
Cervical and Upper Mediastinal Lymph Node Metastasis from Gastrointestinal and Pancreatic Neuroendocrine Tumors: True Incidence and Management

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- BACKGROUND:** The incidence, clinical importance, and optimal management of cervical and upper mediastinal lymph node metastasis from gastrointestinal and pancreatic neuroendocrine tumors (NETs) are largely unknown. Historically, cervical nodes have been regarded as asymptomatic and ignored. We hypothesized that these lesions have clinical implications and should be removed surgically.
- STUDY DESIGN:** Consecutive ^{111}In pentetreotide scans (OctreoScan) performed at our institution from May 2008 to October 2010 were reviewed to determine the incidence of cervical and upper mediastinal lymph node metastases among patients with gastrointestinal and pancreatic NETs. The charts of surgically treated patients were reviewed to evaluate the clinical importance of these metastases and the subsequent outcomes of their surgical treatment.
- RESULTS:** A total of 161 NET patients presented with positive OctreoScans. Fourteen patients (8.7%) scanned positive for cervical and upper mediastinal lymph node metastasis. Nine patients underwent surgical exploration; 8 had successful removal of their metastatic nodes. Seven had clinical symptoms that resolved after surgery.
- CONCLUSIONS:** Cervical and upper mediastinal lymph node metastases from gastrointestinal and pancreatic NETs were seen in up to 8.7% of patients. In the past, these metastases were assumed to be insignificant and ignored. Our study clearly demonstrates that most, if not all, such metastases are symptomatic and their clinical implications should not be overlooked. Notably, these metastases can be easily and safely resected using radioguided surgery. (J Am Coll Surg 2012; 214:1017–1022. © 2012 by the American College of Surgeons)
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Neuroendocrine tumors (NETs) usually present with vague and nonspecific symptoms. Consequently, diagnosis is often delayed until the disease has reached advanced stages. Usually, patients present with distant metastases in-

volving the mesenteric lymph nodes and liver. Occasionally, patients present with cervical or upper mediastinal lymph node metastases that, in general, are considered incidental findings without clinical relevance. However, the true incidence of such metastatic lesions, their clinical significance, and their optimal treatment have not been well studied.

Because of the slow-growing nature of NETs and their prolonged survival rate, treatment has historically been passive and palliative. The wait-and-see approach is often accepted and practiced. Within the last 10 to 15 years, physicians have started to gain a better understanding of the disease and have adopted a more aggressive attitude toward these tumors. This includes debulking even in the presence of nonresectable liver metastasis. However, even with this important conceptual change in thinking about the treatment of NETs in general, the clinical significance of distant metastasis in the neck and mediastinum remains largely unknown and ignored.

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Recently, we have begun to address the clinical significance of finding nodal disease in the lower neck and/or upper mediastinum. We hypothesize that these distant nodal lesions might have significant clinical implications. Therefore, the incidence, clinical significance, and optimal management of these lesions warrant a thorough investigation.

METHODS

Consecutive OctreoScans of NET patients seen at our institution between May 2008 and October 2010 were reviewed by one nuclear medicine physician to determine the incidence of cervical and upper mediastinal lymph node metastasis. The charts of all patients who underwent surgical explorations to remove their metastatic neck and/or upper mediastinal lymph nodes were reviewed to determine the clinical significance of these lymph nodes and the outcomes of their surgical removal.

Radioguided surgery was used for all patients following the protocol developed by Wang and colleagues.¹ All patients were injected with 6.4 mCi ¹¹¹In pentetretotide 7 days before their planned surgery and were then explored with radioisotope guidance using a gamma hand-held probe (Neoprobe, model 2204; Neoprobe Corporation) intraoperatively. A sandostatin drip was used perioperatively to prevent a potential carcinoid crisis. A small (<3 cm) incision was made in the lower neck based on the location of hot spots identified by the hand-held gamma probe. The gamma probe was used to guide the direction of dissection to locate the targeted lymph node(s). The mobility of the lymph node and surrounding tissue, the degree of neck extension, and the relative position of tissue retractors can move the target(s) away from the pointing direction of the hand-held gamma detector and escape detection. Therefore, intermittent gentle digital exploration and palpation with and without the tissue retractor in place can be helpful to locate a positive node. A positive node can be safely retracted with graspers without fear of tumor rupture due to the extensive desmoplastic and fibrotic changes of the node. The procedure is concluded only when the in vivo cavity counts from all directions return to match the background counts.

