International Journal of Inflammation, Cancer and Integrative Therapy

Case Study   Open Access

An Analysis Using Propensity Scores Reveals that Monitoring High-Risk Individuals for Pancreatic Cancer Results in Better Outcomes

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Abstract

Background & Aims: Improved outcomes have been reported by recent high-risk pancreatic cancer surveillance programs. This study looked at whether patients with a CDKN2A/p16 pathogenic variant diagnosed under surveillance had better outcomes for pancreatic ductal adenocarcinoma (PDAC) than those with PDAC diagnosed outside of surveillance.

Method: We compared resectability, stage, and survival in a propensity score-matched cohort using data from the Netherlands Cancer Registry between PDAC patients diagnosed under surveillance and non-surveillance patients. Endurance examinations were adapted to likely impacts of lead time.

Results: The Netherlands Cancer Registry identified 43,762 PDAC patients between January 2000 and December 2020. Based on age at diagnosis, sex, year of diagnosis, and tumor location, 151 non-surveillance patients and 31 patients with PDAC under surveillance were matched 1:15. 5.8% of patients outside of surveillance had stage I cancer, whereas 38.7% of surveillance patients had PDAC (odds ratio [OR], 0.09; (0.04–0.19), 95 percent confidence interval (CI). Overall, a surgical resection was performed on 18.7% of non-surveillance patients versus 71% of surveillance patients (OR, 10.62; 95% CI, 4.56–26.63). With a 5-year survival rate of 32.4% and a median overall survival of 26.8 months, patients on surveillance had a better prognosis than non-surveillance patients, who had a 5-year survival rate of 4.3% and a median overall survival of 5.2 months (hazard ratio, 0.31; 95% CI 0.19–0.50). Surveillance patients had significantly longer survival rates than non-surveillance patients for all adjusted lead times.

Conclusion: Compared to patients with PDAC who are not monitored, those with PDAC who are carriers of a CDKN2A/p16 pathogenic variant experience improved survival, earlier detection, and increased respectability.

Keywords: Pancreatic cancer; Surveillance; High-Risk individual; Survival

Introduction

The majority of patients with pancreatic ductal adenocarcinoma (PDAC) present with either locally advanced, unresectable disease or distant metastasis, highlighting the urgent need for early detection.2 Cancer screening can contribute to reducing cancer mortality and morbidity by detecting either precursor lesions or early invasive tumors [1]. PDAC has the worst outcomes of all cancers and is expected to soon become the second leading cause of cancer-related mortality. Due to the lack of a reliable screening test that can be used for mass screening and the relatively low incidence of PDAC, population-wide pancreatic screening programs are currently unfeasible. Instead, pancreatic surveillance programs concentrate on subgroups of patients who have a high risk of developing PDAC [2].

Carriers of germline pathogenic variants (PVs) in PDAC susceptibility genes or those with a strong family history are eligible for participation in pancreatic surveillance programs. Lifetime risk estimates for PDAC in these high-risk individuals (HRIs) range from 2% for BRCA1 to more than 30% for Peutz-Jeghers syndrome. Guidelines recommend providing certain HRIs with annual imaging by magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography, endoscopic until now, studies assessing the outcomes of surveillance have produced contradictory findings [3]. Some centers reported successful treatment of early-stage PDAC or high-grade precursor lesions, despite the fact that most programs were unable to significantly alter the course of the disease. Most recently, our team reported on the yield and outcomes of 20 years of pancreatic surveillance in a large cohort of germline CDKN2A/p16 PV carriers. We observed a 5-year overall survival (OS) rate of 32%, which appears to be significantly better than the survival outcomes (5%–

10%) When comparing outcomes directly, however, it is important to take into account lead-time bias and potential differences in patient characteristics [4].

PDAC outcomes and control groups of HRIs that do not participate in surveillance should ideally be compared in order to provide additional evidence of the benefits of surveillance. Sadly, adequately huge benchmark groups with long subsequent span are not accessible, and there are moral worries in keeping HRIs from reconnaissance in a (randomized) preliminary setting. Instead, if PDAC diagnosed during surveillance has improved outcomes, a comparison with a control group of patients with similar characteristics from the general population could provide useful information [5].

