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BRCA1/BRCA2 Germline Mutation Carriers and Sporadic Pancreatic Ductal Adenocarcinoma

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Abstract

BACKGROUND: The outcomes of sporadic pancreatic ductal adenocarcinoma (PDAC) patients with germline mutations of *BRCA1/BRCA2* remains unclear. The prognostic significance of *BRCA1/BRCA2* mutations on survival is not well established.

STUDY DESIGN: We performed targeted next-generation sequencing (NGS) to identify *BRCA1/BRCA2* germline mutations in resected sporadic PDAC cases from 2000 to 2015. Germline *BRCA* mutation carriers were matched by age and tumor location to those with *BRCA1/BRCA2* wild-type genes from our institutional database. Demographics, clinicopathologic features, overall survival (OS), and disease-free survival (DFS) were abstracted from medical records and compared between the 2 cohorts.

RESULTS: Twenty-two patients with sporadic cancer and *BRCA1* (n = 4) or *BRCA2* (n = 18) germline mutations and 105 wild-type patients were identified for this case-control study. The *BRCA1/ BRCA2* mutations were associated with inferior median OS (20.2 vs 27.8 months, p = 0.034) and DFS (8.4 vs 16.7 months, p < 0.001) when compared with the matched wild-type controls. On multivariable analyses, a *BRCA1/BRCA2* mutation (hazard ratio [HR] 2.10, p < 0.001), positive margin status (HR 1.72, p = 0.021), and lack of adjuvant therapy (HR 2.38, p < 0.001), were all independently associated with worse survival. Within the *BRCA1/BRCA2* mutated group, having had platinum-based adjuvant chemotherapy (n = 10) was associated with

better survival than alternative chemotherapy (n = 8) or no adjuvant therapy (n = 4) (31.0 vs 17.8 vs 9.3 months, respectively, p < 0.001).

CONCLUSIONS: Carriers of *BRCA1/BRCA2* mutation with sporadic PDAC had a worse survival after pancreatectomy than their *BRCA* wild-type counterparts. However, platinum-based chemotherapy regimens were associated with markedly improved survival in patients with *BRCA1/BRCA2* mutations,with survival differences no longer appreciated with wild-type patients.

Pancreatic ductal adenocarcinoma (PDAC) is a devastating disease with a poor overall survival (OS), partly attributed to late diagnosis, early spread, and relatively ineffective systemic therapies showing benefit in only a subset of patients.[1–4] The genetic and epigenetic heterogeneity of PDAC plays a role in its treatment resistance. Although activating mutations of genes such as *KRAS* and *TP53* are prevalent in PDAC, a multitude of infrequently mutated genes have been identified, along with 4 specific patterns of chromosomal structure variation: stable, locally rearranged, scattered, and unstable.[5,6] As a consequence, biomarkers that can accurately define subgroups of PDAC with different underlying biology are needed to match treatments to their underlying genetic pathway abberations.

Although most commonly observed as a sporadic disease, nearly 10% of PDAC cases are familial, defined as occurring in families with 2 or more affected firstdegree relatives.[7] Within these familial patients, several clusters of germline mutations have been identified that lead to a propensity for malignancy including: *BRCA1, BRCA2, PALB2, ATM*, and DNA mismatch repair genes.[7–9] These inherited familial mutations have also been identified in 3% to 5% of individuals with seemingly sporadic PDAC, perhaps as a result of incomplete penetrance.[10,11]

Germline *BRCA1* and *BRCA2* mutations are found in approximately 5% to 10% of familial PDAC and approximately 3% of apparently sporadic PDAC.[12–15] The *BRCA1* and *BRCA2* proteins are involved in recognition and repair of double-stranded DNA via homologous recombination.[16] DNA maintenance gene inactivation and subsequent repair deficiency may then impart sensitivity to DNA-strand-damaging cytotoxic agents such as platinum-based chemotherapy.[17–19] The use of these platinum-based chemotherapeutics have conveyed a survival advantage in breast and ovarian cancer patients with *BRCA* mutations; however, only limited information has been reported regarding the therapeutic impact of *BRCA* status on platinums in patients with PDAC.[20,21]

The purpose of this study was to retrospectively investigate the association of *BRCA1/BRCA2* mutations with survival in resected sporadic PDAC. Secondly, we aimed to investigate the relation of platinum-based adjuvant chemotherapy and the survival of *BRCA* mutated patients with PDAC.

