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AN EXPERT PANEL CONSENSUS ON MEDICAL TREATMENT OF NON-MIDGUT UNRESECTABLE NEUROENDOCRINE TUMORS

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BACKGROUND

- Gastrointestinal neuroendocrine tumors (NETs) are rare neoplasms that originate from the secretory cells of the neuroendocrine system and produce peptides and neuroamines causing characteristic hormonal syndromes, including carcinoid syndrome.[1,2] Non-midgut, non-pancreatic NETs include those that arise from the rectum, stomach, thymus and lung (excluding small cell).
- The emergence of new therapies has improved the options available to patients, although current treatment guidelines lack specificity in some clinical areas.
- A systematic methodology for group decision-making, such as the RAND/UCLA modified Delphi process,[3] has not previously been used to develop medical management recommendations for non-midgut NETs.[4-8]

OBJECTIVE

- To use the RAND/UCLA modified Delphi panel process to develop a consensus on medical treatment of well-differentiated (grade 1-2 tumors) unresectable non-midgut NETs.

METHODS

The modified RAND/UCLA Delphi process involved recruitment of physician experts, development of patient scenarios, collection of ratings, statistical summary of panel agreement, and development of consensus statements.[3]

Physician Experts

- Thirteen physician experts in treatment of NETs, representing various specialties, were appointed to serve on the study steering committee, on the panel, or both; one physician was assigned the moderator role.
- Experts and the moderator were blinded to the funding source.

Development of Clinical Patient Scenarios

- Following the experts' review of a summary of published evidence on treatment of NETs, we collaborated to develop a comprehensive list of key variables used to construct patient scenarios.

Variables Used to Construct Clinical Patient Scenarios in Non-Midgut NETS

Variable	Range of Values
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 months; every 6 months; every 9 months; every 12 months
Cytoreductive surgery	Appropriateness of initial therapy following: 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	Who previously responded to a lower dose or frequency; who previously did not respond to a lower dose or frequency
Octreotide LAR frequency	Every 2 weeks; every 3 weeks; every 4 weeks
Octreotide LAR dosing	30 mg; 40 mg; 60 mg; 90 mg; 120 mg

Rating of Patient Scenarios

- Experts rated the appropriateness [a] of systematic therapies for each scenario on a scale [b] of 1 to 9.[3]

[a] Appropriate procedure is one in which the expected health benefit exceeds the expected negative consequences by a sufficiently wide margin that the procedure is worth doing, without consideration of cost.

[b] A rating of 1 implied that the expected harms greatly outweighed the expected benefits, a rating of 9 indicated that the expected benefits greatly outweighed the expected harms, and a 5 indicated either that the harms and benefits were equal or that the rater was unable to rate the degree of appropriateness for the patient described in scenario.

- Two rounds of ratings were collected: 1st round before and the 2nd round after a face-to-face panel meeting. [c]

[c] At the meeting, panelists discussed 1st round ratings and decided to include 10 more unique patient scenarios in the 2nd round (i.e., cytotoxic chemotherapy as 3rd line therapy).

Statistical Summary of Panel Agreement

- For every rated scenario, we calculated two statistics: median of the panelists' ratings and absolute deviation (i.e., distance) from every panelist's rating to the median for the particular scenario.
- Using previously established standards for addressing disagreement (i.e., >2 ratings from 1-3 and >2 from 7-9 range), [3] each scenario was scored for appropriateness:
  - *Appropriate*: median rating of 7-9 with no disagreement.
  - *Inappropriate*: median rating of 1-3 with no disagreement.
  - *Uncertain*: median rating of 4-6 with no disagreement.
- Scenarios that were considered to have *disagreement* were not assigned an appropriateness rating.
- All analyses were performed using SAS® version 8.2 (SAS Institute, Cary, NC).

Development of Consensus Statements

- Treatment of consensus statements were drafted based on statistical summary of panel agreement in the 2nd round.

RESULTS

Panelist Characteristics

- The 10 panelists had a mean age of 50.4 years.
- Specialties of panelists included medical and surgical oncology, interventional radiology, and gastroenterology.
- Panelists had practiced between 6-33 years and self-reported on average that 49% of their time was spent seeing patients (range: 15%-60%).
- All panelists self-identified themselves as being part of an academic practice.
- Five panelists were also previously involved with the development of other NET treatment guidelines.

