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META-ANALYSIS

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Histopathological diagnosis of appendiceal neuroendocrine neoplasms: when to perform a right hemicolectomy? A systematic review and meta-analysis

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Abstract

Purpose The European Neuroendocrine Tumor Society (ENETS) guidelines advocate a right hemicolectomy (RHC) only in patients with appendiceal neuroendocrine neoplasms (aNENs) at risk for N+(node positive). The risk is defined using site, size, and grading of tumor as well as mesoappendiceal or lymphovascular invasion.

Methods A systematic review and meta-analysis was carried out. The data were reported using risk difference (RD) to define the risk of N+. The number needed to treat/harm (NNT/NNH) and the likelihood of being helped or harmed (LHH) were calculated using RD. Two strategies were considered: "to treat all" versus "to treat only patients having aNENs with risk stigmata". The aim was to evaluate the harm/benefit ratio related to the use of the ENETS lymph-nodal metastases (N+) risk factors.

Results Six studies were included involving a total of 261 patients. The RD (−0.30; $P < 0.001$) of N+ was significantly lower in aNENs ≤ 20 mm as compared to those >20 mm. One unnecessary RHC every five patients (NNT = 5) could be avoided while 1 patient with N+ every six patients (NNH = 6) remained untreated. The risk was lower than the benefits (LHH = 1.2). The RD NNT, NNH, and LHH values suggested that only a 15 mm cutoff and the presence of lymphovascular invasion could be considered useful.

Conclusions An RHC should be performed in patients with aNENs >20 mm. The use of a 15 mm cutoff criterion had a similar outcome to that of a 20 mm cutoff. Lymphovascular invasion should only be considered a minor criterion. Selection based on other parameters should be avoided

Keywords Appendix · Carcinoid · Neuroendocrine tumor

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Abbreviations

ENETS	European Neuroendocrine Tumor Society
NANETS	North American Neuroendocrine Tumor Society
aNEN	Appendiceal neuroendocrine neoplasm
RHC	Right hemicolectomy
RD	Risk difference
N+	Node positive
NNT	Number needed to treat
NNH	Number needed to harm
LHH	Likelihood of being helped or harmed
WHO	World Health Organization
95% CI	95% Confidence interval
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

Introduction

Appendiceal neuroendocrine neoplasms (aNENs) represent one of most common gastrointestinal endocrine tumors [1], having an incidence rate of ~0.15/100,000/year with a peak in younger patients [2, 3]. The diagnosis has routinely been made by a pathologist after an appendectomy, generating a clinical dilemma: to perfom or not a second surgical look with a right hemicolectomy (RHC) in order to obtain a radical lymphadenectomy. The European Neuroendocrine Tumor Society (ENETS) and the North American Neuroendocrine Tumor Society (NANETS) recently produced guidelines [4, 5], which considered size >20 mm as "high-risk stigmata" for nodal metastases. For this reason, this is the only major criterion for performing an RHC. On the contrary, the presence of an aNEN of between 10 and 20 mm in size, tumor location at the base, mesoappendiceal invasion >3 mm, Ki 67 index >3% (G2 according to the 2010 World Health Organization (WHO) classfication) and lymphovascular invasion represent relative indications for a second surgical look. However, for the physician, some questions still remain under debate. In fact, Heller et al. [6] have recently emphatized that, despite the well-known size-based criteria, one-third of patients could uselessly undergo RHC. Thus, the questions are: first, what is the risk of performing an unnecessary RHC (patients without nodal metastases) using the guidelines? Second, what is the risk of incorrectly leaving patients (patients with nodal metastases) in follow-up using the guidelines? Third, starting from the assumption that a perfect risk factor does not exist, have the guidelines saved additional patients from unnecessaryl surgery as compared to leaving them in follow-up with malignancy or not? In order to answer these three questions, a systematic review and meta-analysis was carried out.

