REVIEW

Open issues on G3 neuroendocrine neoplasms: back to the future

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Abstract

The recent recognition that grade 3 (G3) neuroendocrine neoplasms (NENs) can be divided into two different categories according to the histopathological differentiation, that is G3 neuroendocrine tumors (NETs) and G3 neuroendocrine carcinomas (NECs) has generated a lot of interest concerning not only the diagnosis, but also the differential management of such new group of NENs. However, several issues need to be fully clarified in order to put G3 NETs and G3 NECs in the right place. The aim of this review is to focus on those issues that are still undetermined starting from the current knowledge, evaluating the available evidence and the possible clinical implications.

Key Words

- neuroendocrine tumors
- G3
- diagnosis
- prognosis

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Introduction

Neuroendocrine neoplasms (NENs) are well known to display a wide heterogeneity as concerns histopathology, clinical presentation, treatment and prognosis. Despite their rarity, NENs have drawn a lot of attention due to the newly available therapeutic approaches, that mainly depend on tumor stage and grade (Chan *et al.* 2017*a*,*b*, Cives & Strosberg 2017, Finkelstein *et al.* 2017, Gallo *et al.* 2017, Hilal 2017, Lambrescu *et al.* 2017, Michael *et al.* 2017, Neychev & Kebebew 2017, Rinke & Gress 2017). Since cure is difficult to achieve in most aggressive forms, therapy is mainly aimed at delaying disease progression, in order to improve prognosis. The 2010 World Health Organization (WHO) classification considers neuroendocrine carcinomas (NECs) as a single category on the basis of a Ki-67 labeling index (LI) >20% (Rindi *et al.* 2010). It has recently become apparent that the definition of NEC by the 2010 WHO classification includes a spectrum of different entities that are characterized by different prognosis and response to therapy, depending on tumor morphology (Welin *et al.* 2011, Vélayoudom-Céphise *et al.* 2013, Basturk *et al.* 2015, Heetfeld *et al.* 2015, Hijioka *et al.* 2015, Milione *et al.* 2017) and Ki-67 LI cut-off reassessment (Sorbye *et al.* 2013, Milione *et al.* 2017), suggesting the introduction of a new NEN category characterized by well-differentiated tumor morphology and Ki-67 LI >20%, indicated as G3 well-differentiated neuroendocrine tumors (NETs). This proposal underlines that Ki-67 LI alone is not able to properly describe G3 NEN, which instead appears to be a heterogeneous category, and brings back the definition of these tumors to more morphological grounds, as indicated in the 2000 WHO classification.

Aim

The aim of this review is to summarize the available data on diagnosis, management and prognosis of G3 NETs and

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G3 NECs and to highlight the issues that are still open to debate in the scientific arena.

Methodology

Among the six authors, four (M C Z, E G, E M and F L C) independently searched MEDLINE (PubMed database) to detect articles published in the English language reporting on diagnosis and management of G3 NET and G3 NEC, excluding editorials and letters. The search was last updated 23 October 2017. Additional studies were identified by reviewing the references of all selected articles.

