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REVIEW

Predictors of disease recurrence after curative surgery for nonfunctioning pancreatic neuroendocrine neoplasms (NF-PanNENs): a systematic review and meta-analysis

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Abstract

Purpose Patients submitted to curative surgery for non-functioning pancreatic neuroendocrine neoplasms (NF-PanNENs) exhibit a variable risk of disease relapse. Aims of this meta-analysis were to estimate the rate of disease recurrence and to investigate the risk factors for disease relapse in patients submitted to curative surgery for NF-PanNENs.

Methods Medline/Pubmed and Web of Science databases were searched for relevant studies. A meta-regression analysis was performed to investigate the source of recurrence rate heterogeneity. Pooled hazard ratios (HRs) and 95% confidence intervals (95% CI) were used to assess the effect of each possible prognostic factor on disease-free survival.

Results Fifteen studies, involving 2754 patients submitted to curative surgery for NF-PanNENs, were included. The pooled rate of disease recurrence was 21% (95% CI 15–26%). Study quality (Odds ratio, OR 0.94, $P=0.016$) and G3-PanNENs rate (OR 2.18, $P=0.040$) independently predicted the recurrence rate variability. Nodal metastases (HR 1.63, $P<0.001$), tumor grade G2-G3 (G1 versus G2: HR 1.72, $P<0.001$, G1 versus G3 HR 2.57, $P<0.001$), microvascular (HR 1.25, $P=0.046$) and perineural (HR 1.29, $P=0.019$) invasion were identified as significant prognostic factors. T stage (T1-T2 versus T3-T4, $P=0.253$) and status of resection margins (R0 versus R1, $P=0.173$) did not show any significant relationship with NF-PanNENs recurrence.

Conclusion Disease relapse occurs in approximately one out of five patients submitted to curative surgery for NF-PanNENs. Nodal involvement, tumor grade, microvascular and perineural invasion are relevant prognostic factors, that should be taken into account for follow-up and for possible trials investigating adjuvant or neoadjuvant treatments.

Keywords Pancreatic neuroendocrine neoplasms · Nonfunctioning · Curative surgery · Recurrence · Relapse · Prognostic factors

Introduction

Pancreatic neuroendocrine neoplasms (PanNENs) account for approximately 2–3% of all pancreatic tumors [1]. Despite being still regarded as rare lesions, their incidence has dramatically increased over the last three decades due to the

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widespread use of high-quality imaging techniques [1, 2]. Non-functioning (NF) PanNENs represent the vast majority of these lesions and span a wide range of aggressiveness, including both slow-growing tumors with an indolent biological behaviour and aggressive neoplasms presenting at an advanced stage with local invasion and/or distant metastases [3].

Surgery represents the backbone for the curative treatment of localized NF-PanNENs [4–6]. Moreover, surgical management has been reported to be associated with a survival benefit also in the presence of resectable or potentially resectable liver metastases [7, 8]. The recurrence rate within 5 years after curative surgery has been reported between 10 and 40% [9–11]. Postoperative follow-up plays a pivotal role for the early detection of disease recurrence and its timing should be tailored according to the presence of tumor features of aggressiveness [12]. A number of clinic-pathological features, including presence of symptoms, tumor size and grade, nodal metastases, perineural and microvascular invasion, have been investigated as possible predictors of disease relapse after surgery [13–17]. Furthermore, several retrospective series have developed accurate nomograms that could be of help in predicting the risk of recurrence and consequently in tailoring the follow-up scheme [18–20]. Nevertheless, the features at high-risk for postoperative recurrence are still matter of debate and there is much uncertainty regarding the optimal strategy and timing of surveillance after surgery [4, 5].

The aims of this systematic review and meta-analysis were: (i) to estimate the rate of disease recurrence and (ii) to identify the risk factors for disease relapse in patients submitted to curative surgery for NF-PanNENs.

Methods

The present study was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [21].

Eligibility criteria

Prospective and retrospective cohort studies fulfilling the following PICOTS criteria [22] were considered eligible for the present study:

1. Population (P): patients submitted to surgical resection with curative intent (R0-R1) for NF-PanNENs;
2. Index prognostic factors (I): T stage (T1-T2 versus T3-T4), N stage (N0 versus N+), tumor grade (G1 versus G2, G1 versus G3), resection margin status (R0 versus R1), microvascular invasion (no versus yes), perineural invasion (no versus yes);
3. Comparator prognostic factor (C): none;
4. Outcome (O): disease recurrence after curative surgery;
5. Timing (T): at any time during post-surgical follow-up;
6. Setting (S) and role: estimate of recurrence rate and identification of prognostic factors based on which a tailored follow-up schedule could be developed.

Studies were included if either recurrence rate or Kaplan–Meier curve representing disease-free survival (DFS) were provided. Multivariate hazard ratios (HRs) and 95% confidence intervals (CI) were required to enter the meta-analysis on each prognostic factor. Studies comprising both functioning and non-functioning PanNENs were included only if a sub-analysis for NF-PanNENs was performed. Review articles without original data and small case series including less than ten patients were excluded. Studies analysing secondary recurrences or comprising patients submitted to palliative surgical resection (R2) were excluded as well.

Information sources

A systematic review of the literature was conducted following the recommendations for systematic reviews in surgery provided by Goossen et al. [23]. The MEDLINE/PubMed and Web of Science databases were searched for eligible articles, without any language, publication date, or publication type restriction. The last electronic search was performed on December 28, 2020. The PubMed function "related articles" was used with the aim to expand the search. The reference list of all potentially eligible studies was screened to minimize the retrieval bias. The corresponding authors of two included studies were contacted to retrieve additional information.

