(REVIEW ARTICLE)

Systematic review and meta-analysis on safety and efficacy of immune checkpoint inhibitors and radiotherapy for advanced pancreatic cancer

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Abstract

Objective: The aim of this study is to assess the safety and efficacy of stereotactic body radiotherapy (SBRT) in combination with immune checkpoint inhibitors (ICIs) in patients with advanced pancreatic cancer.

Method: A PRISMA selection protocol was used to identify studies across electronic databases such as; PubMed, Google scholar, Cochrane, Embase, and web of science from inception until November 23, 2022, where data from SBRT studies were compared to data from a combination of SBRT and ICIs for advanced pancreatic cancer. The endpoints recorded after therapy were overall survival (OS), complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), progression-free survival (PFS) and treatment-related adverse effect (TRAE) were collected in each study.

Results: The primary endpoint (OS) retrieved from five studies following SBRT disclosed OS at the rate of one year at 44% as compared to the combination studies of SBRT+ICI with 42%. PFS recorded at the rate of 1 year revealed an outcome of 46% following SBRT. In contrast, PFS in the combination studies recorded SBRT+ICI of 86%. The risk of grade >3 TRAE in the SBRT was 21.5% as compared to the combination studies of 75%. This risk of grade>3 TRAE was reduced as compared to any grade in two studies (Heterogeneity: Chi^2 = 2.78, df = 1 (P = 0.10); I^2 = 64%).

Conclusion: The Combination of SBRT and ICIs demonstrate modest treatment efficiency and acceptable safety profile in patients with advanced pancreatic cancer. However, combination trials are fewer, and further studies are warranted.

Keywords: Radiotherapy; Immune checkpoint inhibitors; Immunotherapy; Pancreatic cancer; Stereotactic body radiation therapy

1. Introduction

In recent years, there has been a significant increase in pancreatic cancer (PC) cases worldwide. In 2021, the National Cancer Center of China released data confirming the occurrence of PC to be 7th in males and 11th in females. PC is also reported to have the sixth highest mortality rate among other malignant cancers(1). Surgical procedures are the main treatment option, but only 15-20% of patients with advanced pancreatic cancer appear to be respectable(2). Survival (5 years) after surgery is usually 10% to 20%, with an average survival time of 24 months(2, 3).

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Radiation therapy (RT) is an effective method used to treat PC at all stages. Scientific studies have indicated an increase in peripheral cancer immunity following RT,and while the exact mechanism is not entirely understood, it is believed to related to cell death caused by radiation(4, 5, 6).This cell death leads to the exposure of tumor antigens, which in turn enhances the intracellular cross-presenting peptide pool and stimulates the function of radiation-killed cells(7).This mechanism can function as an in situ vaccine to combat cancer (8).

Given the controversy surrounding RT in the treatment of PC in the clinical setting, a new application with great potential for RT is its combination with other therapies such as, ICIs(9).Immunotherapy(IT) has recently demonstrated its therapeutic potential in solid tumors. Due to this IT oncology treatments have become more popular (10).Patients with different types of cancer have consistently experienced durable responses when ICIs targeting the CTLA-4,PD-1,or PD-L1 are used(11). However, these successes could not be repeated in PC(12, 13, 14). However, ICIs have only shown benefits in advanced pancreatic cancer that display microsatellite instability(MSI) or mismatch repair (MMR) deficiency (15, 16).

In this study, we reviewed and compared the efficacy and safety of combination therapy with SBRT and ICIs for patients with advanced pancreatic cancer.

2. Material and Method

2.1. Search strategy

The structure of this systematic review and meta-analysis followed the PRISMA guidelines(17). The search was executed to identify comprehensive original published papers involving SBRT and treatment with both SBRT+ICIs for advanced pancreatic cancer. PubMed, Google Scholar, Cochrane, Embase, Medline, and web of science, from inception until November 23, 2022, were systematically queried for human studies, titles, and abstracts. The search strategy contains five keywords: Radiotherapy; Immune checkpoint inhibitors; Immunotherapy; Pancreatic cancer; and stereotactic body radiation therapy.

2.2. Study criteria

2.2.1. Inclusion criteria

- Combination treatment with PD-1, PD-L1, CTLA-4 and radiotherapy (SBRT)
- Only Published English articles
- Histologically confirmed pancreatic adenocarcinoma.
- RCT and non-RCT were used.
- Unresectable advanced, recurrent, or metastatic pancreatic cancer.
- Previous systemic anticancer management administered as prime therapy
- Phase I and II trials, report at least one clinical outcome.
- Implementation ECOG performance status of 0-1.