METHODS

Patient selection

Patients with sporadic PDAC, undergoing resection at the Johns Hopkins Hospital between 2000 and 2015, were selected for targeted next generation sequencing (NGS). Exclusion criteria included known familial pancreatic cancer families (2 or more first degree relatives with PDAC), final pathology other than PDAC, and patients with surgery-related mortality within 90 days of resection. Patients with *BRCA1/BRCA2* mutation were matched with additional patients with wild-type (WT) *BRCA* and other susceptibility genes analyzed in a 32-gene panel in 1:5 ratio. Case matching was performed by age and anatomic tumor location. Institutional Review Board approval was obtained for this study, with informed consent obtained from all patients.

Extraction and sequencing of DNA

Genomic DNA was extracted from banked frozen tissue from resected duodenum, or spleen using QIAamp DNA Micro Kit (QIAGEN) and quantified using Quantifiler (Thermo Fisher) according to the manufacturer's instructions. Somatic tumor tissue was not sequenced for this study. Targeted sequencing was performed using Ion Torrent Proton platform next generation sequencing (Thermo Fisher). A 32-gene panel was used with known pancreatic cancer susceptibility genes (*BRCA2, ATM, PALB2, BRCA1, CDKN2A, MLH1, MSH2, PRSS1*, *STK11*, and *TP53*), known cancer susceptibility genes (*MSH6, PMS2, CDH1, RAD51C, RAD51D, BUB1B,* and *FANCJ*), and candidate pancreatic susceptibility genes (*FANCA, FANCC, FANCG, FANCL, ARID1A, RECQL4, XRCC2, XRCC3, ERCC4, TERT, BAP1, BUB1, BUB3,* and *RNF43*), as described in a previous study.[11] Genetic data were analyzed using NextGENe Software (Soft genetics). Mutations with variants of unknown significance (VUS) were included in this study.

Demographics and clinicopathologic characteristics

Demographics and clinicopathologic features were obtained from a prospectively maintained pancreatic database including: medical history, family history of malignancy, type of operation, and neoadjuvant or adjuvant therapy. All resections were performed at the Johns Hopkins Hospital. Patients were routinely referred for chemotherapy and/or radiation therapy. Platinumbased chemotherapy included the use of cisplatin or oxaliplatin.

The following pathologic features were extracted from final pathology: tumor size, tumor infiltration extension, tumor differentiation grade, presence of lymph node metastases, microscopic perivascular and perineural invasion, and resection margin (R). The pancreatic neck, uncinate, and bile duct margins were assessed by experienced pancreatic pathologists, with R1 defined as a distance of tumor cells <1 mm from the closest resection margin and R0 when the distance was ≥1 mm.

Follow-up and survival

Patients were followed after pancreatectomy with CT scan of the chest, abdomen, and pelvis every 4 to 6 months for the first 2 years and yearly thereafter. Positron emission tomography or MRI were only used occasionally to study suspicious lesions identified on CT.

Recurrence was defined as the imaging observation of distant metastases or progressing radiographic change within the surgical bed including the pancreas remnant or anastomosis sites. Biopsy confirmation of recurrence was not routinely performed. Disease-free survival (DFS) was calculated from the time of surgery to the documented date of recurrence or censored at the last date of follow-up. Overall survival was calculated from the date of diagnosis to the date of death or censored at the date of last follow-up. The date of death was obtained from medical records, local obituaries, or the Social Security Death Index.

