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Efficacy of platinum-based chemotherapy and prognosis of patients with pancreatic cancer with homologous recombination deficiency: comparative analysis of published clinical studies

Ilya Pokataev, Mikhail Fedyanin, Elizaveta Polyanskaya, Anna Popova, Julia Agafonova, Sophia Menshikova, Alexey Tryakin, Alexey Rumyantsev, Sergei Tjulandin

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Department of Clinical Pharmacology and Chemotherapy, FBGU National Medical Research Center of Oncology named after N N Blokhin, Moskva, Russian Federation

Correspondence to
Dr Mikhail Fedyanin;
fedianinmu@mail.ru

ABSTRACT

The aim of our study was to determine the effect of homologous recombination deficiency (HRD) on prognosis and efficacy of platinum-based chemotherapy in patients with pancreatic cancer (PC). We performed PubMed and Embase database queries. We included 4 studies into the meta-analysis and 16 studies in the systematic review. Our systematic analysis showed that the average weighted median overall survival (OS) in patients with HRD with advanced PC was 19.8 and 15.6 months in patients without HRD. With platinum-based chemotherapy, the average weighted median OS in patients with HRD was 23.8 and 17.1 months in patients without HRD. Without platinum-based chemotherapy, the average weighted median OS in patients with HRD was 8.3 and 12.0 months in patients without HRD. For resected PC, our meta-analysis demonstrated that HRD status did not affect the prognosis (HR 1.03, 95% CI 0.46 to 2.33), but results were rather heterogeneous (I^2=83%, p=0.003). Our systematic analysis showed that the average weighted median OS in patients with HRD was 34.6 and 27.0 months in patients without HRD. With platinum-based chemotherapy, the average weighted median OS in patients with HRD was 46.1 and 36.3 months in patients without HRD. Without platinum-based chemotherapy, the average weighted median OS in patients with HRD was 24.2 and 42.9 months in patients without HRD. Results of our meta-analysis and systematic review support the idea of platinum use in patients with HRD both in resected and metastatic PCs, although a randomised trial is warranted to make a more reliable conclusion.

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INTRODUCTION

Pancreatic cancer (PC) is the 11th most common type of cancer with 458 918 new cases registered worldwide in 2018. With 432 242 death cases, it is ranked seventh in the list of the highest mortality rate cancers.[1] Chemotherapy is an important treatment option nearly at any PC stage.[2] Chemotherapy often has a positive impact on the survival of patients with PC but overall results are still poor. Median overall survival (OS) in local PC is 28–54 months,[3 4] while OS for advanced disease is approximately 7–11 months.[5 6]

Homologous recombination is one of the most important mechanisms of DNA repair.[7] Homologous recombination deficiency (HRD) of the DNA has been linked with increased sensitivity of tumour cells to *Poly (ADP-ribose) polymerase* (PARP) inhibitors, platinum derivatives, alkylating agents, mitomycin C and some other antitumour drugs.[8–11] HRD is registered nearly in 5%–9% of patients with PC.[12–14] Since most of HRD target drugs are not routinely used in PC treatment, HRD could potentially serve as a prognostic and predictive biomarker of systemic therapy efficacy in PC setting.

Here, we performed a meta-analysis of recent literature on HRD influence on the prognosis and efficacy of platinum-based chemotherapy in patients with resectable and metastatic PC. Our findings support the idea of platinum use in patients with HRD both in resectable and metastatic settings, but there are still questions that require further investigation.

METHODS

We performed the study in compliance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses() statement.[15] The study protocol was initially registered in International prospective register of systematic reviews.

