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Title Page

Unmet Needs in Appendiceal Neuroendocrine Neoplasms

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Abstract

Appendiceal neuroendocrine neoplasms (ANEN) are mostly discovered coincidentally during appendectomy and usually have a benign clinical course, thus appendectomy alone is considered as curative. However in some cases a malignant potential is suspected and therefore additional operations, such as completion right hemicolectomy, are considered. The existing European Neuroendocrine Tumour Society (ENETS) guidelines provide quite useful data about epidemiology and prognosis, as well as, practical recommendations with regards to the risk factors for a more aggressive disease course and the indications for a secondary operation. However, those guidelines are based on heterogeneous and retrospective studies. Therefore, the evidence does not seem to be robust and there are still unmet needs in terms of accurate epidemiology and overall prognosis, optimal diagnostic and follow-up strategy, and identified risk factors, which would indicate a more aggressive surgical approach at the beginning and a more intense follow-up. In this review, we are attempting a critical approach of ENETS guidelines and published series for ANEN, focusing on the above noted “grey areas”.

Introduction

Appendiceal neuroendocrine neoplasms (ANEN) represent 50-77% of all appendiceal neoplasms [1]. ANEN are mostly discovered coincidentally during appendectomy, run predominantly a benign clinical course, and for that reason, appendectomy alone is, quite often, curative. However, in some cases, a malignant potential is suspected and therefore additional operations, such as completion right hemicolectomy (RHC), are offered to the patients, at the time of diagnosis. The recent European Neuroendocrine Tumour Society (ENETS) guidelines provide quite useful data about epidemiology and prognosis, as well as, practical recommendations with regards to the risk factors for a more aggressive disease course and the indications for a secondary operation [2]. However, ENETS guidelines for ANEN are based mainly on retrospective studies, which quite often include heterogeneous cohorts of patients, consisting of not only ANEN, but also goblet cell appendiceal tumours as well as proximal colon neuroendocrine neoplasms. Therefore, the evidence does not seem to be robust and there are still unmet needs in terms of: a) accurate epidemiology and overall prognosis, b) optimal diagnostic and follow-up strategy, and c) identified substantial risk factors, which would indicate a more aggressive surgical approach at the beginning and a more intense follow-up.

In this review, we are attempting a critical approach of the ENETS guidelines for ANEN, focusing on the above noted “grey areas” and suggesting potential clinical trials for further clarification of the unmet needs. We are also reporting on current practice, as suggested by the members of ENETS Advisory Board, regarding diagnostic evaluation following appendectomy, indications for right hemicolectomy, as well as duration of follow-up.

Methods

An electronic literature search of the PubMed database was performed using the following search terms: 'appendiceal carcinoid' (Title/Abstract), 'carcinoid of the appendix' (Title/Abstract), and "appendiceal neuroendocrine tumors" (Title/Abstract). Only full articles published in peer-reviewed journals and in English were included.

A Web-based survey was constructed, consisting of 5 questions with multiple choice answers and gathering information on: (1) indications for cross-sectional imaging following appendectomy for ANEN, (2) indications for Somatostatin Receptor Imaging following appendectomy for ANEN, (3) indications for a completion RHC, based on one or more risk factors, (4) duration of follow-up of ANEN with positive lymph nodes, following RHC, (5) need/duration of follow-up of ANEN with no lymph node (LN) invasion, following RHC. The Survey was administered via e-mail to 47 members of ENETS Advisory Board, representing the current practice in their Neuroendocrine Tumour Units.

Epidemiology – Prognosis

There are important geographical differences in the incidence of ANEN. In Western countries, ANEN represent about 20% to 25% of all gastrointestinal neuroendocrine tumours (NEN), in contrast to 5-10% in Asian countries. A comparable difference has been found in the SEER registry, in which the incidence of ANEN was found to be very much higher in White and African Americans, than in Asian and Amerindian Americans [1]. Interestingly, the trend of increasing incidence recently observed for many NEN seems not to be verified for ANEN, in which the incidence was found to be stable or even decreasing [3,4].

