Editorial Commentary

Treatment of appendiceal neuroendocrine tumour: a controversial treatment for a misunderstood neoplasm in a mysterious organ

Andy Petroianu^

Department of Surgery, School of Medicine, Federal University of Minas Gerais, Belo Horizonte, Brazil

Correspondence to: Andy Petroianu, MD, PhD. Professor of Surgery, Department of Surgery, School of Medicine, Federal University of Minas Gerais, Rua São Paulo, 925-apt. 802, Belo Horizonte 30170-901, Brazil. Email: petroian@gmail.com.

Comment on: Nesti C, Bräutigam K, Benavent M, *et al.* Hemicolectomy versus appendectomy for patients with appendiceal neuroendocrine tumours 1-2 cm in size: a retrospective, Europe-wide, pooled cohort study. Lancet Oncol 2023;24:187-94.

Keywords: Appendix; neuroendocrine tumour (NET); appendectomy

Submitted Mar 23, 2023. Accepted for publication Jul 16, 2024. Published online Aug 23, 2024.
doi: 10.21037/tcr-23-510
View this article at: https://dx.doi.org/10.21037/tcr-23-510

This outstanding and up-to-date work studied 278 appendiceal neuroendocrine tumours (NETs) of one to two centimetres in size, which were completely resected by means of appendectomy or right-sided hemicolectomy. This retrospective cohort study, assessed patients from 40 hospitals in 15 European countries, considering any age and sex, with more than 10 years of follow-up after the surgical procedure (1).

The appendix is a relatively unknown organ, considering the enigmatic role it plays in the body (2). In spite of the large number of published studies about the appendix, its disorders are still incomprehensible. To reinforce this concept, diseases associated with right-side abdominal pain, having been described for many centuries, are still difficult to identify (3). All theories concerning the appendix are controversial and no symptom or sign may be ascribed to any appendicopathy as pathognomonic. Therefore, the diagnosis of appendiceal disorders continues to be a medical challenge (3,4). Acute appendicitis, which is the most frequent appendiceal disease, is prevalent in white skin patients (74%) with an incidence of 23 per 10,000 people per year (2,5). Radiographic signs suggestive of appendicitis include appendiceal faecalith, gas in the appendix, air-fluid levels or distension of the terminal ileum, caecum, and ascending colon, which are signs of localised paralytic ileum (6). These radiological signs have a sensitivity of 97% and a specificity of 85% (7,8).

The appendiceal characteristics are different from all other digestive organs and do not seem to be linked to digestion. The high amount of neuroendocrine and immune cells in the appendix wall, as well as its disorders, are related to neuroendocrine and immune systems, but not necessarily to inflammation (9,10). More than 20% of all patients with clinical manifestations of appendicitis do not present appendiceal inflammation, but rather a different appendicopathy (11,12). Since the early twentieth century, several studies have ascribed this disease to disorders of neuroendocrine and immune mediators located in the appendix, which occur at a similar age and sex of acute appendicitis. However, the etiology, activating factors, and pathophysiology of this appendicopathy are still unknown (11-14).

Apparently normal appendices removed from patients with clinical manifestations of acute appendicitis have revealed a greater expression in substance P neuroendocrine markers, vasoactive intestinal polypeptide, gastric inhibitory polypeptide, calcium-binding protein, cyclooxygenases 1 and 2, tumour necrosis factor, prostaglandin E2, mast cell tryptase, nitric oxide synthase, CD8 lymphocytes, protein gene product 9.5, vascular endothelial growth factor, class 2 histocompatibility complex, synaptophysin, enolase, and S100 protein (15-17). At least some of these mediators are

^ ORCID: 0000-0002-8659-6866.

© Translational Cancer Research. All rights reserved.

responsible for fever, nausea, vomiting, abdominal pain and diarrhoea. Thus, apparently normal appendices removed from patients with a clinical look of acute appendicitis present neuroendocrine disorders (2,5,11,12).

Patients over 40 years old presenting with appendicitis manifestations and an appendiceal diameter >10 mm seems to have a greater risk of malignancy (3). The presence of an appendiceal malignancy should be considered in the management of older patients with acute appendicitis before indicating non-operative therapy (17). The most frequent cancer of the digestive system is adenocarcinoma, including the goblet cell tumour, which sometimes shows carcinoid-like expansion and may confound the diagnosis. The characteristic appendiceal malignancy is the NET, mainly the carcinoid tumour (18,19). Somatostatinoma and paraganglioma are other rare NETs that may originate in appendices (19,20). More than 80% of all NETs are incidentally found in appendices removed due to a diagnosis of acute appendicitis (18-20). They usually progress indolently and are diagnosed one decade later than acute appendicitis. In fact, the clinical manifestation of acute appendicitis and NET are similar, except for the symptoms due to serotonin secretion of carcinoid tumours, mainly flushing, diarrhoea, and bronchospasm. These clinical manifestations of carcinoid syndrome are mainly found when the NETs are associated with liver metastases (19,21). Their epidemiologic findings of age and sex are also different (21). The acute appendicitis is mainly found between 15 and 30 years, and the NET is between 30 and 40 years (3,13,19,22). The findings of this study confirmed the mean age of patients with NET, which was 36 years (1). The overall lifetime risk of acute appendicitis is 9% for males and 6% for females (2,3,5,11,21). Otherwise, the incidence of NET is 50% higher in females than in males (18-20,22). This result was also found in this study, considering that circa 60% were females and 40% were males (1).