Statistical analysis

Statistical analyses were performed using Stata/MP 12.1 (Stata Corp). Categorical variables were expressed as percentages of the group they were derived from and were compared using a chi-square or Fisher's exact test. Continuous variables were presented as median with interquartile range (IQR), and were compared using a Kruskal-Wallis test. Kaplan-Meier survival curves and a log-rank test were used to estimate median survival and analyze survival outcomes between subgroups. Univariable analyses of demographic and clinicopathologic variables were performed using a Cox proportional hazards model. All factors with a value of $p < 0.10$ in univariable analysis were included as a covariable in multivariable regression analyses. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

A total of 658 patients with resected, presumably sporadic PDAC were included for analysis and sequenced via NGS. Twenty-two patients (3%) had germline *BRCA1/ BRCA2* mutations (*BRCA*+): 4 with *BRCA1* and 18 *BRCA2* (eTable 1 contains further information about these mutations). An additional 213 (32%) patients had mutations (including VUS) identified in the remaining 30 cancer susceptibility genes in our NGS panel and were excluded. The remaining 423 patients (64%) were therefore of confirmed wild-type genotype and were matched by age and anatomic tumor location to the *BRCA1/BRCA2* germline patients. We matched *BRCA* wild-type cases by age and anatomic tumor location (Table 1). Family history of cancer was similar in each group, both for the presence of any cancer (64% *BRCA*+ vs 61% WT, $p = 0.689$) or 1 relative with pancreatic cancer (9% *BRCA*+ vs 12% WT, $p = 0.551$). Neoadjuvant chemotherapy or radiation was received by 23% of the *BRCA*+ group compared with 16% of the WT group ($p = 0.461$). Most patients received adjuvant therapy (73% *BRCA*+ vs 79% WT, $p = 0.648$).

Clinicopathologic characteristics

No significant difference was noted among clinicopathologic characteristics between the 2 groups (Table 2). Patients underwent either a pancreaticoduodenectomy (91% *BRCA*+ vs 90% WT) or a distal pancreatectomy (9% *BRCA*+ vs 10% WT) ($p = 0.950$). Total pancreatectomies were not performed in either group. Detailed pathologic features were well matched between the 2 groups including continuous tumor size, American Joint Committee on Cancer (AJCC) seventh edition T-stage (depth of tumor invasion), differentiation grade,

presence of lymph node metastases, microscopic perivascular and perineural invasion, and resection margin status.

Survival outcomes

Median OS was inferior in patients with a germline *BRCA1/BRCA2* mutation when compared with the matched wild-type control group (20.2 months vs 27.8 months, p = 0.034, Fig. 1). Likewise, median DFS was considerably shorter in those with *BRCA1/BRCA2* mutations (8.4 months vs 16.7 months for WT, p < 0.001, Fig. 2).

A multivariable Cox regression model was generated to describe the strength of association of different mutational statuses with OS (Table 3). Within this model, a *BRCA1/BRCA2* mutation was independently associated with inferior survival compared with the matched wild-type patients with resected sporadic PDAC (hazard ratio 2.10, p < 0.001). A positive microscopic margin status was a significant independent predictor of OS (HR 1.72, p = 0.021). Positive nodal status was included in the model due to an unadjusted univariable association (p = 0.081), but did not reach statistical significance on multivariable analysis (HR 1.44, p = 0.121). A different multivariable Cox regression model was used to assess the variables independently associated with inferior DFS (Table 4). Similarly, a *BRCA1/BRCA2* mutation was associated with inferior DFS when compared with matched wild-type patients (HR 2.48, p < 0.001).

Chemotherapy

In the multivariable Cox regression model, adjuvant chemotherapy was independently associated with prolonged OS (29.9 months vs 16.6 months; HR 0.348, p < 0.001) and longer DFS (15.8 months vs 13.6 months; HR 0.633, p = 0.047). Receipt of neoadjuvant chemotherapy was not associated with DFS or OS. Within wild-type patients, there was no difference in median OS in patients who received platinum-based adjuvant compared with other chemotherapy regimens (33 vs 28 months, p = 0.897). However, within the group of patients with germline *BRCA1/BRCA2* mutations, the use of platinum-based chemotherapy (n = 10) was associated with substantially longer OS than the use of alternative nonplatinum-based agents (n = 8) or failure to receive adjuvant therapy (n = 4) (31.0 vs 17.8 vs 9.3 months, p < 0.001, Fig. 3). Survival in wild-type patients who received chemotherapy was superior to that in *BRCA1/2* mutant patients who underwent similar regimens (28.4 vs 17.8 months, p = 0.002); however, no survival difference was appreciated in patients receiving platinum therapy in both groups (WT, 32.7 months vs *BRCA1/2*, 31.0 months, p = 0.754).

