World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v21.i8.2450

World J Gastroenterol 2015 February 28; 21(8): 2450-2459
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Observational Study

Appropriateness of systemic treatments in unresectable metastatic well-differentiated pancreatic neuroendocrine tumors

Jonathan R Strosberg, George A Fisher, Al B Benson, Lowell B Anthony, Bulent Arslan, John F Gibbs, Edward Greeno, Renuka V Iyer, Michelle K Kim, William J Maples, Philip A Philip, Edward M Wolin, Dasha Cherepanov, Michael S Broder

Jonathan R Strosberg, Department of Gastrointestinal Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL 33612, United States
George A Fisher, Department of Medicine, Division of Oncology, Stanford University Medical Center, Stanford, CA 94305, United States
Al B Benson, Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL 60611, United States
Lowell B Anthony, Department of Internal Medicine, Division of Medical Oncology, University of Kentucky Markey Cancer Center, Lexington, KY 40536, United States
Bulent Arslan, Rush University Medical Center, Chicago, IL 60612, United States
John F Gibbs, Department of Surgery, University at Buffalo - State University of New York, Buffalo, NY 14260, United States
Edward Greeno, Department of Medicine, Division of Hematology, Oncology, and Transplantation, University of Minnesota, Minneapolis, MN 55455, United States
Renuka V Iyer, Department of Medical Oncology, Roswell Park Cancer Institute, Buffalo, NY 14263, United States
Michelle K Kim, Department of Medicine, Gastroenterology Mount Sinai School of Medicine, New York, NY 10029, United States
William J Maples, Mission Health System, Asheville, NC 28801, United States
Philip A Philip, Department of Oncology, Karmanos Cancer Institute, Detroit, MI 48201, United States
Edward M Wolin, Department of Internal Medicine, Division of Medical Oncology, University of Kentucky Markey Cancer Center, Lexington, KY 40536, United States
Dasha Cherepanov, Michael S Broder, Partnership for Health Analytic Research, LLC, Beverly Hills CA 90212, United States
Author contributions: Strosberg JR, Fisher GA, Benson AB, Cherepanov D and Broder MS designed the research, interpreted the findings, and drafted the manuscript; Strosberg JR, Fisher GA and the rest of members of the GEPNET Treatment Consensus Panel; Anthony LB, Arslan B, Gibbs JF, Greeno E, Iyer RV, Kim MK, Maples WJ, Philip PA, Wolin EM performed the research and contributed to interpretation of the findings and review of this research.
Supported by Grants from Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, NJ 07936-1080, United States.

Correspondence to: Michael S Broder, MD, MSHS, Partnership for Health Analytic Research, LLC, 280 South Beverly Drive, Suite 404, Beverly Hills, CA 90212, United States. mbroder@pharllc.com
Telephone: +1-310-8589555
Fax: +1-310-8589552
Received: March 26, 2014
Peer-review started: March 26, 2014
First decision: March 29, 2014
Revised: July 31, 2014
Accepted: October 21, 2014
Article in press: October 21, 2014
Published online: February 28, 2015

Abstract

AIM: To evaluate systemic treatment choices in unresectable metastatic well-differentiated pancreatic neuroendocrine tumors (PNETs) and provide consensus treatment recommendations.

METHODS: Systemic treatment options for pancreatic neuroendocrine tumors have expanded in recent years to include somatostatin analogs, angiogenesis inhibitors, inhibitors of mammalian target of rapamycin

and cytotoxic agents. At this time, there is little data to guide treatment selection and sequence. We therefore assembled a panel of expert physicians to evaluate systemic treatment choices and provide consensus treatment recommendations. Treatment appropriateness ratings were collected using the RAND/UCLA modified Delphi process. After studying the literature, a multidisciplinary panel of 10 physicians assessed the appropriateness of various medical treatment scenarios on a 1-9 scale. Ratings were done both before and after an extended discussion of the evidence. Quantitative measurements of agreement were made and consensus statements developed from the second round ratings.

RESULTS: Specialties represented were medical and surgical oncology, interventional radiology, and gastroenterology. Panelists had practiced for a mean of 15.5 years (range: 6-33). Among 202 rated scenarios, disagreement decreased from 13.2% (26 scenarios) before the face-to-face discussion of evidence to 1% (2) after. In the final ratings, 46.5% (94 scenarios) were rated inappropriate, 21.8% (44) were uncertain, and 30.7% (62) were appropriate. Consensus statements from the scenarios included: (1) it is appropriate to use somatostatin analogs as first line therapy in patients with hormonally functional tumors and may be appropriate in patients who are asymptomatic; (2) it is appropriate to use everolimus, sunitinib, or cytotoxic chemotherapy therapy as first line therapy in patients with symptomatic or progressive tumors; and (3) beyond first line, these same agents can be used. In patients with uncontrolled secretory symptoms, octreotide LAR doses can be titrated up to 60 mg every 4 wk or up to 40 mg every 3 or 4 wk.

CONCLUSION: Using the Delphi process allowed physician experts to systematically obtain a consensus on the appropriateness of a variety of medical therapies in patients with PNETs.

Key words: Unresectable; Neuroendocrine carcinomas; Neuroendocrine tumors; Well-differentiated; Grade 1; Grade 2; Low tumors; Intermediate tumors; Pancreatic neoplasms; Treatment; Consensus; Delphi technique; Expert testimony

Core tip: Using the RAND/UCLA modified Delphi process, physician experts obtained consensus on the appropriateness of various medical therapies in unresectable metastatic well-differentiated pancreatic neuroendocrine tumors. Consensus statements were: (1) it is appropriate to use somatostatin analogs as first-line therapy in patients with hormonally-functional tumors and may be appropriate in asymptomatic patients; (2) it is appropriate to use everolimus, sunitinib, or cytotoxic chemotherapy as first-line therapy in patients with symptomatic or progressive tumors; and (3) beyond first-line, these same agents can be used. In patients with uncontrolled secretory symptoms, octreotide-LAR can be titrated up to 60 mg/4 wk or up to 40 mg/3 or 4 wk.

