

## **Hemicolectomy for patients with appendiceal neuroendocrine tumours**

### **1-2cm in size: a retrospective, Europe-wide, pooled, cohort study**

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## 1 RESEARCH IN CONTEXT

2 **Evidence before this study:** The most pertinent consensus guidelines for European countries  
3 regarding the management of appendiceal neuroendocrine tumours (aNET) 1-2cm in size were  
4 published by the European Neuroendocrine Tumor Society (ENETS). They recommend  
5 oncological right-sided hemicolectomy in cases where one or more histopathological risk factors  
6 are present (positive or unclear margins, deep mesoappendiceal invasion >3 mm, higher  
7 proliferation rate, lymphovascular invasion). Hemicolectomy is associated with higher morbidity  
8 rates and lowered quality of life. We therefore searched PubMed from inception to August 1<sup>st</sup>,  
9 2022, using the terms “neuroendocrine tumour” and “appendix”. While several studies recently  
10 discussed potential global overtreatment by performing oncological resections for aNET 1-2cm,  
11 they are unable to inform treatment decisions due to observational design and low statistical  
12 power.

13 **Added value of this study:** This is by far the largest investigation of a homogeneous, clinically  
14 well-characterized cohort of completely resected aNET 1-2cm in size, supported by ENETS. We  
15 found that long-term overall survival was similar between patients with aNET 1-2cm that  
16 underwent appendectomy as the only measure or right-sided hemicolectomy. Residual regional  
17 lymph node metastases in those that underwent appendectomy as the only measure appeared  
18 clinically irrelevant. No patients developed novel metastases during >10 years follow-up, and  
19 there were no tumour-related deaths.

20 **Implications of all the available evidence:** The role of a systematic lymphadenectomy by right-  
21 sided hemicolectomy following complete resection of the aNET 1-2cm by appendectomy is  
22 debated, but recommended by current guidelines in the presence of histopathological “risk  
23 factors”. The results of the present European multinational cohort study provide the most



24 reliable evidence that right-sided hemicolectomy is not indicated in aNET 1-2cm in size, and that  
25 the potential benefits do not justify the risk of this operation. These findings should inform  
26 consensus best practice guidelines for this typically young group of patients. In view of the low  
27 incidence of the disease and the need for a long-term follow-up, a prospective, randomized trial  
28 on the present research question will likely not be practical.

29

30 **ABSTRACT**

31 **Background:** Awareness of a potential global overtreatment by performing oncological  
32 resections for appendiceal neuroendocrine tumours (aNET) 1-2cm is increasing, but the rarity of  
33 this situation impeded a clear recommendation hitherto. We aimed at assessing the malignant  
34 potential of aNET 1-2cm in patients with or without right-sided hemicolectomy.

35 **Methods:** This retrospective study pooled data from 40 European institutions regarding patients  
36 of any age and performance status with histopathologically confirmed aNET of size 1-2cm and  
37 complete resection of the primary tumour between January 1<sup>st</sup> 2000 and December 31<sup>st</sup> 2010.  
38 The patients either had an appendectomy only or an appendectomy with oncological right-sided  
39 hemicolectomy or ileocecal resection. Predefined primary outcomes were frequency of distant  
40 metastases and tumour-related mortality rate. Secondary outcomes included frequency of  
41 regional lymph node metastases and overall survival with or without right-sided hemicolectomy.  
42 Cox proportional hazards regression was used to estimate the relative all-cause mortality hazard  
43 associated with patients undergoing right-sided hemicolectomy compared to appendectomy  
44 alone.

45 **Findings:** Of 278 patients (110 [39.6%] men and 168 [60.4%] women) with aNET 1-2cm included  
46 in the study, 163 (58.6%) had an appendectomy and 115 (41.4%) right-sided hemicolectomy.  
47 After centralized histopathological review, the aNET was classified as a possible or probable  
48 primary tumour in two patients with distant peritoneal metastases and in two patients with  
49 distant metastases in the liver. All metastases were diagnosed synchronously with no tumour-  
50 related deaths during the follow-up. Regional lymph node metastases were found in 22 (19.6%)  
51 patients with right-sided hemicolectomy. We estimated that 12.8% (95% confidence interval 6.5  
52 - 21.1%) of patients undergoing appendectomy likely had residual regional lymph node

53 metastases based on histopathological risk factors. Overall survival after a median follow-up of  
54 13.0 years was similar between patients with appendectomy and right-sided hemicolectomy  
55 (adjusted hazard ratio .88, 95% confidence interval .36 - 2.17, P = .71).

56 **Interpretation:** This study provides evidence that right-sided hemicolectomy is not indicated  
57 following complete resection of the aNET 1-2cm by appendectomy, that regional lymph-node  
58 metastases of aNET are clinically irrelevant, and that an additional postoperative exclusion of  
59 metastases and histopathological evaluation of risk factors is not supported by the presented  
60 results.

61 **Funding:** Swiss Cancer Research foundation (KFS-4741-02-2019).