Diagnosis

According to the current WHO classification (Rindi *et al.* 2010), the diagnosis of G3 gastroenteropancreatic (GEP) NEN is based on the evaluation of proliferative activity (mitotic count >20/10 high power fields (HPFs) and/or >20% Ki-67 LI) and on cell size (large cell vs small cell). By definition, these are poorly differentiated tumors, whereby they are called NECs and can display two morphologic patterns (Figs 1 and 2). Grade 1 (G1) and grade 2 (G2) NETs are, instead, well-differentiated forms whose diagnosis relies only on Ki-67 LI and/or mitotic activity (NET G1: mitotic count <2/10 HPF and/or ≤2% Ki-67 LI; NET G2: mitotic count 2–20/10 HPF and/or 3–20% Ki-67 LI). Recent evidence shows that G3 neoplasms represent a heterogeneous group of neoplastic proliferations, including both well- and poorly differentiated forms (Vélayoudom-Céphise *et al.* 2013, Basturk *et al.* 2015, Heetfeld *et al.* 2015, Tang *et al.* 2016*a*, Milione *et al.* 2017), with different prognosis and response to medical treatments (Sorbye *et al.* 2013). Based on these observations, a proposal for a new classification has been formulated, that consists of the combination of morphology and proliferative activity (Fig. 3), with the aim of a better prognostic stratification. Three new categories could be identified: NET G3, characterized by well-differentiated morphology and 21–55% Ki-67 LI; NEC G3 that are poorly differentiated and show 21–55% Ki-67 LI and finally NEC G4 that are poorly differentiated and show Ki-67 LI >55% (Fazio & Milione 2016). The new classification of pancreatic NEN (Klöppel *et al.* 2017) has partially upheld this proposal: indeed, the G3 category now includes not only poorly differentiated forms (NEC G3), but also well-differentiated ones (NET G3). These observations have been supported by molecular findings (Girardi *et al.* 2017), but they are still a matter of great debate. Indeed, the proposal to discriminate G3 from

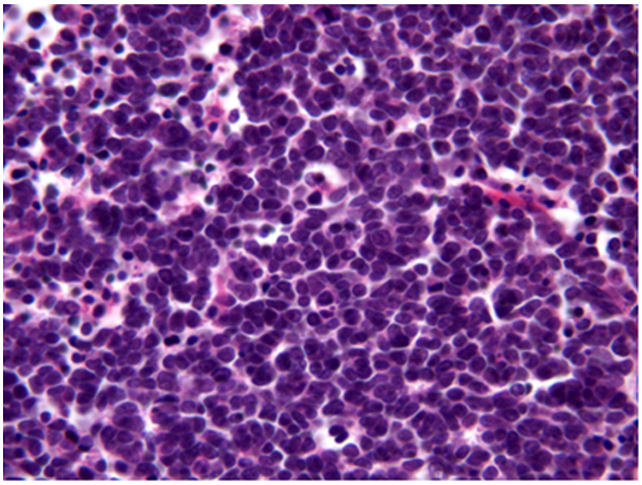

Figure 1
A case of small-cell carcinoma consisting of a dense proliferation of small-sized cells with high nucleus/cytoplasm ratio, nuclear moulding, without prominent nucleoli. (Hematoxylin and eosin stain, 40× magnification.)

G4 NEC only on the basis of Ki67, considering 55% as cutoff, is supported by the evidence provided by a large clinical study (Sorbye *et al.* 2013) but has not been adopted by any consensus group. Therefore, there are open questions that still need to be clarified.

What is meant by 'differentiation'?

A general rule is that the more the neoplasm recapitulates the normal tissue, the more it can be considered as well differentiated. In other sites, specific histological

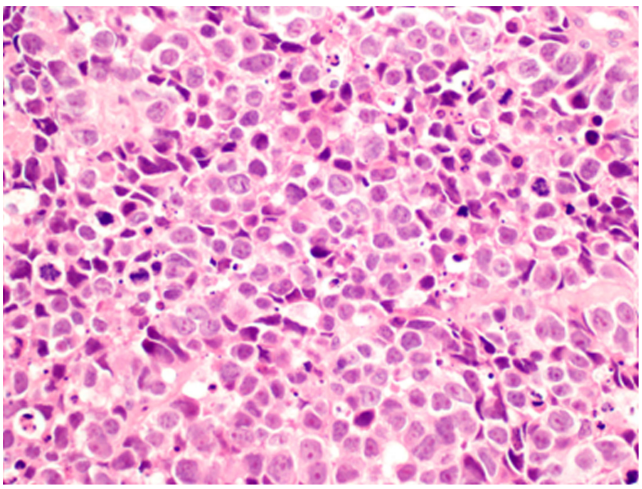

Figure 2
A case of large-cell neuroendocrine carcinoma: large-sized cells with abundant cytoplasm and nuclei with vesicular chromatin and a central nucleolus are typical morphologic features of this NEC subtype. (Hematoxylin and eosin stain, 40× magnification.)

