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Intervention in gastro-enteropancreatic neuroendocrine tumours

Eric Baudin, MD, PhD, Head of the Endocrine Oncology Unit [a,*], David Planchard, MD, PhD, Thoracic Oncologist [b], Jean-Yves Scoazec, MD, PhD, Head of the Translational Research Department [c], Joël Guigay, MD, PhD, Professor of Medicine, Head and Neck Department [b], Clarisse Dromain, MD, Head of the Radiology Department [d], Julien Hadoux, MD, Fellow [a], Thierry Debaere, MD, PhD, Head of the Interventional Radiology Unit [d], Dominique Elias, MD, PhD, Head of the Oncology Surgical Department [e], Michel Ducreux, MD, PhD, Executive Medical Director [b]

[a] *Department of Nuclear Medicine and Endocrine Oncology, Institut Gustave Roussy, 39 rue Camille Desmoulins, 94805 Villejuif Cedex, France*
[b] *Department of Medical Oncology, Institut Gustave Roussy, Villejuif, France*
[c] *Department of Pathology, Institut Gustave Roussy, Villejuif, France*
[d] *Department of Radiology and Interventional Radiology, Institut Gustave Roussy, Villejuif, France*
[e] *Department of Surgery, Institut Gustave Roussy, Villejuif, France*

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A B S T R A C T

Neuroendocrine tumours require dedicated interventions to control their capacity to secrete hormones but also, antitumour growth strategies. Recommendations for early interventions in NET include the management of hormone-related symptoms and poorly differentiated neuroendocrine carcinomas. In contrast, prognostic heterogeneity is a key feature of well differentiated NET that complexified the antitumour strategy whatever the stage in this subgroup of tumour. In this review, timely therapeutic interventions to control hormone-related symptoms and tumour growth in GEP NET patients are discussed. The necessity of

* Corresponding author. Tel.: +33 142116362; fax: +33 142116363.
E-mail addresses: baudin@igr.fr, eric.baudin@igr.fr (E. Baudin), david.planchard@igr.fr (D. Planchard), jean-yves.scoazec@igr.fr (J.-Y. Scoazec), joel.guigay@igr.fr (J. Guigay), clarisse.dromain@igr.fr (C. Dromain), jhadoux@gmail.com (J. Hadoux), thierry.debaere@igr.fr (T. Debaere), dominique.elias@igr.fr (D. Elias), michel.ducreux@igr.f (M. Ducreux).

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controlling hormone-related symptoms as the first step of any strategy affects also the tumour growth control strategy. In the absence of cure at the metastatic stage, progresses are expected in the recognition of well differentiated NET subgroups that display either excellent or poor prognosis.

Introduction

Gastro-enteropancreatic neuroendocrine tumours (GEP NET) constitute a heterogeneous group of tumours responding to a common definition i.e. the expression of specific markers associated with the granules and vesicules characteristic of peptide-producing neuroendocrine cells. They also express common characteristics, including the secretion of hormones, their association as part of inherited syndromes, the existence of common activated molecular pathways but also the expression of specialized membrane receptors like the somatostatin receptors, the presence of a hypervascularized stroma [1,2]. These characteristics translate into a common characterization process but also into common therapeutic targeting [3]. The primary location but also the pathological differentiation, recently incorporated along with the proliferative capacities as part of grading for digestive NET, strongly influence their presentation but also correlate with the stage at diagnosis [1,4–15] (Table 1).

Although NETs were initially thought to pursue an indolent course, successive standardization of pathological and TNM classifications were of major help in outlining the prognostic heterogeneity of this group of tumours. Indeed, even at the metastatic stage, survival ranges between 0 and 100% at five years according to the characteristics of the tumour. In the absence of curative tools at this advanced stage [16] and due to the fact that a large number of randomized trials have not been carried out, prognostic parameters balanced with safety issues remain the decisive elements of the antitumour therapeutic intervention, nowadays.

In this review, the term well differentiated neuroendocrine tumour will apply to G1 and G2 digestive NET but also to typical and atypical bronchial carcinoids. Poorly differentiated neuroendocrine tumour will apply to G3 digestive NEC but also to large cell bronchial carcinoma. The issue of small cell lung carcinoma will not be specifically addressed. Data issued from expert centres, that provide a multivariate analysis, constitute the basis of this review since they provide the most comprehensive and standardized characterization of patients. We will discuss therapeutic interventions to control hormone-related symptoms first and then, tumour growth in GEP NET patients and show how the necessity of controlling hormone-related symptoms as the first step of any strategy affects the tumour growth control strategy.

Intervention in GEP NET for the control of hormone-related symptoms

Functioning syndrome a typical feature of well differentiated NET

One of the most specific features of NETs in oncology is their ability to secrete hormones, creating hormone-related symptoms, also named functioning syndromes. The presence of hormone-related

Table 1
Primary location as a function of presence of distant metastasis and probability of poorly differentiated carcinoma at diagnosis.

TNM stage at diagnosis	Pathological differentiation-grading	
	Probability of poorly differentiated carcinoma $\leq$1%	Probability of poorly differentiated carcinoma >1%
Distant metastasis <15%	Appendix Insulinoma-gastrinoma	Bronchus Rectum Gastric
Distant metastasis >15%	Ileum Other functioning pNET	Pancreas (non-functioning)

pNET = pancreatic neuroendocrine tumour.

symptoms depends on NETs pathological differentiation (recently incorporated in tumour grading), TNM stage and primary location; it is also influenced by tumour load. In brief, functioning syndromes are mainly diagnosed in well differentiated NET, potentially at an early stage in foregut (lung, pancreas, duodenum)-derived NET, but mainly at an advanced metastatic stage especially in midgut (ileum)-derived NET [1,2]. Functioning syndromes affect the quality of life and prognosis of these patients. Indeed, historical reports have clearly demonstrated that presence of hormone secretions may alter the survival of patients before the tumour growth does [17]. Interestingly, in recent prognostic studies, the presence of hormone-related symptoms or increased hormone-related markers together with the TNM stage, were the most powerful prognostic parameters found in some reports dealing with ileum primary [9,18,19] but not pancreatic NET primary [12,20–26]. This result suggests that the prognostic information related to the presence of a functioning syndrome may differ according to the primary.

