Review Article

Appendiceal neuroendocrine tumors: approach and treatment

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ABSTRACT

The incidence of tumors in the appendix has increased over the years, and they are mainly found in the anatomical and pathological examination of appendices operated due to acute appendicitis. The annual incidence of neuroendocrine tumors of the appendix, also called carcinoid tumors, is 0.15–0.16 per 100,000 people. In absolute terms, the incidence of these tumors has increased in the last decade by 70–133%. Appendiceal carcinoid tumors occur more often in women, and are found in 0.3–0.9% of the appendices removed in appendectomies. They appear in the subepithelial neuroendocrine cells and have an indolent course, with the symptoms being indistinguishable from an acute appendicitis. There are two classifications, one presented by the European Neuroendocrine Tumor Society and the other by the American Joint Committee on Cancer. Both classifications use tumor size as a predictor of tumor burden. The classification used by European Neuroendocrine Tumor Society also uses the invasion of the mesoappendix to select the best surgical treatment. However, these classifications require the inclusion of more criteria to define the selection of surgical treatment of tumors between 1 and 2 cm. Thus, along with the size of the tumor and the invasion of the mesoappendix, other factors such as vascular invasion, ki67 index, mitotic index and tumor location should be considered at the time of classification, for a better selection of the treatment and prognostic evaluation.

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Tumores neuroendócrinos do apêndice: abordagem e tratamento

RESUMO

A incidência de tumores no apêndice tem aumentado ao longo dos anos, principalmente encontrados no exame anatomopatológico dos apêndices operados por apendicite aguda. A incidência anual de tumores neuroendócrinos do apêndice, também designados por tumores carcinoides é de 0,15 a 0,16 por 100.000 pessoas. Em termos absolutos, a incidência destes tumores tem aumentado na última década em 70% a 133%. Os tumores carcinoides do apêndice ocorrem mais em mulheres e são encontrados em 0,3%–0,9% dos apêndices.
Neoplasms of the appendix are rare, with an incidence of approximately 1.2 cases per 100,000 inhabitants in the United States. Appendectomy is one of the most frequently performed surgical procedures, with a cumulative lifetime incidence of 12% in men and 23.1% in women, and with an incidence in the general population of 3.9 per 1000 people.

Increased appendectomy may contribute to the increased incidence of appendix tumors.

Tumors of the appendix can be divided into epithelial and non-epithelial tumors. Epithelial tumors are adenocarcinomas and may or may not be mucin-producing. The major non-epithelial tumors are Neuroendocrine Tumors (NETs) and lymphomas.

The adenocarcinomas of the appendix appear between the ages of 62 and 65, with a slight predominance in the male gender, and originate in adenomas, in all similar to colorectal tumors. Non-mucinous adenocarcinomas are histologically and radiologically similar to colorectal adenocarcinomas, radiologically manifesting as a mass and metastasizing preferentially to the lymph nodes, liver, lungs and peritoneum.

Mucinous adenocarcinomas present as cystic enlargement of the appendix due to accumulation of gelatinous material in the lumen, frequently present with abdominal distension, increased abdominal circumference, and impairment of the general condition. Women are often advised to consult a gynecologist for screening to rule out ovarian carcinoma. Inguinal, incisional and umbilical hernias filled with mucin may be another form of presentation. In these cases the tumor may rupture, with release of tumor cells and mucins into the peritoneal cavity, giving rise to peritoneal pseudomixoma.

The extraperitoneal dissemination of mucinous adenocarcinomas is uncommon and therefore the presence of distant metastases at the time of diagnosis is rare. Mucinous adenocarcinomas are present in 0.2–0.3% of the appendices removed by appendectomy, on suspicion of acute appendicitis.

Appendiceal lymphomas are rare, accounting for 0.015% of all cases of gastrointestinal lymphomas. They are more common in men and Caucasians and have a mean age of presentation at age 50, with the exception of Burkitt’s lymphoma that usually arises in the 3rd decade of life. The most common lymphomas in the appendix are diffuse large B-cell lymphomas.

