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Systematic or Meta-analysis Studies

Should platinum-based chemotherapy be preferred for germline BReast CAncer genes (BRCA) 1 and 2-mutated pancreatic ductal adenocarcinoma (PDAC) patients? A systematic review and meta-analysis

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ABSTRACT

Background: Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal cancers worldwide. Recent studies have shown that 4–20% of patients with PDAC have a germline BReast CAncer (g*BRCA*) genes 1 and 2 mutation (m). Because homologous recombination is impaired in patients with g*BRCA*m, some reports suggested that these tumors may be more sensitive to platinum compounds. Therefore, this systematic review and meta-analysis focused on benefit of patients with g*BRCA*m receiving a platinum-based chemotherapy (PtCh) compared with those treated with a non-platinum-based chemotherapy (NPtCh).

Material and methods: The following electronic databases were searched from inception to May 12, 2018: PubMed (MEDLINE), EMBASE, and Cochrane Library. Abstracts from conferences were also reviewed for inclusion. Cohort, case-control and randomized studies of patients with PDAC and g*BRCA*m were eligible for inclusion if they provided data to compare patients receiving PtCh vs NPtCh. The primary endpoint was overall survival (OS) in the PtCh group vs the NPtCh group in patients with clinical stage III (locally advanced) or IV (metastatic) (CS III-IV) PDAC.

Results: Of 112 studies identified, 6 were included (total of 108 patients); of these, 4 provided sufficient data for meta-analysis. Half of the patients were males, with a mean age ranging from 58 to 63 years. The OS in the 85 patients with CS III-IV PDAC was higher in the PtCh group (23.7 vs 12.2 months; mean difference of 10.21 months, 95% confidence interval [CI] 5.05–15.37; $P < 0.001$; very low quality of evidence). PtCh was associated with a lower mortality (62.3 vs 87.5%; relative risk of 0.80, 95%CI 0.66–0.97; $P = 0.021$; very low quality of evidence).

Conclusion: Our study confirmed the hypothesis that patients with CS III-IV g*BRCA*m preferably benefit from a PtCh compared with NPtCh. However the very low quality of evidence should induce to be careful about the risk of potential biases. The generated hypothesis should be prospectively investigated in homogenous clinical settings.

Background

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignancies worldwide, associated with poor prognosis even when diagnosed at an early clinical stage (CS). Despite advances in surgery, radiotherapy, and chemotherapy, the 5-year overall survival (OS) rate is only 7.0–8.5% [1]. FOLFIRINOX (5-fluorouracil, irinotecan, and oxaliplatin) and nab-paclitaxel plus gemcitabine are first-line treatment options in the metastatic setting, with a median overall survival of less than 1 year [2,3]. Deaths from PDAC are projected to increase dramatically in the next 20 years. By 2030, PDAC is expected to become the second leading cause of cancer-related death in the United States [4].

Although most cases of PDAC appear to be sporadic, about 10% occur in patients with a family history of pancreatic cancer. Genetic factors play an important role in the development of PDAC, especially the presence of pathogenic mutations in genes such as BReast CAncer genes 1 and 2 (*BRCA1* and *BRCA2*), PArtner and Localizer of *BRCA2* (*PALB2*), mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*), the ataxia telangiectasia mutated (*ATM*) gene, and the cyclin-dependent kinase inhibitor 2A (*CDKN2A*) gene [5,6]. Germline *BRCA* (g*BRCA*) mutations are the most common genetic alterations known to occur in

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PDAC, inherited in an autosomal dominant pattern with incomplete penetrance. In patients with apparently sporadic PDAC, the prevalence of *BRCA1* and *BRCA2* mutations is about 4.6–7.8%, while in high-risk populations, such as patients of Ashkenazi Jewish descent, prevalence reaches 10–20% [7–13]. The risk of developing PDAC is 2.1–3.5 times higher in *BRCA* mutation carriers [14,15].

The prognosis of PDAC in *BRCA* mutation carriers remains unclear. Evidence suggests a better prognosis in *BRCA1*, *BRCA2*, or *PALB2* mutations, with an OS improvement in carriers compared with non-carriers (21.8 vs 8.1 months; hazard ratio [HR] 0.35, 95% confidence interval [CI] 0.2–0.62; $P < 0.001$) [16]. However, some studies have shown no difference in overall survival [12,14,17] or even suggested a worse prognosis in g*BRCA* mutation carriers [18].