Functioning syndrome, a typical feature of well differentiated NET that requires dedicated interventions

Major medical therapeutic progress has been made in the control of hormone-related symptoms. When such functioning syndromes occur, starting dedicated medical interventions to control hormone-related symptoms are recommended before any antitumour therapeutic intervention [17] (Fig. 1). Somatostatin analogue therapy is given to control carcinoïd, VIPoma, glucagonoma, acromegaly syndromes. Dedicated medical agents such as proton pump inhibitors, cortisol secretion inhibitors, diazoxide are given in the case of gastrinoma, Cushing syndromes or insulinoma, respectively. Recently, promising results have been shown with everolimus in patients with malignant insulinoma to control refractory hypoglycemia [27]. However, it remains that these antisecretory agents allow complete symptomatic response in only rare cases, like in the case of gastrinoma treated with proton pump inhibitors. Therefore, in the case of localized well differentiated NET, surgery remains the only curative option when hormone-related symptoms occur.

In the vast majority of advanced NET, therapeutic dedicated medical interventions to control hormone-related symptoms remain palliative. The absence of hormone level normalization, persistent hormone-related comorbid conditions like the carcinoid heart syndrome or the poor prognosis of malignant insulinomas are evidence that cure of hormone secretions is still an unmet need in NET [17,28,29]. As a consequence, lifelong medical interventions to control hormone-related symptoms are maintained in most cases of functioning unresectable NET. Furthermore, additional tools that typically

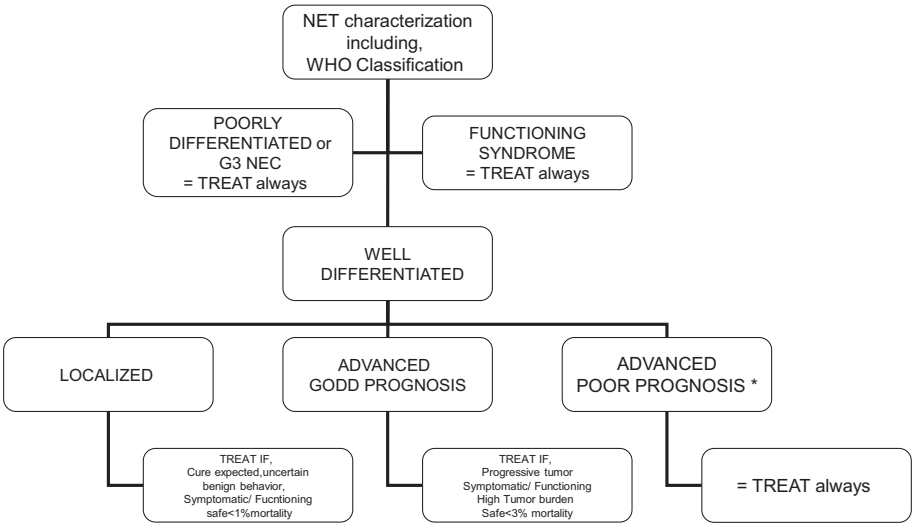

Fig. 1. Interventions in NET. *= G2 (Ki67 > 10–15%) or atypical (mitotic count >5 10 HPF) well differentiated NET and high tumour burden or, ENETS G3 neoplasms.

consist in strategy dedicated to decrease the tumour burden are required to improve such hormone-related symptoms. At that point in time, both antisecretory and antitumour strategies will be combined and the question of the synergism of these combined medical interventions will be raised. The relative contribution of each option in the control of hormone-related symptoms or tumour growth will be unclear if started, concurrently.

Functioning syndrome, a typical feature of NET that requires dedicated interventions that affect antitumour strategy and the design of trials

If the prerequisite of a therapeutic intervention when functioning syndromes are present is widely accepted, it should be kept in mind that such intervention may affect tumour growth. Some examples of this are somatostatin analogue therapy which is used in patients with carcinoid syndrome or everolimus therapy used in patients with malignant insulinomas. Both drugs have antitumour activity as recently demonstrated in placebo-controlled phase III trials [28,30]. Therefore in functioning NET patients, the control of hormone secretion affects directly or indirectly the control of tumour growth, at least in subgroups of patients such as through anti-angiogenic effects [31]. On a routine basis, these results signify that both the antisecretory and antitumour efficacy of each single intervention should be evaluated in each patient but also, should not be considered as separate and independent interventions.

Concerning trial design, a new strategy emerging in NET patients is dedicated to better understanding the respective antisecretory and antitumour roles of each single intervention. Indeed, the recently published RADIANT 2 trial and the ongoing RADIANT 4 trial address the question of the antitumour role of a medical agent, i .e everolimus, in two different populations of well differentiated non-pancreatic NET patients, classified according to their history of functioning syndrome (RADIANT 2) [32] or not (RADIANT4) (NCT01524783). Indeed, in the RADIANT 2 trial, patients with a history of functioning carcinoid syndrome were randomized for: somatostatin analogue therapy combined with everolimus or best supportive care. This study showed a five-month non-significant improvement of PFS in the somatostatin analogue-everolimus arm and leaves unanswered the question of the specific antitumour and or antisecretory roles of everolimus, alone. In addition the potential synergism of the combination of somatostatin analogue therapy and everolimus in these patients could not be determined since most patients received somatostatin analogue therapy prior to the enrolment in the trial to control the functioning syndrome. To get further insights into the antitumour role of Everolimus, as a single agent, the RADIANT 4 trial is ongoing, in non-functioning well differentiated non-pancreatic NET patients, randomized for everolimus alone or best supportive care. Due to the enrolment of non-functioning patients, somatostatin analogue therapy is no longer mandatory and the antitumour efficacy of everolimus alone will be better understood. However, one question at issue is how this new selection of patients, in functioning or non-functioning subgroups, will affect the characteristic of the population enrolled. Indeed, since functioning syndrome has been reported to affect in a negative way the prognosis of non-pancreatic well differentiated NET like ileum NET, it could be hypothesized that the RADIANT 4 trial will enrol patients with less advanced disease in comparison to the RADIANT 2 trial. This hypothesis is reinforced by the analysis of the PROMID study, a placebo phase III trial which evaluated the antitumour impact of somatostatin analogue therapy in midgut NET. In this study, patients enrolled experienced no or mildly functioning ileum NET. Finally, it emerged that 75% of the patients enrolled in the PROMID study experienced a low liver involvement below 10% and low proliferative index in 97% of cases and could finally be therefore classified as 'good prognosis' [28]. A precise characterization of all relevant prognostic parameters is expected to supply answers on this issue and allow comparisons between different trials in the future. This example illustrates how the need to better understand the antisecretory and or antitumour roles of each single therapeutic intervention in NET patients, affects the trial design but also potentially the selection of patients enrolled.