Strosberg JR, Fisher GA, Benson AB, Anthony LB, Arslan B, Gibbs JF, Greeno E, Iyer RV, Kim MK, Maples WJ, Philip PA, Wolin EM, Cherepanov D, Broder MS. Appropriateness of systemic treatments in unresectable metastatic well-differentiated pancreatic neuroendocrine tumors. *World J Gastroenterol* 2015; 21(8): 2450-2459 Available from: URL: http://www.wjgnet.com/1007-9327/full/v21/i8/2450.htm DOI: http://dx.doi.org/10.3748/wjg.v21.i8.2450

INTRODUCTION

Pancreatic neuroendocrine tumors (PNETs) represent approximately 3% of primary pancreatic malignancies[1,2]. Their incidence has increased significantly in recent decades, partially due to incidental detection on imaging studies. PNETs can secrete a variety of peptide hormones including insulin, gastrin, glucagon, and vasoactive intestinal peptide (VIP). In contemporary series, most PNETs are not associated with a hormonal syndrome and are therefore termed "nonfunctional"[3,4]. Prognosis depends on tumor stage as well as tumor differentiation and proliferative activity. Patients who present with hepatic metastases from PNETs have a worse survival than those with midgut neuroendocrine carcinomas[5]. In one large institutional series, the median overall survival was 69 mo for patients with distant metastases (stage Ⅳ disease). Five-year survival rates ranged from 7% for high-grade tumors to 75% for low-grade tumors[6].

The somatostatin analogs (SA), octreotide and lanreotide, have had a profound impact on patients with certain rare hormonally-functioning tumors. Patients with VIPoma and glucagonoma syndromes experience significant palliative benefit from SA therapy[7,8]. The role of SA as antiproliferative agents in nonfunctional tumors has been controversial: phase Ⅱ studies and retrospective series have demonstrated a high-rate of disease stability among patients treated with SA but randomized data was lacking until this year[9-11]. The CLARINET trial recently confirmed the superiority of lanreotide compared to placebo in extending progression free survival (PFS) in nonfunctional gastroenteropancreatic NETs[12]. However, these data were not available at the time of the Delphi consensus panel meeting.

In recent years, a number of novel targeted agents have emerged to provide new treatment options for patients with NETs[13]. Inhibitors of mammalian target of rapamycin (mTOR) are among the most promising of such therapeutic options. Approximately 15% of patients with pancreatic NETs have somatic mutations in enzymes associated with the mTOR pathway[14]. In the randomized RADIANT 3 trial, everolimus, an

oral mTOR inhibitor, was compared to placebo in 410 patients with advanced low and intermediate-grade PNETS[15]. Crossover was permitted upon disease progression. The trial demonstrated an improvement in median progression-free survival from 4.6 mo on the placebo arm to 11 mo on the everolimus arm, thus meeting its primary endpoint. Objective response rates on the everolimus arm were 5%. No improvement in overall survival was observed, possibly due to the crossover design.

PNETs are highly vascular tumors, which frequently overexpress the vascular endothelial growth factor (VEGF) ligand and receptor[16]. Tumor angiogenesis is therefore proving to be a promising treatment target in patients with advanced PNETs. Sunitinib, an oral tyrosine kinase inhibitor, which targets VEGFR-1, -2, and -3 among other receptors, was compared to placebo in a multinational phase Ⅲ study of low and intermediate-grade PNETs[17]. The trial was terminated at midpoint, after accrual of 171 patients, due to improved outcomes on the treatment arm. Median progression free survival increased from 5.5 mo on the placebo arm to 11.4 mo on the sunitinib arm ($P < 0.001$). Response rates on the sunitinib arm were 9.3 percent. There was a trend towards improved overall survival, which was not statistically significant.

Cytotoxic chemotherapy remains an important treatment modality for patients with advanced, progressive PNETs. Streptozocin (STZ) was, for many years, the only agent approved by the Food and Drug Administration for this diagnosis. A randomized trial conducted by the Eastern Cooperative Oncology Group in the 1970s reported response rates of 63% with STZ plus 5-fluorouracil (5-FU) *vs* 36% STZ monotherapy[18]. Another trial, conducted a decade later, reported a response rate of 69% with STZ plus doxorubicin versus 45% with STZ plus 5-FU[19]. These high response rates have been subsequently questioned due to the partial reliance on non-radiographic response criteria. A more recent retrospective study evaluating the combination of STZ, doxorubicin and 5-FU reported a response rate of 39% using modern radiographic response criteria[20].

The clinical use of STZ-based regimens has been limited by toxicity concerns. In recent years, the oral nitrosourea temozolomide has emerged as an active agent. A phase Ⅱ study investigating the combination of temozolomide and thalidomide demonstrated an objective response rate of 45% among 11 patients with PNETs[21]. Another study investigating temozolomide combined with bevacizumab reported a response rate of 33% in this subset[22]. A retrospective study of 30 chemotherapy-naïve patients evaluated the combination of temozolomide and the oral fluoropyrimidine capecitabine[23]. The study reported a response rate of 70% with a median PFS of 18 mo. Recent data suggests that tumoral expression of O-6-methylguanine-DNA-methyltransferase (MGMT) may predict response to temozolomide-based chemotherapy[24].

Although treatment options available to patients with NETs have expanded with the emergence of new therapies, clinicians are faced with the necessity of generating treatment recommendations in the absence of high quality data. The lack of data comparing the effectiveness of the various treatment options in patients with NETs leads to many management decisions being based on physician experience and expert recommendations. Treatment guidelines in NETs have been previously published[25-30].

Strosberg *et al* (2013) have used a systematic methodology for group-decision making involving a RAND/University of California-Los Angeles (UCLA) modified Delphi process[31-33] for evaluation of the appropriateness of various systemic treatments in unresectable metastatic well-differentiated carcinoid tumors. The present study has applied this modified Delphi methodology for evaluation of appropriateness of various treatment regimens for PNET medical management.

The RAND/UCLA modified Delphi process is a valid method for assessing the appropriateness of medical interventions using expert input[31-34]. Our objective was to use this process to develop consensus on the use of systemic treatments for unresectable, metastatic, well-differentiated (grade 1-2) pancreatic neuroendocrine tumors.

MATERIALS AND METHODS

Panelists

A steering committee, consisting of 3 medical oncologists with experience in treating PNETs (Strosberg JR, Fisher GA, Benson AB), developed an a priori list of panelists' attributes aimed at achieving a range of panelist experience, a key feature of the Delphi process. The panelists were selected to include physicians from a variety of geographic regions, practice settings, and clinical specialties. It was a priority to include the specialties of medical and surgical oncology, interventional radiology, gastroenterology, endocrinology, and palliative care. The steering committee identified a group of physicians meeting the various criteria and invited them to participate. This panel was joined by 2 of the steering committee members (Strosberg JR and Fisher GA).