62

## 63 INTRODUCTION

64 Appendiceal neuroendocrine tumours (aNET) are often diagnosed incidentally on  
65 histopathological examination and occur in 1.5% of all appendectomies with an annual incidence  
66 rate of 0.15 – 0.6 per 100,000.<sup>1,2</sup> The most pertinent consensus guidelines for the management  
67 of aNET were published in 2016 by the European Neuroendocrine Tumor Society (ENETS).<sup>2</sup> Simple  
68 appendectomy and oncological right-sided hemicolectomy are undebated surgical procedures  
69 for aNET <1cm and >2cm, respectively, but the treatment of aNET 1-2cm, accounting for 5-25%  
70 of all aNET, is challenging. The ENETS guidelines recommend oncological right-sided  
71 hemicolectomy in cases where one or more histopathological features are present: positive or  
72 unclear margins, deep mesoappendiceal invasion >3 mm, higher proliferation rate (WHO grade  
73 2 [G2]), vascular (V1) and/or lymph vessel (L1) invasion. These factors have been associated with  
74 the presence of lymph node metastases,<sup>3-6</sup> but the prognostic implications of the latter are  
75 unknown.<sup>7</sup> Based on several recent retrospective studies,<sup>3,8-14</sup> there is growing awareness that  
76 there may be overtreatment in this intermediate-risk group. This is important as hemicolectomy  
77 is associated with short-term morbidity rates of 2% and impaired health-related quality of life.<sup>1,6</sup>

78

79 The ability of existing literature to reliably inform treatment guidelines is limited by several  
80 factors. First, the short follow-up (maximum 5 years) of many studies precludes understanding  
81 of long-term safety of either surgical approach, which is compounded by small sample size (less  
82 than 15 patients).<sup>8,10</sup> Second, data on follow-up,<sup>9</sup> risk factors<sup>9,10,13,14</sup> and aNET diameter<sup>9,12,13</sup>  
83 were missing or inconsistently reported. Third, aNET 1-2 cm were combined with the biologically  
84 different goblet cell adenocarcinomas (formerly goblet cell carcinoid), high grade or anaplastic

85 carcinoid tumours <sup>10-13</sup> and aNET <1cm <sup>3,11,14</sup> in the statistical analyses, making inference  
86 regarding the intermediate-risk tumour group difficult.

87 By pooling data from 40 European institutions with >10 years of follow-up, this study seeks to  
88 robustly quantify the malignant potential of aNET 1-2cm in size, and evaluate the  
89 appropriateness of the two typically used treatment approaches.

90

## 91 **METHODS**

### 92 **Study Design and Participants**

93 We conducted a multicentre, international, retrospective cohort study of patients of any age and  
94 performance status with histopathologically confirmed aNET 1-2cm that underwent complete  
95 resection of the primary tumour between January 1<sup>st</sup> 2000 and December 31<sup>st</sup> 2010.

96 The ENETS office invited all 56 ENETS centres of excellence to participate in the present study  
97 and the study was presented in two ENETS advisory board meetings 2019 and 2020. Twenty four  
98 further European institutions were approached by personal contacts. Of the 54 institutions that  
99 agreed to participate, we included 40 institutions in 15 European countries (Austria, Belgium,  
100 Denmark, France, Germany, Greece, Israel, Italy, Netherlands, Norway, Poland, Spain, Sweden,  
101 Switzerland, and United Kingdom). Fourteen institutions were excluded for various reasons  
102 **(appendix p 1 and p2).**

103 This multicentre study was approved by the ethics commission of the canton Bern, Switzerland  
104 (KEKBE 2019-01135) and at each participating centre per their institutional guidelines. Only  
105 anonymized data were shared with the coordinating institution Inselspital Bern, University of  
106 Bern, Switzerland. No written informed consent was necessary. The study is registered with  
107 ClinicalTrials.gov, NCT03852693.

108

### 109 **Procedures**

110 Demographic, clinical, pathologic, treatment, and outcome data were extracted from electronic  
111 medical records at each institution either by C.N. during an on-site visit or by local investigators  
112 with expertise in the treatment of NET. Missing follow-up data were completed by contacting the  
113 family doctor and/or the patients directly. Standardized data collection templates were used.

114 Study data were collected and centrally managed by C.N. using REDCap electronic data capture  
115 tools hosted at CTU Bern, University of Bern.<sup>15,16</sup>

116 Patients were summarized in two subgroups based on surgical approach: (1) Simple  
117 appendectomy or appendectomy during another primary surgery (subsequently named  
118 appendectomy), and (2) appendectomy with oncological right-sided hemicolectomy or ileocecal  
119 resection in one or two stages (subsequently named right-sided hemicolectomy).

