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Prognostic Value of Homologous Recombination Deficiency Identified by Comprehensive Genomic Profiling in Incurable Pancreatic Cancer

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ABSTRACT

Comprehensive genomic profiling (CGP) has been reimbursed by Japan's national health insurance since 2018, yet its practical benefits for patients remain uncertain. To better understand its clinical relevance, we analyzed data from 115 individuals with incurable pancreatic cancer (IPC) who underwent CGP at a Japanese cancer referral hospital between November 2019 and August 2021. Our assessment focused on genomic findings, treatments informed by CGP, and patient survival outcomes. High tumor mutation burden or microsatellite instability (TMB-H/MSI-H) was identified in 6.9% of cases. Mutations in KRAS, TP53, CDKN2A, and SMAD4 were observed in 93.0%, 83.0%, 53.0%, and 25.2% of patients, respectively. Additionally, 21.7% of patients harbored alterations associated with homologous recombination deficiency (HRD). Among those with TMB-H or MSI-H, four patients received pembrolizumab, and two participated in clinical trials. Clinical characteristics did not differ meaningfully between the HRD-mutated and non-mutated groups. Notably, individuals with HRD-related mutations demonstrated significantly longer overall survival (median 749 days) compared with those without such mutations (median 519 days; $p = 0.047$). Multivariate analysis confirmed HRD-associated alterations as an independent predictor of improved survival. These findings suggest that CGP may offer prognostic insight in IPC, particularly through the detection of HRD-related gene changes, while also supporting the identification of potential therapeutic opportunities.

Keywords: Pancreatic cancer, Comprehensive genomic profiling tests, Homologous recombination deficiency

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Introduction

Pancreatic cancer remains one of the most lethal malignancies, with a 5-year survival rate below 10% [1]. Surgical resection offers the only chance for cure; however, early detection is exceedingly difficult [2, 3]. As a result, nearly 80% of patients present with disease that is no longer operable due to extensive local invasion or distant metastasis [4]. Although pembrolizumab has recently been recommended for tumors demonstrating microsatellite instability-high (MSI-H) or high tumor mutational burden (TMB-H), such biomarker-defined cases are rare [5, 6]. Thus, systemic chemotherapy continues to be the primary treatment approach for advanced disease, aiming to extend survival, though the benefit remains limited. Expanding therapeutic options is therefore an urgent need.

Advances in cancer treatment have increasingly centered on exploiting specific genomic alterations. Historically, techniques such as Sanger sequencing, fluorescence in situ hybridization, quantitative RT-PCR, immunohistochemistry, and copy-number microarray analysis were employed to detect pathological genetic changes [7]. The emergence of next-generation sequencing (NGS) has transformed this landscape by allowing large-scale genomic interrogation that is rapid, cost-efficient, and capable of analyzing multiple cancer-associated genes in a single assay, replacing traditional single-gene testing strategies [8]. Genomic instability underlies tumor development in pancreatic ductal adenocarcinoma (PDAC), and is generally classified as either chromosomal

instability or microsatellite instability [9]. In PDAC, chromosomal instability is the predominant driver, as MSI-H tumors account for only around 2.5% of cases [10]. Frequently altered genes include KRAS, TP53, CDKN2A (p16), and SMAD4 (DPC4), whereas mutations in genes such as BRCA2 or ERBB2 occur at much lower frequencies [11]. Rare mutations in genes involved in homologous recombination repair—such as BRCA1/2, ATM, and PALB2—contribute to the considerable genomic diversity observed among PDAC tumors.

Defects in homologous recombination repair (HRD) are clinically relevant, particularly in the context of platinum-based chemotherapy [12, 13]. The FOLFIRINOX regimen has demonstrated superior overall survival compared with gemcitabine in metastatic pancreatic cancer [14], and modified FOLFIRINOX has emerged as a potential option after failure of gemcitabine plus nab-paclitaxel (GnP) [15]. Conversely, in patients previously treated with GnP followed by 5-fluorouracil/L-leucovorin plus nanoliposomal irinotecan, the benefit of FOLFOX appears restricted to those with HRD-associated gene alterations [16]. Therefore, identifying HRD-related mutations may help guide therapeutic decisions. As sequencing technologies continue to advance, comprehensive genomic profiling (CGP) has become increasingly integrated into routine care, permitting broad assessment of HRD-related genes alongside numerous other cancer-related alterations and MSI status.