NETs are found in 1.5% of all appendectomies and are considered to be present in 0.1/100,000 people (9,12,18-20). These neoplasms are epithelial or not specified in 90% of all cases, tubular in 6% and mixed in 4% (18-20). They arise from neuroendocrine cells, including enterochromaffin cells that produce serotonin, L-cells that secrete glucagon-like peptides, pancreatic polypeptides and peptide YY, and tubular cells that produce serotonin and substance P (17-20,23). The NET cells are of architectural complexity with most of the tumour presenting grade 1 atypia, but with some areas of high-grade cytological atypia (enlarged, hyperchromatic and pleomorphic nuclei), mitotic index and Ki67 labelled index higher than 2%, which may be associated with tumour aggressiveness, endocrine atypia and the presence of metastases (17,23-25). The diagnosis of this NET may be confirmed by the markers serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) and chromogranin A (CgA) (17-20,23). In this study, no marker was used to differentiate patients with and without metastases, and to relate them with mortality (1).

The lack of understanding concerning the etiopathogenesis of appendiceal diseases makes appendectomy the standard treatment (3,18,19,21,22,24). The current preference is for laparoscopy, which is initially propaedeutics, may enable a correct diagnosis and confirm the dimensions of the tumour. Hence, adequate treatment is performed in the same laparoscopically procedure. Appendectomy is indicated for less than one-centimetre tumours, which are considered benign or *in situ* neoplasms due to the low risk of metastases (3,18,19,21,22,24). Guidelines indicate hemicolectomy with regional lymphadenectomy, including right mesocolon resection, to treat tumours higher than two centimetres (3,18,19,21,22,24). However, there is controversy in the literature about NET with dimensions between one and two centimetres, considering that patients submitted to hemicolectomy have a worse quality of life than those submitted to appendectomy (3,18,19,21,22,24).

According to this study, 20% had already presented regional lymph node metastases from the appendiceal NET, 29% showed lymphovascular invasion and 2% presented distant metastases at the time of the surgical treatment (1). Mortality due to this tumour increased over the years and, after 10 years, was 4% (1). Even not being significant the difference, more patients died after appendectomy than after hemicolectomy. Nevertheless, in other published series, mortality after appendectomy reached 13% in 10 years and 20% after 20 years (3,18,19,21,22,24,25). Thus, differently from Nesti *et al.* (1), we consider that NETs with one to two centimetres in size must be treated as malignant in order to reduce the high rate of precocious mortality, considering that this disease is mostly found before the age of 40 years. Right hemicolectomy associated with lymphadenectomy and right mesocolon excision provide a greater chance of cure than appendectomy, despite a worse quality of life during a short postoperative period after surgery. Chemotherapy, which is rarely indicated in advanced tumours with metastases, is only able to control the NET for several years, with some severe clinical adverse

© Translational Cancer Research. All rights reserved.

effects (22,24).

In conclusion, NET must be considered in patients with clinical manifestations of acute appendicitis after their thirties, mostly in women and when associated with flushing, diarrhoea and bronchospasm. If the appendiceal specimen reveals a tumour greater than one centimetre, hemicolectomy with regional lymphadenectomy and right mesocolon excision is recommended.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Cancer Research*. The article has undergone external peer review.

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-510/prf

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-510/coif). The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

