

# Management of Appendiceal Neuroendocrine Tumors: Beyond Tumor Size

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## Abstract

**Background:** Appendiceal neuroendocrine tumors (ANETs) less than 2 cm were thought to have no metastatic potential; however, recent evidence including our previous report shows increasing occurrences of regional and metastatic disease in smaller ANETs. We provided an update of patients with ANETs at our institution.

**Methods:** A retrospective review was performed in a follow-up series of patients with ANET who presented to our tertiary referral center from 2019-2020. Demographics, tumor characteristics, treatment, and clinical outcomes were evaluated.

**Cohort update:** In total, 36 patients were included and compared to our previous 114 patients with ANETs who underwent surgical resection. In this updated cohort, we again showed that regional and distant spread is a rare event but can occur in ANETs less than 2 cm. We then discussed the importance of ANET biological factors such as invasion depth, tumor grade, and small vessel invasion and the risk of aggressive disease. Furthermore, we discussed the relevance of lymph node involvement and distant disease as well as the effect of metastasis on outcomes. Lastly, we summarize the work-up and management of a patient with incidental ANET following appendectomy.

**Conclusions:** The complexity of ANET management stems from their incidental discovery, rarity, and overall excellent survival. ANETs less than 2 cm may have metastatic potential and seem to be driven by biological factors such as small vessel invasion, invasion depth, and tumor grade more than primary tumor size. Metastatic disease is the main determinant of survival, whereas the management of regional lymph node metastasis with RH has unproven benefit on long-term outcomes. Patients should be evaluated with individualized care focusing on clinical and pathological risk factors for more aggressive disease which should guide management and surveillance.

## Introduction

In 1987, Charles Moertel and colleagues published a landmark series on 150 patients with appendiceal neuroendocrine tumors (ANET) that showed patients with tumors less than 2 cm in size had no evidence of regional or distant metastasis [1]. This cut-off of 2 cm was a long-carried branch point in ANET management and continues to be a deciding factor for many clinicians to proceed with right hemicolectomy (RH) or stay with appendectomy alone; although, RH was only recommended in select patients with ANETs greater than 2 cm and features of

vascular or mesoappendiceal involvement [1-3]. RH was recommended for ANETs greater than 2 cm to remove potentially involved lymph nodes [1].

The difficulty in studying these patients and establishing concrete recommendations stems from the rarity, incidental discovery, and long-term survival of the disease [4]. Current NCCN guidelines recommend that RH be considered for ANETs that are greater than 2 cm, incompletely resected, with positive nodes, positive margins, or lymphovascular invasion, albeit with a caveat that data is limited concerning survival benefit from RH

[5]. Our group recently published data that supports previous findings that RH showed no survival benefit over appendectomy in our patients with ANETs [6]; however, as in previous studies, a selection bias was present as patients with tumors greater than 2 cm (N=27/30, 90%) or tumors less than 2 cm but with aggressive features were offered RH (N=40/84, 48%) [6-11]. We also observed that 30% (N=34) of our group had regional disease and 18% had metastatic disease (N=20), which are much higher than the rates first reported by Moertel and colleagues [1]. Importantly, when patients were stratified by tumor size (>2 cm, 1-2 cm, or <1 cm), no difference was found in the rate of regional lymph node positivity, metastatic disease, or overall survival (OS). Important findings from our study showed that small ANETs, even less than 1 cm, were capable of regional and distant spread and that features such as small vessel invasion or intermediate tumor grade may be predictive of more aggressive behavior. The important

questions that need to be addressed are (1) which patients are at higher risk for regional and distant spread, (2) does RH change long-term outcome, and (3) does the addition of RH influence ANET morbidity and mortality.

### Cohort Update

Since the completion of our published study consisting of 114 patients evaluated at our institution with a history of surgical resection of ANET, we collected an additional 36 patients as of October 1, 2020 [6]. Again, patients with synchronous or metachronous cancer, with goblet cell carcinoid of the appendix, or with inadequate clinic data were excluded. Table 1 summarizes the demographic and histopathological characteristics of these patients. Median follow-up for this group was only 6 months (range, 1 month – 8 years) as most of these patients have only recently been diagnosed and treated. Most patients underwent

Factors	Previous ANET Cohort N=114	ANET Cohort Update N=36	P value
Mean age at diagnosis, years (SD)	41.04 (17.17)	38.89 (15.48)	0.9
Sex			
Male	32 (28)	14 (39)	0.2
Female	82 (72)	22 (61)	
Surgery			
Appendectomy only	49 (43)	23 (64)	0.04*
Right hemicolectomy	65 (57)	13 (36)	
Mean primary tumor size, cm (SD)	1.48 (1.04)	1.13 (0.86)	0.9
Primary tumor size			
<1 cm	50 (44)	23 (64)	Ref
1-2 cm	34 (30)	8 (22)	0.2
≥2 cm	30 (26)	5 (14)	0.06*
Primary tumor invasion depth			
Muscularis propria	18 (16)	9 (25)	Ref
Subserosa	30 (26)	18 (50)	0.8
Mesoappendix	31 (27)	1 (3)	0.004*
Serosa	28 (25)	7 (19)	0.3
Not assessed	7 (6)	1 (3)	-
Lymphovascular invasion	37 (32)	7 (19)	0.3
Not assessed	10 (9)	6 (17)	

