Curr Oncol Rep (2016) 18: 28
DOI 10.1007/s11912-016-0518-9



# Pathology and Surgical Treatment of High-Grade Pancreatic Neuroendocrine Carcinoma: an Evolving Landscape

**Sven-Petter Haugvik[1,2,3] · Daniel Kaemmerer[4] · Sebastien Gaujoux[5] · Knut Jørgen Labori[1] · Caroline Sophie Verbeke[2,6] · Ivar Prydz Gladhaug[1,2]**

Published online: 16 March 2016


**Abstract** Pancreatic neuroendocrine neoplasms (PNENs) are rare, accounting for less than 5 % of all pancreatic tumors. High-grade pancreatic neuroendocrine carcinomas (hgPNECs) represent about 5 % of all PNENs. They show highly aggressive behavior with dismal prognosis. Throughout the last two decades, there has been a notable progress in basic and clinical research of PNENs and a therapeutic trend towards both more aggressive and minimally invasive surgery. Despite these advances, hgPNECs as a distinct clinical entity remains largely unexplored among surgeons. This review of current development in pathology reporting and surgical treatment of hgPNECs aims at increasing the awareness of an evolving field in pancreatic surgery.

**Keywords** Neuroendocrine tumor · Neuroendocrine neoplasm · Gastroenteropancreatic neuroendocrine tumor · Neuroendocrine carcinoma · Pancreas · Pancreatic neoplasm · Pancreatic surgery · Pancreatic cancer · Review

## Introduction

Pancreatic neuroendocrine neoplasms (PNENs) are rare, accounting for less than 5 % of all pancreatic tumors [1, 2]. They are generally divided into two main, clinically, histologically, and biologically very different entities with a common neuroendocrine histiogenesis—the pancreatic neuroendocrine tumors (PNETs) and the high-grade pancreatic neuroendocrine carcinomas (hgPNECs).

hgPNECs are defined as PNENs with poorly differentiated morphology and a higher proliferation rate than in well-differentiated PNETs [3]. They represent about 5 % of all

This article is part of the Topical Collection on *Gastrointestinal Cancers*

✉ Sven-Petter Haugvik
svhaug@ous-hf.no

Daniel Kaemmerer
daniel.kaemmerer@zentralklinik.de

Sebastien Gaujoux
sebastien.gaujoux@gmail.com

Knut Jørgen Labori
uxknab@ous-hf.no

Caroline Sophie Verbeke
c.s.verbeke@medisin.uio.no

Ivar Prydz Gladhaug
i.p.gladhaug@medisin.uio.no

[1] Department of Hepato-Pancreato-Biliary Surgery, Oslo University Hospital, Rikshospitalet, Postbox 4950, Nydalen 0424, Oslo, Norway

[2] Institute of Clinical Medicine, University of Oslo, Postbox 1171, Blindern 0318, Oslo, Norway

[3] Department of Surgery, Drammen Hospital, Vestre Viken Hospital Trust, Postbox 800, 3004 Drammen, Norway

[4] Department of General and Visceral Surgery, Zentralklinik Bad Berka, Robert-Koch-Allee 9, Bad Berka 99437, Germany

[5] Department of Digestive and Endocrine Surgery, Cochin Hospital, APHP, Université Paris Descartes, 27, rue du Faubourg Saint Jacques, 74014 Paris, France

[6] Department of Pathology, Oslo University Hospital, Rikshospitalet, Postbox 4956, Nydalen 0424, Oslo, Norway

PNENs [4] and are characterized by a highly aggressive behavior and dismal prognosis [5••]. In Norway, the incidence of hgPNEC has remained stable throughout the past two decades with an incidence rate of approximately 0.04 per 100,000 person-years [4]. Most hgPNEC are diagnosed in patients around 60 years of age and with a male predilection (male/female ratio around 1.5) and predominance of tumors located in the pancreatic head (65–70 %) [5••, 6••].

Throughout the last decade, a notable progress has occurred in basic, translational, and clinical research on PNETs [7, 8]. At the same time, there has been a general trend towards both more aggressive and minimally invasive surgery of PNETs [9–13]. In contrast, hgPNECs have not gained much attention although basic and clinical research on hgPNEC has recently started to develop. In addition to clinical trials that focus on cytoreductive treatment, the pathology and surgical treatment of this diverse subgroup of neuroendocrine neoplasms have received increasing interest.

