**The impact of lymph node metastases and right hemicolectomy on outcomes in appendiceal neuroendocrine tumours (aNETs)**

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**Abstract**

**Introduction**: European Neuroendocrine Tumour Society (ENETS) recommends managing appendiceal neuroendocrine tumours (aNET) with appendicectomy and possibly completion right hemicolectomy (CRH). However, disease behaviour and survival patterns remain uncertain.

**Materials and Methods**: We retrospectively assessed the impact of lymph nodes and CRH on outcomes, including survival, in all aNET patients diagnosed between 1990-2016.

**Results**: 102 patients (52F, 50M), median age 39.4 (range 16.3–81.1) years, were diagnosed with aNET. Mean tumour size was 12.7 (range 1-60) mm, most sited in appendiceal tip (63%). Index surgery was appendicectomy in 79% of cases while the remainder underwent colectomy. CRH performed in 30 patients at a median 3.2 (range 1.4–9.8) months post-index surgery yielded residual disease in nine: lymph nodes (n=8) or residual tumour (n=1). Univariate logistic regression showed residual disease was significantly predicted by tumour size ≥2cm (p=0.020). Four patients declined CRH, but did not suffer relapse or reduced survival. One patient developed recurrence after 16.5 years of follow-up and another patient developed a second neuroendocrine tumour after 18.8 years follow-up. There were 5 deaths; one being aNET-related. 5-year and 10-year overall survival were 99% and 92% respectively; 5-year and 10-year relapse-free survival were 98% and 92% respectively. Only 5-year relapse-free survival was affected by ENETS stage (p=0.002).

**Conclusion**: aNETs are indolent with very high rates of overall and relapse-free survival. Recurrence is rare, and in this series only occurred decades later, making a compelling case for selective surveillance and follow-up. The significance of positive lymph nodes and the necessity for completion right hemicolectomy remain unclear.

1. **Introduction**

Appendiceal neuroendocrine tumours (aNETs) are the most common primary tumours of the appendix and are detected in up to 2.3% of all appendectomies (1), usually incidentally in patients with appendicitis. A smaller proportion are found in patients who undergo abdominal surgery for other reasons (2).

The ENETS consensus guidelines recommend completion right hemicolectomy (CRH) for aNETs >2 cm to mitigate the risk of lymph node metastasis, tumour recurrence or distant metastases (3). The survival benefit of completion right hemicolectomy (CRH) over appendicectomy is uncertain. Current evidence guiding the management of aNETs is extracted from cohort studies and in the largest study with the longest follow-up (4), Moertel *et al* reported local recurrence in only one of 12 patients 29 years post-appendicectomy for aNET ≥ 2cm (4). The patient subsequently underwent CRH and was relapse-free 17-years later (4). The other 11 patients who had appendicectomy alone, were relapse-free after a median follow-up of 28 years (5). The Moertel series (4, 5), which has influenced Western treatment recommendations, clearly highlights that relapse-free survival is possible following only appendicectomy for aNET ≥ 2cm. Groth *et al* performed appendicectomy alone in 34/122 patients with aNET ≥ 2cm and did not detect a significant survival difference compared with patients who underwent colectomy (6). Some of the uncertainty surrounding management of aNETs will be resolved by the SurvivApp study which will recruit 700 patients with completely resected aNETs measuring 1-2 cm. The retrospective, observational study proposes that right-sided hemicolectomy has no impact on long-term survival after complete resection of the aNET and results are expected in 2022 (7).

To better understand the impact of either positive lymph nodes or right hemicolectomy on the outcome for patients with aNETs, we have retrospectively analysed recorded data at our tertiary referral centre. These data provide one of the largest contemporary single-centre series, with the longest follow up period, since the original publications of Moertel (4, 5) and Anderson (8) over 30 years ago.