DISCUSSION

The prognostic impact of germline *BRCA1/BRCA2* mutations on sporadic PDAC survival is not well established.

This retrospective, single-institution, case-control study demonstrated, for the first time, that a germline *BRCA1/BRCA2* mutation in patients with resected, sporadic PDAC was independently associated with inferior overall and disease-free survival compared with matched patients with a wild-type genotype. Additionally, *BRCA* mutants who received a

platinum-based adjuvant chemotherapy had improved survival, similar to that of wildtype PDAC counterparts. This finding is of important clinical benefit and provides growing evidence that PDAC patients with a *BRCA* mutation may have inferior outcomes mitigated by "targeted" platinum-based chemotherapy.

Deleterious germline mutations are a well-established risk factor for asubset of PDAC,with many individuals carrying mutations despite not meeting familial criteria for genetic testing.[10,11] Of these, mutations to the *BRCA* tumor suppressor genes are among the most frequently encountered. Mutations in *BRCA* are more commonly studied in the setting of breast or ovarian cancer.[22,23] Although the association between *BRCA* mutations and PDAC in both the familial and seemingly sporadic case is known, the rarity of the diagnosis compounded by the infrequent nature of genetic testing has led to few studies of *BRCA* mutation and its impact on patient survival.[24–28] In theory, *BRCA* mutations in PDAC may fall within the unstable genotype, representing a more mutagenic and aggressive tumor biology and subsequent worse survival.[5]

Multi-institutional studies by Golan and colleagues[25,26] reported OS and clinical characteristics of PDAC in *BRCA* mutation carriers identified via polymerase chain reaction (PCR) analysis. Although a majority of patients in their cohort had unresectable disease, no significant difference was observed in median OS for patients with early stage disease when compared with OS in a matched cohort.[25,26] Of note, in contrast to our study of seemingly sporadic PDAC, 32% of patients had familial PDAC. Their multi-institutional control cases did not have sequencing data to confirm the wild-type status. Furthermore, a large selection of their *BRCA* patients received neoadjuvant or adjuvant platinum-based treatment, perhaps contributing to the exceptional survival.[25,26]

Proteins in *BRCA1* and *BRCA2* are involved in recognition and repair of DNA damage via homologous recombination.[16] Mutations and instability in these genes lead to the inability to repair double-strand DNA breaks and a subsequent sensitivity to platinum-based, DNAstrand-damaging cytotoxic agents.[17–19] Use of these platinum-based chemotherapeutics has been effective in a high proportion of patients with breast and ovarian cancer with *BRCA* mutations, conveying a prolonged survival advantage.[20,21] Given the dismal prognosis of PDAC and its notorious treatment resistance, there is great interest in identifying patient subsets that may have targetable therapeutic vulnerabilities. Promising results of platinumbased chemotherapy and the poly(ADP-ribose) polymerase inhibitors (PARPi) in *BRCA* mutation carriers with PDAC[25,26,29–31] have led to further ongoing clinical trials (NCT02042378, NCT03140670).

Consistent with the current literature,[32–35] we showed that adjuvant chemotherapy was associated with better surival. Certainly retrospective studies are limited due to selection bias. Patients may not make it to adjuvant therapy or have particular regimens selected for multiple reasons including patient performance status. In this study, both platinum-based chemotherapy and other predominately gemcitabine-based chemotherapies were associated with superior survival in wild-type patients than in those who did not recieve adjuvant therapy ($p < 0.001$). No difference was noted between the 2 groups of chemotherapy regimens ($p = 0.897$). However, the use of platinum-based chemotherapy in *BRCA* patients

demonstrated a dramatic survival improvement, with median OS similar to that of WT patients (31.0 months vs 32.7 months, p = 0.754). This provides growing evidence that specific therapies can be targeted for a subset of patients with actionable mutations.