Search

The search was conducted using medical subject headings (MeSH) in combination with free text words. The search strategy used in MEDLINE/PubMed was the following: (Pancreatic Neuroendocrine Neoplasm OR Pancreatic Neuroendocrine Neoplasms OR Pancreatic Neuroendocrine Tumor OR Pancreatic Neuroendocrine Tumors OR Pancreatic Neuroendocrine Tumour OR Pancreatic Neuroendocrine Tumours OR Pancreatic Endocrine Tumor OR Pancreatic Endocrine Tumors OR Pancreatic Endocrine Tumour OR Pancreatic Endocrine Tumours OR Pancreatic Endocrine Neoplasm OR Pancreatic Endocrine Neoplasms OR Adenoma, Islet Cell OR Adenomas, Islet Cell OR Islet Cell Adenomas OR Islet Cell tumor OR Islet Cell Tumors OR Tumor, Islet Cell OR Tumors, Islet Cell OR Island Cell Tumor OR Island Cell Tumors OR Tumor, Island Cell OR Tumors, Islands Cell OR Apudoma OR Carcinoma, Islet

Cell OR Carcinomas, Islet Cell OR Islet Cell Carcinoma OR Islet Cell Carcinomas OR Islet Cell Tumor, Malignant) AND (Disease-Free Survival OR Disease Free Survival OR Survival, Disease-Free OR Survival, Disease Free OR Recurrence OR Relapse).

Study selection

All the records identified through the literature search strategy were screened by two investigators (VA and GG), independently. Titles and abstracts were initially reviewed to remove duplicates and select relevant publications. If the abstract suggested relevance, the full-text paper was assessed for eligibility in accordance with the predefined inclusion criteria.

When multiple articles were published by the same study group and overlapping study periods were reported, either the most recent or the most relevant study was selected to avoid duplication of data. Since two eligible studies [18, 24] had a partially overlapping study population ($n = 39$) and the authors had access to the database related to the publication by Partelli et al. [24], a new survival analysis was performed excluding the overlapping patients from the above-mentioned study. Two series with a minimal, but not quantifiable cohort overlap, were considered as two independent studies [13, 25]. Two studies by Zhou et al. [26, 27] analysed an almost completely overlapping population. For this reason, patients included in these two series were described as a single study cohort [26, 27].

The final decision on eligibility was reached by consensus between the two screening authors (VA and GG). Any disagreement regarding inclusion criteria was solved through discussion or by consulting a third author (SP). Detailed information regarding the screening process are provided in the PRISMA flow diagram (Fig. 1).

Data collection process

Data were extracted from the selected articles using a piloted extraction form by both the screening authors (VA and GG), independently. Extracted data were then compared and any discrepancies were solved through discussion. A third author (SP) was consulted to reach a final consensus and confirm the data, when necessary.

Data items

Data were sought for general information (first author, year of publication, study type and design, study period, institution and country, number of participants), inclusion and

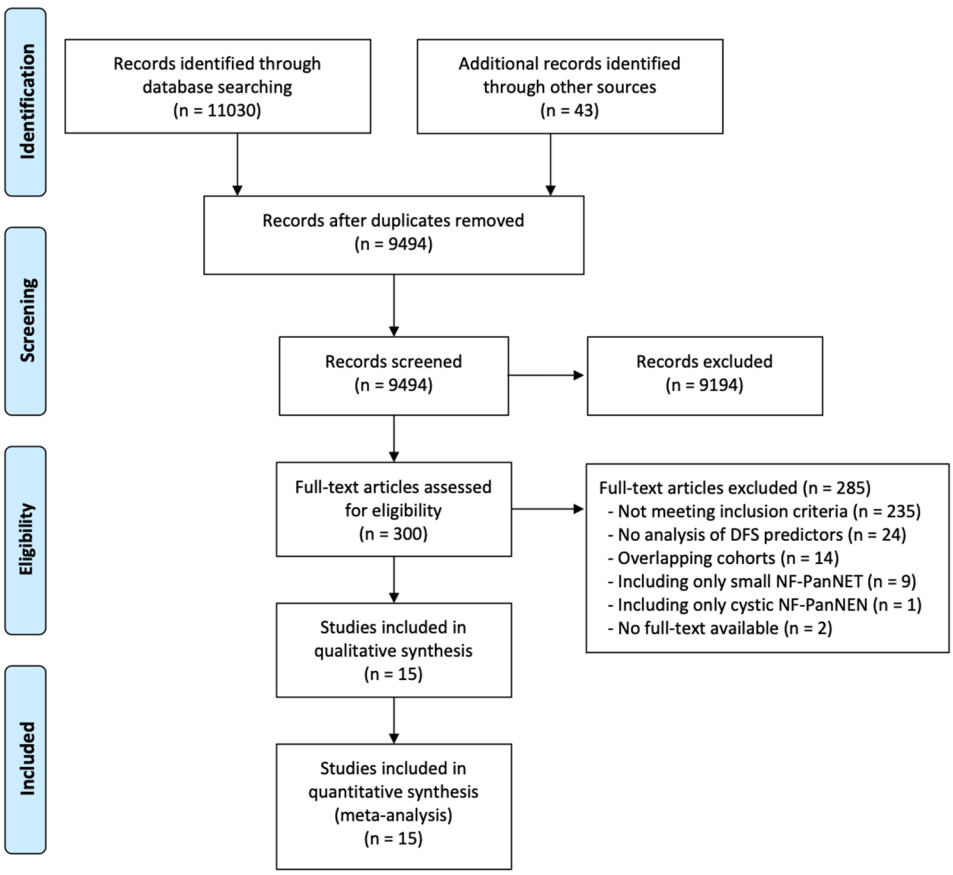

Fig. 1 PRISMA flow diagram illustrating study selection

exclusion criteria, demographics of study participants (gender and age) and follow-up details (recurrence rate, median follow-up and lost rate). Disease recurrence was defined as local recurrence at the pancreatic resection site, newly identified pathological lymph nodes or development of distant metastases. Clinic-pathological characteristics considered as possible predictors of disease recurrence were: T stage (T1–T2 versus T3–T4) and N stage (N0 versus N +) defined according to European Neuroendocrine Tumor Society (ENETS) or to American Joint Committee on Cancer (AJCC) (8th edition) classifications [28, 29], tumor grade (G1 versus G2 and G1 versus G3) defined according to the 2010/2017 World Health Organization (WHO) classification [30, 31], status of resection margins (R0 versus R1), presence of microvascular and perineural invasion.