BRCA1 and *BRCA2* play a critical role in DNA repair via homologous recombination by recognizing and repairing double-stranded DNA. Loss of heterozygosity in the *BRCA* gene due to second allele damage impairs homologous recombination and culminates in genetic instability and chromosomal aberrations involved in the process of tumor development (oncogenesis). This deficiency in the repair of DNA double-strand breaks also increases chemotherapy sensitivity to DNA-damaging agents, such as platinum compounds [19–21]. A whole-genome sequencing analysis of 100 patients with PDAC showed that variation in chromosomal structure is a relevant mechanism of DNA damage in pancreatic carcinogenesis, allowing the classification of PDAC into 4 subtypes: stable, locally rearranged, scattered, and unstable [22]. All deleterious *BRCA* mutations, both somatic and germline, seemed to be characterized by the unstable subtype, in which a large number of structural variation events occur because of defects in DNA maintenance, leading to a potentially better response to DNA-damaging chemotherapy, such as platinum-based chemotherapy (PtCh)—this supports the concept of sensitivity to platinum compounds among patients with *BRCA* mutations [22].

In PDAC, there is no clear evidence for superiority of PtCh over non-platinum-based chemotherapy (NPtCh) as no studies have specifically evaluated *BRCA* mutations in patients with PDAC [23–25]. However, it is conceivable that the use of PtCh in these patients can yield better results. Some promising results have been reported with the use of PtCh in patients with *BRCA*-mutated PDAC, with a response rate up to 76% [12,26]. Case reports of PtCh in PDAC patients with *BRCA* mutations have shown high tumor response and long survival [27–30]. Notably, a case report of a 60-year-old male patient with metastatic PDAC bearing a g*BRCA* mutation showed a complete clinical and radiologic tumor response with the use of PtCh that lasted for 18 months, when the patient had a recurrence and resumed the same protocol, achieving a partial response for an additional 20 months. The patient survived 7 years with a responsive metastatic PDAC [31].

The present study was developed to answer the following research question: Is PtCh more active and effective than NPtCh in patients with PDAC and a g*BRCA* mutation? To this end, a systematic review and meta-analysis was conducted to evaluate the OS of patients with CS III-IV PDAC bearing a g*BRCA* mutation treated with PtCh vs NPtCh. Where available, overall response rate (ORR) and progression-free survival (PFS) were evaluated.

Methods

This systematic review and meta-analysis was conducted following the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Report Items for Systematic Reviews and Meta-analyses (PRISMA) statement [32,33]. The systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42018097048).

Eligibility criteria

Randomized controlled trials, cohort studies and case-control studies of patients with confirmed CS III-IV PDAC and a g*BRCA* mutation who underwent palliative chemotherapy were eligible for inclusion if they provided data on OS or PFS in patients receiving PtCh (intervention group) and NPtCh (control group). Animal studies and studies without a comparison group were excluded.

Data sources and search strategy

The following electronic databases were searched from inception to May 12, 2018: MEDLINE (via PubMed), EMBASE, and the Cochrane Library. Abstracts from conferences were also reviewed, including the (ASCO) and the (ESMO). In addition, other databases identified as relevant by the information specialist were also reviewed. No language restrictions were applied. The following search strategy was used for PubMed and adapted for use in all other databases: (((pancreatic cancer OR pancreatic adenocarcinoma OR pancreatic ductal adenocarcinoma)) AND (platinum OR cisplatin OR carboplatin OR oxaliplatin OR cddp OR cisdiamm*)) AND (BRCA OR BRCA1 OR BRCA2).

Study selection

Two investigators (TR and MP) independently screened the titles and abstracts identified by the initial search. Full text was obtained for all potentially relevant articles to determine whether the study met the eligibility criteria. Disagreements were resolved by consulting a third reviewer for arbitration. In case of duplicate publications, only the most recent was included. Corresponding authors of selected studies were contacted via e-mail for missing data and/or clarification in order to include the studies in the review.

Data extraction

Two reviewers (TR and MF) independently extracted the following data from the selected studies using a standardized form: title of the study; first author; year of publication; country where the study was conducted; study design; total number of patients; number of patients who received PtCh; number of patients who received NPtCh; mean age and sex of the participants; rate of *BRCA1* and *BRCA2* mutations; disease stage; line of therapy; study drugs; mean overall survival of the study population; overall survival and PFS for the use of PtCh as first-line therapy; response rate; and use of poly(ADP-ribose) polymerase (PARP) inhibitors. Any discrepancies were resolved by consensus.

Where available, individual patient data on overall survival and PFS were extracted from survival curves in order to calculate means and standard deviations for these outcomes. If not possible, means and standard deviations were estimated from the medians and interquartile ranges.

Outcomes

The primary endpoint was overall survival (OS) in CS III-IV PDAC. Secondary outcomes were progression free survival (PFS) and overall response rate (ORR) in CS III-IV. Overall survival was defined as either the time from the date of diagnosis of PDAC (in studies by Kondo et al, from the date the first-line chemotherapy started) to the date of death from any cause, or censored until the date of last follow-up. A comparison between patients receiving PtCh (intervention group) and those receiving NPtCh (control group) was performed.