In Japan, insurance coverage for cancer genomic medicine was introduced in June 2019 [17]. Two tissue-based CGP assays—the OncoGuide NCC Oncopanel System and the FoundationOne CDx Cancer Genome Profile—are now widely accessible under the national health insurance program [17, 18]. However, challenges remain, particularly for patients with advanced pancreatic cancer who have limited survival and restricted access to targeted therapies. The clinical impact of CGP testing in this population is not yet fully established. In this study, we examined CGP results and treatment outcomes in patients with incurable pancreatic cancer (IPC) at our institution to assess the real-world value of CGP testing.

Materials and Methods

Study design, patients, and data collection

An overview of the study design is presented in **Figure 1**. We conducted a retrospective analysis of 115 patients with incurable pancreatic cancer who underwent CGP testing at the Osaka International Cancer Institute, a major cancer referral center in Japan, between November 2019 and March 2021. All included patients had histologically confirmed adenocarcinoma. Clinical information for each case was retrieved from electronic medical records. Patient follow-up was censored on 28 February 2022. Data collection and analysis focused on three principal components.

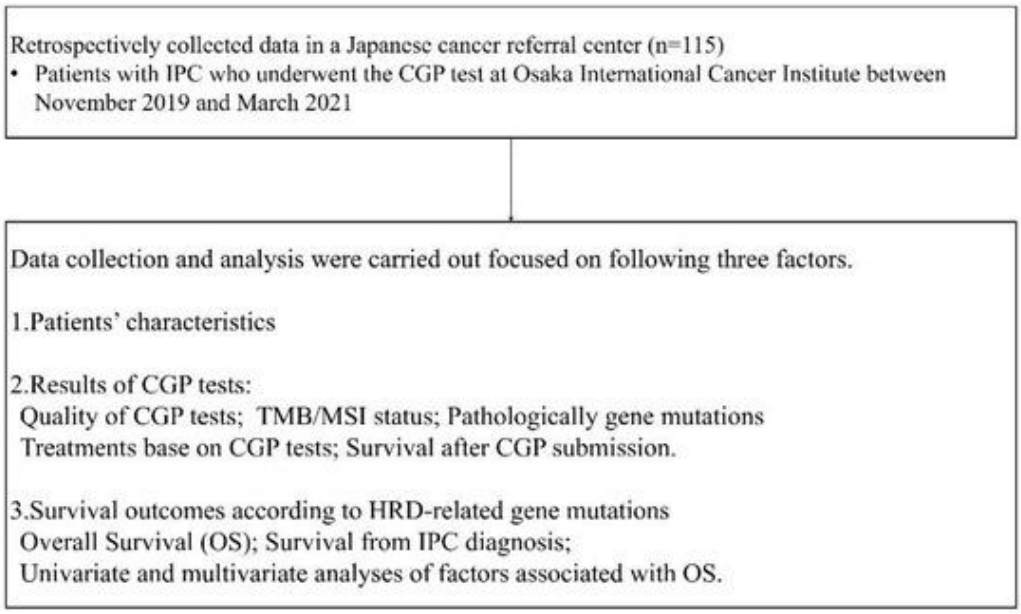

Figure 1. Study design. IPC, incurable pancreatic cancer; CGP, comprehensive genomic profiling; TMB, tumor mutation burden; MSI, microsatellite instability; HRD, homologous recombination deficiency.

Patient characteristics

We gathered a broad set of clinical details for each participant, including demographic information (age and sex), Eastern Cooperative Oncology Group (ECOG) performance status, and the extent of tumor resectability at the time treatment began. Laboratory values such as white blood cell count, hemoglobin, platelets, albumin, and CA19-9 levels were also recorded, along with the specific therapeutic regimens used and their outcomes. Resectability status was assigned based on the National Comprehensive Cancer Network (NCCN) guidelines [19] and categorized as resectable (R), borderline resectable (BR), locally advanced and unresectable (UR-LA), or metastatic and unresectable (UR-M). Patients who initially fell into the R or BR groups underwent CGP only after their cancer was deemed incurable or after postoperative recurrence occurred.