Patient Scenarios Scored: 'Inappropriate', 'Uncertain', 'Appropriate', or 'Disagreement'

	1st Round Results				2nd Round Results			
Agreement	**Freq.**	**Percent**	**Cum. Freq.**	**Cum. Percent**	**Freq.**	**Percent**	**Cum. Freq.**	**Cum. Percent**
Inappropriate	69	35.0	69	35.0	85	42.1	85	42.1
Uncertain	55	27.9	124	62.9	69	34.2	154	76.2
Appropriate	41	20.8	165	83.8	42	20.8	196	97.0
Disagreement	32	16.2	197	100	6	3.0	202	100

- Panelists rated 197 scenarios in the 1st round and 202 in the 2nd round.
- In the 2nd round, 42.1% (85 scenarios) were rated inappropriate, 34.2% (69) were uncertain, and 20.8% (42) were appropriate.
- Among 202 non-midgut rated scenarios, disagreement decreased from 16.2% (32 scenarios) before the meeting to 3% (6) after.

Average Panel Median Rating and Average Absolute Deviation from Median

	1st Round Results					2nd Round Results				
Variable	**N**	**Mean**	**SD**	**Min**	**Max**	**N**	**Mean**	**SD**	**Min**	**Max**
Median	197	4.1	2.4	1.0	9.0	202	3.9	2.5	1.0	9.0
Absolute Deviation	197	1.5	0.6	0.0	3.0	202	0.9	0.5	0.0	2.1

- In the 2nd round:
  - average median rating: was 3.9 (range: 1-9), and
  - average distance from median was 0.9 (range: 0-2.1).

Consensus Statements on the Appropriateness of Medical Therapies in Non-Midgut NETs

Observation without treatment

- 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 months; for patients with progression after prior tests, an appropriate interval is 3-6 months.

First-line medical treatment

- Somatostatin analogs (SSAs) may be appropriate in patients with secretory symptoms.[d] (SSAs may also be appropriate in patients with nonfunctional tumors; however there are limited data to support their use as antiproliferative agents in non-midgut NETs.)

Second-line medical treatment [e]

- In patients with uncontrolled secretory symptoms, increasing the dose/frequency of SSAs is appropriate, particularly among patients who had previously responded to lower dose.
- The panel considered dose escalations of octreotide long-acting release (LAR) up to 60mg every 4 weeks or up to 40mg every 3 or 4 weeks to be reasonable adjustments for refractory carcinoid syndrome.
- Increasing the dose/frequency of SSA s may be considered in patients with radiographic progression, particularly those whose disease was previously stabilized at a lower dose. In these patients, the panel considered an increase in dose/frequency of octreotide LAR up to 40mg every 3 or 4 weeks to be reasonable.[f]
- Everolimus or interferon-α can be considered as second-line agents in patients who progressed radiographically or symptomatically on a somatostatin analog. In patients with carcinoid syndrome, treatment with an SSA should usually be continued beyond the first line.
- Cytotoxic chemotherapy can be considered in cases of uncontrolled tumor-related symptoms or radiographic progression.[g] The panel did not endorse any particular cytotoxic drug or regimen.

Third line medical treatment [e]

- Although randomized data are lacking, accumulating evidence suggests that antiangiogenic therapy may be active in non-midgut carcinoid tumors. At this time, no particular agent can be specifically recommended.

[d] Everolimus can be considered for patients with progressive, symptomatic, or high-volume disease.

[e] If a particular medical treatment was considered appropriate for an earlier line of therapy, then it is assumed appropriate for the next line of therapy if it has not been used before

[f] There is a lack of evidence that increasing the dose/frequency of SSAs slows radiographic progression

[g] Consider also confirming the pathologic diagnosis, including mitotic index

CONCLUSIONS

- **Treatment consensus obtained in this study is concordant with NCCN recommendations.[4]**
- **The consensus statements produced in this study are useful in informing and building on existing guidelines because they address specific scenarios not covered in other guidelines.[4-8]**
- **In this study, we show how an expert panel methodology, namely the RAND/UCLA modified Delphi process, enabled participants to systematically quantify their assessment of the literature in a valid way while improving overall panel consensus on the appropriateness of medical therapies in non-midgut NETs.**
- **The Delphi panel approach resulted in a detailed consensus statement that can inform the development of treatment guidelines and may also guide clinicians in their clinical care decision-making for patients with non-midgut NETs.**

LIMITATIONS

- The panelists relied on information from a variety of data sources, not just from randomized controlled trials.
- Although the Delphi panel method has been shown to be reproducible, all panelists were from academic settings, and a different panel composition may have derived slightly different consensus statements.
- The Delphi panel process does not develop new information; observational and/or prospective studies may also be useful in further evaluating appropriateness of various treatment options.

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