Search strategy

We performed PubMed and Embase database queries. Search criteria included all

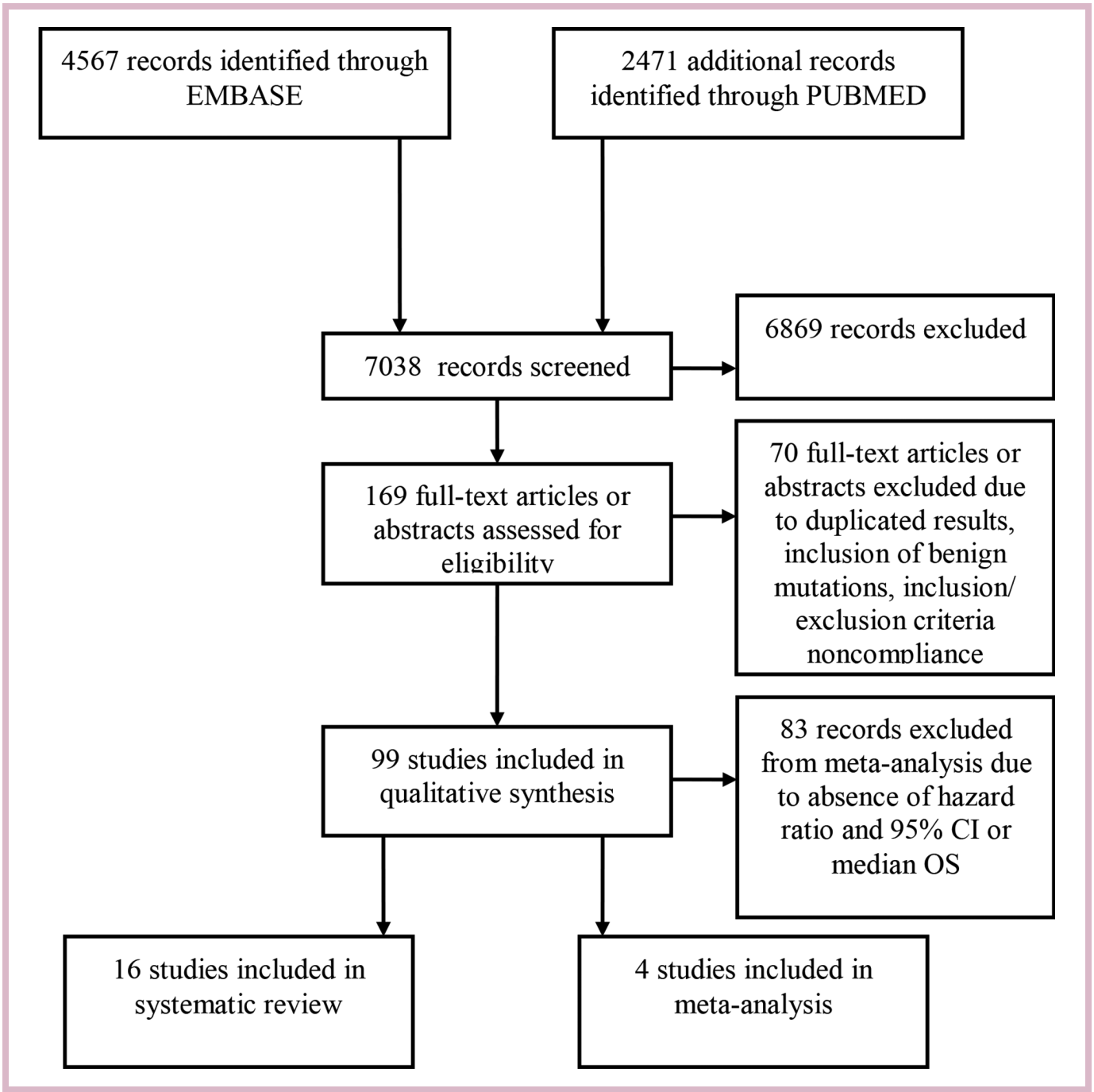

Figure 1 Publication search strategy flowchart.IV, Inverse Variance

prospective and retrospective full-text articles and abstracts published on or before 16 January 2019 in English and Russian languages. Only clinical and observational studies performed on people were included. We excluded surveys, guidelines and other publications that did not contain original data.

For PubMed queries, we searched for word 'pancrea' or 'pancreatic neoplasms' in titles, in combination with one of the following keywords: *BRCA, PALB2*, DNA repair, homologous, *RAD50, RAD51, RAD52, CHEK2, BLM, BARD, NBN, ATM, ATR*, genetic markers, DNA mutational analysis and DNA repair.

For Embase queries, we search word 'pancreatic', in combination with one of the following: *BRCA, PALB2, ATM, ATR, FANC*, DNA repair, homologous, *RAD50, RAD51, RAD52, CHEK2, BLM, BARD, NBN*, genetic markers, DNA mutational analysis and DNA repair.

Inclusion/exclusion criteria

To evaluate prognosis and efficacy of platinum-based chemotherapy in patients with HRD, we included studies

- With patients of any age and family history who had morphologically confirmed pancreatic carcinoma of any subtype.

