



# Journal of Coloproctology

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## Review Article

# Meta-analysis – perineural invasion as prognostic factor in rectal cancer

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### ARTICLE INFO

#### Article history:

Received 26 April 2018

Accepted 1 September 2018

Available online 27 September 2018

#### Keywords:

Rectal cancer

Perineural invasion

Survival

Prognosis

### ABSTRACT

**Objectives:** The aim of this analysis was to determine prognostic value of perineural invasion in rectal cancer.

**Methods:** Medline (PubMed, Ovid), Embase and Cochrane Library were searched for relevant reports published from January 1980 up to December 2017. All clinical trials which studied perineural invasion in rectal cancer, prospective observational studies, clinical registry data and retrospective case series which reported perineural invasion as an outcome were included. Case reports, abstracts, letters and comments were excluded. hazard ratio (HR) with 95% confidence interval (CI) was used to determine the prognostic value.

**Results:** Nineteen studies comprising 6438 patients with rectal cancer were analysed. The results indicate that perineural invasion is a negative prognostic factor as evident from the overall survival (HR = 1.30, 95% CI 1.13–1.50,  $p < 0.01$ ) and disease-free survival (HR = 2.14, 95% CI 2.06–2.22,  $p < 0.01$ ).

**Conclusion:** This study shows that presence of perineural invasion is associated with poor prognosis in rectal cancer.

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<https://doi.org/10.1016/j.jcol.2018.09.001>

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**Metanálise - invasão perineural como fator prognóstico no câncer retal****R E S U M O****Palavras-chave:**

Câncer retal  
 Invasão perineural  
 Sobrevida  
 Prognóstico

**Objetivo:** Este estudo buscou determinar o valor prognóstico da invasão perineural no câncer retal.

**Métodos:** Relatos relevantes publicados entre janeiro de 1980 e dezembro de 2017 foram buscados nas bases de dados Medline (PubMed, Ovid), Embase e Cochrane Library. Todos os ensaios clínicos que avaliaram a IPN no câncer de reto, estudos observacionais prospectivos, dados de registro clínico e séries de casos retrospectivos que relataram IPN como um desfecho foram incluídos. Relatos de casos, resumos, cartas e comentários foram excluídos. A razão de risco (*hazard ratio* [HR]) com intervalo de confiança (IC) de 95% foi usada para determinar o valor prognóstico.

**Resultados:** Foram analisados 19 estudos compreendendo 6.438 pacientes com câncer retal. Os resultados indicam que a invasão perineural é um fator prognóstico negativo, conforme demonstrado pela sobrevida global (HR = 1,30; IC 95%: 1,13-1,50;  $p < 0,01$ ) e sobrevida livre de doença (HR = 2,14; IC 95%: 2,06-2,22,  $p < 0,01$ ).

**Conclusão:** O estudo demonstrou que a presença de invasão perineural está associada a um prognóstico ruim no câncer retal.

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**Introduction**

Rectal cancer shows a gender disparity and is the third most common malignancy in men and the second most common cancer in women.<sup>1</sup> Perineural invasion (PNI) is a pathologic process characterised by invasion of nervous structures by tumour cells and spread along the nerve sheaths.<sup>2</sup> Knowledge of the pathogenesis of PNI is still largely unknown. PNI is known to be a marker of a more aggressive tumour phenotype and usually associated with poor prognosis in tumours of pancreas, head, neck and prostate.<sup>3</sup>

Surgical management of localised cancer of the rectum with curative intent encompasses complete removal of the primary lesion and its draining lymph nodes by total mesorectal excision (TME). Indications for preoperative neoadjuvant chemoradiotherapy for rectal cancer includes the following: T1, T2 tumours which are node +ve, T3, T4 tumours, mid and low rectal tumours, anterior tumours in a male and tumours with threatened circumferential resection margin.

The study of metastasis is important to help find ways to prevent future cancer deaths. There are various ways in which tumour spreads and they include the following: direct spread; haematogenous, lymphatic channels and along nerves and nerve sheaths. The spread along nerves or nerve sheaths is called as perineural invasion (PNI) and should surround >33% of the circumference of the nerve.<sup>2</sup>

The meta-analysis by Knijn et al. showed that PNI rates were higher in rectal cancer (20.6%) as opposed to colonic cancer (14.1%) and this could possibly be attributed to more careful examination of fat in mesorectum in rectal cancer.<sup>4</sup>

Although perineural invasion has been looked at in colonic cancer, its true prognostic value in rectal cancer has not been evaluated in terms of a met-analysis. The American Joint Committee on Cancer Colon and Rectal Cancer staging 7th edition

describes PNI as a site specific accessory factor. There is a significant variance in the definitions used to describe perineural invasion and its potential impact on prognosis.

