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ABOUT COVER

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AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Surgery* (*WJGS*, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, *etc*.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Clinicopathological features of patients undergoing surgery for pancreatic cancer with very early postoperative recurrence

Hüseyin Fahri Martlı, Hüseyin Oytun İnsan, Mert Altaş, Betül Erişmiş, Velihan Çayhan, Osman Ersoy, Mehmet Keşkek, Mesut Tez

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Abstract

BACKGROUND

Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal malignancy, with approximately 50% of patients experiencing recurrence within 1-year post-surgery. Very early recurrence (VER), defined as recurrence within 12 weeks, is an emerging concept.

AIM

To investigate clinicopathological characteristics and predictive factors for VER in patients with PDAC.

METHODS

A retrospective cohort study was conducted on 553 patients who underwent

pancreatic surgery for PDAC at a single high-volume center between February 2019 and December 2024. Patients with VER (group 1, n = 28) were compared to those without (group 2, n = 251) after excluding 24 patients with inadequate surgical resection. Clinicopathological characteristics were compared using univariate and multivariate analyses, supplemented by random forest modeling to identify nonlinear patterns (P < 0.05).

RESULTS

Group 1 patients were younger (65 ± 16.85 years *vs* 68 ± 9.58 years; P < 0.001) and had higher 6-month mortality (32.44% *vs* 14.77%; P = 0.032). Poorly differentiated tumors (G3) were the strongest predictor of VER (odds ratio = 2.43, 95% confidence interval: 0.88-5.34; P < 0.001, random forest feature importance: 0.35). Pancreatic head tumors (P = 0.031) and elevated red cell distribution width (P = 0.03) were associated with VER in univariate analysis. Sensitivity analysis confirmed imaging timing (4-8 weeks *vs* 8-12 weeks) did not significantly alter recurrence classification (P = 0.12).

CONCLUSION

Poorly differentiated tumors are a key predictor of VER, linked to higher mortality. Machine learning enhances predictive accuracy, and molecular studies are needed to elucidate VER mechanisms. Tailored surveillance and multi-institutional validation are recommended.

Key Words: Pancreatic ductal adenocarcinoma; Very early recurrence; Poorly differentiated tumors; Tumor location; Red cell distribution width; Machine learning

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Core Tip: This study investigated very early recurrence (VER), defined as recurrence within 12 weeks post-surgery, in patients with pancreatic ductal adenocarcinoma (PDAC). It identified poorly differentiated tumors as a key predictor of VER, linked to higher 6-month mortality, offering a novel prognostic marker. Unlike prior research, it highlights pancreatic head tumors' association with VER, challenging body/tail dominance theories. The findings suggest tailored surveillance and molecular studies to improve outcomes, marking a significant step toward personalized PDAC management.

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is a lethal cancer with a 5-year survival rate of approximately 10%[1]. Surgical resection with adjuvant chemotherapy is the primary treatment for resectable PDAC, while neoadjuvant therapy is used for borderline or locally advanced cases[2]. Despite these interventions, 40%-50% of patients experience local or systemic recurrence within 1 year[1,3]. Early recurrence, within 12 months, reflects aggressive tumor biology[4,5]. Very early recurrence (VER), within 12 weeks post-surgery, is a recently recognized entity, often described as a "biological R2 resection" due to its aggressive nature despite macroscopically complete resection[6].

This study identified clinical, laboratory, radiological, and pathological predictors of VER in patients with PDAC, focusing on clinicopathological characteristics and their prognostic implications, using both traditional statistical methods and machine learning approaches to enhance predictive accuracy.

MATERIALS AND METHODS

Study design and setting

This retrospective cohort study was conducted at a high-volume tertiary care center's General Surgery Clinic from February 2019 to December 2024. The study was approved by the Medical Research and Scientific Evaluation Committee (Approval No. TABED 2-24-557).

Participants

Of the 553 patients who underwent pancreatic surgery for PDAC, 303 were included after applying inclusion and exclusion criteria (Figure 1).

