The influence of perineural invasion on anal incontinence in postoperative rectal cancer cases by Wexner Score

Firah Diyansah¹, Tomy Lesmana²*, Alphania Rahniayu³, Edwin Danardono⁴, Denny Septarendra⁵

INTRODUCTION
The incidence of rectal cancer, which is currently the third most common cause of cancer-related deaths worldwide, is gradually increasing in developing countries.¹⁻³ For the treatment of rectal cancer, the patients can avoid permanent colostomy associated with an abdominoperineal resection by undergoing Low Anterior Resection (LAR) combined with entire mesorectal excision.⁴⁻⁵ However, LAR can lead to Low Anterior Resection Syndrome (LARS), affecting 80-90% of patients and causing symptoms like anal incontinence.⁶ Perineural invasion (PNI), where cancer cells infiltrate nerves, poses challenges in curative resection and impacts recurrence rates. It alters nerve function, promoting tumor growth along nerves and affecting nerve-cell microenvironments. The denervation process in affected nerves supports tumor proliferation. Mechanisms of PNI involve complex interactions between cancer cells, nerves, and stromal cells, creating a conducive microenvironment for tumor growth. Dying nerves release substances that attract tumors, exacerbating inflammation and directing tumor movement toward nerves.⁶⁻⁸ Given the prevalence of anal incontinence in LARS and the impact of PNI on nerve function, our study aims to explore the relationship between PNI and anal incontinence in postoperative rectal cancer cases following LAR.

METHODS
This study employs an observational analytical approach with a cross-sectional design aiming to examine the correlation between perineural invasion and postoperative anal incontinence in rectal cancer patients. Through a comparative analysis between those with and without perineural invasion post-surgery, the research seeks to understand the impact of perineural invasion on anal incontinence severity. This study occurred at Dr. Soetomo Surabaya Hospital from January 2020 to December 2022.

RESULTS: Characteristics of subjects, considering age and gender, were analyzed to ensure no differences exist between the negative and positive perineural invasion groups. Statistical analyses show similarities in age distribution (p=0.279) and gender distribution (p=1.000) between these groups. Chi-square analysis reveals a significant relationship between perineural invasion and cell differentiation grading (p=0.035). A significantly lower Wexner score was also found in the PNI negative group than in the PNI positive group (p=0.021).

CONCLUSION: A significant correlation was found between PNI, cell differentiation grading, and Wexner score. PNI-positive patients are likely to have incontinence compared with PNI-negative patients.

Keywords: cell differentiation grading, low anterior resection syndrome, perineural invasion, rectal cancer.

The study population comprises rectal cancer patients who underwent surgery and received a pathological diagnosis of perineural invasion, contributing to postoperative anal incontinence. With a minimum sample size of 24 individuals (adjusted to 30 for validation), the study will employ purposive sampling to select patients based on predefined criteria. The inclusion criteria are (1) all rectal cancer patients who underwent surgery and were diagnosed with perineural invasion by histopathological examination and (2) the patient is willing to participate in the study. Patients who had incomplete medical record data were excluded.

Data collection will involve demographic and clinical information retrieval from electronic medical records, including details on perineural invasion and anal incontinence status from histopathological reports and surgical records. Analyses will utilize statistical methods, particularly chi-square correlation tests, conducted using SPSS version 26.0 for Windows.

RESULTS

This study included 30 rectal cancer subjects from the Dr. Soetomo Surabaya Hospital from January 2020 to December 2022. The mean age of the subject in the PNI negative group is 58.87±10.07, and the mean age of the PNI positive group is 54.87±9.78. There is no significant difference between the two groups (p=0.279). No significant difference was found in the study participants’ gender between PNI-negative and PNI-positive patients (p=1.000). Otherwise, histological type shows PNI negative groups tend to have a well-differentiated type (61.9%) compared to the PNI positive group with moderately differentiated histological type (Table 1). A significantly lower Wexner score was found in the PNI-negative group (5.13±1.24) compared to the PNI-positive group (7.00±2.67) (mean differences=1.86; p=0.021; Table 2).