120 All available tissue blocks with missing histopathological risk factors defined by the ENETS  
121 guidelines were reviewed locally by an experienced NET pathologist. In case of deceased or  
122 metastatic patients, all tissue blocks available were reviewed by A.P. at the Institute of Pathology,  
123 University of Bern by using the 2019 World Health Organization (WHO) classification of  
124 gastrointestinal tumours to confirm the diagnosis of the primary tumour and the metastasis and  
125 collect all relevant pathological information. If the aNET was confirmed, the likelihood of the  
126 metastasis originating from the aNET as primary tumour was classified as unlikely (metastasis of  
127 a histopathologically different primary NET/neuroendocrine carcinoma; main tumour mass of the  
128 primary NET in the ileum), possible (no tissue block available) or probable (histopathological  
129 serosal perforation of the aNET with concomitant peritoneal spreading; image guided and clinical  
130 diagnosis of metastases with carcinoid syndrome, while no tissue blocks were available).

131

## 132 **Outcomes**

133 Predefined primary outcomes were the frequency of distant metastases and tumour-related  
134 mortality rate subsequent to complete resection of aNETs 1-2cm in size. Secondary outcomes  
135 were the frequency of patients with regional lymph node metastases in aNETs 1-2cm treated  
136 with right-sided hemicolectomy and the association of regional lymph node metastases with the

137 histopathological risk factors according to the ENETS guidelines. Based on a statistical adjustment  
138 for the latter histopathological risk factors, the frequency of patients with regional lymph node  
139 metastases at the time of diagnosis was estimated for aNET 1-2cm treated with appendectomy.  
140 Additionally, overall survival was assessed for patients with or without right-sided  
141 hemicolectomy.

142

### 143 **Statistical Analysis**

144 We provide descriptive information of the entire patient population and separately for those  
145 with appendectomy and those with right-sided hemicolectomy. Crude comparisons between the  
146 two subgroups are done with t-tests for continuous characteristics and chi-square tests for  
147 categorical characteristics. For the survival analysis, observation time started at the date of  
148 primary surgery and ended at the date of death or last date the patient was known to be alive.  
149 Kaplan-Meier methodology was used to estimate 5-, 10-, 15- and 20-year overall survival after  
150 primary surgery. Cox proportional hazards regression was used to estimate the relative all-cause  
151 mortality hazard associated with patients undergoing right-sided hemicolectomy compared to  
152 appendectomy alone. In order to account for differences in patient and tumour characteristics,  
153 we used multivariable Cox regression where we included age, sex, American Society of  
154 Anaesthesiologists (ASA) score and histopathological risk factors. This was done using hazard  
155 ratios (HRs) and 95% confidence intervals (CIs). The proportional hazards assumption was assessed  
156 via visual inspection of whether the curves are reasonably parallel in the so-called "log-log" plots, i.e. the  
157 plot of the  $\ln\{-\ln(\text{survival})\}$  curves for patient group versus  $\ln(\text{analysis time})$ .  
158 Among the subgroup that underwent right-sided hemicolectomy, we compared the percentage  
159 of patients with and without lymph node metastases stratified by histopathological risk factors.



160 As patients not undergoing completion right-sided hemicolectomy after appendectomy may  
161 have residual, undetected regional lymph node metastases, we sought to estimate this indirectly.  
162 We fitted a logistic regression model (considering tumour location, grade, resection margin,  
163 lymphovascular invasion and mesoappendix infiltration) in this subgroup for having a positive  
164 lymph node, and used the coefficients of this logistic regression model to estimate the proportion  
165 of patients having undetected regional lymph node metastases in the subgroup with  
166 appendectomy only. We used the bootstrap method to obtain a 95% CI for this estimate.<sup>17</sup> A p  
167 value of less than .05 was considered statistically significant. We did all analyses using Stata  
168 (version 17).

169

#### 170 **Role of the Funding Source**

171 The funder of the study had no role in study design, data collection, data analysis, data  
172 interpretation or writing of the report. All authors agreed with the decision to submit for  
173 publication.

174

175 **RESULTS**

176 Of 13 patients with reported metastases, four were excluded (ileal NET with infiltration in the  
177 appendix [two patients], goblet cell adenocarcinoma [one patient] and aNET larger than 2cm [one  
178 patient]). In all, 278 patients with aNET 1-2cm that underwent complete resection of the primary  
179 tumour between January 1<sup>st</sup> 2000 and December 31<sup>st</sup> 2010 were included in the study (**figure 1**).  
180 We identified 163 (58.6%) patients with appendectomy and 115 (41.4%) with right-sided  
181 hemicolectomy (including one patient with ileocecal resection). There were no significant  
182 differences in the two subgroups in terms of age (P = .90), sex (P = .11) and ASA score (P = .62).  
183 We did not collect data on race/ethnicity. Histopathological features differed significantly only in  
184 terms of tumour location (P = .0026) and resection margin (P = .0001) with more tumours at the  
185 base and more positive resection margins in patients with right-sided hemicolectomy (14.8 vs.  
186 6.7% and 13.0 vs. 0.6%, respectively) (**table 1**). In all, 52 (18.7%) patients showed serosal  
187 perforation of the aNET in histopathological examination. All patients had a clinical follow-up,  
188 while a follow-up with computed tomography (CT) or magnetic resonance imaging (MRI) was  
189 performed in 156 (56.1%) patients (75/163 [46.0%] patients with appendectomy and 81/115  
190 [70.4%] with right-sided hemicolectomy). After 10 years or more, 42 (15.1%) patients had a  
191 follow-up with CT or MRI (19/163 [11.7%] patients with appendectomy and 23/115 [20.0%] with  
192 right-sided hemicolectomy).