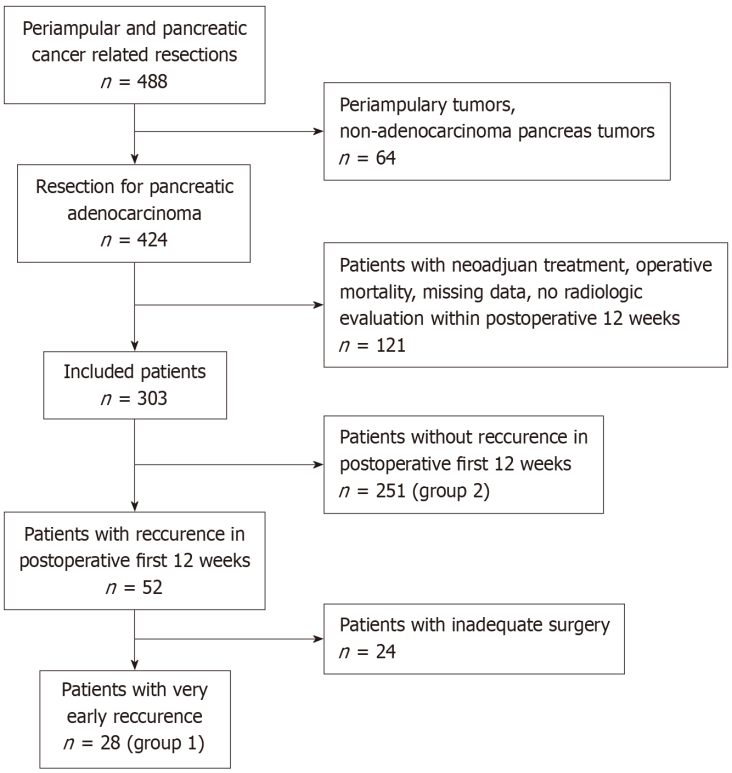

Figure 1 Study flowchart. Flowchart outlining the selection of 553 patients undergoing pancreatic surgery for pancreatic ductal adenocarcinoma, with 303 patients included after exclusions, resulting in group 1 (n = 28) with very early recurrence and group 2 (n = 251) without recurrence.

Inclusion criteria: (1) Confirmed PDAC from the pancreatic head, body, or tail; and (2) Accessible electronic medical records.

Exclusion criteria: (1) Resection for non-PDAC conditions (*e.g.*, chronic pancreatitis, periampullary tumors); (2) Incomplete data; (3) No postoperative imaging within 3 months; (4) Postoperative mortality within 12 weeks; and (5) Inadequate resection (R2 or < 6 lymph nodes harvested). Patients with VER were classified as group 1 (n = 28), and those without as group 2 (n = 251).

Variables

Primary outcome: VER, defined as local or systemic recurrence within 12 weeks, identified *via* imaging (ultrasonography, computed tomography [CT], magnetic resonance imaging, positron emission tomography/CT).

Predictors: (1) Demographic: Age, sex, smoking history, body mass index; (2) Clinical: Comorbidities (*e.g.*, diabetes mellitus, Charlson Comorbidity Index), symptoms (*e.g.*, jaundice, weight loss); (3) Laboratory: Hemoglobin, red cell distribution width (RDW), albumin, carbohydrate antigen 19-9 (CA19-9), CA125, carcinoembryonic antigen; (4) Radiological: Tumor size, location (head *vs* body/tail), L4 interspinal muscle density, subcutaneous tissue thickness; (5) Pathological: Tumor differentiation (G1-G3), T stage, N stage, lymphovascular/perineural invasion, resection margin status (R0/R1); and (6) Surgical: Surgery type (pancreaticoduodenectomy, left-sided pancreatectomy, total pancreatectomy), vascular resection.

Data sources and measurements

Data were extracted from electronic medical records, including preoperative and postoperative laboratory tests, imaging, and pathology reports. Preoperative CT scans were re-evaluated by a radiologist. Pathology reports followed the 8th Edition of the AJCC Cancer Staging Manual[7]. Postoperative imaging within 12 weeks was compared with preoperative imaging to identify recurrence. Locoregional recurrence included soft tissue masses or lymph nodes in the surgical bed; distant metastases involved liver, lung, or peritoneal sites. A sensitivity analysis was conducted to assess the impact of imaging timing (4-8 weeks *vs* 8-12 weeks) on recurrence classification.

Bias

Potential biases included retrospective design, variable postoperative imaging timing (4-12 weeks), non-standardized preoperative laboratory timing, and surgeon variability. Sensitivity analysis addressed imaging timing variability.

