

Review

Neuroendocrine Neoplasms of the Appendix: A Review of the Literature

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Abstract. Appendiceal neuroendocrine neoplasms (ANENs) comprise rare tumors of the appendix, mainly affecting young populations and characterized by a rather favorable prognosis. The aim of this review was to summarize the current knowledge on these neoplasms, focusing on the management and follow-up of such patients, which still remain under debate. ANENs account for 0.16-2.3% of appendectomies and are usually diagnosed incidentally. The histopathological diagnosis includes the immunohistochemical profile of the tumor in regard to synaptophysin and chromogranin A, as well as the Ki-67 index. The surgical management of ANENs is either simple appendectomy or a more extensive oncological operation including right hemicolectomy. This depends on the stage and the presence of risk factors suggesting a more aggressive disease, such as the exact location, mesoappendiceal or lymphovascular invasion, and the proliferative rate of the tumor. Despite their indolent course, ANENs may relapse. Therefore, lifetime observation is necessary for patients with tumors >2 cm and >1 cm plus additional risk factors; however, more studies should be conducted in order to determine the optimal follow-up strategy.

Gastrointestinal neuroendocrine tumors (GI-NETs), otherwise categorized as GI-neuroendocrine neoplasia (GI-

NENs) by the European Neuroendocrine Tumor Society (ENETS) (1), are increasingly diagnosed today with an estimated annual incidence rate of 2-5/100,000 (1-5). Previous epidemiological data showed that appendiceal NENs (ANENs) were the most frequent neuroendocrine neoplasms of the GI tract (6). Nevertheless, their percentage of total GI-NENs has decreased from 17-28% to 2-5%, due to the concomitant overall rise in other types of GI-NEN (7, 8).

ANENs represent the most common tumor of the appendix, found in 0.2-0.7% of all appendectomies (1, 9). Diagnosis most commonly occurs in the second or third decade of life, while ANENs have also been reported in children and young adults (range=4.5-19.5 years) (1, 10, 11). Prognosis of ANENs is greatly dependent on the histological type, malignant potential, stage and grade of the tumor. Importantly, ANENs are associated with the most favorable survival rates compared to other GI-NENs (5).

In 2010, the World Health Organization (WHO) classified ANENs into: well-differentiated NENs/G1 (NET-G1); intermediately differentiated NENs/G2 (NET-G2); poorly differentiated neuroendocrine carcinomas (NEC-G3); and mixed adenoneuroendocrine carcinomas (MANECs) (12). Interestingly, poorly differentiated NECs can be further subdivided into large-cell and small-cell carcinomas (3, 4, 7, 8, 13, 14). Another WHO classification was suggested and was based on the histological type of ANENs (15) as: enterochromaffin cell or serotonin-producing NENs (16), goblet cell carcinoid NETs (GCC) (1), L-cell NENs or glucagon-like peptide-producing and PP/YY-producing NENs (9), and, finally, tubular carcinoid NENs (10).

Regarding their management, a simple appendectomy is generally considered adequate and curative for ANENs smaller than 1 cm, whereas tumors larger than 2 cm may also require right hemicolectomy when the appropriate criteria are

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met (17). Interestingly, there is a grey zone for tumors of 1-2 cm. The aim of this review is to summarize the current knowledge on ANENs, focusing on the management of these tumors.

Epidemiology

The vast majority of the recent epidemiological studies show that the appendix constitutes the third most frequent GI-NEN site (16.7%) with the small bowel (44.7%) and the rectum (19.6%) being the most frequently encountered organs (7, 18). A recent Surveillance, Epidemiology, and End Results (SEER) database analysis, however, classified ANENs in fourth place behind NETs of the small intestine, rectum, pancreas and stomach (5). Despite the fact that ANENs are extremely rare in pediatric populations, studies incorporating such patients rank them in first or second place of GI-NENs (7, 19, 20).

