



Hemicolectomy versus appendectomy alone for appendiceal neuroendocrine tumours between 1–2 cm in size— are we overtreating?

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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: Neuroendocrine tumours; appendix; surgery

Submitted Apr 18, 2023. Accepted for publication Aug 03, 2023. Published online Aug 17, 2023.

doi: 10.21037/tcr-23-655

View this article at: <https://dx.doi.org/10.21037/tcr-23-655>

Recently, a large, retrospective international multicenter study by Nesti *et al.* has been published in the *Lancet Oncology* contributing to the ongoing debate about the optimal treatment strategy for neuroendocrine tumours (NETs) of the appendix (1). NETs of the appendix are very rare with a reported incidence rate of 0.15–0.6 per 100,000 people per year (2). Recommendations regarding its treatment have been formulated by multiple international medical societies namely by the European Neuroendocrine Tumor Society (ENETS), the North American Neuroendocrine Tumor Society (NANETS) and the National Comprehensive Cancer Network® (NCCN®) (2–4). While the recommendations for the treatment of small NETS (<1 cm: solely appendectomy) and large NETs (>2 cm: additional right-sided hemicolectomy) are straightforward and unequivocal, recommendations for the optimal treatment strategy for NETs of the appendix measuring 1–2 cm lack uniformity. In both the ENETS and NANETS guidelines, additional right-sided hemicolectomy is recommended for this group when one or more histopathological risk factors (unclear resection margins, lympho-vascular invasion, high proliferation rate or invasion

of the mesoappendix greater than 3 mm) are present (2,3). On the contrary, in the NCCN guideline, an appendectomy is considered sufficient for this group regardless of the presence of these histopathological risk factors (4). The rationale behind the recommendation for additional right-sided hemicolectomy in these patients is the relatively high incidence of lymph node involvement (5–9).

Yet, right-sided hemicolectomy has not been shown to be associated with improved survival rates in these patients, not even in those with histopathological risk factors (10,11). Based on data recently published by Nesti *et al.* re-evaluation of the recommendations may need to be considered.

Nesti *et al.* performed a large Europe-wide pooled cohort study including 278 patients across 40 institutions from 15 countries. They investigated the beneficial value of additional surgery for patients with appendiceal NETs measuring 1–2 cm (1). They included all patients with a histopathological proven appendiceal NET measuring 1–2 cm, treated between 2000 and 2010 in any of the recruiting centers and compared patients who underwent appendectomy only (n=163) with patients who received an

additional right-sided hemicolectomy (n=115). Primary outcomes were frequency of distant metastases and tumour-related mortality. Secondary outcomes were frequency of regional lymph node metastases in patients treated with right-sided hemicolectomy, overall survival and the association between local lymph node metastases and histopathological risk factors. In patients with metastatic disease and in case of death, the available histopathological tissue blocks were reviewed centrally by an experienced NET pathologist from the University of Bern.

Looking at the general characteristics of the two intervention groups, significantly more patients who underwent additional right-sided hemicolectomy (N=115) had incomplete resection margins after the initial appendectomy compared to those who underwent appendectomy alone (N=163) (13% vs. 1% respectively, P=0.0001). Furthermore, in significantly more patients who underwent additional right-sided hemicolectomy, the NET was located at the base of the appendix (15% vs. 7% respectively, P=0.0026).

In 9/278 (3.2%) patients, distant metastases were diagnosed, of whom four (2.5%) in the appendectomy group and five (4.3%) in the right-sided hemicolectomy group. However, in only four (1.4%) patients the metastases probably or possibly originated from the appendiceal NET. In the remaining five patients, the metastases were ascribed to other diagnoses. In all four patients in whom the metastases were probably or possibly related to NET, metastases occurred synchronously. No metachronous metastases were found during the follow up period [median 13 years; interquartile range (IQR) 11–16 years]. Overall, there were tumour-related deaths in two patients in the right-sided hemicolectomy group (N=115) according to the local hospital. Both of the deceased patients had metastatic disease. However, a central review of the tissue blocks demonstrated that their metastases were unlikely to be related to the appendiceal NET as another diagnosis was made [poorly differentiated small-cell neuroendocrine carcinoma (N=1) and main tumour mass in ileum (N=1) respectively].