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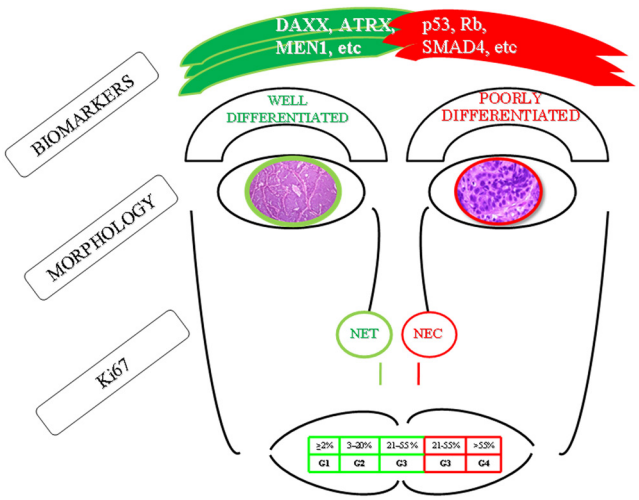

Figure 3
Schematic representation of the new proposed diagnostic algorithm for GEP-neuroendocrine neoplasms that is mainly based on the combination of morphology and Ki-67 labeling Index. In some instances, especially in pancreatic NEN, an integration with immunohistochemical and molecular study of additional biomarkers is needed.

grading scores have been applied for years and have proved to be of great clinical value. Concerning NEN, there is compelling need to make the morphological interpretation of the histological grade homogeneous and reproducible, which is a difficult task to be realized due to their potential ubiquitous localization. Within the same histological grade, morphological features characterizing these tumors are not completely overlapping in all sites. As an example, many site-specific features may be observed in the whole gastrointestinal tract. In the past, an attempt of classification was based on the embryonic origin: foregut tumors are those deriving from thymus, esophagus, lung, stomach, pancreas, gallbladder and duodenum; midgut tumors derive from appendix, ileum, caecum and ascending colon and finally hindgut tumors from distal large bowel and rectum. In the past, well-differentiated tumors (Soga & Tazawa 1971) were divided, on the basis of histological architectural patterns, into type A (insular solid; more common in the small bowel and appendix), type B (trabecular or ribbon-like; in the rectum or sigmoid colon) and type C (glandular; in the ampullary region). Although this division is no longer in use, such a morphological variability is common to both well-differentiated neoplasms and poorly differentiated large-cell carcinomas, mainly concerning cytological features (Fazio & Milione 2016). This morphological diagnostic algorithm, combined with Ki-67 LI evaluation, discriminates well-differentiated high-grade neoplasms (G3 NET) from neuroendocrine carcinoma (G3 NEC) in the gastrointestinal tract (Fig. 3). However, the evaluation of the described features might depend on the operator, especially in the absence of a specific pathology training (Milione & Fazio 2017) or on tumor sampling.

Furthermore, in a large proportion of high-grade NEN of the pancreas, it was shown that additional ancillary information, including clinical findings and biomarker expression, may be of aid in the distinction of NET G3 from NEC G3 to 4 (Basturk *et al.* 2014, Tang *et al.* 2016*b*). Therefore, in pancreatic NEN, molecular information needs to be included in the diagnostic algorithm (Fig. 3).

Are G3 NEN homogeneous?