ANENs are mostly found incidentally in both adults and children, during or after the surgical treatment of appendicitis or other abdominal diseases (7, 17). ANENs comprise 43-57% of the primary tumors of the appendix and are responsible for about 0.16-2.3% of all appendectomies (7, 21). In a large recent review study from three referral centers for NENs, ANENs were diagnosed in 215 out of the 14,850 (1.86%) appendectomies that took place between 2001 and 2015 (22). During 1998-2001, ANENs were the most frequent neoplasms of the appendix (17.3-19.7%), whilst their prevalence decreased to 9.4% in subsequent years when more strict inclusion criteria were applied (23, 24). In another SEER database study concerning ANENs, Hsu *et al.* showed that the most frequent histological type was GCC (59.6%), followed by other malignant NENs (32.1%) and then by mixed GCC (6.9%) (25).

There seems to be a slight female predominance for ANENs, whereas small bowel NENs are more common in men. In contrast to other appendiceal tumors and other NENs, which tend to occur in older patients (7), ANENs show highest incidence rates at 15-19 years of age in women and 20-29 years in men (7, 26). The mean age of patients in the latest study by Pawa *et al.* was 33.2 (range=7-79) years, with a female predominance (60.5%) (22). Other studies suggest a slightly increased age for the development of ANENs (32-42 years of age), including a large series from the Netherlands (7, 27).

Pathogenesis - Histopathology

NENs of the appendix arise from the subepithelial neuroendocrine cells lying on the *lamina propria mucosae* (2) and the submucosal layer of the appendix wall (28, 29). It was in 1928 when Masson first defined these subepithelial cells as the origin of ANENs and also proved their mixed

endocrine and neural nature (30, 31). The tip of the appendix hosts the majority of these cells, while the epithelial neuroendocrine cells are distributed equally throughout the appendix. The number of neuroendocrine cells tends to be low in infancy, and increases over time (29). The distinct features of ANENs, as well as their favorable clinical course when compared to GI-NENs deriving from different anatomic parts of the GI tract, can be attributed to their specific origin (29, 32, 33).

NENs. The histopathological diagnosis of NENs includes determination of the immunohistochemical profile of the tumor in regard to synaptophysin and chromogranin A (CgA), as well as the proliferative marker, the Ki-67 index (1). CgA and synaptophysin are the most common markers to confirm the endocrine nature of the neoplastic cells. According to the current WHO and ENETS grading systems, NET-G1 is designated by a mitotic count of <2 per 2 mm^2 (40 \times magnification) and Ki-67 $\leq 2\%$; NET-G2 by a mitotic count of 2-20 per 2 mm^2 or Ki-67 of 3-20%; NET-G3 by mitotic count of >20 per 2 mm^2 or Ki-67 index $>20\%$.

ANENs are usually well- (G1) or intermediately (G2) differentiated (Ki-67 index $<20\%$) (34). It is suggested that G2 NENs carry a higher risk for relapse and metastasis; however, this remains controversial (35). High-grade cases should raise suspicion of a GCC, a MANEC or a 'true' neuroendocrine carcinoma (NEC-G3); nonetheless the latter is considerably infrequent (1, 17, 36, 37).

Observational studies have shown that G1 and G2 ANENs have an indolent clinical course, and only a minority develop in a more disseminated manner (38). In addition, G1 NENs constitute the vast majority of ANENs, whilst NECs and MANECs are relatively uncommon in the appendix (15). On these grounds, there is a debate on the need for postoperative investigation for residual disease in such patients, as well as about the nature and the duration of their follow-up (39, 40).

Neuroendocrine carcinomas (NECs). NECs are poorly differentiated malignant neoplasms consisting of small or large cells that have a similar immunohistochemical profile to that of NENs and NETs. In particular, diffuse synaptophysin expression and slight or focal chromogranin A expression are evident, along with obvious nuclear atypia, multifocal necrosis and a high mitotic count ($>20/10$ high-power fields) on histological examination.

Appendiceal NECs are extremely rare and share the same histological and immunophenotypic characteristics with the other GI-NECs. Only two cases of appendiceal NECs have been published in bibliography to date. The first case was associated with an adenocarcinoma and the patient survived 65 months after the diagnosis. The second patient had only a 2-month survival postoperatively, highlighting the poor prognosis that accompanies the GI-NECs in general (12, 15).

