Endoscopically removed rectal NETs: a nationwide cohort study

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Abstract

Purpose Rectal neuroendocrine tumours (NETs) often present as an incidental finding during colonoscopy. Complete endoscopic resection of low-grade NETs up to 10 mm is considered safe. Whether this is also safe for NETs up to 20 mm is unclear. We performed a nationwide study to determine the risk of lymph node and distant metastases in endoscopically removed NETs.

Methods All endoscopically removed rectal NETs between 1990 and 2010 were identified using the national pathology database (PALGA). Each NET was stratified according to size, grade and resection margin. Follow-up was until February 2016.

Results Between 1990 and 2010, a total of 310 NETs smaller than 20 mm were endoscopically removed. Mean size of NETs was 7.4 mm (SD 3.5). In 49% of NETs (n = 153), no grade (G) could be assessed from the pathology report, 1% was G2 (n = 3), and the remaining NETs were G1. Median follow up was 11.6 years (range 4.9–26.0). During follow-up, 30 patients underwent surgical resection. Lymph node or distant metastasis was seen in 3 patients (1%) which all had a grade 2 NET. Mean time from endoscopic resection to diagnosis of metastases was 6.1 years (95% CI 2.9–9.2).

Conclusion No lymph node or distant metastases were seen in endoscopically removed G1 NETs up to 20 mm during the long follow-up of this nationwide study. This adds evidence to the ENET guideline that endoscopic resection of G1 NETs up to 20 mm appears to be safe.

Keywords Rectum · Neuroendocrine tumour · Endoscopic resection · Recurrence

Introduction

The increase in incidence of rectal neuroendocrine tumours (NETs) over the last decades is thought to be a consequence of the widespread use of screening endoscopy and improved diagnosis [1–4]. Nonetheless, rectal NETs remain rare, with an estimated incidence of 0.17% [5]. Consequently, many endoscopists will encounter a negligible number of NETs over the course of a career, hindering endoscopic recognition. In addition, rectal NETs often lack distinct endoscopic features, and many are therefore excised at colonoscopy without prior knowledge of their nature.[6]

The biological behaviour of rectal NETs differs greatly with some running an indolent course, while others are more aggressive and metastasize rapidly. Several determinants, including size, have been identified to predict the risk of metastases. Rectal NETs that are smaller than 10 mm and well-differentiated (i.e. grade 1 or 2) are thought to have a very low risk of metastases and can safely be removed endoscopically [7–9]. Conversely, NETs of 20 mm or larger are an indication for surgical therapy, as many studies have demonstrated these lesions to carry a substantial risk of metastasizing.
There is controversy over rectal NETs of intermediate size (10–19 mm). While a number of studies have shown no recurrence or metastatic risk, and endoscopic resection is deemed safe, others have found substantial metastatic risks up to 66%, advocating adjuvant local or radical surgical resection of these intermediate NETs [10–12]. Methodology of these studies differs greatly, contributing to their substantial difference in outcomes.

The aim of the current study is to describe the long-term risk of metastatic recurrence in well-differentiated rectal NETs up to 20 mm, to establish whether these lesions require adjuvant surgical therapy after their endoscopic resection.

Material and methods

Data source and study population

We performed a search of the Dutch Pathology Registry (PALGA), a nationwide registry of histopathology and cytopathology diagnoses, covering the entire population of the Netherlands (approximately 17 million people). In this database, summaries of pathology reports generated by all pathology departments in the Netherlands are centrally archived [13]. Each pathology report in the PALGA can be linked to the database of the Netherlands Cancer Registry (NCR). Using the NCR’s registration and coding manual, trained staff from the NCR collect data from medical records on diagnosis, stage and (surgical) treatment including immuno- and chemotherapy.

None of the data held in PALGA’s database is traceable to individuals. PALGA’s database does not contain identifying patient data, only pseudonyms based on this data. PALGA’s Privacy Committee checks whether the data provision complies with existing Dutch legislation (Medical Treatment Contracts Act and the Personal Data Protection Act). The Medical Research Involving Human Subjects Act is not applicable to this study because data for this study were collected anonymously and no additional patient interventions were performed.

