has not yet to be established.

A randomized, phase III clinical trial to assess the efficacy and safety of sulfatinib, tyrosine kinase inhibitor of VEGFR 1, 2, and 3 and fibroblast growth factor receptor (FGFR) 1, compared to placebo in patients with advanced PanNETs (G1/G2) is currently ongoing (NCT02589821).

In a phase II trial of the combination of mTOR inhibitor (temsirolimus) and the VEGF-A monoclonal antibody (bevacizumab) in patients with well-differentiated PanNETs, there is a response rate of 41%, progression-free survival at 6 months was a notable 79% as well as median overall survival of 34 months [122].

Kunz et al. reported a phase II study that compared bevacizumab plus

FOLFOX (combination of folinic acid, fluorouracil, and oxaliplatin) to bevacizumab plus CapeOX (capecitabine and oxaliplatin) in patients with advanced PanNETs [123]. In bevacizumab and FOLFOX group, the response rate was 41.7% and 1-year progression-free survival was 66.7%, while in bevacizumab and CapeOX group, the response rate was 18.8% and 1-year progression-free survival was 64.3%. As the response rate in the either group was low, only select patients may benefit from oxaliplatin–fluoropyrimidine chemotherapy plus bevacizumab.

In a phase II trial evaluated the clinical effect of combination therapy with sorafenib (tyrosine kinase inhibitor) plus bevacizumab for patients with advanced GEP-NETs, including 13 PanNETs. The disease control rate was 90%, progression-free survival at 6 months was 88.9% [124].

Other phase II trials evaluated numerous new strategies using targeted agents, e.g. axitinib, cabozantinib, and pazopanib (tyrosine kinase inhibitors) or lenvatinib (multiple kinase inhibitor) are currently underway [125].

2.3.1.2.3. Somatostatin analogue

Somatostatin analogue is not only for control of hormonal symptoms but also for improvement of patients' clinical outcome. Somatostatin analogue can develop the

antineoplastic effect via inhibition of mTOR pathway and down regulation of mitogen-activated protein kinase (MAPK). In a placebo-controlled, phase III study (PROMID trial), 85 patients with well-differentiated metastatic midgut NETs were randomly assigned to receive octreotide LAR and placebo [126]. Octreotide LAR significantly extended progression-free survival when compared with placebo (median progression-free survival, 14.3 months versus 6 months). Tumour progression occurred only in 10 out of 42 in octreotide LAR group (in contrast to 23 out of 43 placebo group). However, this trial excluded cases of PanNENs, thus, the evidence from this study cannot be applied to patients with PanNENs.

In a placebo-controlled, phase III study (CLARINET trial), 204 patients, including those with 91 PanNETs, were randomly assigned to an extended-release aqueous-gel formulation of lanreotide (somatostatin analogue) or placebo [127]. Lanreotide was associated with significantly prolonged progression-free survival when compared with placebo (progression-free survival at 24 months, 65.1% versus 33.0%). As this study showed no significant difference in overall survival between groups due to the long life expectancy for patients with a slowly progressive tumour, there is a need to establish the concomitant treatment with somatostatin analogue and other therapies, such as molecular targeted drugs, for patients with a higher risk of progression [127].

As tumour need to express somatostatin receptors for the successful effect of somatostatin analogue, patients must be examined by somatostatin receptor scintigraphy before the treatment.

2.3.1.2.4. Peptide receptor radionuclide therapy

Peptide receptor radionuclide therapy is a radiolabelled somatostatin analogue therapy, which bind to somatostatin receptors. Peptide receptor radionuclide therapy is very effective against somatostatin receptor-positive tumours, and this agent can deliver radionuclides directly to tumour cells expressing somatostatin receptors [128, 129]. Kwekkeboom et al. reported that 30% of 310 patients with somatostatin receptor-positive GEP-NETs treated with [^{177}Lu -DOTA⁰,Tyr³]-octreotate showed complete and partial response [130]. In a clinical phase II single-centre trial, 1,109 patients with metastatic NETs, including 342 PanNETs, were treated with [^{90}Y -DOTA⁰, Tyr³]-octreotide, and the response rate was 34.1% [131]. Furthermore, 229 patients with well-differentiated, metastatic midgut NETs were assigned to receive either [^{177}Lu -DOTA⁰,Tyr³]-octreotate or octreotide LAR alone in a randomized controlled phase III (NETTER-1) trial [132]. [^{177}Lu -DOTA⁰,Tyr³]-octreotate significantly prolonged progression-free survival, as compared with octreotide LAR alone (progression-free