Results of comprehensive genomic profiling

Two nationally insured CGP assays—the OncoGuide™ NCC Oncopanel System and the FoundationOne CDx—were employed in this study. The choice of panel was left to the treating physician and the patient. All tests were conducted using FFPE tissue samples judged suitable for analysis by both clinicians and pathologists. Tissue acquisition methods (e.g., EUS-FNA, needle biopsy, or surgery) were selected according to clinical necessity.

After sequencing, every case was evaluated by a hospital molecular tumor board composed of multiple specialists, including clinicians, pathologists, genetic experts, bioinformaticians, and genetic counselors [20]. This group reassessed the reported variants and determined their pathological and clinical relevance. Because FoundationOne CDx—used in the majority of cases (80.9%)—profiles only tumor-derived DNA, the resulting variants may represent either somatic or germline alterations. Since the testing system cannot routinely distinguish between the two, we classified all clinically meaningful changes as pathogenic tumor mutations.

For the purposes of this study, HRD-associated genes were defined using a previously established list of 17 homologous recombination repair genes: ATM, BAP1, BARD1, BLM, BRCA1, BRCA2, BRIP1, CHEK2, FAM175A, FANCA, FANCC, NBN, PALB2, RAD50, RAD51, RAD51C, and RTEL1 [21]. From the finalized CGP reports, we extracted test quality indicators, MSI/TMB status, the total number of pathogenic alterations, mutation frequencies in key pancreatic cancer genes (KRAS, TP53, CDKN2A, SMAD4), and the presence of HRD-related variants. Treatment actions taken as a consequence of CGP findings were also documented. Survival following CGP submission was defined as the interval between the date the test was submitted and the date of death.

Survival analysis based on HRD status

We assessed two major survival endpoints: overall survival (OS) and survival measured from the point at which pancreatic cancer was designated incurable. OS was calculated beginning from one of the following: the start of first-line chemotherapy for UR-LA or UR-M disease, the date of upfront surgery in the single resectable case, or the start of neoadjuvant therapy for remaining R or BR patients. Survival from IPC diagnosis began at the time the disease was determined to be incurable or when postoperative recurrence was confirmed. We also evaluated factors influencing OS.

The study was approved by the institutional ethics committee (Protocol 20148-3) and complied with the Declaration of Helsinki. Informed consent was waived using an opt-out procedure available via the hospital's website.

Statistical analysis

Categorical variables were summarized as percentages, while continuous values were expressed as medians with ranges. Comparisons between the HRD-positive and HRD-negative groups were conducted using Fisher's exact test or the Yates-corrected chi-square test for categorical variables and the Mann-Whitney U test for continuous variables. Survival curves for OS, IPC-related survival, and post-CGP survival were generated using Kaplan–Meier methods and compared with the log-rank test. To identify prognostic variables, univariate and multivariate Cox proportional hazards models were applied. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were computed, and variables with $p < 0.05$ in univariate testing were entered into multivariate analysis. A significance threshold of $p < 0.05$ was used throughout. All analyses were conducted using JMP version 14.0 (SAS Institute, Cary, NC, USA).

Results and Discussion

Characteristics of CGP testing

A summary of patient characteristics appears in **Table 1**. The cohort had a median age of 63 years (range 37–80), and men represented 54.8% of the participants. More than half of the patients (56.5%) had metastatic, unresectable disease at the time treatment commenced. CGP testing took place during first-line therapy in 26.1% of patients, after progression on first-line therapy in 51.3%, and after progression on second-line or later treatment in 22.6%. Most CGP samples originated from pancreatic tissue (44.4%) or liver lesions (39.1%). EUS-FNA or percutaneous biopsy samples were used for 83.5% of patients, while surgical tissue samples contributed to 20.9%. FoundationOne CDx accounted for the majority of assays (80.9%), with the remaining 19.1% performed using the NCC Oncopanel.

Table 1. Patient characteristics of patients with incurable pancreatic cancer who underwent comprehensive genomic profiling (CGP) tests.