Risk of bias in individual studies, summary measures, and synthesis of results

The qualitative assessment of the studies was carried out based on the methodological index for non-randomized studies (MINORS) [32]. All categorical variables were reported as frequencies and percentages, while continuous variables were presented as means with standard deviations. A dedicated statistical algorithm was used to calculate the mean and standard deviation in studies that presented median and interquartile range [33, 34]. The results were reported as pooling proportion of the recurrence rate, together with a 95% CI. When the recurrence rate was not reported, a dedicated software was used to obtain the crude number of events from Kaplan–Meier curves (GetData Graphical Digitizer@). We also extracted the HRs of multivariate prognostic models predicting DFS, when reported. The HRs together with a 95% CI were converted in logarithimc form and analyzed using a random effect model. The results were reported as cumulative HRs and 95% CI and as fictitiuos median DFS time units. The last measure was calculated assuming that: (1) the hazard rates of the group with lower risk was equal to 1, corresponding to a median DFS of 0.7 fictitious time units. The hazard rate for the group with higher risk was calculated following this formula: $MedianDFS = \frac{\ln(2)}{Hazardrate}$

The meta-analysis was carried out in line with recommendations from the Cochrane Collaboration and Meta-analysis of Observational Studies in Epidemiology guidelines [35, 36] and the Mantel–Haenszel random-effects model was used to calculate effect sizes [37].

Risk of bias across studies and additional analyses

The risk of bias across included studies was tested, measuring both the "between-study heterogeneity" and publication bias. I^2 and Cochran's Q statistics were used to assess heterogeneity [38]. In particular, the value of I^2 describes the percentage of variability in point estimates due to heterogeneity rather than sampling error. When I^2 was $< 50\%$, the risk of "between-study heterogeneity" was judged as low-moderate; if I^2 was $\geq 50\%$, the risk of "between-study heterogeneity" was considered high. The meta-regression analysis was carried out when heterogeneity was high and the result was statistically relevant [39]. The meta-regression was planned only for the primary endpoint (pooling proportion meta-analysis). The meta-regression was based on the use of maximum residual likelihood (REML) [40, 41].

The multivariate model was built using the forward stepwise model.

Firstly, we calculated the distribution of covariates in each study. Secondly, for each covariate, the following parameters were described: odds ratio (OR) with standard error (SE) and R^2. The OR ± SE was related to the change of the recurrence rate: if the OR was > 0, the covariate increase produced a positive modification of the recurrence rate. On the other hand, R^2 indicated the percentage of between-study variance explained by the covariate. A two-tailed P value < 0.05 was considered statistically significant. The publication bias evaluation was made using the Begg and the Egger tests [40], and a P value < 0.05 indicated a non-negligible "small-study effect". A nonparametric "trim and fill" method was used to adjust for the publication bias. The method, a rank-based data augmentation technique, formalizes the use of funnel plots, estimates the number and the outcomes of missing studies, and adjusts the meta-analysis to incorporate the theoretical missing studies. The statistical analysis was carried out using dedicated packages for STATA version 14® (StataCorp, College Station, TX, USA).

Results

Study selection

The PRISMA flow diagram illustrating the study selection process is depicted in Fig. 1. Overall, a total of 11,030 articles were identified using the literature search strategy. Forty-three additional studies were retrieved by means of hand search. Among these, 1579 were excluded, as they were duplicates. The remaining 9494 records were screened by title and abstract for eligibility. Of these, 9194 were excluded because they were not pertinent to the field of the study or did not meet the inclusion criteria. Finally, the full texts of 300 studies were evaluated. Of these, 285 were excluded, 14 of which owing to data duplication (overlapping study cohorts). Eventually, 15 studies fulfilled the inclusion criteria and were suitable for the meta-analysis.

Study characteristics and risk of bias within studies

Fifteen retrospective observational cohort studies, involving a total of 2754 patients submitted to curative surgery for NF-PanNENs, were included [13, 18, 24, 26, 27, 42–52]. All the series were published between 2013 and 2020 and were conducted in nine different countries. Four of these studies were multicentric experiences [13, 18, 24, 47]. The general features and the quality assessment of the included studies are summarized in Table 1. Most of the studies ($n=9$) considered only patients with localized disease, whereas six series included also metastatic patients submitted to curative surgery [26, 43–45, 48, 51]. Two studies considered standard resections only [46, 48], whereas another series established enucleation (but not other parenchyma-sparing resections) as exclusion criterion [13]. Partelli et al. [24] analysed a cohort selectively including patients submitted to pancreaticoduodenectomy. Six studies considered only patients with PanNENs G1-G2 [13, 18, 49–52], whereas nine experiences included also G3 neoplasms. Of these latter, only Capretti et al. [46] applied the latest WHO classification [31] distinguishing between well-differentiated PanNETs G3 and poorly differentiated pancreatic neuroendocrine carcinomas (PanNECs) G3. Inclusion and exclusion criteria of selected studies are reported in Table S1. Other clinic-pathological features are provided in Table 2 and Table S2.

Primary endpoint: recurrence rate

The pooled rate of disease recurrence (Fig. 2), calculated considering all the studies ($n=15$) included in the meta-analysis, was 21% (95% CI 15–26%). Since the "between-study heterogeneity" was high (I^2 92.86%, $P<0.001$), a meta-regression analysis was performed (Table 3). At univariate meta-regression analysis, study quality assessed with MINORS score was significantly related to the variability of the recurrence rate (OR 0.94, SE 0.21, $P=0.033$). This variable alone could explain 33% (R^2) of recurrence rate variability, with a decrease in study quality producing an increase in relapse rate (Fig. S1a). The percentage of G3-PanNENs included in each study showed a trend towards an association with recurrence rate between-study variance (OR 2.31, SE 0.97, $P=0.087$). This variable alone could explain 19% (R^2) of recurrence rate variability, with an increase in the quote of G3 neoplasms producing an increase in the rate of disease relapse (Fig. S1b).

Multivariate meta-regression analysis showed that study quality (OR 0.94, SE 0.01, $P=0.016$) and G3-PanNENs rate (OR 2.18, SE 0.73, $P=0.040$) independently predicted recurrence rate variation. The final multivariable model explained 72.3% of recurrence rate variability.