Neuroendocrine tumors (NETs) can affect several organs. Two-thirds of the neuroendocrine tumors are found in the gastrointestinal tract (54.5%), with the small intestine being the most affected (44.7%), followed by the rectum (19.6%), appendix (16.7%), colon (10.6%), and at last, by the stomach (7.2%).

These tumors originate in neuroendocrine cells, with predominance of enterochromaffin cells or kulchitsky cells, presenting different histopathological characteristics and hormonal secretion capacities due to the primary site of origin of these cells. The percentage of neuroendocrine tumors occurring in the appendix has decreased from 17–28% to 2–5%, which is due to the increased diagnosis of NETs elsewhere in the gastrointestinal tract due to increased endoscopic procedures. However, in absolute terms the incidence of Neuroendocrine Tumors of the Appendix (aNETs) has increased in the last decade by 70–133%. Approximately 1 in 8 gastrointestinal carcinoids occurs in the appendix, and the annual incidence of aNETs is 0.15–0.16 per 100,000 people in agreement with SEER.

aNETs also designated as carcinoid tumors can be divided into island-like carcinoids originating from serotonin-producing enterocromaphine, and tubular carcinoids that grow from Enteroglucagon-producing L-cells and YY peptide. The differential diagnosis with adenocarcinomas is done using immunohistochemistry, with carcinoids being positive for chromogranin A and synaptophysin. Carcinoid tumors can lead to a carcinoid syndrome characterized by flushing, bronchoconstriction, diarrhea, and right valve disease caused by release of vasoactive substances.

aNETs are diagnosed at lower ages compared to the other tumors of the appendix, between 32 and 42.2 years of age. Other studies describe a presentation age between 38 and 51 years old. Neuroendocrine neoplasms of the appendix also occur in the pediatric age with a mean age of presentation between 4.5 and 19.5 years; however there is still no evidence based on the population of this subgroup.

Carcinoid tumors of the appendix occur 1.7 times more in women than in men. They are found in 0.3–0.9% of the appendices removed in appendectomies and correspond to
85% of all appendix neoplasms. These may cause acute appendicitis due to lumen obstruction or the release of vasoactive substances. The symptoms are usually nonspecific and the presentation is usually delayed until the tumor occludes the lumen of the appendix.

The clinical presentation is indistinguishable from acute appendicitis in 50% of cases and approximately 50% of cases are diagnosed in pathological analysis after appendectomy for acute appendicitis. These tumors can invade regionally and/or metastasize at a distance. They have a 5-year survival of more than 90%. An adequate classification is important to establish a good therapeutic plan, a follow-up of the patients, as well as for the prognosis. It is important to evaluate the size, location, histopathological characteristics, invasion of the mesoappendix, vascular invasion, and the presence of distant metastases.

Currently, there are two classifications, ENETS and AJCC/UICC, with the first TNM staging system for neuroendocrine tumors being developed by ENETS in 2006; the second only appeared in the ACJJ 8th Edition, in 2010. The preoperative classification of the appendiceal neuroendocrine tumors is important for the decision of the extension of the surgery to be performed, appendectomy or right hemicolec- tomy with lymphadenectomy, complementary treatment to be implemented, as well as to define a follow-up plan based on the underlying risk (Tables 1–5).

**Materials and methods**

This monograph was prepared using scientific articles, after PubMed bibliographic research, with restriction to articles in Portuguese and English, and time limit from 2007 to 2017. The research was carried out with different combinations of terms, “appendix neoplasm”, “appendix cancer”, “appendix carcinoid”, and “neuroendocrine tumor appendix”. Based on the title and abstract, relevant articles were selected for full reading in the scope of the topic to be developed. Subsequently, articles were read and other articles of interest were searched through bibliographical references. More recent and complete articles were considered more relevant. In total, 31 references were included in this study.