Data extraction and definitions

At the start of the study, registration of pathology reports and the vital status of each patient was known until the 1st of February 2016. To allow sufficient surveillance time after inclusion in the study, a PALGA search of all diagnosed colorectal NETs between 1990 and 2010 was performed.

Each NET was either included or excluded based on its pathology only. Information about the endoscopic procedure was not available. NETs were excluded in the following cases: primary surgical or unknown method of resection, G3 grading (either by Ki67, mitotic index or poor differentiation) or a size of 20 mm or larger. In all other cases, NETs were included; provided endoscopic resection was mentioned in the text of the pathology report. For each included NET, we retrieved all concurrent histopathology reports, starting at the first report and ending on 1 February 2016. Each of these reports was examined for recurrence or metastases, whether obtained endoscopically or surgically. Positive lymph nodes in a surgical specimen were considered metastases.

Each NET was assessed for size, grade (grade 1, 2 or 3), resection margin and presence of lymph vascular invasion (LVI). G1 and G2 NETs were considered well-differentiated. Size was derived from the pathology report and stratified into small (< 10 mm) or intermediate (10–19 mm). In case the specimen was not removed en bloc, each of the fragments mentioned in the pathology report was added up. The sum of these fragments determined whether these NETs were considered small or intermediate.

Grading was based on the Ki67/Mib labelling index, mitotic index or differentiation, provided this was mentioned in the report. If none of these were mentioned in the report, the NET was graded as unknown.

Thirdly, each NET was stratified for resection margin into negative, positive, unknown or unmentioned. All lesions that were not removed en bloc were automatically classified as having an unknown resection margin. Lastly, lymph vascular invasion was noted as present, absent or unmentioned.

Age and gender of the patient were available for each PALGA report. The vital status of each included patient was known through record linkage of the NCR to all municipal population registers in the Netherlands. As this linkage is performed annually, this means that vital status is virtually up to date. The cause of death is not provided in the database.

Statistical analysis

Continuous variables were reported as mean (standard deviation) or median (interquartile range) and compared with the Student t test or Mann-Whitney U test. Long-term overall survival was assessed using the Kaplan Meier analysis. All data analyses were conducted using SPSS Statistical Software (version 24.0; IBM Corp, Armonk, NY).

Results

In total, 1439 colorectal neuroendocrine pathology specimens were identified in PALGA. Of these, 1105 were excluded as the specimens were surgical (n = 365), biopsies (n = 557) or revisions (n = 55). Another 128 specimens were excluded because the mode of resection (i.e. surgical of endoscopic) could not be retrieved from the pathology report. The remaining 334 NETs were all endoscopically removed from the rectum. Of these, 21 NETs were 20 mm or larger and therefore
excluded. Another 3 NETs were excluded because they were grade 3, either based on poor differentiation \( (n = 2) \) or mitotic index \( (n = 1) \).

Mean size of all 310 included rectal NETs was 7.4 mm (SD 3.5) of which 236 (76%) were smaller than 10 mm and 74 (24%) were between 10 mm and 20 mm. The majority of patients was female (167, 53.9%). Mean age at endoscopic resection was 54.2 years (SD 13.8) and did not differ between patients with a small NET (54.7 years) compared to patients with an intermediate NET (52.6 years, \( p = 0.03 \)).

A total of 236 NETs (76%) were removed en bloc, and the remaining 74 were removed using piecemeal resection. Endoscopic resection was radical (R0) in 65 cases (21%), whereas 135 NETs (44%) were unknown or reviewed as uncertain by the pathologist. The remaining 110 NETs (36%) demonstrated positive resection margins. Whether this was positive in the horizontal or lateral margin was mentioned in 20 pathology reports only, all of which were positive in the horizontal or latera l margin was mentioned in 20 pathology reports only, all of which were positive in the horizontal or lateral margin.

