



Clinical Characteristics of Patients With Pancreatic Cancer and Pathogenic ATM Alterations

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Abstract

The Ataxia-Telangiectasia, mutated (*ATM*) gene is involved in a number of DNA damage repair pathways and confers an increased risk for pancreatic ductal adenocarcinoma (PDAC). In this retrospective study, we identified and profiled 22 patients with PDAC and a known somatic or germline pathogenic *ATM* alteration (case patients). These patients were matched 2:1 by age, stage, and year at diagnosis to patients with PDAC without known *ATM* alterations. The median overall survival in patients with *ATM* alterations was 40.2 months compared with 15.5 months in the control population (hazard ratio = 0.14, 95% confidence interval = 0.04 to 0.47, 2-sided $P = .001$). In multivariable analysis, these findings persisted after adjustment for receipt of platinum therapy and Eastern Cooperative Oncology Group status. These findings suggest that pathogenic *ATM* alterations may be prognostic for improved outcomes in patients with pancreatic cancer.

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive and often fatal malignancy with a 5-year overall survival (OS) of 10% across all stages (1). Biological subgroups of pancreatic cancer make up a meaningful portion of the overall patient population (2-5) and may be predictive for treatment response and prognostic for survival. The most well-described patient subgroup consists of patients with pathogenic *BRCA* or *PALB2* mutations whose tumors are well-known to have heightened sensitivity to platinum-based chemotherapy and are sensitive to poly (ADP-Ribose) polymerase (PARP) inhibitors (6-10). Beyond *BRCA* and *PALB2*, alterations in other genes are also associated with pancreatic cancer, yet their impact on prognosis is less well-described. It is estimated that up to 6% of patients with pancreatic cancer may harbor a pathogenic loss or mutation in *ATM* (11), making this a relevant clinical group to study. However, a targeted cohort analysis of patients with pancreatic cancer and alterations in *ATM* has not yet been previously attempted.

The Ataxia-Telangiectasia, mutated (*ATM*) gene is heavily involved in multiple DNA damage repair mechanisms. It encodes for proteins in the PI3/PI4 kinase family and is essential for controlling the cell cycle checkpoints that respond to DNA damage. *ATM* gene products are recruited to repair DNA double-strand breaks through homologous recombination via the *BRCA1* pathway and nonhomologous end-joining as well as cell

cycle checkpoint modulation (12-14). We hypothesized that patients with pathogenic *ATM* alterations have improved outcomes compared with those without such alterations.

We conducted a single-institution retrospective study of patients with confirmed pathogenic or likely pathogenic germline or somatic *ATM* alterations and pancreatic cancer. This study was approved by our institutional review board and waiver of consent was obtained. We queried the University of Pennsylvania patient electronic medical record for patients with PDAC treated at our institution between January 1, 2014, and December 31, 2019. Cases were defined as those with a known pathogenic germline or somatic *ATM* loss or mutation. Controls were noncarriers or those who had not been tested. Baseline covariates, treatment history, and date of death or last follow-up were recorded, with a cutoff date of June 20, 2020. Each case patient was matched to 2 control patients queried from the Penn Medicine Cancer Registry by age, American Joint Committee on Cancer (AJCC) stage, and year, all at time of diagnosis. The primary outcome was OS. Two-sided Fisher exact and Wilcoxon rank sum tests were performed for dichotomous and nonnormal continuous variables, respectively. A P value of less than .05 was considered statistically significant. Hazard ratios (HRs) and 95% confidence intervals (CI) were calculated using the Cox proportional hazards model, and assumption of

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Table 1. Baseline characteristics and therapy administered in our cohort