Data analysis

Results were presented qualitatively for each identified study. Meta-analysis of available data was performed using a random-effects model. Crude data were used in the analysis in the absence of adjusted estimates for the intended comparison. Relative risks (RRs) with 95% CIs were calculated for categorical outcomes, while mean differences (MDs) with 95% CIs were calculated for continuous outcomes. Heterogeneity between studies was assessed by I^2 statistic, and potential sources of heterogeneity were assessed by sensitivity analysis. In addition, a sensitivity

analysis was performed excluding studies that accounted for patients with *BRCA* variants of unknown significance (VUS).

The quality of evidence from observational studies was assessed using the Newcastle-Ottawa scale [34,35]. Overall quality of evidence was assessed using the GRADE approach [36]. Publication bias was not assessed because of the small number of studies.

All analyses were performed using R statistical software version 3.3.3, with meta package version 4.8–1 [37,38].

Role of the funding source

There was no funding source for this review and *meta*-analysis.

Results

The search strategy yielded a total of 112 publications. Fig. 1 provides an overview of the literature search and study selection. After removal of duplicates, 95 studies remained for the screening of titles and abstracts. Of these, 23 potentially relevant publications were selected for full-text reading. The corresponding authors of 4 studies [12,16,26,39] were contacted for further information, and 2 of them responded providing additional unpublished data [16,26]. After full-text screening, 6 studies were included in the systematic review [16,26,40–43], and 4 of them provided sufficient data for quantitative synthesis of overall survival of CS III-IV PDAC patients by meta-analysis. Excluded studies are listed in Appendix A.

The main characteristics of the included studies are shown in Table 1. The studies enrolled a total of 108 patients, with mean age ranging from 57.6 to 62.6 years; approximately 50% were males. Patients who had not been treated with chemotherapy and 1 patient whose treatment information was not available were excluded from the analysis. The most common mutated gene was *BRCA2*, in 70% of patients, followed by *BRCA1* in 28%, and *BRCA1* + *BRCA2* in 2%. Almost half of the patients were of Jewish descent. Detailed data on family and personal history of cancer and Jewish heritage are reported in Appendix B.

It was possible to pool OS data of patients with CS III-IV PDAC from 4 out of the 6 included studies [16,26,41,43]. Of these 4 studies, a total of 85 *BRCA*-mutated PDAC patients were included in the meta-analysis: 53 (62.4%) receiving PtCh and 32 (37.6%) receiving NPtCh. Vyas et al [42] and Lowery et al [40] only provided data to assess PFS when platinum was used as first-line therapy.

The primary endpoint of OS in patients with CS III-IV PDAC was evaluated in 85 patients. PtCh was associated with lower mortality (62.3 vs 87.5%; RR 0.80, 95%CI 0.66–0.97; $P = 0.02$; very low quality of evidence, i.e., patients who received PtCh had 20% lower mortality than those who received NPtCh during the study period. Overall survival was 10 months longer with PtCh than with NPtCh (23.7 vs 12.2 months; MD 10.21 months, 95%CI 5.05–15.37; $P < 0.001$; very low quality of evidence) (Fig. 2). Preplanned subgroup analyses according to the use of PARP inhibitors and ORR were not performed because of data unavailability.

When the impact of using PtCh vs NPtCh as first-line treatment was evaluated for patients with CS III-IV PDAC, the difference in PFS

