Review Article

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

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e Campbelltown Hospital, Campbelltown, Australia

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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Introduction

Rectal cancer shows a gender disparity and is the third most common malignancy in men and the second most common cancer in women.\(^1\) Perineural invasion (PNI) is a pathologic process characterised by invasion of nervous structures by tumour cells and spread along the nerve sheaths.\(^2\) 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.\(^3\)

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.\(^4\)

The meta-analysis by Knijin 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.\(^5\)

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, lymphvascular 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 systematically 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,
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,
An additional two studies, did these epidemi-}

...screening for systematic review, after excluding further 34 articles. Ninety articles were considered eligible for search. There were a total of 124 articles once duplicates from PubMed and another additional ten from manual screening from ten studies and the number of patients included in these 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).

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

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>Heterogeneity:</th>
<th>Test for overall effect:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poeschl 2010</td>
<td>-0.133</td>
<td>0.264</td>
<td>0.5%</td>
<td>0.88</td>
<td>[0.52,1.47]</td>
<td></td>
<td>Z = -3.65 (p &lt; 0.0003)</td>
</tr>
<tr>
<td>Peng 2011</td>
<td>0.04</td>
<td>0.38</td>
<td>0.3%</td>
<td>1.04</td>
<td>[0.49,2.19]</td>
<td></td>
<td>Z = 3.65 (p &lt; 0.0003)</td>
</tr>
<tr>
<td>Ueno 1995</td>
<td>0.3</td>
<td>0.182</td>
<td>1.2%</td>
<td>1.35</td>
<td>[0.94,1.93]</td>
<td></td>
<td>Z = 3.65 (p &lt; 0.0003)</td>
</tr>
<tr>
<td>Lee 2011</td>
<td>0.42</td>
<td>0.3</td>
<td>0.4%</td>
<td>1.52</td>
<td>[0.85,2.74]</td>
<td></td>
<td>Z = 3.65 (p &lt; 0.0003)</td>
</tr>
<tr>
<td>Lim 2007</td>
<td>0.693</td>
<td>0.28</td>
<td>0.5%</td>
<td>2.00</td>
<td>[1.16,3.46]</td>
<td></td>
<td>Z = 3.65 (p &lt; 0.0003)</td>
</tr>
<tr>
<td>Liebig 2009</td>
<td>0.77</td>
<td>0.02</td>
<td>95.8%</td>
<td>2.16</td>
<td>[2.06,2.25]</td>
<td></td>
<td>Z = 3.65 (p &lt; 0.0003)</td>
</tr>
<tr>
<td>Ruller 2008</td>
<td>0.8</td>
<td>0.24</td>
<td>0.7%</td>
<td>2.23</td>
<td>[1.39,3.56]</td>
<td></td>
<td>Z = 3.65 (p &lt; 0.0003)</td>
</tr>
<tr>
<td>Dhadda 2014</td>
<td>1.09</td>
<td>0.28</td>
<td>0.5%</td>
<td>2.97</td>
<td>[1.72,5.15]</td>
<td></td>
<td>Z = 3.65 (p &lt; 0.0003)</td>
</tr>
<tr>
<td>Peng 2010</td>
<td>1.66</td>
<td>0.718</td>
<td>0.1%</td>
<td>5.26</td>
<td>[1.29,21.48]</td>
<td></td>
<td>Z = 3.65 (p &lt; 0.0003)</td>
</tr>
<tr>
<td>Stewart 2008</td>
<td>2.64</td>
<td>0.57</td>
<td>0.1%</td>
<td>14.01</td>
<td>[4.59,42.83]</td>
<td></td>
<td>Z = 3.65 (p &lt; 0.0003)</td>
</tr>
</tbody>
</table>

Total (95% CI): 100.0% 2.14 [2.06, 2.00]