Five studies (Vélayoudom-Céphise *et al.* 2013, Basturk *et al.* 2015, Heetfeld *et al.* 2015, Tang *et al.* 2016*a*, Milione *et al.* 2017) investigated the role of morphology in G3 NENs, mostly of the gastrointestinal tract. All of them provide data supporting the evidence that the current WHO G3 category is heterogeneous, containing at least two different groups of tumors. On a total of 461 analyzed cases (Table 1), G3 NETs were more often observed in the pancreas, representing 43% of G3 pancreatic NENs. The second most common site of this new category is the ileum (35% of ileal G3 NENs) and then the stomach (18%). Therefore, most of the knowledge concerning G3 NETs originates from the pancreatic site. Moreover, in this context, G3 NEC represents a peculiar entity, accurate diagnosis of which is not straightforward, because of the wide range of differential diagnoses to be taken into consideration (G3 NET, acinar cell carcinoma, mixed acinar-NEC and primitive neuroectodermal tumor) (Basturk *et al.* 2014). Site-specific distribution of high- and low-grade NEN throughout the gastrointestinal tract may be explained by the different histological conformation of various districts. In the esophagus, for example, well-differentiated NETs are uncommon, probably because normal tissue does not contain a significant neuroendocrine population (Odze & Goldblum 2015). Interestingly, in one of the five case series that studied G3 NEN (Milione *et al.* 2017), it was observed that midgut and/or hindgut sites of origin statistically correlated with a worse survival as compared with foregut. Given the heterogeneity of G3 NEN, much has yet to be clarified as concerns differential diagnosis and sub-categorization into G3 NET and G3 NEC in the various tumor sites of origin. On top of these difficulties lays the well-known intra-tumoral NEN heterogeneity. Indeed, these neoplasms may display areas characterized by high grade with foci showing low/intermediate grade, especially in the settings

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Table 1 Studies evaluating site-specific distribution of G3 NEN, with detail of G3 NET.

Site	G3 NEN	Total	G3 NET	Total (%)
Esophagus	8[d]+5[e]	13	0[d]+0[e]	0
Stomach	17[d]+28[e]	45	3[d]+5[e]	8 (18)
Pancreas	9[a]+62[b]+21[c]+65[d]+33[e]	190	7[a]+1[b]+21[c]+24[d]+11[e]	82 (43)
Duodenum	7[d]+5[e]	12	1[d]+0[e]	1 (8)
Ileum	6[c]+11[d]+17[e,*]	34	6[c]+2[d]+4[e]	12 (35)
Colon	31[d]+46[e]	77	0[d]+4[e]	4 (5)
Biliary ducts	2[c]+2[e]	4	2[c]+0[e]	2 (n.e.)
Rectum	2[c]+24[d]+1[a]	27	2[c]+3[d]+0[a]	5 (19)
Lung	2[a]	2	1[a]	1 (n.e.)
Thymus	2[a]	2	2[a]	2 (n.e.)
Larynx	3[a]	3	1[a]	1 (n.e.)
Unknown	7[a]+28[d]	35	1[a]+0[d]	1 (3)
Others	4[a]+13[d]	17	0[a]+1[d]	1 (6)

*Ileum + cecum + appendix; [a]Vélayoudom-Céphise *et al.* (2013); [b]Basturk *et al.* (2015); [c]Tang *et al.* (2016*a*,*b*); [d]Heetfeld *et al.* (2015); [e]Milione *et al.* (2017). n.e., not evaluable.

of a well-differentiated NET G1–2 progressing to a NET G3 (Tang *et al.* 2016*a*). Therefore, the correct characterization of G3 NEN remains a matter of great debate.

Staging system: what staging for G3 NET?

According to the European Neuroendocrine Tumor Society, all NENs are classified in a single system (Rindi *et al.* 2006). The American Joint Committee on Cancer (AJCC), on the other hand, in the seventh (Edge *et al.* 2010) and in the eighth edition (Asare *et al.* 2017), applies this system only to G1 and G2 NETs. Concerning G3 NEC, the AJCC recommends to classify them according to the TNM staging of adenocarcinomas of the site of origin (Edge *et al.* 2010, Asare *et al.* 2017). G3 NETs are still in a grey zone since they represent 'high-grade, well-differentiated forms', whose biological behavior is quite similar to G2 NET in the first 2 years from diagnosis in terms of overall survival (OS) (Milione *et al.* 2017). Indeed, the AJCC suggests to use the parameters of well-differentiated forms in staging the rare G3 NET, rather than those of poorly differentiated carcinomas (Asare *et al.* 2017).

Lung and thorax 'G3' NEN: more morphology, less proliferation!