MANEC and GCCs. MANECs have both malignant exocrine and endocrine components; it is mandatory for each of these components to exceed 30% of the tumor in order for the diagnosis of MANEC to be established. Therefore, simply identifying scattered neuroendocrine cells in immunohistochemistry does not meet the requirements of this definition (41). Malignant elements from squamous carcinomas are uncommon.

In the appendix, the term “MANEC” has been introduced to define a carcinoma which is the result of the progression of a GCC (34); nevertheless, signet-ring cells or cells typical of a poorly differentiated adenocarcinoma can also be found (15, 34, 42). The latter type is usually characterized by the immunohistochemical expression of p53 and mucin 1 (MUC1), along with loss of MUC2 expression (34). These carcinomas occur without obvious neoplastic alterations in the mucosal epithelium of the appendix (43).

GCCs, as well as the composite goblet cell carcinoid adenocarcinomas, belong to the MANEC family. GCCs consist of cells with partial neuroendocrine differentiation mixed with nests/clusters of mildly or intermediately dysplastic signet-ring cells (43). These irregular-shaped tumors, are typically characterized by submucosal development and concentric infiltration of the appendiceal wall; the mucosa is free of disease, with exception of the interactions between the cell nests of the tumor and the crypt bases. The cells are generally mildly to intermediately atypical, show slight mitotic activity (Ki-67 index <20%) and are focally positive for synaptophysin, CgA and CD56, whilst they are diffusely positive for cytokeratin 20 and MUC2 (44).

GCCs are more aggressive than the other appendiceal carcinoids and have usually already developed metastases at the time of diagnosis in approximately 20% of cases (24, 34). Hence, it is not uncommon for such tumors to be misdiagnosed as adenocarcinomas of the appendix. Until recently, GCCs were histologically subdivided into typical GCCs, signet-ring cell adenocarcinomas and poorly differentiated adenocarcinomas; each of these categories meant a different prognosis for the patient (34). Goblet cell carcinomas (GCCs and composite goblet cell carcinoid adenocarcinomas) are no longer considered as a type of ANEN, even though they share some ANEN characteristics due to their significantly different clinical course, treatment and prognosis (45).

Clinical Presentation of ANENs

There are no classic symptoms specifically attributed to ANENs. The most common presentation of these neoplasms is acute appendicitis (54%) (46, 47), which results either from obstruction of the appendiceal lumen by the tumor (25%) (48) or alternative etiology, since the majority of ANENs are located in the appendiceal apex and, hence, blockage cannot

be caused by the tumor mass (1, 7, 49). Infrequently, ANENs can present as a vague abdominal pain located in the right lower quadrant as a result of the incomplete or periodic obstruction of the lumen (47, 48, 50, 51). Carcinoid syndrome is a much rarer consequence of ANENs, which appears after distant metastases have developed, similarly to the other GI-NEN cases (40, 52); carcinoid syndrome is more likely to be related to a small intestine-NEN (1).

Diagnosis

Histology is crucial for the establishment of ANEN diagnosis and most lesions are found incidentally following appendectomy. Endoscopy is of no great benefit for the diagnosis of ANENs, since it detects only large tumors infiltrating the cecum (17). On the other hand, colonoscopy is necessary for colorectal cancer screening, since patients with ANEN may simultaneously have other neoplasms of the GI tract in up to 18% of cases (53).

Biochemical tests – Markers. CgA can be used as a tumor marker in ANENs, as well as in small intestine-NENs. Taking into account the relatively raised levels of CgA in ANENs, it could prove of some help in the differential diagnosis from GCCs (54, 55). There is a clear relationship between the CgA level and the tumor load; therefore, in patients with ANENs, the CgA level can be in the normal range when ANENs are generally sized <2 cm, while larger tumors may be related to higher CgA values (8, 40, 46, 56). Unlike other GI-NENs, however, the role of CgA in monitoring a possible relapse of the disease has not yet been established (8, 57). Measurement of 5-Hydroxyindoleacetic acid (5-HIAA) in the urine is mandatory in the case of carcinoid syndrome (58).

A great variety of histopathological markers have been found to be helpful in identification of NETs, although non-specific. In >83% of ANEN cases, CgA was immunohistochemically detected to a greater extent than 50% of the tumor cells (59); additionally, neuron-specific enolase and CD56 also stained positively (60). Other immunohistochemical markers, such as secretoneurin, Homeobox protein CDX2 and catestatin have also been described in the diagnostic approach to ANENs (7).