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. 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, cholangiocarcinomas, 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. 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>
<thead>
<tr>
<th>References</th>
<th>Year published</th>
<th>Country</th>
<th>N</th>
<th>Study design</th>
<th>M/F</th>
<th>Med age (years)</th>
<th>Follow up mean ± SD</th>
<th>Number PNI +ve (%)</th>
<th>Neoadjuvant treatment</th>
<th>TNM edition</th>
<th>Stage grouping</th>
<th>Outcome</th>
<th>JS</th>
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<tbody>
<tr>
<td>Bentzen⁶</td>
<td>1988</td>
<td>Denmark</td>
<td>494</td>
<td>Prospective</td>
<td>258/236</td>
<td>64.1</td>
<td>NR</td>
<td>129 (26.11)</td>
<td>A</td>
<td>Duke</td>
<td>Duke B/C</td>
<td>OS</td>
<td>3</td>
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<tr>
<td>Ceyhan⁷</td>
<td>2010</td>
<td>Germany</td>
<td>296</td>
<td>Retrospective</td>
<td>184/112</td>
<td>62.8</td>
<td>60</td>
<td>73 (24.7)</td>
<td>P</td>
<td>UICC 2009</td>
<td>Ila</td>
<td>OS</td>
<td>3</td>
</tr>
<tr>
<td>Chandrasinge⁸</td>
<td>2013</td>
<td>Sri Lanka</td>
<td>226</td>
<td>Retrospective</td>
<td>123/103</td>
<td>59</td>
<td>60</td>
<td>25 (11.06)</td>
<td>P</td>
<td>AJCC</td>
<td>AJCC I/II/III/IV</td>
<td>OS</td>
<td>2</td>
</tr>
<tr>
<td>Dresen⁹</td>
<td>2009</td>
<td>Netherlands</td>
<td>277</td>
<td>Retrospective</td>
<td>163/104</td>
<td>62</td>
<td>66</td>
<td>20 (7.22)</td>
<td>P</td>
<td>UICC</td>
<td>I/II/III</td>
<td>OS</td>
<td>2</td>
</tr>
<tr>
<td>Guillem¹⁰</td>
<td>2005</td>
<td>USA</td>
<td>297</td>
<td>Retrospective</td>
<td>186/111</td>
<td>62</td>
<td>44</td>
<td>27 (9.09)</td>
<td>P</td>
<td>AJCC</td>
<td>AJCC I/II/III/IV</td>
<td>OS</td>
<td>2</td>
</tr>
<tr>
<td>Kim¹¹</td>
<td>2011</td>
<td>Korea</td>
<td>797</td>
<td>Prospective</td>
<td>515/282</td>
<td>59</td>
<td>44.7</td>
<td>215 (26.9)</td>
<td>A</td>
<td>AJCC</td>
<td>AJCC I/II/III</td>
<td>OS</td>
<td>2</td>
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<tr>
<td>Knudsen¹²</td>
<td>1983</td>
<td>Denmark</td>
<td>682</td>
<td>Retrospective</td>
<td>324/358</td>
<td>67 (mean)</td>
<td>NR</td>
<td>34.4 (Dukes), N</td>
<td>Duke/</td>
<td>Dukes A/B/C</td>
<td>OS</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Lim¹³</td>
<td>2012</td>
<td>Singapore</td>
<td>320</td>
<td>Prospective</td>
<td>212/108</td>
<td>64</td>
<td>45</td>
<td>48 (15)</td>
<td>P</td>
<td>AJCC</td>
<td>I/II/III</td>
<td>OS/DFS</td>
<td>2</td>
</tr>
<tr>
<td>Peng¹⁴</td>
<td>2011</td>
<td>China</td>
<td>173</td>
<td>Retrospective</td>
<td>109/64</td>
<td>57</td>
<td>49</td>
<td>42 (24.28)</td>
<td>N</td>
<td>NR</td>
<td>II</td>
<td>OS/DFS/ Recurrence</td>
<td>2</td>
</tr>
<tr>
<td>Poeschl¹⁵</td>
<td>2010</td>
<td>Austria</td>
<td>381</td>
<td>Retrospective</td>
<td>NR</td>
<td>NR</td>
<td>56</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>OS/DFS</td>
<td>2</td>
</tr>
<tr>
<td>Ruiller¹⁶</td>
<td>2005</td>
<td>France</td>
<td>495</td>
<td>Prospective</td>
<td>313/182</td>
<td>65 (mean)</td>
<td>48</td>
<td>31(15.5)</td>
<td>A</td>
<td>5th UICC</td>
<td>I/II/III</td>
<td>OS/DFS</td>
<td>2</td>
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<tr>
<td>Ueno¹⁷</td>
<td>2001</td>
<td>Japan</td>
<td>364</td>
<td>Prospective</td>
<td>222/142</td>
<td>60.6 (mean)</td>
<td>92</td>
<td>52 (14)</td>
<td>N</td>
<td>NR</td>
<td>NR</td>
<td>OS/Recurrence</td>
<td>2</td>
</tr>
<tr>
<td>Peng¹⁸</td>
<td>2011</td>
<td>China</td>
<td>124</td>
<td>Retrospective</td>
<td>53/71</td>
<td>50</td>
<td>72 (median)</td>
<td>12 (9.7)</td>
<td>N</td>
<td>AJCC</td>
<td>I</td>
<td>OS/DFS</td>
<td>3</td>
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<tr>
<td>Stewart¹⁹</td>
<td>2008</td>
<td>USA</td>
<td>304</td>
<td>Retrospective</td>
<td>157/147</td>
<td>66</td>
<td>27 (median)</td>
<td>11 (5.21)</td>
<td>P</td>
<td>6th AJCC</td>
<td>I/II/III/IV</td>
<td>DFS</td>
<td>3</td>
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<tr>
<td>Lee²⁰</td>
<td>2012</td>
<td>Korea</td>
<td>328</td>
<td>Prospective</td>
<td>222/106</td>
<td>59</td>
<td>45 (median)</td>
<td>66 (20.3)</td>
<td>A</td>
<td>7th AJCC</td>
<td>I/II/III</td>
<td>OS, DFS</td>
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<td>Dhadda²¹</td>
<td>2014</td>
<td>UK</td>
<td>158</td>
<td>Prospective</td>
<td>105/53</td>
<td>65</td>
<td>40</td>
<td>58 (17.72)</td>
<td>A</td>
<td>NR</td>
<td>II/III</td>
<td>DFS</td>
<td>2</td>
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<td>Bognel²²</td>
<td>1995</td>
<td>France</td>
<td>339</td>
<td>Retrospective</td>
<td>166/173</td>
<td>61.8</td>
<td>61</td>
<td>115 (34)</td>
<td>P</td>
<td>Astler-Coller A/B/C</td>
<td>OS</td>
<td>2</td>
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<tr>
<td>Liebig²³</td>
<td>2009</td>
<td>USA</td>
<td>66</td>
<td>Retrospective</td>
<td>NR</td>
<td>NR</td>
<td>81</td>
<td>19 (30)</td>
<td>NR</td>
<td>TNM</td>
<td>I/II/III/IV</td>
<td>DFS, OS</td>
<td>2</td>
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<tr>
<td>Vlad²⁴</td>
<td>2012</td>
<td>Romania</td>
<td>317</td>
<td>Prospective</td>
<td>201/116</td>
<td>54 (mean)</td>
<td>66</td>
<td>60 (19)</td>
<td>P</td>
<td>TNM</td>
<td>I/II/III/IV</td>
<td>DFS, OS</td>
<td>3</td>
</tr>
</tbody>
</table>

* 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.34 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.

**REFERENCES**