Methods

The study was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [7], and a PRISMA flowchart was formulated (Fig. 1) in order to obtain the transparency of the conclusions reached by the Authors. Eligibility criteria, information sources, study selection, inclusion and exclusion criteria, the data collection process, and statistical analyses are reported in Supplementary file. Briefly, the terms for the search strategy were the following: (neuroendocrine tumor OR neuroendocrine tumors OR neuroendocrine tumor OR neuroendocrine tumors OR carcinoid tumor OR carcinoids tumors OR carcinoid OR carcinoids OR gastrointestinal endocrine tumors OR gastrointestinal endocrine tumors OR argentaffinoma OR argentaffinomas OR goblet cell carcinoid OR goblet cell carcinoids OR apudoma OR apudomas) AND (appendix OR appendiceal). The last search was conducted on 15 December 2018. This study used the meta-analytic data regarding the risk of nodal metastasis in aNEN patients. The parameters for classifying aNENs "at risk" were size (20, 15, and 10 mm cutoffs), site (middle/tip versus base), grading (G2 versus G1) and mesoappendiceal or lymphovascular involvement according to the ENETS guidelines [4]. The risks were reported using risk difference (RD) together with a 95% confidence interval (95% CI). Using the RDs, two competitive strategies for the management of aNENs after appendectomy were compared. The strategies were "to treat all aNENs" (referent or A strategy) with a second surgical look (RHC) and "to treat only aNENs at risk" (experimental or B strategy). The primary endpoint was to evaluate the risk-benefit ratio using a 20 mm cutoff in order to select the patients who were candidates for RHC. The secondary endpoints were to evaluate the other ENETS risk parameters. The benefits, risks, and risk/benefit ratios were reported as the number needed to treat (NNT) and to harm (NNH), and the likelihood of being helped or harmed (LHH) [8].

Results

The results of the systematic search are reported in Supplementary Fig. 1. The details regarding the systematic search and the studies included are reported in Supplementary file. The characteristics of the studies selected are summarized in Supplementary Table 1.

Meta-analysis of the primary endpoint

The data were derived from six studies [9–14] involving a total of 265 patients, having an overall lymph node

