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The Role of Inflammatory Markers in Predicting Resectability of Pancreatic Ductal Adenocarcinoma

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Rezumat

Rolul markerilor inflamatori în prezicerea rezecabilității adenocarcinomului ductal pancreatic

Context: Adenocarcinomul pancreatic încă este considerat unul dintre cele mai agresive cancere, cu procente scăzute de rezectabilitate, în ciuda progreselor diagnostice recente. Evaluarea markerilor inflamatori preoperatori poate creşte ratele de rezecabilitate.
Metode: Studiul este unicentric, s-a desfăşurat pe o perioadă de 2 ani şi include pacienți cu adenocarcinom pancreatic potențial rezecabil. Un număr de 96 de pacienți au fost eligibili pentru analiză.
Rezultate: CRP, d-dimerii şi nivelurile de fibrinogen au fost similare între cele două grupuri. Pe de altă parte, au existat diferențe semnificative statistic în ceea ce priveşte indicele nutrițional prognostic (PNI) şi raportul neutrofile-limfocite (NLR).
Concluzii: Markerii inflamatori pot acționa ca un instrument suplimentar în prezicerea rezecabilității la pacienții cu adenocarcinom pancreatic.

Cuvinte cheie: pancreas, cancer, inflamație, rezecabilitate

Abstract

Background: Pancreatic adenocarcinoma is still considered as one of the most aggressive cancers with low percentages of respectability, despite recent advances in diagnosis. Assessment of preoperative inflammatory markers can increase the rates of resectability.
Methods: Patients with potentially resectable pancreatic adeno-

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carcinoma in a single pancreatic unit were included. Ninety-six patient during a one year period were eligible for analysis.
Results: CRP, d-dimers, and fibrinogen levels were similar between the two groups. On the contrary, there were statistically significant differences regarding the prognostic nutritional index (PNI) and neutrophil-to-lymphocyte ratio (NLR).
Conclusions: inflammatory markers can act as an additional tool in predicting resectability in patients with pancreatic adenocarcinoma.

Keywords: pancreas, cancer, inflammation, resectability

Introduction

Pancreatic cancer is generally recognized as one of the most aggressive cancers, with a rising incidence over the past decades. Late diagnosis, low rates of resectability, and poor overall survival rank pancreatic adenocarcinoma as the fourth leading cause of cancer-related mortality (1). Although implementation of standardized perioperative care protocols has improved short-term surgical outcomes, little progress has been made in terms of resectability and long-term survival. Only 20% of patients with pancreatic cancer have upfront resectable disease (2) and 5-year survival rarely exceeds 15-20% even in subgroups with favorable prognostic features (3).

During the past decade, efforts have been made to increase resectability rates. Prognostic indices (4), laparoscopy (5), novel regimens of neoadjuvant chemotherapy, along with the introduction and definition of new terms like borderline resectable cancer (6), have been implemented to overcome the barriers of the aggressive nature of pancreatic cancer. These efforts aim at identifying those subgroups of patients that can truly benefit from a difficult and sometimes painful multimodality treatment.

Anti-inflammatory agents have been proven to be effective in the chemoprevention of several cancers like colon and breast (7). A significant correlation has also been identified between inflammation and pancreatic cancer development and metastasis. Several markers like the neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), and the modified Glasgow Prognostic Score (mGPS) have been used in an attempt to stratify patients and increase resectability, ultimately gaining benefit to survival and recurrence rates.

The aim of this study was to validate various preoperative inflammatory markers that may predict resectability in a cohort of patients with initially operable pancreatic cancer. These markers could potentially aid in the perioperative assessment of these patients, but also improve and potentially alter their treatment outcome.

Patients and Methods

All patients diagnosed with potentially resectable pancreatic neoplasms in the pancreatic unit of Konstantopouleio general Hospital, as of January 2017, were prospectively entered in the institutional electronic database. Included in the final analysis were all consecutive adult patients with pancreatic adenocarcinoma, operated on between January 2017 and December 2018. Histological types other than adenocarcinoma were excluded, as they involve different treatment pathways.