Interventions in GEP NET for the control of tumour growth

One of the most challenging features of NET consists in their heterogeneous prognosis. Indeed, within the spectrum of well differentiated NET, 100% survival at five-years is achievable whatever the TNM stage, at least in subgroups of patients [33]. In addition, no means exist that procide cure at this

stage [16]. These simple observations make clear the fact that the decisive elements of any therapeutic decision in NETs should be based on the adequate balance between benefits expected from therapeutic intervention and safety. The low number of randomized trials and therefore the low level of evidence-based medicine, also argue in favour of the benefit–risk ratio as a critical parameter in the therapeutic-making decision. Finally, a few predictors of tumour response are used in NET and no one is definitely validated.

Prognostic heterogeneity as a key feature of NET even at the metastatic stage: refinements expected per WHO subgroups and TNM stages

Due to multiple facets of NET but also multiple primary locations and only recently established TNM classifications, the key prognostic determinants of this group of tumours were difficult to establish. Indeed, parameters playing a putative prognostic role are numerous in NET and include at least, parameters like: functioning syndromes and/or hormone levels, inherited syndromes, pathological differentiation and/or grading, TNM stage and finally, the primary location. Interestingly, the fact that NET definition describes a network of tumours and not a single organ tumour creates a unique level of complexity. Indeed, specific features of NET are highly interrelated with the primary location, as illustrated in Table 1 [7,8,11–14]. Taking into account studies from expert centres, that characterized in a standardized manner most of these parameters, pathological differentiation renamed grading for digestive primaries and, TNM stage emerged as the two most important prognostic parameters. Poorly differentiated NEC are characterized by a poorer outcome in comparison with well differentiated NET whatever the TNM stage and the primary location [11,12,15,23,34–38]. In this subgroup of poorly differentiated NEC, a homogeneous aggressive prognostic course has been described, as illustrated by a five-year overall survival below 10% in the case of metastatic presentation. As a result, urgent therapeutic intervention is recommended, as soon as, the diagnosis is ascertained on adequate specimen by skilled pathologists [3,39] (Fig. 1). TMM stage constitutes the second most powerful prognostic parameter whatever the primary [18,40–42].

In contrast, with poorly differentiated NEC, the prognosis of well differentiated metastatic NET remains broadly heterogeneous. Interestingly, in recent recommendations, watch and see policy is considered an option in subgroups of well differentiated GEP NET [3]. The heterogeneity of well differentiated GEP NET is illustrated in metastatic patients by a five-year survival of 30%–78 % or, a median overall survival that ranges from of 10.8–74 months from the time of diagnosis or therapeutic intervention [33,43–59] (Table 2). This heterogeneity in prognosis makes comparison of historical results impossible and, the timely decision to initiate the treatment a critical question in well differentiated NET. Recently, placebo-controlled trials in metastatic well differentiated NET reported in placebo arms, a 74-months median OS in ileum well differentiated NET and, median OS in progressive pancreatic NETs superior to 26 months [28,60]. Further prognostic studies are therefore expected to refine, stage by stage, the prognostic outcome of this subgroup of patients.

Towards the recognition of NET subgroups that display either excellent or poor prognosis as defined by more than 90% or less than 30% survival at five-year: preliminary results

Well differentiated Grade 1 (G1) digestive NET or typical bronchial carcinoid [61], without lymph node extension and distant metastasis experience the best outcome. Surgery is recommended when cure is expected but, is also key to refining the pTNM and pathological classifications [62,63]. After surgery, patients with low proliferative index, absence of angioinvasion, N0 and R0 resections constitute the most favourable subgroup of patients in terms of prognostic behaviour [8,11,12,24,26,34–36,64–69]. However, the absence of a routine use of lymph node dissection in digestive NET, the evolving classifications or, recent implementation of R0 status in studies together with the prolonged survival of these patients explain why no single NET prognostic study has taken into account such a comprehensive panel of markers. Interestingly, the excellent survival of these patients, more than 95% probability at ten years, challenges the routine use of surgery. Such challenges happen for instance, when, the preclinical condition highly suggests a benign behaviour like in type 1 gastric carcinoids or, in patients in whom the

Table 2
Survival of stage IV well differentiated NET at the time of diagnosis or therapeutic intervention.