Variables	Controls (n = 44)	Cases (n = 22)	P ^a
Baseline characteristics			
Age at diagnosis, median (IQR), y	63.4 (57.5-70.0)	64 (58.8-67.1)	.95
Males, No. (%)	27 (61.4)	16 (72.1)	.36
Year of diagnosis, median (IQR)	2017 (2014-2018.5)	2017 (2015-2019)	.44
Caucasian race, No. (%)	39 (88.6)	20 (90.9)	1.00
Stage at diagnosis, No. (%)			1.00
Stage I	2 (4.5)	1 (5)	
Stage II	13 (29.5)	6 (27)	
Stage III	9 (20.5)	5 (23)	
Stage IV	20 (45.5)	10 (45.5)	
Family history of any cancers, No. (%)	29 (65.9)	15 (68.2)	.83
Family history of BRCA-related cancers, No. (%)	26 (59.1)	19 (86.4)	.06
Personal history of other cancers, No. (%)	6 (13.6)	6 (27.3)	.12
Breast	3 (6.8)	0 (0)	
Ductal carcinoma in-situ	0 (0)	1 (4.5)	
Chronic myelomonocytic leukemia	0 (0)	1 (4.5)	
Endometrial	1 (2.3)	0 (0)	
Hodgkins lymphoma	1 (2.3)	0 (0)	
Melanoma	0 (0)	2 (9.1)	
Prostate	1 (2.3)	1 (4.5)	
Thyroid	0 (0)	1 (4.5)	
Two or more previous cancers	1 (2.3)	2 (9.1)	
No previous cancers	38 (86.4)	16 (72.7)	
ECOG performance status, No. (%)			.46
0	13 (29.5)	9 (40.9)	
1	25 (56.8)	12 (54.5)	
2	3 (6.8)	0 (0)	
3	1 (2.3)	0 (0)	
Unknown	2 (4.5)	1 (4.5)	
Therapy administered, No. (%)			
Any systemic therapy	37 (84.1)	22 (100)	.048
Any platinum therapy	23 (52.3)	19 (86.4)	.007
FOLFIRINOX	15 (34.1)	16 (72.7)	.003
FOLFOX	9 (20.5)	4 (18.2)	.83
Gemcitabine/cisplatin	1 (2.3)	3 (13.6)	.07
Other platinum therapy	10 (22.7)	5 (22.7)	1.00
Gemcitabine alone	24 (54.5)	14 (63.6)	.48
Gemcitabine/abraxane	15 (34.1)	11 (50)	.21
Other nonplatinum therapy	24 (54.5)	10 (45.5)	.49
Multiple therapies	26 (59.1)	15 (68.2)	.47
Surgical resection	15 (34.1)	12 (54.5)	.11
Any neoadjuvant systemic treatment	7 (15.9)	4 (18.2)	.82
Platinum based	5 (11.4)	4 (18.2)	.45
Nonplatinum based	2 (4.5)	0 (0)	.31
Any adjuvant systemic treatment	18 (40.9)	12 (54.5)	.29
Platinum-based	4 (9.1)	4 (18.2)	.29
Nonplatinum based	14 (31.8)	8 (36.4)	.71

^aTwo-sided P values were calculated using Fisher exact and Wilcoxon rank sum tests for dichotomous and continuous variables, respectively. ECOG = Eastern Cooperative Oncology Group; FOLFIRINOX = Folinic acid, 5-Fluorouracil, Irinotecan, Oxaliplatin; FOLFOX = Folinic acid, 5-Fluorouracil, Oxaliplatin; IQR = interquartile range.

proportional hazards was verified using Schoenfeld residuals. Survival curves for time-to-event variables were estimated using the Kaplan-Meier method.

The study population included a total of 66 patients with PDAC (22 case patients and 44 control patients). Sixteen cases had germline ATM alterations. The median age was 63.4 years (interquartile range = 48.8-75.6), 65.2% were male, and 93.9% reported an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1. Median time of follow-up was 19.6 months (interquartile range = 1.5-56.8). Age, stage, and year at time of diagnosis were well-matched between cases and controls

(Table 1). Cases were statistically significantly more likely to receive platinum chemotherapy (86.4% vs 52.3%, $P = .007$), especially FOLFIRINOX therapy (72.7% vs 34.1%, $P = .003$).