The current WHO Classification of lung and thorax NEN (Brambilla *et al.* 2015) catalogues four categories on the basis of morphological parameters (well-differentiated/high-grade neoplasm, absence/presence of necrosis and mitotic activity): typical carcinoid; atypical carcinoid; large-cell neuroendocrine carcinoma (LCNEC); small-cell lung carcinoma (SCLC). No role is recognized for Ki-67 LI, while, unlike GEP NEN, in this classification, morphology alone plays an essential role. Attempts to introduce a three-tiered grading based on Ki-67 LI, together with mitotic count and necrosis, were performed, but no clinical utility was achieved before the approval of the last classification. A new proposal for a diagnostic algorithm is emerging for lung NEN that is, just as for the GEP district, an integration of morphology (necrosis and mitoses) and proliferation (Ki-67 LI), aimed at identifying three NEN categories: Lu-NET G1, Lu-NET G2 and Lu-NET G3 (Rindi *et al.* 2013). This proposal would allow to handle tumors with similar behavior according to their own biological potential. Furthermore, it would be worth to consider the mitotic count among the diagnostic criteria. Indeed, NET G3 are often diagnosed only on the basis of Ki-67 LI, but a low mitotic count (<20 mitosis/10 HPF) in a case with elevated Ki-67 LI (>20%) could be helpful in identifying a well-differentiated form of high-grade NEN.

Molecular characteristics

A recently published comprehensive genomic analysis of 102 clinically sporadic pancreatic NETs disclosed the presence of genetic alterations affecting DNA damage and repair, chromatin remodeling, telomere maintenance and mammalian target of rapamycin (mTOR) signaling (Scarpa *et al.* 2017), providing a significant contribution to the understanding of this disease and helping in risk stratification and treatment. However, only 5% of the investigated pancreatic NETs were G3, and there is no specification as to whether they were well- or poorly differentiated neoplasms. Therefore, this study cannot help in differentiating G3 NEN in the proposed sub-categories. Conversely, in the field of NEN, most of the

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detected molecular alterations involve NECs. Mutations in *TP53*, *BRAF* or *RAS* genes, aberrations in the p16/Rb/cyclin D1 signaling pathway and microsatellite instability are the most frequently reported molecular derangements (Pizzi *et al.* 2003, Kimiloglu Sahan *et al.* 2015, Vijayvergia *et al.* 2016). These features are often shared by both adenocarcinomas and NEC components of mixed adenoneuroendocrine carcinomas, as it was shown mostly in cases of colorectal NEC (Takizawa *et al.* 2015, Woischke *et al.* 2017), and almost never detected in NET (Takizawa *et al.* 2015). These proofs strongly suggest that NECs and NETs belong to two different families, linked by some histologic overlap and expression of neuroendocrine markers, but differing substantially in terms of their genomic bases, clinical presentation and relationship to non-NE neoplasms. In addition, a recent retrospective study found that pancreatic G3 NET display *DAXX*, *ATRX* and *MEN1* gene mutations, similarly to well-differentiated G2 NET, and not *RB1* or *TP53* gene mutations, commonly found in G3 NEC (Hijioka *et al.* 2015, Tang *et al.* 2016*a*,*b*). Therefore, the characterization of such molecular derangements may help in differentiating G3 NET from G3 NEC when morphology is not sufficient (Tang *et al.* 2016*b*, Konukiewitz *et al.* 2017). Along this line, in pancreatic NET loss-of-function mutations in *DAXX* and *ATRX* genes have been described, with consequent loss of expression of their related proteins by immunohistochemistry (Yachida *et al.* 2012). Inactivating mutations of these genes were exclusive of this form, since they have not been detected either in small-cell or in large-cell NEC. This finding could suggest that well-differentiated NETs are genetically distinct from poorly differentiated forms. In the thoracic district, comparative genomic hybridization studies and gene-expression profiling data have shown that carcinoids are biologically different from NECs of the lung (Swarts *et al.* 2012), and may help in further characterizing lung NENs. Despite these promising results, the applied methodology is not widely available and validation studies are still lacking. In a large series of LCNECs (Rekhtman *et al.* 2016), three tumor subsets were identified on the basis of their genomic signatures: a major group, characterized by *TP53*+*RB1* co-mutation/loss and other SCLC-type alterations (e.g. *MYCL* amplification), another major group with NSCLC-like genetic profile, characterized by the lack of co-altered *TP53*+*RB1* and the occurrence of NSCLC-type mutations (*STK11*, *KRAS*, *KEAP1*) and, finally, a minor group, carcinoid-like, characterized by *MEN1* mutations and low mutation burden.

