

Neuroendocrine tumors (NETs) of unknown primary: is early surgical exploration and aggressive debulking justifiable?

Yi-Zarn Wang¹, Aman Chauhan², Jeffrey Rau¹, Anne E. Diebold¹, Adwoa Opoku-Boateng³, Thiagarajan Ramcharan¹, J. Philip Boudreaux¹, Eugene A. Woltering⁴

¹Division of Surgical Oncology, ²Department of Internal Medicine, Louisiana State University Health Sciences Center, New Orleans, LA, USA;

³Department of Surgery, Ochsner Medical Center, New Orleans, LA, USA; ⁴Neuroendocrine Tumor Clinic, Ochsner Medical Center, Kenner, LA, USA

Contributions: (I) Conception and design: YZ Wang; (II) Administrative support: None; (III) Provision of study materials or patients: YZ Wang, A Chauhan, J Rau, A Opoku-Boateng, T Ramcharan, JP Boudreaux, EA Woltering; (IV) Collection and assembly of data: A Chauhan, J Rau, AE Diebold, A Opoku-Boateng, T Ramcharan, JP Boudreaux, EA Woltering; (V) Data analysis and interpretation: YZ Wang, A Chauhan, J Rau, AE Diebold; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Professor Yi-Zarn Wang, DDS, MD. 200 West Esplanade, Suite 200, Kenner, LA 70065, USA. Email: Ywang@lsuhsc.edu.

Background: Neuroendocrine tumors (NETs) are rare tumors that often present with vague symptoms. Identification and localization of the primary NET can be challenging and the true incidence remains unclear. These patients have been thought to have a poor prognosis compared to those patients with a known primary. Therefore, traditionally the treatments for patients with unknown primaries have been passive and directed towards symptom control and/or cytoreduction of metastatic disease. We hypothesized that NET of unknown primary are predominantly low-grade and easily located surgically and therefore are amendable to surgical debulking and cytoreduction, which will likely increase survival in these patients.

Methods: The charts for all 342 surgical patients, seen in our clinic at Ochsner–Kenner between 1/2009 and 9/2012 were retrospectively reviewed to determine which patients had a pre-operative diagnosis of a “NET with unknown primary”. Twenty-two patients (6.4%) were identified. For these patients, the rate of successful surgical exploration in which a primary site was identified was recorded. Survival for these “unknown primary” patients were compared to a large similar group of NET patients from a recent study collected from this same Ochsner clinic group.

Results: Twenty-two (22/342, 6.4%) NET patients with a pre-operative diagnosis of an unknown primary were explored and cytoreduced. The primary tumor site was identified in all 22 patients (100%). The primary sites identified for these patients were 19 small intestines (86.4%) and 3 pancreatic (13.6%). All 22 patients had low-grade tumors and all were still alive as of 9/2012, not allowing for a survival curve to be generated.

Conclusions: Unknown primary NETs are not associated with a poor prognosis as previously reported. Timely surgical exploration and debulking always results in the identification of the primary and a maximum cytoreduction. Early surgical exploration with aggressive debulking is indicated for the treatment of these patients, as for the known counterpart.

Keywords: Tumor of unknown primary; neuroendocrine tumor (NET); carcinoids

Submitted Aug 09, 2015. Accepted for publication Dec 30, 2015.

doi: 10.3978/j.issn.2304-3865.2016.02.03

View this article at: <http://dx.doi.org/10.3978/j.issn.2304-3865.2016.02.03>

Introduction

Neuroendocrine tumors (NETs) are relatively rare oncologic pathology. NETs with an unknown primary are even rarer which only accounts for less than 5% of all unknown primary gastrointestinal cancers. According to the Surveillance, Epidemiology and End Results (SEER) program data, primary tumor location could not be identified in 4,752 cases among the 35,618 (13%) NETs registered over the last 31 years (1).

NETs of unknown origin were thought to be mostly (90%) poorly differentiated and therefore more aggressive. Polish and colleagues cautioned that the search for the primary in these cases must be weighed against the need to initiate a prompt treatment (2), and NCCN guidelines recommend octreotide therapy, observations, or resection if possible only for metastatic well or moderately differentiated NETs (3). Polish and colleagues also conclude that frequently, the primary tumor site cannot be found despite comprehensive workup (2). We hypothesize that NETs of unknown primary are predominantly low grade, easily localizable surgically, amendable to timely surgical debulking and cytoreduction, which will increase survival in these patients.