Table 1 Overall survival depending on HRD status in patients with locally advanced or metastatic pancreatic cancer

	HRD genotype			Non-HRD genotype			
Study	n	Pt-based CT (%)	Median OS (months)	n	Pt-based CT (%)	Median OS (months)	P value
O'Reilly *et al*[27]	9	100	23.3	7	100	11	ND
Ferrone *et al*[28]	8	ND	6	145	ND	16	0.35
Reiss *et al*[17]	18	100	>20	28	100	15.5	0.002
Reiss *et al*[17]	11	0	6.1	30	0	2.8	0.12
Pishvaian *et al*[29]	54	100	28.4	258	100	17.4	<0.0001
Pishvaian *et al*[29]	19	0	9.1	114	0	14.4	0.11
Lowery *et al*[14]	63	ND	33.5	229	ND	23.1	0.42
Cheng *et al*[25]	22	ND	4.7	166	ND	5.6	0.771
Holter *et al*[13]	10	ND	7.7	ND	ND	ND	
Lowery *et al*[30]	10	70	13.2	ND	ND	ND	
Aung *et al*[31]	20	100	15.3	ND	ND	ND	
Aung *et al*[31]	12	0	8.3	ND	ND	ND	
Golan *et al*[32]	22	100	22	ND	ND	ND	
Golan *et al*[32]	21	0	9.0	ND	ND	ND	
Faluyi *et al*[33]	7	100	33	ND	ND	ND	
Faluyi *et al*[33]	6	0	7.3	ND	ND	ND	
Total	312		19.8	977		15.6	

HRD, homologous recombination deficiency; n, number of patients; ND, no data provided; Pt-based CT, per cent of patients who underwent platinum-based chemotherapy.

- Where tumour or normal tissue was evaluated for deleterious mutations in homologous recombination genes.

We excluded studies that

- Included patients with benign and/or mutations of unknown significance[16] in survival analysis.
- Included mutations not related to homologous recombination in survival analysis.
- Did not provide OS data.
- Reported OS results without differentiating between resectable and advanced PCs.
- Included fewer than five patients.

Data extraction (selection and coding)

Two authors independently screened the retrieved titles and/or abstracts of studies to identify studies that potentially met the inclusion criteria. Then they retrieved full texts of these potentially eligible studies and independently assessed them for eligibility. To avoid repetitive data from studies performed on the same clinical material, we further evaluated inclusion criteria and timing of recruitment. If an intersection of the patient cohort was detected, we favoured the most recent publication or the publication with the largest number of included

Table 2 Overall survival due to HRD status in patients with locally advanced or metastatic pancreatic cancer treated with platinum-based chemotherapy

	HRD		Non-HRD		
Study	n	Median OS (months)	n	Median OS (months)	P value
O'Reilly *et al*[27]	9	23.3	7	11.0	ND
Reiss *et al*[17]	18	>20	28	15.5	0.002
Pishvaian *et al*[29]	54	28.4	258	17.4	<0.0001
Lowery *et al*[31]	7	20.4	ND	ND	
Aung *et al*[31]	20	15.3	ND	ND	
Golan *et al*[32]	22	22	ND	ND	
Faluyi *et al*[33]	7	33	ND	ND	
Total	137	23.8	293	17.1	

HRD, homologous recombination deficiency; n, number of patients; ND, no data provided.

Table 3 Overall survival due to HRD status in patients with locally advanced or metastatic pancreatic cancer not treated with platinum-based chemotherapy

	HRD		Non-HRD		
Study	n	Median OS (months)	n	Median OS (months)	P value
Reiss *et al*[17]	11	6.1	30	2.8	0.12
Pishvaian *et al*[29]	19	9.1	114	14.4	0.11
Aung *et al*[31]	12	8.3	ND	ND	
Golan *et al*[32]	21	9.0	ND	ND	
Faluyi *et al*[33]	6	7.3	ND	ND	
Total	69	8.3	144	12.0	

HRD, homologous recombination deficiency; n, number of patients; ND, no data provided.

patients. We extracted the following information: study type, patient population, patient inclusion criteria, characteristics, type of genetic testing (PCR for founder mutations or next-generation sequencing (NGS)), carcinoma subtype, evaluated genes, types of mutations (pathogenic/benign/unknown and germline/somatic), regimen of chemotherapy and response rate. We also extracted the information about patient outcomes: median OS with 95% CI; OS of 1, 2 or 5 years; and hazard ratio (HR) and 95% CI for comparison of OS between patients with and without HRD, and between platinum and non-platinum chemotherapy in patients with HRD.