193

194 In the histopathological review of the nine patients with metastatic disease (four patients with  
195 appendectomy and five patients with right-sided hemicolectomy), the aNET 1-2cm was classified  
196 as unlikely to be the origin of metastases in five patients, possible in one patient, and probable  
197 in three patients (**table 2**). Of the latter four patients, metastases were diagnosed synchronously

198 with the aNET 1-2cm. Two patients had a histopathological serosal perforation and peritoneal  
199 spreading. Distant peritoneal metastases were successfully treated without recurrence by  
200 electrocoagulation and oncological right-sided hemicolectomy, respectively. In one patient, a  
201 liver metastasis was successfully treated by radiofrequency ablation, followed by Peptide  
202 Receptor Radionuclide Therapy (PRRT), without previous biopsy. In one patient with bilobar liver  
203 metastases and a lymph node metastasis in the transverse mesocolon, new regional and distant  
204 metastases occurred despite three doses of PRRT, followed by selective internal radiation  
205 therapy (SIRT). No tissue samples were available. The patient is alive after a follow-up of 11 years.  
206 In both patients with liver metastases, the only histopathological risk factor according to the  
207 ENETS guidelines was lymphovascular invasion of the primary tumour.

208 Overall, tumour-related death was attributed to the aNET 1-2cm by the local treating institution  
209 in two patients. However, our central histopathological review suggested that their metastases  
210 were likely unrelated to the aNET 1-2cm (one patient had a poorly differentiated small-cell  
211 neuroendocrine carcinoma without any known metastases of a well differentiated NET and  
212 another had a main tumour mass in the ileum thought to be the primary).

213

214 Regional lymph node metastases were found in 22 (19.6%) patients with right-sided  
215 hemicolectomy (in three patients with right-sided hemicolectomy no lymph nodes were  
216 evaluated). Regarding the histopathological risk factors defined by the ENETS guidelines, their  
217 occurrence was significantly associated with the resection margin only ( $P = .023$ ; **appendix p 3**)  
218 with a higher proportion of patients with R0 resection margin in patients without lymph node  
219 metastases (87.8 vs. 63.6%).

220 Since no lymph nodes were retrieved in patients with appendectomy only, the presence of lymph  
221 node metastases was estimated in this group. **Appendix p 3** shows the logistic regression model  
222 fitted for having regional lymph node metastases in patients with right-sided hemicolectomy.  
223 Based on the coefficients of this model, we estimated that 12.8% (95% CI 6.5 - 21.1%) of patients  
224 undergoing appendectomy likely had undetected residual regional lymph node metastases at the  
225 time of diagnosis.

226

227 The median follow-up was 13.0 years (interquartile range, 11.0 – 15.6 years). In 163 patients with  
228 appendectomy only, 20 deaths were recorded in 20 years resulting in estimates of overall survival  
229 after 5, 10, 15 and 20 years of 95.6% (95% CI 90.9-97.9%), 91.6% (95% CI 85.9-95.0%), 87.1% (95%  
230 CI 80.1-91.8%) and 80.4% (95% CI 69.5-87.8%). In 115 patients with right-sided hemicolectomy,  
231 13 deaths were recorded in 20 years resulting estimates of overall survival after 5, 10, 15 and 20  
232 years of 93.9% (95% CI 87.6-97.0%), 91.2% (95% CI 84.2-95.2%), 87.4% (95% CI 79.1-92.6%) and  
233 87.4% (95% CI 79.1-92.6%). Kaplan-Meier estimates of overall survival were similar between  
234 patients with appendectomy and right-sided hemicolectomy (HR .88, 95% CI .44 - 1.75, P = .71;  
235 **figure 2**) with reasonably parallel lines in the "log-log" plots. They were also similar in multivariable  
236 cox regression analysis including histopathological risk factors (tumour location, tumour grade,  
237 resection margin, lymphovascular invasion and mesoappendix infiltration) (adjusted HR .88, 95%  
238 CI .41 - 1.89, P = .75) and including both histopathological risk factors and patient characteristics  
239 (age, sex and ASA score) (adjusted HR .88, 95% CI .36 - 2.17, P = .79). There was no surgical  
240 mortality.