The two main controversial points in ANEN epidemiology are: a) whether ANEN are truly associated with a risk of distant metastases, which will affect the overall prognosis and b) whether there is a risk of regional LN metastases, if tumours are measuring < 1 cm. A small percentage of distant metastases from ANEN has been reported in several series, but it is not clear in any of the reports, whether those metastases were associated with well differentiated (WD) NEN. In Yao's paper from the SEER database published in the "Journal of Clinical Oncology" in 2008, that is the largest series of NEN ever published, ANEN were representing 12% of all NEN, but it is not clear whether all of them were WD NEN as several ICD-O codes were utilized, including those of "goblet cell", "adenocarcinoid" and carcinoid [1]. Quaevedlie et al reported that 1.5% of ANEN presented with distant metastases [5]. The authors of that study reported that ICD-O code for goblet cell carcinoid (GCC) was not considered, therefore those should be all ANEN. However, in that study, it was not clear: a) if some of the tumours were poorly differentiated (PD), b) what was the tumours' size and c) whether in the two cases of advanced ANEN, distant metastases were synchronous or metachronous. Hsu et al. reported that "malignant appendiceal carcinoid tumors (MCT), identified with ICD-O-3 code 8240, had distant metastases in 1.9 % of cases, and this was noted more frequently when the primary tumor was > 2 cm. Unfortunately, no related references were mentioned [6].

In a recent paper, based on a two decade-analysis of 977 pathological reports of ANEN in The Netherlands, 1% of well differentiated ANEN were reported as metastatic, whereas 25% of large cell neuroendocrine carcinomas (only 8 cases out of a total of 977) were metastatic at diagnosis [3].

In a recently published series, Pawa et al [7], reported that 0.9% of a homogeneous cohort of ANEN had distant metastases at the time of diagnosis. One of the 2 patients, had a Grade 2 tumour with Ki67: 8%, that was T3N1, (as per TNM staging). The other patient, surprisingly, had a Grade 1 and T2N0 tumour (TNM), which, however, had displayed invasion into muscularis propria and mesoappendix.

Regional LN metastases from ANEN, measuring < 1cm, were reported in up to 17% [8,9]. Groth et al. reported that for RHC patients who had at least 12 lymph nodes (LN) examined, patients with LN metastases had poorer specific survival rates (74.3%; 95% CI: 47.9 – 88.7%) as compared with patients without LN metastases (93.4%; 95% CI: 80.2 – 97.9%) [8]. Mullen et al. reported a 15% risk of LN metastases from < 1 cm ANEN, but no difference in terms of survival was observed, with 100 % survival at 10 years for both ANEN with positive and negative LN metastases [9]. Interestingly, while in the Groth's paper, the ICD-O3 codes, that were utilized, included also mixed carcinoid tumors (codes 8243 and 8245), in Mullen's study only typical ANEN were included (codes 8240 and 8241). Furthermore in Groth's study, the odds for LN metastasis in patients with tumours measuring 1.0 – 1.9 cm was not significantly different than tumours <1.0 cm. Finally, in the 2017 publication of SEER database including 674 patients with ANEN, 11% of patients with tumours measuring < 1cm, had LN metastases. However, in that database the presence of LN metastases does not seem to have any implication to the overall prognosis, as the 10-year survival rate of the whole group of patients with ANEN was 92.6% [10].

ANEN, may rarely coexist with other neuroendocrine or non-neuroendocrine malignancies. In the series of Pawa et al, 1.86% of their patients had synchronous neoplasms (ileal neuroendocrine neoplasms or colonic adenocarcinomas) [7].

Finally, in terms of overall survival, associated to the surgical intervention that was carried out, McGory reported a 5-y survival rate of 94% in patients, who had undergone appendectomy vs. 83% for those with RHC [11]. Similar trend was observed by Groth, who reported a 10-y survival rate of 85% for patients, who had undergone appendectomy vs. 72% for those with RHC [8]. Again, it is not clear, whether in those series only well-differentiated ANEN were included.