Robust knowledge of the histologic characteristics and defining criteria of hgPNEC is a prerequisite for the understanding of oncologic outcomes after surgery. The review will therefore provide an overview of the histologic diagnostic and staging criteria of PNENs, including hgPNEC, followed by a discussion of the surgical treatment of hgPNEC.

## Surgical Pathology

As hgPNECs are morphologically and biologically heterogeneous [14••], thorough and standardized histopathologic reporting is of great importance for treatment planning and prognostic evaluation of patients. Due to the low incidence of hgPNEC and ensuing risk of misdiagnosis, cases should be reviewed by pathologists with expertise in the evaluation of gastroenteropancreatic (GEP) NENs [5••]. Histopathologic characterization of hgPNEC follows the general classification systems that apply for PNENs. The latter are diagnosed based on morphologic appearance and immunohistochemistry, graded and classified according to the tumor-node-metastasis (TNM) staging system. While the characterization of neuroendocrine cell morphology and evaluation of immunohistochemistry in hgPNEC remain the domain of pathologists [15] that will not be further discussed in this review, pancreatic surgeons should have a thorough understanding of the grading and TNM staging of PNENs, including hgPNECs.

## Grading

According to the 2010 World Health Organization (WHO), grading of GEP NENs, including hgPNEC, is based on the mitotic rate (number of mitotic figures per 10 high-power fields) and/or the Ki-67 index (percentage of tumor cells with nuclear staining for Ki-67) [3]. A mitotic rate of <2 and/or Ki-67 index of ≤2 corresponds to a NET G1, and a mitotic rate of 2–20 and/or Ki-67 index of 2.5–20 characterizes a NET G2, while a mitotic rate and/or Ki-67 index of >20 defines a NEC G3 (Table 1). NECs are further subdivided into a small and large cell subtype based on the morphology of the tumor. The genetics of hgPNEC differ from those of PNETs (G1 and G2) [16, 17••], indicating that hgPNEC does not usually develop by genetic progression of G1–G2 PNET [5••, 17••]. Small and large cell morphology is not a prognostic factor for patients with hgPNEC [6••]. It is important to note that grading of a neuroendocrine neoplasm is determined by the highest mitotic rate or Ki-67 index, irrespective of whether this is found in the primary tumor or a metastatic deposit.

A discrepancy in grading defined by mitotic rate and Ki-67 has been observed in up to 44 % of PNENs [18]. PNENs with a mitotic rate within the G2 range and a Ki-67 index corresponding to G3 have been described [14••, 19, 20••]. Such "grade-discordant" PNENs were found to have better prognosis compared with true hgPNECs (median survival 54 versus 11 months), but a worse outcome compared with "grade-concordant" PNENs (median survival 54 versus 68 months) [14••]. A further recent observation that exemplifies the heterogeneity of hgPNEC is the difference in response rate to first-line platinum-based systemic chemotherapy among patients with a GEP NEC depending on whether they had a Ki-67 index above or below 55 %. Interestingly, the response rate correlated with the Ki-67 value (response rate 42 % with Ki-67 above 55 % versus 14 % with Ki-67 below 55 %) [21••]. Both observations, i.e., the existence of a "grade-discordant" group of hgPNEC with unique clinical features and the association between the Ki-67 index and effect of platinum-based chemotherapy of hgPNEC, imply the need for modification of the current WHO 2010 grading system for PNENs [22].

## TNM Staging

PNENs, including hgPNECs, are classified according to their tumor-node-metastasis (TNM) pattern, as defined by validated TNM staging systems [23]. There is no separate TNM

**Table 1** WHO 2010 grading system for pancreatic neuroendocrine neoplasms

| Grade | Mitotic count (10 HPF)[a] | Ki-67 index (%)[b] |
|---|---|---|
| G1 | <2 | ≤2 |
| G2 | 2–20 | 2.5–20 |
| G3 | >20 | >20 |

Table modified from Bosman et al. [3]

[a] 10 HPF, high-power field = 2 $mm^2$, at least 40 fields (at ×40 magnification) evaluated in areas of highest mitotic density

[b] MIB1 antibody, % of 2000 tumor cells in areas of highest nuclear labeling

classification for hgPNECs. There are currently two TNM staging systems for staging of PNENs. The first classification was recommended by the European Neuroendocrine Tumor Society (ENETS) in 2006 [24] and is predominant in Europe. This was followed by the classification suggested by the American Joint Cancer Committee and International Union for Cancer Control (AJCC/UICC) in 2009 [25], which is now widely used in the North American region. The ENETS and AJCC/UICC classification systems for PNENs differ in their definition of the T stage as shown in Table 2.