RAND/UCLA modified delphi panel method

Key features of the method include[31-34]: (1) quantitative ratings: presented with a scenario, each panelist rates a given therapy's appropriateness anonymously, preventing a single individual's opinions from dominating the group; (2) controlled feedback: once first round ratings are submitted by the whole panel, panelists hold an in-person meeting to review all ratings and work out disagreements; (3) iteration: further ratings are given, so panelists may make any changes following the group discussion; and (4) statistical group response: the degree to which panelists agreed is determined through

Table 1 Variables used to construct clinical patient scenarios in unresectable metastatic well-differentiated pancreatic neuroendocrine tumors

Variable	Range of values
Anatomic site	Pancreatic neuroendocrine tumors
Line of treatment	Observation; first-line treatment; second-line treatment; third-line treatment
Patient's primary problem	Uncontrolled secretory symptoms; uncontrolled tumor-related symptoms; rapid radiographic progression; nonrapid radiographic progression; no symptoms and no radiographic progression; no symptoms
Postmarker and postscan testing status	No progression from prior marker and scan; progression after prior marker and scan
Frequency of testing a patient with markers and scans	Every 3 mo; every 6 mo; every 9 mo; every 12 mo
Cytoreductive surgery	Optimal cytoreductive surgery; suboptimal cytoreductive surgery; not a candidate for surgery
Systemic therapy	Somatostatin analog; everolimus; sunitinib; cytotoxic chemotherapy; interferon-α; temozolomide-containing regimen; streptozotocin-containing regimen
Response to lower octreotide LAR dose	Previously responded to a lower dose or frequency; previously did not respond to a lower dose or frequency
Octreotide LAR frequency	Every 2 wk; every 3 wk; every 4 wk
Octreotide LAR dosing	30 mg; 40 mg; 60 mg; 90 mg; 120 mg

statistical analysis.

Development of patient scenarios

A summary of published evidence about PNETs was collected by the moderator, steering committee, and researchers trained in the Delphi method (Cherepanov D, Broder MS) and provided to the panelists. The intent was to consider both medical and liver directed therapies, but the limited time available for the in-person meeting led to a focus on only medical therapy. A set of variables was developed by the steering committee, which represented the range of patient presentations in clinical practice (*e.g.,* anatomic site, line of treatment, presence or absence of secretory symptoms) (Table 1). A list of 197 patient scenarios was developed from these variables. Each patient scenario described the clinical circumstances of a patient with PNET (*e.g.,* a patient whose primary problem is uncontrolled secretory symptoms who has had suboptimal cytoreductive surgery) and gave choices for medical treatment (*e.g.,* SA, everolimus, no treatment). The scenarios were reviewed and refined iteratively with the steering committee.

Rating of patient scenarios and development of consensus statements

Panelists ranked (on a 1-9 scale) the appropriateness of multiple treatment options for each patient scenario, using the definition that an appropriate treatment is one for which the expected health benefit outweighs the expected detriment by a wide enough margin that it is worth doing, without consideration of cost[33]. A rating of 1 indicated an inappropriate treatment, meaning one for which the expected harms greatly outweighed the expected benefits; a rating of 9 indicated an appropriate treatment for which expected benefits greatly outweighed expected harms; a 5 indicated either an equal tradeoff between harms and benefits or that the scenario could not be rated for appropriateness.

The first round of ratings was completed in early October 2011, and the panelists met face-to-face on October 18, 2011 in Minneapolis, Minnesota. At this meeting, panelists reviewed the initial survey results then participated in a moderated discussion to determine areas of agreement or disagreement. During the discussion, panelists added 5 additional unique patient scenarios for the second round of ratings. After the discussion, panelists rated the appropriateness of clinical management options for each patient scenario a second time. The second round results were summarized, and the steering committee compiled the data into consensus statements about systemic treatments for patients with PNETs.

Statistical analysis

The median of the 10 panelists' ratings and the absolute deviation from each panelist's rating to the median were calculated for every patient scenario. For both the pre-meeting and final surveys, median and mean distance from the median were calculated for each scenario. Median was used to measure central tendency because the responses are ordinal and the distance between points on the scale is not fixed (*e.g.*, 8 and 9 might be closer together than 4 and 5). Average distance from the median was used to measure dispersion. Whether respondents agreed or disagreed on each item was reported, with disagreement defined as > 2 ratings from 1 to 3 and > 2 from 7 to 9 on the same item. Statistics summarizing appropriateness and agreement over the entire survey were also calculated. Clinical management for each scenario was categorized as appropriate (a median rating of 7-9 with no disagreement), inappropriate (a median rating of 1-3 with no disagreement), and uncertain (a median rating of 4-6 with no disagreement). All data and statistical analyses were performed using SAS® version 9.2 (SAS Institute, Cary, NC).

Blinding and role of the funder

Novartis selected the research company that organized the meeting and determined the topic of the Delphi

Table 2 Number of indications scored as "inappropriate", "uncertain", "appropriate", or as "disagreement" in unresectable metastatic well-differentiated pancreatic neuroendocrine tumors

Agreement	First Round Results				Second Round Results			
	Frequency	Percent	Cumulative Frequency	Cumulative Percent	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Inappropriate	73	37.1	73	37.1	94	46.5	94	46.5
Uncertain	39	19.8	112	56.9	44	21.8	138	68.3
Appropriate	59	29.9	171	86.8	62	30.7	200	99.0
Disagreement	26	13.2	197	100.0	2	1.0	202	100.0

Table 3 Average panel median rating and absolute deviation for clinical scenarios in patients with unresectable metastatic well-differentiated pancreatic neuroendocrine tumors

Variable	First round results					Second round results				
	Number of Scenarios	Mean	SD	Minimum	Maximum	Number of Scenarios	Mean	SD	Minimum	Maximum
Median	197	4.3	2.6	1.0	9.0	202	4.1	2.9	1	9.0
Absolute deviation	197	1.6	0.5	0.1	2.7	202	0.8	0.6	0	2.2

panel. A steering committee, which did not know the funding source, consisted of 3 medical oncologists experienced in treating PNETs (Strosberg JR, Fisher GA, Benson AB). At no point were potential panelists told the funder, nor asked their views of drugs marketed by the funder. Although Novartis saw the final list of panelists, all selections were made independently by the steering committee. An independent moderator who was experienced in the Delphi method and did not know the funding source was selected. The funder paid travel and honoraria for the panel members and the moderator, but did not discuss the panel content with panelists or the moderator before, during, or after the meeting. During the meeting, Novartis had no representation. Novartis read the panel results, but did not direct or modify these analyses. Results were also shared with the panelists. Until the manuscript was fully drafted, the moderator, steering committee, and panelists all remained blinded to the funder. Novartis reviewed the manuscript prior to submission but did not edit or amend or make suggestions that resulted in changes to the manuscript.