Histopathologic Features of High-risk Neoplasms and Prognostic Factors

After the histopathological diagnosis of an ANEN, many parameters have to be taken into account for the distinction of tumors with a mild clinical course from those with a more aggressive potential carrying a higher risk for locoregional relapse and distant metastasis. These include the tumor size and its exact location, as well as the extent of infiltration of the appendix wall or possible vascular invasion (Table I).

Table I. Prognostic factors of appendiceal neuroendocrine neoplasms (ANENs).

Factor	Comments
Size	
<1 cm	Most common; 100% survival post-appendectomy (11).
1-2 cm	5-25% of ANENs; rarely accompanied with lymph node metastases, especially if >1.5 cm (11)
2 cm	<10% of ANENs. Up to 40% risk for systematic dissemination (65-67)
Location	
Tip of the appendix	Most common location (60-75%)
Body of the appendix	Frequency 5-20%
Base of the appendix	Frequency <10%. Associated with higher risk for R1 or R2 tumor resection
Mesoappendiceal invasion	
Mesoappendiceal invasion >3 mm	Higher risk of vascular or lymphatic invasion. More aggressive neoplasm (11, 68)
Proliferative rate	
Ki-67 index >2%	Higher metastatic potential (55); increased risk for lymph node disease and for vascular or perineural infiltration (43)

Size. ANENs measuring <1 cm in maximum diameter (T1a tumors according to TNM staging system American Joint Committee and T1 according to ENETS TNM guidelines) (1) have the best survival rates of all ANENs, at around 100% post-appendectomy in both adults and children (1). There is a discrepancy among various studies concerning the possibility for these neoplasms to metastasize to lymph nodes (33, 38, 61, 62). The greatest debate and controversy considering decision-making comes with ANENs sized from 1 cm to 2 cm (T1b and T2 according to UICC/AJCC and ENETS TNM staging systems, respectively). This subgroup constitutes 5-25% of ANENs and only rarely is accompanied by lymph node disease, mostly seen in carcinomas >1.5 cm (1). Fewer than 10% of ANENs refer to tumors larger than 2 cm (T2 in UICC/AJCC staging system and T3 in ENETS guidelines). These neoplasms carry a substantially higher risk for systemic dissemination (up to 40%) (63-65) and, therefore, a broader oncological procedure as well as longer follow-up time are warranted (65, 66). ANENs of higher stages which have already spread beyond the appendix either invading the peritoneum or other adjacent organs (T4 in all TNM staging systems) or the lymph nodes (stage N1), or tumors that have metastasized to distant locations (stage M1) are considered systemic disease and require a multidisciplinary team approach for adequate treatment (1, 34, 36).

Location. Most ANENs are located in the tip of the appendix (60-75%), they can also be found, however, in the appendiceal body (520%) or base (<10%). A clear relationship between prognosis and the exact part of the appendix with an ANEN has not been established. However, neoplasms located in the appendiceal base are associated with higher risk for incomplete tumor excision (R1 or R2), which means a worse prognosis for the patient (1, 36, 62).

Mesoappendiceal invasion. Invasion of the mesoappendix is a feature highlighted by the ENETS guidelines for the characterization of T2 and T3 tumors (1, 67). Whilst penetration of the appendiceal serosa is not associated with worse prognosis, tumors infiltrating the mesoappendix are related to higher risk of vascular (V1) or lymphatic (L1) dissemination of the disease. Depth of invasion exceeding 3 mm is another feature associated with a more aggressive course, and, therefore, is applied by ENETS for the distinction of T3 from T2 tumors, even if their size is less than 2 cm (1, 67). In that context, patients with such stage tumors should have a longer and more frequent follow-up (20% adults, 40% children) (1).