There is an ongoing debate as to which of the two staging systems is the most precise in terms of prognostic stratifications, with some studies demonstrating similar strength [26] and others indicating superiority of the ENETS over the AJCC/UICC TNM staging system [27, 28].

As two different TNM staging systems are currently being used, publications should report the tumor features on which the T stage classifications are based, such that translation between ENETS and AJCC/UICC classifications can be made [29]. This is all the more important, in view of the likely future adaptions of current staging systems when more clinical follow-up data have been gathered [28].

## Future Directions

Upcoming trials on surgical treatment of PNENs, including hgPNEC, should report histopathological features as outlined above. A modification of the WHO 2010 grading system of PNENs with inclusion of the "grade-discordant" group of hgPNEC as a new subgroup is likely. Moreover, there is a need for one internationally accepted TNM staging system in order to avoid confusion and misinterpretation among researchers and clinicians. There is also a need to clarify whether staging should be the same for PNETs (G1–G2) and hgPNECs (G3) as clinical behavior of these PNEN subgroups is very diverse. Future studies should report Ki-67 values of both primary and metastatic diseases, if available, as discordance of histologic grade between primary and metastatic PNENs is sometimes observed [30]. This is probably more relevant for metachronous than synchronous metastases, as there is often an increase in Ki-67 over time [30]. Multicenter studies should include central slide review by pathologists with expertise in the field. The use of digital image analysis should be further explored [31]. With the increasing knowledge about the molecular and genetic aberrations in hgPNEC, current classification systems are likely to change.

## Surgical Treatment

Surgical resection is the only curative treatment option for pancreatic NETs (G1 and G2) and remains the therapeutic cornerstone, even for patients with advanced disease [12, 13]. In contrast, the role of surgery in the treatment of hgPNEC remains unclear [6••]. This may be explained by the common presence of synchronous metastatic disease and rapid progression of hgPNECs, which traditionally has supported a treatment choice of palliative systemic chemotherapy [21••]. However, less than half of patients with hgPNEC respond to such treatment regimens and alternative treatment options are urgently needed. A novel interest in surgical treatment of hgPNEC has recently been noted [6••, 32••, 33, 34], as shown in Table 3, although the underlying clinical evidence for a surgical approach is still scarce and prospective trials on surgery for hgPNEC are lacking. Nevertheless, efforts should be made to increase the attention of surgeons to the treatment of hgPNEC as a possible measure to improve patient survival. In the following sections, different aspects of surgical treatment for hgPNEC will be discussed.

## Localized Disease

Surgery of localized nonmetastatic disease, defined as T stage T1 or T2, combined with chemotherapy seems to improve overall survival despite the presence of a recurrent disease, compared with chemotherapy alone (median survival 23 versus 13 months) [6••]. Surgical resection of localized nonmetastatic disease has also been associated with a relatively high 5-year survival of 43 % [33]. For patients with localized hgPNEC ≤2 cm who underwent resection, median survival was 29 months, while patients who were left to best supporting care had a median survival of 5 months [34]. The case number of patients with localized hgPNEC undergoing surgery in these studies was generally low ranging from 20 to 26.

**Table 2** Comparison of the criteria for the T category in the ENETS and AJCC/UICC TNM classifications of pancreatic neuroendocrine neoplasms

| | ENETS TNM [24] | AJCC/UICC [25] |
|---|---|---|
| T1 | Confined to pancreas, <2 cm | Confined to pancreas, <2 cm |
| T2 | Confined to pancreas, 2–4 cm | Confined to pancreas, >2 cm |
| T3 | Confined to pancreas, >4 cm, or invasion of duodenum or bile duct | Extension beyond pancreas, but without involvement of celiac axis or superior mesenteric artery |
| T4 | Invasion of adjacent organs or major vessels | Involvement of celiac axis or superior mesenteric artery |

*ENETS* European Neuroendocrine Tumor Society, *AJCC/UICC* American Joint Cancer Committee and International Union for Cancer Control