Methods

The charts of all 346 surgical patients, seen in our clinic at Ochsner-Kenner between 1/2009 and 9/2012 were retrospectively reviewed to determine the incidence of unknown primary. The rate of successful primary tumor localization and resection was then recorded. Survival for these “unknown primary” patients were then compared to that of a large group of NET patients with a pre-operatively known primary from the same institutional data base. The mortality, the grade of the tumor, and the ability to locate the primary surgically were the main focus of our observation. Institutional Review Board (IRB) approval was obtained to collect the data from patient charts for the research purposes.

Results

A total of 342 patients were seen during the 45-month time span (*Figure 1*). Twenty-two patients (6.4%) were identified with a pre-operative diagnosis of a “NET with unknown primary”. All of these patients had a biopsy proven carcinoid/neuroendocrine

tumor diagnosis and all underwent surgical intervention. The patient demographics are shown in *Table 1*. There are 10 females and 12 males in the study group with an average age of 56. The average length between diagnosis and surgical intervention was 11 months. The primary tumor sites were identified in all 22 patients (100%)—and they were 19 small intestines (86.4%) and 3 pancreatic (13.6%). There is no difference in surgical complications or survival rate while compared to their known counterpart. All 22 patients had low-grade tumors and all are still alive as of 9/2012.

Discussion

Mid gut carcinoid tumors make up the majority of the NETs and are the most commonly occurring intestinal endocrine tumors. The incidence of mid gut carcinoid is estimated to be approximately 1.5 cases per 100,000 of the general population (4). The slow growth rate of most NETs and their nonspecific clinical presentations often allow the disease to progress undetected until late and/or while an acute clinical manifestation such as bowel obstruction or liver metastasis induced carcinoid syndrome occurs. The recently revised general goal for treating these patients is an aggressive one. The focus is now on resecting the primary tumor and regional lymph nodes in conjunction with resection or cytoreduction of the distant metastases (5). Resection of the primary tumor and the mesenteric lymph nodes can lead to a significant reduction in the tumor-related symptoms and result in a survival advantage (6). This survival advantage of the aggressive surgical cytoreduction has been extended even into patients with unresectable metastatic disease (7). Many nonsurgical treatment modalities like chemoembolization and somatostatin analogs therapy can often be adopted to complement the surgical debulking (5). This combination therapy has been proven to further enhance the survival advantage of NETs patients with advance disease (8).

“NETs of unknown primary are a rare “zebra” amongst “zebras”. Attempts were made to identify biological markers to guide the clinical approach to these minority patients. Tumor grade has become the most commonly used marker in helping direct patient management based on its prognostic value (9). In general, the consensus have always been against the surgical exploration and debulking for high grade tumors (2).

It is unclear if unknown primary NET tumors are biologically different from those of known primary sites (10). Nonetheless, they were often labeled as poorly differentiated

and aggressive tumors presumptively. Some clinicians believed and claimed that having an unknown primary site is indicative of a high-grade tumor and are associated with poorer prognosis. As a result of these permissive erroneous observation and assumption, treatment for patients with metastatic NETs of unknown primary has been passive, especially for those who are clinically “stable” or asymptomatic. In rare occasion, the treatments were started

but often only focused on symptomatic control and aiming toward addressing the distant disease without the attempt of identifying and removal of the primary tumor. Platinum based chemotherapy has been recommended for metastatic poorly differentiated disease (11).

Many NETs patients, especially those with unknown primary, are often deemed “unresectable” or declared to be non-surgical candidates by clinicians who are not familiar with the current array of treatments that have been developed (5). Current NCCN guidelines recommends management decision based on grade of differentiation of NET with unknown primary (12). Well differentiated NET are treated with carcinoid tumor protocol whereas poorly differentiated NET are only resected if tumor is local or loco-regional. Metastatic disease is often deemed non-surgical and only chemotherapy is recommended (3).