Perineural invasion	31 (27)	7 (19)	0.4
Not assessed	25 (22)	7 (19)	
Mesoappendiceal invasion	67 (59)	19 (53)	0.6
Not assessed	5 (4)	1 (3)	
Tumor grade			
Low	82 (72)	33 (92)	Ref
Intermediate	16 (14)	3 (8)	0.3
Not assessed	15 (13)	0	-

**Table 1:** Demographics and histopathological characteristics of cohort update (N=36) compared to previous ANET cohort (N=114).

appendectomy only (N=23, 64%), while 11 patients (31%) also received additional RH; 2 patients (6%) underwent upfront RH due to 1) ANET diagnosed during colonoscopy and 2) an appendiceal mass incidentally found on imaging. Preoperative diagnoses from the initial appendectomy were as follows: appendicitis (N=28, 82%), appendiceal mass (N=4, 12%), and small bowel obstruction (N=2, 6%). Mean tumor size was  $1.1 \pm 0.9$  cm, which was comparable to our previous cohort with mean tumor size of  $1.5 \pm 1.0$  cm. In addition, 3 patients (8%) had grade 2 (G2) tumors, and utilizing the AJCC 8<sup>th</sup> Edition TNM Staging System, 9 (25%) patients had T1 or T2 lesions, 20 patients (56%) had T3 lesions; and 7 (19%) had T4 lesions. By last follow-up, only one out of 36 patients had positive regional lymph nodes and 2 had metastatic disease. Because of the technique of simple appendectomy, lymph nodes were not present in 29 appendectomy specimens (81%), and of the 11 patients who went on to RH, only one patient had positive lymph nodes. The indications for RH in these 11 patients were: T3 or T4 tumor (N=11), size greater than 1.5 cm (N=5), intermediate grade (N=1), or both size greater than 1.5 cm and intermediate grade (N=1). Both patients with metastatic disease had evidence of peritoneal involvement and both had a T4, low grade tumor; one patient had a 1.5 cm ANET with positive regional lymph nodes, lymphovascular and perineal invasions, and the other had a 3.2 cm ANET with negative lymph nodes and positive perineural invasion. All patients included in the new cohort were alive at the conclusion of this study.

## Biological Aspects of Appendiceal Neuroendocrine Tumors

In our previous paper, our aim was to evaluate the biological aspects and metastatic potential of ANETs and identify potential risk factors for metastatic disease and worse outcomes [6]. Our hypothesis was that in ANETs, characteristics such as small vessel invasion, grade, and

depth of invasion were important prognostic factors and could delineate patients with aggressive disease at increased risk for disease spread. ANET surgical management has been driven by primary tumor size so we first wanted to identify if primary tumors less than 2 cm were capable of lymph node and distant metastasis. Unfortunately, since lymph nodes are rarely observed in appendectomy specimens, our lymph node evaluation was limited mostly to RH specimens, and we did not find any significant predictors of lymph node metastasis. However, we observed that of the 34 patients with involved regional lymph nodes, 50% (N=17) had primary tumors less than 2 cm in size. Additionally, a third of the patients with involved regional lymph nodes (N=11) had primary tumors less than 1 cm in size. When we evaluated risk factors for distant metastatic disease at diagnosis, patients were more likely to be older at diagnosis (mean age 54 vs 38 years old,  $p < 0.0001$ ) and have aggressive biological features such as serosal invasion (HR 9.4,  $p = 0.03$ ), lymphovascular invasion (HR 3.6,  $p = 0.02$ ) perineural invasion (HR 3.0,  $p = 0.08$ ), intermediate tumor grade (HR 3.9,  $p = 0.03$ ), and regional lymph node involvement (HR 11.6,  $p = 0.0001$ ). Importantly, larger primary tumor size was not predictive for metastatic disease at diagnosis as 55% of patients (N=11) with metastatic disease at diagnosis had primary tumors less than 2 cm in size. Lastly, on multivariate analysis, when comparing larger tumor size and other risk factors, intermediate tumor grade trended for worse OS (HR 5.1,  $p = 0.06$ ). Even though ANET grade appears to be a risk factor for metastatic disease and survival, the AJCC Staging System does not yet include grade in ANET prognostic staging groups [12]. In addition, male patients also had worse survival (HR 4.8,  $p = 0.08$ ), however, the reason for this is not well elucidated as men were not more likely than women to have metastatic disease at diagnosis. Although regional lymph node involvement was not associated with worse survival, distant metastatic disease was significant for worse OS (HR 24.4,  $p = 0.008$ ).