**Table 3** Summary of the current surgical series for patients with high-grade pancreatic neuroendocrine carcinoma

| Study | Country | Study design | Patients with hgPNEC | Patients with hgPNEC undergoing surgery | Conclusion |
|---|---|---|---|---|---|
| Crippa et al. 2015 [32••] | Italy | Retrospective multicenter | 59 | 23 | Radical resection of nonmetastatic disease is associated with improved survival compared with no resection. |
| Fischer et al. 2014 [33] | Germany | Retrospective single-center | 24 | 24 | Surgery may be considered as a treatment option for patients with hgPNEC. |
| Haugvik et al. 2015 [6••] | Norway, Sweden, Denmark, Finland | Retrospective multicenter | 119 | 28 | Resection of the primary tumor is an independent prognostic factor of improved survival for patients with hgPNEC at different disease stages. Patients selected for combined treatment with surgery and chemotherapy seem to have better survival than chemotherapy alone. |
| Sharpe et al. 2015 [34] | USA | Retrospective multicenter | 30 | 20 | Surgical resection of nonmetastatic hgPNEC ≤2 cm seems to improve survival compared with no resection |

According to the current ENETS consensus guidelines for high-grade GEP NECs, combination of postoperative platinum-based chemotherapy with local treatment consisting of surgery, radiotherapy, or both probably offers the greatest likelihood of long-term survival for patients with localized disease irrespective of the exact site of the primary [35••]. As prognosis of GEP NECs correlates with the Ki-67 index, tumors with a very high Ki-67 are more aggressive than tumors with a Ki-67 just above 20 % [21••, 36]. At the same time, GEP NECs with a high Ki-67 (≥55 %) do respond better on systemic platinum-based chemotherapy than GEP NECs with a low Ki-67 (<55 %) [21••]. Based on these observations, we would recommend upfront radical surgery for hgPNECs with a Ki-67 <55 % and neoadjuvant systemic platinum-based chemotherapy for hgPNECs with a Ki-67 ≥55 %.

## Peripancreatic Lymphadenectomy

The risk of peripancreatic lymph node metastasis in patients with PNENs correlates with increasing tumor size and tumor grading [37]. Presence of regional lymph node metastasis is independently associated with decreased disease-specific survival in patients with PNENs, including patients with hgPNEC [37, 38]. There is an ongoing debate as to whether or not peripancreatic lymphadenectomy should be performed routinely in patients with PNENs [38–43]. It is unknown if peripancreatic lymphadenectomy improves survival in patients with hgPNEC since no trial has evaluated this. However, as lymph node stage predicts prognosis, peripancreatic lymphadenectomy should probably be performed routinely in patients undergoing surgery for hgPNEC.

## Locally Advanced Disease

The impact of surgery on the prognosis of patients with locally advanced hgPNEC, defined as T-stage T3 or T4, has not been evaluated yet. However, there are indications that surgery may improve survival in locally advanced disease when compared with chemotherapy alone, as shown by a recent report on 19 patients with stage T3 or T4 disease [6••]. The current North American Neuroendocrine Tumor Society (NANETS) consensus guidelines provide only an expert opinion on this matter, which supports radical surgery, if the risk of morbidity is low and the risk of intestinal obstruction is high [44]. Our experiences are in accordance with this recommendation. Furthermore, we would suggest surgery for radically resectable locally advanced nonmetastatic hgPNEC for selected patients, despite a higher risk for a margin-positive resection. This is supported by the observed improved survival after R0/R1 resections of hgPNEC, compared with R2 resections [32••]. As mentioned earlier, we would recommend neoadjuvant systemic platinum-based chemotherapy for hgPNECs with a Ki-67 ≥55 %.

## Preoperative and Postoperative Chemotherapy

There are no systematic studies on the use of preoperative chemotherapy in patients with localized hgPNEC. Most localized hgPNECs will recur or metastasize within 1 year after resection [6••]. This might suggest the presence of occult metastases at diagnosis. Thus, postoperative platinum-based chemotherapy should always be considered for patients with hgPNEC, regardless of the stage of the disease and provided the treatment is tolerated [6••, 35••]. It seems that >4 courses

of postoperative chemotherapy is a significant factor of improved survival compared with 1–4 courses [6••]. Based on the limited clinical evidence available, we recommend upfront radical surgery of localized disease with postoperative platinum-based systemic chemotherapy of more than four courses [6••]. This is also supported by an expert opinion reported in the current NANETS guidelines [44]. Given the early manifestation of a recurrent disease after surgery for localized nonmetastatic hgPNEC, it remains to be established whether chemotherapy should also be given in a neoadjuvant setting.