Ki-67 index. The metastatic potential of an individual ANEN is related to its proliferative rate. A high Ki-67 index is indicative of an aggressive tumor and is accompanied by worse prognosis (52). Thus, it is suggested that tumors with excessive mitotic count or substantial Ki-67 index should be treated with right hemicolectomy (17, 56). Recently, in a multi-institutional study concerning ANENs treated with right hemicolectomy, it was noted that 17% of the study population expressed Ki-67 at an extent >2% and 50% of them (2/4) had metastatic lymph node disease (40). In the same study, vascular infiltration was found in 10 patients (3.6%) and six of them (60%) had nodal infiltration, whilst perineural infiltration (six patients) was associated with nodal involvement in 33% (40). On the other hand, there are studies that do not support these findings. A large multicenter study from France showed that right hemicolectomy is of no benefit in terms of survival when compared with simple appendectomy for the treatment of ANENs (10).

The effect of all these risk factors has not yet been definitely proven since they have not been prospectively

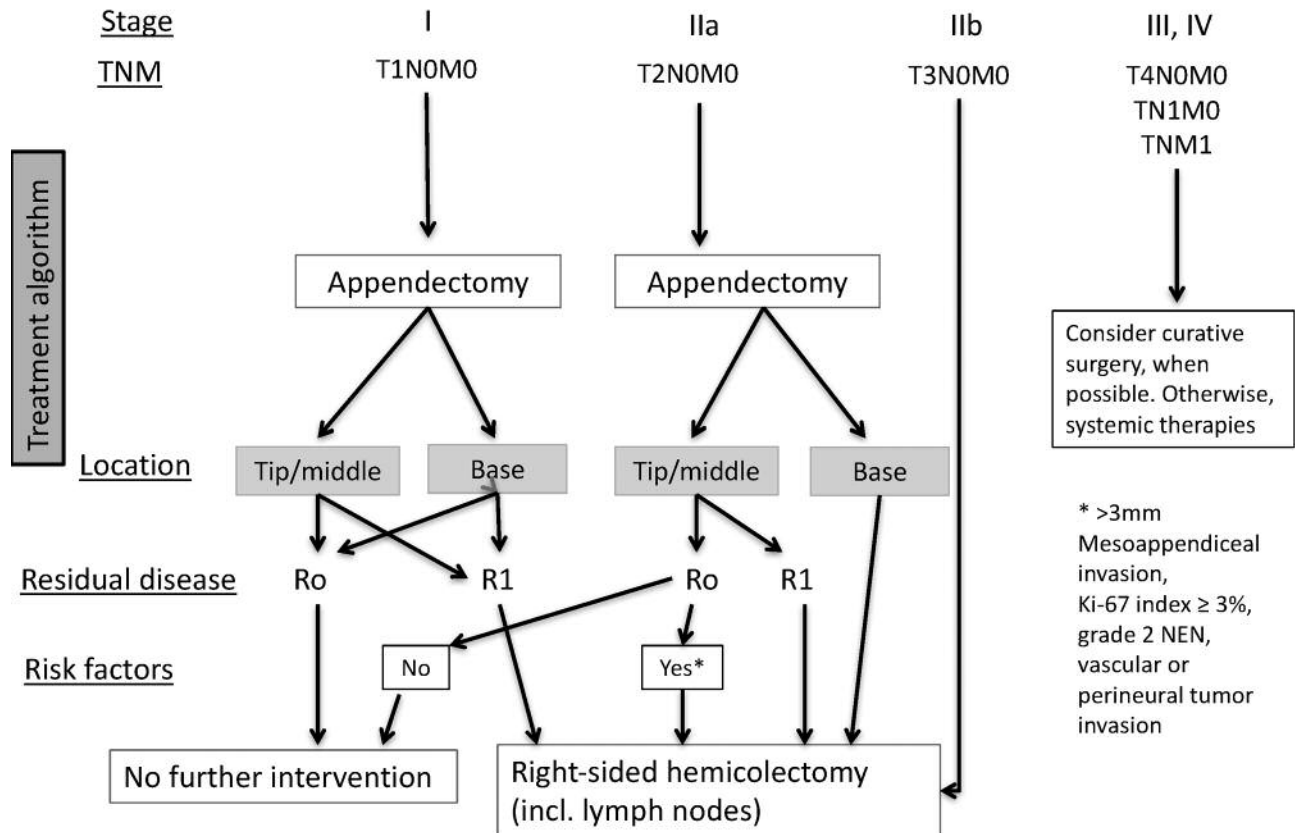


Figure 1. Proposed algorithm for the management of appendiceal neuroendocrine neoplasms (NENs).

evaluated. Therefore, the decisions depend on the attending physician's judgement. However, for more accurate treatment planning, the pathological report should definitely contain comments on the risk factors mentioned above.