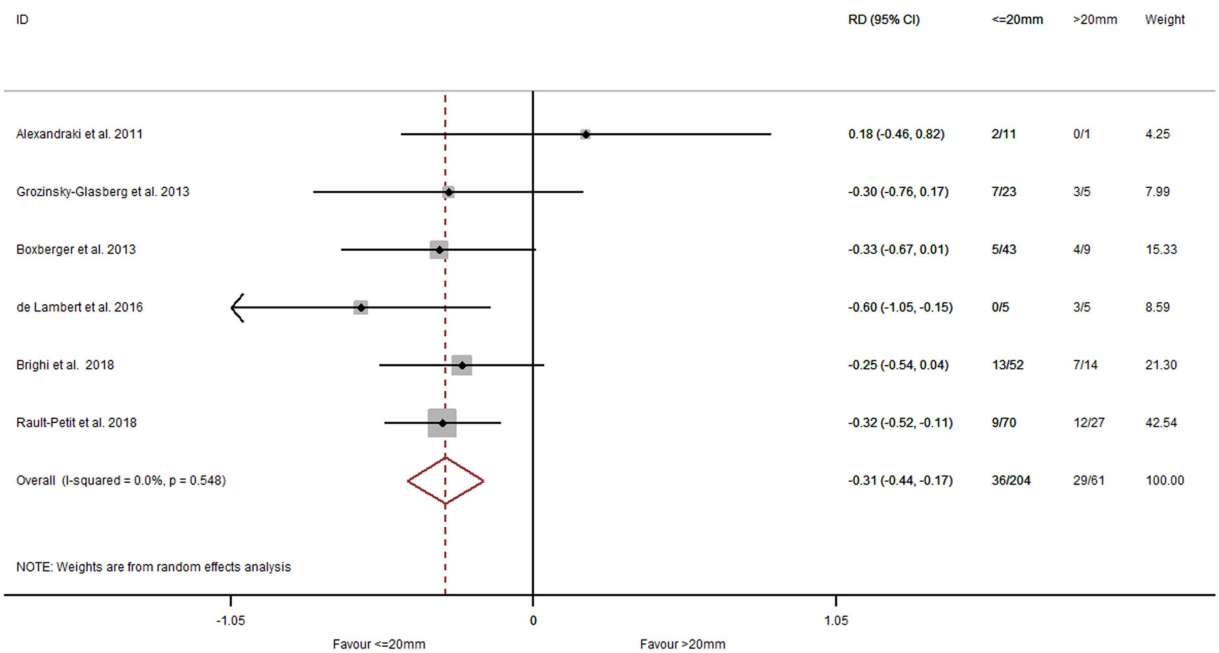

Fig. 1 Forest plot showing the risk difference for the lymph-nodal metastatic rate between small (≤20 mm) and large (>20 mm) appendiceal neuroendocrine neoplasms (aNENs). RD: risk difference; 95% CI: 95% confidence interval; I-squared: between study heterogeneity according to the Higgins's test; *P*: *P*-value referred to the Q Cochran test; gray square: risk difference of each study; size of square: weight of each study in the analysis; solid black line: 95% confidence interval for each study; red diamond: the pooled risk difference

metastasis rate of 24.5%. Patients having an aNEN ≤ 20 mm had a statistically significant reduced risk of nodal metastasis with respect to those having an aNEN >20 mm (RD −0.30; −0.43 to −0.17 95% CI) (Fig. 1 and Table 1). Using the 20 mm cutoff, the risk of an unnecessary RHC was reduced by 23% (9 to 36%, 95% CI). The NNT was 5 (3 to 11, 95% CI), i.e., using this parameter, for every five patients managed, one additional patient could avoid an unnecessary RHC (Table 2). In the same way, this strategy increased the risk of leaving some malignant aNENs in follow-up (17%; 12 to 23%, 95% CI). The related NNH was 6 (4 to 8, 95% CI), i.e., using a 20 mm cutoff, for every six patients managed, one additional patient with nodal metastases could be incorrectly left in follow-up (Table 3). The LHH was 6/5 (1.2), suggesting that the benefits related to the adoption of a 20 mm cutoff were very close to the risk related.

Meta-analysis of the secondary endpoints

Supplementary Fig. 2, panels A to F, show the forest plots of the other risk parameters while the detailed results are reported in Tables 1–3. Data regarding the 15 and 10 mm cutoffs were available in only four studies involving 158 and 254 patients, respectively. The RDs were statistically significantly different in the two groups using both the 15 (RD = −0.26; −0.47 to −0.06, 95% CI) and the 10 mm cutoffs (RD = −0.23; −0.47 to −0.06, 95% CI). For the 15 mm cutoff, the NNT, NNH, and LHH were 6 (3 to 23, 95% CI), 8 (5 to 15, 95% CI) and 1.3, respectively. For the 10 mm cutoff, the NNT was not clearly related to a benefit because it included the 0 value in the confidence interval (NNT = 16;7 to −50, 95% CI). The NNH was 14 (7 to 88, 95% CI), suggesting that for every 14 patients managed, one additional patient could be left in follow-up with a nodal metastasis. The LHH was not calculated. The absence of lymphovascular invasion significantly decreased the risk of lymph-nodal disease (RD = −0.24; −0.47 to −0.06, 95% CI). The related NNT, NNH, and LHH were 6 (3 to 22, 95% CI), 6 (4 to 9, 95% CI), and 1, respectively. The site of the lesions, the presence of mesoappendiceal invasion, and grading did not significantly influence the risk of lymph-nodal metastasis. A strategy based on these parameters never produced a clear benefit (no reduction of unnecessary RHCs); however, at the same time, it could be harmful (patients with nodal metastasis in follow-up), having an NNH of 4 (3 to 6, 95% CI), 6 (4 to 9, 95% CI) and 4 (3 to 5 95% CI) for site, mesoappendiceal status and grading, respectively. The related LHHs were not calculated.