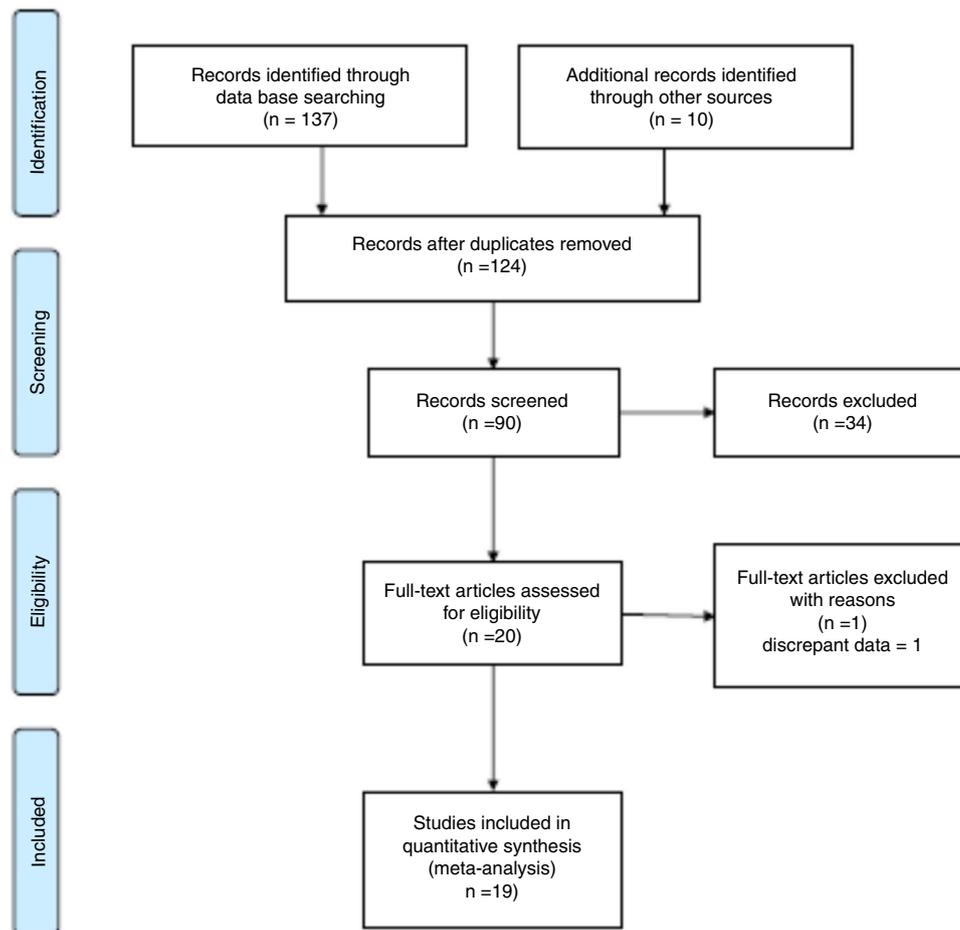
Other well recognised prognostic markers in rectal cancer include tumour differentiation, depth of invasion, lymphovascular invasion (LVI), lymph node metastasis and extramural vascular invasion. In order to establish the significance of PNI in rectal cancer, we systematically reviewed the available evidence on PNI in rectal cancer. The endpoints of this study to predict prognosis are local recurrence, 5-year disease-free survival and 5-year overall survival.

Patients with rectal cancer who have perineural invasion are at higher risk of local recurrence and should be considered for adjuvant treatment. Hence, the objective of this study was to systemically review prevailing information on perineural invasion in rectal cancer to evaluate its prognostic significance.

**Methods**

The analysis in this study was done using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (Fig. 1). A thorough search of literature was performed using Medline (PubMed, Ovid), Embase and Cochrane Library with the following keywords: rectal cancer, perineural invasion, survival, survival benefit and prognosis. The search included literature published from January 1980 through December 2017. The computer search was augmented with manual search of both published and unpublished studies restricted to the English language. All reference lists of selected studies were reviewed and checked.