Number of patients, n	115
Median age (range), y.o	63 (37–80)
Sex	
Male, n (%)	63 (54.8)
Female, n (%)	52 (45.2)
Diagnosis at the start of treatment	
R or BR, n (%)	26 (22.6)
UR-LA, n (%)	24 (20.9)
UR-M, n (%)	65 (56.5)
Timing of submitting cancer gene panel tests	
During 1st-line treatment, n (%)	30 (26.1)
After disease progression of 1st-line treatment, n (%)	59 (51.3)
After disease progression of 2nd-line treatment, n (%)	26 (22.6)
Samples for CGP tests	
Pancreas, n (%)	51 (44.4)
Liver, n (%)	45 (39.1)
Lymph node, n (%)	7 (6.1)
Gastrointestinal tract, n (%)	5 (4.3)
Lung, n (%)	4 (3.5)
Peritoneum, n (%)	3 (2.6)
Sampling methods	
EUS-FNA, n (%)	44 (38.3)
Percutaneous needle biopsy, n (%)	42 (36.5)
Surgery, n (%)	24 (20.9)
Forceps biopsy, n (%)	5 (4.3)
Kinds of cancer gene panel tests	
FoundationOne CDx, n (%)	93 (80.9)
NCC Oncopanel, n (%)	22 (19.1)

R, resectable; BR, borderline resectable; UR-LA, unresectable-locally advanced; UR-M, unresectable-metastatic; EUS-FNA, endoscopic ultrasound-guided fine-needle aspiration.

Results of CGP testing

Table 2 outlines the findings from the CGP analyses. Most tissue specimens—98 cases (85.2%)—met the quality requirements for either the FoundationOne CDx or the NCC Oncopanel platforms. The remaining 17 samples (14.8%) were labeled as "qualified," indicating reduced sensitivity for detecting TMB, MSI, gene mutations, or copy-number alterations.

A total of eight patients (6.9%) showed high tumor mutation burden and/or high microsatellite instability. The expert panel identified a median of four pathogenic alterations per patient (range 1–10). The most frequently altered genes were KRAS in 107 patients (93.0%), TP53 in 96 (83.0%), CDKN2A in 61 (53.0%), and SMAD4 in 29 (25.2%).

HRD-associated mutations were observed in 25 patients (21.7%). These included variants in BRCA1/2 (11 patients, 9.6%), ATM (4 patients, 3.5%), RAD51C (3 patients, 2.6%), PALB2 (2 patients, 1.7%), and several less common HRD-related genes (5 patients, 4.3%).

Only six individuals (5.2%) ultimately received a matched therapy informed by the CGP results. Four patients with TMB-H/MSI-H tumors (3.5%) were treated with pembrolizumab, while two patients (1.7%) enrolled in clinical trials targeting their specific alterations—one receiving a KRAS G12C inhibitor and another an ROS1 inhibitor.

Across the cohort, the median survival from CGP test submission was 182 days (95% CI: 150–227). Sixteen patients (13.9%) died within 90 days.

Table 2. The results of comprehensive genomic profiling (CGP) tests.

Quality control	
Pass/met the criteria, n (%)	98 (85.2)
Qualified, n (%)	17 (14.8)
TMB-H or MSI-H, n (%)	8 (6.9)
Pathological gene mutations (range), n	4 (1–10)
KRAS mutations, n (%)	107 (93.0)
TP53 mutations, n (%)	96 (83.0)
CDKN2A mutations, n (%)	61 (53.0)
SMAD4 mutations, n (%)	29 (45.2)
HRD-related genes mutations, n (%)	25 (21.7)
BRCA1/2 mutations, n (%)	11 (9.6)
ATM mutations, n (%)	4 (3.5)
RAD51C mutations, n (%)	3 (2.6)
FANCA mutations, n (%)	2 (1.7)
Others mutations, n (%)	5 (4.3)
Administration of pembrolizumab, n (%)	4 (3.5)
Clinical Trial Participation, n (%)	2 (1.7)

TMB-H, tumor mutation burden-high; MSI-H, microsatellite instability-high; HRD, homologous recombination deficiency.

Survival outcomes according to HRD-related gene mutations

We next assessed the clinical relevance of HRD-associated gene alterations. **Table 3** presents the baseline characteristics of patients stratified by the presence or absence of HRD-related mutations. Median age did not differ meaningfully between the groups (61 years, range 38–78, in the HRD-positive group vs. 65 years, range 37–80, in the HRD-negative group; p = 0.585).

No statistically significant differences were observed between the groups with respect to sex distribution, disease resectability at treatment initiation, the occurrence of TMB-H or MSI-H tumors, performance status, prior curative surgery, or laboratory markers including WBC, hemoglobin, platelet count, albumin, and CA19-9.