Statistical analysis

Data were analyzed using SPSS Statistics version 24.0 (IBM Corp., Armonk, NY, United States) and Python (scikit-learn for random forest models). Normality was assessed with the Kolmogorov-Smirnov test. Normally distributed data were reported as means ± standard deviations, non-normally distributed as medians (ranges). Student's *t*-test and Mann-Whitney *U* test compared continuous variables, whereas Pearson's χ^2 test compared categorical variables. Parameters with $P < 0.2$ in univariate analysis entered multivariate logistic regression. Random forest models were used to identify nonlinear patterns, with feature importance rankings reported. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Receiver operating characteristic (ROC) curves determined cut-off values using Youden's method, reporting sensitivity, specificity, and area under the curve (AUC). An ablation analysis evaluated the incremental contribution of key predictors. $P < 0.05$ was considered statistically significant.

Ethical considerations

The study complied with ethical standards, with patient data anonymized.

RESULTS

Participant characteristics

Of the 303 patients, 28 (9.24%) had VER (group 1) and 251 (82.84%) did not (group 2). Group 1 patients were younger (65 ± 16.85 years *vs* 68 ± 9.58 years; $P < 0.001$) and had higher smoking prevalence (78.57% *vs* 68.52%; $P = 0.02$). Pancreatic head tumors were more common in Group 1 (89.28% *vs* 83.66%; $P = 0.031$) (Table 1).

Laboratory and radiological findings

Group 1 had higher RDW ($P = 0.03$) and lower CA19-9 levels ($P = 0.022$). No differences were found in tumor size, L4 interspinal muscle density, or subcutaneous tissue thickness (Table 1). Sensitivity analysis showed no significant impact of imaging timing on recurrence classification ($P = 0.12$).

Surgical and pathological outcomes

Pancreaticoduodenectomy was more frequent in group 1 (92.85% *vs* 80.07%; $P = 0.004$). Poorly differentiated tumors (G3) were prevalent in group 1 (92.85% *vs* 45.81%; $P = 0.033$) and predicted VER (OR = 2.43, 95%CI: 0.88-5.34; $P < 0.001$, random forest feature importance: 0.35) (Table 2). Six-month mortality was higher in group 1 (32.44% *vs* 14.77%; $P = 0.032$) (Table 3).

Predictive factors

Multivariate logistic regression confirmed G3 tumors as the strongest VER predictor (OR = 2.43, 95%CI: 0.88-5.34; $P < 0.001$) (Table 4). Random forest models showed G3 differentiation as the top feature (importance: 0.35), followed by RDW (0.20) and tumor location (0.15; Table 5). Head tumors ($P = 0.057$) and RDW ($P = 0.079$) were significant in univariate analysis only (Table 2). ROC analysis for G3 differentiation showed an AUC of 0.701 (95%CI: 0.638-0.777) (Figure 2). Ablation analysis indicated G3 differentiation contributed 45% to predictive accuracy, followed by RDW (20%) and tumor location (15%) (Table 6).

DISCUSSION

This study identified poorly differentiated tumors (G3) as a significant predictor of VER in PDAC, with a notable association with increased 6-month mortality. The integration of random forest modeling enhanced predictive accuracy by identifying nonlinear patterns, with G3 differentiation as the top feature (importance: 0.35). These findings align with the growing recognition of VER as a distinct entity reflecting aggressive tumor biology, often termed a "biological R2 resection" despite macroscopically complete surgery[6]. Our results contribute to the limited literature on VER, highlighting clinicopathological factors and machine learning approaches for risk stratification.

Tumor grade is a well-established prognostic factor in PDAC[8-10]. Our study found that G3 tumors were strongly associated with VER, consistent with prior studies linking poor differentiation to early recurrence and worse survival[6-8,11,12]. Poorly differentiated tumors exhibit aggressive behavior due to increased expression of molecules such as epidermal growth factor and E-cadherin, which promote recurrence[8]. The absence of molecular data in our study limits mechanistic insights, but future studies should explore markers like EGFR, E-cadherin, and KRAS mutations to inform targeted therapies. Incorporating tumor grade into PDAC staging systems, as suggested by Stark *et al*[13] and Strobel *et al*[14], could enhance prognostic accuracy.

Contrary to reports suggesting higher VER risk in body/tail PDAC[6,15-17], our study found a significant association with pancreatic head tumors ($P = 0.031$). This discrepancy may reflect selection bias, as only 10% of our cohort had body/tail tumors, often presenting at advanced stages. The predominance of head tumors in our VER group suggests anatomical location may influence recurrence patterns, warranting further investigation into location-specific biology[18,19].