Author	Patients (*n*)	Primary location	Therapeutic setting	Overall survival (%)	Median overall survival (months)
Yu et al 1999 [52]	37	Gastrinoma	Diag of stage IV	Five-year OS: 61%	ND
Clancy et al 2006 [45]	137	Various	Diag of stage IV	Six-year OS: 67%	Six years
Ahmed et al 2009 [9]	112	Ileum	Diag of stage IV	Five-year OS: 78%	5.95 years
Durante et al 2009 [33]	118	Various	Diag of stage IV	Five-year OS: 54%	ND
Stosberg et al 2011 [12]	146	Ileum	Diag of stage IV	Five-year OS: 57%	69 mo
Hentic et al 2011 [43]	63	Various	Diag of stage IV	Five-year OS: 52%	ND
Kölby et al 2003 [55]	68	Midgut	Octreotide or, IFN Randomized trial	Five-year OS: 46.5% (Oc: 36%, Oc + IFN: 56%)	ND
Arnold et al 2005 [80]	109	Various	Octreotide or IFN-octreotide randomized	ND	Oc: 35 mo Oc + IFN: 51 mo
Rinke et al 2009 [28]	90	Midgut	Octreotide or placebo randomized	ND	Octreotide: 73.7 mo Placebo: Not estimated
Que et al 1995 [81]	74	Various	Liver surgery	Four-year OS: 73%	Not reached
Elias et al 2003 [82]	47	Various	Liver surgery	Five-year OS: 71%	91 mo
Sarmiento et al 2003 [53]	170	Various	Liver surgery	Five-year OS: 61%	81 mo
Mayo et al 2011 [83]	753	Various	Liver surgery or liver intra-arterial therapy	Five-year OS 61.7 % (Surgery: 74%, IAT: 30%)	54.9 mo
Bushnell et al 2010 [84]	90	Carcinoïds	PRRT phase II	ND	26.9 mo
Moertel et al 1979 [46]	89	Various	STZ-EDX or STZ-5FU randomized	ND	STZ-EDX: 12.5 mo STZ-5FU: 11.2 mo
Moertel et al 1980 [47]	103	Pancreas	STZ or 5FU-STZ randomized	ND	STZ: 16 mo 5FU-STZ: 26 mo
Engstrom et al 1984 [48]	172	Carcinoids	5Fu-STZ or Dox randomized	ND	5FU-STZ: 16 mo Doxorubicin: 12 mo
Bukowski et al 1987 [49]	65	Carcinoids	5-FU-EDX-STZ +/− Dox phase II	ND	10.8 mo
Moertel et al 1992 [78]	125	Pancreas	CZT or 5FU-STZ or Doxo-STZ randomized	ND	CZT: 1.4 year 5FU-STZ: 1.5 year Doxo-STZ: 2.2 years
Bukowski et al 1992 [85]	51	Pancreas	5FU-CZT phase II	ND	25 mo
Ramanathan et al 2001 [86]	54	Pancreas	DTIC phase II	ND	19.3 mo
Delaunoit et al 2004 [56]	45	Pancreas	DDR STZ retrospective	Three-year OS: 24.4%	24 mo
Kouvaraki et al 2004 [76]	84	Pancreas	STZ, 5FU-DXR retrospective	Two-year OS: 74%	37 mo
Sun et al 2005 [79]	176	Various Non pancreas	5FU-dox or 5FU-STZ randomized	ND	Overall: 18.4 mo Dox-STZ: 16 mo 5FU-STZ: 24 mo
Dahan et al 2009 [57]	64	Various Non pancreas	5FU-STZ or IFN randomized	Overall: Two-year OS: 70%	5FU-STZ: 30 mo IFN: 44 mo
Meyer T et al [59]	86	Various	Cap-STZ-CDDP or Cap-STZ randomized	OS-one yr 72 or 73%	–
Raymond et al 2011 [58,60]	171	Pancreas	Sunitinib or placebo randomized phase III	ND	Sunitinib: 33.0 mo Placebo: 26.7 mo NS

OS = Overall survival, Oc = octreotide, IFN = interferon, LR = lanreotide, Oc LAR = octreotide long-acting release, PRRT = peptide receptor radionuclide therapy, STZ = streptozotocin, EDX = cyclophosphamide, 5FU = 5 fluorouracil, Dox = doxorubicin, CZT = chlorozotocin, Cap = capecitabine, CDDP = cisplatinum, pts = patients, NA = not applicable, NR = not reported, ND = not determined.

mortality rate of the surgery is expected to be above 1%, like in patients with a sporadic or inherited pancreatic NET localized in the head of the pancreas [63,70].

Remarkably, a good prognosis as defined by an expected five-year survival above 90% at five-years, can also be achieved in subgroups of patients with metastatic well differentiated G1 digestive NET or, typical bronchial carcinoid [8,11,24,26,34–36,64–68,71,72]. However, the uncertain reproducibility of

the proliferative index determination at the metastatic stage makes additional parameters required to secure the very good prognostic classification of this subgroup [33]. The growth curve of the tumour shown by the imaging procedures at three to six-month intervals can be used to refine the prognostic classification [33,52]. In addition, the tumour burden defined by the number of tumour organs and/or tumour liver involvement allows a better identification of patients in whom such a watchful strategy can be confirmed and maintained [28,33,43–45]. Typically, asymptomatic patients with ileum well differentiated NET or typical bronchial carcinoid as defined by low mitotic count and/or Ki 67 index (in the range of G1 digestive NET or typical bronchial carcinoid), non progressive at two morphological evaluations at three months should be considered as belonging to this group of patients. Indeed within the scope of digestive NET, metastatic midgut primary have been shown to pursue a less aggressive course than hindgut or foregut-derived NET including pancreatic primary [33,40,43,73,74]. Other prognostic parameters like the control of hormone-related symptoms [17,18,29,33,44], low level of chromogranin A [18,33], absence of bone metastases, primary resectability help confirming the good prognosis of this subgroup of patients. Of note, although the classifications of lung or digestive NETs use strict thresholds of proliferative indexes to categorize each tumour subgroups, it may be anticipated that patients who present with proliferative indexes in the low range of the G2 classification of digestive NET or atypical bronchial carcinoid subgroup definitions may also benefit from such a cautious management [11,75]. In these patients, watchful follow up plus or minus locoregional options, constitute an adequate strategy. A constant effort to avoid the risk of definitive toxicity and to assure a mortality rate below 3% should drive the strategy.

By contrast, metastatic poorly differentiated NEC patients indisputably constitute the subgroup of most aggressive neuroendocrine tumours, in which early therapeutic intervention is mandatory whatever the primary location as strongly suggested by recommendations [3,39] (Fig. 1). Similarly, subgroups of patients with metastatic well differentiated G2 NET and high liver tumour burden may also require early therapeutic intervention when a poor outcome is expected as illustrated by a five-year survival below 30%. Definitions of significant liver involvement such as more than ten metastases, bilateral liver involvement, increased alkaline phosphatase levels or, >25–75% liver involvement have been proposed which require further standardization [33,43–45,76]. In addition, a mitotic index above ten or Ki67 index above 10–20% have also been proposed as thresholds to qualify aggressive subgroups of well differentiated tumours [11,15,33,43,72]. A combination of these parameters: markers of high tumour burden and high proliferative index or, a progressive slope in a given patient constitute the most accurate definition of a poor prognosis in well differentiated NET defined by a five-year survival below 30%. Metastatic G2 pancreatic or rectum digestive NET or atypical bronchial or thymic carcinoid with such high tumour burden and proliferative index constitute examples of subgroups of NET candidates for an early therapeutic intervention. Recent studies suggest that advanced NEN with high proliferative indexes, in the G3 ENETS grading range, whatever the pathological differentiation should also be considered as of poor prognostic NET requiring an early therapeutic intervention [8,9,12,15] (Fig. 1).