**Results and discussion**

**Histology and epidemiology**

Neuroendocrine tumors of the appendix originate from subepithelial neuroendocrine cells present in the lamina propria and submucosa of the appendix wall. These cells exist in greater quantity at the end of the appendix, and this location, as well as their reduced size and presentation at earlier ages may explain their indolent course and good prognosis. These tumors, which are marked with immunohistochemistry, synaptophysin, and chromogranin A can be divided into classic or insular and tubular, being radiologically indistinguishable, and having similar clinical evolutions. As previously mentioned, these tumors may be associated with a carcinoid syndrome that occurs in less than 10% of all neuroendocrine tumors in the appendix, usually associated with the presence of liver metastases.

aNETs have an annual incidence of 0.4–0.6 per 100,000 people with a slight predominance in females. Other studies show an annual incidence of aNETs of 0.15–0.16 per 100,000 people in agreement with the SEER. In a study conducted in Qatar, neuroendocrine tumors of the appendix were found in 0.23% of appendectomies, consistent with other studies carried out in Belgium (0.4%), the United Kingdom (0.62%) and United Arab Emirates (0.93%). Another study showed that carcinoid tumors were found in 0.5% of the appendices removed by appendectomy, which is in line with the prevalence found in the literature of 0.3–0.9%. The differences in the incidence of aNETs may be due to the fact that the disease is mostly asymptomatic for many years, and the incidence may be underestimated in most studies.

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**Table 1 – TNM classification of neuroendocrine tumors of the appendix according to ENETS.**

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM classification of neuroendocrine tumors of the appendix according to ENETS.</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor ≤1 cm with submucosa and muscular propia invasion</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor ≤2 cm with submucosa, muscular propia invasion, and subserosa/mesoappendix invasion up to 3 mm</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor &gt;2 cm and/or invasion &gt;3 mm of subserosa/mesoappendix</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor invades peritoneum or other organs</td>
</tr>
</tbody>
</table>

**Table 2 – TNM stages of neuroendocrine tumors of the appendix according to ENETS.**

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM stages of neuroendocrine tumors of the appendix according to ENETS.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>Tis N0, M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T1, N0, M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T2, N0, M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>T3, N0, M0</td>
</tr>
<tr>
<td>Stage V</td>
<td>T4, N0, M0</td>
</tr>
<tr>
<td>Stage VI</td>
<td>Any T, N1, M0</td>
</tr>
</tbody>
</table>

**Table 3 – TNM classification of neuroendocrine tumors of the appendix according to UICC/AJCC.**

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM classification of neuroendocrine tumors of the appendix according to UICC/AJCC.</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a</td>
<td>Tumor ≤1 cm in its larger dimension</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor &gt;1 cm and ≤2 cm in its larger dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor &gt;2 cm and &lt;4 cm or cecum invasion</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor &gt;4 cm or with extension to the ileum</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor perforates the peritoneum or invades organs or adjacent structures</td>
</tr>
</tbody>
</table>

**Table 4 – TNM stages of neuroendocrine tumors of the appendix according to UICC/AJCC.**

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM stages of neuroendocrine tumors of the appendix according to UICC/AJCC.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T1, N0, M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T2–3, N0, M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T4, N0, M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T, N1, M0</td>
</tr>
</tbody>
</table>

**Table 5 – Classification based on the proliferative capacity of neuroendocrine tumors of the appendix according WHO criteria.**

<table>
<thead>
<tr>
<th>Ki67 index</th>
<th>Mitotic index</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤2%</td>
<td>&lt;2</td>
</tr>
<tr>
<td>3%–20%</td>
<td>2–20</td>
</tr>
<tr>
<td>&gt;20%</td>
<td>&gt;20</td>
</tr>
</tbody>
</table>

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Diagnosis

The preoperative diagnosis of aNETs is difficult because these tumors have an indolent course and the symptoms may be indistinguishable from acute appendicitis. In fact, 50% of cases are diagnosed in pathological analysis after appendectomy for acute appendicitis.\(^\text{17}\)