There were a total of two investigators involved in this study. Data on the type of study, total number of patients in the study, study design, number of male and female patients,



**Fig. 1 – PRISMA 2009 flow diagram.**

median age, follow up mean, number of patients with PNI +ve tumour and stage grouping were obtained from the included studies by the above reviewers. In order to reduce reviewer bias, data that was obtained were extracted separately by the team. For the purposes of this study, the author's names were blinded and the materials and results section were reviewed. Inconsistencies were sorted after thorough discussion and a consensus between the reviewers. All the statistical test results that were obtained from the articles were entered onto a data sheet that was specifically designed for the purposes of this study.

#### **Inclusion criteria**

Published between January 1980 and December 2017.

Aims to determine the prognostic value of perineural invasion in rectal cancer, with the diagnosis based on pathological assessment.

Overall survival or disease free survival was reported.

Hazard ratio (HR) with 95% confidence interval (CI) was reported.

If HR and CI not available, then it should have enough information to allow estimation of HR and CI.

#### **Exclusion criteria**

Case reviews, abstract, editorials, letters, comments.

Studies which had conflicting information in the report.

Duplicate reports.

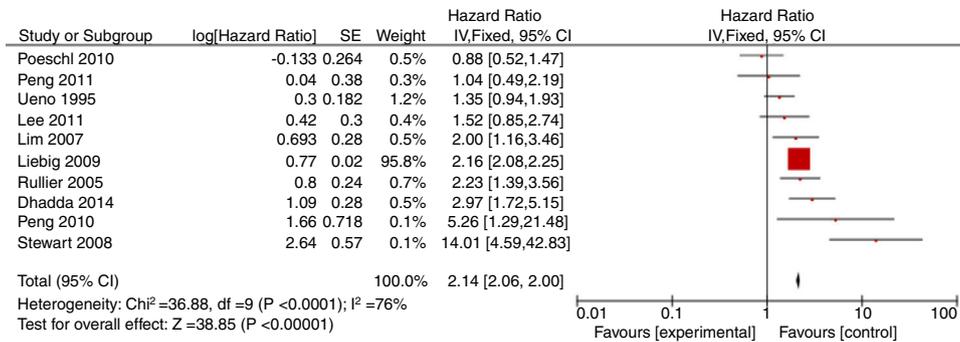
#### **Statistical analysis**

The statistical analysis was done with the use of Review Manager 5.2 software. HR and 95% CI were determined using inverse variance. The *p*-value was fixed at 0.05. If the studies did not report the HR, we estimated the HR and 95% CI manually.

Both  $\chi^2$  test and  $I^2$  were used to assess the heterogeneity among the various included studies. A funnel plot was used to detect publication bias. Only a univariate analysis was performed and no other subgroup analysis was done.

#### **Results**

Nineteen studies comprising 6438 patients with rectal cancer were analysed. The results indicate that PNI is a negative prognostic factor as evident from the overall survival (HR = 1.30,



**Fig. 2 – Forest plot of the hazard ratio for the association of perineural invasion with disease free survival in rectal cancer patients.**

95% CI 1.13–1.50,  $p<0.01$ ) and disease-free survival (HR = 2.14, 95% CI 2.06–2.22,  $p<0.01$ ).

One hundred and thirty seven studies were generated from PubMed and another additional ten from manual search. There were a total of 124 articles once duplicates were excluded. Ninety articles were considered eligible for screening for systematic review, after excluding further 34 articles. Of the 90 articles, 20 were found to have full text. Of this one was excluded as it had discrepant data. Finally, a total of 19 studies met the inclusion criteria (Fig. 2).

The 19 studies included in the analysis yielded 6438 patients who had resection for rectal cancer and diagnosis was based on pathological assessment. Nine of these studies were conducted in Europe (2 in Denmark, France; 1 from Germany, UK, Romania, Austria and Netherlands), while seven were from Asia (2 in Korea and China, 1 from Singapore, Japan and Sri Lanka) and three from USA. The median ages of the cohorts were between 54 and 66. These characteristics are further elucidated in Table 1.