**2. Materials and methods**

2.1 Data Collection

We identified all aNET patients from a prospectively maintained database at our ENETS Centre of Excellence between 1990 and 2016. No paediatric patients were included. We excluded patients with mixed adeno-neuroendocrine carcinomas, neuroendocrine carcinomas and goblet cell carcinomas. Inclusion relied upon on confirmation of original histology diagnosing aNET. Tumours were classified using the 2017 WHO classification system for gastro-enteropancreatic neuroendocrine neoplasms (9). Patients had surgery in our tertiary centre, but some underwent primary resection elsewhere before referral to us. We recorded post-operative mortality and complications using Clavien-Dindo (10) grading. Histology of all specimens was reviewed by an experienced neuroendocrine tumour histopathologist at our ENETS centre. Patients with aNETs ≥2cm in size, mesoappendiceal or lymphovascular involvement underwent octreotide scan to rule out metastatic disease. Post-operative surveillance involved 6- to 12-monthly clinic review and radiological imaging using MRI, CT or transabdominal ultrasound scanning at intervals based on clinician’s discretion. Follow-up was calculated from index aNET resection, and time to recurrence from aNET resection or CRH. We assessed and recorded all patient, tumour, and treatment characteristics. The project was registered at our institution as a retrospective audit.

2.2 Statistical analysis

Continuous variables were analysed using Student’s t-test and categorical data by Fisher’s exact test. Survival was analysed by Kaplan-Meier method, with comparisons between groups performed by log-rank test. Statistical significance was taken at the 5% level. All analyses were performed using R version 3.6.1 (The R Foundation, Vienna, Austria) and SAS version 9.4 (SAS UK, Marlow, UK).

**3. Results**

3.1 Patient characteristics

102 patients (52F, 50M) presented with aNET at a median age of 39.4 (range 16.3 – 81.1) years. Primary resections performed in all 102 patients included appendicectomy (n=81), right hemicolectomy (n=19), and subtotal colectomy (n=2) indicated by suspected appendicitis (n=80), the presence of an abdominal mass on imaging (n=7), or incidental finding at surgery (n=15). Operations which incidentally diagnosed aNETs were surgery for inflammatory bowel disease (n=4), colorectal cancer (n=4), inguinal hernia (n=2), gynaecological conditions (n=2), colonic polyps (n=1), cholecystitis (n=1), or bowel ischaemia (n=1). Patient characteristics are summarised in Table 1.

The majority of patients (60%, n=61) underwent diagnostic surgery elsewhere before referral to our tertiary centre. Following index surgery, 2 patients had Clavien-Dindo Grade III complications: stump appendicitis (n=1) or pelvic collection (n=1) following laparoscopic appendicectomy, and post-operative bleeding following open appendicectomy (n=1). These complications were respectively managed with interval surgery to excise appendiceal stump, re-look laparotomy for washout of collection, and re-look laparotomy for haemostasis. There were no other complications for which further intervention was required and mortality was 0%. The clinically relevant (Clavien-Dindo Grade II – IV) complication rate was thus 3%.

3.2 aNET Histology

All aNETs were well differentiated and mean tumour size was 12.7 (range 1 - 60) mm; distribution as follows: <1cm (n=44), 1-2cm (n=43), and >2cm (n=15). Tumours were mainly located at the tip of the appendix (n=64) but also in the body (n=27), base (n=9) or were multifocal (n=2). All patients were staged by ENETS TNM classification (11): stage 1 (n=26), stage 2a (n=35), stage 2b (n=14), stage 3a (n=13), stage 3b (n=11), and stage 4 (n=3). Most tumours were grade G1 (n=96), and a minority grade G2 (n=5) or G3 (n=1). Patients had median follow-up of 6.2 (0.8 – 27.8) years.

3.3 Completion surgery

The NET MDT recommended CRH for 34 patients based on the presence of one or more at-risk ENET criteria (3); mainly tumour size (n=15) and involved margins (n=8). CRH in 30/34 patients at median 3.2 (range 1.4 – 9.8) months after appendicectomy was performed laparoscopically in 16 patients of which 9 had their appendicectomy also performed laparoscopically. CRH was declined by 4 patients with G1 tumours due to concomitant pregnancy (n=2) or personal preference (n=2). None of these 4 patients subsequently suffered relapse or reduced survival in median follow-up of 4.7 (range 4.3-12.9) years. Logistic regression identified patient and tumour traits which predicted selection for completion surgery (**Table 2**).