In 49% of NETs \( (n = 153) \), no grade (G) could be assessed from the pathology report, 1% was G2 \( (n = 3) \), and the remaining NETs were G1. Lymph vascular invasion was mentioned in only 19 pathology reports (6.1%) and therefore excluded for further analysis. Histopathologic characteristics are shown in more detail in Table 1. Median follow-up of all included NETs was 11.6 years (range 4.9–26.0).

Data on (neo) adjuvant therapy was missing in 11 patients (4%). None of the other 299 patients received NET-related (neo) adjuvant or palliative systemic therapy during follow-up.

**Characteristics small NETs \(< 10 \text{ mm}\)**

Small NETs accounted for 236 out of the 310 included NETs. Of the small NETs, 40 (17%) had a negative resection margin.

| Table 1 | Histopathology characteristics of small and intermediate NETs |
|---|---|
| **Histopathology rectal NETs** | |
| Size | \(< 10 \text{ mm}\) | 10–19 mm |
| Number | 236 (76%) | 74 (24%) |
| Resection margin | |
| Negative | 40 (17%) | 25 (34%) |
| Positive | 83 (35%) | 27 (36%) |
| Unsure | 23 (10%) | 12 (16%) |
| Unknown | 90 (38%) | 10 (14%) |
| Grading | |
| G1 | 117 (50%) | 37 (50%) |
| G2 | 0 (0%) | 3 (4%) |
| Unknown | 119 (50%) | 34 (46%) |
| Assessment grading | |
| Number of mitoses | 77 (33%) | 26 (35%) |
| Ki67/MiB | 30 (13%) | 13 (18%) |
| Differentiation | 10 (4%) | 1 (1%) |
| Not available | 119 (50%) | 34 (46%) |

Grading of 119 (50%) small NETs could not be retrieved from the pathology report and was classified as unknown in these cases; the remaining 117 small NETs were G1.

A total of 17 patients (7%) with a small rectal NET underwent consecutive surgical resection. The indication for consecutive surgical resection could not be retrieved from the pathology reports. Endoscopic characteristics of these NETs and their surgical specimens are described in Table 2. Median interval between endoscopic resection and surgical resection was 91 days (IQR 57–244). Remnant neuroendocrine tissue is found in 6 surgical specimens which previously had a positive \( (n = 2) \) or unknown \( (n = 4) \) endoscopic resection margin (Fig. 1).

Surgical resection consisted of transanal endoscopic microsurgery (TEM, \( n = 12 \)) or a low anterior resection (LAR, \( n = 5 \)). None of the LAR specimens demonstrated lymph node metastasis. None of the 236 patients with a small NET developed lymph node or distant metastases during the median follow-up of 11.1 years (IQR 8.2–17.6).

**Characteristics intermediate NETs \(10–19 \text{ mm}\)**

A total of 74 NETs (24%) were intermediate in size, and 25 (34%) of these demonstrated a negative resection margin. Grading of 34 (46%) intermediate NETs could not be retrieved from the pathology report; another 37 were G1 and the remaining 3 NETs were G2.

A total of 13 patients (18%) with an intermediate rectal NET underwent consecutive surgical resection. Endoscopic characteristics of these NETs and their surgical specimens are described in Table 2. Median interval between endoscopic resection and surgical resection was 72 days (IQR 36–161). Remnant neuroendocrine tissue is found in 7 surgical specimens who previously had a negative \( (n = 1) \), positive \( (2) \), or unknown \( (n = 4) \) endoscopic resection margin (Fig. 1).

Surgical resection consisted of TEM \( (n = 8) \) or a LAR \( (n = 5) \). One of the LAR specimens demonstrated lymph node metastasis originating from a G2 NET. None of the intermediate G1 NETs developed lymph node or distant metastases.

| Table 2 | Histopathology characteristics of NETs with subsequent surgical therapy |
|---|---|
| Surgical specimen \( (n = 30) \) | |
| Size | \(< 10 \text{ mm} \ (n = 17)\) | 10–19 mm \( (n = 13)\) |
| Endoscopic resection margin | |
| Negative | 1 | 7 |
| Positive | 8 | 1 |
| Unknown | 8 | 5 |
| Remnant in surgical specimen | |
| Yes | 6 (35%) | 7 (54%) |
| No | 11 (65%) | 6 (46%) |

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during the median follow-up of 13.0 years (IQR 8.8–18.3), while all 3 G2 NETs developed distant metastases during follow-up. The interval between endoscopic resection and metastases ranged from 193 days to 8.8 years. Characteristics of all G2 NETs are described in more detail in Table 3.