Secondary endpoints: predictors of disease recurrence

A meta-analysis based on multivariate HRs and 95% CI extraction was performed to evaluate the effect of each covariate (T stage, N stage, tumor grade, resection margin status, microvascular invasion and perineural invasion) on disease recurrence (Table 4).

Three studies [13, 24, 42], including 399 patients, reported T stage dichotomized as T3–T4 versus T1–T2 [28]. The pooled HR was 1.16 (95% CI 0.90–1.50), indicating that T category was not a significant prognostic factor ($P=0.253$) (Fig. 3a). The median DFS for T1–T2 and T3–T4 tumors was similar (0.7 versus 0.6 time units).

Ten series [13, 18, 24, 27, 42, 45, 47, 49, 51, 52], including 2045 patients, evaluated N category (N0 versus N+) as prognostic variable. The pooled HR was 1.63 (95% CI 1.38–1.92), indicating that nodal involvement was a significant predictor of recurrence ($P<0.001$) (Fig. 3b). The median DFS was longer in N0 tumors than in N+ (0.7 versus 0.5 time units).

Nine studies considered tumor grade as prognostic variable [13, 18, 24, 27, 45, 47, 49–51]. Overall, 1218 patients had a PanNEN G1, 722 had a PanNEN G2 and 61 had a PanNEN G3. The pooled HR for G1 versus G2 was 1.72 (95% CI 1.41–2.10), thus indicating that G2 tumors have a significantly higher risk of recurrence compared to G1 tumors ($P<0.001$) (Fig. 3c). After adjustment for publication bias, the pooled HR was 1.66 (95% CI 1.37–2.01). Four series [24, 27, 45, 47] considered also the comparison G1 versus G3. The pooled HR for G1 versus G3 was 2.57 (95% CI 1.53–4.34, $P<0.001$) (Fig. 3d). The median DFS were 0.7, 0.4 and 0.3 time units for G1, G2 and G3 lesions, respectively.

Three series [13, 47, 48], including 1096 patients, considered the prognostic role of microscopic margin involvement (R0 versus R1). The pooled HR was 1.24 (95% CI 0.92–1.67) (Fig. 3e), indicating that microscopic involvement of the resection margin was not a significant prognostic variable ($P=0.173$). The median DFS was similar in patients who underwent R0 and R1 resection (0.7 versus 0.7 time units).

Five studies [13, 24, 42, 47, 51], including 1405 patients, considered the prognostic role of microvascular invasion. The pooled HR was 1.25 (95% CI 1.00–1.55) (Fig. 3f), indicating that microvascular invasion was a significant predictor of disease recurrence ($P=0.046$). The related median DFS were 0.7 and 0.6 time units in the absence or presence of microvascular invasion, respectively.

Seven series [13, 18, 24, 42, 47, 50, 51], including 1947 patients, considered the prognostic role of perineural invasion. The pooled HR was 1.29 (95% CI 1.04–1.60) (Fig. 3g), indicating that perineural invasion was a significant predictor

Table 1 Characteristics of the studies included in the meta-analysis ($n = 15$)

Year	Authors	Study type	Study design	Center(s) (Country)	Study period	Patients enrolled	Recurrences *n* (%)	Median follow-up, months	Lost rate	Multivariate models	Study quality[a]
2013	Partelli et al.[13]	Retrospective	Multicentric	Verona University Hospital (Italy), Hospital Beaujon (France)	1993–2009	181	23 (13)	55	0	Yes	11
2015	Jiang et al.[42]	Retrospective	Monocentric	Ruijin Hospital Affiliated to Shanghai Jiaotong University School of Medicine (China)	2004–2014	100	21 (21)	n.e	6 (6)	Yes	10
2015	Sallinen et al.[43]	Retrospective	Monocentric	Helsinki University Hospital (Finland)	2000–2013	44	11 (25)	24	0	No	12
2017	Choi et al.[44]	Retrospective	Monocentric	Asan Medical Center (South Korea)	2004–2013	162	34 (21)	29	0	No	10
2017	Zhou et al.[26, 27]	Retrospective	Monocentric	First Affiliated Hospital, Zhejiang University School of Medicine (China)	2003–2016	125	47 (38)	n.e	0	Yes	10
2018	Bu et al.[45]	Retrospective	Monocentric	Samsung Medical Center (South Korea)	1995–2013	166	40 (24)	47	0	Yes	10
2018	Genc et al.[18]	Retrospective	Multicentric	Erasmus Medical Center (Netherlands), Academic Medical Center (Netherlands), San Raffaele Hospital (Italy)	1992–2015	211	35 (17)	51	0	Yes	10
2018	Partelli et al.[24]	Retrospective	Multicentric	San Raffaele Hospital (Italy), Johns Hopkins University Hospital (USA), Varese University Hospital (Italy)	2005–2015	118	24 (20)	43	0	Yes	11
2019	Capretti et al.[46]	Retrospective	Monocentric	Humanitas Research Hospital (Italy)	2011–2016	77	8 (10)	n.e	0	No	12
2019	Dong et al.[47]	Retrospective	Multicentric	US Neuroendocrine Tumor Study Group	1997–2016	842	344 (41)	34	0	Yes	9
2019	Feretis et al.[48]	Retrospective	Monocentric	Addenbrooke's Hospital (UK)	2002–2015	73	12 (16)	49	0	Yes	10
2019	Izumo et al.[49]	Retrospective	Monocentric	Tokyo Woman's Medical University (Japan)	2000–2016	74	12 (16)	62	0	Yes	11
2019	Landoni et al.[50]	Retrospective	Monocentric	Verona University Hospital (Italy)	1990–2015	331	45 (14)	67	0	Yes	11
2020	Gong et al.[51]	Retrospective	Monocentric	Fudan University Shanghai Cancer Centre (China)	2008–2018	164	35 (21)	43	0	Yes	9
2020	Tan et al.[52]	Retrospective	Monocentric	West China Hospital, Sichuan University (China)	2009–2017	88	12 (14)	49	7 (8)	Yes	10

n.e. not extractable

[a]Study quality evaluated with MINORS score [32]

Table 2 Overview of clinical and staging details reported by the studies ($n=15$) included in the meta-analysis