RESULTS

A total of 161 NET patients presented with positive OctreoScans, of which 14 (8.7%) presented with cervical and upper mediastinal lymph node metastasis. Nine of the 14 patients (64%) had left neck and upper mediastinum metastasis (Fig. 1), 3 patients (21%) had right neck metastasis (Fig. 2), and 2 patients (14%) had bilateral disease (Fig. 3). Following our institutional protocol, all patients were sequentially operated on to remove and deb-

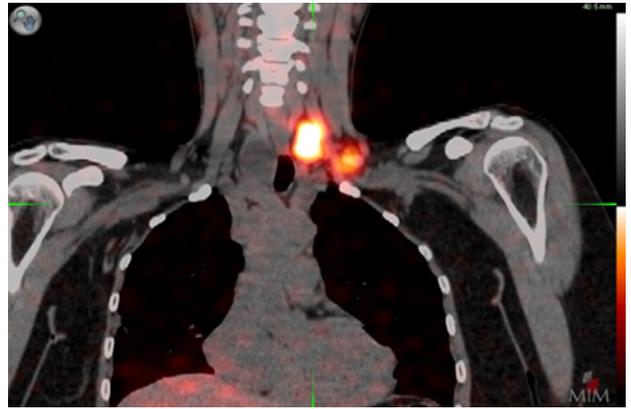


Figure 1. Infusion scan of tumors in left lower neck and upper mediastinum.

ulk the primary tumor as the first-phase operation, with concurrent or staged liver-directed treatment (second phase) to address liver metastases. Patients were then recommended for surgery targeting their cervical and mediastinal lymph node metastasis after recovering from their major abdominal debulking as either a phase 2 or 3 operation.

Nine of the 14 patients (64.3%) underwent surgical explorations; 6 for left neck/upper mediastinum metastatic disease, 1 for bilateral disease, and 2 for right-sided disease based on their preoperative scans. Of the 14 patients, 1 was African American and 13 were white. Their ages ranged from 41 to 73 years. Twelve patients had midgut primary tumors, 1 patient had a pancreatic primary tumor, and 1 patient's primary was unknown (Table 1).

Eight of the 9 patients (88.9%) had successful explorations resulting in the speedy and safe removal of their lymph node(s) (Fig. 4). Operating time varied between 40 and 70 minutes with minimal blood loss. There were no perioperative complications associated with any of the neck and or mediastinal explorations. Eight patients were discharged on postoperative day 1, and 1 patient was discharged on postoperative day 2 due to a more extensive mediastinal exploration.

Patient 1 had a long-term (ie, 7 years) debilitating pulsatile tinnitus, which resolved postoperatively; patient 2 regained food-taste sensation, which had been impaired for 5 years before the procedure; patient 3 had resolution of carcinoid syndrome, including diarrhea 4 to 5 times daily that had persisted even after an extensive abdominal debulking operation; patient 4 experienced relief of radicular pain of the shoulder; patient 5 had elimination of aerodigestive tract—compression symptoms; patient 6 had suffered from a transient ischemic attack that led to an emergent subclavian—carotid bypass 1 year earlier that conceivably could have been avoided if the compressing

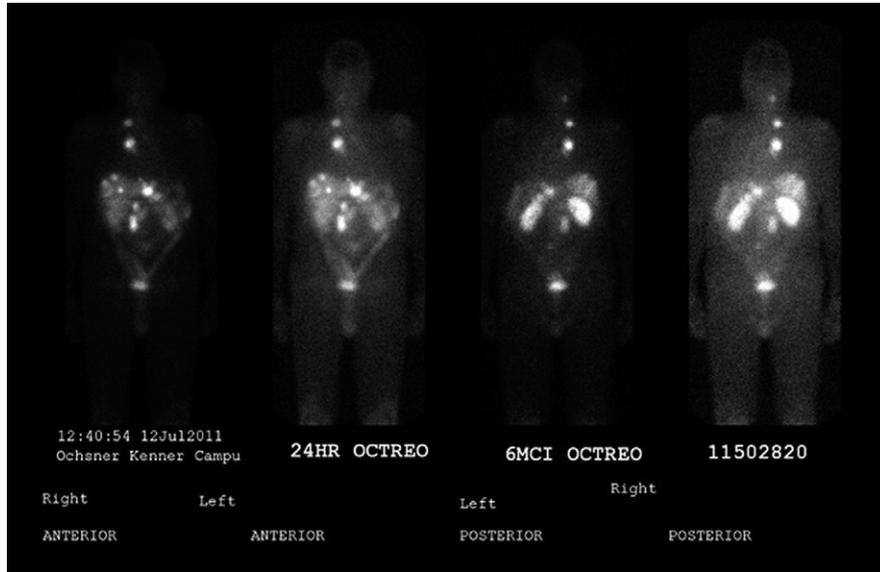


Figure 2. Positive scan of right neck.

tumor been removed earlier; patient 7 regained food-taste sensation, which had been impaired for 15 years; and patient 8 had resolution of voice hoarseness that developed 6 months before the procedure. In contrast, 1 of the 2 patients explored for a positive right neck scan had a negative exploration in which no metastatic lymph nodes were identified. Instead, a cervical bony metastasis was identified (Table 1).