Publication bias and heterogeneity

Publication bias (Begg and Egger tests) and heterogeneity tests (Cochran-Q test and I^2 tests) are reported in Table 1. The regression line of the Egger test is plotted in Supplementary Fig. 3 (panels A to G). No publication bias for

Table 1 Meta-analysis of risk factors predicting lymph node metastasis in appendiceal Neuroendocrine Neoplasm (aNENs)

Outcomes of interest	No. of studies	Lymph node status			RD	95% CI	*P*-value	Heterogeneity *P* of C-Q, I^2%	*P* for reporting bias[a]	
		Total	N1	N0						
Size cutoff: 20mm										
≤20 mm (%)	6	204	36 (17.6)	168 (82.4)	−0.30	−0.43 to −0.17	<0.001	0.54, 0%	0.826	0.734
>20 mm (%)		61	29 (47.5)	32 (52.4)						
Size cut-off: 15 mm										
≤15mm (%)	4	95	13 (13.7)	82 (86.3)	−0.26	−0.47 to −0.06	0.013	0.09, 52.3%	0.021	1.000
>15mm (%)		63	28 (44.4)	44 (55.5)						
Size cutoff: 10 mm										
≤10mm	4	69	5 (7.2)	64 (92.7)	−0.23	−0.37 to −0.12	0.004	0.04, 60%	0.671	0.734
>10 mm		185	50 (27.1)	135 (72.9)						
Site										
Middle-Tip	4	120	31 (25.8)	89 (74.2)	0.01	−0.26 to 0.29	0.938	0.08, 54.9%	0.938	0.497
Base		36	7 (19.4)	29 (80.6)						
Mesoappendiceal invasion										
No	5	89	17 (19.1)	72 (80.9)	−0.08	−0.21 to 0.05	0.212	0.35, 10.4%	0.051	0.142
Yes		145	38 (26.2)	107 (73.8)						
Grading according to the 2010 WHO guidelines										
G1	4	154	39 (25.3)	115 (74.7)	−0.08	−0.26 to 0.09	0.332	0.71, 0%	0.442	0.602
G2		35	13 (37.1)	22 (62.9)						
Lymphovascular invasion										
No	5	150	26 (17.3)	124 (82.7)	−0.24	−0.37 to −0.10	0.001	0.55, 0%	0.278	0.624
Yes		65	28 (43.1)	37 (56.9)						

aNENs appendiceal neuro-endocrine neoplasms, *RD* risk difference; *95% CI* 95% confidence interval; *P of C-Q* = *P*-value using the Cochran-Q method to test the heterogeneity of the pooled data (values <0.10 indicate substantial heterogeneity), I^2 Higgin's index for heterogeneity and values >50% indicate substantial heterogeneity, *WHO* World Health Organization

[a]*P*-values for testing publication/reporting bias using the Egger's test (left column) and the Begg test (right column) and $P < 0.1$ indicates significant bias; N1: lymph-nodal metastases; G1–G2: grading of the disease according to the 2010 WHO grading system

either the primary or the secondary endpoints was found except for a 15 mm cutoff and mesoappendiceal invasion. For the 15 mm cutoff, reducing the study sample size resulted in a softening of the effect (beta = 1.93 ± 0.06; *P* = 0.021). On the contrary, for the mesoappendiceal invasion, reducing the study sample size resulted in a magnification of the effect (beta = −2.04 ± 0.64; *P* = 0.051). The heterogeneity was low for the 20 mm cutoff, grading, and mesoappendiceal and lymphovascular invasion while it was moderate for the 15 mm and the 10 mm cutoffs and sites.