Analysis of the results of therapeutic interventions are based on low level of evidence

Surgery remains the only curative option in localized NET and strategy at the metastatic stage remains palliative. The number of randomized studies in NET remains low and only two have enrolled more than 100 patients per arm [30,77]. Improved overall survival has been reported in well differentiated pancreatic NET treated with the doxorubicin–streptozotocin combination and, in functioning well differentiated NET treated with the fluorouracil–streptozotocin combination but the results were never confirmed [78,79]. Finally, strategies in NET are mainly based on expert-based recommendations. Absence of a large number of randomized trials in NET can be considered a direct consequence of its historical complexity but also of heterogeneous prognosis and prolonged survivals that make this group of tumours one of the most complex to treat. Nowadays, the number of predictors that can help to select the best strategy in these patients is still limited. Prescription of cisplatinum-based regimen in case of poorly differentiated NEC, higher response rate to cytotoxic chemotherapy in well differentiated NET of pancreatic origin, higher response rate to peptide receptor radionuclide therapy in case of high uptake at the somatostatin receptor scintigraphy and low tumour burden as a predictor of response to locoregional therapy or somatostatin analogue therapy are the most frequently cited predictors [3].

Summary

Objectives of interventions in NET patients are both to control hormone-related symptoms and tumour growth. This is best achieved in localized well differentiated NET by surgery which remains the only curative option. The aggressiveness of poorly differentiated neuroendocrine carcinoma warrants early medical interventions. Interventions in advanced well differentiated NET should take into account presence of functioning syndromes but also their strong heterogeneous prognosis, and absence of curative options. Prognostic factors for each TNM stage according to WHO classification, level evidence associated with each intervention, predictors of response remain major unanswered questions.

Conflict of interest

None.

Practice points

The standardized characterization of NET patients in expert centres for the following parameters: functioning syndrome, chromogranin A levels, inherited syndromes, WHO pathological differentiation and or grading, TNM stage, tumour burden and slope at the metastatic stage and finally, the primary location is a prerequisite before any therapeutic intervention.

Therapeutic interventions for functioning syndromes and poorly differentiated neuroendocrine carcinoma constitute consensual recommendations.

In well differentiated NET, the benefit over risk ratio is the main determinant of the treatment initiation : surgery is proposed in most localized NET.

Research agenda

Randomized trials in well characterized NET patients.
Prognostic studies according to each TNM stage and WHO classification categories.
Common terminologies whatever the primary location.

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To the nurses of the endocrine oncology unit.

References

[1] Baudin E. Gastroenteropancreatic endocrine tumors: clinical characterization before therapy. Nat Clin Pract Endocrinol Metab 2007;3:228–39.
[2] Modlin IM, Oberg K, Chung DC, Jensen RT, de Herder WW, Thakker RV, et al. Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol 2008;9:61–72.
[3] Pavel M, Baudin E, Couvelard A, Krenning E, Öberg K, Steinmüller T, et al. ENETS Consensus Guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut, and unknown primary. Neuroendocrinology 2012;95:157–76.
[4] Moertel CG, Weiland LH, Nagorney DM, Dockerty MB. Carcinoid tumor of the appendix: treatment and prognosis. N Engl J Med 1987;317:1699–701.
[5] Söreide JA, van Heerden JA, Thompson GB, Schleck C, Ilstrup DM, Churchward M. Gastrointestinal carcinoid tumors: long-term prognosis for surgically treated patients. World J Surg 2000;24:1431–6.
[6] Fahy BN, Tang LH, Klimstra D, Wong WD, Guillem JG, Paty PB, et al. Carcinoid of the rectum risk stratification (CaRRs): a strategy for preoperative outcome assessment. Ann Surg Oncol 2007;14:1735–43.
[7] Fischer L, Kleeff J, Esposito I, Hinz U, Zimmermann A, Friess H, et al. Clinical outcome and long-term survival in 118 consecutive patients with neuroendocrine tumours of the pancreas. Br J Surg 2008;95:627–35.