2.2.2. Exclusion criteria

- Animal studies
- Reviews
- Case reports
- Articles written in a language other than English were excluded.

2.3. Data Extraction

We extracted data from selected literature. The authors, publication year, study design, trial phase, clinical trial number, number of patients in SBRT and number of patients included in combination therapy (PD-1, PD-L1, CTLA-4 and SBRT) as shown in Table 1. OS, CR, PR, SD, PD, PFS, and TRAE were all considered as the post-therapy outcomes, as shown in Table 2. Data from studies that collected SBRT were compared to data retrieved from combination of both SBRT and ICIs.

2.4. Statistical Analysis

Statistical analysis was performed using the Cochrane Collaboration's Software Review Manager (RevMan) version 5.4. Odds ratios (OR) with 95% confidence intervals (CI) were used to pool dichotomous variables. Random-effects and

fixed-effects (OR or RR) models were calculated using the Mantel-Haenszel statistical method. The consistency statistic (I^2) was used to assess heterogeneity between studies. Pooled results were considered significant and heterogeneous when I^2 was 50%. A random effects model was then applied. A P-value < 0.05 was considered statistically significant.

2.5. Quality Assessment

This study independently assessed study quality using the Cochrane Handbook for Systematic Reviews of Interventions version 5.1 risk of bias tool. Sequence generation, allocation concealment, blinding, incomplete data, selective reporting, and other sources of bias were assessed. The term 'high risk' was used to denote studies at high risk of bias in one or more important areas. A study was classified as 'low risk' if it had a low risk of bias in all major domains. Otherwise, it was classified as 'unknown' as shown in Figures 3a and b. Disagreements between researchers were resolved through discussion with the corresponding author.

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3. Results

A total number of 500 studies were searched, of which 63 of the studies were fully examined in detail. Finally, 11 articles including 363 patients were included in the studies. These studies comprise five studies with 174 patients describing SBRT and 189 patients reporting SBRT in combination with ICIs, as shown in Fig. 1. Of the 11 studies, 5 were non-randomized control trials, and 6 were randomized control trials. Studies reported endpoints such as OS, PFS, CR, PR, SD, PD, and TRAE, shown in Table 2.

3.1. Study Endpoints Assessments

The primary endpoint was OS for one year. Which is defined as the time between treatment and death. The secondary endpoints were PFS, CR, PR, SD, and PD. PFS, defined as the time from enrolment to the first documented disease progression. The CR, PR, SD and PD were evaluated according to RECIST 1.1(18). CR is defined as no radiographic detectable evidence of tumor.CR is generally measured through imaging studies. PR is defined as at least a 30% decrease in the sum of the target lesions.SD is defined as fitting the criteria neither for progressive disease nor a PR. PD is when at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. Safety endpoints included TRAE. TRAEs identified in the study were analyzed using the National Cancer Institute's Common Terminology Criteria version 4.0(19). Table 2

3.2. Overall Survival (OS): Primary endpoint

The use of SBRT was recorded in five studies with total of 174 patients. The primary endpoint was OS which was collected from five studies (20, 21, 22, 23, 24). OS was calculated from the end of SBRT to death(24). The OS from the time of SBRT for one year was 44%. However, four studies (25) with a sum of 146 patients used a combination of SBRT+ICI in their treatment and the OS was 42%.

3.3. Progression-free survival (PFS), Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD): Secondary endpoint

PFS was calculated from the end of SBRT to the disease progression data (24). However, three studies (20, 23, 24) with a total of 83 patients collected PFS at the rate of 1 year, and the overall outcome was 46% after SBRT. Conversely, PFS recorded in three studies(25, 26, 27) with a total of 116 patients after SBRT in combination with ICI displayed 86% . Two studies(22, 24) with total of 51 patients recorded CR of 7.8% following SBRT. Meanwhile in the combination therapy of SBRT +ICI in one study (28),including 10 patients recorded a CR of 70%. Four studies(20, 22, 23, 24) with a sum of 103 patients recorded total PR of 44% when SBRT was used. But PR after the SBRT+ICI in two studies(26, 29) with 67 patients indicated a PR of 9%. Three studies(22, 23, 24) with total of 81 patients received SBRT and the SD was 29.6%.However,combination therapy of SBRT+ICI collected from three studies(26, 28, 29) with a total of 77 patients resulted in 25% . One study(22) involving 20 patients received SBRT and the records revealed a PD of 15%.Though PD in the combination treatment with SBRT+ICI among 67 patients revealed 54% in two studies(26, 29). Table 2