### Metastatic Disease

Most patients with hgPNEC develop distant metastases, which is often already present at the time of diagnosis [45]. This reduces the prospects for long-term survival. The current ENETS and NANETS guidelines do not recommend surgery for distant metastasis or debulking surgery for hgPNEC [35••, 44]. This is also supported by the guidelines of the Nordic Neuroendocrine Tumor Group (NNTG) from 2014 [46] and by a recent international consensus conference on the treatment of neuroendocrine liver metastasis [47].

However, there is evidence that surgery of metastatic hgPNEC may improve survival. In one study, overall survival was 24 months with a 5-year survival of 21 % among 13 patients who underwent surgery for liver metastasis [48]. In another study, overall survival after surgery of metastases was 29 months with a 3-year survival of 69 % among 12 patients [6••].

Resection of the primary tumor is an independent prognostic factor for improved survival in patients with hgPNEC at different disease stages [6••]. This has also recently been demonstrated for PNENs across all stages of disease [13, 49] and suggests that resection of the primary tumor should always be considered, even in patients with metastatic disease. Aggressive locoregional treatment of liver metastases (debulking surgery, radiofrequency ablation, and liver-directed intra-arterial intervention) of hgPNEC may improve survival [50••]. Another important and recent finding is that surgical treatment combined with systemic chemotherapy may improve the survival of patients with metastatic hgPNEC compared with chemotherapy alone [6••].

As the current guidelines are exclusively based on expert opinions and considering the latest clinical data on this matter that diverge from the guidelines' recommendations, we could expect that the expert opinions may be modified in the near future as more clinical data on surgery of hgPNEC become available.

### Future Directions

The therapeutic approach for localized hgPNEC is at present neither consistent nor uniform [46]. Future studies on surgical treatment of hgPNEC should focus on the establishment of standardized sequences of treatment for hgPNEC, especially the combined use of platinum-based chemotherapy pre- and postoperatively [51]. High-grade PNECs should be studied as a separate entity with precise reporting of their characteristics in future trials [52]. Moreover, initiatives should be undertaken to carry out to plan and conduct prospective multicenter studies. We propose the need for a prospective trial on neoadjuvant platinum-based chemotherapy for nonmetastatic hgPNEC with a Ki-67 index above 55 %. We would also suggest the need for a prospective study on radical surgical treatment combined with platinum-based chemotherapy of resectable metastatic disease versus platinum-based chemotherapy alone.

### Prognosis and Surveillance

Median survival for patients with hgPNECs receiving best supportive care is 2 months, 13 months for those receiving chemotherapy, and 23 months if treated with combined chemotherapy and surgery [6••].

There is no evidence as to how the follow-up of patients with hgPNECs should be planned and conducted. Hence, recommendations concerning surveillance are based on expert opinion. According to the current recommendations of the NNTG, radically treated patient should undergo surveillance with a CT scan of the abdomen and chest, alternatively MRI, every 3 months [46]. The most recent ENETS guidelines support this scheme and recommend that if the patient is in remission 2–3 years postoperatively, surveillance intervals can be prolonged to 6–12 months during the following 5 years [35••]. Surveillance of patients with metastatic disease should be decided individually with a general recommendation of CT/MRI every 2–3 months while undergoing treatment. Recurrent disease is typically distant and not local [6••].

## Conclusion

High-grade PNECs represent a rare and diverse group of PNENs, both histopathologically and clinically, which warrants special attention from pancreatic surgeons. Recent novel findings support the notion of surgery as a principle of treatment for patients with hgPNEC. As treatment options are limited, initiatives should be made to further evaluate the role of surgery in this aggressive group of malignancies.

#### Compliance with Ethical Standards

**Conflict of Interest** Sven-Petter Haugvik, Daniel Kaemmerer, Sebastien Gaujoux, Knut Jørgen Labori, Caroline Sophie Verbeke, and Ivar Prydz Gladhaug declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

## References

Papers of particular interest, published recently, have been highlighted as:
•• Of major imprtance