[8] Pape U-F, Jann H, Müller-Nordhorn J, Bockelbrink A, Berndt U, Willich SN, et al. Prognostic relevance of a novel TNM classification system for upper gastroenteropancreatic neuroendocrine tumors. Cancer 2008;113:256–65.
[9] Ahmed A, Turner G, King B, Jones L, Culliford D, McCance D, et al. Midgut neuroendocrine tumours with liver metastases: results of the UKINETS study. Endocr Relat Cancer 2009;16:885–94.
[10] Rindi G. The ENETS guidelines: the new TNM classification system. Tumori 2010;96:806–9.
[11] Scarpa A, Mantovani W, Capelli P, Beghelli S, Boninsegna L, Bettini R, et al. Pancreatic endocrine tumors: improved TNM staging and histopathological grading permit a clinically efficient prognostic stratification of patients. Mod Pathol 2010;23: 824–33.
[12] Strosberg JR, Cheema A, Weber J, Han G, Coppola D, Kvols LK. Prognostic validity of a novel American Joint Committee on Cancer Staging Classification for pancreatic neuroendocrine tumors. J Clin Oncol 2011;29:3044–9.
[13] Zerbi A, Capitanio V, Boninsegna L, Pasquali C, Rindi G, Delle Fave G, et al. Surgical treatment of pancreatic endocrine tumours in Italy: results of a prospective multicentre study of 262 cases. Langenbecks Arch Surg 2011;396:313–21.
[14] Jann H, Roll S, Couvelard A, Hentic O, Pavel M, Müller-Nordhorn J, et al. Neuroendocrine tumors of midgut and hindgut origin: tumor-node-metastasis classification determines clinical outcome. Cancer 2011;117:3332–41.
[15] Panzuto F, Boninsegna L, Fazio N, Campana D, Pia Brizzi M, Capurso G, et al. Metastatic and locally advanced pancreatic endocrine carcinomas: analysis of factors associated with disease progression. J Clin Oncol 2011;29:2372–7.
[16] Elias D, Lefevre JH, Duvillard P, Goéré D, Dromain C, Dumont F, et al. Hepatic metastases from neuroendocrine tumors with a « thin slice » pathological examination: they are many more than you think. Ann Surg 2010;251:307–10.
[17] Jensen RT, Cadiot G, Brandi ML, de Herder WW, Kaltsas G, Komminoth P, et al. ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms: functional pancreatic endocrine tumor syndromes. Neuroendocrinology 2012;95:98–119.
[18] Janson ET, Holmberg L, Stridsberg M, Eriksson B, Theodorsson E, Wilander E, et al. Carcinoid tumors: analysis of prognostic factors and survival in 301 patients from a referral center. Ann Oncol 1997;8:685–90.
[19] Burke AP, Thomas RM, Elsayed AM, Sobin LH. Carcinoids of the jejunum and ileum: an immunohistochemical and clinicopathologic study of 167 cases. Cancer 1997;79:1086–93.
[20] Lo CY, van Heerden JA, Thompson GB, Grant CS, Söreide JA, Harmsen WS. Islet cell carcinoma of the pancreas. World J Surg 1996;20:878–83 [discussion 884].
[21] Pelosi G, Bresaola E, Bogina G, Pasini F, Rodella S, Castelli P, et al. Endocrine tumors of the pancreas: Ki-67 immunoreactivity on paraffin sections is an independent predictor for malignancy: a comparative study with proliferating-cell nuclear antigen and progesterone receptor protein immunostaining, mitotic index, and other clinicopathologic variables. Hum Pathol 1996; 27:1124–34.
[22] Gentil Perret A, Mosnier JF, Buono JP, Berthelot P, Chipponi J, Balique JG, et al. The relationship between MIB-1 proliferation index and outcome in pancreatic neuroendocrine tumors. Am J Clin Pathol 1998;109:286–93.
[23] Madeira I, Terris B, Voss M, Denys A, Sauvanet A, Flejou JF, et al. Prognostic factors in patients with endocrine tumours of the duodenopancreatic area. Gut 1998;43:422–7.
[24] Hochwald SN, Zee S, Conlon KC, Colleoni R, Louie O, Brennan MF, et al. Prognostic factors in pancreatic endocrine neoplasms: an analysis of 136 cases with a proposal for low-grade and intermediate-grade groups. J Clin Oncol 2002;20:2633–42.
[25] Tomassetti P, Campana D, Piscitelli L, Casadei R, Santini D, Nori F, et al. Endocrine pancreatic tumors: factors correlated with survival. Ann Oncol 2005;16:1806–10.
[26] Ekeblad S, Skogseid B, Dunder K, Oberg K, Eriksson B. Prognostic factors and survival in 324 patients with pancreatic endocrine tumor treated at a single institution. Clin Cancer Res 2008;14:7798–803.
[27] Kulke MH, Bergsland EK, Yao JC. Glycemic control in patients with insulinoma treated with everolimus. N Engl J Med 2009; 360:195–7.
[28] Rinke A, Müller H-H, Schade-Brittinger C, Klose K-J, Barth P, Wied M, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. J Clin Oncol 2009;27:4656–63.
[29] Møller JE, Pellikka PA, Bernheim AM, Schaff HV, Rubin J, Connolly HM. Prognosis of carcinoid heart disease: analysis of 200 cases over two decades. Circulation 2005;112:3320–7.
[30] Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med 2011;364:514–23.
[31] Scoazec J-Y. Angiogenesis in neuroendocrine tumors: therapeutic applications. Neuroendocrinology 2013;97:45–56.
[32] Pavel ME, Hainsworth JD, Baudin E, Peeters M, Hörsch D, Winkler RE, et al. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. Lancet 2011;378:2005–12.
[33] Durante C, Boukheris H, Dromain C, Duvillard P, Leboulleux S, Elias D, et al. Prognostic factors influencing survival from metastatic (stage IV) gastroenteropancreatic well-differentiated endocrine carcinoma. Endocr Relat Cancer 2009;16:585–97.
[34] Travis WD, Rush W, Flieder DB, Falk R, Fleming MV, Gal AA, et al. Survival analysis of 200 pulmonary neuroendocrine tumors with clarification of criteria for atypical carcinoid and its separation from typical carcinoid. Am J Surg Pathol 1998; 22:934–44.
[35] Rindi G, Azzoni C, La Rosa S, Klersy C, Paolotti D, Rappel S, et al. ECL cell tumor and poorly differentiated endocrine carcinoma of the stomach: prognostic evaluation by pathological analysis. Gastroenterology 1999;116:532–42.
[36] Lim E, Yap YK, De Stavola BL, Nicholson AG, Goldstraw P. The impact of stage and cell type on the prognosis of pulmonary neuroendocrine tumors. J Thorac Cardiovasc Surg 2005;130:969–72.
[37] Asamura H, Kameya T, Matsuno Y, Noguchi M, Tada H, Ishikawa Y, et al. Neuroendocrine neoplasms of the lung: a prognostic spectrum. J Clin Oncol 2006;24:70–6.
[38] Faggiano A, Sabourin J-C, Ducreux M, Lumbroso J, Duvillard P, Leboulleux S, et al. Pulmonary and extrapulmonary poorly differentiated large cell neuroendocrine carcinomas: diagnostic and prognostic features. Cancer 2007;110:265–74.
[39] Strosberg JR, Coppola D, Klimstra DS, Phan AT, Kulke MH, Wiseman GA, et al. The NANETS consensus guidelines for the diagnosis and management of poorly differentiated (high-grade) extrapulmonary neuroendocrine carcinomas. Pancreas 2010;39:799–800.