241

242 Patients with incidental appendectomy performed during primary surgery for another indication  
243 and those with appendectomy as a consequence of primary oncological right-sided  
244 hemicolectomy or ileocecal resection might have had advanced tumours of different entities,  
245 leading to a bias in the overall survival. After excluding these patients (41 [25.2%] patients with  
246 appendectomy and 22 [19.1%] patients with right-sided hemicolectomy), Kaplan-Meier  
247 estimates of overall survival were still similar between patients with appendectomy and right-  
248 sided hemicolectomy (HR .81, 95% CI .19 - 3.41, P = .78; **figure 3**) with 5 (4.1%) deaths reported  
249 after appendectomy and 3 (3.2%) deaths reported after right-sided hemicolectomy. They were  
250 also similar in multivariable cox regression analysis for the latter two groups of patients including  
251 histopathological risk factors (tumour location, tumour grade, resection margin, lymphovascular  
252 invasion and mesoappendix infiltration) (adjusted HR 1.19, 95% CI .21 - 6.90, P = .84) and  
253 including both histopathological risk factors and patient characteristics (age, sex and ASA score)  
254 (adjusted HR .67, 95% CI .02 - 18.07, P = .81).

255 **DISCUSSION**

256 The aim of this Europe-wide retrospective ENETS study was to quantify the malignant potential  
257 of aNET 1-2cm. The summarized results include two main statements: first, regional lymph node  
258 metastases of aNET 1-2cm are clinically not relevant and not associated with reduced tumour-  
259 specific survival; second, right-sided hemicolectomy has no benefit on long-term survival  
260 following complete resection of the primary tumour by appendectomy.

261  
262 These two statements with practical implication need further discussion. Brighi et al. found a  
263 difference in disease-specific survival of 78 vs. 141 months in patients with aNET and regional  
264 lymph node metastases compared to those without nodal involvement, although this difference  
265 was not statistically significant.<sup>3</sup> However, histopathological slides have not been reviewed and  
266 it is unclear how many of these patients had aNET >2cm. Also, no patient developed relapse  
267 during follow-up in this study, irrespective of appendectomy with or without hemicolectomy.  
268 Other studies,<sup>10,12-14</sup> as well as our own results, do not show survival differences depending on  
269 presence or absence of lymph node metastases. We found regional lymph node metastases in  
270 19.6% of patients with right-sided hemicolectomy, a similar range as previously reported.<sup>1,4,12,18</sup>  
271 Corrected for the histopathological risk factors defined in the ENETS guidelines, we would expect  
272 residual lymph node metastases in 12.8% of the patients with appendectomy in the present study  
273 population. Nevertheless, the overall survival after a median follow-up of 13 years was similar  
274 with or without resection of regional lymph nodes, and no tumour relapse or tumour-related  
275 death occurred. Consequently, completion right-sided hemicolectomy following the ENETS  
276 guidelines in aNET 1-2cm would lead to overtreatment with unnecessary morbidity. Since lymph  
277 node metastases seem clinically irrelevant, this finding might be extrapolable to aNET >2cm.

278 Additionally, a recent study found a lowered health-related quality of life due to impaired social  
279 functioning and development of diarrhea after oncological right-sided hemicolectomy in aNET  
280 patients.<sup>6</sup>

281 Importantly, no patient with aNET 1-2cm developed metachronous distant metastasis during >10  
282 years of follow-up. Distant metastases reported at time of appendectomy turned out to be most  
283 frequently metastases of concomitant ileal NET in centralized histopathological review.  
284 Interestingly, the only distant metastases clearly related to aNET 1-2cm were peritoneal  
285 metastases, and they were associated with serosal perforation of the primary tumour. Even this  
286 feature, which is associated with NET induced death in pancreatic and ileal NET, was controlled  
287 by loco-ablative techniques in one patient and by performing right-sided hemicolectomy in the  
288 second patient.

289 The risk for further distant metastases in aNET 1-2cm is very low. In the present study we only  
290 found two patients with synchronous distant metastases in the liver, leading to a risk for distant  
291 metastases other than peritoneal metastases of 0.7%. Importantly, the diagnosis could not be  
292 confirmed histopathologically due to missing tissue samples in both patients.

293  
294 At this point the question about strengths and limitations of our study arises: the strengths  
295 include a well characterized cohort of 278 patients with aNET 1-2cm, standardized data collection  
296 by on-site visits of C.N. or dedicated local investigators with expertise in the treatment of NET,  
297 and the long median follow-up. The vast majority of available relative survival data are based on  
298 cancer registries, such as the Surveillance, Epidemiology, and End Results (SEER) program<sup>12-14,19</sup>  
299 or the National Cancer Data Base (NCDB),<sup>10</sup> suffering from coding issues in the presence of  
300 combined ileal and aNET and from nomenclature changes, as goblet cell adenocarcinomas used

301 to be classified as NET in earlier days. This is an important issue with regard to the results of our  
302 centralized histopathological review: In 13 patients with the external diagnosis of aNET 1-2cm  
303 with metastases, four were reclassified to a different primary tumour or a size >2cm, and in  
304 another five the metastases were judged as unlikely from the aNET, accounting for 69.2% of all  
305 metastasized patients. Another strength is that long-term overall survival rates up to 10 years are  
306 rarely described,<sup>11,12,19</sup> but are of utmost importance in this tumour of young patients. The  
307 appendectomy is a standardized procedure. Therefore, the results of the present study are  
308 generalizable to non-specialised institutions around the world.