Another open issue concerns the role of immunocheckpoints in NEN. Recently, programmed death-ligand 1 (PD-L1) expression was assessed in 32 GEP NET (Kim *et al.* 2016), where it was found to associate with progression-free survival (PFS) and OS. Others found PD-L1 to be expressed only in high-grade forms (Li *et al.* 2016). In the lung, PD-L1 expression was apparent in 10.4% of LCNECs and 5.8% of SCLCs and was not observed in carcinoid tumors (Tsuruoka *et al.* 2017), therefore suggesting that PD-L1 staining might help in differentiating poorly from well-differentiated lung NETs.

Does microenvironment have a role in NENs?

It is not clear why tumors arising in different tissues have different metastasizing behavior. Tumor progression depends on complex biochemical and biological changes occurring in cancer cells and in the associated stroma. In addition, the immune system has a critical role providing defense actions and attack mechanisms against cancer (Weinberg 2014). The existence of an interconnection between the neuroendocrine system and the microenvironment has been studied for years. Chromogranin A, one of the major circulating NEN markers, is believed to be able to influence neoplastic stroma and tumor growth (Corti *et al.* 2010, Marotta *et al.* 2018). Moreover, neuroendocrine mediators are able to enhance inflammatory states and to interfere with the immune response (Zappalà *et al.* 2013). In addition, the issue of epigenetic influence on metastatic behavior of low-to-intermediate grade NEN, rather than a genetic drive, is still open. Heterogeneity in the epigenetic profiles of different primary sites has been shown in NEN, thus suggesting the presence of underlying differences in tumorigenic processes, microenvironment-driven modulation of epigenetic states and/or their possible correlation with the biological aggressiveness of these diverse neoplasms (Cives *et al.* 2016). The clinical influence of this finding is under investigation: the definition of an epigenetic fingerprinting could provide a more successful prognostic stratification than those based on grade, site and differentiation.

Management

In non-metastatic NET G3, surgery appears as the first option, but, at the same time, the least frequent; therefore, systemic therapy is often necessary. Generally, chemotherapy regimen in pancreatic NET G3 is similar to

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that implemented in NET G1/2 when Ki-67 LI is <55%, while it is similar to the NEC chemotherapy regimen when Ki-67 LI is >55%. Literature reports describe many different medical treatments for these tumors, ranging from somatostatin analogs (SSAs), to platinum-based regimens and molecular targeted drugs.

As concerns NET G3, a study evaluating 30 patients mostly affected with GEP tumors demonstrated the efficacy of SSAs in obtaining disease control (considered as stable disease and partial/complete response) in 70% of the cases (Aparicio *et al.* 2001). A further study employed SSA in combination with fluorouracil (5-FU) in 29 GEP NET G3 patients, showing disease control in 93% of the cases (Brizzi *et al.* 2009). On the other hand, in studies employing chemotherapy including variable regimens (5-FU, streptozotocin, platinum-based drugs alone or in combination with etoposide, capecitabine and/or vincristine) disease control was achieved in ~50% of the patients (Moertel *et al.* 1991, Mitry *et al.* 1999, Bajetta *et al.* 2007, Turner *et al.* 2010).