1. Milan SA, Yeo CJ. Neuroendocrine tumors of the pancreas. Curr Opin Oncol. 2012;24:46–55.
2. Fitzgerald TL, Hickner ZJ, Schmitz M, Kort EJ. Changing incidence of pancreatic neoplasms: a 16-year review of statewide tumor registry. Pancreas. 2008;37:134–8.
3. Bosman FT, Carneiro F, Hruban RH. WHO classification of tumours of the digestive system. Lyon: International Agency for Research on Cancer (IARC); 2010.
4. Boyar CR, Aagnes B, Thiis-Evensen E, Tretli S, Bergestuen DS, Hansen S: Trends in incidence of neuroendocrine neoplasms in Norway: a report of 16,075 cases from 1993 through 2010. *Neuroendocrinology* 2015.
5.•• Basturk O, Tang L, Hruban RH, Adsay V, Yang Z, Krasinskas AM, et al. Poorly differentiated neuroendocrine carcinomas of the pancreas: a clinicopathologic analysis of 44 cases. Am J Surg Pathol. 2014;38:437–47. **Most hgPNECs are diagnosed in patients around 60 years of age with a male predilection and predominance of tumors located in the pancreatic head. hgPNECs are often misdiagnosed by pathologists.**
6.•• Haugvik SP, Janson ET, Osterlund P, Langer SW, Falk RS, Labori KJ, et al: Surgical treatment as a principle for patients with high-grade pancreatic neuroendocrine carcinoma: a Nordic multicenter comparative study. Ann.Surg.Oncol. 2015. **Resection of the primary tumor is an independent prognostic factor of improved survival for patients with hgPNEC at different disease stages. Patients selected for combined treatment with surgery and chemotherapy had better survival than chemotherapy alone.**
7. Chabot J: Pancreatic neuroendocrine tumors: Primum non nocere. Surgery 2015.
8. Kulke MH. Are neuroendocrine tumors going mainstream? J Clin Oncol. 2013;31:404–5.
9. Norton JA, Harris EJ, Chen Y, Visser BC, Poultsides GA, Kunz PC, et al. Pancreatic endocrine tumors with major vascular abutment, involvement, or encasement and indication for resection. Arch Surg. 2011;146:724–32.
10. Bertani E, Fazio N, Botteri E, Chiappa A, Falconi M, Grana C, et al. Resection of the primary pancreatic neuroendocrine tumor in patients with unresectable liver metastases: possible indications for a multimodal approach. Surgery. 2014;155:607–14.
11. Fernandez-Cruz L, Molina V, Vallejos R, Jimenez CE, Lopez-Boado MA, Ferrer J. Outcome after laparoscopic enucleation for non-functional neuroendocrine pancreatic tumours. HPB (Oxford). 2012;14:171–6.
12. Haugvik SP, Labori KJ, Edwin B, Mathisen O, Gladhaug IP. Surgical treatment of sporadic pancreatic neuroendocrine tumors: a state of the art review. Sci World J. 2012;2012:357475.
13. Huttner FJ, Schneider L, Tarantino I, Warschkow R, Schmied BM, Hackert T, et al. Palliative resection of the primary tumor in 442 metastasized neuroendocrine tumors of the pancreas: a population-based, propensity score-matched survival analysis. Langenbecks Arch Surg. 2015;400:715–23.
14.•• Basturk O, Yang Z, Tang LH, Hruban RH, Adsay V, McCall CM, et al. The high-grade (WHO G3) pancreatic neuroendocrine tumor category is morphologically and biologically heterogenous and includes both well differentiated and poorly differentiated neoplasms. Am J Surg Pathol. 2015;39:683–90. **PNENs with a mitotic rate within the G2 area and a Ki-67 index within the G3 represent a distinct subgroup of hgPNEC**.
15. Campbell F, Verbeke CS. Pathology of the pancreas: a practical approach. London: Springer; 2013.