Statistical methods

HR was presented as a death risk ratio of compared groups with 95% CI. Standard error (SE) was calculated from 95% CI. Statistical analysis included I^2 test to confirm homogeneity of the study results included in the meta-analysis. For research results with no statistically significant heterogeneity (p>0.1), the 'generic inverse variance' method with a fixed effect was used to assess the relationship between the risks of progression and death and to construct 95% CI. We applied random effect in the absence of significant heterogeneity of results of included studies in the meta-analysis. To avoid biases associated with publication, a funnel-shaped graph was constructed (with the SE values (log HR) on the ordinate axis and the HR). Meta-analysis was performed with Review Manager (computer program) V.5.3 (Nordic Cochrane Center, Copenhagen).

RESULTS

Requests to Embase and PubMed databases identified 7038 records (figure 1). We reviewed all of these records and excluded 6869 of them from further analysis due to noncompliance with the inclusion/exclusion criteria based on the abstract analysis. We analysed the remaining 169 records in detail, screening the full texts and additional posters in case of conference/congress abstracts.

We excluded further 70 full-text articles or abstracts due to duplicated results, inclusion of benign mutations in survival analysis or noncompliance with the inclusion/exclusion criteria. We included the remaining 99 papers in qualitative synthesis. Of these, only four papers reported a comparative analysis of prognosis of patients with and without HRD, which indicated HR and 95% CI. We included these four papers into the meta-analysis. Additionally, 16 studies were included in the systematic review.

Overview of studies included in the meta-analysis of the effect of HRD status on the OS prognosis

Our meta-analysis of OS prognosis in PC due to HRD status included four retrospective studies that reported HR and 95% CI.

The study by Reiss *et al*[17] included 29 patients with advanced PC with germline mutations in *BRCA1*, *BRCA2* or *PALB2*. They were matched 2:1 to patients who were non-carriers or untested (controls). The HRD group underwent platinum-based chemotherapy in 72% of

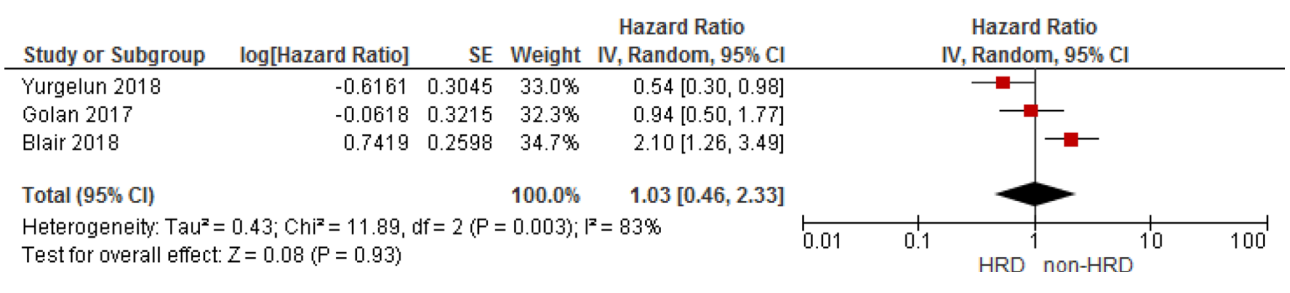

Figure 2 HR for death in patients with resected pancreatic cancer due to HRD. HRD, homologous recombination deficiency.

Table 4 Overall survival due to HRD status in patients with resected pancreatic cancer

	HRD			Non-HRD			
Study	n	Pt-based CT (%)	Median OS (months)	n	Pt-based CT (%)	Median OS (months)	P value
Blair *et al*[19]	22	45	20.2	105	ND	27.8	0.034
Pishvaian *et al*[29]	49	100	52.2	220	100	36	0.1
Pishvaian *et al*[29]	14	0	21.6	94	0	45	0.76
Golan *et al*[20]	14	0	36	40	0	38	0.983
Golan *et al*[20]	10	100	43.8	7	100	44.4	0.775
McKay *et al*[26]	23	ND	20.3	369	ND	20.5	0.978
Yurgelun *et al*[18]	19	26	34.4	244	ND	19,1	0.05
Lucas *et al*[34]	8	ND	61.7	ND	ND	ND	
Aung *et al*[31]	24	ND	19.5	ND	ND	ND	
Total	183		34.6	1079		27.0	