[40] Onaitis MW, Kirshbom PM, Hayward TZ, Quayle FJ, Feldman JM, Seigler HF, et al. Gastrointestinal carcinoids: characterization by site of origin and hormone production. Ann Surg 2000;232:549–56.
[41] Kirshbom PM, Kherani AR, Onaitis MW, Feldman JM, Tyler DS. Carcinoids of unknown origin: comparative analysis with foregut, midgut, and hindgut carcinoids. Surgery 1998;124:1063–70.
[42] Musunuru S, Chen H, Rajpal S, Stephani N, McDermott JC, Holen K, et al. Metastatic neuroendocrine hepatic tumors: resection improves survival. Arch Surg 2006;141:1000–4 [discussion 1005].
[43] Hentic O, Couvelard A, Rebours V, Zappa M, Dokmak S, Hammel P, et al. Ki-67 index, tumor differentiation, and extent of liver involvement are independent prognostic factors in patients with liver metastases of digestive endocrine carcinomas. Endocr Relat Cancer 2011;18:51–9.
[44] Ho AS, Picus J, Darcy MD, Tan B, Gould JE, Pilgram TK, et al. Long-term outcome after chemoembolization and embolization of hepatic metastatic lesions from neuroendocrine tumors. AJR Am J Roentgenol 2007;188:1201–7.
[45] Clancy TE, Sengupta TP, Paulus J, Ahmed F, Duh M-S, Kulke MH. Alkaline phosphatase predicts survival in patients with metastatic neuroendocrine tumors. Dig Dis Sci 2006;51:877–84.
[46] Moertel CG, Hanley JA. Combination chemotherapy trials in metastatic carcinoid tumor and the malignant carcinoid syndrome. Cancer Clin Trials 1979;2:327–34.
[47] Moertel CG, Hanley JA, Johnson LA. Streptozocin alone compared with streptozocin plus fluorouracil in the treatment of advanced islet-cell carcinoma. N Engl J Med 1980;303:1189–94.
[48] Engstrom PF, Lavin PT, Moertel CG, Folsch E, Douglass Jr HO. Streptozocin plus fluorouracil versus doxorubicin therapy for metastatic carcinoid tumor. J Clin Oncol 1984;2:1255–9.
[49] Bukowski RM, Johnson KG, Peterson RF, Stephens RL, Rivkin SE, Neilan B, et al. A phase II trial of combination chemotherapy in patients with metastatic carcinoid tumors. A Southwest Oncology Group Study. Cancer 1987;60:2891–5.
[50] Saltz L, Trochanowski B, Buckley M, Heffernan B, Niedzwiecki D, Tao Y, et al. Octreotide as an antineoplastic agent in the treatment of functional and nonfunctional neuroendocrine tumors. Cancer 1993;72:244–8.
[51] Weber HC, Venzon DJ, Lin JT, Fishbein VA, Orbuch M, Strader DB, et al. Determinants of metastatic rate and survival in patients with Zollinger-Ellison syndrome: a prospective long-term study. Gastroenterology 1995;108:1637–49.
[52] Yu F, Venzon DJ, Serrano J, Goebel SU, Doppman JL, Gibril F, et al. Prospective study of the clinical course, prognostic factors, causes of death, and survival in patients with long-standing Zollinger-Ellison syndrome. J Clin Oncol 1999;17:615–30.
[53] Sarmiento JM, Heywood G, Rubin J, Ilstrup DM, Nagorney DM, Que FG. Surgical treatment of neuroendocrine metastases to the liver: a plea for resection to increase survival. J Am Coll Surg 2003;197:29–37.
[54] Faiss S, Pape U-F, Böhmig M, Dörffel Y, Mansmann U, Golder W, et al. Prospective, randomized, multicenter trial on the antiproliferative effect of lanreotide, interferon alfa, and their combination for therapy of metastatic neuroendocrine gastroenteropancreatic tumors – the International Lanreotide and Interferon Alfa Study Group. J Clin Oncol 2003;21:2689–96.
[55] Kölby L, Persson G, Franzén S, Ahrén B. Randomized clinical trial of the effect of interferon alpha on survival in patients with disseminated midgut carcinoid tumours. Br J Surg 2003;90:687–93.
[56] Delaunoit T, Ducreux M, Boige V, Dromain C, Sabourin J-C, Duvillard P, et al. The doxorubicin-streptozotocin combination for the treatment of advanced well-differentiated pancreatic endocrine carcinoma; a judicious option? Eur J Cancer 2004;40:515–20.
[57] Dahan L, Bonnetain F, Rougier P, Raoul J-L, Gamelin E, Etienne P-L, et al. Phase III trial of chemotherapy using 5-fluorouracil and streptozotocin compared with interferon alpha for advanced carcinoid tumors: FNCLCC-FFCD 9710. Endocr Relat Cancer 2009;16:1351–61.
[58] Raymond E, Dahan L, Raoul J-L, Bang Y-J, Borbath I, Lombard-Bohas C, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med 2011;364:501–13.
[59] Meyer T, Caplin M, Reed N, Qian W, Lao-Siriex S, Armstrong G, et al. Treatment of advanced neuroendocrine tumors: final results of the UKINETS and NCRI randomised phase II NET01 trial. ESMO Meeting Abstracts 2012;23:ix378–9.
[60] Vinik A, Van Cutsem E, Niccoli P, Raoul J-L, Bang Y-J, Borbath I, et al. Updated results from a phase III trial of sunitinib versus placebo in patients with progressive, unresectable, well-differentiated pancreatic neuroendocrine tumor (NET). ASCO Meeting Abstracts 2012;30:4118.
[61] Rindi G, Arnold R, Bosman F. Nomenclature and classification of neuroendocrine neoplasms of the digestive system. In: Bosman F, Carneiro F, Hruban R, Theise N, editors. WHO classification of tumors of the digestive system. Lyon: IARC; 2010.
[62] Pape U-F, Perren A, Niederle B, Gross D, Gress T, Costa F, et al. ENETS Consensus Guidelines for the management of patients with neuroendocrine neoplasms from the jejuno-ileum and the appendix including goblet cell carcinomas. Neuroendocrinology 2012;95:135–56.
[63] Falconi M, Bartsch DK, Eriksson B, Klöppel G, Lopes JM, O'Connor JM, et al. ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms of the digestive system: well-differentiated pancreatic non-functioning tumors. Neuroendocrinology 2012;95:120–34.
[64] Martini N, Zaman MB, Bains MS, Burt ME, McCormack PM, Rusch VW, et al. Treatment and prognosis in bronchial carcinoids involving regional lymph nodes. J Thorac Cardiovasc Surg 1994;107:1–6 [discussion 6–7].
[65] Thomas Jr CF, Tazelaar HD, Jett JR. Typical and atypical pulmonary carcinoids: outcome in patients presenting with regional lymph node involvement. Chest 2001;119:1143–50.
[66] Mezzetti M, Raveglia F, Panigalli T, Giuliani L, Lo Giudice F, Meda S, et al. Assessment of outcomes in typical and atypical carcinoids according to latest WHO classification. Ann Thorac Surg 2003;76:1838–42.
[67] Cardillo G, Sera F, Di Martino M, Graziano P, Giunti R, Carbone L, et al. Bronchial carcinoid tumors: nodal status and long-term survival after resection. Ann Thorac Surg 2004;77:1781–5.
[68] García-Yuste M, Matilla JM, Cueto A, Paniagua JMR, Ramos G, Cañizares MA, et al. Typical and atypical carcinoid tumours: analysis of the experience of the Spanish Multi-centric Study of Neuroendocrine Tumours of the Lung. Eur J Cardiothorac Surg 2007;31:192–7.
[69] La Rosa S, Inzani F, Vanoli A, Klersy C, Dainese L, Rindi G, et al. Histologic characterization and improved prognostic evaluation of 209 gastric neuroendocrine neoplasms. Hum Pathol 2011;42:1373–84.