Time to completion surgery exceeded 3 months in 17/30 patients who had CRH at median 4.3 (range 3.1 to 9.8) months, but this did not adversely affect survival or risk of relapse (p=1.000).

Completion right hemicolectomy was not associated with any Clavien-Dindo Grade II - IV complications and mortality was 0%.

CRH histology showed residual NET in 9/30 patients: lymph nodes alone (n=8) or residual tumour in caecum (n=1). 7/30 patients who underwent CRH had tumour size ≥2cm and all had residual disease. Univariate logistic regression confirmed size ≥2cm significantly predicted residual disease (**Table 3**).

3.4 Management of patients with 1-2cm aNETs

Five out of the 43 pateints with aNETs sized 1-2cm underwent initial right hemicolectomy. Of the remaining 38 patients with aNETs measuring 1-2 cm in size, 13 underwent CRH indicated by T4 tumour (n=2), R1 index resection (n=3), caecal pole residual disease on octreotide scan (n=1), patient preference (n=3), or ‘younger’ age (n=4). The median age of the latter group of ‘younger’ patients was 24.9 (range 17.3 - 31.8) years. The only patient with residual disease in this group was a 56-year-old female with a 19mm grade G1 appendiceal body tumour completely excised at appendicectomy without any evidence of invasion. CRH was indicated by patient preference based on borderline size and residual disease was present in the peri-caecal lymph nodes.

3.5 Disease relapse and metachronous NETs

All patients with aNET > 1cm had baseline cross-sectional imaging and somatostatin receptor imaging to rule out residual disease/metastases. According to ENETS guidance and based on clinician discretion at bi-annual or annual clinical review; patients had radiological imaging with CT, MRI, USS or further cross-sectional imaging or further somatostatin receptor imaging to rule out recurrent disease. The two recurrences in our cohort were diagnosed via symptomatic presentation and no asymptomatic recurrences were detected by radiological surveillance modalities.

Only one patient experienced disease relapse: a male patient whose 40mm G1 ENETS stage 3b aNET showing lymphovascular and perineural invasion was completely excised with right hemicolectomy at 43-years age. His retroperitoneal relapse, diagnosed at presentation with weight loss 16.5 years later, was treated with a palliative chemotherapy regimen of cisplatin and etoposide, but he died 12 months later. The recurrent retroperitoneal tumour expressed carcinoembryonic antigen (CEA) unlike the primary aNET and had a comparatively higher Ki67 (10% vs ≤2%).

Another patient developed a second primary neuroendocrine tumour 18.8 years after appendicectomy at age 16 years to completely excise a 10mm G1 ENETS stage 2b aNET showing lymphovascular invasion. Staging In111 Octreotide scan for the primary aNET had previously excluded other disease sites. This second primary was a right middle ear carcinoid tumour causing hearing loss and was curatively excised. No further disease has been detected during 7 years of subsequent follow-up.

3.6 Survival

There were 5 deaths in our series; only 1 of which was NET-related. The was the previously described 43-year old patient who developed relapse 16.5 years after complete excision of a 40mm G1 stage 3b aNET. Patients’ 5-year and 10-year relapse-free and overall survival estimates were 98% and 92%, and, 99% and 92% respectively (**Figure 1 & Figure 2**). The 5-year relapse-free survival was significantly affected by ENETS stage (p=0.002), but neither the 10-year relapse-free nor the 5-year overall and 10-year overall survivals were significantly affected by ENETS stage (p=0.089, p=0.700 and p=0.693 respectively). The relapse-free and overall survivals were also not significantly affected by type of surgery (p=0.522), resection margin status (p≥0.213), or by age, gender, MAI, LVI, PNI, Ki67, or relapse (all p=1.000).

