Meta Narrative Review of Programmed Cell Death Protein 1 and Programmed Cell Death Protein Ligand 1 as a Diagnostic Tool for Pancreatic Cancer and Non-Small Cell Lung Cancer Utilizing Immunohistochemical Staining.

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What is PD-1?

- Programmed cell death protein.
- Cell surface receptor found on many APCs, notably T cells. (Jiang, Y., Chen, M., Nie, H., & Yuan, Y. (2019).
- Has many inhibitory functions.
- PD-1 expression is hallmark of T cell exhaustion.

PD-L1 – Ligand

- Plays a role in T cell activation and proliferation
- Cancer cells expressing high levels of PD-L1 are able to inhibit T cell activation and effectively escape the T cell response.
Immunohistochemical (IHC) Staining

- Immunohistochemical staining is a method used in histopathology and utilizes antibodies to retrieve specific antigens in the tissue sample.
- Immunohistochemical staining has recently been utilized to evaluate expression of specific biomarkers in various malignancies.
Research Question:

What is the application and efficacy of programmed cell death 1 protein utilizing immunohistochemical staining as a diagnostic tool for Non-Small Cell Lung Cancer and Pancreatic Cancer?
METHODOLOGY

• The topic of this study is to evaluate the efficacy of these proteins as diagnostic tools in cancer at various stages to see if any correlating trends emerge. Meta-narrative review allows one to compare data on efficacy in relevant studies in order to analyze how the variables impact the results. By analyzing many sources, bias is decreased as opposed to focusing on results from one study.

• Articles are selected to specified cancers (non-small cell lung cancer and pancreatic cancer) and the expression of programmed cell death protein 1 (PD-1) and programmed cell death ligand 1 (PD-L1) in various stages of each cancer.

• Documents included for research meta-analysis are published within the last five years and are peer reviewed for validity.
➢ Information extracted includes prognosis, diagnostic information, survival rate, stages of cancer, and charts, statistics, and conclusions from relevant articles.

➢ Limitations and inconsistencies of this technique can be found in the articles with a focus on the diagnostic process.

➢ Survival rate is a factor to show the intensity of the cancers and detecting them as early as possible is important.

➢ Stages of each cancer are important to see if they influence the expression of programmed cell death protein 1 and programmed cell death ligand protein 1. This will supplement our research on the efficacy of programmed death and programmed death L1 in diagnosing the two chosen cancers.
This immunotherapy prevents the binding of PD-L1 (expressed in cancerous and healthy cells) to PD-1 (an immune regulatory protein). Cancer cells have been able to bypass the immune cell surveillance by binding their PD-L1 with PD-1. By blocking these checkpoints and inhibitory signals, it led to apoptosis of Tregs and increased immune response of effector T cells against tumoral antigens (Mucileanu, A., Chira, R., & Mircea, P. A. (2021).

In treatment for pancreatic cancer, it was generally considered to be a non-immunogenic tumor and thus PD-1/PD-L1 inhibitors provided poor results in pancreatic cancer, excepting some patients with MSI/dMMR (microsatellite instability/deficient mismatch repair) (Mucileanu, A., Chira, R., & Mircea, P. A. (2021).

PD-1/PD-L1 immunotherapy is FDA approved for the public usage under the name "Pembrolizumab" for treatment of many cancers including Non-Small Cell Lung Cancer.
**PD-1 Immunotherapy Vs Chemotherapy**

2018 Nobel Prize Winner Dr. Jim Allison, is an MD Anderson Researcher who worked with CTLA-4 immunotherapy.

Figure shows the efficacy of the anti-PD-1 treatment specifically for Non-small Cell Lung Cancer patients with high (>50%) IHC expression of PD-1. The figure shows chemotherapy as a control and combination with other immunotherapy, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). (Linardou, et al, 2021; Nesline, et al, 2023)
• Regarding the poor results of the use of PD-1/PD-L1 as a diagnostic tool for pancreatic cancer, it could be due to its ability to suppress cells of the immune response and remain undetected by PD-1/PD-L1. Alternative forms of diagnosis such as CT, MRI and PET scan are more successful in detecting pancreatic cancer.

• Non-small cell lung cancer has had promising results to these biomarkers. It has become standard that PD-L1 levels are checked in all lung cancer patients at the time of diagnosis. This impact has a considerable significance as PD-1/PD-L1 understanding could pave the way for more forms of IHC staining in diagnosing patients with Non-small cell lung cancer.
Strengths and Limitations

Strengths:
• PD-1/PD-L1 has been effective in diagnosing cancers such as bladder cancer, kidney cancer, breast cancer, non-small lung cancer…etc.
• One of the few biomarkers approved for clinical usage.
• Generally, a "next day" test and is relatively a quick read.

Limitations:
• PD-L1 is expressed on various cell types in the body, not just cancerous cells so one of the side effects could be development of autoimmune diseases. (Li, Y., Yan, B., & He, S. 2023)
• PD-1/PD-L1 expression changes spontaneously throughout a patient's clinical course, so not all patients respond to immunotherapy selected based on PD-1 expression. IHC results lack consistency specifically when it comes to pancreatic cancer.
• Limitation of the present statistical data is that it is biased towards patients expressing high levels of PD-1 who were selected for the trials.
• The lack of companion assays to confirm the efficacy of IHC for evaluating PD-1 levels. IHC biomarker is a relatively new strategy in cancer diagnosis. The mechanism of PD-1/PD-L1 pathway is not fully understood.
**Conclusion**

**Pancreatic Cancer**

- Shows little to no promising results
- Aggressive "silent" cancer that spreads rapidly
- Alternative forms of diagnosis are more successful

"Non-immunogenic" (no immune response) causes cancer to be nearly undetectable.

**Non-Small Cell Lung Cancer**

PD-L1 with immunotherapy can "train" the immune system.

- Has promising results with PD-1/PD-L1
- PD-1/PD-L1 levels are checked routinely with NSCLC at the time of diagnosis.
Future Implications

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<tr>
<th>Non-Small Cell Lung Cancer (NSCLC)</th>
<th>Pancreatic Cancer</th>
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<tbody>
<tr>
<td>• Integrating PD-1/PD-L1 with other forms of diagnosis and treatment. (RNA sequencing, Chemotherapy and immunotherapy)</td>
<td>• Mortality and Incidence is expected to increase due to lack of early detection</td>
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<tr>
<td>• Will improve patient care in regard to diagnosis and monitoring.</td>
<td>• Finding more effective forms of diagnosis.</td>
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<td>• 22 other biomarkers showed promising results</td>
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