Discussion

The management of aNENs, incidentally discovered after appendectomy, represent one of most important challenges for modern oncologists. Both ENETS [4] and NANETS [5] guidelines have suggested that only aNENs >20 mm should be treated with an RHC. In fact, the 20 mm cutoff is the only worldwide accepted "high-risk stigmata" for lymph-nodal metastases. Nevertheless, several other parameters have been described as factors capable of predicting nodal involvement, such as size >10 or 15 mm, location on the base, grading G2, and mesoappendiceal or lymphovascular invasion. Moreover these "minor" parameters are frequently used in the clinical practice in order to select patients who are candidate for RHC as recently reported by Heller et al. [6]. In fact, when one or more of these coexist, the guidelines recommend discussing the possibility of a second surgical look with the patient. Unfortunately, the guidelines rest on questionable bases due to the lack of high-level studies. For this reason, all oncologists have experienced a certain degree of difficulty in choosing whether or not to recommend an RHC after the pathological diagnosis of an aNEN. In fact some questions remain unaddressed. What is the risk of performing an unnecessary RHC? What is the risk of incorrectly leaving a patient in follow-up? Have the ENETS recommendations saved additional patients from unnecessary surgery as compared to leaving them in follow-up with malignancy or not? In this study, the Authors attempted to answer these questions, carrying out a systematic review and meta-analysis for the first time. Moreover, the meta-analytic data were translated into clinical practice using very useful statistical tools, such as NNT, NNH, and LHH. These measurements were used to compare two competitive strategies: "to treat all aNENs" versus "to treat only aNENs at risk".

Table 2 Number needed to treat (NNT) comparing two competitive strategies

Parameters for selecting patients for an RHC	No. of studies	Strategy A	Strategy B	"A vs. B"	
		Unnecessary RHC (%)	Unnecessary RHC (%)	ARR (95% CI)	NNT (95% CI)
Primary endpoint					
Size cutoff >20 mm	6	200/265 (75.5%)	32/61 (52.5%)	0.23 (0.09 to 0.36)	5 (3 to 11)
Secondary endpoints					
Size >15 mm	4	117/158 (74.1%)	35/63 (55.6%)	0.19 (0.04 to 0.32)	6 (3 to 23)
Size >10 mm	4	192/254 (75.6%)	128/185 (69.2%)	0.08 (−0.02 to 0.14)[a]	16 (7 to −50)[b]
Site (base)	4	118/156 (75.6%)	29/36 (80.6%)	−0.05 (−0.02 to 0.10)[c]	−21 (10 to −50)[b]
Mesoappendiceal (invasion)	5	179/234 (76.5%)	107/145 (73.8%)	0.03 (−0.06 to 0.12)[a]	38 (5 to −17)[b]
Grading (G2)	4	137/139 (72.5%)	22/35 (62.9%)	0.10 (−0.08 to 0.27)	11 (4 to −13)[b]
Lymphovascular invasion (Yes)	5	161/215 (74.9%)	37/65 (56.9%)	0.18 (0.05 to 0.31)	6 (3 to 22)

The population at risk consists of patients having an aNEN (after appendectomy) who are candidates for a right hemicolectomy (RHC). The target event was the unnecessary RHC rate (i.e., RHC performed in patients without lymph-nodal metastasis). The referent strategy (strategy A) was "to treat all aNENs"; the experimental strategy (strategy B) was "to treat only patients having an aNEN at risk"

aNENs appendiceal neuroendocrine neoplasms, 95% CI 95% confidence interval, *ARR* absolute risk reduction (this value is equal to the Control event rate—experimental event rate) and, when positive, indicates a reduction in the risk in target event; *NNT* number needed to treat: (this value is equal to 1/ARR and indicates the number of patients who would have to be exposed to the experimental strategy (instead of to the control strategy) to avoid an unnecessary hemicolectomy)

[a]Confidence interval including 0 means that the risk of target event is not clearly lower when adopting the experimental strategy

[b]Confidence interval including 0 means that the alternative strategy is not associated with an increase in benefit