16. Yachida S, Vakiani E, White CM, Zhong Y, Saunders T, Morgan R, et al. Small cell and large cell neuroendocrine carcinomas of the pancreas are genetically similar and distinct from well-differentiated pancreatic neuroendocrine tumors. Am J Surg Pathol. 2012;36:173–84.
17.•• Tang LH, Untch BR, Reidy DL, Eileen OE, Dhall D, Jih L, et al: Well differentiated neuroendocrine tumors with a morphologically apparent high grade component: a pathway distinct from poorly differentiated neuroendocrine carcinomas. Clin Cancer Res 2015. **The etiology of PNETs (G1 and G2) is genetically different from that of hgPNEC.**
18. Khan MS, Luong TV, Watkins J, Toumpanakis C, Caplin ME, Meyer T. A comparison of Ki-67 and mitotic count as prognostic markers for metastatic pancreatic and midgut neuroendocrine neoplasms. Br J Cancer. 2013;108:1838–45.
19. La RS, Sessa F. High-grade poorly differentiated neuroendocrine carcinomas of the gastroenteropancreatic system: from morphology to proliferation and back. Endocr Pathol. 2014;25:193–8.
20.•• Velayoudom-Cephise FL, Duvillard P, Foucan L, Hadoux J, Chougnet CN, Leboulleux S, et al. Are G3 ENETS neuroendocrine neoplasms heterogeneous? Endocr Relat Cancer. 2013;20:649–57. **PNENs with a mitotic rate within the G2 area and a Ki-67 index within the G3 represent a distinct subgroup of hgPNEC**.
21.•• Sorbye H, Welin S, Langer SW, Vestermark LW, Holt N, Osterlund P, et al. Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): the NORDIC NEC study. Ann Oncol. 2013;24:152–60. **Gastroenteropancreatic NECs with a Ki-67 value > 55% behave clinically differently than those with a Ki-67 value < 55%**.
22. Sorbye H, Strosberg J, Baudin E, Klimstra DS, Yao JC. Gastroenteropancreatic high-grade neuroendocrine carcinoma. Cancer. 2014;120:2814–23.
23. Rindi G. The ENETS guidelines: the new TNM classification system. Tumori. 2010;96:806–9.
24. Rindi G, Kloppel G, Alhman H, Caplin M, Couvelard A, de Herder WW, et al. TNM staging of foregut (neuro) endocrine tumors: a consensus proposal including a grading system. Virchows Arch. 2006;449:395–401.
25. Sobin LH, Gospodarowicz MK, Wittekind C. UICC: TNM classification of malignant tumours, edn 7th. edn. Oxford: Wiley-Blackwell; 2009.
26. Ellison TA, Wolfgang CL, Shi C, Cameron JL, Murakami P, Mun LJ, et al. A single institution's 26-year experience with nonfunctional pancreatic neuroendocrine tumors: a validation of current staging systems and a new prognostic nomogram. Ann Surg. 2014;259:204–12.
27. Rindi G, Falconi M, Klersy C, Albarello L, Boninsegna L, Buchler MW, et al. TNM staging of neoplasms of the endocrine pancreas: results from a large international cohort study. J Natl Cancer Inst. 2012;104:764–77.
28. Qadan M, Ma Y, Visser BC, Kunz PL, Fisher GA, Norton JA, et al. Reassessment of the current American Joint Committee on Cancer staging system for pancreatic neuroendocrine tumors. J Am Coll Surg. 2014;218:188–95.
29. Kloppel G, Rindi G, Perren A, Komminoth P, Klimstra DS. The ENETS and AJCC/UICC TNM classifications of the neuroendocrine tumors of the gastrointestinal tract and the pancreas: a statement. Virchows Arch. 2010;456:595–7.
30. Adesoye T, Daleo MA, Loeffler AG, Winslow ER, Weber SM, Cho CS. Discordance of histologic grade between primary and metastatic neuroendocrine carcinomas. Ann Surg Oncol. 2015;22(3):817–21.
31. Tang LH, Gonen M, Hedvat C, Modlin IM, Klimstra DS. Objective quantification of the Ki67 proliferative index in neuroendocrine tumors of the gastroenteropancreatic system: a comparison of