This study has several limitations worthy of mention. Due to its retrospective nature, it relied on self-reported family history when determining our seemingly sporadic cohort. Additionally, only the patients who proceeded to the operating suite for resection were included in analysis, excluding those with rapidly progressive or metastatic biology in both the wild-type and *BRCA* mutated groups. In-depth analysis of the impact of different neoadjuvant and adjuvant chemotherapy or chemoradiation regimen were beyond the scope of this study, as a large degree of chemotherapy heterogeneity existed within the total cohort. Furthermore, because our center is a tertiary surgical referral center, many patients opt for chemotherapy at local institutions, where the dosage and treatment details are difficult to obtain. The mitigation in worse OS and DFS observed in *BRCA1/2* mutated patients who received platinum-based chemotherapy is certainly limited by selection bias in this retrospective study setting. Of note, 9 cases of *BRCA* mutations were variants with unknown significance (Table 1). The significance of VUS in *BRCA* remains unknown and clearly represents a clinical challenge; nonetheless, a correlation with worse outcomes was found in this study. In this study, only the germline was sequenced and biallelic inactivation of *BRCA* was not assessed within the tumor. Future efforts may show some of these patients with germline VUS to have tumor gene inactivation, potentially identifying additional pathogenic mutations. Finally, randomized controlled trials are necessary to prospectively assess the benefit of platinum agents in sporadic patients with *BRCA1/2* mutations.

The growing ease and decreasing cost of gene sequencing in parallel with our growing knowledge of subsets of potentially targetable mutations further increases a push toward more ubiquitous sequencing of PDAC patients, even those without suspected familial disease. The outcomes presented from this study were all associations with solely germline mutations, so a sample of saliva or a simple cheek swab is all that is necessary to obtain information that could potentially assist with treatment direction and a survival impact. Hopefully, with further prospective study and technologic advancement, the future of PDAC treatment will follow this path, where germline sequencing may allow guidance to targeted therapy, such as platinum agents in *BRCA* carriers.

CONCLUSIONS

Our study demonstrated for the first time, that a germline *BRCA1* or *BRCA2* mutation in patients with resected sporadic PDAC infers an inferior overall and diseasefree survival when compared to survival in wild-type matched controls. However, the use of platinum-based chemotherapy was associated with improved survival, equivalent to that of wild-type counterparts. Prospective randomized trials will help further illuminate a potential treatment advantage in these select groups of patients.

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Abbreviations and Acronyms

BRCA1	breast cancer 1
BRCA2	breast cancer 2
DFS	disease-free survival
HR	hazard ratio
NGS	next-generation sequencing
OS	overall survival
PDAC	pancreatic ductal adenocarcinoma
VUS	variants of unknown significance
WT	*BRCA1/BRCA2* wild-type

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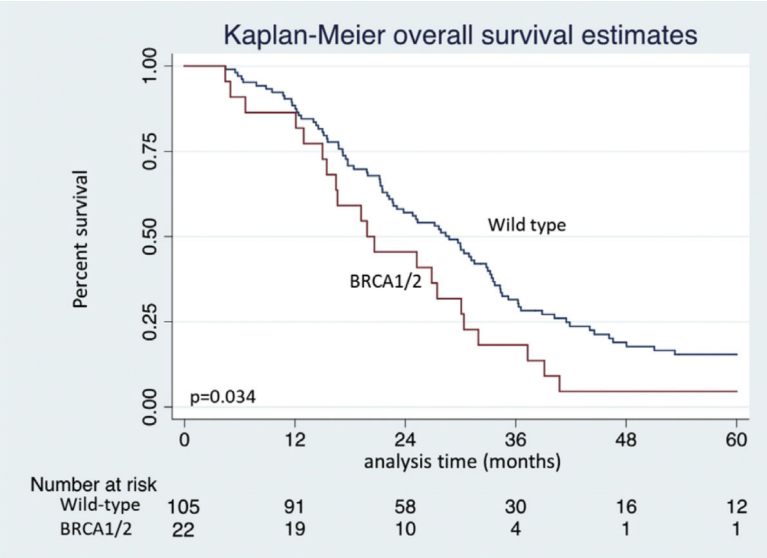

Figure 1.