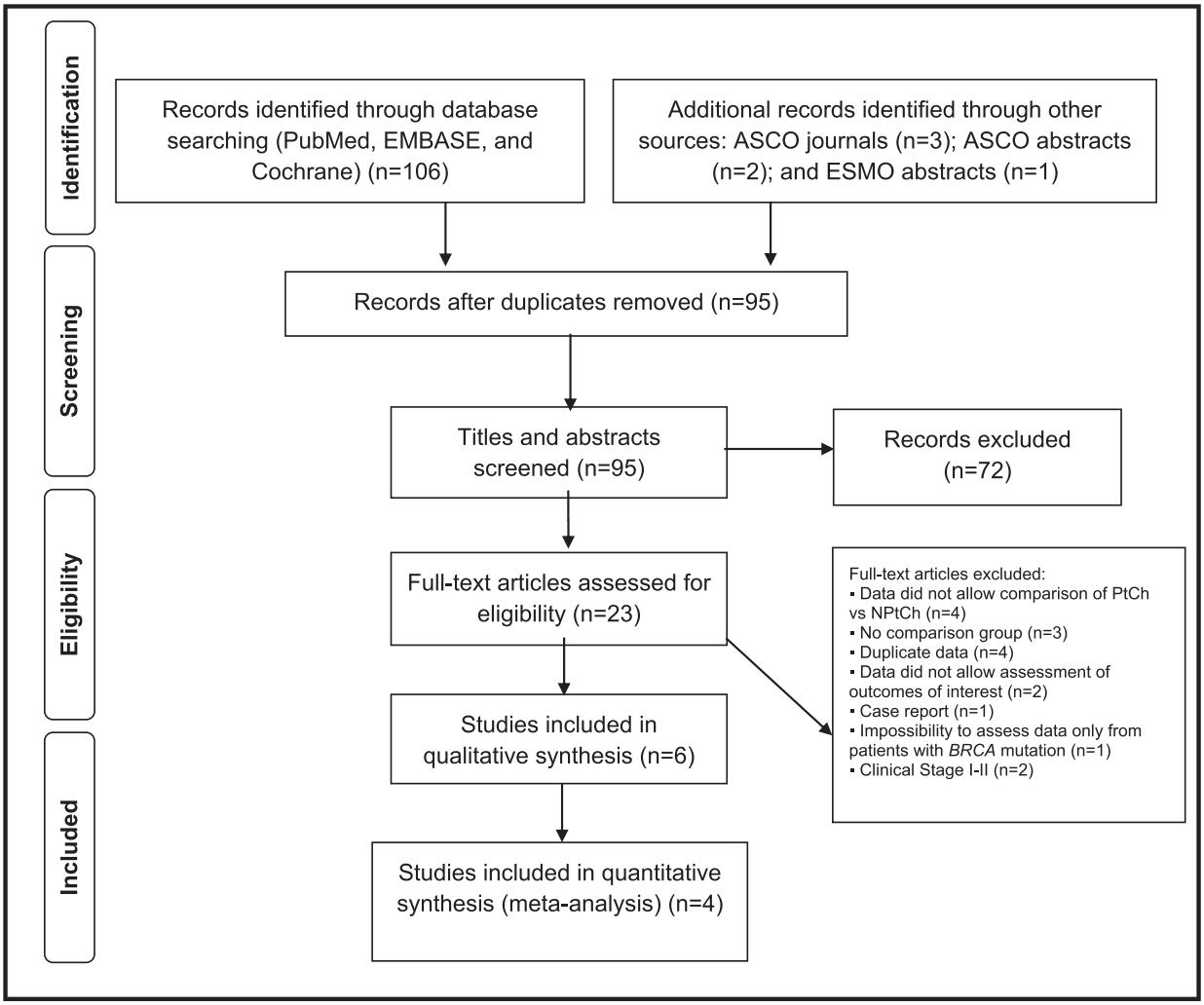

Fig. 1. Study selection. PRISMA flow chart summarizing the process of selection of eligible studies. (ASCO) American Society of Clinical Oncology; (ESMO) European Society for Medical Oncology; (PtCh) platinum-based chemotherapy; (NPtCh) non-platinum-based chemotherapy.

Table 1
Main characteristics of included studies.

Author, year, country	N	Design	Age (years), mean (range)	Male, n (%)	Mutation (%)	Clinical stage, n (%)	Interventions	Co-intervention (n)
Lowery, 2011, United States [1]	15 patients **-10 patients** 8 (PtCh) 1 (NO) 1 (NA)	Cohort	Median: 62¥	5 (33%)¥	BRCA1: 30% BRCA2: 70%	III: 2 (20%) IV: 8 (80%)	***Intervention:*** FOLFOX, gemcitabine and cisplatin, gemcitabine and oxaliplatin ***Control:*** gemcitabine, docetaxel and capecitabine, PARP inhibitors and gemcitabine, gemcitabine and capecitabine	Radiation (2) PARP inhibitors (2): combined with chemotherapy
Golan, 2014 Israel, Canada, United States [2]	71 patients **-43 patients** 22 (PtCh) 21 (NPtCh)	Cohort	61.6 (33–82)	41 (58%)	BRCA1: 30% BRCA2: 69% BRCA1/2: 1%	III: 15 (35%) IV: 28 (65%)	***Intervention:*** gemcitabine and oxaliplatin (1), FOLFIRINOX (3), gemcitabine and cisplatin (18) ***Control:*** Alternative non-platinum-based agents NS	PARP inhibitors (12): excluded from analysis
Vyas, 2015, United States [1]	**9 patients** 6 (PtCh) 3 (NPtCh)	Cohort	57.6 (42–71)	3 (33%)	BRCA2: 100%	III: 1 (10%) IV: 8 (80%)	***Intervention:*** FOLFOX (1), gemcitabine and oxaliplatin (3), gemcitabine-cisplatin (3) ***Control:*** Gemcitabine-docetaxel-irinotecan, FOLFIRI, irinotecan-erlotinib, PARP inhibitors	PARP inhibitors (1)
Smith, 2018 Canada	**11 patients** 9 (PtCh) 2 (NPtCh)	Cohort	59.7 (29–79)	8 (72%)	BRCA1: 19%[a] BRCA2: 81%	III: 3 (27%) IV: 8 (73%)	***Intervention:*** FOLFIRINOX (9), cisplatin and gemcitabine (6) ***Control:*** gemcitabine and nab-paclitaxel (3)	PARP inhibitors (1)
Reiss, 2018 United States **	**27 patients** 16 (PtCh) 7 (NPtCh) 4 (NO)	Cohort	62 (41–81)	15 (55%)	BRCA1: 45% BRCA2: 55%	III: 5 (18.5%) IV: 22 (81.5%)	***Intervention:*** FOLFOX (5), FOLFIRINOX (5), cisplatin and gemcitabine or other platinum (6) ***Control:*** Gemcitabine (4), gemcitabine and paclitaxel (2), multiple therapies (5)	PARP inhibitors: 6 (33%)
Kondo, 2018 Japan	**8 patients** 6 (PtCh) 2 (NPtCh)	Cohort	62.6 (44–81)	5 (62%)	BRCA1: 12.5%[b] BRCA2: 75% BCRA1/2: 12.5%	III-IV: 8 (100%)	***Intervention:*** FOLFIRINOX (3), SOX (3) ***Control:*** Gemcitabine (1), gemcitabine and nab-paclitaxel (1)	