For each eligible patient, demographic characteristics and operative data were collected. Furthermore, preoperative inflammatory markers for all patients undergoing surgical exploration were gathered to identify markers useful in predicting resectability. Blood samples were collected on the day before surgery.

The main inflammatory markers investi-

gated were CRP, NLR, platelet-to-lymphocyte ratio (PLR), and the mGPS score, which combines CRP and albumin levels (8). Moreover, Onodera's prognostic nutritional index (PNI) score was also studied, calculated as 10 × serum albumin (g/dL) + 0.005 × total lymphocyte count (per mm^3), along with D-Dimers and Fibrinogen, markers that have been proven of potential value in predicting metastasis and therefore resection rates. Based on previously published studies, cut-off values were 10 mg/dl for CRP, 5 for NLR, 150 for PLR, 0.55 μg/l for d-dimers, 400 mg/dl for fibrinogen and 45 for the PNI score, whereas the scale from 0-2 was used for the mGPS score.

All patients underwent preoperative staging using Computer Tomography (CT) or Magnetic Resonance Imaging (MRI), whereas additional investigations like Endoscopic Ultrasound (EUS) or Endoscopic Retrograde Cholangiopancreatography (ERCP) were selectively used. All cases were discussed preoperatively in the multidisciplinary team meeting and the optimal treatment strategy for each patient was decided. Two experienced HPB surgeons performed standardized pancreatectomies (pylorus-preserving or Whipple's pancreatoduodenectomy, distal pancreatectomy or total pancreatectomy with or without spleen preservation).

Patients with potentially resectable pancreatic cancer were divided into two subgroups. Group R(esection) included those patients who underwent resection and Group E(xploration) those who underwent surgical exploration without tumor resection, due to locally advanced or metastatic disease. Patients who did not undergo resection had intraoperative biopsies taken either from the tumor or the metastases to confirm the diagnosis of pancreatic cancer.

Statistical Analysis

Statistical analysis was performed on SPSS v. 21 (IBM, Chicago, USA). Non-parametric variables are expressed as median and range, while parametric variables as mean ± SD. Normality of distribution was tested with the Kolmogorov-Smirnoff test. Mann-Whitney U test or Student's t test were used to compare non-parametric and parametric continuous variables, respectively. Categorical variables were expressed as frequency or percentage, and were compared using Chi-square (or Fisher's exact test where appropriate). All comparisons between groups were made on an intention-to-treat basis. Statistical significance was set at $p<0.05$.

Results

In total, 96 patients underwent surgical exploration due to potentially resectable pancreatic adenocarcinoma and fulfilled the inclusion criteria. Seventy-two patients underwent resection (Group R), while 24 were judged to be unresectable (Group E). Pylorus-preserving pancreatoduodenectomy, Whipple's pancreatoduodenectomy, distal pancreatectomy and total pancreatectomy were performed for 40 (55.6%), 5 (6.9%), 13 (18.1%), and 14 (19.4%) patients, respectively. In Group E, 12 (50%) patients were deemed unresectable due to locally advanced tumors, and another 12 (50%) due to liver or peritoneal metastases found upon laparotomy. In 13 (54.2%) patients with unresectable disease, the procedure was completed by gastrojejunostomy, biliary bypass or both. All unresectable cases had biopsies taken to confirm histology (*Table 1*).

Table 1. Demographic and operative characteristics

	Group R (esection)	Group E (xploration)	p
No	72	24	
Sex			0.813
male	42 (58.3%)	15 (62.5%)	
female	30 (41.7%)	9 (37.5%)	
Age mean (sd)	65.54 (8.966)	65.71 (9.594)	0.675
Ca 19-9 mean (sd)	336.66(745)	302.47(306)	0.148
Location of tumour			
Head	50 (69.4%)	21 (87.5%)	
Body/tail	22 (30.6%)	3 (12.5%)	
Type of resection			
Pylorus-preserving	40 (55.6%)		
Whipple's	5 (6.9%)		
Distal	13 (18.1%)		
Total	14 (19.4%)		