All 9 patients reported to be symptom free preoperatively (except for patient 3, who suffered from carcinoid

syndrome with daily diarrhea). Similar to many hyperparathyroidism patients, symptom improvement or resolution was only recognized postoperatively by our patients and was attributed to the successful surgical removal of the offending nodes.²

DISCUSSION

Gastrointestinal and pancreatic NETs are uncommon tumors that affect only 1 to 4 per 100,000 people.^{3,4} The

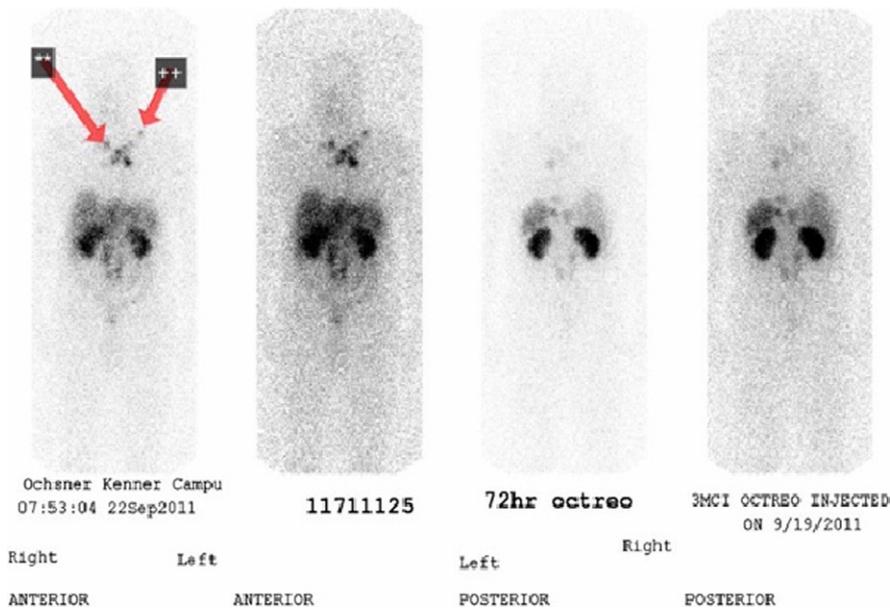


Figure 3. Positive scan of bilateral neck.

Table 1. Characteristics of Patients Operated on for Cervical/Upper Mediastinal Lymph Node Metastases

Patient no.	Race	Sex	Age, y	Ki-67	Location of primary	Primary resected?	Distant metastatic sites	Treated	Location of neck node	Node removed	Successful removal	Clinical symptoms
1	Black	F	59	1	Midgut	Yes	Mesentery, lymph nodes, ovary, various sites within the midgut	Yes	Left neck	Yes	Yes	Pulsatile tinnitus
2	White	F	63	NA	Pancreas	Yes	Mesentery, lymph nodes, ovary, liver, breast, bone, various sites within the midgut	Yes	Left neck	Yes	Yes	Loss of taste
3	White	F	65	1	Midgut	Yes	Mesentery, lymph nodes, liver	Yes	Left neck	Yes	Yes	Extensive carcinoid syndrome
4	White	F	73	4	Midgut	Yes	Mesentery, lymph nodes	Yes	Left neck	Yes	Yes	Shoulder pain
5	White	M	70	1	Midgut	Yes	Mesentery, lymph nodes, liver	Yes	Left neck	Yes	Yes	Aerodigestive tract compression symptoms
6	White	F	49	NA	Midgut	Yes	Mesentery, lymph nodes, ovary, liver	Yes	Left neck	Yes	Yes	Transient ischemic attack 1 year before
7	White	M	70	1	Midgut	Yes	Mesentery, lymph nodes, liver	Yes	Right neck	Yes	Yes	Loss of taste
8	White	M	54	2	Midgut	Yes	Mesentery, lymph nodes	Yes	Bilateral neck	Yes	Yes	Voice hoarseness
9	White	F	52	1	Midgut	Yes	Mesentery, lymph nodes, liver	Yes	Right neck	Yes	No*	NA

*No metastatic nodes identified.
F, female; M, male; NA, not available.