Initial diagnostic work-up

Following confirmation of ANEN in post-appendectomy specimens, there is a question whether estimation of NEN biomarkers [such as Chromogranin-A (CgA) levels or 5-HIAA (5-hydroxy-indol-acetic-acid) in a 24h urine sample or in plasma] is justified. Even in the presence of regional lymphadenopathy, CgA will most likely be normal, whilst ANEN are very rarely functional and thus 5-HIAA will not be raised either. Those biomarkers, however, may be utilized in the rare scenario of distant metastases at presentation.

With regards to cross-sectional imaging, while it has been suggested that all patients with ANEN measuring > 2 cm and those with > 3mm mesoappendiceal infiltration or angioinvasion need to undergo either CT or MRI, it is not clear whether imaging studies are indicated in ANEN, measuring between 1-2 cm. The majority of NEN physicians (66.6%) who participated in the web survey, would request cross-

sectional imaging studies in patients with ANEN measuring 1-2 cm, in the presence of any of the following risk factors: Grade 2 tumours, tumours located in appendiceal base, and tumours with deep mesoappendiceal infiltration or angio- or lymphatic invasion.

However, it would be useful to identify whether cross-sectional imaging studies are able to detect regional lymph nodes in those scenarios and therefore justify the need for an additional operation. Only 4.1% of the Web-survey participants would request cross-sectional imaging in ANEN, measuring < 1cm (in the absence of other risk factors), and this approach has not been supported by the current ENETS guidelines.

Finally, although it has been recommended by ENETS guidelines that Somatostatin Receptor Imaging (SRI) needs to be performed in ANEN measuring > 2 cm and those with > 3mm mesoappendiceal invasion or angioinvasion, 20.8% of the Web-survey participants do not feel that extra radiation exposure (especially in young patients) through SRI is justified.

Risk factors – Criteria for a completion Right Hemicolectomy

In recent and previous ENETS guidelines, a set of criteria have been proposed for a completion RHC, as several risk factors had been identified that could be associated with loco-regional spread and potentially more aggressive disease course. Those factors are associated with: a) tumour size, b) meso-appendiceal invasion, c) tumour grade, d) tumour location, e) angio- or lymphatic invasion. Those factors were identified in retrospective series, which reported synchronous LN or synchronous/metachronous distant metastases, when any of those factors were present. Although tumour size > 2cm seems to be the most established risk factor, the importance of each one of the others remains debatable.

- Tumour size

Tumour size is the most used stratification factor in patients with ANEN. Whereas in small tumours ≤ 1 cm the risk of LN metastases is low [12] and the risk of distant metastases is negligible, tumours of > 2cm are associated with increased risk of regional LN involvement (30-80%) [12,13] and distant metastases (4.1%) [6]. Therefore, appendectomy alone is the standard surgical approach for ANEN ≤ 1 cm and appendectomy followed by completion RHC is performed for ANEN >2cm, although a survival benefit for RHC versus appendectomy is not proven. Interestingly, a recently published multicenter retrospective study, including 435 patients, suggested the new cutoff of 1.55 cm, as one of the independent predictors of LN involvement [14]. The intermediate size (1-2 cm) is indeed challenging. In a recently reported series [7], LN metastases were revealed at 24.1% with ANEN between 1 and 2 cm in size, who underwent a subsequent RHC, based on other risk factors. Therefore, most authors recommend a simple appendectomy for that category, unless any of the other risk factors like any mesoappendiceal invasion, angioinvasion or increased proliferation rate is present [2]. On the contrary, in a recently published large series, none of the above noted risk factors seem to be associated with lymph node involvement in ANEN measuring 1-2 cm. In particular, 21.4% of patients with tumours 1-2 cm had LN involvement but none of the risk factors present, whereas 6 of 7 patients with more than 2 risk factors had no invasion of lymph nodes at RHC [15].