Although not significant, a greater proportion of HRD-positive patients received platinum-based chemotherapy (84.0%) compared with HRD-negative patients (66.7%) (p = 0.136).

Overall, patient demographics and treatment patterns were comparable between individuals with and without HRD-related mutations.

Table 3. Comparison of patient characteristics between the patients who had homologous recombination deficiency (HRD)-related genetic mutations (HRD (+)) and those who did not (HRD (−)).

	HRD (+)	**HRD (−)**	**p-Value**
Number of patients, n	25	90	
Median age (range), y.o.	61 (38–78)	64 (37–80)	0.585 †
Sex			0.822 §
Male, n (%)	13 (52.0)	50 (55.6)	
Female, n (%)	12 (48.0)	40 (44.4)	
Operability at the time of diagnosis			
R or BR, n (%)	5 (20.0)	22 (24.4)	0.658 §
UR-LA, n (%)	6 (42.0)	18 (20.0)	
UR-M, n (%)	14 (56.0)	50 (55.6)	

TMB-H or MSI-H, n (%)	1 (4.0)	7 (7.8)	1.000 §
Performance status			0.691 §
0	16 (64.0)	60 (66.7)	
1-	5 (20.0)	21 (23.3)	
NA	4 (16.0)	9 (10.0)	
Platinum-based regimen, n (%)	21 (84.0)	60 (66.7)	0.136 §
Curative resection, n (%)	4 (16.0)	24 (26.7)	0.429 §
Median WBC (range), /μL	5380 (2970–10,490)	5420 (2530–19,910)	0.929 †
Median Hb (range), g/dL	12.8 (9.4–15.0)	12.5 (8.2–15.1)	0.265 †
Median Platelet (range), 10^4/μL	20.5 (15.1–44.9)	22.8 (9.7–49.7)	0.610 †
Median Albumin (range), mg/dL	3.8 (2.8–4.5)	3.8 (2.3–5.5)	0.187 †
Median CA19-9 (range), mg/dL	503 (2–100,000)	368 (2–100,000)	0.741 †

†, Wilcoxon test; §, Fisher's test. HRD, homologous recombination deficiency; R, resectable; BR, borderline resectable; UR-LA, unresectable-locally advanced; UR-M, unresectable-metastatic; TMB-H, tumor mutation burden-high; MSI-H, microsatellite instability-high; NA, not assessed; WBC, white blood cell; Hb, hemoglobin; CA19-9, carbohydrate antigen 19-9.

Treatment outcomes according to HRD-related genetic mutations

The HRD-positive group showed longer survival than patients without these mutations. Their median overall survival was 749 days (95% CI: 487–958), compared with 516 days (95% CI: 440–598) in the HRD-negative group, which was statistically significant (p = 0.047). A similar pattern was observed when measuring survival from the time incurable pancreatic cancer was diagnosed: the HRD-positive patients had a median survival of 636 days (95% CI: 422–958), whereas the HRD-negative patients lived a median of 441 days (95% CI: 382–510) (p = 0.002).

To identify factors influencing overall survival, several clinical variables were assessed individually. Three factors showed significant associations: starting treatment with metastatic disease rather than resectable, borderline-resectable, or locally advanced tumors (HR 1.82; 95% CI: 1.25–2.66; p = 0.002), the presence of an HRD-related alteration (HR 0.63; 95% CI: 0.44–0.99; p = 0.049), and the baseline hemoglobin value (HR 1.58; 95% CI: 1.08–2.30; p = 0.018). These variables were then included in the multivariate model, where all three continued to show independent prognostic value. HRD-related mutations remained associated with improved survival (HR 0.60; 95% CI: 0.34–0.96; p = 0.035), while metastatic disease at diagnosis (HR 1.97; 95% CI: 1.34–2.92; p < 0.001) and hemoglobin levels (HR 1.54; 95% CI: 1.06–2.23; p = 0.025) were linked to worse outcomes.