Authors	Gender M/F *n* (%)	Age Years Mean (SD)	Symptoms No/Yes *n* (%)	MEN-1 No/Yes *n* (%)	T stage[a] T1-T2/T3-T4 *n* (%)	N stage[a] N0/N1 *n* (%)	M stage[a] M0/M1 *n* (%)	Tumor grade[c] G1/G2/G3 *n* (%)
Partelli et al.[13]	93/88 (51/49)	59 (11)	94/87 (52/48)	181/0 (100/0)	121/60 (67/33)	126/55 (70/30)	181/0 (100/0)	111/70/0 (61/39/0)
Jiang et al.[42]	46/54 (46/54)	n.e	47/53 (47/53)	100/0 (100/0)	64/36 (64/36)	80/20 (80/20)	100/0 (100/0)	61/24/15 (61/24/15)
Sallinen et al.[43]	n.e	n.e	29/15 (66/34)	35/9 (80/20)	35/9 (80/20)	35/9 (80/20)	n.e	17/22/5 (39/50/11)
Choi et al.[44]	n.e	n.e	n.e	162/0 (100/0)	n.r	142/20 (88/12)	n.e	n.e
Zhou et al.[26, 27]	64/61 (51/49)	53 (13)	54/71 (43/57)	125/0 (100/0)	111/14 (89/11)[b]	98/27 (78/22)	110/15 (88/12)	41/62/22 (33/50/17)
Bu et al.[45]	81/85 (49/51)	54 (11)	106/60 (64/36)	166/0 (100/0)	108/58 (65/35)[b]	142/24 (86/14)[e]	162/4 (98/2)	82/72/12 (50/43/7)
Genc et al.[18]	103/108 (49/51)	59 (12)	n.r	211/0 (100/0)	n.r	160/51 (76/24)	211/0 (100/0)	139/72/0 (66/34/0)
Partelli et al.[24]	55/63 (47/53)	58 (14)	n.r	118/0 (100/0)	90/28 (76/24)	75/43 (64/36)	118/0 (100/0)	70/42/6 (59/36/5)
Capretti et al.[46]	45/32 (58/42)	57 (15)	n.r	77/0 (100/0)	46/31 (60/40)	52/25 (68/32)	77/0 (100/0)	36/37/4 (47/48/5)[d]
Dong et al.[47][f]	431/411 (51/49)	57 (n.r.)	363/473 (43/57)	764/64 (92/8)	n.r	525/191 (73/27)	842/0 (100/0)	449/198/22 (67/30/3)
Feretis et al.[48]	38/35 (52/48)	58 (10)	n.r	73/0 (100/0)	67/6 (92/8)[b]	43/30 (59/41)	73/0 (100/0)	56/13/4 (77/18/5)
Izumo et al.[49]	28/46 (38/62)	59 (12)	63/11 (85/15)	67/7 (91/9)	n.r	61/13 (82/18)	74/1 (99/1)	61/13/0 (82/18/0)[d]
Landoni et al.[50]	n.e	n.e	n.e	331/0 (100/0)	n.r	n.e	331/0 (100/0)	217/114/0 (66/34/0)
Gong et al.[51][g]	62/102 (38/62)	54 (10)	n.r	164/0 (100/0)	n.r	125/26 (83/17)	157/7 (96/4)	74/89/0 (45/55/0)[d]
Tan et al.[52]	46/42 (52/48)	52 (12)	40/48 (45/55)	88/0 (100/0)	57/31 (65/35)	75/13 (85/15)	88/0 (100/0)	32/56/0 (36/64/0)

M male, *F* female, *MEN-1* multiple endocrine neoplasia type 1, *n.r.* not reported, *n.e.* not extractable

[a]According ENETS-TNM staging system [28]

[b]According to AJCC classification 7th edition [58]

[c]According to WHO 2010 classification [30]

[d]According to WHO 2017 classification [31]

[e]N0 included also Nx patients who underwent atypical resection without preoperative evidence of lymph node metastases

[f]Missing: $n=6$ presence of symptoms; $n=14$ genetic syndrome; $n=126$ N stage; $n=173$ tumor grade

[g]Missing: $n=13$ N stage; $n=1$ tumor grade

of disease recurrence ($P=0.019$). The median DFS in the absence or presence of perineural invasion were 0.7 versus 0.5 time units.

Heterogeneity and publication bias

Heterogeneity between studies was low-moderate ($I^2<50\%$) for T stage ($I^2=0\%$), resection margin status ($I^2=37\%$) and microvascular invasion ($I^2=38\%$). On the contrary, heterogeneity between included series was high ($I^2\geq 50\%$) for nodal status ($I^2=52\%$), tumor grade (G1 versus G2, $I^2=54\%$; G1 versus G3, $I^2=72\%$) and perineural invasion ($I^2=59\%$) (Table 4). No "small study effect" was observed for any of the investigated variables using both visual assessment (Fig. S2, panels a-g) and Begg and Egger tests (Table 4). HRs and 95% CI adjusted for publication bias are reported in Table 4.

Discussion

The present study comprehensively assessed the prognosis of patients submitted to curative surgery for NF-PanNENs. The analysis showed that the pooled recurrence rate after