Median OS among patients with pathogenic ATM alterations was 40.2 months compared with 15.5 months for patients without known alterations (HR = 0.14, 95% CI = 0.04 to 0.47, $P = .001$) (Figure 1, A). Rates of 5-year survival were 38.3% for patients with ATM mutations and 6.6% for patients without known mutations. This difference persisted after adjustment for receipt of platinum therapy and ECOG performance status in a multivariable analysis (HR_{adj} = 0.20, 95% CI = 0.05 to 0.74,

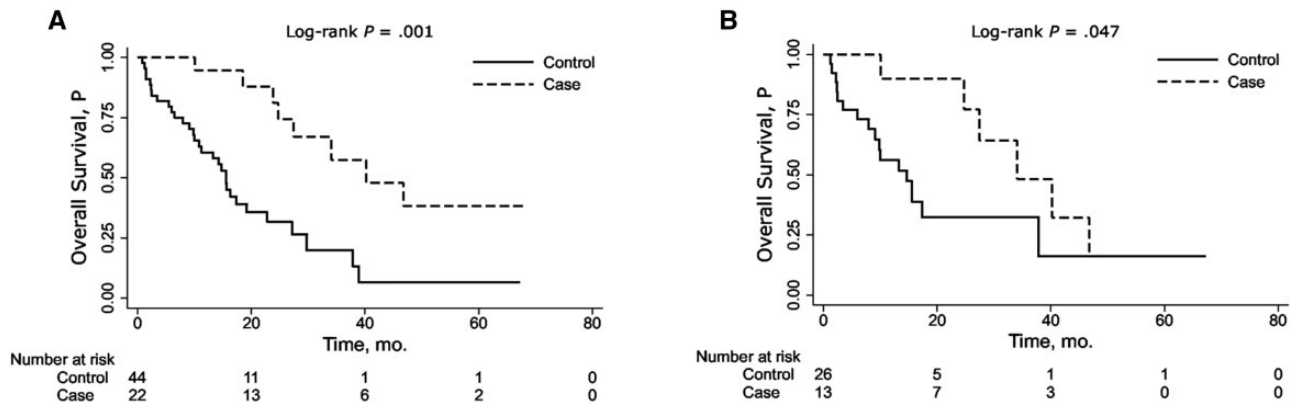


Figure 1. Kaplan-Meier survival curves estimating overall survival of (A) the full cohort and (B) case patients who received genetic testing within 6 months of diagnosis and their matched controls. P values were calculated using a 2-sided log-rank test.

$P = .02$). The median OS for patients with metastatic disease at diagnosis was 24.7 vs 6.0 months (HR = 0.16, 95% CI = 0.04 to 0.71, $P = .02$). Given the potential for immortal time bias, we performed a sensitivity analysis by evaluating only patients whose time between diagnosis and genetic testing was less than 6 months. The OS for this subgroup was 34.0 vs 14.7 months (HR = 0.28, 95% CI = 0.08 to 0.98, $P = .047$) (Figure 1, B), consistent with magnitude of difference found in our full patient cohort.

This is the first cohort study to focus solely on patients with pancreatic cancer and pathogenic ATM alterations. In matched patients, we observed a statistically significantly longer OS in those with ATM alterations compared with control patients. Our findings persisted after adjustment for receipt of platinum therapy, suggesting that ATM alterations may be prognostic for survival independent of treatment selection. Notably, 93.9% of the patients in the entire cohort were ECOG 0-1, suggesting that poor performance status was not a reason for the observed difference between groups. Finally, in a sensitivity analysis to assess the potential for immortal lead time bias, our results continued to show a persistent statistically significant survival difference when we limited the analysis to patients who had received genetic testing within 6 months of diagnosis.