The 3 patients in our cohort with ENETS stage 4 aNETs remain alive in follow-up. The first of these is a male patient who underwent appendicectomy for a G1 aNET at age 81-years and was diagnosed with right iliac fossa residual disease on Gallium-68 DOTATATE PET/CT scan. He declined completion right hemicolectomy so was commenced on Somatostatin analogue therapy (SSA). He has remained asymptomatic during 2-years of follow-up. The second is a male patient who had a right hemicolectomy for a G1 aNET at age 60-years before thoracic spinal metastases were diagnosed with on 111In-octreotide scan. He received spinal fixation, radiotherapy, and somatostatin analogues. The third is a female patient diagnosed with a G1 aNET during total abdominal hysterectomy and bilateral salpingo-oophorectomy for perimenopausal symptoms at age 40-years. She subsequently had CRH, resection of liver metastases and was commenced on Somatostatin analogues. No further relapse has been detected in either of the latter 2 patients after 8 years of follow-up.

**4.0 Discussion**

In this large, single centre retrospective analysis of patients with aNETs, we highlight their indolent behaviour, characterised by very high rates of overall and relapse-free survival. We note that recurrence rarely occurs, and when it does so, it may occur decades later, thus making a case for selective long-term clinical, biochemical and radiological surveillance. The prognostic significance of positive lymph nodes in the original histological specimen, and the necessity for completion right hemicolectomy, remain questionable.

The representative cohort created by the wide geographical coverage of our tertiary referral service has similar diagnostic features, patient demographic traits, and the good prognosis of the typical aNET patient cohort described in the ENETS consensus guidelines (3). The breadth of our representative cohort is further evidenced by the detection of associated colorectal neoplasia, infrequently reported by others (12), and our detection of the very rarely reported Amyand’s hernia containing aNET (13).

Population-based studies highlight variations in the histological reporting of aNETs (14) hence all histological specimens were reviewed by our specialist histopathologists to ensure consistency. This approach was particularly relevant for those patients diagnosed and treated out within our own ENETS Centre.

Analysis of criteria on which we based our selection of patients for CRH showed strong adherence to ENETS guidelines for aNETs (3), but we additionally selected patients based on their young age as has been described in other series (4, 15, 16). Logistic regression analysis showed that aNET size ≥ 2cm significantly predicted the likelihood of detecting residual disease at CRH (p≤0.001), but we also detected residual disease in one patient who had a <2cm diameter aNET. The rationale for right hemicolectomy is to excise loco-regional lymph nodes and mitigate the risk of recurrence or metastases in order to improve survival (3). In our cohort, CRH detected residual disease in 54% (7 of 13) of patients with aNET ≥2cm. Other series have shown variable incidence of residual disease at completion surgery for aNET ≥2cm ranging from 0%to 46% (1, 2, 17-20).

Similar to other recent series (2), CRH was safe in our cohort, but its benefit is unclear in our cohort and the published literature lacks evidence that CRH for aNET ≥ 2cm improves survival when compared to appendicectomy alone (6, 15). Our series includes 4 patients who declined CRH despite it being clinically indicated, but none of these patients have consequently suffered relapse or adverse survival during 13 years of follow-up. ENETS guidelines recommend CRH within 3 months of initial appendicectomy (3), but 17 patients in our cohort had delayed times to completion surgery of up to 10 months without any adverse impact on overall or relapse-free survival.

The only patient who developed tumour relapse in our cohort received palliative chemotherapy and died 12 months later. The patient’s recurrent tumour appeared to show more aggressive tumour biology as unlike the primary aNET, it expressed colonic adenocarcinoma antigen (CEA) and had a higher proliferative index. The current ENETS guidelines recommend continued follow-up, at least annually, of patients with aNETs >2cm but acknowledges that there has been no validation of this approach (3). The relapse rate was very low in our series with follow-up of up to 27.8 years (median 6.2 years). This compares favourably with the studies by Moertel *et al* (4) with median follow-up of 26 years and Anderson *et al* (8) with average length of follow-up of 7.4 years; both showing there is a very low risk of relapse following index resection surgery and relapse only occurs after a long latency period following index resection surgery.

A single patient developed a right middle ear carcinoid tumour nearly 2 decades after curative appendicectomy for a low-risk aNET. The middle ear carcinoid was curatively excised and felt to be unrelated to the original aNET. Primary middle-ear carcinoids are very rare, typically present with hearing loss and are treated by surgical excision (21). There are no previous reports of middle ear carcinoids occurring in aNET patients and we are not aware of any association between these NET types.