3.4. Safety Assessment

Several patients were lost to follow-up due to deterioration or mortality in the various studies(20). The incidence of grade>3 acute and late toxicities such as nausea, fever, vomiting, diarrhea, weight loss, fatigue, abdominal pain, and constipation was recorded. Toxicities were seen in a total of 121 patients collected from three studies(21, 22, 23) after SBRT and the total risk of grade>3 TRAE was 21.5%.Four studies(27, 28, 29, 30) were collected for TRAE, including 138 patients and total risk of TRAE recorded was 75%. But, no treatment-related deaths were seen during the combination trial of SBRT and ICI in each study. Some adverse events recorded were fatigue, diarrhea, adrenal

insufficiency, colitis, arthralgia, myalgia, increased serum aspartate aminotransferase levels, lymphopenia, anemia, thrombocytopenia, pruritus, hyponatremia, hypoalbuminemia, leukopenia, skin rashes, and fever. All patients experience at least one treatment-related adverse event. Table 2

Meta-analysis of TRAE for risk of any grade, grade>1(1-2), and grade>(3-4) was analyzed after administration of SBRT and ICI.Two studies(26, 29) reported TRAE of any grade(67 patients) and grade>3(67patients).The was a significant difference between two groups. The risk of grade>3 TRAE was decrease after SBRT in combination with ICI. Heterogeneity: Chi^2 = 2.78, df = 1 (P = 0.10); I^2 = 64%. Test for overall effect: Z = 4.59 (P < 0.00001).Figure 2a

Two studies(27, 28) recorded the incidence of fatigue, nausea and fever .There was a significant difference between the two grades. The risk of grade>3 was decrease as compared to grade>1.Fatigue(Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.50, df = 1 (P = 0.48); I^2 =0%. Test for overall effect: Z = 6.19 (P < 0.00001)Figure 2b, Nausea (Heterogeneity: Tau^2 = 0.02; Chi^2 = 3.42, df = 1 (P = 0.06); I^2 = 71%. Test for overall effect: Z = 2.05 (P = 0.04)Figure 2c and Fever (Heterogeneity: Tau^2 = 0.01; Chi^2 = 1.97, df = 1 (P = 0.16); I^2 = 49%. Test for overall effect: Z = 2.63 (P = 0.009) Figure 2d.

Table 1 General Characteristics of Patients

Author	Study Year	Nationality	Study Design	Trial Phase	Clinical Trial Number	Median Age(range)years	SBRT	ICIs+SBRT
Morten Hoyer (20)	2005	Denmark	nRCT	II	-	-	22	-
Jean-Claude Rwigema (21)	2010	USA	nRCT	II	-	71(33-91)	71	-
K Goyal(22)	2014	USA	nRCT	-	-	74(54-91)	20	-
Youngsek Seo(23)	2009	Korea	nRCT	-	-	-	30	-
T.Comito (24)	2016	Italy	nRCT	-	-	69(40-87)	31	-
Aparna R.Parikh (25)	2022	USA	nRCT	II	NCT03104439	60(32-75)	-	25
Inna M.Chen (29)	2022	Denmark	RCT	II	NCT02866383	63(37-80)	-	41
Inna M.Chen(26)	2022	Denmark	RCT	II	NCTO4258150	62(54-71)	-	26
Changqing Xie(28)	2020	-	RCT	-	NCT02311361	61.5(48-77)	-	10
Jennifer Wu(30)	2020		RCT	Ib	-	-	-	2
Xiaofei Zhu(27)	2021	China	RCT	II	NCT02704156	65(54-74)	-	85