RESULTS

Panelist demographics

The 10 panelists had a mean age of 50.4 years and included members from the Northeast, Midwest, South, and West regions of the United States. Specialties represented included medical and surgical oncology, interventional radiology, and gastroenterology. The panel's single selected endocrinologist could not attend the meeting. Panelists had practiced for a mean of 15.5 years (range: 6-33 years) and an average of 49% of their time was spent seeing patients (range: 15%-60%), with 30%-100% of that time spent caring for NET patients. All panelists were part of academic practices. Five of the panelists were previously involved with the development of other NET treatment guidelines [*e.g.*, North America Neuroendocrine Tumor Society and National Comprehensive Cancer Network (NCCN)].

Consensus results

Among 197 patient scenarios rated in the first round, 37.1% (73 scenarios) were rated as inappropriate, 19.8% (39) were uncertain, and 29.9% (59) were appropriate (Table 2). In the second round of ratings, 46.5% (94 scenarios) were rated inappropriate, 21.8% (44) were uncertain, and 30.7% (62) were appropriate. The proportion for which there was disagreement decreased from 13.2% (26 scenarios) before the meeting to 1.0% (2 scenarios) after. Average median rating was 4.1 (range: 1-9) and average distance from median was 0.8 (range: 0-2.2) in the 2nd round (Table 3). A summary of interventions rated "appropriate" in the management of pancreatic NETs is as follows:

Observation without treatment (Tables 4 and 5): Observation may be appropriate for patients with no symptoms and low-volume radiographically-stable disease. For patients with no progression from prior tests, markers and scans may be obtained every 3-12 mo; for patients with progression after prior tests, an appropriate interval is 3-6 mo.

First-line medical treatment (Table 6): Somatostatin analogs (SA) are appropriate in hormonally functional tumors (particularly VIPomas and glucagonomas). SA may also be appropriate in patients with nonfunctional tumors; however, there have been limited data to support their use as antiproliferative agents in pancreatic NETs. Everolimus is an appropriate agent in patients with symptomatic or progressive tumors. Sunitinib is an appropriate agent in patients with symptomatic or progressive tumors. Cytotoxic chemotherapy (*i.e.*, streptozocin or temozolomide-based regimens as recommended by NCCN) is appropriate, particularly in

Table 4 Observation in patients with unresectable metastatic well-differentiated pancreatic neuroendocrine tumors

Rate the appropriateness of observation without regional or medical therapy	In a patient whose primary problem is:				
	Uncontrolled secretory symptoms	Uncontrolled tumor-related symptoms	Rapid radiographic progression	Nonrapid radiographic progression	No symptoms and no radiographic progression
	1.0[1] (0.0)	1.0[1] (0.0)	1.0[1] (0.0)	4.3[2] (1.2)	8.0[3] (1.3)

The medians of ratings represents the type of panel consensus that was reached for the particular patient scenario (cell). [1]Median rating 1-3 and no disagreement[4] = "inappropriate"; [2]Median rating 4-6 and no disagreement[4] = "uncertain"; and [3]Median rating 7-9 and no disagreement[4] = "appropriate"; [4] > 2 responses in the range 1-3 and > 2 responses in the range 7-9 = "disagreement".

Table 5 Observation in patients with unresectable metastatic well-differentiated pancreatic neuroendocrine tumors

Rate the appropriateness of the frequency of testing in an asymptomatic patient	Markers and scans			
Who has had	Every 3 mo	Every 6 mo	Every 9 mo	Every 12 mo
A. No progression from prior marker and scan	7.0[3] (1.5)	6.5[3] (1.8)	5.0[2] (1.5)	3.5[2] (1.7)
B. Progression after prior marker and scan	9.0[3] (0.2)	6.5[3] (1.6)	2.0[1] (1.0)	1.0[1] (0.5)

The medians of ratings represents the type of panel consensus that was reached for the particular patient scenario (cell): [1]Median rating 1-3 and no disagreement[4] = "inappropriate"; [2]Median rating 4-6 and no disagreement[4] = "uncertain"; and [3]Median rating 7-9 and no disagreement[4] = "appropriate"; [4] > 2 responses in the range 1-3 and > 2 responses in the range 7-9 = "disagreement".

Table 6 First-Line treatment in patients with unresectable metastatic well-differentiated pancreatic neuroendocrine tumors

Rate the appropriateness of the following initial treatment options		In a patient whose primary problem is:		
		Uncontrolled secretory symptoms	Uncontrolled tumor-related symptoms	No symptoms
No systemic therapy	Following optimal cyto-reductive surgery	1.0[1] (0.0)	1.0[1] (0.0)	8.5[3] (1.5)
Somatostatin analogue		9.0[3] (0.0)	7.0[3] (1.1)	5.0[2] (0.7)
Everolimus		7.0[3] (0.5)	7.0[3] (0.9)	1.0[1] (0.4)
Sunitinib		7.0[3] (0.7)	7.0[3] (0.9)	1.0[1] (0.3)
Cytotoxic chemotherapy		5.0[2] (1.2)	7.5[4] (2.2)	1.0[1] (0.2)
No systemic therapy	Who had suboptimal cytoreductive surgery	1.0[1] (0.0)	1.0[1] (0.0)	5.0[2] (1.2)
Somatostatin analogue		9.0[3] (0.0)	6.0[2] (1.7)	5.0[2] (0.3)
Everolimus		7.0[3] (0.4)	7.0[3] (0.6)	5.0[2] (1.1)
Sunitinib		7.0[3] (0.5)	7.0[3] (0.5)	5.0[2] (1.2)
Cytotoxic chemotherapy		7.0[3] (1.0)	7.0[3] (0.9)	2.0[1] (1.2)
No systemic therapy	Who is not a candidate for surgery	1.0[1] (0.0)	1.0[1] (0.0)	5.0[2] (0.3)
Somatostatin analogue		9.0[3] (0.0)	5.0[2] (1.5)	6.5[3] (1.2)
Everolimus		7.0[3] (0.6)	8.0[3] (0.6)	5.0[2] (1.1)
Sunitinib		7.0[3] (0.8)	8.0[3] (0.4)	5.0[2] (1.2)
Cytotoxic chemotherapy		6.5[3] (1.1)	9.0[3] (0.8)	5.0[2] (1.5)

The medians of ratings represents the type of panel consensus that was reached for the particular patient scenario (cell): [1]Median rating 1-3 and no disagreement[4] = "inappropriate"; [2]Median rating 4-6 and no disagreement[4] = "uncertain"; and [3]Median rating 7-9 and no disagreement[4] = "appropriate"; [4] > 2 responses in the range 1-3 and > 2 responses in the range 7-9 = "disagreement".

patients with rapidly progressive tumors, or in cases where tumor burden is high. There were no significant differences in ratings between sunitinib, everolimus and cytotoxic chemotherapy for most scenarios. The exception was for patients with non-rapidly progressive tumors where cytotoxic chemotherapy was rated as less appropriate than either sunitinib or everolimus.