HRD, homologous recombination deficiency; n, number of patients; ND, no data provided; Pt-based CT, per cent of patients who underwent platinum-based chemotherapy.

cases and controls in 61% . Patients with mutations had overall OS benefit (HR 0.35, 95% CI 0.2 to 0.62, p<0.001) with a median OS of 21.8 vs 8.1 months, respectively. With platinum exposure, only mutation-positive patients had a significant OS benefit as compared with controls (HR 0.25, 95% CI 0.1 to 0.61, p=0.002). Without platinum exposure, there was no OS difference between groups (HR 0.54, 95% CI 0.25 to 1.17, p=0.12).

The study by Yurgelun *et al*[18] included 289 patients with resectable PC who underwent surgical treatment. Their tissues then were analysed for HRD mutations with NGS. They found that 21 patients had HRD mutations (*BRCA1*, *BRCA2*, *ATM*, *BRIP1*, *CHEK2*, *NBN*, *PALB2*, *RAD50* or *RAD51C*). Compared with non-carriers, these patients had significantly longer OS (HR 0.54, 95% CI 0.30 to 0.99, p=0.05) with a median of 34.4 vs 19.1 months, respectively. Unfortunately, the authors provided no details about adjuvant chemotherapy and its personalisation due to mutational status.

The study by Blair *et al*[19] included patients with local PC. Of them, 22 had germinal *BRCA* mutations and 105 had *BRCA* wild type. Patients with *BRCA1/BRCA2* mutations had inferior median OS when compared with the matched wild-type controls (20.2 vs 27.8 months, p=0.034). When analysing the *BRCA*-mutated group, patients with adjuvant platinum-based chemotherapy (n=10) had better OS than patients with no platinum (n=8) or no chemotherapy at all (n=4) (31.0 vs 17.8 vs 9.3 months, p<0.001).

The study by Golan *et al*[20] included patients with local PC whose blood samples were tested for *BRCA* mutations. Of them, 25 had *BRCA* mutations and 49 had *BRCA* wild type. The *BRCA*-mutant group received platinum-based neoadjuvant or adjuvant chemotherapy in 40% of cases and in 14.9% of controls (p=0.012). There was no OS difference observed in both groups (37.1 vs 38.8 months, p=0.838). There also was no OS difference with platinum neoadjuvant or adjuvant chemotherapy compared in *BRCA*-mutated group and controls (43.8 vs 44.4 months, p=0.775).

HRD and prognosis of advanced PC

There is only one study that reported HR of death and 95% CI in patients with locally advanced or metastatic PC due to HRD status.[17] The results showed that patients with HRD had a more favourable prognosis (HR 0.35, 95% CI 0.20 to 0.62).

Since the other studies did not indicate HR and 95% CI in patients due to HRD status, we conducted a systematic review of these studies (table 1). Our analysis showed

Table 5 Overall survival due to HRD status in patients with resected pancreatic cancer treated with platinum-based chemotherapy

	HRD		Non-HRD		
Study	n	Median OS (months)	n	Median OS (months)	P value
Pishvaian *et al*[29]	49	52.2	220	36	0.1
Golan *et al*[20]	10	43.8	7	44.4	0.775
Blair *et al*[19]	10	31	ND	ND	
Yurgelun *et al*[18]	5	20.9	ND	ND	
Total	74	46.1	227	36.3	

HRD, homologous recombination deficiency; n, number of patients; ND, no data provided.

Table 6 Overall survival due to HRD status in patients with resected pancreatic cancer treated without platinum-based chemotherapy

	HRD		Non-HRD		
Study	n	Median OS (months)	n	Median OS (months)	P value
Pishvaian *et al*[29]	14	21.6	94	45	0.76
Golan *et al*[20]	14	36	40	38	0.983
Blair *et al*[19]	8	17.8	ND	ND	
Yurgelun *et al*[18]	8	14.4	ND	ND	
Total	44	24.2	134	42.9	

HRD, homologous recombination deficiency; n, number of patients; ND, no data provided.

that the average weighted median OS in patients with HRD (n=312) was 19.8 months, and that in patients without HRD (n=977) was 15.6 months. With platinum-based chemotherapy, the average weighted median OS in patients with HRD (n=137) was 23.8, and that in patients without HRD (n=293) was 17.1 months (table 2). Without platinum-based chemotherapy, the average weighted median OS was 8.3 in patients with HRD (n=69) and and that in patients without it (n=144) was 12.0 months (table 3).