[c]Negative ARR means an absolute risk increase

Table 3 Number needed to harm (NNH) comparing two competitive strategies

Patients without risk signs	No. of studies	Strategy A	Strategy B	"A vs. B"	
		Untreated N+ patients (%)	Untreated N+ patients (%)	ARR (95% CI)	NNH (95% CI)
Primary endpoint					
Size ≤20 mm	6	0/204 (0%)	36/204 (17.6%)	−0.18 (−0.12 to −0.23)	6 (4 to 8)
Secondary endpoints					
Size ≤15 mm	4	0/95 (0%)	13/95 (13.7%)	−0.14 (−0.07 to −0.21)	8 (5 to 15)
Size ≤10 mm	4	0/69 (0%)	5/69 (5.6%)	−0.07 (−0.01 to −0.13)	14 (7 to 88)
Site: middle-tip	4	0/120 (0%)	31/120 (25%)	−0.26 (0.18 to 0.34)	4 (3 to 6)
Mesoappendiceal (no invasion)	5	0/89 (0%)	17/89 (19.1%)	−0.19 (−0.11 to 0.28)[a]	6 (4 to 9)
Grading (G1)	4	0/154 (0%)	39/154 (25.3 %)	−0.25 (−0.18 to −0.32)	4 (3 to 5)
Lymphovascular invasion (No)	5	0/150 (0%)	26/150 (17.3%)	−0.17 (−0.11 to −0.23)	6 (4 to 9)

The population at risk consists of patients having an aNEN without risk signs. The target event was the rate patients were incorrectly included in a follow-up program (i.e., with lymph-nodal metastases). The target event was the unnecessary RHC rate (i.e., RHC performed on patients without lymph-nodal metastases). The referent strategy (strategy A) was "to treat all aNENs"; the experimental strategy (strategy B) was "to treat only patients having an aNEN at risk"

aNENs appendiceal neuroendocrine neoplasms, 95% CI 95% confidence interval; ARR absolute risk reduction (this value is equal to the control event rate- experimental event rate and, when negative is called absolute risk increase (ARI), indicating an increase in the risk in the target event); NNH number needed to harm (this value is equal to 1/ARI and indicates the number of patients who would have to be exposed to an experimental strategy (instead of a control strategy) to result in an incorrect follow-up program)

[a]Confidence interval including 0 means that the risk of the target event is not clearly superior when adopting the experimental strategy

As a primary endpoint, the utility of only "high-risk stigmata" (i.e., size of the tumor >20 mm), produced some interesting findings. First, patients having aNENs >20 mm had a really significantly increased risk (+30%) of nodal involvement with respect to those having aNENs ≤ 20 mm. Second, this RD was sufficiently large to be useful in clinical practice as a selection parameter, reducing unnecessary RHCs (one less for every five patients managed). Third, at the same time, a selection based on the 20 mm cutoff led to a risk otherwise nonexistent in the strategy "to treat all": for every six managed, one patient with nodal involvement could be left in follow-up. Thus, combining the risk and the benefit using the LHH (1.2) indicated that the use of a 20 mm cutoff was slightly more frequently related to a "good choice", saving additional patients from unnecessary surgery as compared to those who were left with a malignancy in follow-up.

Regarding the secondary endpoints, when lowering the size cutoff to 15 mm, the RD remained statistically significant (+26% for the tumors >15 mm), and this difference seemed to be useful in clinical practice, producing an NNT and an NNH of 6 and 8, respectively. Using a 15 mm instead of a 20 mm cutoff, the number of patients who underwent an unnecessary RHC did not increase very much (one patient saved for every six managed instead of for every five) while it was possible to reduce the risk of leaving the patients with nodal involvement (one patient with nodal involvement for every eight managed instead of for every six) untreated in follow-up. Thus, the benefit/risk ratio (LHH = 1.3) seemed to be higher when using the 15 mm cutoff with respect to the 20 mm cutoff.