digital image analysis with manual methods. Am J Surg Pathol. 2012;36:1761–70.

32.•• Crippa S, Partelli S, Bassi C, Berardi R, Capelli P, Scarpa A, et al: Long-term outcomes and prognostic factors in neuroendocrine carcinomas of the pancreas: morphology matters. Surgery 2015. **Radical resection of nonmetastatic hgPNEC is associated with improved survival compared with no resection. R0/R1 resections of hgPNEC is associated with better oncologic outcome than R2 resections.**

33. Fischer L, Bergmann F, Schimmack S, Hinz U, Priess S, Muller-Stich BP, et al. Outcome of surgery for pancreatic neuroendocrine neoplasms. Br J Surg. 2014;101:1405–12.

34. Sharpe SM, In H, Winchester DJ, Talamonti MS, Baker MS. Surgical resection provides an overall survival benefit for patients with small pancreatic neuroendocrine tumors. J Gastrointest Surg. 2015;19:117–23.

35.•• Garcia-Carbonero R, Sorbye H, Baudin E, Raymond E, Wiedenmann B, Niederle B, et al: Consensus guidelines for high grade gastro-entero-pancreatic (gep) neuroendocrine tumours and neuroendocrine carcinomas (nec). Neuroendocrinology 2016. **The current guidelines of the European Neuroendocrine Tumor Society represent the most comprehensive of existing guidelines in the management of patients with gastroenteropancreatic NECs.**

36. Heetfeld M, Chougnet CN, Olsen IH, Rinke A, Borbath I, Crespo G, et al. Characteristics and treatment of patients with G3 gastroenteropancreatic neuroendocrine neoplasms. Endocr Relat Cancer. 2015;22:657–64.

37. Curran T, Pockaj BA, Gray RJ, Halfdanarson TR, Wasif N. Importance of lymph node involvement in pancreatic neuroendocrine tumors: impact on survival and implications for surgical resection. J Gastrointest Surg. 2015;19:152–60.

38. Hashim YM, Trinkaus KM, Linehan DC, Strasberg SS, Fields RC, Cao D, et al. Regional lymphadenectomy is indicated in the surgical treatment of pancreatic neuroendocrine tumors (PNETs). Ann Surg. 2014;259:197–203.

39. Ferrone CR. Lymphadenectomy for pancreatic neuroendocrine tumors: is that the relevant debate? Ann Surg. 2014;259:213–4.

40. Ricci C, Casadei R, Taffurelli G, Buscemi S, D'Ambra M, Monari F, et al. The role of lymph node ratio in recurrence after curative surgery for pancreatic endocrine tumours. Pancreatology. 2013;13:589–93.

41. Stabile BE. When pNETs bust out of their shells. Arch Surg. 2012;147:828.

42. Krampitz GW, Norton JA, Poultsides GA, Visser BC, Sun L, Jensen RT. Lymph nodes and survival in pancreatic neuroendocrine tumors. Arch Surg. 2012;147:820–7.

43. Yoo YJ, Yang SJ, Hwang HK, Kang CM, Kim H, Lee WJ. Overestimated oncologic significance of lymph node metastasis in G1 nonfunctioning neuroendocrine tumor in the left side of the pancreas. Medicine (Baltimore). 2015;94, e1404.

44. Kunz PL, Reidy-Lagunes D, Anthony LB, Bertino EM, Brendtro K, Chan JA, et al. Consensus guidelines for the management and treatment of neuroendocrine tumors. Pancreas. 2013;42:557–77.

45. Shiba S, Morizane C, Hiraoka N, Sasaki M, Koga F, Sakamoto Y, et al: Pancreatic neuroendocrine tumors: a single-center 20-year experience with 100 patients. Pancreatology. 2015.

46. Janson ET, Sorbye H, Welin S, Federspiel B, Gronbaek H, Hellman P, et al. Nordic guidelines 2014 for diagnosis and treatment of gastroenteropancreatic neuroendocrine neoplasms. Acta Oncol. 2014;53:1284–97.

47. Frilling A, Modlin IM, Kidd M, Russell C, Breitenstein S, Salem R, et al. Recommendations for management of patients with neuroendocrine liver metastases. Lancet Oncol. 2014;15:e8–e21.

48. Partelli S, Inama M, Rinke A, Begum N, Valente R, Fendrich V, et al. Long-term outcomes of surgical management of pancreatic neuroendocrine tumors with synchronous liver metastases. Neuroendocrinology. 2015;102:68–76.

49. Keutgen XM, Nilubol N, Glanville J, Sadowski SM, Liewehr DJ, Venzon DJ, et al: Resection of primary tumor site is associated with prolonged survival in metastatic nonfunctioning pancreatic neuroendocrine tumors. Surgery 2015.

50.•• Du S, Ni J, Weng L, Ma F, Li S, Wang W, et al. Aggressive locoregional treatment improves the outcome of liver metastases from grade 3 gastroenteropancreatic neuroendocrine tumors. Medicine (Baltimore). 2015;94:e1429. **Combined surgical treatment and chemotherapy of metastatic gastroenteropancreatic NECs may improve survival compared with chemotherapy alone**.

51. Labori KJ, Haugvik SP, Line PD. Letter to the editor: Multidisciplinary management of pancreatic neuroendocrine tumors—the importance of an aggressive surgical approach. Scand J Gastroenterol. 2016;51:383–4.

52. Kulke MH, Siu LL, Tepper JE, Fisher G, Jaffe D, Haller DG, et al. Future directions in the treatment of neuroendocrine tumors: consensus report of the National Cancer Institute Neuroendocrine Tumor clinical trials planning meeting. J Clin Oncol. 2011;29:934–43.