- Mesoappendiceal invasion

Any mesoappendiceal invasion (MAI) by ANEN can be demonstrated in 30–40% of children and 33–57% of adults [13]. The possibility of LN metastases from ANEN with any MAI was initially estimated as ~ 1% [16], however at least three reports demonstrated a higher potential for metastatic spread with tumours in the setting of any MAI, of up to 38% [17–19]. Moreover, in a review of 414 cases of ANEN reported in the literature, both tumours > 2 cm and MAI were related to metastatic disease [16]. In contrast, other studies did not find that MAI predicts residual or metastatic disease. In the analysis by Moertel et al. [12] of 86 patients followed for > 10 years, 7% had lesions at the base of the appendix and 64% had involvement of the MAI or the peritoneum, however none have recurrent or metastatic disease following simple appendectomy.

In a paediatric series, 30% of 23 patients had MAI, and despite the fact that only two children underwent a RHC and one more underwent removal of a residual appendiceal stump, no extra-appendiceal disease was found in the RHC specimens and no metastatic disease was identified after a median follow-up period of 26 years [22]. The prognostic significance of MAI remains controversial, but its relationship to distant metastases development has been reported as up to 4.1% and cannot be ignored [12,16]. MAI was reported as the only aggravating factor to suggest potentially aggressive behaviour in one case report with liver metastasis occurring after appendectomy from a 0.6 cm ANEN [21]. In the current ENETS guidelines, an MAI depth of > 3mm is utilized as a criterion to distinguish T2 to T3 tumours in TNM classification [2]. It seems though, that the 3 mm limit has been set up, rather arbitrarily, as there are no clear data in the literature to substantiate that 3 mm is the valid size limit for performing or not performing an extended operation. In a multicenter study including adult patients, five of 13 patients with a tumour size between 1 and 2 cm (38%) presenting with MAI <3 mm had metastatic disease to the lymph nodes at RHC [20]. On the contrary, despite MAI being present in 39.3% of their patients, the authors of the large, recently published, retrospective study from Italy, did not find any association with LN involvement at multivariate analysis [14]. Among the web-survey participants, only 20.8% of the will recommend RHC in any MAI, whilst the vast majority (75%) will accept only deep MAI (> 3mm), as a risk factor.

Tumour grade

Tumour proliferation markers may predict metastatic potential [23–26], and a high Ki-67 proliferation index has been shown to be predictive of aggressive biological behaviour in gastro-entero-pancreatic NEN [27]. Almost all ANEN are well-differentiated. Hence, it has been suggested that a raised mitotic index and/or a high Ki-67 may be indicative of a more malignant behaviour and could thus also be considered as an indication for RHC [2]. Initial results in ANEN demonstrated that, increased Ki-67 was associated with decreased survival [21], but no clear correlation

was demonstrated between Ki-67 and tumour size or presentation with metastatic disease.

Also, in a multicenter retrospective study of 138 ANEN, the authors suggested that WHO 2010 NEN grading system (in contrast to TNM staging) is not a predictor of adverse clinical outcome [28].

However, more recent data from multicenter studies, demonstrate that ANEN of > G1 have got a high metastatic potential, at least, for regional LN metastases. Grozinsky-Glasberg S et al, reported that 17% of the patients of their series, had a Ki-67 >2% and 50% of them (2 of 4) had lymph node metastases [20].

Also Pawa et al showed that all 4.7% of their patients had G2 and G3 ANEN, and all of those patients had locoregional lymph node metastases at RHC [7]. The majority (68.7%) of the web-survey participants would recommend a right hemicolectomy for any ANEN of Grade 2 or Grade 3.

- Additional risk factors

Vascular invasion has been considered as another risk factor, which would indicate the need an additional operation. Grozinsky-Glasberg et al reported vascular invasion in 3.6% of their series and in 60% of them, LN metastases were revealed [20]. Kleiman et al [29], demonstrated that even for ANEN measuring <2cm, there is increased incidence of LN dissemination when the angioinvasion was present, despite the absence of other worrisome pathologic features. Disease recurrence was noted only in 1 of their 8 patients with LN metastases (liver metastases developed approximately 6 months after primary surgery) and in none of the patients with localized ANEN. However, the overall survival was 100% in both groups.