References

1. Nesti C, Bräutigam K, Benavent M, et al. Hemicolectomy versus appendectomy for patients with appendiceal neuroendocrine tumours 1-2 cm in size: a retrospective, Europe-wide, pooled cohort study. Lancet Oncol 2023;24:187-94.
2. Ferris M, Quan S, Kaplan BS, et al. The Global Incidence of Appendicitis: A Systematic Review of Population-based Studies. Ann Surg 2017;266:237-41.
3. Naar L, Kim P, Byerly S, et al. Increased risk of malignancy for patients older than 40 years with appendicitis and an appendix wider than 10 mm on computed tomography scan: A post hoc analysis of an EAST multicenter study. Surgery 2020;168:701-6.
4. Petroianu A, Villar Barroso TV. Pathophysiology of Acute Appendicitis. JSM Gastroenterol Hepatol 2016;4:1062.
5. Petroianu A, Oliveira-Neto JE, Alberti LR. Comparative incidence of acute appendicitis in a mixed population, related to skin color. Arq Gastroenterol 2004;41:24-6.
6. Petroianu A. Diagnosis of acute appendicitis. Int J Surg 2012;10:115-9.
7. Petroianu A, Alberti LR, Zac RI. Fecal loading in the cecum as a new radiological sign of acute appendicitis. World J Gastroenterol 2005;11:4230-2.
8. Petroianu A, Alberti LR, Zac RI. Assessment of the persistence of fecal loading in the cecum in presence of acute appendicitis. Int J Surg 2007;5:11-6.
9. Güller U, Oertli D, Terracciano L, et al. Neurogenic appendicopathy: a frequent, almost unknown disease picture. Evaluation of 816 appendices and review of the literature. Chirurg 2001;72:684-9.
10. Kooij IA, Sahami S, Meijer SL, et al. The immunology of the vermiform appendix: a review of the literature. Clin Exp Immunol 2016;186:1-9.
11. Di Sebastiano P, Fink T, di Mola FF, et al. Neuroimmune appendicitis. Lancet 1999;354:461-6.
12. Petroianu A, Barroso TVV, Buzelin MA, et al. Neuroendocrine apendicopathy in morphologically normal appendices of patients with diagnosis of acute appendicitis: Diagnostic study. Ann Med Surg (Lond) 2020;60:344-51.
13. Sesia SB, Mayr J, Bruder E, et al. Neurogenic appendicopathy: clinical, macroscopic, and histopathological presentation in pediatric patients. Eur J Pediatr Surg 2013;23:238-42.
14. Ruiz J, Ríos A, Oviedo MI, et al. Neurogenic ppendicopathy. A report of 8 cases. Rev Esp Enferm Dig 2017;109:180-4.
15. Barroso TVV, Sales PGO, Petroianu A. Assesment of the Vasoactive Intestinal Polypeptide (VIP) in Morphologically Normal Appendices Removed from Patients with Clinical Diagnosis of Acute Appendicitis. Emerg Med 2015;5:1000256.
16. Villar Barroso TV, Petroianu A. Neuroimmunoendocrine

© Translational Cancer Research. All rights reserved.

peptides on inflammed and morphologically normal appendices removed due to clinical acute appendicitis. Int J Surg 2019;67:76-8.
17. Skendelas JP, Alemany VS, Au V, et al. Appendiceal adenocarcinoma found by surgery for acute appendicitis is associated with older age. BMC Surg 2021;21:228.
18. Moris D, Tsilimigras DI, Vagios S, et al. Neuroendocrine Neoplasms of the Appendix: A Review of the Literature. Anticancer Res 2018;38:601-11.
19. Bell PD, Pai RK. Goblet cell adenocarcinoma of the appendix: an update and practical approach to diagnosis and grading. Hum Pathol 2023;132:183-96.
20. Terzioğlu SG, Kılıç MÖ, Öksüz P, et al. Appendiceal neuroendocrine neoplasia: analysis of 50 patients. Neoplasia neuroendocrina apendicular: análisis de 50 pacientes. Cir Cir 2022;90:75-80.
21. Luiz do Nascimento Junior P, Teixeira Brandt C, Petroianu A. Differences between inflamed and non inflamed appendices diagnosed as acute appendicitis. Ann Med Surg (Lond) 2021;62:135-9.
22. Muñoz de Nova JL, Hernando J, Sampedro Núñez M, et al. Management of incidentally discovered appendiceal neuroendocrine tumors after an appendicectomy. World J Gastroenterol 2022;28:1304-14.
23. Solis-Pazmino P, Oka K, La K, et al. Incidence rate and histology of appendiceal neoplasms in complicated versus uncomplicated appendicitis: A meta-analysis and systematic review. Langenbecks Arch Surg 2023;408:432.
24. Mohamed A, Wu S, Hamid M, et al. Management of Appendix Neuroendocrine Neoplasms: Insights on the Current Guidelines. Cancers (Basel) 2022;15:295.
25. Du R, Xiao JW. Prognostic impact of number of examined lymph nodes on survival of patients with appendiceal neuroendocrine tumors. World J Clin Cases 2022;10:10906-20.

Cite this article as: Petroianu A. Treatment of appendiceal neuroendocrine tumour: a controversial treatment for a misunderstood neoplasm in a mysterious organ. Transl Cancer Res 2024;13(8):3940-3943. doi: 10.21037/tcr-23-510

© Translational Cancer Research. All rights reserved.