Kaplan-Meier overall survival estimates of *BRCA1/BRCA2* germline mutation vs wild-type control patients after resection of pancreatic adenocarcinoma.

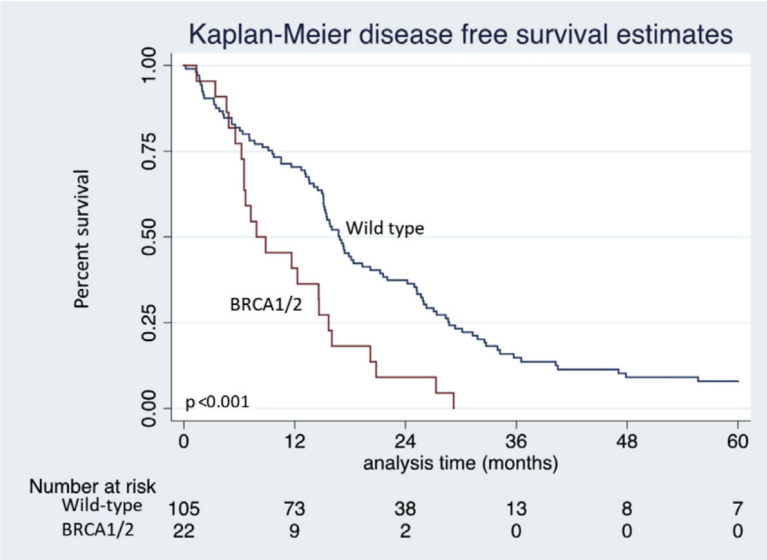

Figure 2.

Kaplan-Meier disease-free survival estimates of *BRCA1/BRCA2* germline mutation vs wild-type control patients after resection of pancreatic adenocarcinoma.

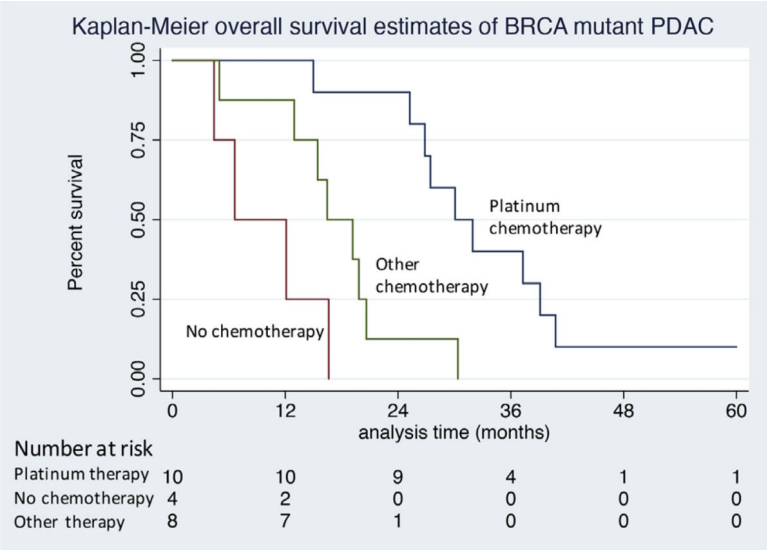

Figure 3.

Kaplan-Meier overall survival estimates of *BRCA1/BRCA2* germline mutated patients after resection of pancreatic adenocarcinoma stratified by type of chemotherapy received. Platinum-based chemotherapy vs other chemotherapy ($p < 0.01$) vs no chemotherapy ($p < 0.01$). Other chemotherapy vs no chemotherapy ($p = 0.053$).

Table 1.

Demographics of *BRCA*-Mutated and Wild-Type Patients

Variable	*BRCA* (n = 22)	Wild-type (n = 105)	p Value
Age, y, median (IQR)	61 (57–65)	61 (55–66)	0.990
Male sex, n (%)	14 (64)	48 (46)	0.126
Race, n (%)			0.765
Caucasian	19 (86)	88 (84)	
Non-Caucasian	3 (14)	17 (16)	
History of diabetes, n (%)	6 (27)	25 (24)	0.566
History of smoking, n (%)	6 (27)	29 (28)	0.369
Family history of cancer, n (%)			
Any cancer	14 (64)	64 (61)	0.689
Pancreatic cancer	2 (9)	13 (12)	0.551
Neoadjuvant therapy, n (%)	5 (23)	17 (16)	0.461
Adjuvant therapy, n (%)	16 (73)	83 (79)	0.648

Table 2.