Nesti *et al.* reported regional lymph nodes in 22/112 patients (19.6%) who underwent right-sided hemicolectomy. Incomplete resection (R1) was identified as the only histopathological risk factor associated with the occurrence of regional lymph node metastases. In the present study, overall survival was reported to be excellent and similar in both intervention groups (adjusted hazard ratio 0.88; 95% CI: 0.44–1.75; P=0.71). Overall survival

rates at 5, 10, 15 and 20 years were 96% vs. 94%, 92% vs. 91%, 87% vs. 87% and 80% vs. 87% for the appendectomy and right-sided hemicolectomy group, respectively.

Based upon these data, the authors concluded that regional lymph node metastases in patients with an appendiceal NET of 1–2 cm are clinically not relevant and not associated with reduced survival. In addition, they concluded that right-sided hemicolectomy was not beneficial in terms of long-term survival after complete resection of the NET by appendectomy. Their findings strengthen the idea that routine additional surgery for appendiceal NETs of 1–2 cm might be unnecessary (1).

With this study, new important evidence has become available for the ongoing debate whether or not additional right-sided hemicolectomy should be recommended for patients with appendiceal NETs measuring 1–2 cm. Nesti *et al.* carefully defined and investigated a homogenous study population by adhering to the accepted ENETS guideline for risk assessment of appendiceal NETs (1,2). Their international collaboration has resulted in a relatively large cohort of patients with a long follow up period (1). Another strength of the study is the fact that central review of the histopathological specimens available was performed in case of death or metastatic disease to rule out other diagnoses.

When evaluating these new data and their practical implications, we need to keep the following limitations of this study in mind. (I) Only 40 of the 80 institutions (50%) approached for participation, actually participated. It would be of interest to know how many patients were excluded due to non-participation to estimate the magnitude of selection bias. (II) The number of patients with metachronous distant metastases might be underreported due to lack of routine imaging studies in the follow-up period. (III) Although the follow up period of median 13 years seems long in comparison to other studies, we need to consider that appendiceal NET is an indolent disease. Distant metastases related to appendiceal NETs may occur decades later. (IV) The two intervention groups differed significantly with respect to incomplete resection margins after initial appendectomy and in terms of location of the NET (location at the base of the appendix was significantly more common in the group of patients who underwent additional surgery). Therefore, it is unclear if outcomes were truly equal for both treatment options, or if these results may have been affected by comparison of two distinct patient groups. (V) Regarding the statistical analysis, the low incidence of the primary outcome could cause a potential problem with the number of confounding factors used for adjustment. A

propensity score method could have been used alongside for comparison. (VI) It needs to be taken into consideration that a part of the research population (those treated between 2000 and 2010) was treated in an era before the implementation of international guidelines for treatment of appendiceal NETs (2-4). In this time frame, decision-making for patients with appendiceal NET was mostly determined by institution and/or surgeons' preferences and a large variety in clinical practice existed, which could have influenced results. The implementation of international guidelines led to more uniformity and less clinical practice variation. Of last concern are the applicability and generalizability of this study. Data can only be extrapolated to patients with NET of the appendix and not for other appendiceal neoplasms. Furthermore, patients with grade 2 NET were relatively underrepresented in this study.