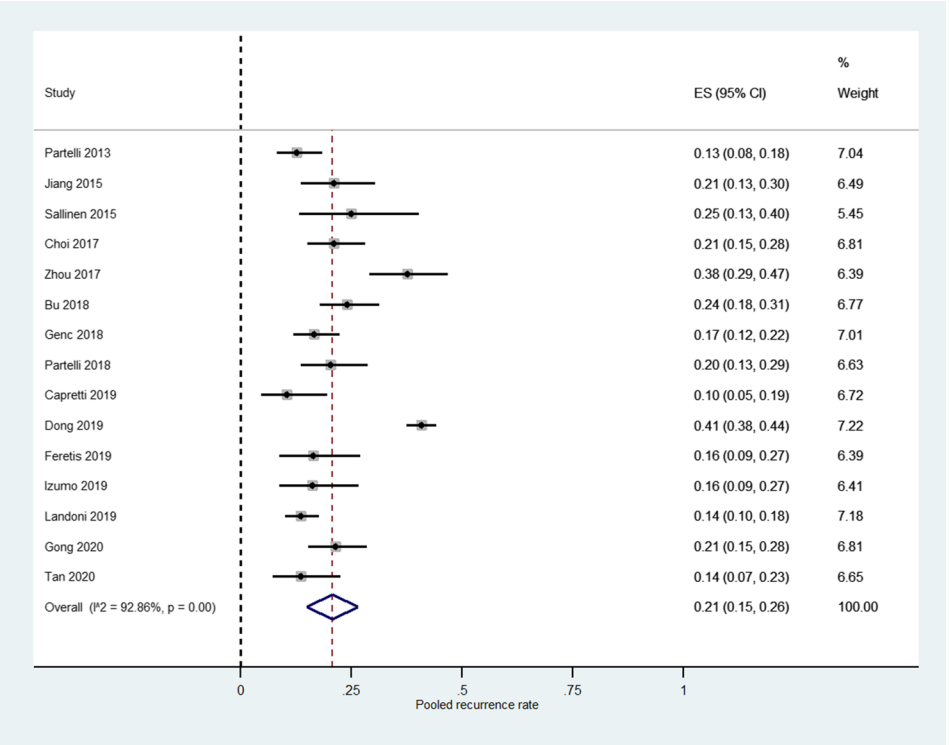

Fig. 2 Forest plot of the pooled recurrence rate of patients submitted to curative surgery for nonfunctioning pancreatic neuroendocrine neoplasms (NF-PanNENs)

Table 3 Univariate and multivariate meta-regression analysis

Covariates	Number of studies	Univariate analysis			Multivariate analysis		
		OR (SE)	Adjusted R^2 (%)	*P* value	OR (SE)	Adjusted R^2 (%)[c]	*P*-value[c]
Study quality (MINORS score), points	15	0.94 (0.21)	33	0.033	0.94 (0.01)	72.3	0.016
Male gender, rate	12	0.92 (0.48)	94	0.891	–	–	–
Age (years), mean	11	0.98 (0.01)	13	0.140	–	–	–
Symptoms, rate	8	0.76 (0.23)	− 4	0.423	–	–	–
MEN-1, rate	15	1.93 (0.93)	12	0.195	–	–	–
T1-T2, rate[a]	6	1.75 (0.47)	81	0.109	–	–	–
N0, rate[a]	14	0.92 (0.26)	− 8	0.780	–	–	–
M0, rate[a]	13	0.22 (0.16)	11	0.101	–	–	–
G1, rate[b]	14	0.78 (0.14)	6	0.202	–	–	–
G2, rate[b]	14	0.94 (0.18)	− 6	0.755	–	–	–
G3, rate[b]	14	2.31 (0.97)	19	0.087	2.18 (0.73)	72.3	0.040
R0, rate	11	1.01 (0.19)	− 10	0.987	–	–	–
No microvascular invasion, rate	8	1.04 (0.28)	− 17	0.840	–	–	–
No perineural invasion, rate	8	1.33 (0.52)	− 13	0.506	–	–	–
Follow-up (months), median	12	0.99 (0.01)	38	0.101	–	–	–

MINORS methodological index for non-randomized studies, *MEN-1* multiple endocrine neoplasia type 1, *OR* odds ratio, *SE* standard error, *Adjusted R2* adjusted residual that represents the proportion of between-study heterogeneity explained by the covariate

[a]According to ENETS-TNM [28]

[b]According to WHO 2010/2017 classifications [30, 31]

[c]The values are referred to the entire multivariate model

– Covariate not included in the multivariate model

Table 4 Meta-analysis based on multivariate hazard ratios (HRs) extraction

Covariates	Number of studies	HR (95% CI)	*P* value	Heterogeneity I^2 (%); *P*-value of C-Q	*P* value for reporting bias[c]		Adjustment bias		Median DFS in fictitious time units[d]
					Egger	Begg	Trim/fill	Adj HR	
T1-T2 vs. T3-T4[a]	3	1.16 (0.90–1.50)	0.253	0; 0.533	0.438	1.000	0	1.16 (0.90–1.50)	0.7 vs. 0.6
N0 vs. N + [a]	10	1.63 (1.38–1.92)	< 0.001	52; 0.028	0.403	0.107	+ 2	1.54 (1.30–1.83)	0.7 vs. 0.5
G1 vs. G2[b]	9	1.72 (1.41–2.10)	< 0.001	54; 0.025	0.506	0.348	+ 1	1.66 (1.37–2.01)	0.7 vs. 0.4
G1 vs. G3[b]	4	2.57 (1.53–4.34)	< 0.001	71; 0.025	0.335	0.734	0	2.57 (1.53–4.34)	0.7 vs. 0.3
R0 vs. R1	3	1.24 (0.92–1.67)	0.173	37; 0.203	1.000	0.602	+ 2	1.02 (0.75–1.40)	0.7 vs. 0.7
Microvascular invasion (No vs. Yes)	5	1.25 (1.00–1.55)	0.046	38; 0.165	0.963	0.806	0	1.25 (1.00–1.55)	0.7 vs. 0.6
Perineural invasion (No vs. Yes)	7	1.29 (1.04–1.60)	0.019	59; 0.023	0.954	0.764	0	1.29 (1.04–1.60)	0.7 vs. 0.5

HR hazard ratio, *95% CI* confidence interval at 95%, *Adj* adjusted, I^2 Higgins test, *C–Q* Cochran's test, *vs.* versus

[a]According to ENETS-TNM [28]

[b]According to WHO 2010/2017 classifications [30, 31]

[c]A reporting bias is considered non negligible for *P* values < 0.100

[d]The median time unit of recurrence was obtained assuming that Hazard rate of group with lower risk was equal to 1 corresponding to 0.7 fictitiuos time units

curative resection was 21% and that study quality and G3-PanNENs proportion were the main determinants of recurrence rate variability across studies. Tumor grade, nodal involvement, microvascular and perineural invasion were identified as significant predictors of disease relapse.