Clinicopathologic Features of *BRCA*-Mutated and Wild-Type Patients

Variable	BRCA (n = 22)	Wild-type (n = 105)	p value
Operation procedure, n (%)			0.950
Pancreaticoduodenectomy	20 (91)	95 (90)	
Distal pancreatectomy	2 (9)	10 (10)	
Tumor size, cm, median (IQR)	3 (2.5–3.7)	3 (2.3–3.5)	0.987
Lymph nodes, median (IQR)	20 (13–23)	18 (14–26)	0.674
Positive nodal metastases, n (%)	14 (64)	76 (72)	0.412
Grade, n (%)			0.202
1	0 (0)	7 (7)	
2	14 (64)	47 (46)	
3	8 (36)	49 (48)	
T-stage, n (%)			0.799
T1	2 (9)	8 (8)	
T2	5 (23)	31 (30)	
T3	15 (68)	64 (61)	
T4	0 (0)	2 (2)	
Perivascular invasion, n (%)			0.599
Yes	7 (32)	55 (52)	
No	8 (36)	47 (45)	
Perineural invasion, n (%)			0.937
Yes	19 (86)	90 (86)	
No	3 (14)	15 (14)	
Resection margin, n (%)			0.577
R0	17 (77)	75 (71)	
R1	5 (23)	30 (29)	

IQR, interquartile range.

Table 3.

Univariable and Multivariable Cox Regression Analyses of Overall Survival in Patients Who Underwent Resection for Pancreatic Adenocarcinoma

Clinical characteristic	Cohort(n = 127)	Univariable p Value
Mutation		
Wild-type	105 (83)	Reference
BRCA1/BRCA2	22 (17)	0.036*
Hazard ratio	2.10	
95% CI	1.26–3.49	
Multivariable p value	<0.001*	
Age, n (%)		
<60 y	64 (50)	Reference
≥60 y	63 (50)	0.395
Sex, n (%)		
Male	62 (49)	Reference
Female	65 (51)	0.315
History of diabetes, n (%)	31 (24)	0.826
History of smoking, n (%)	35 (28)	0.624
Family history of cancer, n (%)		
Any cancer	78 (67)	0.410
Pancreatic cancer	15 (12)	0.432
Neoadjuvant therapy, n (%)	22 (17)	0.313
Adjuvant therapy, n (%)	99 (80)	<0.001*
Hazard ratio	0.348	
95% CI	0.22–0.56	
Multivariable p value	<0.001*	
Operative procedure, n (%)		
Pancreaticoduodenectomy	115 (91)	Reference
Distal pancreatectomy	12 (9)	0.776
Positive nodal metastases, n (%)	90 (71)	0.081*
Hazard ratio	1.44	
95% CI	0.91–2.29	
Multivariable p value	0.121	
Grade, n (%)		
1	7 (6)	Reference
2	61 (48)	0.821
3	57 (45)	0.601
T-stage, n (%)		
T1	10 (7)	Reference

Clinical characteristic	Cohort(n = 127)	Univariable p Value
T2	36 (28)	0.822
T3	79 (63)	0.370
T4	2 (2)	0.350
Perivascular invasion, n (%)		
No	55 (43)	Reference
Yes	62 (49)	0.194
Perineural invasion, n (%)		
No	18 (14)	Reference
Yes	109 (86)	0.891
Resection margin, n (%)		
R0	92 (72)	Reference
R1	35 (28)	0.032 *

* Statistically significant.

Table 4.