Table 2. Preoperative inflammatory markers in Groups R and E

Value, mean(sd)	Group R (esection)	Group E (xploration)	p
CRP (mg/dl)	9.46(17.83)	14.6(19.65)	0.609
mGPS	0.71(0.837)	0.88(0.850)	0.626
D-Dimers (μg/l)	0.834(0.99)	1.38(1.41)	0.072
Fibrinogen (mg/dl)	498.74(143.22)	517.17(151.46)	0.784
NLR	3.53(3.06)	4.58(2.79)	0.017
PLR	172.31(122.72)	207.37(96.94)	0.098
PNI	44.23(6.25)	41.02(6.903)	0.03

CRP: C reactive protein, mGPS: modified Glasgow Prognostic Score, NLR: Neutrophil-to-Lymphocyte Ration, PLR: Platelet-to-Lymphocyte ratio, PNI: Prognostic Nutritional Index

Regarding baseline demographic characteristics, both groups were comparable in terms of age, gender, and preoperative Ca19-9 values (*Table 1*). As far as preoperative inflammatory markers are concerned, CRP, d-dimers, and fibrinogen levels were similar between the two groups (*Table 2*). Moreover, no difference could be identified in PLR and mGPS score.

On the contrary, our analysis revealed statistically significant differences for the NLR (Group R 3.53±3.06 vs Group E 4.58±2.79, p=0.017) and the PNI score (Group R 44.23±6.25 vs Group E 41.02±6.903, p=0.03) (*Table 2*).

Discussion

The focus of this paper was to identify preoperative inflammatory markers that may predict resectability of pancreatic adenocarcinoma. The rationale behind targeting the inflammatory process is based upon the fact that up to 20% of cancers are related to chronic inflammation, an association very well-established so far in gastric and hepatocellular carcinoma. Although acute inflammation is an important aspect of the normal host defenses, chronic inflammation has been shown to play a key role in tumorigenesis. Cancer-related inflammation includes both inflammatory cells and mediators, which interfere with cell proliferation, tumor development, angiogenesis, and metastasis (9,10).

Chronic exposure to inflammatory mediators like Tumor Necrosis Factor (TNF) and Interleukin 8 (IL-8) can lead to tumorigenesis through various cellular pathways. Inflammatory mediators can induce DNA damage by producing NO, a mutagenic agent that can oxidize DNA, and damage to DNA repair proteins, resulting in genomic instability. In addition, tumor suppressor gene p53 mutations, presumably caused by oxidative damage due to a cytokine called migration inhibitory factor, can lead to the inactivation or bypass of this protein, which in turn can give rise to cell proliferation and metastasis. TNF can also stimulate vascular endothelial growth factor (VEGF), produce tumor growth factor (TGF) and by direct or indirect ways influence microvascular endothelial cells resulting in angiogenesis. Last but not least, chemokines and TNF can induce protease production, necessary for tumor growth, along with using their molecular tools and migrating ability for lymphovascular dissemination (9-11).

Only few studies in the literature have examined the correlation of inflammatory markers with pancreatic cancer resectability. Ong et al. found that Ca 19-9, along with PLR and NLR had significant differences in patients with unresectable disease (2). Karachristos et al (12) suggested that prediction of resectability is more accurate when Ca 19-9 and NLR are combined, whereas similar conclusions were drawn by Smith et al. when combining Ca 19-9 and PLR (4). In a recent consensus statement, inflammatory markers are considered of great value when dealing with borderline resectable pancreatic cancer in order to stratify management and treatment (6).

Our study examined several inflammatory markers to correlate their preoperative levels with the outcome of surgery for pancreatic adenocarcinoma. Our study did not reproduce the results of previous research, regarding the predictive role of CRP, PLR, fibrinogen, and d-dimers. Moreover, neither mGPS score nor Ca 19-9 showed any statistical difference between the two study subgroups. However, a significant difference was identified when comparing NLR and PNI scores. These differences could imply that inflammation may

indeed have a role in predicting resectability.