The results from our study have revealed and confirmed our hypothesis that NETs of unknown primary are

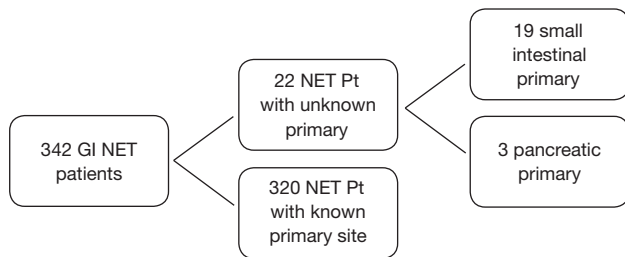


Figure 1 Flowchart illustrating patient distribution. GI, gastrointestinal; NET, neuroendocrine tumor; Pt, patients.

Table 1 Demographics and results of the unknown primary patients

Patient number	Sex	Age at surgery	Diagnosis	Surgery	Interval (months)	Postop primary
1	F	43	5/31/11	7/21/11	2	TI
2	F	66	5/23/07	5/21/09	24	TI
3	M	50	12/15/10	4/28/11	5	TI
4	M	70	10/14/09	3/14/12	29	TI (in Meckels)
5	M	71	3/05/10	11/10/10	8	TI
6	M	67	5/10/10	6/09/11	13	TI
7	F	56	2/26/10	10/28/10	8	TI
8	F	54	7/15/11	3/29/12	8	Pancreas
9	F	46	1/18/08	11/30/11	46	TI
10	F	57	12/01/10	2/16/11	2	TI
11	M	55	7/20/10	11/18/10	4	TI
12	F	48	12/30/11	4/26/12	4	Small bowel
13	M	57	11/29/11	2/29/12	3	Pancreas
14	M	55	2/23/11	2/23/11	0	Pancreas
15	F	45	7/14/09	9/21/09	2	TI
16	M	50	3/17/09	4/07/11	25	Jejunum
17	M	60	5/02/11	9/14/11	4	TI
18	F	57	8/15/11	2/02/12	6	TI
19	M	61	1/28/11	6/30/11	5	TI
20	M	57	3/01/12	3/28/12	1	TI
21	F	60	6/08/10	11/02/11	17	TI
22	M	57	8/24/09	8/24/11	24	TI/Appendix

Interval is the time between the diagnosis date and surgery date. TI, terminal ileum.

predominantly low grade and the primary site can be easily identified by a surgeon with experience. A study from Oregon Health & Science University (OHSU) found that laparoscopic surgical exploration had the highest diagnostic sensitivity (79%) in locating unknown primary NET as compared to radiological imaging, endoscopy or colonoscopy (13). Wang *et al.* were able to successfully locate 86.7% of their GI NET with unknown primary on surgical exploration (14). Molecular fingerprinting techniques via next-generation sequencing, polymerase chain reaction (PCR), immunohistochemistry etc. have been increasingly used for not only finding disease characteristics but also predicting the location of tumors of unknown primary. Although promising, molecular profiling is still in infancy owing to lack of substantial data (15). Molecular fingerprinting is expensive and the routine adaptation preoperatively for tumor localization will further increase the cost of care to NETs patients.

Our data also shows that the surgical outcomes of patients with distant metastasis from an unknown primary appear to be no worse than that of the known group as previously reported (8). The survival for our NETs patients overall have also been proven to be better than that reported and this survival advantage has been attributed to our multi-disciplinary approach and adaptation of a timely aggressive surgical debulking (8). Therefore, we advocate, NET patients with unknown primary who are low risk surgical candidate be aggressively debulked surgically in a timely fashion without the utilizations of any additional costly and low yield pre-op localization studies.

We recognize the limitation of our study, being a retrospective, one with a short follow-up and a small cohort. It is further hampered by the fact that a survival curve couldn't be generated at this time due to the indolent nature of low grade NETs in combination with a short follow-up.

A future longitudinal study with a larger cohort and a longer follow up time will be needed to further endorse our current recommendation in dealing with NETs patients of unknown primary.

Conclusions

Unknown primary NETs are not associated with a poor prognosis as previously reported. Early surgical exploration with aggressive debulking is indicated for the treatment of these patients, as for their known counterparts. All NETs patients with an unknown primary who are low risk surgical candidates should be explored timely.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Wang YZ, Chauhan A, Rau J, Diebold AE, Opoku-Boateng A, Ramcharan T, Boudreaux JP, Woltering EA. Neuroendocrine tumors (NETs) of unknown primary: is early surgical exploration and aggressive debulking justifiable? *Chin Clin Oncol* 2016;5(1):4. doi: 10.3978/j.issn.2304-3865.2016.02.03