survival at 20 months, 65.2% versus 10.8%). However, as this phase III study did not include cases with PanNENs, further study is needed to clarify the effect on [^{177}Lu -DOTA⁰,Tyr³]-octreotate for patients with PanNENs. As side effects, such as nephrotoxicity and haematotoxicity are usually mild and reversible, peptide receptor radionuclide therapy would be an effective treatment option for unresectable and/or metastatic PanNENs [128]. As well as achieving oncologic control, the efficacy of peptide receptor radionuclide therapy was shown in treating functional syndrome, particularly for insulinomas, gastrinomas, and glucagonomas [133].

2.3.2. *Well-Differentiated PanNET (PanNET G3)/Poorly-Differentiated PanNEC (PanNEC)*

PanNETs G3 and PanNECs showed not only distinct histological morphology and genetic mutations, but also distinct response to chemotherapy and clinical outcome [102, 134–138]. Sorbye et al. reported that patients having GEP-NECs (according to WHO 2010 classification) with Ki-67 labelling index <55% had a lower response rate to platinum-based chemotherapy than patients with Ki-67 labelling index $\geq 55\%$ (response rate, 15% versus 42%), but has better survival (median overall survival, 14 months versus 10 months) [134]. Although the morphological comparison was not performed

in this study, the result indicated that platinum-based chemotherapy should not be performed uniformly to patients having GEP-NENs with Ki-67 index >20%. Hijioka et al. analyzed 70 PanNENs G3 (21 PanNETs G3 and 49 PanNECs) and also revealed that overall survival for patients with PanNECs was significantly shorter than that for patients with PanNETs G3 (median overall survival, 8.5 months versus 41.8 months) and response rate to platinum-based chemotherapy was significantly higher in PanNECs group than in PanNETs G3 group (response rate, 55.9% versus 0%) [135]. Rb protein loss and mutated *KRAS* that are the characteristics of PanNECs were predictors of the response to platinum-based chemotherapy in patients with PanNENs G3 (response rate, 80% in Rb loss group versus 24% in Rb positive group; 77% in mutated *KRAS* group versus 23% in wild type *KRAS* group) [135]. Thus, it is essential to differentiate patients having PanNECs from PanNETs G3 in order to select the appropriate therapeutic strategies. In addition, some PanNECs did not response to platinum-based chemotherapy. Thus, PanNECs could be classified into subgroups, and treatment for PanNETs G1/G2/(G3), such as everolimus, sunitinib, or streptozocin-/temozolomide-based cytotoxic agents might be more effective for PanNECs that do not response to platinum-based chemotherapy [135].

2.3.2.1. Cytotoxic agent

PanNECs are rare neoplasms and account for only 1 to 7.5% of all PanNENs [105, 139–141]. Many cases are unresectable, and even if complete resection is performed in resectable cases, most of the cases encounter the recurrence and/or distant metastases within one year after surgery [9, 75, 108]. The standard chemotherapy regimens based on a large randomized controlled trial have not been established because of the limited number of PanNECs. However, most of patients with advanced PanNECs are treated with the chemotherapy along the regimens for small cell lung carcinoma [20, 31, 35, 108]. The current standard regimens for small cell lung carcinoma are cisplatin plus etoposide (EP regimen) or cisplatin plus irinotecan (IP regimen). In retrospective studies, the response rate in patients with advanced GEP-NECs receiving EP or IP regimen were 14–67% and 7–58%, and median overall survival were 5.5–19 months and 11–13 months, respectively [134, 142–144]. Yamaguchi et al. investigated 258 patients with unresectable or recurrent NECs of the gastrointestinal tract and hepato-biliary-pancreatic system, including 35 patients with PanNECs [142]. The number of patients treated with IP/EP regimen were 160/46 respectively, and patients with IP regimen showed a better response rate and longer overall survival than those with EP regimen (response rate, 50%/28%; median overall survival, 13.0 months/7.3 months, respectively). Sorbye et al. studied the clinical

outcomes of patients with advanced GEP-NECs (according to WHO 2010 classification) treated with EP regimen (129 patients), carboplatin plus etoposide (67 patients), and carboplatin/etoposide/vincristine (28 patients) [134]. The response rate/median progression-free survival/median overall survival of all the patients were 31%/4 months/11 months, respectively. There were no significant differences among three platinum-based regimen groups. Currently, a randomized phase III comparative study of EP and IP regimens for unresectable/recurrent NECs of gastrointestinal and hepatobiliary pancreas is ongoing by the Japan Clinical Oncology Group (JCOG 1213). A randomized phase II trial is also underway evaluating the efficacy of temozolomide and capecitabine compared to EP regimen in patients with advanced non-small cell GEP-NECs (NCT 02595424).