The minority of ANEN (7-10%) are located at the base of the appendix. In that location, incomplete resections may occur and this may explain the presence of LN metastases, as shown in the studies of Alexandraki et al and Grozinsky-Glasberg et al [25,20]. Both series reported residual LN disease in 40% and 44% of patients respectively. However, there is no information whether those findings affected the overall patients' prognosis. The importance of regional LN metastases, in relation to the overall disease prognosis, has also been questioned in the series of Pawa et al [7]. Although 24.4% of their ANEN patients were found to have LN metastases at completion RHC (based on existing Guidelines), no recurrence and no disease related deaths was noted in any of those patients.

Finally, it has not been clear whether a completion RHC is needed in tumours, which despite measuring < 1cm, they have been classified as T4 in TNM staging, based on serosal breach in the appendectomy specimen. As per ENETS guidelines, any T4 ANEN are not considered a limited disease and therefore an additional operation seems to be justified [2]. In the large study published from the French Group for the study of Neuroendocrine Tumours, 13 patients had T4 disease. However, of those, 9 underwent RHC and LN involvement was noted in only 33%, whilst no tumour recurrence was noted in those 4 patients, who did not have an additional surgical procedure [15].

Follow-up strategy

Clinical utility of follow-up of patients after resection of ANEN is closely coupled to prognosis. It has to be taken into account that prognostic scores are based on retrospective series and registry data, mostly on the basis of pathological diagnosis after initial surgery. In addition, overall survival is usually registered without any information on disease-free survival.

Furthermore, it is currently unclear whether early detection of disease recurrence will alter patients' prognosis.

- Indications for follow-up

It has been widely accepted that: a) follow-up of ANEN < 2cm without risk factors, is not needed, as appendectomy alone is considered as curative and b) in the rare scenario of distant metastases associated with ANEN or whenever ANEN co-existed with other NEN, long-term follow-up is mandatory and needs to be similar to that of patients with advanced small bowel NEN.

For the other groups, such as: a) patients who, for some reason, had just an appendectomy, despite the presence of risk factors, b) patients who had RHC, because of any risk factors, but without LN metastases and c) patients who had RHC, because of any risk factors and were found to have lymph nodal metastases in the resected specimen, the decision for follow-up is based upon the presumed importance of each risk factor and the association of regional LN metastasis with the disease outcome and overall prognosis.

Based on the current ENET guidelines, no follow-up is needed in patients who did not have LN invasion at the time of RHC [2]. However, the long term risk of local/distant disease recurrence in that group and whether the absence of regional LN invasion excludes the subsequent development of distant metastases, remain unclear. Interestingly, whilst 35% of the web-based questionnaire participants would not follow-up those patients, the majority would be rather concerned and follow them up for, either 5 years (35%), 10 years (17%), or even 15 years (13%).

The guidelines suggest that all patients with documented LN metastases will need to be followed-up. However, the duration of follow-up and the appropriate follow-up modalities are still not entirely clear. Among the web-based questionnaire participants, 42% would follow-up those patients life-long, whilst 17% only for 5 years, 31% for 10 years and 10% for 15 years.

- Follow-up modalities

As noted in the initial diagnostic work-up, the utility of the established NEN biomarkers that are routinely used in small bowel NEN, is doubtful. 5-HIAA would be normal in the absence of carcinoid syndrome and CgA may be still within normal limits, even in presence of loco-regional metastases, especially if the tumour load is low. The decision for imaging modalities needs to be adapted to patients' age and comorbidities. Patients with ANEN are often diagnosed at a young age and recurrence may occur after a long period of time. In low risk groups and young age, radiation should be avoided rendering sonography and MRI preferred methods. SRS imaging should be reserved for patients with known focal lesions. In older patients and patients with high risk or distant metastases CT or MRI together with SRS imaging are the methods of choice.