As concerns NEC G3, a study employing SSA showed disease control in only one patient out of the five treated (Aparicio *et al.* 2001). Two studies including 464 bronchopulmonary NECs (Mavroudis *et al.* 2001, Hanna *et al.* 2006) showed a very limited efficacy of the diverse chemotherapeutic regimens employed (platinum-based drugs alone or in combination with etoposide, irinotecan or paclitaxel), with disease control limited to 36% of the patients. As for GEP-NEC G3, 9 studies employed chemotherapy including 386 patients treated with variable regimens (5-FU, streptozotocin, platinum-based drugs alone or in combination with etoposide, capecitabine and/or vincristine), showing disease control in ~65% of the patients (Moertel *et al.* 1991, Mitry *et al.* 1999, Brenner *et al.* 2004, Hainsworth *et al.* 2006, Bajetta *et al.* 2007, Iwasa *et al.* 2010, Turner *et al.* 2010, Welin *et al.* 2011).

Therefore, these studies support the hypothesis that NET G3 may be managed by SSA, in association or not with chemotherapy, obtaining an overall good disease control rate. On the contrary, NEC G3 seems to respond better to chemotherapy, mostly platinum-based compounds in combination with different other drugs. Conversely, bronchopulmonary NECs display a lower sensitivity to chemotherapy as compared to NEC of GEP origin. Platinum-based chemotherapy appears to be better than other types of chemotherapy for LCNEC, although there are no randomized studies indicating that platinum is the treatment of choice for these tumors. Thang and coworkers explored peptide receptor radionuclide therapy (PRRT) efficacy in G3 NEN, evaluated by response evaluation criteria in solid tumors (RECIST) 1.1 criteria and toxicity (Thang *et al.* 2018). They observed a longer PFS (12 months) and OS (46 months) in 22 patients with Ki-67 LI ≤55% as compared to 6 patients with Ki-67 LI >55% (4 and 7 months, respectively). Patients with FDG-avid disease, likely less differentiated, showed progression, but clinically significant response (partial response + disease stabilization) was obtained in 74% of the other 23 patients. Therefore, even though evidence is not very strong, PRRT may be considered as a potential therapeutic strategy also for G3 NEN. It should be underlined, however, that only few of the evaluated studies were performed by dividing G3 NEN on the basis of the new concepts of differentiation. Available literature was analyzed by dissecting the studies and taking into consideration those reporting grade and differentiation, trying to draw conclusions that, of course, cannot provide solid information, but only general indications. Only prospective studies will provide definitive information concerning the most appropriate therapeutic regimen for NET G3 and for NEC G3.

Prognosis

In keeping with the evidence that one of the main prognostic markers in NEN is represented by cell differentiation (Madeira *et al.* 1998, Faggiano *et al.* 2007), NET G3 displays less aggressive features as compared to NEC G3 but worse outcome as compared to NET G2, with a disease-specific survival ranging from 41 to 55 months (Vélayoudom-Céphise *et al.* 2013, Sorbye *et al.* 2014, Basturk *et al.* 2015, Crippa *et al.* 2016*a*). A recent study retrospectively evaluating 136 G3 GEP-NEC patients with a median follow-up of 81 months, showed an independent prognostic value for Ki-67 LI, mismatch repair proteins, stage and CD117 expression (Milione *et al.* 2017). The authors provided support for a sub-classification of G3 NEN in three 'types', on the basis of morphology and Ki-67 LI, which are associated with different prognosis. They indeed identified: type A neoplasms, represented by well-differentiated tumors with a Ki-67 LI = 20–55% and median OS of 43.6 months; type B, represented by poorly differentiated neoplasms with a Ki-67 LI = 20–55% and median OS of 24.5 months; type C, represented by poorly differentiated neoplasms with a Ki-67 LI ≥55% and median OS of 5.3 months. In addition, NET G3 may include patients with well-differentiated NET showing <20 mitoses/10 HPF

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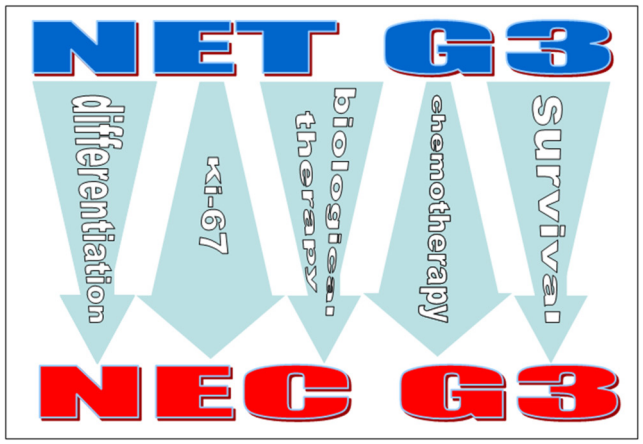

Figure 4
The different spectrum of G3: NET to NEC.