DISCUSSION

A pathologic process known as PNI involves the spread of tumor cells along the sheaths surrounding nerves, resulting in the invasion of neurological tissues. PNI is recognized as an indicator of a more aggressive tumor phenotype and is typically linked to a dismal prognosis for some types of tumors.9 PNI has a reported incidence of colorectal cancer ranging from 9% to 30%. It is more common in the advanced stages of the disease. According to studies, PNI can occur in 10% of stage I–II disease, 30% of cases of stage III disease, and 40% of cases of stage IV disease.10,11 In line with this study, it was found that PNI-negative patients are more likely to have a well-differentiated cancer type than moderate or poorly differentiated cancer cells. Meanwhile, some of the PNI-positive patients are likely to have a worse differentiated cancer cell, which may lead to a worse prognosis because of the nature of the badly differentiated cancer cell. A study by Liebig et al. shows that the incidence of PNI was higher in rectal cancers than in colon cancers. They speculate that the observed higher PNI-positive rates in rectal cancers may help to partially explain why rectal cancers have worse outcomes stage-by-stage than colon cancers since the PNI is linked to a more aggressive disease.10 Furthermore, Knijn et al. conducted a meta-analysis and systematic review, which included 58 studies involving 22,900 colorectal cancer patients in all stages. They found that PNI is linked to reduced 5-year overall survival, disease-free survival, and cancer-specific survival.12

The Cleveland Clinic Florida Incontinence Score (CCFIS), or Wexner Score, is a scoring system that can be used to determine the severity of fecal incontinence. The Wexner Score consists of five frequencies and five. The total Wexner Score ranges from 0, which shows a full continence condition, to 20, which shows a complete incontinence. Wexner Score is a highly used scoring system because of its easy-to-understand nature and ability to correlate with patients’ subjective symptom perception.13 This study found that the PNI-negative group has a lower Wexner Score than the PNI-positive group. It shows that PNI also affects the patient’s quality of life. As far as we know, our study is the first to explore the relationship between PNI and Wexner score. A previous study by Bozbıyık et al. only evaluated the outcomes of patients who underwent intersphincteric resection without evaluating the patient’s PNI status. They found that 20 patients who still had functional anastomosis had a mean Wexner score of 8.35, whereas the other 13 patients had a good continence status.14 In a study by Özgen et al. which evaluates the long-term effects of neoadjuvant chemoradiotherapy followed by sphincter-preserving resection among locally advanced rectal cancer patients found that neoadjuvant chemoradiotherapy and sphincter preserving surgery have substantial late-life negative effects on bowel dysfunction and quality of life (showed by a high Wexner score) in

Table 1. Characteristics of study participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PNI negative</th>
<th>PNI positive</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Mean ± SD) (years)</td>
<td>58.87 ± 10.07</td>
<td>54.87 ± 9.78</td>
<td>0.279</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 (50%)</td>
<td>8 (50%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Rectal cancer histological type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well-differentiated</td>
<td>13 (61.9%)</td>
<td>8 (38.1%)</td>
<td>0.035*</td>
</tr>
<tr>
<td>Moderately differentiated</td>
<td>1 (12.5%)</td>
<td>7 (87.5%)</td>
<td></td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>1 (100%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
</tbody>
</table>

Note: *Significant (p<0.05)

Table 2. Wexner score differences

<table>
<thead>
<tr>
<th>Variable</th>
<th>Wexner score (Mean ± SD)</th>
<th>Mean differences</th>
<th>CI 95%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNI-negative</td>
<td>5.13 ± 1.24</td>
<td>1.86</td>
<td>0.30-3.42</td>
<td>0.021*</td>
</tr>
<tr>
<td>PNI-positive</td>
<td>7.00 ± 2.67</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Note: *Significant (p<0.05)
patients with rectal cancer, especially when there is concurrent urgency symptoms. However, they did not explore the relationship between PNI and Wexner score.\(^{15}\)

This research still has limitations. The small number of samples will certainly affect the results of data analysis. Multicenter studies with a larger sample size will show better results. In addition, we also did not exclude patients with special conditions that could affect incontinence, so there is still the potential for bias in sample selection.

**CONCLUSION**

A significant correlation was found between PNI and cell differentiation grading and the Wexner score. PNI-positive patients are likely to have incontinence compared with PNI-negative patients.

**DISCLOSURES**

**Ethical Approval**
The Committee of Medical Research Ethics of Dr. Soetomo Surabaya Hospital has approved our research protocol with letter No. 0793/KEPK/X/2023.

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**Conflicts of Interests**
There are no potential conflicts of interest to declare.

**Author Contribution**
Firah Diyansah contributed to the study protocol, analysis, manuscript writing, and main idea conceptualization. Tomy Lesmana contributed to supervising study protocol, statistical analysis, and conceptualization. Alphania Rahniayu contributed to histology interpretation. All authors prepare the manuscript and agree for this final version to be submitted to this journal.

**REFERENCE**