Radical surgical resection represents the cornerstone for the curative treatment of NF-PanNENs. However, a relevant proportion of patients still experience disease relapse during postoperative follow-up. In this regard, a number of clinic-pathological features have been investigated as possible predictors of disease recurrence. Nevertheless, the rarity of the disease and the heterogeneity in terms of study populations and follow-up length still make it challenging to extrapolate a reliable recurrence rate (10–25%) as well as to draw firm conclusions regarding the most relevant prognostic factors after NF-PanNENs curative resection [9, 10]. Therefore, an accurate stratification of the recurrence risk is currently lacking and there is no tailored follow-up strategy based on the individual risk of recurrence [4, 12].

The present meta-analysis showed that approximately one out of five patients submitted to curative surgery for a NF-PanNEN experiences a disease relapse during follow-up. This rate is higher compared to that reported in a recent meta-analysis published by Li et al. [53], who described a 13% relapse rate after curative surgery for well-differentiated PanNENs. Two main reasons can explain this divergent data: first, the present study included NF-PanNENs only, whereas Li et al. considered both NF and functioning tumors. In this regard, it has been widely reported that functioning PanNENs have a different biological behaviour and a significantly better prognosis compared to NF-PanNENs [19, 54]. Therefore, the selective inclusion of NF neoplasms represents a strength of the present study, as there are no previous meta-analyses evaluating prognostic factors on a homogeneous cohort of curatively resected NF-PanNENs. Second, also G3 neoplasms were considered in this study, while the previous experience limited the analysis to G1-G2 tumors [53]. Consistently, the rate of G3 neoplasms was identified as an independent determinant of recurrence rate variability across the included studies, with a higher rate of G3 PanNENs being associated with an increased rate of disease relapse. The other significant factor explaining recurrence rate heterogeneity was study quality (assessed with MINORS score), with higher recurrence rates in the presence of lower study quality. Of note, the presence of distant metastases was not identified as a predictor of recurrence rate variability, probably due to the low rate of M1 patients included in the present meta-analysis. The use of a meta-regression analysis to identify the main determinants of recurrence rate variability represents another strength of the present study, as it has never been performed in this setting. In addition, most of the included studies ($n = 9$) had a follow-up length greater than 40 months, which improves the reliability of the present findings.

The results of this study also validate the prognostic role of several clinic-pathological features. The presence of nodal involvement was confirmed to be associated with a poorer DFS, with nine out of ten series agreeing about the significant prognostic role of nodal metastases. Only Gong et al. [51] reported a discordant result, possibly due to low

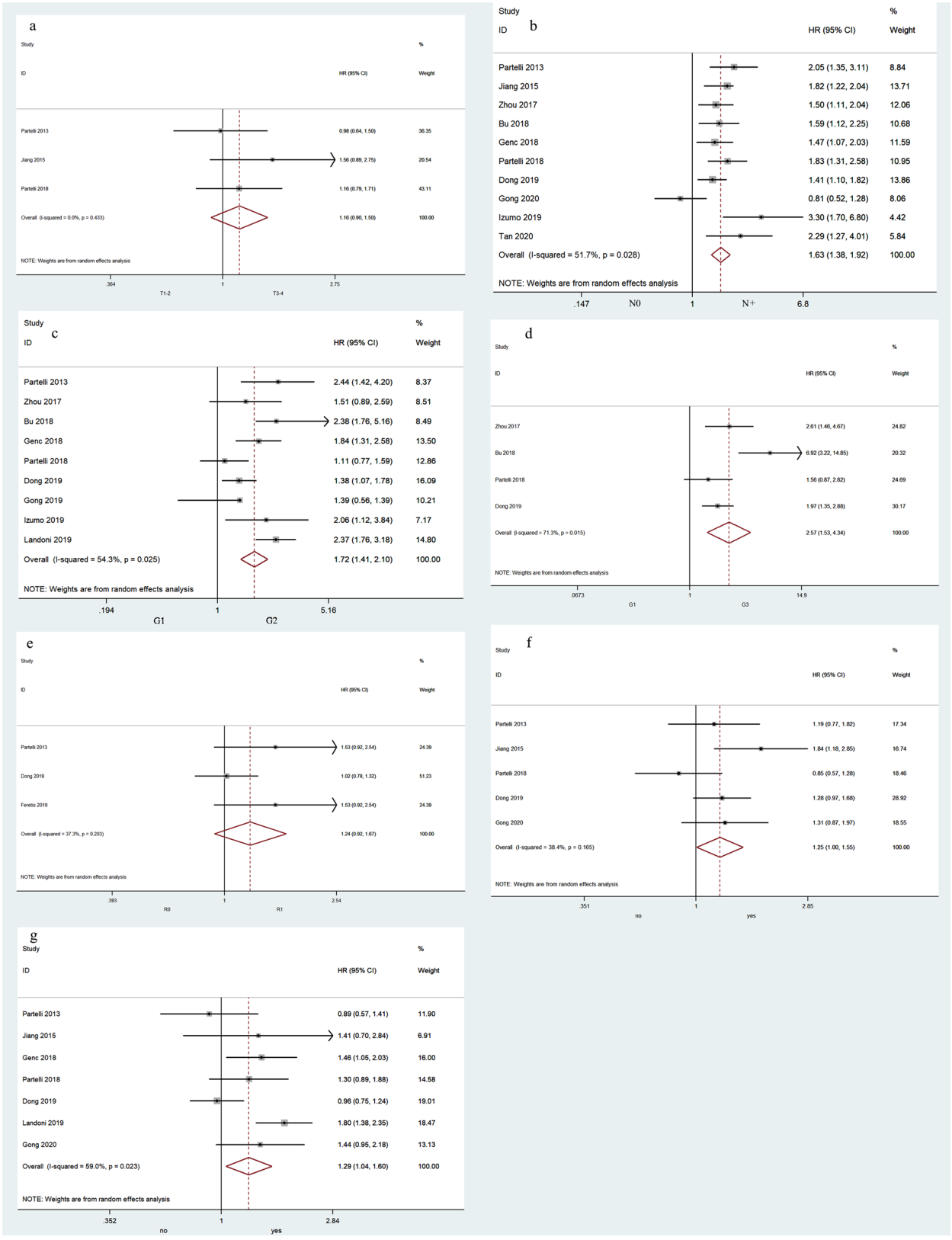

Fig. 3 Forest plots of studies showing the effect pathological factors on disease recurrence (**a**: T stage—T1-T2 versus T3-T4; **b**: N stage—N0 versus N+; **c**: tumor grade—G1 versus G2; **d**: tumor grade—G1 versus G3; **e**: status of resection margins—R0 versus R1; **f**: microvascular invasion—no versus yes; **g**: perineural invasion—no versus yes)