(G2 by mitotic count) but Ki-67 LI >20%. These grade-discordant NETs have been shown to display a worse prognosis as compared to grade-concordant G2 NETs (54 vs 68 months) (Basturk *et al.* 2014). In keeping with the bad prognosis of poorly differentiated cancers, NEC G3 represents a group of very aggressive neoplasms. Pancreatic NEC G3 behaves similar to SCLC: they display lymph node and distant metastases since diagnosis and are associated with a median survival of ~1 year (Basturk *et al.* 2014, Crippa *et al.* 2016*b*). Most of these patients may die few weeks after diagnosis, even if treated with aggressive systemic chemotherapy (Sorbye *et al.* 2013). Therefore, it is apparent that still a lot of work has to be done in order to better characterize these tumors and provide clinically useful information, especially for treatment purposes.

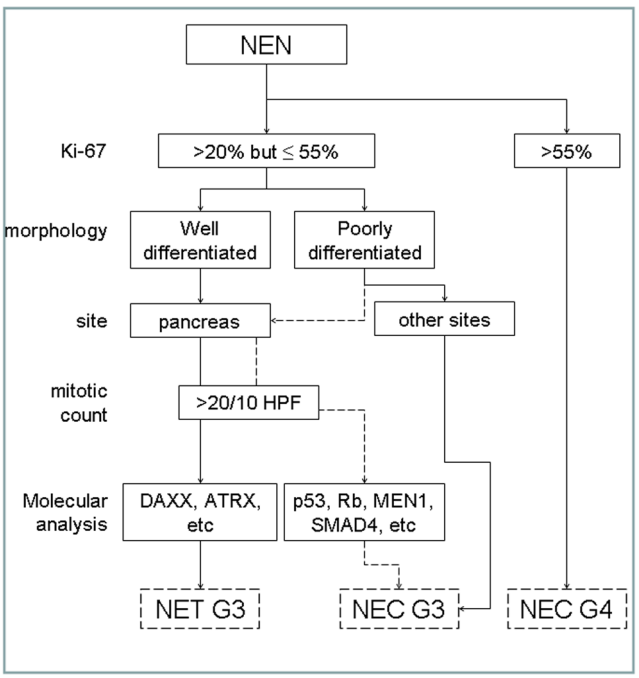

Figure 5
Indicative flow-chart for NEN G3 diagnosis.

Conclusions

The available studies highlight the rapid evolution in defining and characterizing NEN categories on the basis of the growing amount of evidence in this field. G3 NEN diagnostic criteria need to be refined in order to better address treatment on the basis of differential outcomes of these tumors. Going back to highlight the importance of morphological differentiation may represent an important indication in the difficult management of these tumors (Fig. 4). It is indeed crucial to gather as much information as possible in order to ensure the best and quickest diagnostic path to these patients, that need to be promptly (and frequently aggressively) treated (Fig. 5).

Only prospective studies will allow us to respond to the several questions raised by our analysis.

Declaration of interest
M C Zatelli has received consultant fees from Novartis, Pfizer and Genzyme. The other authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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Author contribution statement
Maria Chiara Zatelli wrote the Abstract, the Introduction, the Aim and Methodology, the part related to Management and Prognosis, the Conclusions and revised the manuscript; Elia Guadagno: wrote the part related to Diagnosis; Erika Messina helped in analyzing the literature on treatment of G3 NET/NEC and corrected the references; Fabio Lo Calzo helped in analyzing the literature on treatment of G3 NET/NEC and provided a critical review; Antongiulio Faggiano proof-read the manuscript; Annamaria Colao supervised the project.

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