Metastatic disease. Lymph node metastatic disease in patients with ANENs has only been studied in case reports (7). In a review of the literature (68), lymph node metastases were seen in 50% of cases in which the tumor diffusely infiltrated the appendiceal wall. There are no clear data in the literature concerning the distant metastatic potential of such tumors. Although this metastatic capability seems to exist, it is probably very low (1.6%) as indicated by a large series of 619 patients from the Netherlands (27).

Treatment of ANENs

Surgical treatment. The surgical treatment of ANENs mainly depends on the stage of the disease (Figure 1). For early-stage tumors, the optimal procedure choice is between simple appendectomy and right hemicolectomy, after other factors, such as such tumor size and the depth of invasion

have been evaluated (2). Given that these tumors are usually of small size and their diagnosis is often made after the appendectomy has been performed, no further treatment is required in a considerable number of cases. Appendectomy is the gold standard treatment for stage I, according to the ENETS TNM staging system (17, 22).

In more advanced disease, as for other GI-NENs (69), a wider oncological operation is recommended along with systematic or targeted adjuvant treatment. Treatment planning is more complicated in patients with ENETS TNM system stage IIa tumors. Small tumors (≤ 2 cm) infiltrating the submucosa, the muscularis, the subserosa layer or the mesoappendix (up to 3 mm in depth) or tumors 1-2 cm especially located in the base of the appendix or those invading the mesoappendix should be treated with right hemicolectomy (40). Additionally, right hemicolectomy could be a reasonable choice after an incomplete (R1) tumor excision, although this is rather rare (89). Other factors suggesting right hemicolectomy as the best treatment option would be a Ki-67 index of 3% or higher, a NEN-G2 or vascular or perineural tumor invasion (17, 22, 52).

For IIb ENETS TNM stage tumors characterized by a high risk for lymph node involvement, increased possibility of disease relapse and development of distant metastases, right hemicolectomy is also recommended. However, pathological identification of residual disease after an appendectomy was noted in 12-36% of patients who underwent right hemicolectomy as a complementary procedure (8, 40, 70). Therefore, unlike previous studies suggesting appendectomy as adequate treatment for such tumors (29), nowadays, right hemicolectomy is considered the treatment of choice, especially in young patients (7).

No guidelines have been issued concerning patients with appendiceal perforation in the case of ANEN. Only a relevant single case report was published by Marthur *et al.*, which suggested supplemental right hemicolectomy as a means of minimizing the possibility of disease dissemination (71); however, no data from large cohort studies on appendiceal perforation exist to date.

Of note, Sutton *et al.* suggested that right hemicolectomy is the best treatment option when the following criteria are met: ANEN larger than 2 cm, located at the base, mesoappendix infiltration, vascular or perineural infiltration or a Ki-67 index >2%. Two studies were conducted to examine the adequacy of right hemicolectomy when one of the Sutton *et al.* criteria is met (17, 72). However, these studies failed to prove that this approach increases survival or prevents disease dissemination (8, 38, 40). In a recent SEER database study concerning the type of procedure followed in patients with ANEN (73), out of the 510 patients with confined disease, 7.8% underwent simple appendectomy, 50.2% right hemicolectomy and the remaining 43% another type of procedure. On the other hand, in patients with regional disease, only 2.6% had an appendectomy, the great majority had a right hemicolectomy (70.7%) and 26.7% a different operation. All patients with distant metastases underwent cytoreductive surgical operations.

Only a small minority of patients with ANENs present with advanced disease (stage III or IV). For these patients, curative surgery should always be considered when possible, while currently a variety of systemic approaches is available with good results (8, 17). In a recent survey on advanced stage ANENs (40), therapy with somatostatin analogs (SSAs) was related to longer survival with stability of the disease compared to placebo (17). When treatment with SSAs fails to inhibit the progress of the tumor, there are further therapeutic options, such as locoregional treatment with embolism, or radiofrequency or microwave ablation along with hepatectomy in patients with hepatic metastases, as well as molecular targeted therapies (17). Although GI-NENs are traditionally considered non-chemosensitive tumors, besides those located in the pancreas, new data suggest that patients could respond to chemotherapy based on temozolomide (74, 75). In functional ANENs, which are rather uncommon,

treatment with SSAs should be administered (8, 76, 77); however, due to their rarity, no definite guidelines have been established regarding the exact indications and the length of the treatment (17).