309 The study also has limitations: first, the observational nature with the need to retrospectively  
310 compare patients with appendectomy and right-sided hemicolectomy; second, not all aNET have  
311 been reviewed histopathologically and not all histopathological risk factors could be obtained;  
312 third, all patients had a clinical follow-up, but only few patients had a follow-up by CT or MRI  
313 after 10 years or more; fourth, despite the important support of ENETS, the Europe-wide  
314 participation of institutions and the inclusion of patients over a period of 11 years, the study  
315 group is relatively small given by the low incidence of the disease. The approximate incidence  
316 rate for aNET independent of size is 0.15-0.6/100,000/year.<sup>2</sup>

317  
318 The results of the present European multinational cohort study provide the most reliable  
319 evidence that right-sided hemicolectomy is not indicated in aNET 1-2cm in size, that the potential  
320 benefits do not justify the risk of this operation, and that an additional postoperative exclusion  
321 of metastases by a further medical imaging and histopathological evaluation of risk factors is not  
322 supported by the presented results and may therefore not be necessary. These findings should  
323 inform consensus best practice guidelines for this typically young group of patients.



325 **Contributors:** AP and RMK contributed equally to this work. CN and RMK had full access to all the  
326 data and verified the data in the study. CN and RMK take responsibility for the integrity of the  
327 data and accuracy of the data analysis.

328 *Concept and design:* RMK, AP, MZ.

329 *Acquisition, analysis, or interpretation of data:* All authors.

330 *Drafting of the manuscript:* RMK, CN, AP, MZ.

331 *Critical revision of the manuscript for important intellectual content:* All authors.

332 *Statistical analysis:* MZ.

333 *Obtained funding:* RMK, AP, MZ.

334 *Administrative, technical, or material support:* AP, RMK.

335 *Supervision:* AP, RMK.

336 All authors had access to all the data reported in the study. The corresponding author had full  
337 access to all of the data and the final responsibility to submit for publication.

338

339 **Data sharing:** The de-identified individual-level patient data, data dictionary, and protocol for  
340 this study can be provided to researchers upon written request 24–36 months after publication  
341 of this article. Please send enquiries to the corresponding author. A detailed proposal for how  
342 the data will be used is required and we will assess applications on a case-by-case basis, and only  
343 for the purpose of individual participant data meta-analysis. A data access agreement must be  
344 signed for these data to be released.

345

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358 Roche. GC reports, outside the submitted work, grants/contracts from AAA, consulting fees from  
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361 travel from AAA, Ipsen and Keocyt. MP reports, outside the submitted work, payments for  
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367 president, ESMO Education Committee, ESMO scientific steering committee NET track, advisor  
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370 work, being an ENETS Advisory Board member. TV reports, outside the submitted work, payment

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## FIGURE LEGENDS

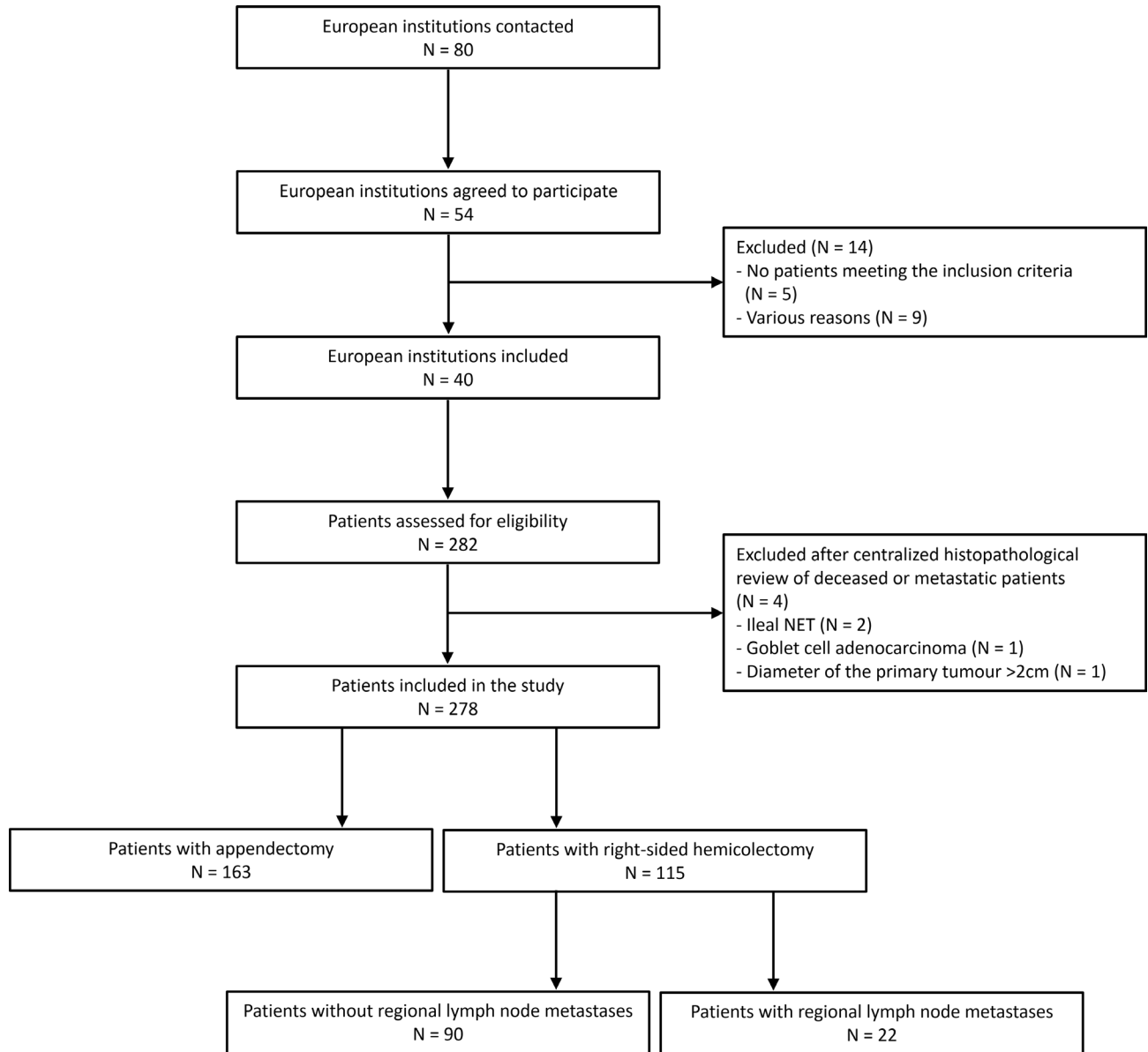
**Figure 1.** Study flow chart.