The highly favourable relapse-free and overall survivals in our cohort are similar to those reported by Pawa *et al* in a recent multicentre series of 215 patients (2). These findings demonstrate that most aNETs are indolent and patients rarely die from metastatic or recurrent disease. In strong support, a registry study based in Switzerland demonstrated that the 10-year relative survival rate after resection of aNET did not differ from the survival of the average national population matched by age and gender (22).

The biological significance of positive lymph nodes related to aNETs is uncertain. The presence of lymph node metastases correlated with tumour size ≥ 2cm in our cohort, but we did not observe any difference in survival (p=0.556) when patients were compared by lymph node status, nor were lymph node metastases predictive of disease relapse (p=0.383). The very good prognosis for aNETs sized 1-2cm in our cohort was unaffected by residual lymph nodes being detected in the single patient who underwent CRH. Studies have not demonstrated any significant effect of positive lymph nodes on outcome of patients with aNETs (18, 23, 24). ENETS guidelines recommend right hemicolectomy for large aNETs ≥ 2cm, which are more likely to have lymph node metastasis, in order to negate the risk of long-term relapse and metastases (3). From a tumour biology perspective however, right hemicolectomy is likely to serve two functions: lymph node harvest for prognostication and mitigating risk of local disease recurrence. The prognostic role of lymph nodes is well-established in most abdominal cancers for which lymphadenectomy is routinely performed as part of tumour resection surgery in order to identify patients with positive lymph nodes who will be offered adjuvant chemotherapy. A previous study has however demonstrated that there is no significant difference in overall survival when comparing patients with node-negative and node-positive aNETs, regardless of tumour size (16). This finding is surprising as lymph node involvement generally signifies poor prognosis in other NETs (25) and in colorectal cancers (26). Epidemiological studies show only a small proportion of aNETs, just 3%, actually develop metastases unlike 41% of small intestinal NETs (27). The apparent lack of effect of CRH and lymphadenectomy on aNET patient may be explained by lymph node involvement being inconsequential in such an indolent disease process. The true benefit of lymphadenectomy in aNETs is thus questionable, but it is reasonable to undertake CRH to achieve clear resection margins. In‘t Hof *et al* suggested performing a more limited ileocaecal resection instead of right hemicolectomy for tumours >2cm (17). The key treatment recommendations from published papers are summarised in table 3 (**Table 4**).

The main limitation of our study is potential referral bias as some patients with small tumours may not have been referred to our tertiary referral centre, especially in the earlier years of the study. It is thus possible that we have not captured some small aNETs, but this is likely to also be the same limitation experienced by other similarly designed cohort studies.

**5.0 Conclusion**

When aNETs were ≥ 2cm in size, there was a significantly greater risk of detecting involved lymph nodes at completion right hemicolectomy. However, the prognostic significance of positive lymph nodes is unclear considering lymph node status did not influence clinical outcomes. Furthermore, our data, consistent with those of others, do not support a beneficial role for completion right hemicolectomy and question the value of the current ENETS guidance on routine follow-up following aNET resection.

**6.0 Acknowledgements**

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| **Variable** | **Detail** |
| Gender n (F, M) | 52, 50 |
| Median (range) age | 39.4 (16.3 – 81.1) years |
| Median (range) follow-up | 6.2 (0.8 – 27.8) years |
| Mean (range) size | 12.7 (1 - 60) mm |
| Indication for surgery | Appendicitis (n=80), suspicious mass (n=7), or incidental finding at surgery (n=15) |
| Index surgery | Appendicectomy (n=81), right hemicolectomy (n=19), or subtotal colectomy (n=2) |
| aNET location | Tip 63%, body 26%, base 11% |
| Grade | G1 (n=96), G2 (n=5), G3 (n=1) |
| ENETS Stage | 1 (n=26), 2a (n=35), 2b (n=14), 3a (n=13), 3b (n=11), 4 (n=3) |
| IHC markers (n, sensitivity) | CgA (54, 94%), CD56 (35, 97%), SYP (46, 98%), CDX2 (2, 100%) |

**Table 1: Summary of NET patient characteristics.** ENETS (European Neuroendocrine Tumour Society), IHC (Immunohistochemistry), CgA (Chromogranin A), SYP (Synaptophysin)