Second-line options were reported in only a few small retrospective studies and the response rate/median progression-free survival of second- or third-line treatment after first-line treatment failure were 0–40%/1.9–6 months [134, 142, 145–150]. The most used regimens of second-line therapy were; i) irinotecan-based chemotherapy (FOLFIRI; combination of folinic acid, fluorouracil, and irinotecan), ii) oxaliplatin-based chemotherapy (FOLFOX), iii) temozolomide-based chemotherapy, or iv) reintroduction of cisplatin or carboplatin plus etoposide after a treatment break (usually

for at least 3 months). Temozolomide-, amrubicin-, irinotecan-, or topotecan-alone failed to demonstrate the efficacy; all response rates of these regimens were less than 5% [142, 145, 147, 148]. A randomized phase II study are going on, investigating the effect of bevacizumab in combination of FOLFIRI compared to FOLFIRI alone after failure of cisplatin (or carboplatin) and etoposide as first-line palliative chemotherapy in patients with advanced GEP-NECs (NCT02820857) [151].

Considering a high rate of recurrence after surgery, adjuvant therapy should be considered in patients with PanNECs after complete resection in order to have a clinical outcome benefit (disease-free survival and overall survival). Pokrzywa et al. reported that 29% of patients with PanNECs (24 out of 82) received adjuvant chemotherapy after surgery, however, receipt of this therapy did not significantly prolong overall survival of these patients [105]. In contrast, postoperative chemotherapy with 4 to 6 cycles of cisplatin or carboplatin and etoposide is recommended [35], thus, further prospective trials would be needed in the future.

The appropriate treatment strategy should be established for patients with PanNETs G3 immediately due to a lower response rate to platinum-based chemotherapy compared to that of PanNECs. As the biology of PanNETs G3 is considered closer to PanNETs G2 than to PanNECs, treatment options for patients with PanNETs G2 are

currently used for those with PanNETs G3, such as temozolomide-/streptozocin-based chemotherapy, or peptide receptor radionuclide therapy in somatostatin receptor-positive cases [145]. Specific trials for PanNETs G3 are urgently needed. A phase II trial using a combination of temozolomide and everolimus in patients with advanced GEP-NENs with Ki-67 labelling index of 20–55% (NCT02248012) are ongoing. This trial would provide further information for treatment options of patients with PanNETs G3.

2.3.2.2. Immunotherapy

In small cell lung carcinoma, new systemic therapeutic strategies targeting immune checkpoints, such as programmed death 1 (PD-1), programmed death ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) are being established. In a randomized, placebo-controlled, phase III (IMpower133) trial, patients with extensive-stage small cell lung carcinoma who were treated with atezolizumab (PD-L1 inhibitor antibody) plus carboplatin and etoposide showed the prolonged overall survival as compared to patients with placebo plus carboplatin and etoposide (median overall survival, 12.3 months versus 10.3 months) [152]. In contrast, a phase III study of ipilimumab (CTLA-4 inhibitor antibody) in combination

with platinum and etoposide (cycle 3) versus placebo plus platinum/etoposide failed to improve overall survival over chemotherapy alone (median overall survival, 11 months versus 10.9 months) [153]. In a phase I/II trial of nivolumab (PD-1 inhibitor antibody) monotherapy and nivolumab plus ipilimumab (CheckMate 032), the response rate was achieved in 23% of patients with receiving nivolumab plus ipilimumab, while only 10% in nivolumab alone group [154]. In a phase I trial testing pembrolizumab, another monoclonal antibody against PD-1 (KEYNOTE 028), the response rate/median progression-free survival/median overall survival were 33.3%/1.9 months with 1-year progression-free survival, 23.8%/9.7 months with 1-year overall survival, 37.7%, respectively [155]. Although negative results were reported, several phase II/III trials are currently ongoing in small cell lung carcinoma [156]. Thus, new immune checkpoint inhibitors might be potential agents for patients with PanNECs based on the evidence of small cell lung carcinoma, which has a similar genetic background.