Abbreviations: (PtCh) platinum-based chemotherapy; (NPtCh) non-platinum-based chemotherapy; (NO) no chemotherapy treatment; (NA) not available; (NS) not specified; (FOLFIRINOX) fluorouracil, leucovorin, oxaliplatin, and irinotecan; (FOLFOX) fluorouracil, leucovorin, and oxaliplatin; (FOLFIRI) fluorouracil, leucovorin, and irinotecan; (PARP) poly(ADP-ribose) polymerase; (SOX) S-1 and oxaliplatin; 1- Lowery (2011) and Vyas (2015): studies not included in the *meta*-analysis; 2- Golan (2014): *meta*-analysis used data from 43 of 71 patients, representing patients with clinical stage III-IV and available data on *BRCA* mutation and use of platinum-based therapy; patients using PARP inhibitors were excluded; *Clinical stage was classified according to AJCC 7th edition; ** The median overall survival was not reached in the final analysis, and the 20.1-month follow-up was then used. Reiss (2018) originally included 29 patients in the study, but 2 patients with *PALB2* mutation were excluded based on information provided by the author; ¥ data from all cohort; a: VUS were assessed for pathogenicity using in silico prediction algorithms; b: 4 of the patients harboring VUS.

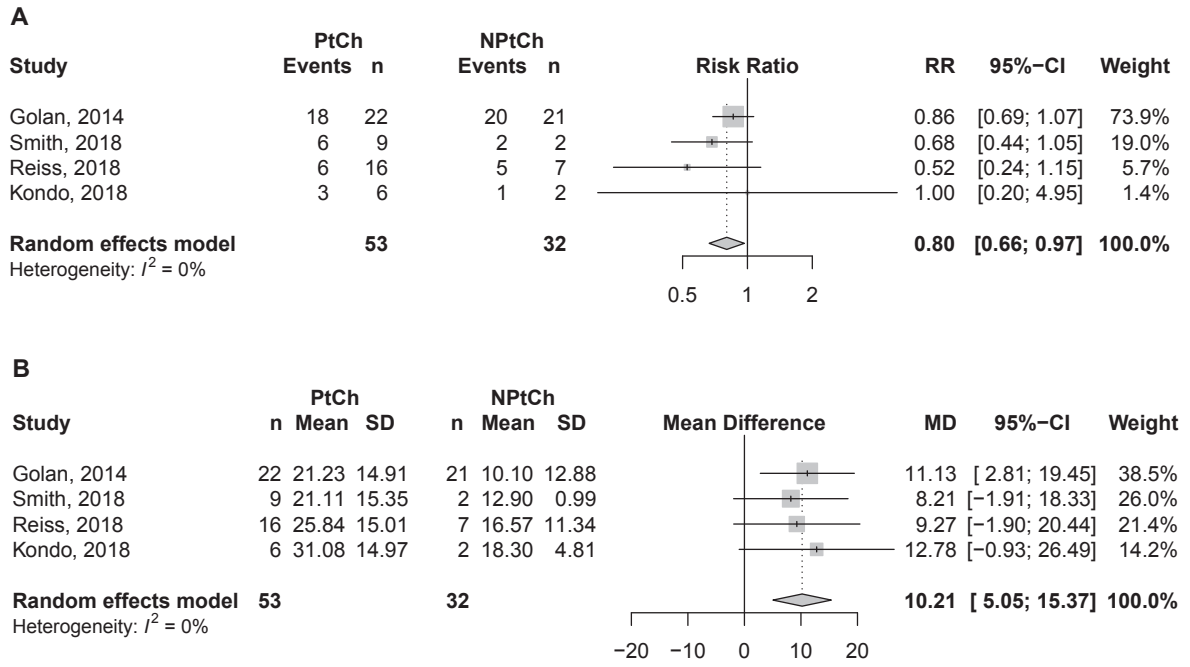

Fig. 2. Overall survival of patients with clinical stage III-IV pancreatic ductal adenocarcinoma. (A) Relative risk for overall survival with platinum-based chemotherapy (PtCh) vs non-platinum-based chemotherapy (NPtCh). (B) Mean difference in overall survival (months) between PtCh and NPtCh.

between the groups was 4.14 months in favor of the PtCh group (95%CI − 4.86 to 13.15; $P = 0.37$; very low quality of evidence), but this difference was not statistically significant (Fig. 3).

Most studies included patients with well-known pathogenic g*BRCA*m. However, Kondo et al. [26] included *BRCA* VUS mutations in their cohorts. Smith et al. [43] also evaluated VUS carriers, and these VUS were assessed for pathogenicity using in silico prediction algorithms. Although knowledge of the real meaning of VUS mutations in PDAC is scarce, even with the exclusion of the study by Kondo et al from the meta-analysis, there was still a benefit from using platinum (RR 0.79, 95%CI 0.65–0.97; $P = 0.03$ and MD 9.78 months, 95%CI 4.21–15.35; $P < 0.001$) (Appendix C).

Studies had a high risk of bias, and the overall quality of evidence was considered very low. Detailed data of the Newcastle-Ottawa scale for quality assessment and GRADE for quality of evidence are reported in Appendix D and Appendix E, respectively.