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| --- | --- | --- | --- | --- | --- |
| **Variable** | |  | **Odds Ratio (95% Cl)** |  | **P-Value** |
|  | |  |  |  |  |
| Male (vs. Female) | |  | 0.24 (0.10 - 0.59) |  | 0.002 |
| Age at diagnosis | |  | 0.96 (0.94 - 0.99) |  | 0.002 |
| Mesoappendiceal invasion (vs. none) | |  | 1.39 (0.53 - 3.64) |  | 0.504 |
| Lymphovascular invasion (vs. none) | |  | 1.41 (0.46 - 4.33) |  | 0.554 |
| Resection margin involvement (vs. none) | |  | 6.87 (2.18 - 21.72) |  | 0.001 |
| Size ≥ 2cm (vs. < 2cm) | |  | 6.10 (2.16 – 17.23) |  | 0.001 |
| ENETS stage 2a ENETS stage 2b ENETS stage 3a ENETS stage 3b ENETS stage 4 (vs. ENETS stage 1) |  | | 10.00 (1.19 – 84.07) 62.50 (6.20 – 630.13) 21.43 (2.20 – 208.85) 43.75 (4.19 – 456.97) 0.00 (0.00 - ∞) |  | 0.034 <0.001 0.008 0.002 0.992 |
| Grade ≥ G2 (vs. G1) | |  | 2.10 (0.40 – 10.99) |  | 0.381 |
| Base of appendix involvement (vs. none) | |  | 6.67 (1.64 - 27.11) |  | 0.008 |

**Table 2: Univariate logistic regression showing predictors of selection for completion surgery.** ENETS (European Neuroendocrine Tumour Society)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Variable** |  | **Odds Ratio (95% Cl)** | |  | **P-Value** |
|  |  |  | |  |  |
| Male (vs. Female) |  | 1.25 (0.23 - 6.70) |  | | 0.794 |
| Age at diagnosis |  | 1.02 (0.96 - 1.08) |  | | 0.521 |
| Resection margin involvement (vs. none) |  | 0.46 (0.08 - 2.81) |  | | 0.404 |
| Size ≥ 2cm (vs. < 2cm) |  | 8.75 (1.40 - 54.80) |  | | 0.020 |
| Mesoappendiceal invasion (vs. none) |  | 1.60 (0.29 - 8.86) |  | | 0.590 |
| Lymphovascular invasion (vs. none) |  | 0.53 (0.05 - 5.55) |  | | 0.597 |
| Base of appendix involvement (vs. none) |  | 1.21 (0.20 - 8.22) |  | | 0.842 |