**Figure 2.** Kaplan-Meier estimates of overall survival for patients treated with appendectomy vs. right-sided hemicolectomy.

**Figure 3.** Kaplan-Meier estimates of overall survival for patients treated with appendectomy vs. right-sided hemicolectomy excluding patients with advanced tumours of different entities.

## FIGURES

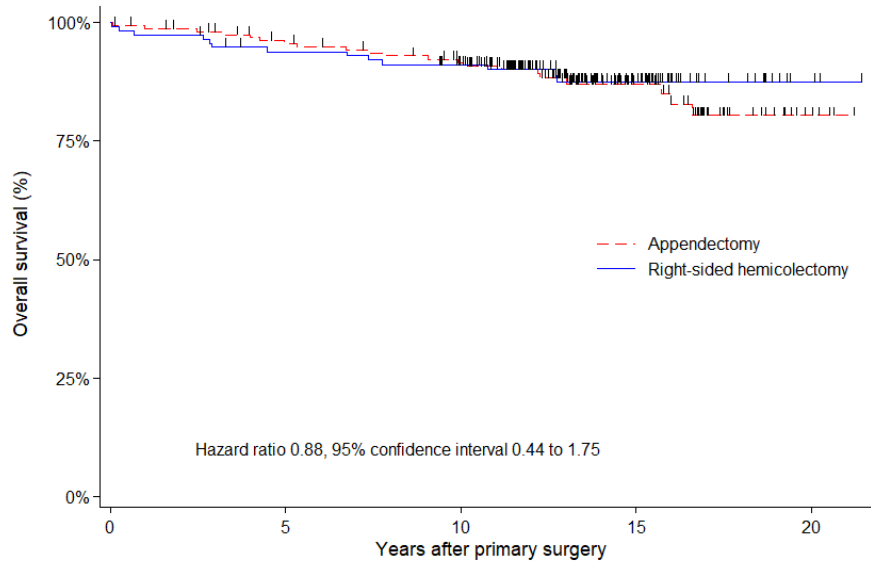
Figure 1.



Abbreviation: NET, neuroendocrine tumour.



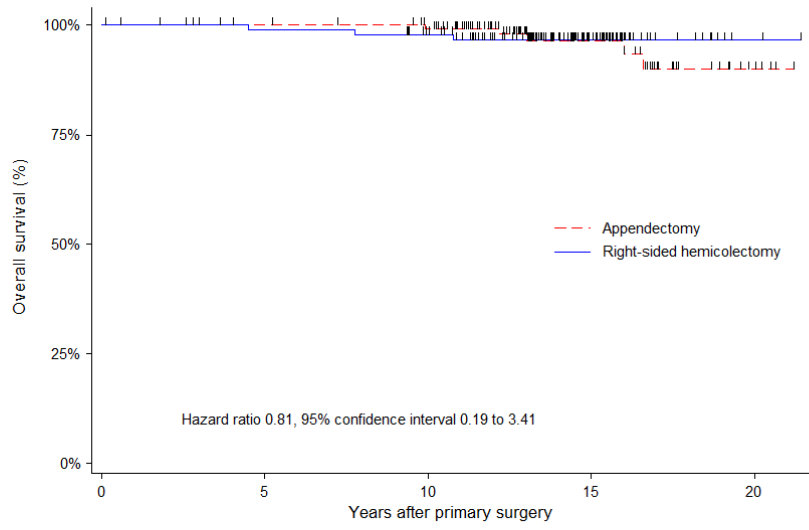
Figure 2.