[70] Delle Fave G, Kwekkeboom DJ, Van Cutsem E, Rindi G, Kos-Kudla B, Knigge U, et al. ENETS Consensus Guidelines for the management of patients with gastroduodenal neoplasms. Neuroendocrinology 2012;95:74–87.
[71] Strosberg JR, Fine RL, Choi J, Nasir A, Coppola D, Chen D-T, et al. First-line chemotherapy with capecitabine and temozolomide in patients with metastatic pancreatic endocrine carcinomas. Cancer 2011;117:268–75.
[72] 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.
[73] Greenberg RS, Baumgarten DA, Clark WS, Isacson P, McKeen K. Prognostic factors for gastrointestinal and bronchopulmonary carcinoid tumors. Cancer 1987;60:2476–83.
[74] Panzuto F, Nasoni S, Falconi M, Corleto VD, Capurso G, Cassetta S, et al. Prognostic factors and survival in endocrine tumor patients: comparison between gastrointestinal and pancreatic localization. Endocr Relat Cancer 2005;12:1083–92.
[75] Beasley MB, Thunnissen FB, Brambilla E, Hasleton P, Steele R, Hammar SP, et al. Pulmonary atypical carcinoid: predictors of survival in 106 cases. Hum Pathol 2000;31:1255–65.
[76] Kouvaraki MA, Ajani JA, Hoff P, Wolff R, Evans DB, Lozano R, et al. Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. J Clin Oncol 2004;22:4762–71.
[77] Yao JC, Lombard-Bohas C, Baudin E, Kvols LK, Rougier P, Ruszniewski P, et al. Daily oral everolimus activity in patients with metastatic pancreatic neuroendocrine tumors after failure of cytotoxic chemotherapy: a phase II trial. J Clin Oncol 2010; 28:69–76.
[78] Moertel CG, Lefkopoulo M, Lipsitz S, Hahn RG, Klaassen D. Streptozocin-doxorubicin, streptozocin-fluorouracil or chlorozotocin in the treatment of advanced islet-cell carcinoma. N Engl J Med 1992;326:519–23.
[79] Sun W, Lipsitz S, Catalano P, Mailliard JA, Haller DG. Phase II/III study of doxorubicin with fluorouracil compared with streptozocin with fluorouracil or dacarbazine in the treatment of advanced carcinoid tumors: Eastern Cooperative Oncology Group Study E1281. J Clin Oncol 2005;23:4897–904.
[80] Arnold R, Rinke A, Klose K-J, Müller H-H, Wied M, Zamzow K, et al. Octreotide versus octreotide plus interferon-alpha in endocrine gastroenteropancreatic tumors: a randomized trial. Clin Gastroenterol Hepatol 2005;3:761–71.
[81] Que FG, Nagorney DM, Batts KP, Linz LJ, Kvols LK. Hepatic resection for metastatic neuroendocrine carcinomas. Am J Surg 1995;169:36–42 [discussion 42–43].
[82] Elias D, Lasser P, Ducreux M, Duvillard P, Ouellet J-F, Dromain C, et al. Liver resection (and associated extrahepatic resections) for metastatic well-differentiated endocrine tumors: a 15-year single center prospective study. Surgery 2003; 133:375–82.
[83] Mayo SC, de Jong MC, Bloomston M, Pulitano C, Clary BM, Reddy SK, et al. Surgery versus intra-arterial therapy for neuroendocrine liver metastasis: a multicenter international analysis. Ann Surg Oncol 2011;18:3657–65.
[84] Bushnell Jr DL, O'Dorisio TM, O'Dorisio MS, Menda Y, Hicks RJ, Van Cutsem E, et al. 90Y-edotreotide for metastatic carcinoid refractory to octreotide. J Clin Oncol 2010;28:1652–9.
[85] Bukowski RM, Tangen C, Lee R, Macdonald JS, Einstein Jr AB, Peterson R, et al. Phase II trial of chlorozotocin and fluorouracil in islet cell carcinoma: a Southwest Oncology Group study. J Clin Oncol 1992;10:1914–8.
[86] Ramanathan RK, Cnaan A, Hahn RG, Carbone PP, Haller DG. Phase II trial of dacarbazine (DTIC) in advanced pancreatic islet cell carcinoma. Study of the Eastern Cooperative Oncology Group-E6282. Ann Oncol 2001;12:1139–43.