Future developments

The majority of ANEN measure < 2cm, do not harbor any risk factors and appendectomy alone is curative. However, several controversies remain for some patients, in whom several risk factors have been identified. Those patients may have to undergo an additional operation and a proportion of them will need long term follow-up, as per the existing guidelines. Although data from recently published large and homogeneous series seem to agree that tumour size (> 1.55 cm), lymphovascular invasion and > G1 tumours are associated with the development of loco-regional metastases [7,14,15], the true importance of the other risk factors is not entirely clear. Also, the true prognostic implication of regional LN metastases and their definite association with a risk of subsequent development of distant metastases needs to be better defined. Those concerns are supported by the absence of loco-regional or distant recurrence, in some patients, who, did not have (for any reason) a RHC, despite the presence of the known risk factors [7,15].

Good quality studies need to be designed, as they may resolve those "grey areas". For example, a multicenter international large retrospective trial could include all patients who underwent a completion RHC (or a limited ileo-caecal resection) for any of the known risk factors, addressed in the existing guidelines. The presence of LN metastases, post RHC, could then help to identify the predictive role of each one of the risk factors, for that loco-regional spread. Also, taking into account, that patients with LN metastases would have been followed-up by the vast majority of the NEN Units, information could be obtained, with regards to the risk of disease recurrence. It would be interesting also to identify: a) what should be the standard approach of lymphadenectomy during the prophylactic operation and b) whether a more limited ileo-caecal resection, rather than an oncological right hemicolectomy, would be sufficient in some patients.

Furthermore, novel serum biomarkers such as circulating transcripts and molecular markers, including tissue expression of NAP1LI, MAGE-D2, and MTA1 may provide more information in the future, with regards to identification of residual disease post-appendectomy and overall disease prognosis [30,31]. However, more data are needed, before establishment of those new biomarkers in clinical practice.

Finally, the benefit of adjuvant medical treatment in patients who are found to have lymph node metastases at RHC (as per current practice in appendiceal adenocarcinomas) could be assessed in prospective studies.

The resolving of controversies in ANEN is mandatory, as many of these patients are young and some of them may be over-treated, through an additional operation. Although RHC is not a technically challenging procedure nowadays and almost always performed laparoscopically, its morbidity/mortality cannot be ignored. All decisions ideally should be individualized, well-supported and balanced between the risks and benefits. Finally, well-designed clinical trials, with long-term patients' follow-up are required to identify accurately the most important risk factors which could be associated with regional or distant metastases and potentially adverse outcomes.

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.
2. Pape UF, Niederle B, Costa F, Gross D, Kelestimur F, Kianmanesh R, Knigge U, Öberg K, Pavel M, Perren A, Toumpanakis C, O'Connor J, Krenning E, Reed N, O'Toole D: ENETS Consensus Guidelines for Neuroendocrine Neoplasms of the Appendix (Excluding Goblet Cell Carcinomas). *Neuroendocrinology* 2016, 103(2):144-152.
3. Korse CM, Taal BG, van Velthuisen ML, Visser O. Incidence and survival of neuroendocrine tumours in the Netherlands according to histological grade: experience of two decades of cancer registry. *Eur J Cancer*. 2013. May;49(8):1975-83
4. Mocellin S, Nitti D. Gastrointestinal carcinoid: epidemiological and survival evidence from a large population-based study (n = 25 531). *Ann Oncol*. 2013 Dec;24(12):3040-4.
5. Quaedvlieg PF, Visser O, Lamers CB, Janssen-Heijen ML, Taal BG: Epidemiology and survival in patients with carcinoid disease in the Netherlands. An epidemiological study with 2,391 patients. *Ann Oncol* 2001;12:1295–1300.
6. Hsu C, Rashid A, Xing Y, Chiang YJ, Chagpar RB, Fournier KF, Chang GJ, You YN, Feig BW, Cormier JN.: Varying malignant potential of appendiceal neuroendocrine tumors: Importance of histologic subtype. *J Surg Oncol* 2013;107:136-143.