Discussion

The present review and meta-analysis showed a significant improvement in OS in patients with CS III-IV gBRCAm PDAC treated with PtCh compared with patients who received NPtCh. This confirms the hypothesis that g*BRCA*m PDAC is more sensitive to platinum than to non-platinum compounds [7,10,22,28,30,31]. However, this conclusion should be carefully considered, as the type and heterogeneity of the studies and the very small number of patients evaluated expose to a high risk of biases.

We are fully aware that this systematic review and meta-analysis has several limitations, including the retrospective design of the studies, the variety of clinical settings, the heterogeneity of chemotherapy regimens, and unbalanced patient and tumor characteristics between the 2 groups analyzed (PtCh vs NPtCh). A further potential bias may be related to the fact that the intervention group received polychemotherapy more often that the control group. In addition, adjusted estimates were not available.

An interesting feature raised by the present study was the high proportion of patients of Ashkenazi Jewish descent, in whom 3 predominant *BRCA1* (185delAG, 5382InsC) and *BRCA2* (6174delT) mutations were most commonly detected [44]. However, studies conducted in different countries and involving patients with sporadic PDAC harboring different mutations were also included in this review. Therefore, we believe that the results of the present meta-analysis can be applied to patients harboring g*BRCA* mutations regardless of their ethnicity.

An emerging personalized treatment strategy in this scenario is the use of PARP inhibitors. In PDAC, some clinical trials exploring the combined or sequential use of PtCh and PARP inhibitors are ongoing [45,46]. The recently published POLO (Pancreas Cancer Olaparib Ongoing) trial showed a PFS benefit with a maintenance olaparib compared with placebo in patients who had not progressed during a first-line PtCh. However an interim analysis (data maturity, 46%) showed no difference in OS between the 2 groups (median, 18.9 months for olaparib vs 18.1 months for placebo) [46]. The POLO trial design is outside the focus of our meta-analysis and therefore the results of this trials did not change our conclusions.

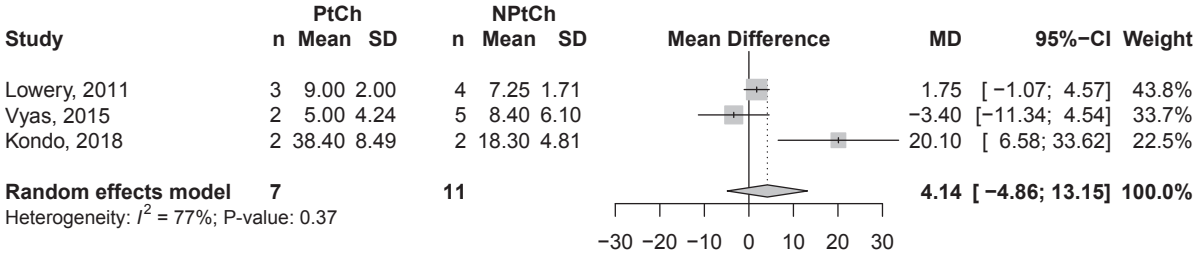

Fig. 3. Progression-free survival for platinum-based chemotherapy (PtCh) as first-line treatment.