Second-line therapy and beyond (Tables 7-9): Everolimus, sunitinib, and cytotoxic chemotherapy (temozolomide or streptozocin-based regimens) are appropriate in the refractory setting. However, there are no studies guiding the appropriate sequence of treatments. There were no significant differences in the appropriateness ratings of sunitinib, everolimus and cytotoxic chemotherapy for most scenarios. The exception was for patients with non-rapidly progressive tumors where cytotoxic chemotherapy was rated as less appropriate than either sunitinib or everolimus. In patients with uncontrolled secretory symptoms, increasing the dose/frequency of SA is appropriate, particularly among patients who had previously responded to lower dose. The panel considered dose escalations of octreotide LAR up to 60 mg every 3 or 4 wk regardless of previous response to somatostatin

Table 7 Second-line treatment in patients with unresectable metastatic well-differentiated pancreatic neuroendocrine tumors

Rate the appropriateness of the following as a second-line medical treatment in a patient who has had an initial adequate trial of a somatostatin analogue	In a patient whose primary problem is:				
	Uncontrolled secretory symptoms	Uncontrolled tumor-related symptoms	Rapid radiographic progression	Nonrapid radiographic progression	No symptoms and no radiographic progression
Higher dose/frequency of somatostatin analogue (*e.g.*, > 30 mg dose or < 4 wk dosing of octreotide LAR)	9.0[3] (0.2)	3.0[1] (0.8)	2.0[1] (0.8)	5.0[2] (1.4)	1.0[1] (1.0)
Everolimus	8.0[3] (0.4)	9.0[3] (0.4)	8.0[3] (0.5)	8.0[3] (0.6)	1.5[1] (1.1)
Sunitinib	8.0[3] (0.7)	8.5[3] (0.8)	7.5[3] (0.7)	7.0[3] (0.7)	1.5[1] (1.0)
Cytotoxic chemotherapy	7.0[3] (0.8)	8.5[3] (0.8)	7.5[3] (1.4)	6.0[2] (1.0)	1.0[1] (0.8)
Interferon	5.0[2] (1.1)	4.0[2] (0.9)	4.0[2] (1.3)	3.5[2] (1.7)	1.0[1] (0.3)

The medians of ratings represents the type of panel consensus that was reached for the particular patient scenario (cell): [1]Median rating 1-3 and no disagreement[4] = "inappropriate"; [2]Median rating 4-6 and no disagreement[4] = "uncertain"; and [3]Median rating 7-9 and no disagreement[4] = "appropriate"; [4] > 2 responses in the range 1-3 and > 2 responses in the range 7-9 = "disagreement".

Table 8 Second-line treatment in patients with unresectable metastatic well-differentiated pancreatic neuroendocrine tumors

Rate the appropriateness of increasing the dose or frequency of octreotide lar beyond 30 mg every 4 wk		Every 4 wk				Every 3 wk					Every 2 wk				
In a patient whose primary problem is:		40 mg	60 mg	90 mg	120 mg	30 mg	40 mg	60 mg	90 mg	120 mg	30 mg	40 mg	60 mg	90 mg	120 mg
Uncontrolled secretory symptoms	Who previously responded to a lower dose or frequency	9.0[3] (0.7)	7.0[3] (0.7)	1.0[1] (0.5)	1.0[1] (0.3)	8.0[3] (0.8)	7.0[3] (0.6)	5.5[2] (1.5)	1.0[1] (0.6)	1.0[1] (0.4)	5.0[2] (2.0)	4.5[2] (2.2)	3.0[1] (1.9)	1.0[1] (0.1)	1.0[1] (0.1)
Uncontrolled tumor-related symptoms		6.0[2] (1.7)	5.0[2] (1.8)	1.0[1] (0.4)	1.0[1] (0.3)	5.5[2] (2.0)	4.5[2] (1.9)	3.5[2] (1.8)	1.0[1] (0.5)	1.0[1] (0.4)	1.0[1] (1.5)	1.0[1] (1.4)	1.0[1] (0.6)	1.0[1] (0.1)	1.0[1] (0.1)
Radiographic progression		5.0[2] (1.1)	4.5[2] (1.6)	1.0[1] (0.3)	1.0[1] (0.3)	5.0[4] (2.2)	4.0[2] (1.9)	2.5[1] (1.8)	1.0[1] (0.5)	1.0[1] (0.5)	1.0[1] (1.7)	1.0[1] (1.6)	1.0[1] (0.5)	1.0[1] (0.1)	1.0[1] (0.1)
Uncontrolled secretory symptoms	Who previously did not respond to a lower dose or frequency	7.0[3] (0.9)	7.0[3] (0.9)	1.0[1] (0.5)	1.0[1] (0.3)	6.0[2] (1.1)	6.0[2] (0.9)	3.5[2] (1.6)	1.0[1] (0.4)	1.0[1] (0.5)	3.0[1] (2.0)	2.5[1] (1.6)	2.0[1] (0.8)	1.0[1] (0.1)	1.0[1] (0.1)
Uncontrolled tumor-related symptoms		3.5[2] (1.4)	3.0[1] (1.5)	1.0[1] (0.3)	1.0[1] (0.2)	2.5[1] (1.0)	3.0[1] (1.0)	1.5[1] (0.5)	1.0[1] (0.2)	1.0[1] (0.2)	1.0[1] (0.7)	1.0[1] (0.4)	1.0[1] (0.3)	1.0[1] (0.1)	1.0[1] (0.1)
Radiographic progression		3.0[1] (1.4)	3.0[1] (1.5)	1.0[1] (0.2)	1.0[1] (0.2)	2.0[1] (0.7)	2.5[1] (1.1)	1.0[1] (0.6)	1.0[1] (0.3)	1.0[1] (0.3)	1.0[1] (0.6)	1.0[1] (0.4)	1.0[1] (0.2)	1.0[1] (0.1)	1.0[1] (0.1)

The medians of ratings represents the type of panel consensus that was reached for the particular patient scenario (cell): [1]Median rating 1-3 and no disagreement[4] = "inappropriate"; [2]Median rating 4-6 and no disagreement[4] = "uncertain"; and [3]Median rating 7-9 and no disagreement[4] = "appropriate"; [4] > 2 responses in the range 1-3 and > 2 responses in the range 7-9 = "disagreement".