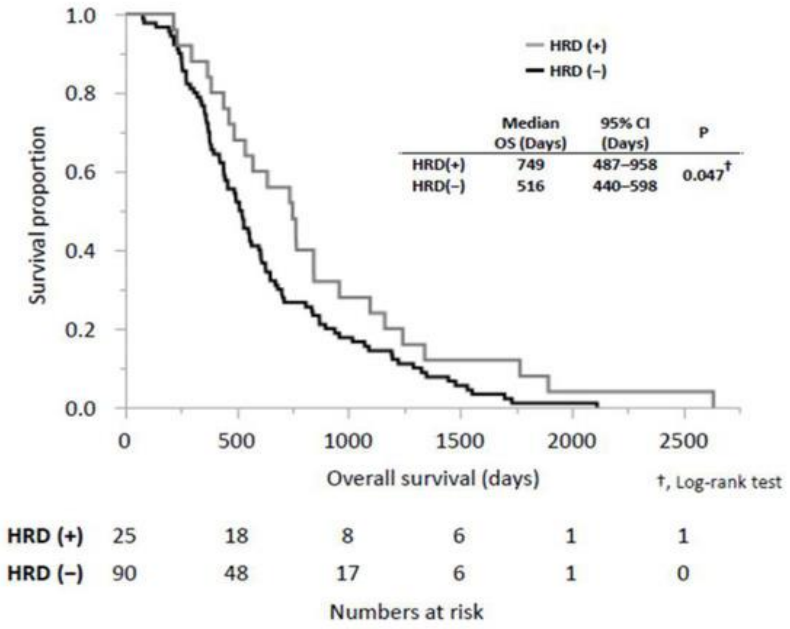

Figure 2. Comparison of overall survival (OS) between the patients who had homologous recombination deficiency (HRD)-related genetic mutations (HRD (+)) and those who did not (HRD (−)). †, Log-rank test; OS, overall survival; HRD, homologous recombination deficiency; CI, confidence interval.

Table 4. Univariate and multivariate analyses of factors associated with overall survival (OS).

	Univariate Analysis			Multivariate Analysis		
	HR	**95% CI**	**p-Value**	**HR**	**95% CI**	**p-Value**
Age (>70 vs. ≤70, y.o.)	0.65	0.43–1.00	0.051			
Male vs. Female	0.73	0.51–1.08	0.114			
PS (1- and NA vs. 0)	1.43	0.96–2.11	0.078			
Operability at the time of diagnosis. (UR-M vs. R, BR, and UR-LA)	1.82	1.25–2.66	**0.002**	1.97	1.34–2.92	**<0.001**
HRD related gene mutation (HRD (+) vs. HRD (−))	0.63	0.40–0.99	**0.049**	0.60	0.34–0.96	**0.035**
Platinum-based regimen (Y vs. N)	0.97	0.64–1.50	0.876			
Baseline WBC (>5420 vs. ≤5420, /μL)	0.92	0.63–1.34	0.673			
Baseline Hb (<12.7 vs. ≥12.7, g/dL)	1.58	1.08–2.30	**0.018**	1.54	1.06–2.23	**0.025**
Baseline Platelet (<22.6 vs. ≥22.6, $\times 10^4$/μL)	0.98	0.67–1.43	0.915			
Baseline albumin (<3.8 vs. ≥3.8, U/mL)	1.45	0.99–2.12	0.056			
Baseline CA19-9 (>400 vs. <400, U/mL)	1.41	0.96–2.06	0.078			

OS, overall survival. PS, performance status; NA, not assessed; R, resectable; BR, borderline resectable; UR-LA, unresectable-locally advanced; UR-M, unresectable-metastatic; WBC, white blood cell; Hb, hemoglobin; CA19-9, carbohydrate antigen 19-9.

Discussion

In this study, we assessed the practical utility of comprehensive genomic profiling (CGP) in patients with inoperable pancreatic cancer (IPC). Approximately 85% of patients met the quality criteria for CGP testing, indicating that the results largely reflected the pathogenic mutations present in each tumor. Additionally, the mutation frequencies of the "big four" genes—KRAS, TP53, CDKN2A, and SMAD4—were consistent with previously reported data [6], demonstrating that CGP reliably identified relevant gene alterations. Based on these findings, the clinical utility of CGP testing can be considered from two perspectives.