Previous guidelines recommended genetic testing for patients with a diagnosis of PDAC, especially those with a family history of cancer, of Ashkenazi Jewish descent or young patients. However, the prevalence of patients with PDAC harboring pathogenic germline mutations (including *BRCA* mutation) without a family history of cancer or Ashkenazi Jewish heritage is higher than expected [47]. A recent study demonstrated that, of 122 patients with exocrine pancreatic neoplasms (108 with PDAC) and germline alterations, 41.8% did not meet previous guidelines for germline testing [12]. Likewise, a study evaluating 306 patients with incident PDAC identified 14 patients (4.6%) with g*BRCA* mutations; of these, 8 (57%) did not meet previous *BRCA* genetic testing criteria of the National Comprehensive Cancer Network (NCCN) and 9 (64%) did not meet the criteria of the Ontario Ministry of Health and Long-Term Care [7]. The latest NCCN guideline recommends that all patients with pancreatic cancer at any age should be encouraged to perform a genetic risk assessment. Assuming that patients with PDAC would have a better prognosis if provided with personalized treatment regimens, the identification of these patients may be key to such an improvement. Therefore, we underscore the importance of considering genetic testing in every patient with PDAC.

Other genetic mutations that interfere with homologous recombination have been studied, such as *PALB2* and *ATM* mutations, and it is possible that patients harboring these mutations may also benefit from the PtCh strategy. Similarly, somatic *BRCA1/2* mutations presumably also have high sensitivity to platinum compounds, although further studies are warranted to clarify this issue.

In conclusion, the findings of this systematic review and meta-analysis confirmed the hypothesis that a PtCh is more effective than NPtCh for patients with gBRCAm PDAC, showing a significant OS benefit in favor of PtCh-treated patients. However at the same time our study remarked the very low level of evidence about this topic, coming from the very low number of evaluable patients, heterogeneity and type of studies, all of them exposing to a high risk of biases. Therefore this hypothesis needs to be investigated with randomized trials in homogenous clinical settings.

Contributors

TR, NF, MP, FS, CAC, AL and SP participated in the conception of the study. All authors designed the study, interpreted the data and wrote the manuscript. TR, MP and MF collected the data. TR and MF performed the statistical analysis. All authors reviewed the manuscript and approved the final version.

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Disclosure

The authors have declared no conflicts of interests.

Appendix A

List of excluded studies after full-text screening.

Study	Reason for exclusion
Lowery MA	Presented data did not allow comparison of platinum vs non-platinum therapy (no information about treatment or no treatment in control group)
O'Reilly EM	No comparison group
Lundberg J	No comparison group and impossibility to assess data only from patients with *BRCA* mutation
Waddell N	No comparison group and xenograft group
Leung K	Duplicate data
Kondo T	Duplicate data and presented data did not allow comparison of platinum vs non-platinum therapy
Connor A	Presented data did not allow comparison of platinum vs non-platinum therapy
Rahib L	Presented data did not allow assessment of outcomes of interest
Golan T	Duplicate data
Mathew B	Case report
Hingorani SR	Presented data did not allow assessment of outcomes of interest
O'Kane GM	Duplicate data and impossibility to assess data only from patients with *BRCA* mutation
Aung KL	Duplicate data (overlap of patients from same center of other studies)
Faluyi OO	Duplicate data (overlap of patients from same center of other studies)
Shahda S	Presented data did not allow comparison of platinum vs non-platinum therapy
Golan	Clinical Stage I-II
Blair	Clinical Stage I-II