**Table 3: Univariate logistic regression showing predictors of residual disease at completion surgery.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |
| **Authors, year** | **Type** | **Age in years** | **N** | **CRH performed (residual disease)** | **Follow-up** | **Key message(s)** |
|  |  |  |  |  |  |  |
| Anderson 1985(8) | Single centre | Mean 30 (range 12-82) | 147 | n/s | Average 7.4 (2-14) years | CRH recommended if size > 1-5 cm |
| Moertel 1987(4) | Single centre | Median if: <2cm/ no metastases = 42 ≥2cm/ no metastases = 31 or ≥2cm/ metastases = 29 | 150 | n/s | Median 29 years | Appendicectomy sufficient unless size >2cm in young patient |
| Bamboat and Berger, 2006(15) | Single centre | Mean 41 (11-86) | 48 | 6 (0) | Mean 18 (range 1-25) years | Appendicectomy sufficient unless size >2cm in young patient |
| O'Donnell 2007(28) | Single centre | Mean 43 (range 14–81) | 9 | 0 | Mean 63 (range 1-125) months | Appendicectomy sufficient for small aNETs <2 cm at the tip of the appendix, with a low proliferative index, no angiolymphatic and no MAI. Consider adjuvant chemotherapy for advanced disease. |
| In't Hof 2008(17) | Single centre | Mean 32.7 (range 20–59) | 7 | 5 (0) | Mean 65 (range 25–92) months | Limited ileocaecal resection suggested as alternative to formal right hemicolectomy in cases appropriate for CRH |
| Boudreaux 2010(29) | NANETS guidelines | n/a | n/a | n/a | n/a | Appendicectomy sufficient unless size >2cm, or if <2cm with risk factors (invasion of appendix base, tumour size indeterminable, LVI, MAI, or intermediate/ high-grade tumours) |
| Alexandraki 2010(1) | Single centre | Median 25 (range 18-38) | 12 | 12 (3) | n/s | Appendicectomy sufficient unless size >2cm, or if 1-2cm with risk factors (tumour at base of appendix, infiltration of caecum, positive resection margin, MAI, or undifferentiated/ poorly differentiated cells) |
| Groth 2011(6) | SEER cohort | Mean (± SD) if: Appendicectomy = 47 (± 17.3) Right hemicolectomy = 50.1 (± 14.4) | 576 | n/s | n/s | There is no significant difference in survival with CRH vs. appendectomy alone |
| Mullen 2011(16) | SEER cohort | n/s | 89 | n/s | n/s | Appendicectomy sufficient unless size >2cm, or if 1-2cm with risk factors (young patient, MAI) |
| Grozinsky-Glasberg 2013(20) | Multi-centre | n/a | 28 | 28 (8) | Median 3.6 years | CRH for involved surgical margins, extensive MAI, vascular invasion, Ki-67 ≥2%, or size ≥2 cm. |
| Steffen 2015(22) | Multi-centre | Mean 44.6 | 79 | 6 (n/s) | Median 12.1 (1.6–22.4) years | No conclusive survival difference if CRH vs. appendicectomy alone |
| Kleiman 2015(24) | Single centre | Mean 43.6 (SD, ± 19.1) | 79 | 8 (4) | Median (months) if: Metastatic = 18 Localized = 5.5 | Tumours <2 cm with small-vessel invasion should be considered for CRH as they have similar metastatic potential as tumours ≥2 cm |
| Pape 2016(3) | ENETS guidelines | n/a | n/a | n/a | n/a | Appendicectomy sufficient for well-differentiated aNET <2 cm regardless of tumour location. CRH needed tumours 1–2 cm with risk factors (positive/ unclear margins, deep MAI, G2/G3 or vascular invasion) or for tumours >2 cm. |
| Sarshekeh 2017(30) | SEER cohort |  | 658 | 194 (106) | Median 44 months | Tumour size predicts LN metastasis but CRH may not improve outcome vs. appendicectomy alone |
| Pawa 2018(2) | Multi-centre | Mean 33.2 (range 9-79) | 215 | 49/64 | Median 38.5 (range 1-192) months | CRH might overtreat some patients as oncological relevance of nodal metastases is uncertain |
| Galanopoulos 2019(31) | Single centre | Mean 42 (range 15–81) | 263 | 72 (23) | n/a | Prognosis is significantly affected by higher tumour grade and LVI but not tumour size |
| Rault-Petit 2019(18) | French registry | Median 27 | 403 | 80 (n/s) | Median 3 (0-84) months | Tumour size (cut-off at 1.95cm), LVI and PNI predict lymph node metastases but the survival impact of CRH is uncertain |
| Brighi 2020(23) | Multi-centre | Median 29 (range 21-41) | 435 | 69 (21) | n/s | Oncological resection if tumour size >15.5 mm, G2, or presence of LVI which all independently relate to nodal metastases. |
| Alexandraki 2020(32) | Multi-centre | Mean 31 ± 16 | 166 | 58 (20) | Mean 50.9 ±  54 months | The value of CRH for aNETs <20 mm is challenged |

**Table 4:** Key treatment recommendations from published papers**.** aNET (Appendiceal neuroendocrine tumour), SEER (Surveillance, Epidemiology, and End Results Program), ENETS (European Neuroendocrine Tumour Society), NANETS (North American Neuroendocrine Tumour Society), CRH (Completion right hemicolectomy), MAI (mesoappendiceal invasion), LVI (lymphovascular invasion), PNI (perineural invasion).

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Figure 1: 5-year overall survival by ENETS TNM stage. (Numbers at risk are shown).

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Figure 2: 5-year relapse-free survival by ENETS TNM stage. Numbers at risk are shown.