HRD and prognosis of resected PC

Three studies reported HR of death and 95% CI in patients with resected PC due to HRD status (figure 2). Our meta-analysis included data on 65 patients with HRD and 396 patients without HRD and demonstrated that HRD did not affect the prognosis (HR 1.03, 95% CI 0.46 to 2.33). However, the results were rather heterogeneous (I^2=83%, p=0.003). For example, one study[19] showed that the OS in patients with HRD was significantly lower than that in patients without HRD (HR 2.10, 96% CI 1.26 to 3.49). Another study[18] claimed that patients with HRD had a statistically significantly better prognosis compared with patients without mutations (HR 0.54, 95% CI 0.30 to 0.98). The last study[20] revealed no difference in prognosis due to HRD status (HR 0.94, 95% CI 0.50 to 1.77).

We performed a systematic review of studies that compared OS in patients with resected PC due to HRD (table 4). Our analysis showed that the average weighted median OS in patients with HRD (n=183) versus patients without HRD (n=1079) was 34.6 vs 27.0 months. With platinum-based chemotherapy, the average weighted median OS was 46.1 months in patients with HRD (n=74) and 36.3 months in patients without HRD (n=227) (table 5). Without platinum-based chemotherapy, the average weighted median OS was 24.2 in patients with HRD (n=44) and 42.9 months in patients without HRD (n=134) (table 6).

Two studies reported HR and 95% CI in patients with HRD and resected PC due to the use of platinum-containing chemotherapy[18 20] (figure 3). Meta-analysis included 37 patients and showed that platinum-based therapy is associated with a slightly more favourable prognosis in patients with HRD and resectable PC. However, the difference was not statistically significant (HR=0.60, 95% CI 0.36 to 1.33, p=0.27).

DISCUSSION

HRD is of great clinical importance for different types of tumours since it is associated with better efficacy of PARP inhibitors, platinum derivatives, alkylating agents, mitomycin C and some other antitumour drugs. For example, it increases the efficacy of platinum-containing chemotherapy regimens in breast and ovarian cancers with HRD.[11 21]

About 5%–9% of patients with PC have HRD.[12–14] Randomised studies show no gain in OS with platinum when added to gemcitabine in unselected patients with PC.[22 23] Therefore, platinum doublets are not routinely recommended in clinical practice.[2] FOLFIRINOX is the only standard regimen for PC therapy which contains oxaliplatin as one of the components.[5] However, given the resistance of PC to the vast majority of cytostatics, lack of targeted drugs and any predictive biomarkers useful

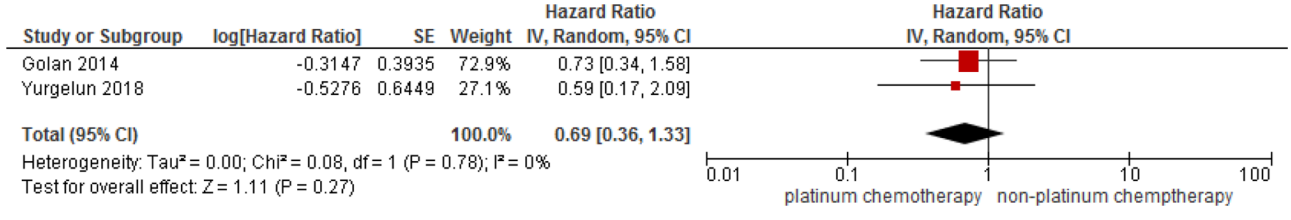

Figure 3 HR for death in patients with resected pancreatic cancer due to HRD and use of platinum chemotherapy. HRD, homologous recombination deficiency.

for clinical practice, it seems reasonable to evaluate HRD as a possible prognostic and predictive biomarker.