For an accurate classification of tumors, an imaging and histological evaluation is important. Computed tomography and magnetic resonance imaging are gold-standard imaging tests to assess the tumor burden of a patient with neuroendocrine tumor\(^\text{25}\), and are important to rule out regional involvement and distant metastases. Abdominal ultrasound can be used, and despite user- and patient's profile-dependent limitations, it has the advantage of being a less invasive procedure.\(^\text{4}\) However, computed tomography and magnetic resonance imaging have higher sensitivity and specificity.\(^\text{25}\) aNETs are difficult to be radiologically visualized because of their size, and generally present as submucosal masses or nodular thickening of the wall.\(^\text{5}\)

These tumors are associated with a higher incidence of metachronous and synchronous lesions, requiring investigation and surveillance of the gastrointestinal tract.\(^\text{16}\) Colonoscopy, capsule examination, DOTA-NOC scintigraphy and serum determination of chromogranin A should be performed.\(^\text{4}\) One study showed an incidence of 15% of patients with metastatic tumors.\(^\text{2}\)

Histology is essential to establish the diagnosis. Immunohistochemical marking for chromogranin A and synaptophysin, the count of mitoses per 10 HPF (2 mm\(^2\), at least 40 fields at 40× magnification) evaluated in areas of high mitotic density, and finally the evaluation of the Ki-67 index, which determines the proliferative capacity of the tumor, are essential for diagnosis and define the therapeutic strategy.\(^\text{19}\) The histopathological classification allows a good classification according to the criteria of the World Health Organization (WHO). Chromogranin A can be used as a tumor marker, especially in neoplasms with metastases,\(^\text{4}\) may reflect tumor size and degree of invasion, and also be used in the evaluation of tumor growth rate, as well as in the context of follow-up.\(^\text{22}\) Neurospecific enolase may be used as an additional marker in poorly differentiated tumors\(^\text{25}\); however, it has less sensitivity than chromogranin A in the evaluation of aNETs.\(^\text{25}\)

5-HIAA is the metabolite excreted in the urine resulting from the metabolism of serotonin, and can be evaluated in 24-h urine collection in the presence of carcinoid syndrome. It has a sensitivity and specificity of 70% and 90%, respectively. When metastatic lesions are present, chromogranin A is more sensitive than 5-HIAA.\(^\text{26}\)

Chromogranin A may be elevated in patients with chronic gastritis type A atrophy, renal failure, and those medicated with proton pump inhibitors, and histamine H2 receptor blockers.\(^\text{25}\) Urinary 5-HIAA is influenced by numerous dietary factors, such as avocado, banana, tomato, among others, and by drugs such as coumarin, acetaminophen, phenacethin, aspirin, among others.\(^\text{25}\) In this context, when these measurements are taken, dietary and drug restrictions should be made so as not to influence the results.\(^\text{19}\)

Somatostatin Receptor Imaging (SRI) using somatostatin-111-indium (SRS) scintigraphy, and Positron Emission Tomography (PET) using gallium-68 with somatostatin analogues (octreotide) are used in patients where curative resection has not been achieved or when there is suspicion of metastasis.\(^\text{4}\) In some centers, PET is preferred with gallium-68 (GALLIUM-DOTA-NOC PET) compared to scintigraphy with octreotide because of its greater sensitivity and consequent detection of more lesions using this technique.\(^\text{25}\)

Classification and treatment

Currently there are two classifications, the one presented by European Neuroendocrine Tumor Society (ENETS) and the one by American Joint Committee on Cancer (AJCC). Tumor size is the most important indicator for surgery decision-making,\(^\text{16}\) and the main indicator of metastatic disease,\(^\text{14}\) thus defining the criteria for the elaboration of both classifications. Surgery is the only curative treatment for neuroendocrine tumors, being incurable when there is unresactable metastatic disease.\(^\text{27}\)

A study conducted in Qatar found an average size of 4.86 mm, consistent with other studies conducted in Belgium (6 mm), the United Kingdom (5 mm) and the United Arab Emirates (3.3 mm).\(^\text{22}\) One study demonstrated that 80% of the neuroendocrine tumors of the appendix have less than 1 cm, 14% have between 1 and 2 cm, and the tumors larger than 2 cm correspond to only 6%.\(^\text{16}\)