**Survival**

At the end of the follow-up on February 2016, 64 (21%) patients had deceased. In the small NET group, 45 patients (19%) deceased vs. 19 patients (26%) in the intermediate NET group. Overall survival between the small NET group and the intermediate did not differ significantly ($p = 0.367$). The 10-year survival of each group is outlined in Fig. 2. Mean age at time of death in the small NET group was 72.5 years (SD 11.8) versus 71.6 years (SD 12.5) in the intermediate NET group which was not significantly different ($p = 0.76$). All 3 patients with metastases were still alive.

**Discussion**

The present study identified 310 endoscopically removed rectal NETs prospectively registered in our nationwide database. With a long median follow-up of over 11 years and the availability of all subsequent pathology reports, this study provides an insight into the biological behaviour of rectal NETs.

While many rectal NETs behave in an indolent fashion, there appears to be a subset that behaves more aggressively. None of the intermediate G1 NETs in our study developed lymph node or distant metastases during the long follow-up, though metastases were seen in all 3 G2 NETs. Several studies have found a similar low metastatic risk after resection of intermediate G1 NETs [14–17]. Others on the other hand have demonstrated poor survival or high percentages of lymph node metastases up to 66% [10–12, 18, 19]. This discrepancy in outcome can be attributed to several differences in study design and inclusion. Gleeson et al. included only 6 intermediate NETs, and their size was based on estimation by the
endoscopist, which is often imprecise [20]. More importantly, no grading of these NETs was performed, meaning potential inclusion of G2 or G3 NETs could explain the more aggressive course of NETs in their study. Similarly, Weinstock and colleagues found significant differences between size grouping < 1 and > 1 cm [21]. In their study, half of all intermediate NETs were removed surgically which are thought to have lymph vascular invasions more frequently compared to endoscopically removed cases, possibly caused by their deeper infiltration into the submucosal layer [11]. Overall, tumour-specific features in many studies are not similar or remain unmentioned, making comparison of survival or metastatic risk in each of these studies challenging.

Endoscopic resection is by definition confined to the mucosa or submucosa, which could be an important factor contributing to the excellent long-term outcomes in our cohort. Similar to T1 colorectal carcinomas, several studies have demonstrated depth of NET invasion to be predictive of outcome [11, 22, 23]. One of these was a Japanese analysis of 849 rectal NETs demonstrating a 98% 5-year overall survival rate for NETs confined to the submucosa, while the overall survival rate of rectal NETs was 88% [23]. Similarly, Fahy et al. found a 30% 5-year recurrence-free survival rate in rectal NETs growing into the muscularis mucosa compared to 88% in tumours limited to the (sub) mucosa [24]. Interestingly, two recently large cohort studies found a higher 5-year NET-free survival or overall survival in the locally excised group compared to the group that underwent radical surgery, again confirming the better outcome of superficial NETs [25, 26].

**Table 3** Characteristics of 3 patients demonstrating metastases during follow-up

| Size (mm) | Endoscopic resection margin | Grade | Surgical specimen | Remnant in surgical specimen | Time to surgical specimen (days) | Location of metastasis | Time to metastasis (days) | Follow-up after metastasis (days) |
|----------|-----------------------------|-------|------------------|-----------------------------|---------------------------------|------------------------|--------------------------|-------------------------------|
| 1 | 12 | Positive | G2 (Ki67) | No | - | - | Lymph node obturator | 193 | 1798 |
| 2 | 17 | Negative | G2 (Ki67) | Yes | Yes | 1696 | Liver | 3213 | 1778 |
| 3 | 12 | Positive | G2 (Ki67) | Yes | No | 46 | Liver | 2413 | 783 |