7. Pawa N, Clift AK, Osmani H, Drymoussis P, Cichocki A, Flora R, Goldin R, Patsouras D, Baird A, Malczewska A, Kinross J, Faiz O, Antoniou A, Wasan H, Kaltsas GA, Darzi A, Cwikla JB, Frilling A. Surgical Management of Patients with Neuroendocrine Neoplasms of the Appendix: Appendectomy or More. *Neuroendocrinology*. 2018;106(3):242-251.
8. Groth SS, Virnig BA, Al-Refaie WB, Jarosek SL, Jensen EH, Tuttle TM.: Appendiceal carcinoid tumors: Predictors of lymph node metastasis and the impact of right hemicolectomy on survival. *J Surg Oncol* 2011; 103:39–45.
9. Mullen JT, Savarese DM.: Carcinoid tumors of the appendix: a population-based study. *J Surg Oncol*. 2011 Jul 1;104(1):41-4.
10. Mehrvarz Sarshekeh A, Advani S, Halperin DM, Conrad C, Shen C, Yao JC, Dasari A. Regional lymph node involvement and outcomes in appendiceal neuroendocrine tumors: a SEER database analysis. *Oncotarget*. 2017 Aug 19;8(59):99541-99551.
11. McGory ML, Maggard MA, Kang H, O'Connell JB, Ko CY.: Malignancies of the appendix: Beyond case series reports. *Dis Colon Rectum* 2005;48:2264 – 2271.
12. Moertel CG, Weiland LH, Nagorney DM, Dockerty MB: Carcinoid tumor of the appendix: treatment and prognosis. *N Engl J Med* 1987, 317(27):1699-1701.
13. Mullen JT, Savarese DM: Carcinoid tumors of the appendix: a population-based study. *J Surg Oncol* 2011, 104(1):41-44.
14. Brighi N, La Rosa S, Rossi G, Grillo F, Pusceddu S, Rinzivillo M, Spada F, Tafuto S, Massironi S, Faggiano A, Antonuzzo L, Santini D, Sessa F, Maragliano R, Gelsomino F, Albertelli M, Vernieri C, Panzuto F, Fazio N, De Divitiis C, Lamberti G, Colao A, Fave GD, Campana D. Morphological Factors Related to Nodal Metastases in Neuroendocrine Tumors of the Appendix: A Multicentric Retrospective Study. *Ann Surg*. 2018 Jul 10. doi: 10.1097/SLA.0000000000002939. [Epub ahead of print]
15. Rault-Petit B, Do Cao C, Guyétant S, Guimbaud R, Rohmer V, Julié C, Baudin E, Goichot B, Coriat R, Tabarin A, Ramos J, Goudet P, Hervieu V, Scoazec JY, Walter T. Management and Predictive Factors of Lymph Node Metastasis of Appendix Neuroendocrine Tumors: A National Study from the French Group of Endocrine Tumors(GTE). *Ann Surg*. 2018 Mar 19. doi: 10.1097/SLA.0000000000002736. [Epub ahead of print]
16. Alexandraki KI, Kaltsas G: Gastroenteropancreatic neuroendocrine tumors: new insights in the diagnosis and therapy. *Endocrine* 2012, 41(1):40-52.
17. Rossi G, Valli R, Bertolini F, Sighinolfi P, Losi L, Cavazza A, Rivasi F, Luppi G: Does mesoappendix infiltration predict a worse prognosis in incidental neuroendocrine tumors of the appendix? A clinicopathologic and immunohistochemical study of 15 cases. *American journal of clinical pathology* 2003, 120(5):706-711.
18. Ponka JL: Carcinoid tumors of the appendix. Report of thirty-five cases. *American journal of surgery* 1973, 126(1):77-83.
19. Syracuse DC, Perzin KH, Price JB, Wiedel PD, Mesa-Tejada R: Carcinoid tumors of the appendix. Mesoappendiceal extension and nodal metastases. *Annals of surgery* 1979, 190(1):58-63.
20. Grozinsky-Glasberg S, Alexandraki KI, Barak D, Doviner V, Reissman P, Kaltsas GA, Gross DJ: Current size criteria for the management of neuroendocrine tumors of the appendix: are they valid? Clinical experience and review of the literature. *Neuroendocrinology* 2013, 98(1):31-37.