study quality and missing data regarding nodal status in 10% of cases [51]. The present data are concordant with those reported by previous meta-analyses considering resected PanNENs regardless of functional status [53, 55]. Moreover, a recent meta-analysis by Tanaka et al. found a significant association between nodal involvement and decreased survival outcomes in patients with resected NF-PanNENs, highlighting a non-negligible rate of nodal metastases (10%) also in small (< 2 cm) and G1 NF-PanNENs [56]. Based on these findings, an oncological resection with lymphadenectomy seems justified to properly stage patients submitted to surgery for NF-PanNENs and to accurately stratify their risk of disease relapse. Of note, also patients with small NF-PanNETs showing features of aggressiveness (i.e., presence of symptoms, dilation of main pancreatic duct/bile duct) should be managed by formal resection with lymphadenectomy. On the other hand, parenchyma-sparing resections can be considered as a valid option for selected patients with indolent NF-PanNETs ≤ 2 cm, when a conservative management cannot be pursued (i.e., for patient's choice).

Consistently with previous reports [53, 55], also tumor grade was identified as a relevant predictor of DFS, with G2 and G3 neoplasms having an increasingly higher risk of disease relapse compared to G1 tumors. Indeed, G2 tumors represent a large fraction of PanNENs and include both aggressive and indolent neoplasms encompassing a wide range of Ki67 [10, 15]. Therefore, the between-study heterogeneity hereby reported might be explained by different distributions of Ki67 within the G2 category. The risk of recurrence was even higher in patients with G3 PanNENs, who were also identified as those experiencing the earliest disease relapse (0.3 versus 0.7 time units for G1 tumors). This evidence strengthens the need for a closer postoperative follow-up schedule, based on high-quality morphological and functional imaging, for patients with high-grade neoplasms [20]. However, the number of patients with G3 PanNENs included in the present meta-analysis was pretty low, and no analysis stratified by cell differentiation was performed. Therefore, further assessments distinguishing between G3 PanNETs and PanNECs are now required to draw firm conclusions on this aspect.

Finally, also microvascular and perineural invasion were identified as significant prognostic factors, suggesting that these features should be routinely assessed and systematically reported. This evidence, which is in line with previous findings [16, 17], supports the hypothesis that vessels and nerves could represent a route of metastatic spread and should be consequently regarded as indicators of an aggressive biological behaviour [10]. On the other hand, T stage and status of resection margins did not show any significant relationship with recurrence at pooled analysis. Li et al. reported a similar finding for tumor size, but recognized positive resection margins as a significant risk factor for disease relapse [53]. Of note, in the present meta-analysis, only three studies were considered for the evaluation of these features and sample size was consequently limited. The reason explaining the low number of series available for T stage analysis is that only homogeneous studies applying either the ENETS classification or the AJCC classification 8th edition were considered as eligible [13, 24, 42]. Also, T1–T2 neoplasms may comprise patients with small PanNETs that were not managed conservatively due to the presence of aggressiveness features. Therefore, a selection bias towards aggressive small PanNETs being treated by surgery might explain the lack of a significant association between T stage and disease relapse. Regarding resection margin status, it is currently matter of debate whether R1 resection represents an independent predictor of poorer DFS. In this regard, a recent study showed that re-resection of an initially positive surgical margin to achieve a R0 resection did not improve survival outcomes in patients with PanNENs [57].

The present meta-analysis has several limitations. First, all the included studies are retrospective and this might lead to biases in the collection and reporting of data. Second, inclusion criteria vary across the studies and this represents a relevant source of heterogeneity. In particular, several series considered also metastatic patients submitted to curative surgery. However, the low number of M1 PanNENs prevented from performing a separate analysis to investigate this factor as predictor of disease relapse. Third, most of the included studies applied the 2010 WHO classification for tumor grade, without distinguishing between well- and poorly differentiated G3-PanNENs [30]. Also, the inclusion of series adopting either the 2010 or the 2017 WHO classifications led to a variable categorization (G2 or G1) of patients with Ki67 proliferative index comprised between 2 and 3%. Fourth, there are other relevant prognostic factors, including presence of symptoms, necrosis and DAXX/ATRX status, that were not analysed due to the limited number of series assessing these parameters. Also, the number of harvested lymph nodes could not be evaluated as predictor of disease relapse, due to heterogeneous reporting and lack of data stratified according to the type of surgical resection. Fifth, the number of studies that could be included in the evaluation of T stage and resection margin status is limited, which leads to a decreased reliability of these results. In addition, there is variability in terms of multivariate regression model construction, and this could partially explain the high heterogeneity of the pooled HRs observed for several prognostic factors. Last, fictitiuos median DFS time units, calculated from HRs, were used to estimate the time to disease recurrence for each prognostic factor, as median DFS expressed in months were not available in most of the included studies.

In conclusion, the present study found that disease recurrence is not a rare event, as it occurs in approximately 20%

of patients submitted to curative surgery for NF-PanNENs. Nodal involvement, tumor grade G2–G3, microvascular and perineural invasion were identified as the most relevant risk factors for disease relapse. Moreover, patients with G3 PanNENs were identified as the group experiencing the earliest disease relapse. These findings might represent the cornerstone for the establishment of a tailored follow-up schedule. In addition, the accurate stratification of patients' risk could be useful for designing future trials investigating adjuvant treatments for PanNENs. Prospective studies are needed to confirm the validity of the present findings and assess their implications in the clinical practice.

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Code availability Not applicable.

Declarations

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

Ethical approval This meta-analysis is based on published studies performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki.

Research involving human participants and/or animals As this meta-analysis is performed based on published studies, no ethical approval was required.

Consent to participate Not applicable.

Consent for publication As this meta-analysis is based on published studies, no patient consent for publication was required

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