In the included 19 studies, there were 5 studies where all patients in the study had neo-adjuvant treatment.<sup>6,11,16,20,21</sup> The number of patients in the above group was 2272. Four of these were prospective studies while one was a retrospective study.

In two of the nineteen studies, none of the patients had neo-adjuvant treatment.<sup>12,14</sup> An additional two studies, did not report use of neo-adjuvant treatment in their patients.<sup>3,15</sup> In the remaining ten studies, some of the patients had accepted neo-adjuvant treatment.

PNI positivity ranged from 5% to 34% among the included studies with a follow up mean which ranged from 27 months to 92 months.

While most of the studies used American Joint Committee on Cancer classification, some used Dukes, Broders and Astler-Coller. The stage groupings ranged from Stage I to IV. The quality of the studies was assessed using the Jadad score or the Oxford quality scoring system. The scores ranged from 1 to 3 among the included studies. A funnel plot was obtained and the results were symmetrical.

#### Effect of PNI on overall survival (OS)

Data on the effect of PNI on the overall survival was obtained from ten studies and the number of patients included in these

studies was 3487. Univariate analysis of the studies showed that the overall survival was reduced in patients with PNI +ve rectal cancers (HR=1.30; 95% CI 1.13–1.50;  $p<0.01$ ). A funnel plot showed no evidence that there was significant publication bias. Also there was no significant heterogeneity in the studies included ( $\chi^2=36.88$ ,  $df=9$ ,  $p<0.0001$ );  $I^2=76\%$ ; total overall effect:  $Z=38.85$  ( $p<0.00001$ ).

#### Effect of PNI on disease free survival (DFS)

Data on the effect of PNI on the disease free survival was obtained from nine studies and the number of patients included in these studies was 2951. Univariate analysis of the studies showed that the disease free survival was reduced in patients with PNI +ve rectal cancers (HR=2.14, 95% CI 2.06–2.22,  $p<0.01$ ). A funnel plot showed no evidence that there was significant publication bias in the included studies. Also there was no significant heterogeneity in the studies included ( $\chi^2=38.54$ ,  $df=11$ ,  $p<0.0001$ );  $I^2=71\%$ ; total overall effect:  $Z=3.65$  ( $p<0.0003$ ).

### Discussion

Malignancies such as pancreatic cancer, cholangio-carcinomas, prostatic cancer and gastric cancers (60%) have a much higher incidence of PNI. The incidence in rectal cancer on the other hand is much lower.

The incidence rates of rectal cancer increase with age and is usually detected between the ages of 60–80 years old. It occurs twice as frequently in males than in females.<sup>1</sup> These epidemiologic data correlate with the results of this review. Female patients composed less than 40% of the cohorts while median age at detection of the primary ranged from 54 to 66 years.

Due to the nature of the disease, early detection of resectable rectal cancer is of utmost importance for a better prognosis. Hence, compliant screening programs are required in high risk countries to reduce the associated mortality.

To the best of our knowledge, this meta-analysis is the first study to methodically assess the association between the presence of PNI and the prognosis of patients with rectal cancer.

Rectal cancer has a greater incidence of PNI than colon cancers, which may partly be explained by the fact that rectum