21. MacGillivray DC, Synder DA, Drucker W, ReMine SG: Carcinoid tumors: the relationship between clinical presentation and the extent of disease. *Surgery* 1991, 110(1):68-72.
22. Moertel CL, Weiland LH, Telander RL: Carcinoid tumor of the appendix in the first two decades of life. *Journal of pediatric surgery* 1990, 25(10):1073-1075.
23. Solcia E, Rindi G, Paolotti D, La Rosa S, Capella C, Fiocca R: Clinicopathological profile as a basis for classification of the endocrine tumours of the gastroenteropancreatic tract. *Annals of oncology : official journal of the European Society for Medical Oncology* 1999, 10 Suppl 2:S9-15.
24. Liu E, Telem DA, Hwang J, Warner RR, Dikman A, Divino CM: The clinical utility of Ki-67 in assessing tumor biology and aggressiveness in patients with appendiceal carcinoids. *Journal of surgical oncology* 2010, 102(4):338-341.
25. Alexandraki KI, Griniatsos J, Bramis KI, Ballian N, Dimitriou N, Giannakakis T, Tsigris C, Felekouras E, Kaltsas GA: Clinical value of right hemicolectomy for appendiceal carcinoids using pathologic criteria. *Journal of endocrinological investigation* 2011, 34(4):255-259.
26. Pape UF, Perren A, Niederle B, Gross D, Gress T, Costa F, Arnold R, Denecke T, Plockinger U, Salazar R, Grossman A. ENETS Consensus Guidelines for the management of patients with neuroendocrine neoplasms from the jejunum-ileum and the appendix including goblet cell carcinomas. *Neuroendocrinology* 2012, 95(2):135-156.
27. Van Eeden S, Quaedvlieg PF, Taal BG, Offerhaus GJ, Lamers CB, Van Velthuysen ML: Classification of low-grade neuroendocrine tumors of midgut and unknown origin. *Human pathology* 2002, 33(11):1126-1132.
28. Volante M, Daniele L, Asioli S, Cassoni P, Comino A, Coverlizza S, De Giuli P, Fava C, Manini C, Berruti A, Papotti M. Tumor staging but not grading is associated with adverse clinical outcome in neuroendocrine tumors of the appendix: a retrospective clinical pathologic analysis of 138 cases. *Am J Surg Pathol.* 2013 Apr;37(4):606-12.
29. Kleiman DA, Finnerty B, Beninato T, Zarnegar R, Nandakumar G, Fahey TJ, Lee SW: Features Associated With Metastases Among Well-Differentiated Neuroendocrine (Carcinoid) Tumors of the Appendix: The Significance of Small Vessel Invasion in Addition to Size. *Dis Colon Rectum* 2015 Dec;58:1137-43.
30. Modlin IM, Kidd M, Latich I, Zikusoka MN, Eick GN, Mane SM, Camp RL. Genetic differentiation of appendiceal tumor malignancy: a guide for the perplexed.. *Ann Surg.* 2006 Jul;244(1):52-60.
31. Modlin IM, Frilling A, Salem RR, Alaimo D, Drymoussis P, Wasan HS, Callahan S, Faiz O, Weng L, Teixeira N, Bodei L, Drozdov I, Kidd M. Blood measurement of neuroendocrine gene transcripts defines the effectiveness of operative resection and ablation strategies. *Surgery.* 2016 Jan;159(1):336-47.

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