Table 9 Third-line treatment in patients with unresectable metastatic well-differentiated pancreatic neuroendocrine tumors

Rate the appropriateness of the following as a third-line medical treatment in a patient who has had an adequate trial of two agents, one of which was a somatostatin analogue. Assume for each question that the agent being rated was not previously used	In a patient whose primary problem is:				
	Uncontrolled secretory symptoms	Uncontrolled tumor-related symptoms	Rapid radiographic progression	Nonrapid radiographic progression	No symptoms and no radiographic progression
Higher dose/frequency of somatostatin analogue (*e.g.*, > 30 mg dose or < 4 wk dosing of octreotide LAR)	9.0[3] (0.4)	3.0[1] (1.6)	2.5[1] (1.0)	4.5[2] (1.8)	1.0[1] (0.4)
Everolimus	9.0[3] (0.7)	9.0[3] (0.7)	8.0[3] (0.8)	7.0[3] (0.6)	1.0[1] (0.7)
Sunitinib	8.5[3] (0.7)	9.0[3] (0.7)	8.0[3] (0.8)	7.0[3] (0.7)	1.0[1] (0.7)
Interferon	5.0[2] (0.9)	4.5[2] (1.3)	4.0[2] (1.0)	3.0[1] (1.7)	1.0[1] (0.4)
Temozolomide-containing regimen	7.5[3] (1.4)	7.5[3] (1.2)	7.5[3] (1.5)	5.0[2] (1.3)	1.0[1] (0.6)
Streptozotocin-containing regimen	5.5[2] (1.3)	7.0[3] (1.4)	6.5[3] (1.2)	4.5[2] (1.6)	1.0[1] (0.4)
Cytotoxic Chemotherapy	6.5[3] (1.3)	8.0[3] (1.1)	8.0[3] (1.2)	5.5[2] (1.5)	1.0[1] (0.9)

The medians of ratings represents the type of panel consensus that was reached for the particular patient scenario (cell): [1]Median rating 1-3 and no disagreement[4] = "inappropriate"; [2]Median rating 4-6 and no disagreement[4] = "uncertain"; and [3]Median rating 7-9 and no disagreement[4] = "appropriate"; [4] > 2 responses in the range 1-3 and > 2 responses in the range 7-9 = "disagreement".

analog or up to 40 mg every 2 wk in those who previously responded to a lower dose to be reasonable adjustments. The hormonal syndromes most likely to respond to SA therapy are associated with secretion of glucagon and VIP. Caution should be used in administration of SA in patients with insulinoma, which may result in worsening of hypoglycemia.

DISCUSSION

While the data surrounding the management of unresectable metastatic PNETs is limited, this study was able to systematically derive specific and actionable consensus statements for management using the expert panel methodology. In distinction to other approaches for eliciting treatment recommendations[25-30], the Delphi process combines literature review, multiple rounds of quantitative ratings of specific clinical scenarios, and face-to-face discussions[31-34]. Moreover, this process allows for a statistical summary of the resultant body of evidence rather than a qualitative extrapolation of a literature review alone. The Delphi process enables elicitation of the collective opinion of experts, rather than forcing a consensus. The results include detailed statements that can inform the development of treatment guidelines and may also guide clinicians in their clinical care.

A limitation of this approach is that the information is aggregated across data sources rather than relying solely on data from randomized controlled trials (RCTs), and panelists must make a decision about each treatment scenario, even in the absence of high quality evidence. Clinical practice requires similar decision-making and the results of the panel may therefore be of particular interest to practicing clinicians.

The panel developed a number of consensus statements with very low levels of disagreement. These included statements regarding the appropriateness of observation of patients with stable, asymptomatic tumors; use of SAs in patients with certain hormonally functional tumors; and use of everolimus, sunitinib and streptozocin or temozolomide-based chemotherapy in patients with progressive tumors. Appropriateness levels were similar for sunitinib and everolimus in all scenarios, reflecting the similarity of outcomes when these agents were compared to placebo in phase Ⅲ studies. Cytotoxic drugs were considered less appropriate than targeted agents for patients with slowly progressive tumors.

A limitation of this consensus is that the panel convened prior to the report of the CLARINET trial, which confirmed the superiority of lanreotide compared to placebo in extending PFS in nonfunctional gastroenteropancreatic NETs[12]. Additionally, therapeutic use of somatostatin analogues linked to radioactive isotopes, known as peptide receptor radiation therapy, is approved for use in Europe but is not available in the United States. Though it is clear that such treatment can be effective in PNETs, the fact that it is simply unavailable in this country is the reason it was omitted as an option in this analysis. Overall, consensus statements developed by the panel are consistent with the NCCN guidelines, and further complement the guidelines by adding clarity on sequencing of available systemic treatment options, given the lack of RCTs based on clinical experience and incorporation of eligibility used in trials. Future research should consider collecting treatment appropriateness ratings from physician experts on additional unique PNET patient scenarios not considered in this study, such as patient scenarios with moderately differentiated (intermediate grade or G2) PNETs and poorly differentiated (high grade or G3) PNETs[35,36].

In conclusion, bringing together an expert physicians panel as described by the RAND/UCLA modified Delphi process allowed us to obtain appropriateness ratings of a variety of medical therapies in PNETs. In the absence of high-quality RCTs, the consensus process can help clinicians choose the most appropriate therapy for patients with this rare condition.

COMMENTS

Background

Treatment options available to patients with pancreatic neuroendocrine tumors (NETs) have expanded with the emergence of new therapies, yet clinicians are faced with the necessity of generating treatment recommendations in the absence of high quality data. Treatment guidelines in NETs have been previously published[25-30] but the lack of data comparing the effectiveness of the various treatment options in patients with NETs leads to many management decisions being based on physician experience and expert recommendations.

Research frontiers

In the absence of high-quality RCTs, this consensus process can help clinicians choose the most appropriate therapy for patients with this rare condition. The detailed consensus statements resulting from this process can also inform the development of new treatment guidelines.

Innovations and breakthroughs

The RAND/UCLA modified Delphi process is a valid method for assessing the appropriateness of medical interventions using expert input[31-34]. Present study used this process to develop consensus on the use of systemic treatments for unresectable, metastatic, well-differentiated (grade 1-2) pancreatic neuroendocrine tumors.