**Fig. 2** 10-year survival of small vs intermediate NETs

| Number of patients at risk |
|---------------------------|
| 5 years | 7.5 years | 10 years |
| Small | 236 (100%) | 187 (79%) | 134 (57%) |
| Intermediate | 74 (100%) | 63 (85%) | 47 (64%) |
In our study, 30 out of 310 patients underwent surgical resection which demonstrated positive or uncertain resection margins in 29/30 of the endoscopy pathology reports. Remnant neuroendocrine tissue was found in 13/30 surgical specimens. All but one of these had a positive or uncertain endoscopic resection margin. Meanwhile, many other patients with a positive resection margin (whether horizontal or lateral) did not undergo surgery. Hence, the indication for consecutive surgical resection was performed at the discretion of the treating physician, which may have been caused by the lack of guidelines in previous years. Even so, this provides an insight into the biological behaviour of rectal NETs histologically incompletely removed. None of the 210 G1 NETs having positive or unknown resection margins appeared to reveal metastases during follow-up. Even though this demonstrates their indolent behaviour, the importance of negative resection margins remains as recurrence can evolve after many years, and follow-up in our study might have been too short.

All three patients in our cohort that developed metastases had a G2 grading based on the Ki67 index. Metastases arose at different intervals ranging from 6 months to nearly 9 years. The ENETS guideline regarding the treatment of G1 vs. G2 NETs is practically similar except for its emphasis on the need of complete (local) resection in G2 NETs [7]. The number of G2 NETs in our study is too small to draw conclusions, but other authors have also found G2 NETs to demonstrate a less indolent behaviour than G1 NETs. Weinstock et al. found a significant difference in 5-year survival rate between rectal G1 and G2 NETs, respectively, 87.7% and 47.6% [21]. Similarly, Kojima et al. found a higher rate of lymph node metastases in rectal G2 NETs up to 20 mm compared to G1 NETs [11]. Also, in the stratification model of Fahy et al., G2 grading—though assessed through mitotic index rate—was found to be an independent predictor on recurrence-free survival and disease-specific survival [24]. Although each of these studies has a low number of G2 rectal NETs, it remains to be seen whether G2 rectal NETs, now more accurately assessed through Ki67 index, require a similar treatment as G1 NETs.

The current study has several limitations. Firstly, grading on histopathology was absent in a large proportion of the examined histopathology reports providing no Ki67, Mib or mitotic index. This could have led to inclusion of G3 NETs which were meant to be excluded. Considering the long-term outcomes of our cohort, however, inclusion of many G3 NETs appears unlikely. Secondly, local and metastatic recurrence was based on subsequent pathology reports only. Potentially, a number of patients had an undiagnosed recurrence at the end of follow-up. Similarly, lymph node or distant metastases may have been present in our cohort but still undiagnosed at the end of the study. In addition, metastases could have been diagnosed by means of octreotide or DOTATE scans without biopsy. We know however that at least 96% of the cohort did not undergo systemic therapy during follow-up, suggesting this to be an unlikely scenario. Thirdly, only a small number of rectal NETs in our cohort were assessed for lymph vascular invasion. Although challenging to assess in small rectal NETs, several studies have demonstrated lymph vascular invasion to be an independent risk factor for lymph node involvement [15, 19, 24, 27]. Lack of knowledge on lymph vascular invasion could have led to an underestimation of the malignant potential of included NETs, but as none of the G1 NETs demonstrated metastasis during their long follow-up, this seems improbable.

In conclusion, using a nationwide pathology registry, local recurrence was seen in a small number of endoscopically removed G1 rectal NETs up to 20 mm. More importantly, during a long follow-up of over 11 years, no lymph node or distant metastases were reported in G1 NETs up to 20 mm, adding evidence to the ENET guideline that endoscopic resection of G1 NETs up to 20 mm appears to be safe.

Authors’ contributions T Kuiper: Study concept and design; acquisition of data; analysis and interpretation of data; statistical analysis; drafting of the manuscript
M G H van Oijen: Study concept and design; analysis and interpretation of data; statistical analysis; critical revision of the manuscript
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