As a result, we compared patients diagnosed outside of surveillance in the general population to a high-risk cohort of germline CDKN2A/p16 PV carriers to determine whether or not pancreatic cancer surveillance led to a stage shift, improved respectability, and lead-time adjusted survival of PDAC [6].

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Materials and Methods

Preparation and data sources

Clinical data and transcriptomic information were obtained from the TCGA and GEO databases, and GSCAlite was used primarily for pancancer analysis. Figure depicts our analysis methodology. The in-depth procedures for our data acquisition and processing are included in the supplementary materials and methods.

Identification of various necroptosis statuses and immunophenotypes

30 necroptosis-related biomarkers were found in the MSigDB and GeneCards databases, which we used to identify various immunophenotypes and necroptosis statuses in pancreatic cancer. We used the MSigDB database and previous research to identify 31 immune-related processes and immune cell scores, which we used to identify immune-related phenotypes. Using the R package "ConsensusClusterPlus," an unsupervised clustering algorithm (consensus clustering, K-Means, Euclidean distance) was used to identify the disease's status and perform immunophenotyping. Information and specifics about clustering are included in the supplementary materials and methods.

Identification of a necroptosis-immune phenotype and NI scoring system

Necroptosis status and immune phenotype were combined to create a more comprehensive new phenotype known as the necroptosis-immune phenotype, which was used in the NI scoring system. Patients were divided into four groups based on their various immunity and necroptosis statuses: high necroptosis and low immunity, high necroptosis and low immunity, and high necroptosis and low immunity. The mixed status group was formed by combining the two middle statuses [7]. The necroptosis-immunity score (NI score) was then derived from the differentially expressed genes between the low necroptosis-low immunity group and the high necroptosis-high immunity group. Multiple steps, including univariate analysis, random forest and Lasso regression, and multivariate regression analysis, were used to screen for biomarkers that had prognostic significance and necroptosis and immune properties. Using univariate analysis (R packages "survminer 0.4.9" and "survival 3.3.7"), we first identified two-dimensional phenotypic differential genes with prognostic significance for pancreatic cancer. Next, Lasso regression (R packages "glmnet" (version 4.1.2, nfold=1000, family = "cox") and random forest (version 2.12.0, set.seed= 60, ntree = 100, nsplit = The NI scoring system is a risk score system that indicates the patient's death risk.

Results

Pancancer evaluation of necroptosis-related molecules at the transcriptomic level

We investigated the multiomic variation of thirty molecules that are related to necroptosis and represent necroptotic characteristics in cancer. Figure depicts the effect of necroptosis on the tumor immune microenvironment. The tumor immune microenvironment and the progression of the tumor may both benefit from necroptosis. On the one hand, the activation of CD8+ T cells, NKT cells, cytotoxic T lymphocytes, etc., promotes the activation of the tumor-killing effect and a tumor-suppressive immune microenvironment through the release of some cytokines [8]. On the other hand, necroptosis's release of DAMPs and ROS may encourage tumor progression through angiogenesis, genomic instability, and MDSC activation. A total of 1502 samples with at least one of the aforementioned gene mutations were evaluated as part of our subsequent pancancer investigation of these molecules related to necroptosis. The waterfall plot depicts the mutational profiles of the ten molecules with the highest mutation rates among these molecules. 787.7% of all mutations were caused by these molecules' mutations. CHL1 had the most noteworthy change rate, and roughly one-fifth of growth patients had this transformation.

In the majority of cancers, the methylation level of necroptotic molecules was inversely correlated with their expression levels, as determined by the assessment of methylation correlation. Additionally, tumors have significantly higher methylation levels of a number of molecules related to necroptosis than normal tissue. A positive correlation between CNV levels and the expression levels of the majority of necroptosis-related molecules was found when we further investigated the alterations in necroptosis indicators at the level of copy number variations (CNVs) across cancers [9]. The current investigation centered on the functions and alterations of molecules related to necroptosis in pancreatic cancer. The majority of molecules related to necroptosis were found to be predictive of pancreatic cancer prognosis in a univariate Cox regression analysis. In addition, the majority of these molecules were elevated in cancer, and their expression in cancer samples was noticeably different from that of normal samples. In conclusion, we examined the mutation, methylation, and CNV profiles of necroptosis-related molecules in a variety of cancers and discovered that these molecules have prognostic significance in pancreatic cancer as well as differential expression .