Number at risk (number censored)

Appendectomy	163 (0)	147 (9)	134 (16)	50 (95)	4 (141)
Right-sided hemicolectomy	115 (0)	105 (3)	96 (9)	38 (65)	3 (101)

**Figure 3.**



Number at risk (number censored)	0	5	10	15	20
Appendectomy	122 (0)	115 (7)	109 (12)	41 (78)	4 (116)
Right-sided hemicolectomy	93 (0)	91 (1)	85 (6)	35 (56)	2 (89)

## TABLES

**Table 1.** Patient Characteristics

	Overall (N = 278)	Appendectomy (N = 163)	Right-sided hemicolectomy (N = 115)	P Value
Age at initial surgery, mean (SD), y	36.0 (18.2)	36.2 (18.4)	35.9 (17.9)	.90
Sex, No. (%)				
Male	110 (39.6)	71 (43.6)	39 (33.9)	.11
Female	168 (60.4)	92 (56.4)	76 (66.1)	
ASA score, No. (%)				
I	147 (52.9)	82 (50.3)	65 (56.5)	.62
II	36 (13.0)	21 (12.9)	15 (13.0)	
III	18 (6.5)	11 (6.8)	7 (6.1)	
IV	1 (0.4)	1 (0.6)	0 (0.0)	
V	1 (0.4)	0 (0.0)	1 (0.9)	
Not available	75 (27.0)	48 (29.5)	27 (23.5)	
Histopathological features, No. (%)				
Tumour location				
Tip/middle	227 (81.7)	144 (88.3)	83 (72.2)	.0026
Base	28 (10.1)	11 (6.7)	17 (14.8)	
Not available	23 (8.3)	8 (4.9)	15 (13.0)	
Tumour grade				
Grade 1	235 (84.5)	142 (87.1)	93 (80.9)	.36
Grade 2	25 (9.0)	12 (7.4)	13 (11.3)	
Not available	18 (6.5)	9 (5.5)	9 (7.8)	
Resection margin				
R0	252 (90.6)	156 (95.7)	96 (83.5)	.0001
R1	16 (5.8)	1 (0.6)	15 (13.0)	
Not available	10 (3.6)	6 (3.7)	4 (3.5)	
Lymphovascular invasion				
Yes	61 (21.9)	28 (17.2)	33 (28.7)	.073
No	191 (68.7)	119 (73.0)	72 (62.6)	
Not available	26 (9.4)	16 (9.8)	10 (8.7)	
Mesoappendix infiltration				
≤3mm	80 (28.8)	42 (25.8)	38 (33.0)	.10
>3mm	28 (10.1)	13 (8.0)	15 (13.0)	
Not available	170 (61.2)	108 (66.3)	62 (53.9)	
Tumour size				
1.0-1.5mm	221 (79.5)	135 (82.8)	86 (74.8)	.10
1.6-2.0mm	57 (20.5)	28 (17.2)	29 (25.2)	

Abbreviations: ASA, American Society of Anaesthesiologists.

**Table 2.** Histopathological review of deceased or metastatic patients

Patient no.	Likelihood of metastases due to a NET 1-2cm <sup>a</sup>	Time point of diagnosis <sup>b</sup>	Tumour-related death <sup>c</sup>	Histopathological review
1	Unlikely	Follow-up	Yes	Liver metastasis of poorly differentiated small-cell NEC
2	Unlikely	Initially	Yes	Diffuse infiltration of the ileum most probably due to ileal NET (main tumour mass in ileum)
3	Unlikely	Follow-up	No	Additional ileal NET found in follow-up
4	Unlikely	Initially	No	Primary tumour most probably ileal NET
5	Unlikely	Follow-up	No	Metastasis in the renal hilum due to colon NET
6	Possible	Initially	No	Liver metastasis diagnosed by (68)Gallium-DOTATATE PET-CT and successfully ablated with subsequent PRRT without previous biopsy
7	Probable	Initially	No	Distant peritoneal metastases
8	Probable	Initially	No	Distant peritoneal metastases
9	Probable	Initially	No	Concomitant metastases in liver and transverse mesocolon with the clinical diagnosis of a carcinoid syndrome and without second primary tumour

<sup>a</sup>The likelihood of the aNET as primary tumour for diagnosed metastases was classified as unlikely, possible or probable based on the centralized histopathological review.

<sup>b</sup>Time point at which metastases were diagnosed the first time (at initial presentation or in the follow-up).

<sup>c</sup>Diagnosis by the local treating institution (before centralized histopathological review).

Abbreviations: NEC, neuroendocrine carcinoma; NET, neuroendocrine tumour; PRRT, Peptide Receptor Radionuclide Therapy.