Applications

The expert panel reached consensus on appropriateness of a variety of medical therapies in PNETs, which included the following consensus statements: (1) it is appropriate to use somatostatin analogs as first line therapy in patients with hormonally functional tumors and may be appropriate in patients who are asymptomatic; (2) it is appropriate to use everolimus, sunitinib, or cytotoxic chemotherapy therapy as first line therapy in patients with symptomatic or progressive tumors; and (3) beyond first line, these same agents can be used. In patients with uncontrolled secretory symptoms, octreotide LAR doses can be titrated up to 60 mg every 4 wk or up to 40 mg every 3 or 4 wk. The consensus statements developed by the panel are consistent with the NCCN guidelines, and further complement the guidelines by adding clarity on sequencing of available systemic treatment options.

Peer review

This study is meaningful and innovative in applying the RAND/UCLA modified Delphi process to assist NET physician experts in obtaining consensus on the appropriateness of various medical therapies in unresectable metastatic well-differentiated PNETs under varied clinical scenarios.

REFERENCES

1 **Yao JC**, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, Abdalla EK, Fleming JB, Vauthey JN, Rashid A, Evans DB. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol* 2008; **26**: 3063-3072 [PMID: 18565894 DOI: 10.1200/JCO.2007.15.4377]

2 **Fesinmeyer MD**, Austin MA, Li CI, De Roos AJ, Bowen DJ. Differences in survival by histologic type of pancreatic cancer. *Cancer Epidemiol Biomarkers Prev* 2005; **14**: 1766-1773 [PMID: 16030115]

3 **Strosberg J**, Gardner N, Kvols L. Survival and prognostic factor analysis in patients with metastatic pancreatic endocrine carcinomas. *Pancreas* 2009; **38**: 255-258 [PMID: 19066493 DOI: 10.1097/MPA.0b013e3181917e4e]

4 **Halfdanarson TR**, Rabe KG, Rubin J, Petersen GM. Pancreatic neuroendocrine tumors (PNETs): incidence, prognosis and recent trend toward improved survival. *Ann Oncol* 2008; **19**: 1727-1733 [PMID: 18515795 DOI: 10.1093/annonc/mdn351]

5 **Johanson V**, Tisell LE, Olbe L, Wängberg B, Nilsson O, Ahlman H. Comparison of survival between malignant neuroendocrine tumours of midgut and pancreatic origin. *Br J Cancer* 1999; **80**: 1259-1261 [PMID: 10376980 DOI: 10.1038/sj.bjc.6690494]

6 **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**: 3044-3049 [PMID: 21709192 DOI: 10.1200/JCO.2011.35.1817]

7 **Maton PN**. Use of octreotide acetate for control of symptoms in patients with islet cell tumors. *World J Surg* 1993; **17**: 504-510 [PMID: 8395751]

8 **di Bartolomeo M**, Bajetta E, Buzzoni R, Mariani L, Carnaghi C, Somma L, Zilembo N, di Leo A. Clinical efficacy of octreotide in the treatment of metastatic neuroendocrine tumors. A study by the Italian Trials in Medical Oncology Group. *Cancer* 1996; **77**: 402-408 [PMID: 8625251]

9 **Saltz L**, Trochanowski B, Buckley M, Heffernan B, Niedzwiecki D, Tao Y, Kelsen D. Octreotide as an antineoplastic agent in the treatment of functional and nonfunctional neuroendocrine tumors. *Cancer* 1993; **72**: 244-248 [PMID: 8389666]

10 **Arnold R**, Trautmann ME, Creutzfeldt W, Benning R, Benning M, Neuhaus C, Jürgensen R, Stein K, Schäfer H, Bruns C, Dennler HJ. Somatostatin analogue octreotide and inhibition of tumour growth in metastatic endocrine gastroenteropancreatic tumours. *Gut* 1996; **38**: 430-438 [PMID: 8675099]

11 **Tomassetti P**, Migliori M, Corinaldesi R, Gullo L. Treatment of gastroenteropancreatic neuroendocrine tumours with octreotide LAR. *Aliment Pharmacol Ther* 2000; **14**: 557-560 [PMID: 10792118]

12 Caplin M, Ruszniewski P, Pavel M, Cwikla J, Phan A, Raderer M, Sedlackova E, Cadiot G, Wall L, Rindi G, Liyanage N, Blumberg J. A randomized, double-blind, placebo-Controlled study of Lanreotide Antiproliferative Response in patients with gastroenteropancreatic NeuroEndocrine Tumors (CLARINET). Program and abstracts of the Annual Meeting of the European Society for Medical Oncology; September 27-October 1, 2013; Amsterdam, The Netherlands. Abstract E17-7103

13 **Strosberg JR**, Cheema A, Kvols LK. A review of systemic and liver-directed therapies for metastatic neuroendocrine tumors of the gastroenteropancreatic tract. *Cancer Control* 2011; **18**: 127-137 [PMID: 21451455]

14 **Jiao Y**, Shi C, Edil BH, de Wilde RF, Klimstra DS, Maitra A, Schulick RD, Tang LH, Wolfgang CL, Choti MA, Velculescu VE, Diaz LA, Vogelstein B, Kinzler KW, Hruban RH, Papadopoulos N. DAXX/ATRX, MEN1, and mTOR pathway genes are frequently altered in pancreatic neuroendocrine tumors. *Science* 2011; **331**: 1199-1203 [PMID: 21252315 DOI: 10.1126/science.1200609]

15 **Yao JC**, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, Hobday TJ, Okusaka T, Capdevila J, de Vries EG, Tomassetti P, Pavel ME, Hoosen S, Haas T, Lincy J, Lebwohl D, Öberg K. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med* 2011; **364**: 514-523 [PMID: 21306238 DOI: 10.1056/NEJMoa1009290]

16 **Terris B**, Scoazec JY, Rubbia L, Bregeaud L, Pepper MS, Ruszniewski P, Belghiti J, Fléjou J, Degott C. Expression of vascular endothelial growth factor in digestive neuroendocrine tumours. *Histopathology* 1998; **32**: 133-138 [PMID: 9543669]

17 **Raymond E**, Dahan L, Raoul JL, Bang YJ, Borbath I, Lombard-Bohas C, Valle J, Metrakos P, Smith D, Vinik A, Chen JS, Hörsch D, Hammel P, Wiedenmann B, Van Cutsem E, Patyna S, Lu DR, Blanckmeister C, Chao R, Ruszniewski P. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med* 2011; **364**: 501-513 [PMID: 21306237 DOI: 10.1056/NEJMoa1003825]