Our study has several important limitations. This is a single-institution, retrospective analysis and is therefore hypothesis generating only. Second, our small sample size limited our ability to perform subgroup analyses, which would have allowed us to further examine several variables more closely. Third, we observed a lower median OS in the metastatic control group than would be expected based on published data. We attribute this to our small sample size and unmeasured variables that may have influenced treatment decisions and patient survival. Finally, a portion of the patients in the control group had not undergone genetic testing, but this would plausibly bias toward the null hypothesis. Larger and prospective studies of patients with ATM mutations are needed to confirm and further explore our preliminary findings.

In conclusion, we demonstrate for the first time, to our knowledge, that patients with pancreatic cancer and a pathogenic ATM alteration have improved OS compared with matched controls and that this persists when adjustments are made for receipt of platinum-based therapy. Prospective studies to further align these findings with optimal therapeutic strategies are ongoing.

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Role of the funder: The funder had no role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the manuscript; and the decision to submit the manuscript for publication.

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Data Availability

Deidentified data that support the findings of this study are available on request from the corresponding author, K.A.R.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA A Cancer J Clin*. 2020; 70(1):7–30.
2. Holter S, Borgida A, Dodd A, et al. Germline BRCA mutations in a large clinic-based cohort of patients with pancreatic adenocarcinoma. *J Clin Oncol*. 2015; 33(28):3124–3129.
3. Salo-Mullen EE, O'Reilly EM, Kelsen DP, et al. Identification of germline genetic mutations in patients with pancreatic cancer. *Cancer*. 2015;121(24): 4382–4388.
4. Toss A, Venturelli M, Molinaro E, et al. Hereditary pancreatic cancer: a retrospective single-center study of 5143 Italian families with history of BRCA-related malignancies. *Cancers*. 2019;11(2):193.
5. Blanco A, de la Hoya M, Osorio A, et al. Analysis of PALB2 gene in BRCA1/BRCA2 negative Spanish hereditary breast/ovarian cancer families with pancreatic cancer cases. *PLoS One*. 2013;8(7):e67538.

6. Golan T, Hammel P, Reni M, et al. Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. *N Engl J Med.* 2019;381(4):317–327.
7. O'Reilly EM, Lee JW, Zalupski M, et al. Randomized, multicenter, phase II trial of gemcitabine and cisplatin with or without veliparib in patients with pancreas adenocarcinoma and a germline BRCA/PALB2 mutation. *J Clin Oncol.* 2020;38(13):1378–1388.
8. Wattenberg MM, Asch D, Yu S, et al. Platinum response characteristics of patients with pancreatic ductal adenocarcinoma and a germline BRCA1, BRCA2 or PALB2 mutation. *Br J Cancer.* 2020;122(3):333–339.
9. Yu S, Agarwal P, Mamtani R, et al. Retrospective survival analysis of patients with resected pancreatic ductal adenocarcinoma and a germline BRCA or PALB2 mutation. *J Clin Oncol Precis Oncol.* 2019;3:1–11.
10. Bailey P, Chang DK, Nones K, et al.; Australian Pancreatic Cancer Genome Initiative. Genomic analyses identify molecular subtypes of pancreatic cancer. *Nature.* 2016;531(7592):47–52.
11. Park W, Chen J, Chou JF, et al. Genomic methods identify homologous recombination deficiency in pancreas adenocarcinoma and optimize treatment selection. *Clin Cancer Res.* 2020;26(13):3239–3247.
12. Savitsky K, Bar-Shira A, Gilad S, et al. A single ataxia telangiectasia gene with a product similar to PI-3 kinase. *Science.* 1995;268(5218):1749–1753.
13. Watters D, Khanna KK, Beamish H, et al. Cellular localisation of the ataxia-telangiectasia (ATM) gene product and discrimination between mutated and normal forms. *Oncogene.* 1997;14(16):1911–1921.
14. Roberts NJ, Jiao Y, Yu J, et al. ATM mutations in patients with hereditary pancreatic cancer. *Cancer Discov.* 2012;2(1):41–46.