Tumors <1 cm classified as T1 by ENETS and T1a by UICC/AJCC are treated with appendectomy only, with no follow-up, and a 100% survival at 5 years.\(^\text{19}\)

Tumors >1 cm and <2 cm, T2 by ENETS and T1b by UICC/AJCC are a group where the decision for treatment with simple appendectomy or right hemicolectomy is more difficult. Tumors in this group correspond to 5–25% aNETs, and up to 10% of the cases are associated with metastasis.\(^\text{19}\) The ENETS classification distinguishes T2 and T3 by the invasion of the mesoappendix, with the cut-off being of 3 mm, not considered in the classification presented by UICC/AJCC. The invasion of the mesoappendix, as opposed to the degree of invasion of the serosa, is associated with greater lymphatic invasion. In these cases, the invasion of the mesoappendix occurs up to 20% in adults and up to 40% in children.\(^\text{15}\) Thus, when present, the invasion of the mesoappendix correlates well with lymph node metastases and tumor size.\(^\text{16}\)

Another criterion to define a surgical approach in patients with tumors between 1 and 2 cm is Ki67. When Ki67 >3%, there is indication for right hemicolectomy. There is insufficient evidence to demonstrate that Ki67 is a prognostic factor in well differentiated NETs.\(^\text{14}\)\(^\text{19}\) It is also equally important to evaluate the mitotic index in the histopathological evaluation of tumors included in this group.

For the surgical decision, the location of the tumor is also important; 60–75% of the tumors are located at the end of the appendix, 5–20% in the body of the appendix, and less than 10% at the base.\(^\text{19}\) Tumors at the base are more likely to be of incomplete resection, but there are no studies in the literature to validate this.\(^\text{14}\)\(^\text{19}\)

Lymph node invasion may also be a factor to be taken into account in this decision, since the main form of metastasis is lymphatic.\(^\text{16}\) Recent studies have shown that approximately half of the patients with neuroendocrine tumors of
the appendix of 1–2 cm had ganglion metastases at the time of surgery.\textsuperscript{28,29} Regional involvement decreases survival in localized tumors,\textsuperscript{29} and the risk of ganglion invasion increases as the size of the tumor increases.\textsuperscript{17} To evaluate lymph node invasion, a suitable lymphadenectomy should be performed, and the minimum of isolated lymph nodes should be 12.\textsuperscript{30} The number of lymph nodes evaluated is important to negate lymph node involvement, and we consider positive lymph node involvement whenever there is involvement of at least one ganglion.\textsuperscript{30} Regional lymphadenectomy should include all lymph nodes in the ileocolic pedicle, right colon, and right branch of medium colon.\textsuperscript{28}

Lymphatic permeation is associated with a 30% risk of lymph node metastasis, negatively influencing survival in these patients.\textsuperscript{14}

Thus, the surgical decision by appendectomy or right hemicolectomy with lymphadenectomy is difficult, and the only validated parameters are tumor size and invasion of the mesoappendix; however, the evaluation of other factors, such as lymph node and venous invasion, ki67, mitotic index and tumor location should be considered.

In T3 and T4 tumors by ENETS, or T2, T3 and T4 by UICC/AJCC, a right hemicolectomy with lymphadenectomy is indicated because of the increased risk of lymph node invasion, recurrence and distant metastases.\textsuperscript{19}

Neuroendocrine tumors of the appendix can still be classified according to WHO histopathology. Tumors with ki67 index ≤2%, and mitotic index (mitoses/10 HPF) <2 are classified as G1 and have a low proliferation rate. Tumors with ki67 index <3% and <20% and mitotic index (mitoses/10 HPF) between 2 and 20 are classified as G2. Finally, tumors with a ki67 index <20%, and a mitotic index (mitoses/10 HPF) <20 are classified as G3.\textsuperscript{19}

As previously mentioned, tumors classified as G2 and G3 have a higher proliferation rate; as such, in tumors between 1 and 2 cm, this classification may serve as a support to help the decision between a simple appendectomy and a right hemicolectomy with lymphadenectomy.