The necroptosis-resistant aggregate gatherings contrast in oncogenic flagging and metabolic qualities

We additionally focused on the varieties in oncogenic flagging and metabolic qualities among these aggregates. According to research on pancancers, the RAS/MAPK signaling pathway, apoptosis, and EMT pathways were found to be activated, whereas the PI3K/AKT pathway, the TSC/MTOR pathway, and the cell cycle pathway were found to be inhibited in many cancers. TSC/mTOR pathways, the hormone ER, and PI3K/AKT are also activated in pancreatic cancer [10]. When we compared the differences in ten key tumorigenic signaling pathways, the Wnt, TP53, TGF-, PI3K, Notch, Hippo, and cell cycle signaling pathways revealed significant differences between the three subtypes. For differential gene analysis, we selected the most distinct HNHI and LNLI phenotypes to further investigate the differences in pathways and biological processes among the two-dimensional phenotypes. We compared these two-dimensional phenotypes' molecular mechanisms and signaling pathways through enrichment analysis. Through GO investigation, the organic cycles that we found to contrast between the two aggregates (HNHI, LNLI) were predominantly "receptive oxygen species metabolic interaction", "glucose metabolic interaction", "retinoid metabolic interaction" and other digestion related processes. T-cell activation and macrophage migration, two immune-related processes, were also significantly enriched.

Discussion

Patients with pancreatic cancer have very different outcomes, according to increasing evidence. For patients with pancreatic cancer, it is essential to develop a trustworthy system for categorizing subtypes and risk factors. This will make it possible to provide patients with individualized treatment and precise follow-up. High-throughput bioinformatics investigation in view of sequencing information has been progressively broadly used to lay out disease risk scores [11]. However, multifactor risk factor classification systems are still rarely investigated. As of late, necroptosis has turned into a significant subject

of examination; However, most basic research has focused on cellular studies of a single gene. The expression of a single gene is frequently not representative of the overall level of necroptosis in patients. However, integration and typing of multiple distinct patterns of necroptosis-associated genes using bioinformatics approaches may be able to model the level of necroptosis in patients [12]. Different necroptosis-associated genes frequently exhibit effects that either promote or inhibit necroptosis. In this exploration, we previously examined the pancancer highlights of necroptotic particles and distinguished unmistakable necroptotic status as well as safe status in pancreatic disease. Based on necroptosis and immunity phenotypes, we developed a novel two-dimensional phenotype and prognostic classification system. We investigated its application to immunotherapy and chemotherapy-based precision therapy.

In the development and progression of pancreatic cancer, necroptosis regulation and immunological microenvironmental characteristics play crucial roles. It is common belief that necroptosis enhances antitumor immunity and inhibits the activity of tumor cells. The activation of MLKL phosphorylation and the level of protein expression may be related to the level of intracellular necroptosis [13]. Mechanistically, necroptosis is linked to the activation of RIPK3 and MLKL. Multiple studies have demonstrated that pancreatic cancer patients have elevated levels of the necroptosis-associated molecules RIPK3 and RIPK1, which may cause CXCL1 activation to promote pancreatic cancer proliferation. Likewise, Ando et al. found that RIPK3 and MLKL expression was higher in cancerous tissues than in healthy pancreatic tissues. Aside from that, it's possible that RIPK1 inhibition won't affect the growth of pancreatic tumors. The findings of Akimoto et al. found that AdipoR encourages the RIPK1/ERK pathway to be activated, which in turn causes necroptosis and stops pancreatic cancer cells from growing. This suggests that genes related to necroptosis play two roles in pancreatic cancer. Pancreatic cancer progression and immunotherapy failure are linked to suppression of immune regulation and depletion of immune infiltration in the immune microenvironment [14]. Patients with pancreatic cancer's necroptosis and immunity phenotypes were found to be correlated with prognosis in our study. Moreover, pancreatic disease patients with various necroptosis situations with safe subtypes displayed totally unique microenvironmental qualities. As a result, developing a brand-new risk categorization system and two-dimensional phenotype based on these two characteristics may offer new advantages in terms of individualizing treatment and accurately distinguishing patients' risk levels. Patients were effectively differentiated based on their inflammatory microenvironment characteristics using the new two-dimensional classification method. In the HNHI group, many inflammatory factors that suppress tumours were upregulated, suggesting a better outcome.

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