Despite these limitations, this study adds considerably to the debate on whether patients with appendiceal NETs measuring 1–2 cm should be performed a right-sided hemicolectomy. In line with previous studies, lymph node metastases are found in approximately 20% of these patients (12-15). Previously, rates up to 38–47% have been reported, although these high numbers should be interpreted with caution as in some studies other more malignant forms of neuroendocrine neoplasms were also included (5,16). Despite the high rate of lymph node involvement, excellent overall survival rates have been reported. Even for patients with appendiceal NETs measuring 1–2 cm with histopathological risk factors treated with appendectomy alone (10,11,17,18). There seems to be no beneficial value of additional right-sided hemicolectomy in this group of patients in terms of improved survival rates, as was confirmed by the recent study from Nesti *et al.* (1). When no benefit of additional surgery is present in these patients, we need to re-evaluate its necessity and take into account other outcome variables. Especially since right-sided hemicolectomy is associated with surgery related complications, like anastomotic leakage, anastomotic stenosis, superficial/deep site infection and bleeding etcetera. Recently, Alexandraki *et al.* published a paper reporting on the health-related quality of life (HRQoL) in patients treated with right-sided hemicolectomy for appendiceal neuroendocrine neoplasms. They found that patients who underwent additional right-sided hemicolectomy more frequently reported impaired social functioning, diarrhea and financial difficulties (12). Hence, additional surgery comes with a price. Outcomes such as costs, HRQoL and patient preference should therefore also

be taken into account when the role of additional surgery for these patients is determined. It may be valuable to develop individual treatment plans based on shared-decision making. Furthermore, it might be interesting to investigate the potential effect of age at diagnosis and treatment of intermediate appendiceal NET and their outcomes in terms of disease free survival. As already mentioned, current literature is very scarce and therefore large international cohort studies are needed for this purpose. Parallel to the discussion about treatment, the role of routine intensive follow up should also be discussed. If overall survival is excellent, metachronous distant metastases are rare and there is no influence of lymph node metastases on these outcomes, it may be questioned whether or not follow-up with biomarkers and imaging studies is needed. The data shown by Nesti *et al.* demonstrate that an unclear resection margin after appendectomy is the only histopathological risk factor associated with regional lymph node metastasis. However, this does not seem to influence survival. It is imaginable that these patients would benefit from close monitoring as they seem at risk for developing late distant metastases or disease recurrence (19). However, the optimal follow-up strategy remains a topic of discussion. Follow-up with imaging studies such as computed tomography (CT) or magnetic resonance imaging (MRI) and blood markers such as CgA or 5-HIAA have been described in some studies, but have not been compared with each other to assess their sensitivity in detecting metastases or disease recurrence (20-25). An argument can be made to opt for MRI in young patients due to the radiation impact of repetitive CT scanning (20). Patient factors and preferences should also be taken into account when new recommendations on this topic are formulated.

To conclude, with the arrival of the study by Nesti *et al.* new evidence has become available questioning the role of right-sided hemicolectomy for patients with an appendiceal NET, measuring 1–2 cm. Although the results of this study should be interpreted with care, these should incur the re-evaluation of current guidelines on the treatment of this specific group of patients.

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-23-655/prf>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-23-655/coif>). IJNK, MFR and RRG are recipients of the KiKa research grant paid to the institution especially as investment for the multicenter NET trial. IJNK reports that he receives funding from the Hartwig Foundation and EuroQoL, which are related to other research projects, not related in any manner to the topic of this manuscript. RRG reports that he receives the grant paid to the institution from Zonmw for the APAC trial, RCT on optimal treatment strategy for simple appendicitis in children (operative *vs.* non-operative) and the grant paid to the institution from LTC for the CAPP trial, Prospective cohort study on the optimal treatment strategy for complex appendicitis in the pediatric population. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are 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.

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Cite this article as: Bachiri S, van Amstel P, Koppen IJN, van der Weide MC, Raphael MF, Gorter RR. Hemicolectomy versus appendectomy alone for appendiceal neuroendocrine tumours between 1–2 cm in size—are we overtreating? *Transl Cancer Res* 2023;12(9):2420-2424. doi: 10.21037/tcr-23-655