In patients with distant metastases, somatostatin analogues may be beneficial in relieving the symptoms of carcinoid syndrome. Somatostatin binds to somatostatin receptors and blocks the release of growth hormone, insulin, gastrin and glucagon. These receptors are found in more than 80% of these tumors.\textsuperscript{24}

Octreotide is a somatostatin analog and in this study it was effective in decreasing symptoms in 88% of patients and urinary excretion of 5-HIAA in 72% of patients. Patients with progressive or non-responsive carcinoid syndrome may benefit from alpha interferon and hepatic artery occlusion with adjuvant chemotherapy.\textsuperscript{16}

Loco regional therapies with embolization and/or radiofrequency ablation can be used in patients with aNETs, mainly with metastases.\textsuperscript{10}

One study demonstrated a risk of lymph node metastases of 16.7% in tumors smaller than 1 cm, 29.9% in tumors between 1 and 1.9 cm, and 40.6% in tumors larger than 2 cm.\textsuperscript{37}
aNETs are more aggressive in pediatric ages than in adults, and in adults there is involvement of adipose tissue in 10% of the cases and the serosa layer in 20% of cases, while in children there is involvement in 30% and 40%, respectively.\textsuperscript{16}

A study conducted in Sweden showed an increased risk of neuroendocrine neoplasms of the appendix in individuals with first-degree relatives with a history of neuroendocrine tumors, neoplasms of the nervous system, urinary tract, breast, and endocrine glands.\textsuperscript{31}

Carcinoid syndrome is one of the complications of aNETs and occurs in less than 10% of patients.\textsuperscript{6} Carcinoid syndrome was a frequent cause of morbidity and mortality; however, with the introduction of new treatments such as somatostatin analogues, currently it rarely occurs, and organ failure is now the leading cause of mortality in patients with neuroendocrine tumors resulting from the invasion of other organs, and it occurs only at an advanced stage of the disease.\textsuperscript{27}

Follow-up should be performed with CT or MRI, abdominal ultrasound 6 months after surgery. If negative, it should be repeated after another 6 months, and then with 1-year intervals. In the case of disease stabilization, longer intervals may be used.\textsuperscript{23} Scintigraphy with octreotide should be done after surgery and then with intervals of 2 years, and adjustments can be made according to the stabilization of the disease.\textsuperscript{25}

In the case of malignant tumors, G2 or G3, CT, MRI or abdominal ultrasound should be performed in periods of 3 months for an indefinite period. Scintigraphy with octreotide should be performed 3 and 12 months after surgery. It should be performed earlier if new lesions arise during CT/MRI or ultrasound.\textsuperscript{25}

As previously reported, octreotide scintigraphy can be replaced by GALLIUM-DOTA-NOC PET, which has higher sensitivity.\textsuperscript{25} Chromogranin A and 5-HIAA can be measured periodically, but only in the presence of tumor imaging. Finally, neurospecific enolase may be required in less differentiated tumors.\textsuperscript{25}

Finally, due to the higher incidence of metachronous tumors in patients with neuroendocrine tumors,\textsuperscript{2} colonoscopy should be an examination to be more regularly requested compared to the rest of the population, in the context of follow-up.

**Conclusion**

Neuroendocrine tumors have increased in incidence over the last few years, and this makes them an increasingly frequent problem in clinical practice. The guidelines that guide diagnosis, classification and treatment are not uniform and are based on few criteria to ensure a correct approach to these patients. Therefore, further studies are necessary to assess the risk underlying these tumors more accurately. The criteria defining the classification and surgical approach, such as Ki67, tumor location, mitotic index, vascular invasion, and mesoappendix invasion need to be validated with scientific evidence, in order to enable the clinician to evaluate and make the most supported and correct decision and therefore improve these patients prognosis.

**Prognosis and follow-up**

The prognosis of aNETs is generally favorable when compared to other neoplasms in the appendix. One study showed that aNETs have a 5-year survival rate greater than 90%.\textsuperscript{18} Another study showed a survival rate of 96% at 10 years.\textsuperscript{2}
Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES