

Prognostic impact and implications of extracapsular lymph node involvement in colorectal cancer: a systematic review with meta-analysis

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Background: The extranodal extension (ENE) of nodal metastasis (i.e. the extension of tumor cells through the nodal capsule into the perinodal adipose tissue) has recently emerged as an important prognostic factor in different types of malignancies. However, the tumor–node–metastasis (TNM) staging system for colorectal cancer does not consider it as a prognostic parameter. Therefore, we conducted a systematic review and meta-analysis to determine the prognostic role of ENE in patients with lymph node-positive colorectal cancer.

Materials and methods: Two independent authors searched PubMed and SCOPUS until 7 January 2015 without language restrictions. Prospective studies reporting data on prognostic parameters in subjects with colorectal cancer, comparing participants with the presence of ENE (ENE+) versus only intranodal extension (ENE–) were eligible. Data were summarized using risk ratios (RRs) for the number of deaths/recurrences and hazard ratios (HRs) together with 95% confidence intervals (CIs) for time-dependent risk related to ENE+, adjusted for potential confounders.

Results: Thirteen studies including 1336 patients were identified with a median follow-up of 4.7 years. ENE was associated with a higher T stage and tumor grading. In addition, ENE was associated with a significantly increased risk of all-cause mortality (RR = 1.75; 95% CI 1.42–2.16, $P < 0.0001$, $I^2 = 60\%$; HR = 1.69, 95% CI 1.32–2.17, $P < 0.0001$, $I^2 = 46\%$) and of recurrence of disease (RR = 2.07, 95% CI 1.65–2.61, $P < 0.0001$, $I^2 = 47\%$; HR = 2.31, 95% CI 1.54–3.44, $P < 0.0001$, $I^2 = 48\%$).

Conclusions: Based of these results, in colorectal cancer, ENE should be considered from the gross sampling to the pathology report, as well as in future oncologic staging systems.

Key words: extranodal extension, extracapsular extension, lymph node metastasis, colon cancer, rectal cancer

introduction

Colorectal cancer is the third most common cancer in the United States and Europe [1]. The pathologic stage at diagnosis is the best indicator of prognosis [2, 3]. The classic staging system for colorectal cancer is the tumor–node–metastasis (TNM) staging system, in which the N category is divided in N1 and N2, and tumor deposits represent N1c subcategory (supplementary Table S1, available at *Annals of Oncology* online) [2]. Thus, not only T and N status, but even the free tumor deposits in the adipose tissue are recognized as important prognostic

parameters. Although the majority of patients with colorectal carcinoma display lymph node involvement, little attention has been paid to the histologic features of lymph node metastasis. Specifically, the TNM system does not consider as a prognostic parameter in N+ patients the extranodal extension (ENE), which is the extension of tumor cells through the nodal capsule into the perinodal fatty tissue (Figure 1). Given this, ENE has recently emerged as an important prognostic factor in several types of malignancies [4–8]. A previous systematic review with a last search date of almost a decade old [4] considered the evidence on ENE as a prognostic factor in all the gastrointestinal malignancies, yet only identified four colon and/or rectal cancer series with a total 502 node-positive patients, suggesting ENE to be a valuable prognostic factor for such cancers. While this review was helpful and advanced the field of study, no formal

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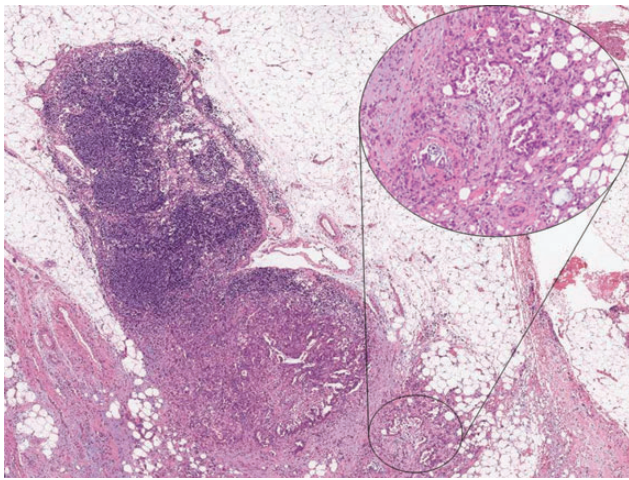


Figure 1. Extranodal extension of lymph node metastasis. A classic example of ENE is here shown. The cells of lymph node metastasis go through the nodal capsule into the perinodal fatty tissue (original magnifications: $\times 4$ entire lymph node, $\times 10$ detail).

meta-analysis currently exists on this topic. The potential of tumor cells to invade through the lymph node capsule may reflect the aggressiveness of the primary tumor [9]. Therefore, the detection and quantification of ENE in the surgical specimen of colorectal cancer can be helpful from investigating tumor biology to assess correctly the staging system and to determining adjuvant treatment strategies. Since several new studies in the last years have investigated this topic and the last review date was over a decade old, we aimed to clarify the prognostic role of ENE in patients with lymph node-positive colorectal cancer and conduct the first meta-analysis on this topic. Within our meta-analysis, we sought to take into consideration potentially important prognostic factors, including namely overall survival (OS), disease-free survival (DFS) and cancer-specific survival in patients with (ENE+) or without (ENE-) ENE.

materials and methods

This systematic review adhered to the MOOSE guidelines [10] and PRISMA statement [11], following a predetermined protocol.

inclusion and exclusion criteria

Studies were considered eligible for inclusion meeting the following criteria: (i) prospective, observational cohort studies, (ii) contained a comparison of prognostic factors between ENE+ and ENE-, (iii) diagnosis of cancer of colon and/or rectum, (iv) contained data about mortality or recurrence of disease, (v) were published in a peer-review journal or published abstract.

Exclusion criteria were: (i) no presence of cancer, (ii) no data about prognostic parameters in the title/abstract, (iii) comparison between ENE+ and no lymph nodes metastases, (iv) diagnosis of nonepithelial malignancies (i.e. lymphomas) and (v) *in vitro* or animal studies. We considered articles in any language.

data sources and literature search strategy

Two investigators (CL, NV) independently searched PubMed and SCOPUS until 7 January 2015. The search terms used in PubMed

included combinations of the following keywords: ((extracapsular OR pericapsular OR extranodal OR perilymphatic OR perinodal OR 'extra capsular' OR 'peri-capsular' OR 'extra nodal' OR 'peri lymphatic' OR 'peri nodal' OR 'extra-capsular' OR 'peri-capsular' OR 'extra-nodal' OR 'peri-lymphatic' OR 'peri-nodal') AND (colon OR colonic OR rectum OR rectal OR colorectal) AND (mortality OR mortalities OR fatality OR fatalities OR death* OR survival OR prognosis OR 'hazard ratio' OR HR OR 'relative risk' OR RR OR prognosis OR progression OR recurrence)). A similar search was carried out in SCOPUS. We considered the reference lists of all included articles and of previous related reviews.

study selection

Following the searches as outlined above, after removal of duplicates, two independent reviewers screened titles and abstracts of all potentially eligible articles. The two authors applied the eligibility criteria, considered the full texts and a final list of included articles was reached through consensus.

data extraction

Two authors were involved in data extraction in a predetermined database. Specifically, one author (AN) extracted data from the included articles and a second independent author (MS) validated the data. For each article, we extracted information about authors, year of publication, country, location of cancer, exclusion criteria, number of females, T stage, tumor grading, number of patients with metastatic lymph nodes, age, concomitant analysis of free tumor deposits, number of adjustments in survival analyses and duration of follow-up.

outcomes

The primary outcomes were the number of deaths independently from the cause (all-cause mortality), number of deaths due to cancer and number of recurrences after treatment during follow-up period in those with ENE+ versus ENE-. Secondary outcomes were hazard ratios (HRs), adjusted for the maximum number of confounders available, about the same issues taking those with ENE- as reference.

assessment of study quality

We used the Newcastle-Ottawa Scale (NOS) [12] to evaluate study quality. The NOS provides an assessment of the methodological quality of nonrandomized trials and its content validity and reliability have been established [12]. Included studies are judged on eight items across three key areas: selection of the participants, comparability of the participants and outcomes. Two authors (CL, NV) completed the NOS and each study receives an overall score for methodological quality of up to 9 points with a score of ≤ 5 (out of 9) indicating high risk of bias (supplementary Tables S2 and S3, available at *Annals of Oncology* online).

data synthesis and statistical analysis

All analyses were carried out using Comprehensive Meta-Analysis (CMA) software version 3. For continuous variables, normality was assessed using the Shapiro-Wilk test. If normality was satisfied the variables were presented as mean \pm standard

deviation (and compared with independent Student's *t*-test) or as median with range if normality not satisfied. Categorical variables were presented as number and percentage and compared using χ^2 test.

In our primary analyses, pooled risk ratios (RRs) and 95% confidence intervals (CIs) of all-cause mortality, cancer-specific mortality and recurrences of disease between ENE+ and ENE- were calculated using DerSimonian-Laird random-effect models [13]. In secondary analyses, pooled, HRs with 95% CIs adjusted for the maximum number of covariates, available in the articles, were also calculated for providing additional information if the relationship between ENE status and outcomes was influenced by potential confounders. Heterogeneity across studies was assessed by the I^2 metric and χ^2 statistics [14]. In the presence of significant heterogeneity ($P < 0.05$) [14], we conducted a series of meta-regression analyses according to ENE status and each of prognostic parameters considered. The following moderators were tested: location of cancer (colonic, rectal or colorectal), sample size, concomitant analysis of free tumor deposits, percentage of females and age of the sample as whole, T stage, percentage of metastatic lymph nodes, median follow-up period of observation, NOS, number of adjustments, country (categorized as Europe versus Asia). For significant moderators at meta-regression analysis, a further stratification analysis was made, using the median value in case of a continuous variable.

Finally, we investigated publication bias for our primary meta-analysis with a visual inspection of funnel plots and with the Begg-Mazumdar Kendall's tau [15] and Egger's bias test [16]. Moreover, in the presence of publication bias for the main analyses, we conducted a trim-and-fill-adjusted analysis [17] to remove the most extreme small studies from the positive side of the funnel plot, and recalculated the effect size at each iteration, until the funnel plot was symmetric about the (new) effect size.

results

search results

Altogether, 210 nonduplicated articles were identified through the literature search. After excluding 189 articles based on title/abstract review, 21 articles were retrieved for full-text review and following the application of the inclusion criteria, 13 unique articles were eligible for the meta-analysis [18–30] (supplementary Figure S4, available at *Annals of Oncology* online).

study and patient characteristics

The studies were conducted in Europe (7 studies, 53.8%) [18–20, 22, 25, 26, 29] or in Japan (6 studies, 46.2%) [21, 23, 24, 27, 28, 30], with no studies from America or other continents. The studies included a higher proportion of men (57.7%) than women, with a mean age of 64.0 ± 12.2 years. Four studies specifically investigated colon cancer [18, 20, 26, 29], five considered the rectum only [19, 22, 23, 25, 28] and four considered both the colon and the rectum [21, 24, 27, 30]. Furthermore, four studies have considered even tumor-free deposits as prognostic parameter [18, 26, 28, 29].

The median NOS score was 7 points (range: 6–8) with no studies at possible high risk of bias for quality (i.e. NOS score ≤ 5) (supplementary Tables S2 and S3, available at *Annals of Oncology* online).

Nine of 13 studies assessed ENE with a classic definition [18–20, 22, 25, 26, 28–30], which is the extension of lymph node metastatic cells through the nodal capsule into the perinodal fatty tissue. The remaining four studies [21, 23, 24, 27] used alternative definitions of ENE. For Fuji et al. [21], ENE is defined as an extension of lymph node metastatic cells through the nodal capsule into the perinodal fatty tissue and/or extranodal location of tumor cells; for Komori et al. [23], it is an extension of lymph node metastatic cells through the nodal capsule into the perinodal fatty tissue or extranodal location of tumor cells continuously; Komuta et al. [24] defined ENE as the extension of lymph node metastatic cells through the nodal capsule into the perinodal fatty tissue, distinguishing two subcategories: < 5 cells or more than 5 cells out of metastatic lymph node; lastly, Suzuki et al. [27] defined ENE as an invasive cancer showing penetration at least of the nodal capsule or extending through the nodal capsule into the perinodal adipose tissue. All the alternative definitions of ENE are present in studies from Japan.

Regarding characteristics of ENE+ versus ENE- patients, no significant differences emerged for mean age ($P = 0.67$) or gender ($P = 0.82$). Regarding T stage, ENE+ patients have, however, a significant major proportion of a higher T stage than ENE- (T3–T4 of ENE+: 94.9% versus T3–T4 of ENE-: 79.9%, $P < 0.0001$). A similar figure emerged regarding high tumor grading (G3 of ENE+: 24.2% versus G3 of ENE-: 14.3%, $P < 0.0001$) (supplementary Table S2, available at *Annals of Oncology* online).

risk ratios on overall survival and disease-free survival

Pooling data from eight studies reporting data on mortality [18, 19, 23–28], 70.0% with ENE+ were dead versus 39.5% with ENE-, leading to a significant increased risk of all-cause mortality (RR = 1.75; 95% CI 1.42–2.16, $P < 0.0001$, $I^2 = 60\%$) (Table 1, Figure 2A).

ENE+ was further associated to a significant higher risk of recurrence of disease (9 studies [18, 20–22, 25, 29, 30]); 64.7% in ENE+ versus 30.0% in ENE-; equating to a RR = 2.07 (95% CI 1.65–2.61, $P < 0.0001$, $I^2 = 47\%$) (Table 1; Figure 2B).

The funnel plot of the studies taking as outcome OS or DFS included in our meta-analysis (supplementary Figure S5, available at *Annals of Oncology* online) indicated publication bias, as confirmed by the Egger's test (bias = 3.00; 95% CI 0.70–5.29, $P = 0.001$ for both outcomes) and Begg-Mazumdar test (Kendall's $\tau = 0.61$, $P = 0.01$ for both outcomes), likely due to the inclusion of works reporting a significant association between ENE+ and OS/DFS (right side of the mean).

Given the publication bias observed, we calculated the trim-and-fill-adjusted analysis [17]. However, after the adjustment for publication bias, our results remained unchanged.

adjusted hazard ratios on overall survival and disease-free survival

In our secondary analyses, we investigated whether using HRs (adjusted for the maximum number of the covariates available in each study) instead of RRs could influence our results. In the survival analyses, the median number of adjustments used was 4 (range: 2–9) (supplementary Tables S2 and S6, available at *Annals of Oncology* online).

Table 1. Pooled risk ratio estimates for overall and disease-free survival according to the presence or not of extranodal extension

Parameter	N Studies	N of Events in ENE+	N of No ENE+	N of Events in ENE-	N of ENE-	Risk ratio (95% CI)	P value	Heterogeneity
Overall survival	8	278	397	186	471	1.75 (1.42–2.16)	<0.0001	$I^2 = 0.05$; $\chi^2 = 17.60$, $df = 7$ ($P = 0.01$); $I^2 = 60\%$
Disease-free survival	9	255	394	134	447	2.07 (1.65–2.61)	<0.0001	$I^2 = 0.05$; $\chi^2 = 15.20$, $df = 7$ ($P = 0.06$); $I^2 = 47\%$

df, degrees of freedom; ENE, extranodal extension.

Table 2 shows the adjusted HRs according to ENE status. ENE + was associated to a significant poorer prognosis, being associated to higher risk of both all-cause mortality (5 studies [18, 19, 23, 26, 27]; HR = 1.69, 95% CI 1.32–2.17, $P < 0.0001$, $I^2 = 46\%$) (Figure 3A) and recurrence of disease (5 studies [18, 20, 23, 26, 30]; HR = 2.31, 95% CI 1.54–3.44, $P < 0.0001$, $I^2 = 48\%$) (Figure 3B).

Only one study [30] reported data about cancer-specific survival, indicating that ENE increased such type of risk (HR: 2.513; 95% CI 1.001–6.307; $P = 0.05$), precluding meaningful meta-analysis.

No publication bias evident using adjusted HRs instead of RR for OS (Egger's test: bias = -0.98; 95% CI -4.17 to 2.19, $P = 0.40$; Begg-Mazumdar test: Kendall's $\tau = 0.02$, $P = 0.80$) or DFS (Egger's test: bias = 3.80; 95% CI 1.93–5.77, $P = 0.0008$; Begg-Mazumdar test: Kendall's $\tau = 0.50$, $P = 0.22$) (supplementary Figure S5, available at *Annals of Oncology* online).

meta-regression and sensitivity analyses

Only RRs for all-cause mortality reported high heterogeneity ($I^2 \geq 50\%$ and $P \leq 0.05$). Meta-regression established that only the consideration of free tumor deposits in perinodal fatty tissue emerged as a significant moderator for RRs of all-cause mortality (slope = -0.384 ± 0.180 , $P = 0.03$) (supplementary Table S7, available at *Annals of Oncology* online). However, the stratification for this factor seems to poorly affect our findings since, in the five studies [18, 26, 28, 29] analyzing free tumor deposits, the RR for OS was 2.14 (95% CI 1.56–2.93, $P < 0.0001$, $I^2 = 59\%$) and, in those without this parameter [19–25, 27, 30], the RR was 1.39 (1.18–1.65, $P < 0.0001$, $I^2 = 0\%$). Finally, stratifying according to the definition of ENE (classical versus other definition) does not significantly change our findings (supplementary Table S8, available at *Annals of Oncology* online).

discussion

In this meta-analysis, we examined 13 observational studies involving 1336 patients affected by colon and/or rectal cancer with metastatic lymph node(s), of which 611 presented ENE of lymph node metastasis while 725 showed only intranodal metastasis. Our results have demonstrated the important weight of ENE in the prognosis of such malignancies. Particularly, our findings suggest that the presence of ENE is associated to a poor prognosis in terms of overall mortality and recurrence of diseases, the most important indicators of prognosis and also of life's quality in patients with colon cancer. Furthermore, the majority of outcomes were not characterized by a high heterogeneity, reinforcing the robustness of our findings. Furthermore, ENE emerged as a hallmark of a more advanced tumor stage: indeed, ENE+ patients have a higher T stage than ENE- ($P < 0.001$); furthermore, ENE can be considered also a hallmark of aggressiveness, since it is associated with a higher percentage of high-grade tumor.

An important implication derived from this study regards the surgical pathology approach and, in particular, the gross sampling. Indeed, on the basis of the shown importance of ENE in colorectal cancer, and knowing that ENE can be very focal, a mandatory consequence is that all the lymph nodes with their

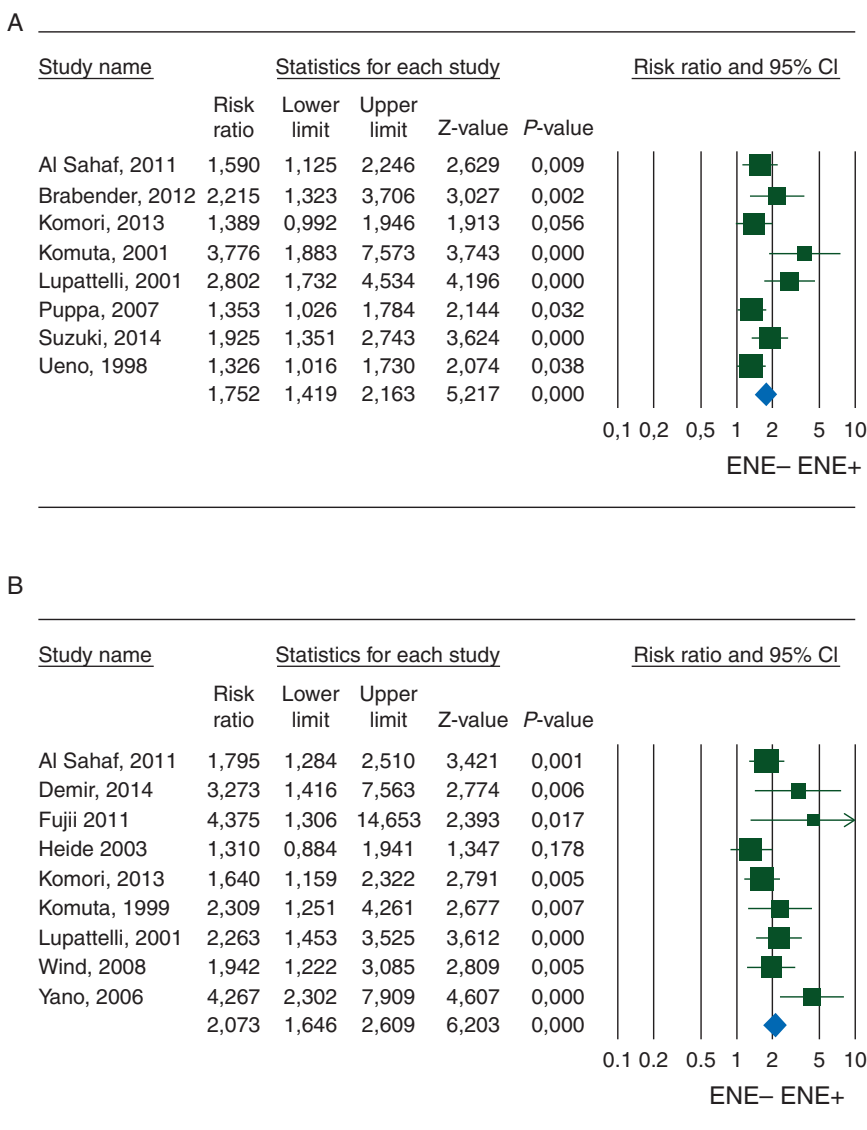


Figure 2. Forest plot of pooled risk ratios taking all-cause mortality (A) and recurrence of disease (B) as outcomes.

Table 2. Pooled risk ratio estimates for adjusted hazard ratios for overall and disease-free survival according to the presence or not of extranodal extension

Parameter	N Studies	Hazard ratios (95% CI)	P value	Heterogeneity
Overall survival	5	1.69 (1.32–2.17)	<0.0001	$\tau^2 = 0.03$; $\chi^2 = 7.41$, df = 4 ($P = 0.11$); $I^2 = 46\%$
Disease-free survival	5	2.31 (1.54–3.44)	<0.0001	$\tau^2 = 0.11$; $\chi^2 = 8.34$, df = 4 ($P = 0.08$); $I^2 = 48\%$

df, degrees of freedom; ENE, extranodal extension.

surrounding adipose tissue have to be completely included. A common gross approach tends to start with the manual isolation of lymph nodes, or with the sampling of only a portion of lymph nodes with metastatic aspect. However, on the basis of this systematic review and meta-analysis, a complete inclusion of all the lymph nodes, even if very large, and of the perinodal fatty tissue is suggested. Following the TNM staging system, it is important looking for free tumor deposits in the adipose tissue,

and on the basis of our shown results, also looking for ENE is very important.

Furthermore, another aspect that needs to be clarified is a standard definition of ENE, since these parameters should be included, in our opinion, in the final pathology report. Nine of 13 meta-analyzed studies assessed ENE with a classic definition, considering it as the extension of lymph node metastatic cells through the nodal capsule into the perinodal fatty tissue.

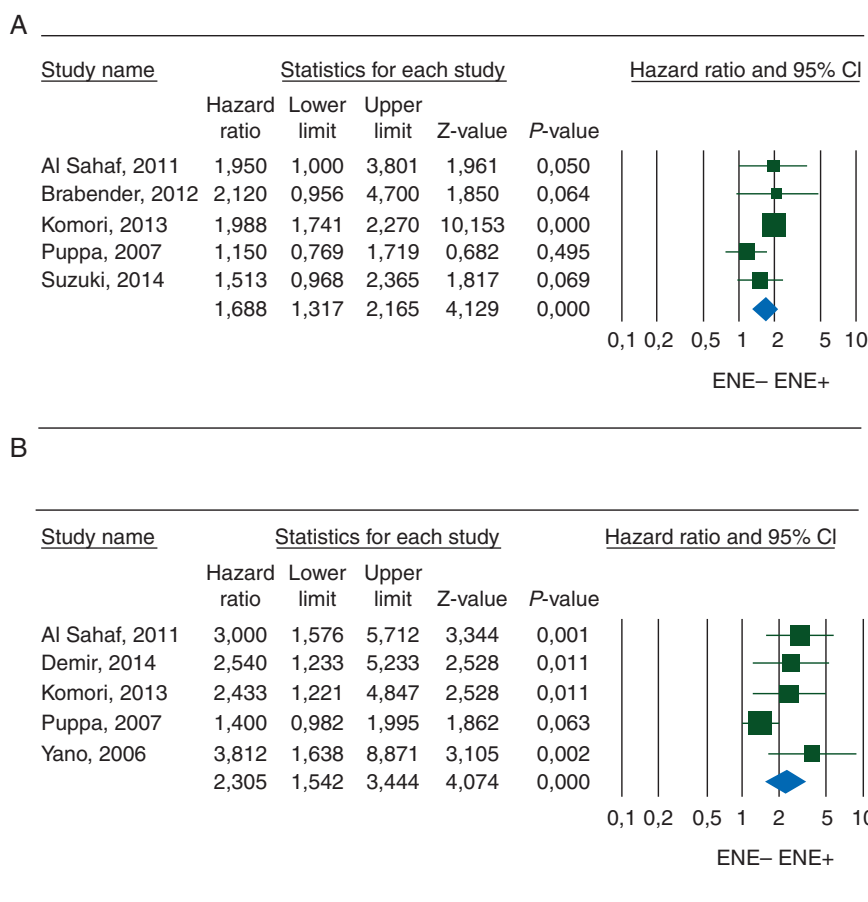


Figure 3. Forest plot of pooled adjusted hazard ratios taking all-cause mortality (A) and recurrence of disease (B) as outcomes.

The remaining four studies used alternative ENE definitions, without significant alteration in the meaning with the exception of the study by Fujii et al. [21]. In that paper, indeed, ENE was defined as an extension of lymph node metastatic cells through the nodal capsule into the perinodal fatty tissue and/or extranodal location of tumor cells [21]. Using this definition, it is possible that in ENE category have been included also free tumor deposits, with a possible bias. However, the global results of our meta-analysis are too robust to be affected significantly by this issue. Furthermore, this point emphasizes the necessity of reaching a standard definition of ENE. We suggest to consider as true ENE for colorectal cancer only, a nondebatable ENE. It has to be demonstrated histologically, documenting a structural rupture of the lymph node capsule by the metastasis. Neoplastic emboli even outside the lymph node, as well as metastasis in the marginal sinus or free tumor cells deposits in soft tissue, should not be considered as true ENE.

ENE, indicated recently as a prognostic factor for cancers in several organs [4–8], has also been taken into account in the last staging systems of squamous cell carcinoma of the vulva [2, 31]. It is likely that the better prediction of prognosis of vulvar cancer by these new staging systems could be partly due even to the consideration of the importance of ENE. According to our findings, and if further studies and/or nomograms will confirm these results, we suggest to include ENE as a prognostic parameter in future colorectal staging system, also considering that, for a

histologically similar aspect to ENE, the free tumor deposits, it has been already designed a specific N subcategory (N1c) in the current TNM staging system.

Notably, in this meta-analysis, only one parameter, the RRs for all-cause mortality, reported high heterogeneity. This aspect consolidates our findings, emphasizing the importance of ENE as prognostic parameter. In our meta-regression analysis for all-cause mortality RRs, only the consideration of free tumor deposits in perinodal fatty tissue emerged as a significant moderator, although its role seems to be limited in magnitude since, also in studies not considering this factor, the presence of ENE was associated with a significant higher risk of death. Furthermore, considering for all-cause mortality RRs all the studies with the exception of the one by Komuta et al. [24], the heterogeneity becomes not of a high level.

While the results of this meta-analysis are novel, it is important to consider a number of limitations, which are largely reflected by those within the primary studies. First, data about other co-morbidities (like cardiovascular diseases) were not reported, but it is known that they play an important prognostic role also in patients with cancer. We also encountered some heterogeneity but were able to investigate sources of this within meta-regression. Finally, we encountered evidence of publication bias in our main analysis, but our results remained unchanged after we adjusted for this. Nevertheless, allowing for these caveats, in conclusion our results suggest that ENE seems to be associated with a poorer prognosis in colorectal cancer

also independent of potential confounders. Since this condition is present in a remarkable proportion of the patients affected by such malignancy, its consideration becomes mandatory from the gross sampling to the histopathological evaluation and the oncologic staging. Thanks to the recent development of techniques of next-generation sequencing, it has been already proposed to integrate a complete molecular characterization of cancer in pathology report [32]; however, before this, all the prognostic roles of the pure histologic features and of the morphologic aspects, as ENE, should be clarified.

disclosure

The authors have declared no conflicts of interest.

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