C-reactive protein (CRP) is an acute phase protein produced by the hepatocytes mainly under the control of circulating Interleukin 6 (IL 6). Elevated CRP in cases of resectable or even advanced pancreatic cancer has an adverse effect on survival reflecting a more aggressive tumor or a high tumor burden along with increased tissue necrosis (13). In our study, CRP values did not differ between the two study groups. Even after combining CRP with albumin, the so-called modified Glasgow prognostic score (mGPS), no difference was found in predicting resectability rates.

However, mGPS has been validated in a series of studies providing solid evidence on its prognostic value irrespective of tumor site. Especially in pancreatic cancer this score has been shown to influence survival irrespective of other tumor-related characteristics, such as stage and lymph node count. For example, no long-term (>48 months) survivors could be identified in cases of elevated preoperative mGPS score. Proponents of this score suggest that the combination of CRP and albumin reflects both the induced inflammatory response and the progressive nutritional decline of patients with pancreatic cancer, providing a more accurate survival prognostic tool (14).

Other widely used inflammatory markers are the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR). Cancer-related neutrophilia and lymphocytopenia predispose to impaired systemic immune response and predict response to therapy. In patients with pancreatic cancer, NLR can predict overall and disease-free survival; simultaneously NLR could be a useful follow-up tool, having also a predictive value on recurrence rates (15,16). NLR has been associated with more aggressive tumor characteristics, such as poor differentiation, as well as poor patient performance status (17,18). Furthermore, platelet count may also serve as a surrogate inflammatory response index in pancreatic malignancies. In vitro studies have shown that antiplatelet agents may inhibit the invasive potential of pancreatic cancer cells and that PLR can be strongly related with overall survival in patients with resectable pancreatic cancer (19).

In addition, fibrinogen has not only been associated with increased metastatic potential of tumor cells in mice, by impeding tumor cell clearance by Natural Killer (NK) cells (20) but it also seems that elevated plasma levels are strongly associated with more advanced stages in pancreatic cancer (21). Finally, d-dimers are associated with increased metastatic potential of pancreatic cancer, particularly when their levels are increased in the portal circulation (22).

On the other hand, nutritional status plays a significant role in postoperative outcomes. Onodera's prognostic nutritional index (PNI) has also been used as a prognostic tool. Especially in pancreatic cancer, a malignancy that causes profound cachexia and weight loss, impaired nutrition can contribute to tumor spread and metastasis, mainly due to impaired host immunity. PNI has been found to strongly correlate with overall survival in patients with resectable pancreatic cancer (23).

Our study has several limitations. First of all, staging laparoscopy is not routinely performed in our department, to assess pancreatic cancer resectability, according to the guidelines in cases with elevated Ca 19-9 or large tumor size. By assessing pre-operative imaging studies alone, our experienced and dedicated pancreatic radiology colleagues are able to identify unresectable cases with reasonable accuracy and within the international standards of 20-70% (24). Secondly, the number of patients was relatively low, which may lead in an underpowered sample for analysis. Last but not least, inflammatory markers are generally non-specific and are influenced by a variety of causes, among which biliary obstruction and jaundice, acute cholangitis and preoperative biliary stenting. These conditions were not included in the exclusion criteria per se, however patients with preoperative blood tests outside the relevant reference range were excluded, as per study protocol. While patients cannot be

excluded from surgical exploration solely on the basis of inflammatory marker levels, these markers could point towards a more individualized approach in patient diagnosis and treatment.

For example, in cases of elevated inflammatory markers, further imaging could potentially help towards avoiding unnecessary surgical explorations. Moreover, targeted therapies, including neoadjuvant chemotherapy and anti-inflammatory drugs, could increase overall resectability rates. Finally, preoperative recognition of an ongoing inflammatory process and association with surrogate pathology markers, like perineural and lymphovascular invasion, can be helpful in individualizing adjuvant therapy. Further ideas for future research could include correlation of these markers with postoperative complications, recurrence rates, and overall survival.

In conclusion, information about the preoperative systemic inflammatory status could be useful in stratifying patients with pancreatic adenocarcinoma. Our results imply that inflammatory markers may have a role not only in predicting survival or postoperative complications, as described in the literature so far, but also in predicting resectability. Large registries are required to validate these preliminary conclusions.

Conflict of Interest

The authors declare that they have no conflict of interest.

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