**Table 1 – Characteristics of cohorts in the included studies.**

References	Year published	Country	N	Study design	M/F	Med age (years)	Follow up mean ± SD	Number PNI +ve (%)	Neoadjuvant treatment	TNM edition	Stage grouping	Outcome	JS <sup>a</sup>
Bentzen <sup>6</sup>	1988	Denmark	494	Prospective	258/236	64.1	NR	129 (26.11)	A	Duke	Duke B/C	OS	3
Ceyhan <sup>7</sup>	2010	Germany	296	Retrospective	184/112	62.8	60	73 (24.7)	P	UICC 2009	IIa	OS	3
Chandrasinghe <sup>8</sup>	2013	Sri Lanka	226	Retrospective	123/103	59	60	25 (11.06)	P	AJCC	AJCC I/II/III/IV	OS	2
Dresen <sup>9</sup>	2009	Netherlands	277	Retrospective	163/104	62	66	20 (7.22)	P	UICC	I/II/III	OS	2
Guillem <sup>10</sup>	2005	USA	297	Retrospective	186/111	62	44	27 (9.09)	P	AJCC	AJCC I/II/III/IV	OS	2
Kim <sup>11</sup>	2011	Korea	797	Prospective	515/282	59	44.7	215 (26.9)	A	AJCC	AJCC I/II/III	OS	2
Knudsen <sup>12</sup>	1983	Denmark	682	Retrospective	324/358	67 (mean)	NR	34.4 (Dukes), 33.1 (Broders)	N	Duke/ Broders	Dukes A/B/C, Broders I/II/III/IV	OS	2
Lim <sup>13</sup>	2012	Singapore	320	Prospective	212/108	64	45	48 (15)	P	AJCC	I/II/III	OS/DFS	2
Peng <sup>14</sup>	2011	China	173	Retrospective	109/64	57	49	42 (24.28)	N	NR	II	OS/DFS/ Recurrence	2
Poeschl <sup>15</sup>	2010	Austria	381	Retrospective	NR	NR	56	NR	NR	NR	NR	OS/DFS	2
Rullier <sup>16</sup>	2005	France	495	Prospective	313/182	65 (mean)	48	31(15.5)	A	5th UICC	II/III	OS/DFS	2
Ueno <sup>17</sup>	2001	Japan	364	Prospective	222/142	60.6 (mean)	92	52 (14)	N	NR	NR	OS/Recurrence	2
Peng <sup>18</sup>	2011	China	124	Retrospective	53/71	50	72 (median)	12 (9.7)	N	AJCC	I	OS/DFS	3
Stewart <sup>19</sup>	2008	USA	304	Retrospective	157/147	66	27 (median)	11 (5.21)	P	6th AJCC	I/II/III/IV	DFS	3
Lee <sup>20</sup>	2012	Korea	328	Prospective	222/106	59	45 (median)	66 (20.1)	A	7th AJCC	I/II/III	OS, DFS	2
Dhadda <sup>21</sup>	2014	UK	158	Prospective	105/53	65	40	58 (17.72)	A	NR	II/III	DFS	2
Boguel <sup>22</sup>	1995	France	339	Retrospective	166/173	61.8	61	115 (34)	P	Astler-Coller	A,B,C	OS	2
Liebig <sup>5</sup>	2009	USA	66	Retrospective	NR	NR	81	19 (30)	NR	TNM	I/II/III/IV	DFS, OS	2
Vlad <sup>23</sup>	2012	Romania	317	Prospective	201/116	54 (mean)	66	60 (19)	P	TNM	I/II/III/IV	DFS, OS	3

<sup>a</sup> A, all the patients undergo treatment; AJCC, American Joint Committee on Cancer; DFS, disease-free survival; N, none of patients accept the therapy; NR, not reported; OS, overall survival; S, some of the patients undergo treatment; PNI+, rectal cancer with perineural invasion; R, rectum; SD, standard deviation; UICC, Union for International Cancer Control.

is quite well supplied by autonomic nerve plexus (Liebig). In the present setting, there is no standard definition for PNI. Although several studies have described PNI, it is the study by Peng et al. that looks at PNI in a different perspective and analysed two tumour and nerve relationships in rectal cancer namely surrounding the nerve sheath (SS-PNI) and invading through the nerve sheath (TS-PNI) and their outcomes separately. Patients in both the above groups had higher 5-year local recurrence rates than tumours which were PNI negative.<sup>14</sup> Hence, in the absence of a standard definition for PNI, the above methods should be looked at while analysing PNI.

In our study, a funnel plot was used to evaluate for the potential risk of publication bias. The funnel plots obtained were symmetrical and there was no noticeable publication bias.

### Limitation

Rectal cancer was staged according to different classifications in the various included studies. Also, some of the hazard ratios were calculated from the original data, and they might be less consistent than hazard ratios from the included studies. However, the study was done in an unprejudiced manner and all authors in this study had no conflict of interest.

### Conclusions

There is no consensus regarding the prognostic value of perineural invasion in rectal cancer. Based on the paramount evidence obtained in this meta-analysis, the obvious results indicate that perineural invasion is a poor prognostic factor and its presence should be considered an indication for further adjuvant treatment in patients with rectal cancer.

### Recommendations for further research

Further appraisal encompassing a bigger cohort of patients using a prospective multicentre randomised controlled study will provide more robust evidence on the prognostic value of perineural invasion in rectal cancer. There is surely a need for further research on this topic.

### Conflicts of interest

The authors declare no conflicts of interest.

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