Univariable and Multivariable Cox Regression Analyses of Disease-Free Survival in Patients That Underwent Resection for Pancreatic Adenocarcinoma

Clinical characteristic	Cohort(n = 127)	Univariable p Value
Mutation		
Wild-type	105 (83)	Reference
BRCA1/BRCA2	22 (17)	<0.001 *
Hazard ratio	2.48	
95% CI	1.50–4.07	
Multivariable p value	<0.001 *	
Age, n (%)		
<60 y	64 (50)	Reference
≥60 y	63 (50)	0.392
Sex, n (%)		
Male	62 (49)	Reference
Female	65 (51)	0.492
History of diabetes, n (%)	31 (24)	0.502
History of smoking, n (%)	35 (28)	0.296
Family history of cancer, n (%)		
Any cancer	78 (67)	0.553
Pancreatic cancer	15 (12)	0.949
Neoadjuvant therapy, n (%)	22 (17)	0.847
Adjuvant therapy, n (%)	99 (80)	0.080 *
Hazard ratio	0.633	
95% CI	0.40–0.99	
Multivariable p value	0.047 *	
Operative procedure, n (%)		
Pancreaticoduodenectomy	115 (91)	Reference
Distal pancreatectomy	12 (9)	0.684
Positive nodal metastases, n (%)	90 (71)	0.236
Grade, n (%)		
1	7 (6)	Reference
2	61 (48)	0.936
3	57 (45)	0.688
T-stage, n (%)		
T1	10 (7)	Reference
T2	36 (28)	0.984
T3	79 (63)	0.531
T4	2 (2)	0.549

Clinical characteristic	Cohort(n = 127)	Univariable p Value
Perivascular invasion, n (%)		
No	55 (43)	Reference
Yes	62 (49)	0.429
Perineural invasion, n (%)		
No	18 (14)	Reference
Yes	109 (86)	0.975
Resection margin, n (%)		
R0	92 (72)	Reference
R1	35 (28)	0.132

*Statistically significant.

eTable 1.

Mutation Detail of BRCA-Mutated Patients

Patient#	Age, y	Gene	Chromosome position	Amino acid change	Nucleotide change	Function
1	66	BRCA2	13:32911298–9	p.K936Kfs	c.2808_2811delACAA	Frameshift*
2	60	BRCA2	13:32911298–9	p.K936Kfs	c.2808_2811delACAA	Frameshift*
3	83	BRCA2	13:32911419	p.S976Sfs	c.2928delC	Frameshift*
4	63	BRCA2	13:32914401	p.S1970X	c.5909C>AC	Nonsense*
5	62	BRCA2	13:32914438	p.S1982Rfs	c.5946delT	Frameshift*
6	61	BRCA2	13:32914438	p.S1982Rfs	c.5946delT	Frameshift*
7	57	BRCA2	13:32914438	p.S1982Rfs	c.5946delT	Frameshift*
8	60	BRCA2	13:32914438	p.S1982Rfs	c.5946delT	Frameshift*
9	59	BRCA2	13:32932067	Splice	c.7805+1G>A	Noncoding*
10	65	BRCA2	13:32972626	p.K3326X	c.9976A>T	Nonsense*
11	65	BRCA2	13:32972626	p.K3326X	c.9976A>T	Nonsense*
12	76	BRCA2	13:32893421	p.Q92R	c.275A>G	Missense†
13	68	BRCA2	13:32912190	p.A1233V	c.3698C>T	Missense†
14	58	BRCA2	13:32911703	p.H1071Y	c.3211C>T	Missense†
15	66	BRCA2	13:32911794	p.H1101R	c.3302A>G	Missense†
16	54	BRCA2	13:32912586	p.C1365Y	c.4094G>A	Missense†
17	56	BRCA2	13:32915133	p.T2214I	c.6641C>T	Missense†
18	49	BRCA2	13:32931943	p.Q2561R	c.7682A>G	Missense†
19	50	BRCA1	17:41243887	p.E1221X	c.3661C>A	Nonsense*
20	58	BRCA1	17:41276034	fs	c.70_80delCAGATGGGACA	Frameshift*
21	61	BRCA1	17:41245975	p.V525I	c.1573C>T	Missense†
22	57	BRCA1	17:41245975	p.V525I	c.1573C>T	Missense†

*Known pathogenic variant.

†Variant with unknown significance (VUS).