associated symptoms are usually vague and nonspecific, which, in general, results in delayed diagnosis. Patients are usually diagnosed at an advanced stage when extensive metastasis to the mesenteric lymph nodes, peritoneum, and liver are already present. For years, treatment for NETs has been passive and palliative. Surgical intervention was used only to address acute complications resulting from advanced disease, such as an ischemic bowel or bowel obstruction. Only within the last 10 to 15 years have physicians begun to adopt more aggressive treatment measures for this relatively indolent disease. A few experts in the treatment of NETs from medical centers around the world have reported that aggressive debulking or cytoreductive surgery is beneficial to the patients, even in the presence of nonresectable liver metastasis.⁵⁻⁹ However, the distant metastatic disease in the neck and mediastinum were still largely assumed to be medically insignificant and commonly ignored. As a result, there is no solid information about the incidence, possible associated symptoms, and optimal treatment strategy for these lesions.¹⁰ Our study clearly demonstrated that the incidence of such metastasis is much higher (8.7%) than previously assumed and accepted (3% to 4%) by experts in the field. However, no formal large population studies have been conducted to confirm this number. In addition, most of these metastases, if not all, are symptomatic and these

symptoms can be resolved after successful surgical removal of the diseased tissue.

Upper mediastinal and lower neck lymph node metastases have always been assumed to be asymptomatic. However, the anatomic location of these nodal metastases allows for the development of many diversified and unrecognizable symptoms. The tumor can compress the carotid or vertebral arteries and produce neurological symptoms, such as a transient ischemic attack (patient 6) or even a stroke.^{11,12} Additionally, this compression could cause turbulent blood flow within the arteries, leading to debilitat-



Figure 4. Mediastinal lymph node and scalene fat pad.

Table 2. Characteristics of Patients Not Yet Operated on for Cervical/Upper Mediastinal Lymph Node Metastases

Patient no.	Race	Sex	Age, y	Ki-67	Location of primary	Primary resected	Distant metastatic sites	Treated	Location of neck node	Node removed
10	White	M	51	3	Midgut	Yes	Mesentery, lymph nodes	Yes	Left neck	No
11	White	M	71	1	Midgut	Yes	Mesentery, lymph nodes, liver, various sites within the midgut	Yes	Left neck	No
12	White	M	41	1	Midgut	Yes	Mesentery, lymph nodes, various sites within the midgut	Yes	Left neck	No
13	White	M	48	NA	Midgut	Yes	Mesentery, lymph nodes, various sites within the midgut	Yes	Left neck	No
14	White	F	70	NA	Unknown	No	Mesentery, liver	No	Right neck	No

F, female; M, male; NA, not available.

ing pulsatile tinnitus (patient 1).¹³ Compression of the glossopharyngeal nerve near the carotid body can cause disturbance of taste because the general sensation for the posterior third of the tongue is supplied by this nerve (patients 2 and 7).^{14,15} Compression of the recurrent laryngeal nerve can cause voice hoarseness (patient 8). If the metastatic nodes are numerous or boggy and biologically active in producing serotonin, the patient can suffer from carcinoid syndrome (patient 3). Obviously, with the tumor infringing on nerves, radicular pain (patient 4) and aerodigestive tract—compression symptoms (patient 5) are easily conceivable.

Most of the patients in our series have left-sided neck/upper mediastinum lymph node metastasis simply because the major lymphatic drainage channel of gastrointestinal tract, namely the thoracic duct, is located in the left upper mediastinum and lower neck. With extensive lymphatic node metastasis, the thoracic duct can be compressed and/or obstructed, which in turn results in the shunting of lymphatic drainage to the right neck and a bilateral positive OctreoScan. However, patients that present with an isolated positive scan of the right neck require additional imaging studies before surgical exploration because the thoracic duct, in general, does not traverse the right neck.

Five of the 14 patients in our series continue to elude surgical exploration because either the patient or their referring physician believes these metastases are inconsequential and can be ignored (Table 2). This demonstrates that reports of the clinical implications of cervical and upper mediastinal lymph node metastases are needed to educate and change the mindset of patients and, more importantly, the physicians taking care of these patients.

CONCLUSIONS

For years, metastatic NETs to the neck or upper mediastinum have been assumed to be asymptomatic and ig-

nored. The true incidence of these metastases among NET patients who have positive OctreoScans was never truly defined and, consequently, neither was their proper management. Our study revealed that the incidence of cervical and upper mediastinal lymph node metastasis from gastrointestinal and pancreatic NETs is up to 8.7% and most of these metastases were symptomatic. The clinical implications of these lesions should not be overlooked and radioguided surgery provides an easy method of resection and symptom resolution. However, a positive OctreoScan of the right neck calls for additional studies before exploration.

Author Contributions

Study conception and design: Wang, Mayhall, Anthony, Campeau, Woltering

Acquisition of data: Wang, Mayhall, Campeau, Boudreaux
Analysis and interpretation of data: Wang, Mayhall, Anthony

Drafting of manuscript: Wang, Mayhall, Woltering

Critical Revision: Wang, Anthony, Campeau, Boudreaux, Woltering

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