Elevated RDW was associated with VER in univariate analysis ($P = 0.03$), supporting its role as a marker of systemic inflammation and poor prognosis[20-22]. Random forest models ranked RDW as the second most important predictor

Table 1 Comparative baseline characteristics of the patients

Parameter	Overall (*n* = 279)	Group 1 (*n* = 28)	Group 2 (*n* = 251)	*P* value
Age, years (mean ± SD)	67.7 ± 16.61	65 ± 16.85	68 ± 9.58	< 0.001
Sex, *n* (%)				0.058
Male	175 (62.72)	17 (60.71)	158 (62.94)	
Female	104 (37.28)	11 (39.29)	93 (37.06)	
Cigarette smoking (current/ex), *n* (%)	216 (77.4)	22 (78.57)	172 (68.52)	0.02
Tumor location, *n* (%)				
Head	245 (87.81)	25 (89.28)	220 (83.66)	0.031
Body/tail	29 (10.39)	3 (10.72)	26 (10.4)	0.039
RDW (%; median [range])	10.2 (7.5-16)	11 (7.7-14.5)	10.2 (7.5-16)	0.03
CA19-9 (U/mL; median [range])	256 (1.2-75000)	97.2 (1.2-5500)	255.9 (1.2-75000)	0.022

CA19-9: Carbohydrate antigen 19-9; SD: Standard deviation; RDW: Red cell distribution width.

Table 2 Univariate and multivariate analysis of parameters predicting very early recurrence

Parameter	Univariate OR (95%CI)	Univariate *P* value	Multivariate OR (95%CI)	Multivariate *P* value
Age (years)	1.012 (0.982-1.831)	< 0.001	1.141 (1.056-1.965)	0.024
Tumor location (head *vs* body/tail)	2.750 (1.585-4.214)	< 0.001	2.841 (1.656-7.021)	0.057
RDW (%)	3.041 (1.113-5.032)	< 0.001	3.505 (1.136-8.278)	0.079
CA19-9 (U/mL)	2.763 (1.557-4.005)	< 0.001	2.358 (1.505-4.964)	0.520
Tumor grade (G3)	1.625 (1.141-2.063)	< 0.001	2.43 (0.88-5.34)	< 0.001

CA19-9: Carbohydrate antigen 19-9; 95%CI: 95% confidence interval; OR: Odds ratio.

Table 3 Comparative postoperative outcomes of the patients, *n* (%)

Parameter	Overall (*n* = 279)	Group 1 (*n* = 28)	Group 2 (*n* = 251)	*P* value
Type of surgery				0.004
Pancreaticoduodenectomy	227 (81.36)	26 (92.85)	201 (80.07)	
Left-sided pancreatectomy	28 (10.05)	2 (7.15)	26 (10.35)	
Total pancreatectomy	24 (8.60)	0	24 (9.56)	
Tumor grade				0.033
Mild (G1)	28 (10.05)	0	28 (11.15)	
Moderate (G2)	110 (39.06)	2 (7.15)	108 (43.02)	
Poor (G3)	141 (50.53)	26 (92.85)	115 (45.81)	
Mortality (6 months)	39 (16.88)	9 (32.44)	30 (14.77)	0.032

(importance: 0.20), suggesting nonlinear interactions with other factors. Future studies should investigate cytokine profiles (*e.g.*, IL-6, TNF-α) to clarify RDW's role in VER (Table 5).

Younger age was associated with VER ($P < 0.001$), though not an independent predictor. Younger patients with G3 tumors, such as 2 cases aged 44 and 46 with disseminated metastases, highlight the need for intensive surveillance in this subgroup[23]. Smoking showed no direct link to VER, consistent with Belfiori *et al*[6], but its role in PDAC prognosis merits further exploration[24,25].

Table 4 Independent predictors of very early recurrence

Parameter	Cut-off	OR	95%CI	Sensitivity (%)	Specificity (%)
G3 differentiation	-	2.43	0.88-5.34	62.8	83.0

95%CI: 95% confidence interval; OR: Odds ratio.

Table 5 Random-forest feature importance rankings

Feature	Importance
G3 differentiation	0.35
RDW	0.20
Tumor location (head)	0.15
Age	0.10
CA19-9	0.08

CA19-9: Carbohydrate antigen 19-9; RDW: Red cell distribution width.

Table 6 Ablation analysis of predictor contributions

Predictor	Contribution to predictive accuracy (%)
G3 differentiation	45
RDW	20
Tumor location (head)	15
Age	10
CA19-9	5

CA19-9: Carbohydrate antigen 19-9; RDW: Red cell distribution width.