To date, several studies discuss the effect of HRD status on the prognosis and efficacy of platinum therapy in PC. For locally advanced and metastatic PC, there is only one study reporting HR of death and 95% CI[17]. This study demonstrated that patients with HRD had a more favourable prognosis and benefited more with platinum-based therapy (HR 0.25, p=0.002). Our systematic review showed that the average weighted median OS in patients with HRD is slightly higher than that in non-HRD-mutant patients (19.8 vs 15.6 months). Furthermore, the increase in OS can be improved by incorporating platinum-based chemotherapy. The increase of the average weighted median OS in patients with HRD who underwent platinum-based treatment was 23.8 vs 17.1 months in non-mutant patients. Without platinum exposure, the average weighted median OS in patients with HRD was worse than that in non-mutant patients (8.3 and 12.0 months, respectively).

For resectable PC, our meta-analysis based on studies with known HR does not allow us to conclude unequivocally that platinum-based therapy increases the survival rate. The OS difference between HRD-mutant patients and their non-mutant counterparts was not statistically significant (HR 0.60, p=0.27). At the same time, our systematic analysis showed that patients with HRD who had platinum therapy had a higher average weighted median OS than those who did not have platinum therapy (46.1 vs 24.2 months, respectively). Patients without HRD had shorter average weighted median OS with platinum-based chemotherapy compared with platinum-naïve patients (36.3 vs 42.9 months, respectively).

The main limitations of our analysis are the small number of patients and the retrospective nature of the included studies. HRD is a rare condition in PC, and it translates into a small number of included patients. This results in a disproportion of such key prognostic factors as age, stage, carbohydrate antigen (CA) 19.9 level, lymphocytic to neutrophilic ratio and others. Besides this, not all studies reported the type of the analysed HRD mutations. Germinal or somatic (especially monoallelic) HRD mutations could have different clinical significance.[24] Another limitation is that studies do not allow comparison of the efficacy of FOLFIRINOX and platinum doublets in patients with and without HRD.

Analysis of the prognosis of HRD-mutant patients is limited by conflicting results reported in the literature. For example, the study by Blair *et al*[19] revealed statistically significantly worse prognosis for patients with HRD. On the contrary, the study by Yurgelun *et al*[18] showed a statistically significantly more favourable prognosis in patients with HRD. Other studies reported no differences in survival between mutant and non-mutant patients.[20 25 26] Despite the researchers' attempts to adequately match the studied groups, the retrospective nature of their studies also translated into disproportion of patients according to the main clinical and laboratory parameters.

We identified only one study that discussed prognosis in locally advanced and metastatic PC with HR. This study showed that patients with HRD had a more favourable prognosis (HR 0.35).[17] Our systematic analysis also demonstrated that metastatic patients with HRD have a higher average weighted median OS (19.8 vs 15.6 months, respectively). In resected PC, the meta-analysis showed that prognosis was the same regardless of the mutational status (HR 1.03, 95% CI 0.46 to 2.33). At the same time, our systematic review indicated that the average weighted median OS for patients with HRD was 34.6 vs 27.0 months for non-patients with HRD. We hypothesise that this effect could be linked to the disproportion in platinum use. This could be indirectly confirmed by the fact that similar data were obtained for ovarian cancer in patients with *BRCA* mutations.[11] Better prognosis in *BRCA*-mutant patients can be attributed to better efficacy of platinum chemotherapy. However, after the 5-year follow-up, the survival curves intersect and the prognosis of patients with *BRCA* becomes worse than that of non-mutant patients.[11]

In summary, the results of our meta-analysis and systematic review support the idea of platinum use in patients with HRD PC, although published data with a small sample size and heterogeneous population allowed us to identify only a trend towards longer OS with the use of platinum in the HRD group compared to non-platinum therapy.

However, several questions require further investigation. Firstly, the available data do not allow for a comparison of the efficacy of platinum-based therapy in patients with *BRCA* or other HRD mutations. Secondly, platinum efficacy also remains unclear in case of monoallelic *BRCA* mutation in tumour cells, which is known to occur in PC. Finally, available studies do not report what platinum regimens (triplets or doublets) were used, and, specifically, it is not possible to compare efficacy of cisplatin-based or oxaliplatin-based doublets.

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Contributors All authors of this research paper have directly participated in the planning, execution, analysis of this study results and the manuscript writing, and have read and approved the final version submitted.

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ORCID iD
Mikhail Fedyanin http://orcid.org/0000-0001-5615-7806

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