Survival and Prognosis

Neuroendocrine neoplasms carry the best survival rates (>95%) compared to all other tumor types located in the appendix (24, 78). These favorable outcomes may be attributed to the localization, prompt identification, diagnosis and excision, the biopathology of the tumor itself or the usual size that characterize ANENs (23, 31, 48, 79, 80). The young age of the patients that are mostly affected by ANENs and an early stage of the disease at the time of diagnosis further justify the high 5-year survival rates (Table II). Even patients with locoregional disease seem to have approximately the same prognosis as those suffering from tumors confined to the appendix (27). SEER database studies, as well as smaller series (7), report 5-year survival rates of 94% for confined lesions, 84.6% for locoregional disease and 33.7% when distant metastases are present (31, 81). There are only a few reports describing death as a result of an ANEN (82, 83).

A multicenter observational study from Germany has shown that patients with ANENs have a 5-year overall survival of 83.1% compared to 49.2% for those with non-carcinoid tumors of the appendix (80). Several large studies from the SEER database (64), as well as a recent survey by Shaib *et al.* (73), failed to show any difference between patients treated with right hemicolectomy and others who were managed with simple appendectomy in terms of overall survival. This could mean either that right hemicolectomy offers no superior benefits in the treatment of ANENs or that it is more useful in cases of higher stage.

The excellent prognosis of the disease was verified in a previously mentioned study by two referral centers from London and Warsaw that described 5- and 10-year overall survival rates of 99.05% with no reported relapse (22). There have been some reports regarding relapse of this disease, although in patients with prolonged follow-up period. In a series of 64 patients who were diagnosed with an ANEN at an age younger than 40 years and were followed-up for 10-33 years after surgery, relapse was noted only in one patient who suffered from a tumor larger than 2 cm with regional metastases (84). Liver metastases developed 6 years postoperatively in a patient who was included in a small series of seven patients. This patient had a tumor larger than 2 cm with mesoappendiceal invasion and lymph node metastases, and was treated with right hemicolectomy (65). This phenomenon was observed in another patient from Greece with mesoappendiceal invasion who developed pulmonary metastases 2 years after right hemicolectomy (85). Another report from the Duke Hospital demonstrated

Table II. Survival among studies reporting on patients with appendiceal neuroendocrine tumors.

Author, year (Ref)	Years of enrollment	Institution/database	Outcome	Results
Pawa <i>et al.</i> (2017)	2001-2015	St Mark's Hospital, London, UK, Imperial College London Healthcare NHS Trust, London, UK and Maria Skłodowska-Curie Memorial Cancer Center, Warsaw, Poland	5-Year OS 10-Year OS	99.05% 99.05%
Shaib <i>et al.</i> (2016)	1973-2011	SEER database	OS	No significant difference in survival for TNET and GCC patients based the type of surgery, appendectomy or RHC ($p=0.21$ and $p=0.94$, respectively). Statistically significant difference in survival for SRCC patients treated with hemicolectomy compared to appendectomy ($p=0.01$).
Groth <i>et al.</i> (2011)	1988-2005	SEER database	5-Year OS 10-Year OS	Appendectomy versus RHC: 89% versus 84%, $p=0.18$ Appendectomy versus RHC: 82% versus 72%, $p=0.18$
Benedix <i>et al.</i> (2010)	2000-2004	German multicenter study	5-Year OS	All stages: 83.1%
McGory <i>et al.</i> (2005)	1973-2001	SEER database	5-Year OS	All stages: 83% Localized: 94% Regional: 83% Distant: 31%
Modlin <i>et al.</i> (1997)	1973-1991	SEER database	5-Year OS	All stages: 85.9%
Sandor <i>et al.</i> (1998)	1950-1991	SEER database, Third National Cancer Survey of the National Cancer Institute	5-Year OS	Localized: 94% Regional: 84.6% Distant: 33.7%

SEER database: Surveillance Epidemiology and End Results (SEER) database; OS: overall survival; TNET: typical neuroendocrine tumor; GCC: goblet cell carcinoid; RHC: right hemicolectomy; SRCC: signet-ring cell cancer.

that for 1- to 2-cm appendiceal carcinoids, formal resection of the right colon does not appear to improve survival, even for those with higher grade tumors. Collectively, these findings imply that resection of the primary tumor alone is possibly adequate for all carcinoids <2 cm (86).