First, the proportion of patients receiving gene-matched therapies based on CGP results was limited. Among eight patients identified as TMB-high (TMB-H) and/or MSI-high (MSI-H), four received pembrolizumab, while only two patients (1.7%) were enrolled in clinical trials. Tumor MSI status and TMB are known to influence the response to immune checkpoint inhibitors [22, 23], and pembrolizumab has been approved for MSI-H solid tumors since 2017 and for TMB-H solid tumors since 2020 [24, 25]. In Japan, approval for MSI-H solid tumors occurred in December 2018 and for TMB-H tumors in February 2022 [25, 26]. Reported frequencies of TMB-H and MSI-H in pancreatic cancer range from 1.4–27.9% and 0–1.3%, respectively [18]. Despite similar frequencies in our cohort, half of the eligible patients did not receive pembrolizumab, likely due to poor general condition or comorbidities. Overall, six patients (5.2%) underwent gene-matched therapy based on CGP, aligning with prior reports of 5–10% [21, 27]. Studies from the United States suggest that IPC patients receiving gene-matched therapy based on molecular profiling have improved prognosis [21]. However, access to clinical trials in Japan remains limited due to factors such as the small number of investigational drugs, regional variations in trial sites, and rapid deterioration in patients' general condition. In our cohort, CGP testing was submitted after progression on first-line therapy in 73.9% of patients, and 16 patients (13.9%) died within 90 days of test submission, underscoring the importance of timely CGP testing. Early testing may facilitate better treatment planning under favorable patient conditions, as second-line chemotherapy offers limited survival benefits, with OS and PFS ranging between 4.1–9.9 months and 1.4–3.1 months, respectively [28–31].

Second, we evaluated the prevalence and prognostic significance of HRD-related gene mutations. Overall, 21.7% of patients carried HRD-related mutations, comparable to previous reports in advanced pancreatic cancer (19%), which included 15% germline and 4% somatic mutations [21]. Patients with HRD mutations had significantly longer overall survival, and multivariate analysis identified HRD as an independent prognostic factor. Prior non-randomized studies have also suggested HRD as a predictor of response to platinum-based chemotherapy [21, 32]. The identification of HRD status offers two potential clinical advantages: (1) for patients receiving platinum-based regimens like FOLFIRINOX, managing adverse effects such as peripheral neuropathy is critical for long-term therapy; (2) for those initially treated with non-platinum regimens, platinum-based therapy may be prioritized as second-line treatment, as patients with HRD mutations may lose the opportunity for platinum therapy due to disease progression. Thus, HRD status can guide the selection of second-line regimens, and early CGP testing may support timely and appropriate chemotherapeutic decisions.

This study has several limitations. It is a retrospective analysis conducted at a single center, and multicenter studies with larger patient populations are needed. Additionally, outcomes were analyzed only for patients who underwent CGP; IPC patients unable to undergo testing were not included. Finally, the low number of patients receiving gene-matched therapy may reflect limited access to clinical trials, which varies by location and trial availability.

Conclusion

In summary, although CGP testing for IPC currently offers limited opportunities for gene-matched therapies under existing insurance and trial structures, expanding clinical trials in the future may improve these prospects. The findings also indicate that CGP has meaningful value in identifying HRD-related mutations, which may serve as a prognostic marker and support treatment decisions. Because this research reflects results from a single-institution retrospective study, broader multicenter investigations with larger cohorts are needed to validate these observations.

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Conflict of Interest: Yamai reports honoraria for lectures from Taiho Pharmaceutical and Yakult Honsha. Ikezawa honoraria for lectures from Taiho Pharmaceutical, Yakult Honsha, Ono Pharmaceutical, MSD and Incyte Biosciences Japan, and research funding from ASKA Pharmaceutical. Sugimoto reports honoraria for lectures from Chugai Pharm, Daiichi Sankyo, Ono and Eli Lilly, and research funding from Chugai Pharm, Daiichi Sankyo, MSD Pfizer, and Seagen. Takada reports honorarias for lecture from Hisamitsu Pharmaceutical, Novartis and TEIJIN PHARMA. Kunimasa reports honoraria for lectures from Chugai Pharma, and Novartis Pharma. Ohkawa reports honoraria for lectures from Eisai, Chugai Pharmaceutical, Yakult Honsha, Incyte Biosciences Japan, Takeda, Gilead and Hisamitsu, and research grants from Towa Pharmaceutical and Sumitomo Chemical. The other authors have no conflict of interest.

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Ethics Statement: This study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Ethical Review Committee of the Osaka International Cancer Institute (No. 20148-3, approved on 12 October 2020).
The requirement for informed consent was waived by the opt-out method of our hospital's website. A waiver of informed consent was granted by institutional review board of the Institutional Review Board of Osaka International Cancer Institute.

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