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Appendix B

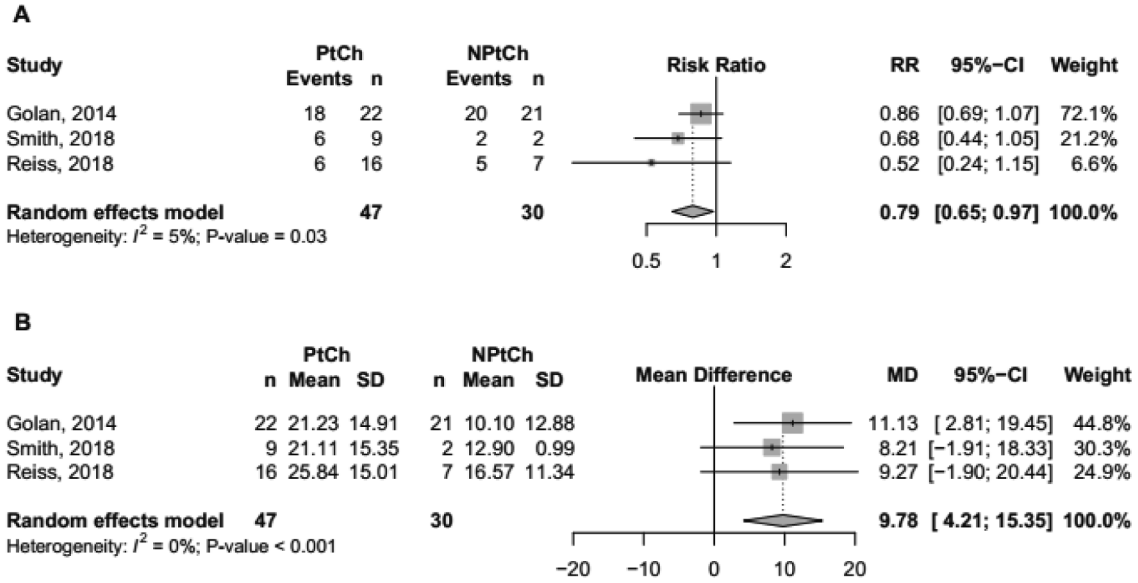
Data on family and personal history of cancer and Jewish heritage.

Author, year, country	Personal history of malignancy, n (%)	Family history of cancer, n (%)	Jewish heritage (%)
Lowery, 2011, United States	9 of 15 (60%) *	12 (80%) FDR with breast, ovarian, prostate, or pancreatic cancer *	8 (53%) *
Golan, 2014 Israel, Canada, United States	26 of 71 (37%)*	58 of 70 (82%) * − 91% (53/58) FDR	52 out of 71 (73%), of whom 47 (90.4%) were Ashkenazi Jews *
Vyas, 2015, United States	4 (40%)*	NA	4 (40%)*
Smith, 2018 Canada	4 (19%)*	7 (33%) ≥ 1 FDR/SDR with PDAC* 14 (66%) ≥ 2 FDR/SDR breast, ovarian, or prostate cancer, or PDAC *	3 (16%)*
Reiss, 2018 United States	11 (41%)	25 (96%)	NA
Kondo, 2018Japan	NA	5 (62%)	NA

Abbreviations: (FDR) first-degree relative; (SDR) second-degree relative; (NA) not available; (PDAC) pancreatic ductal adenocarcinoma; * total study sample.

Appendix C

Relative risk for overall survival with platinum-based chemotherapy (PtCh) vs non-platinum-based chemotherapy (NPtCh) in patients with confirmed pathogenic germline *BRCA* mutation, without variants of unknown significance (VUS).



Appendix D

Quality assessment by the Newcastle-Ottawa scale

Study	Selection				Comparability	Outcome		
	Representativeness of the exposed cohort	*Selection of the nonexposed cohort*	*Ascertainment of exposure*	*Outcome of interest not present at start of study*	*Control for important factor or additional factor*	*Assessment of outcome*	*Follow-up long enough from outcomes to occur*	*Adequacy of follow-up cohorts*
Lowery, 2011	*	–	*	*	–	–	*	*
Golan, 2014	*	–	*	*	–	*	*	*
Vyas, 2015	*	–	*	*	–	–	*	*
Smith, 2018	*	*	*	*	–	*	*	*
Reiss, 2018	*	*	*	*	–	*	–	*
Kondo, 2018	*	–	*	*	–	*	*	*

Appendix E

Quality of evidence by the GRADE approach

Platinum-based chemotherapy compared to non-platinum-based chemotherapy for pancreatic ductal adenocarcinoma with germline *BRCA* mutation

Certainty assessment							Summary of findings				
No. of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With non-platinum-based chemotherapy	With platinum-based chemotherapy		Risk with non-platinum-based chemotherapy	Risk difference with platinum-based chemotherapy
Stage III-IV: Overall survival (months)											
85 (4 observational studies)	serious [a]	not serious	not serious	not serious	none	⊕○○○ VERY LOW	32	53	–	The mean overall survival (months) was 12.20 months	MD 10.21 months more (5.05 more to 15.37 more)
Stage III-IV: Progression free survival (months)											
18 (3 observational studies)	serious [a,b]	not serious	not serious	serious	none	⊕○○○ VERY LOW	7	11	–	The mean progression-free survival (months) was 9.78 months	MD 4.14 months more (4.86 fewer to 13.15 more)

Abbreviations: (CI) confidence interval; (MD) mean difference; (RR) risk ratio.

Explanations: a. Estimates are based on crude analyses, since adjusted analyses were not possible. Patients receiving platinum-based chemotherapy may have received more intensive chemotherapy regimens, and it is possible that these patients had better performance status; b. Progression-free survival was not adjudicated by independent outcome assessors.

Appendix F. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctrv.2019.101895.

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