Follow-up

Follow-up for patients with small tumors (<1 cm) treated with appendectomy and excised in clear margins (R0) is not suggested by the ENETS guidelines (1, 17). Furthermore, follow-up is also not mandatory for ANENs larger than 1 cm for which right hemicolectomy was implemented, no additional risk factors were present and no lymphovascular invasion or residual disease were identified in the histological examination (1).

On the contrary, although not completely evidence-proven, according to the latest guidelines, long-term follow-up is needed when lymph node involvement is present, locoregional disease is identified postoperatively, as well as in cases in which the tumor is of high stage (1, 17). Regular monitoring is necessary for patients with tumors sized between 1 and 2 cm with features indicating a higher risk for

lymph node dissemination of the disease, such as mesoappendiceal invasion >3 mm, localization in the base of the appendix, vascular infiltration or intermediate differentiation (G2) (1).

The postsurgical follow-up of patients with ANENs includes the measurement of certain biochemical markers as well as regular imaging. The only serum marker that has systemically been evaluated in GI-NEN is CgA (8, 40); therefore, yearly CgA assessment is suggested in such patients. Nonetheless, the value of CgA measurement for the identification of disease relapse has not yet been proven. In patients with clinical symptoms of carcinoid syndrome, urine 5-HIAA should be assessed (87).

There are insufficient data supporting the use of imaging in the detection of residual disease. The most efficient method of imaging (computerized tomography, magnetic resonance imaging or ultrasound) is yet to be identified and there are still issues concerning the adequate follow-up length of monitoring as well as the proper number of tests in that period. As far as CT is concerned, concerns are raised due to the accumulating radiation that these patients will receive. Despite this, there is a growing use of CT and MRI in children, without any substantial benefit, however, since

in this population, simple appendectomy is almost always curative (11). As noted, ANENs are usually of early stage and small size and, therefore, are highly unlikely to be detected by ultrasound. Positron-emission tomography using Ga-octetotide could overcome these drawbacks; yet further studies are needed in this direction (59). In addition, the role of colonoscopy has not been confirmed. In that context, MRI appears to be the most effective imaging tool for patients requiring prolonged follow-up. Perhaps a transabdominal ultrasound could be introduced in the observation plan in order to prolong the intervals between MRIs or CTs. Although still not proven, a reasonable follow-up strategy would be monitoring at 6 and 12 months postoperatively and yearly afterwards (1). Despite their indolent course, ANENs may relapse. Therefore, lifetime observation is necessary for those with tumors >2 cm, or >1 cm with additional risk factors (1, 17, 88).

Conclusion

Appendiceal NENs are rare neoplasms accompanied by excellent prognosis. The treatment of choice is either simple appendectomy or right hemicolectomy; right hemicolectomy is considered the treatment of choice for tumors > 2 cm or 1-2 cm with at least one risk factor especially invasion of the mesoappendix, regardless of the depth. There is not enough evidence to predict which patients require extensive surgery for disease control. Improved patient selection for more extensive surgery may be possible with multi-factorial tumor assessment integrating morphological and molecular analyses. Follow-up strategy is also a matter of debate. No observation is suggested for low-risk patients (<1 cm maximal diameter of the tumor, no mesoappendiceal invasion, low Ki-67 index and localization in the tip or body of the appendix). Likewise, patients at greater risk require no follow-up, provided that they underwent a R0 right hemicolectomy. On the other hand, high-risk patients with R1 tumor resection or not having undergone right hemicolectomy should be regularly monitored with yearly CgA evaluation and possibly MRI, at least for the early postoperative period.

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