The risk of nodal involvement also remained statistically significant for patients having an aNEN <10 mm (−23%). However, the adoption of the size cutoff (10 mm) did not produce a clear clinical benefit. In fact, a selection strategy based on this cutoff could be similar to the "to treat all aNENs" strategy in terms of unnecessary RHCs but, at the same time, the risk of leaving patients with nodal involvement in follow-up was not 0 (NNH = 14) as it was in the referent strategy. Considering the other "worrisome features", only lymphovascular invasion seemed to identify a subgroup of aNENs with a significantly increased risk of nodal involvement (+24%). A selection strategy based on this risk parameter could produce some benefit with respect to a "to treat all aNENs strategy" quantifiable in one additional patient saved from an unnecessary RHC for every six managed. At the same time, this selection strategy could be equally harmful, leaving some patients with nodal metastasis in follow-up (NNH = 6 and LHH = 1). A selection strategy based on the site of the tumor, mesoappendiceal invasion or grading was not related to clinical benefit with respect to a "treat-all strategy" but could produce harm, leaving some patients with nodal involvement in follow-up.

In interpreting these results, it should be taken into account that this meta-analysis had some limitations. First, the data were derived only from patients who underwent an RHC and, for this reason, they represented a surgically selected population. This could represent a limitation because this was a subgroup of patients judged "at risk" by physicians and, probably, the overall rate of nodal metastases could be lower than 24.5%.

Second, it was impossible to establish interaction on the part of the risk factors using meta-analytic data; for example, it would be very useful to determine whether or not lymphovascular invasion represented itself and independent risk factors. In fact, Brighi et al. [14]. have suggested that lymphovascular invasion did not independently predict the presence of nodal metastases but, at the same time, it represented an independent prognostic factor for survival.

Third, the secondary endpoints were studied in a smaller population with respect to the primary endpoint (six studies involving 265 patients). In particular, the 15 mm cutoff "meta-population" represented the smallest (only four studies involving 158 patients).

Fourth, the results of some secondary endpoints, such as a 15 mm size cutoff or mesoappendiceal invasion, have to be interpreted with caution due to significant "small size effect". In fact, the impact of a 15 mm cutoff in predicting nodal metastases was reduced in small studies [9, 10] with respect to larger studies [13, 14], suggesting that nodal involvement remained a relatively rare event, observable only in large populations.

Fifth, the surgical risk of the meta-population was unknown and was not included in calculating the NNTs and NNHs. However, the mean age of the patients included reflected the state of health and life expectancy of an average patient eligible for surgery without increased surgical risk. Moreover, an RHC represented very low-risk surgery having a mortality rate of 0.3% [14] and, for this reason, was negligible in balancing the risks and benefits of an approach based on oncologic parameters. Finally, no studies are available, which really compare the surgical approach versus conservative management in terms of disease-specific survival. However, the role of lymph node metastasis, also in reducing survival in resected patients is well known [14, 15]. Nevertheless, any speculation regarding the safety of conservative management has be careful interpreted, since it derives only from pathological data. In fact, conservative management could play an important role in low risk, small (<20 mm) a-NENs as well as in small pancreatic NENs [16].

In conclusion, despite its limitations, the present study, analyzing the knowledge currently available, answered our questions. Regarding the first question, the data suggested that a selection based on the size of the tumor could be helpful in reducing the unnecessary RHCs. Both 20 and 15 mm cutoffs had a similar performance in reducing the unnecessary second surgical look while the adoption of a 10 mm cutoff did not produce a significant advantage with respect to the "to treat all" strategy. Of the other parameters, only lymphovascular invasion seemed to be helpful in avoiding unnecessary surgery. Regarding the second question, adopting a selection based on ENETS risk factors, there was a non-negligible risk of leaving some malignant aNENs in follow-up. All parameters performed similarly, except for the 10 mm cutoff, which rarely left metastatic aNENs in follow-up. Finally, when balancing risk and benefit, the selection of patients for an RHC should be based on size (20 or 15 mm cutoffs) or on the presence of lymphovascular invasion. However, the physician had to take into account that the risk of leaving some patients with malignancy in follow-up was not 0 and, for this reason, an adequate follow-up should be carried out. Lowering the cutoff to 10 mm, the benefit disappeared with only a small risk remaining. Finally, any choice based on location of the tumor, grading or mesoappendiceal invasion could not only be worthless but also harmful.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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