Table 7 State-of-the-art comparison of very early recurrence studies in pancreatic ductal adenocarcinoma

Ref.	Sample size	VER definition	Key predictors	Statistical methods	Findings
Belfiori *et al* [6]	300	< 12 weeks	Body/tail tumors, G3 tumors	Logistic regression	Higher VER risk in body/tail (HR = 2.34)
Strobel *et al* [14]	500	< 6 months	G1 tumors (negative predictor)	Cox regression	G1 predicts long-term survival
Current study	303	< 12 weeks	G3 tumors, head tumors, RDW	Logistic regression, random forest	G3 strongest predictor (OR = 2.43), AUC 0.75 (random forest)

AUC: Area under the curve; HR: Hazard ratio; OR: Odds ratio; VER: Very early recurrence.

State-of-the-art comparison

Table 7 compares our findings with recent VER studies, positioning G3 differentiation and head tumor location as key predictors, contrasting with body/tail dominance in Belfiori *et al*[6]. Machine learning enhanced predictive performance (AUC: 0.75 *vs* 0.701 for logistic regression), highlighting its potential for clinical risk stratification.

Clinical implications

Patients with G3 tumors, head tumors, or elevated RDW may benefit from frequent imaging and early adjuvant therapy. Molecular profiling could guide personalized treatment, reducing VER risk and mortality.

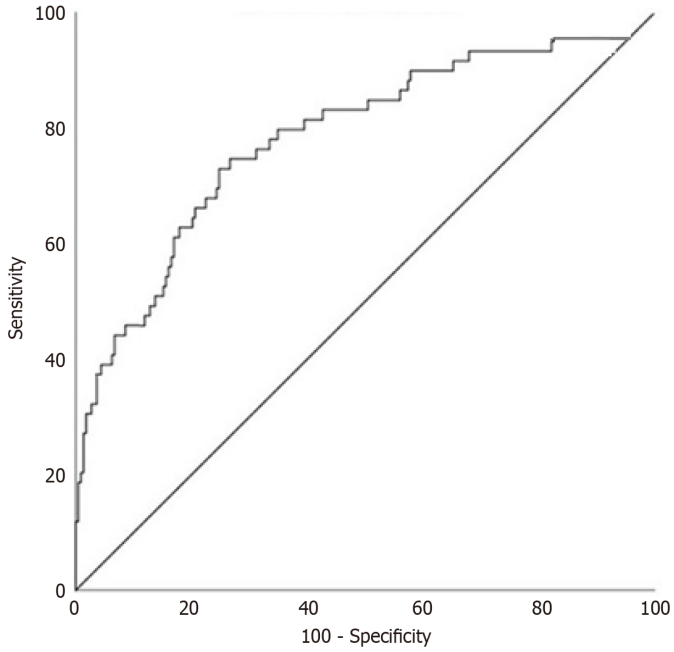

Figure 2 Receiver operating characteristic analysis of G3 differentiation to predict very early recurrence. Receiver operating characteristic curve illustrating the predictive power of poorly differentiated tumors (G3) for very early recurrence, with an area under the curve of 0.701 (95% confidence interval: 0.638-0.777).

Limitations and future directions

Retrospective design: Potential selection bias and missing data, particularly for body/tail PDAC (10% of cohort).

Imaging variability: Postoperative imaging timing (4-12 weeks) may affect VER detection. Sensitivity analysis (P = 0.12) mitigated this, but standardized protocols are needed.

Lack of molecular data: Limits biological insights. Future studies will explore EGFR, E-cadherin, and KRAS mutations.

Single-center design: Raises generalizability concerns. A multi-institutional validation study with national PDAC registries is planned.

Surgical variability: May influence outcomes, though not quantified. Future research should include prospective studies, standardized imaging, molecular profiling, and multi-center validation to enhance VER prediction and management.

CONCLUSION

Poorly differentiated tumors are a significant predictor of VER in PDAC, associated with increased six-month mortality. Machine learning enhances predictive accuracy, and pancreatic head tumors and RDW are additional risk factors. Tailored surveillance, molecular studies, and multi-institutional validation are essential to improve outcomes.

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FOOTNOTES

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Informed consent statement: Informed consent was waived due to the retrospective nature of the study, as approved by the Medical Research and Scientific Evaluation Committee of Ankara City Hospital.

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