As the genetic and molecular backgrounds of PanNECs are being understood steadily, new noble candidates of drug, including molecular targeted drugs and immune checkpoint inhibitors, might be developed in the future. The current treatment strategies for PanNET G1–G3 and PanNEC were summarized in Figure 2.

Figure 2. Current treatment strategies for PanNET G1–G3 and PanNEC.

PanNET: pancreatic neuroendocrine tumour; PanNEC: pancreatic neuroendocrine carcinoma; LN: lymph node; LD: lymph node dissection; PPI: proton pump inhibitor; AA: amino acid; SSA: somatostatin analogue.

2.3.3. Mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN)

Pokrzywa et al. reported that some patients with mixed acinar-neuroendocrine carcinomas (total, n=515) received neo-adjuvant or adjuvant chemotherapy (8% and 41%, respectively) [105]. Frizziero et al. also revealed that approximately 60% of patients with MiNENs who had undergone curative surgery received neo-adjuvant/adjuvant treatment [157]. However, receipt of perioperative treatment (versus surgery alone) did not improve the patients' recurrence-free survival and overall survival. Thus, further studies are needed to find out the appropriate candidates who

could benefit from neo-adjuvant/adjuvant therapy. Appropriate agents for MiNENs have not been established as well as surgical procedures. In general, the decision of a regimen for MiNENs should be based on histopathological findings, serum tumour markers, and imaging [106, 158]. If MiNENs is diagnosed via resected specimens, a regimen for the predominant component might be indicated as adjuvant therapy. On the other hand, receipt of palliative active treatment (versus best supportive care) prolonged progression-free survival and overall survival in patients with unresectable lesion diagnosed with MiNENs [157]. A regimen should be decided considering histopathological findings obtained by EUS-guided fine-needle aspiration and/or serum tumour markers, such as neuron-specific enolase (NSE) for a neuroendocrine component and carcinoembryonic antigen (CEA) for a ductal adenocarcinoma or acinar cell carcinoma component. If a predominant component is detected by histopathological findings, a regimen targeting for the component would be indicated. Likewise, a regimen should be based on an increase in serum tumour markers. A regimen often needs to be changed due to progression of tumour or an increase in serum markers; e.g. the NEC-targeted regimen to the adenocarcinoma-targeted regimen. Thus, frequent imaging examinations and blood tests are required. EUS-guided fine-needle aspiration may also help to decide the regimen [106, 158].

3. Conclusion

The incidence of PanNENs was increasing steadily due to increased clinical vigilance resulting in incidental detection of small and asymptomatic lesions [159]. The use of diagnostic platforms with improved sensitivity, such as ^{68}Ga -DOTATATE positron-emission tomography/computed tomography or the combined use of serum NSE with chromogranin-A could also help the detection of smaller lesions [160].

The current WHO classification of PanNENs reflects the biological characteristics of neoplasms, thus, it is very useful for clinicians to decide the management strategies according to the classification. Further advances in genomic analysis and prospective clinical trials for some PanNENs (such as PanNETs G3, MiNENs, etc) are needed to establish the appropriate treatment strategies for them. There are several issues that should be addressed in the future which should include, i) criteria for observation, especially in patients with small non-functional PanNETs discovered incidentally, ii) development of minimally invasive (laparoscopic/robot-assisted) surgery for PanNENs, iii) establishment of debulking/conversion surgery or neo-adjuvant/adjuvant therapy, iv) introducing new agents or effective combination therapy, and v) appropriate selection of agents according to tumour grading, genetic mutations, tumour volume, or proliferative activity of neoplasms. As biological

characteristics of PanNENs are diverse, treatment stratification or personalisation also needs to be developed. Thus, data of personal genetic mutations or biomarkers that could predict prognosis of the patient should be incorporated into clinical information in order to decide the treatment option. Thus, further establishment of appropriate management strategies is urgent.

Funding sources

The research is supported by funding from Mr Nigel Chamier AO DUniv, Chair of Menzies Health Institute Queensland Advisory Board.

Conflict of interest

There is no conflict of interest in submission of the above-mentioned manuscript for publication in Critical Reviews in oncology/hematology

Acknowledgements

The research is supported by funding from Mr Nigel Chamier AO DUniv, Chair of Menzies Health Institute Queensland Advisory Board.

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