18 **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**: 1189-1194 [PMID: 6252466]

19 **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**: 519-523 [PMID: 1310159]

20 **Kouvaraki MA**, Ajani JA, Hoff P, Wolff R, Evans DB, Lozano R, Yao JC. Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. *J Clin Oncol* 2004; **22**: 4762-4771 [PMID: 15570077]

21 **Kulke MH**, Stuart K, Enzinger PC, Ryan DP, Clark JW, Muzikansky A, Vincitore M, Michelini A, Fuchs CS. Phase II study of temozolomide

and thalidomide in patients with metastatic neuroendocrine tumors. *J Clin Oncol* 2006; **24**: 401-406 [PMID: 16421420]

22 **Chan JA**, Stuart K, Earle CC, Clark JW, Bhargava P, Miksad R, Blaszkowsky L, Enzinger PC, Meyerhardt JA, Zheng H, Fuchs CS, Kulke MH. Prospective study of bevacizumab plus temozolomide in patients with advanced neuroendocrine tumors. *J Clin Oncol* 2012; **30**: 2963-2968 [PMID: 22778320 DOI: 10.1200/JCO.2011.40.3147]

23 **Strosberg JR**, Fine RL, Choi J, Nasir A, Coppola D, Chen DT, Helm J, Kvols L. First-line chemotherapy with capecitabine and temozolomide in patients with metastatic pancreatic endocrine carcinomas. *Cancer* 2011; **117**: 268-275 [PMID: 20824724 DOI: 10.1002/cncr.25425]

24 **Kulke MH**, Hornick JL, Frauenhoffer C, Hooshmand S, Ryan DP, Enzinger PC, Meyerhardt JA, Clark JW, Stuart K, Fuchs CS, Redston MS. O6-methylguanine DNA methyltransferase deficiency and response to temozolomide-based therapy in patients with neuroendocrine tumors. *Clin Cancer Res* 2009; **15**: 338-345 [PMID: 19118063 DOI: 10.1158/1078-0432.CCR-08-1476]

25 **Boudreaux JP**, Klimstra DS, Hassan MM, Woltering EA, Jensen RT, Goldsmith SJ, Nutting C, Bushnell DL, Caplin ME, Yao JC. The NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: well-differentiated neuroendocrine tumors of the Jejunum, Ileum, Appendix, and Cecum. *Pancreas* 2010; **39**: 753-766 [PMID: 20664473 DOI: 10.1097/MPA.0b013e3181ebb2a5]

26 **Maroun J**, Kocha W, Kvols L, Bjarnason G, Chen E, Germond C, Hanna S, Poitras P, Rayson D, Reid R, Rivera J, Roy A, Shah A, Sideris L, Siu L, Wong R. Guidelines for the diagnosis and management of carcinoid tumours. Part 1: the gastrointestinal tract. A statement from a Canadian National Carcinoid Expert Group. *Curr Oncol* 2006; **13**: 67-76 [PMID: 17576444]

27 **Kulke MH**, Anthony LB, Bushnell DL, de Herder WW, Goldsmith SJ, Klimstra DS, Marx SJ, Pasieka JL, Pommier RF, Yao JC, Jensen RT. NANETS treatment guidelines: well-differentiated neuroendocrine tumors of the stomach and pancreas. *Pancreas* 2010; **39**: 735-752 [PMID: 20664472 DOI: 10.1097/MPA.0b013e3181ebb168]

28 **Strosberg JR**, Coppola D, Klimstra DS, Phan AT, Kulke MH, Wiseman GA, Kvols LK. The NANETS consensus guidelines for the diagnosis and management of poorly differentiated (high-grade) extrapulmonary neuroendocrine carcinomas. *Pancreas* 2010; **39**: 799-800 [PMID: 20664477 DOI: 10.1097/MPA.0b013e3181ebb56f]

29 National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Neuroendocrine Tumors. Version 2.2014. Available from: URL: http://www.NCCN.org

30 **Vinik AI**, Woltering EA, Warner RR, Caplin M, O'Dorisio TM, Wiseman GA, Coppola D, Go VL. NANETS consensus guidelines for the diagnosis of neuroendocrine tumor. *Pancreas* 2010; **39**: 713-734 [PMID: 20664471 DOI: 10.1097/MPA.0b013e3181ebaffd]

31 **Shekelle PG**, Kahan JP, Bernstein SJ, Leape LL, Kamberg CJ, Park RE. The reproducibility of a method to identify the overuse and underuse of medical procedures. *N Engl J Med* 1998; **338**: 1888-1895 [PMID: 9637810]

32 **Hemingway H**, Crook AM, Feder G, Banerjee S, Dawson JR, Magee P, Philpott S, Sanders J, Wood A, Timmis AD. Underuse of coronary revascularization procedures in patients considered appropriate candidates for revascularization. *N Engl J Med* 2001; **344**: 645-654 [PMID: 11228280]

33 **Fitch K**, Bernstein SJ, Aguilar MS, Burnand B, LaCalle JR, van het Loo M, McDonnell J, Vader JP, Kahan JP. The RAND/UCLA Appropriateness Method User's Manual. Santa Monica, CA: RAND; 2001: 1–123. Available from: URL: http://www.rand.org/content/dam/rand/pubs/monograph_reports/2011/MR1269.pdf Accessed August 18, 2014.

34 **Strosberg JR**, Fisher GA, Benson AB, Malin JL, Cherepanov D, Broder MS, Anthony LB, Arslan B, Fisher GA, Gibbs JF, Greeno E, Iyer RV, Kim MK, Maples W, Philip PA, Strosberg J, Wolin EM. Systemic treatment in unresectable metastatic well-differentiated carcinoid tumors: consensus results from a modified delphi process. *Pancreas* 2013; **42**: 397-404 [PMID: 23211372 DOI: 10.1097/MPA.0b013e31826d3a17]

35 **Klimstra DS**, Modlin IR, Coppola D, Lloyd RV, Suster S. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. *Pancreas* 2010; **39**: 707-712 [PMID: 20664470 DOI: 10.1097/MPA.0b013e3181ec124e.]

36 **Strosberg JR**, Nasir A, Hodul P, Kvols L. Biology and treatment of metastatic gastrointestinal neuroendocrine tumors. *Gastrointest Cancer Res* 2008; **2**: 113-125 [PMID: 19259290]

P- Reviewer: Cheon YK, Zhang ZM
S- Editor: Qi Y **L- Editor**: A **E- Editor**: Liu XM

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 1007-9327