## Metastatic Disease

Patients with ANETs, like all patients with cancer, fear disease spread, either to regional lymph nodes or distant sites. We and other studies have questioned the effect of involved lymph nodes on ANET patient survival [6,7,9]. Our previous study showed that about a third of patients who had lymph node evaluation, either at the time of appendectomy or RH, had lymph node involvement [6]. The problem with lymph node evaluation in patients with ANETs is the lack of lymph nodes in most appendectomy specimens; therefore, patients may have involved regional lymph nodes with no evidence of disease progression by the end of our study. In addition, patients with involved regional lymph nodes were mostly discovered from the RH specimens. Because of the retrospective nature of our study, we were not able to ascertain if involved regional lymph nodes were an indicator of metastatic spread or determine if RH and removal of the ileocolic nodal basin was beneficial to ANET survival. Removing locoregional lymph nodes in gastrointestinal cancers serves two main purposes: to adequately stage the patient by AJCC criteria and for locoregional control of disease [13,14]. Unlike most gastrointestinal cancers, the overall indolent nature of most ANETS makes long term survival possible even with nodal involvement, making any survival benefit to additional surgery with RH more difficult to prove. In most gastrointestinal cancers, lymph node involvement is an independent predictor of the risk of future metastatic disease [13,14]. However, all ANET patients with metastatic disease in our study had M1 disease at diagnosis, and during our study period none of the patients with regional nodal involvement but nonmetastatic at presentation progressed to distant metastasis by end of study. This again raises the question of whether the biology of disease and risk of metastatic disease is dictated by the histopathologic features of the primary tumor and that locoregional lymph node sampling by RH is merely an additional staging tool without an impact on outcome. To address this clinical question would require a large, multi-institutional randomized trial comparing observation-only versus RH following appendectomy in ANET patients with an endpoint of disease specific survival. The rarity of the tumor and the indolent nature of most ANETs would make this difficult if not impossible to achieve.

The most important determinant of survival in patients with ANETs is distant metastatic disease; however, even in the metastatic setting, ANET patients often achieve long-term survival [4]. In our previous study, only 8 of the 20 patients with metastatic disease died by end of study with a median time to death of 6.3 years from metastatic ANET diagnosis [6]. In addition, the remaining patients with metastatic ANET were alive at a median of 8.4 years after diagnosis and remain alive at last follow-up. We observed that most patients with metastatic ANET

in our cohort had metastasis to the liver (N=13, 65%) or intra-peritoneal metastasis (N=15, 75%), including in the peritoneum, ovary, mesentery, and fallopian tube. Metastatic disease is an uncommon finding in ANETs and the long-term survival in this setting makes management and surveillance complex.

## Patient Care

Patients with ANET were most often diagnosed following appendectomy from an outside hospital for appendicitis with an incidental ANET, as high as 78% in our initial study and 82% in our updated cohort. Features such as tumor size, grade, small vessel invasion, margin status, and depth of invasion should be made available for more informed patient management; if these are not reported, these features can be requested by pathology. Unfortunately, most appendectomy specimens will not contain lymph nodes for evaluation and management guidance, up to 66% in our initial study and 86% in our updated cohort. Following an incidental ANET diagnosis, a thorough history and physical should be performed focusing on metastatic symptoms consisting of fatigue, weight loss, chronic abdominal pain, or early satiety and carcinoid symptoms consisting of facial flushing, diarrhea, and dyspnea [5]. In the absence of conclusive evidence showing a benefit of RH in the setting of localized ANETs with high-risk features, the risks and benefits of RH should be discussed with patients and at a multidisciplinary conference for individualized patient care. Colonoscopy should be discussed with patients diagnosed with ANET who are over the age of 50 [15], as we observed 9 patients (8%) with a synchronous or metachronous colorectal adenocarcinoma by the end of the study. Observation and surveillance of ANETs may be a valid option in many patients, especially those with (1) less aggressive features/low risk of metastasis, (2) older age, (3) comorbidities and/or (4) high operative morbidity [15]. There is insufficient data to support routine screening with biochemical testing or NET specific imaging in patients with ANETs, especially in patients without high-risk features [5,15]. Postoperative surveillance commonly consists of annual examinations with optional biological testing and/or NET-specific imaging for patients with high-risk features or advanced disease [5,15].

## Concluding Note

In conclusion, the lack of level 1 evidence in the management of ANETs is a result of the incidental discovery, rarity, and overall excellent survival, even in the metastatic setting. ANETs less than 2 cm (even less than 1 cm) may have metastatic potential and seem to be driven by biological factors such as small vessel invasion, invasion depth, and tumor grade more than primary tumor size. Metastatic ANET is the main determinant of

survival, whereas the management of regional lymph node metastasis with RH has unproven benefit on long-term outcomes. Treatment decisions should weigh the potential benefits versus the known morbidities of RH. Patients should be evaluated with individualized care focusing on clinical and pathological risk factors for more aggressive disease which should guide management and surveillance. A large, multi-institutional randomized trial comparing observation-only versus RH following appendectomy in patients diagnosed with localized ANET would be necessary to delineate the role of RH in ANETs.

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