Table 2 Post Therapy Outcome

| Author	Intervention	OS	CR	PR	SD	PD	PFS	TRAE
Morten Hoyer (20)	SBRT(Gy) n=22	1(5 %)	-	2(9%)	-	-	2(9%)	-
Jean-Claude Rwigema (21)	SBRT(Gy) n=71	29(41%)	-	-	-	-	-	3(4.2%)
K Goyal(22)	SBRT(Gy) n=20	11(56%)	2(13%)	5(31%)	6(38%)	3(15%)	-	3(16%)
Youngsek Seo (23)	SBRT(Gy) n=30	18(60%)	-	17(68%)	3(12%)	-	21(70.2%)	20(66.7%)
T.Comito (24)	SBRT(Gy) n=31	17(58%)	2(6%)	11(35%)	15(48%)	-	15(48%)	-
Total		76/174(44%)	4/51(7.8%)	35/103(44%)	24/81(29.6%)	3/20(15%)	38/83(46%)	26/121(21.5%)
Aparna R.Parikh (25)	ICIs+SBRT n=25	2(8%)	-	-	-	-	11(43%)	-
Inna M.Chen (29)	ICIs+SBRT(Gy)n=41	-	0	1(2.4%)	6(14.6%)	28(68.3%)	-	30/41(73.2%) Any versus grade >3
Inna M.Chen(26)	ICIs+SBRT(Gy)26	1(4%)		5(19%)	12(46%)	8(31%)	1(4%)	Any versus grade >3
Changqing Xie (28)	ICIs+SBRT(Gy)n=10	10/8(80%)	7(70%)	0	1(12%)	-	-	3/10(33.3%) Grade>1versus grade >3
Jennifer Wu (30)	ICIs+SBRT(Gy)n=2	-	-	-	-	-	-	1(50%)
Xiaofei Zhu(27)	ICIs+SBRT(Gy)85	48(56.5%)	-	-	-	-	74(87.1%)	70(82%) Grade>1versus grade >3
Total		61/146(42%)	7/10(70%)	6/67(9%)	19/77(25%)	36/67(54%)	86/116(74%)	104/138(75%)
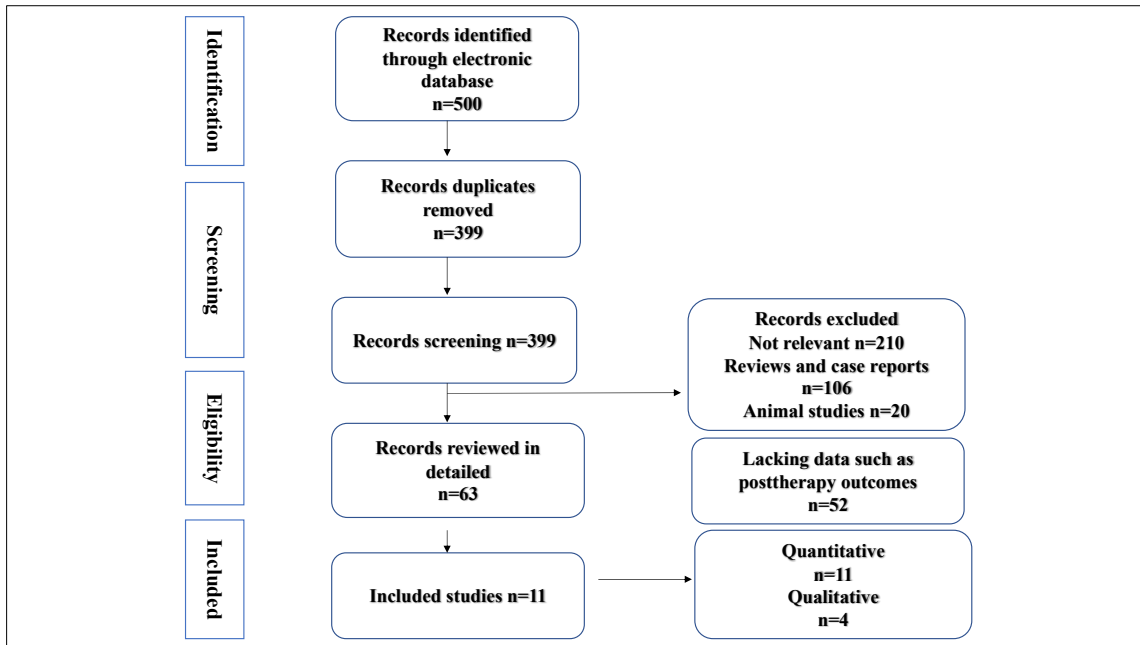
Figure 1 Flow diagram for selected studies

3.5. Meta-analysis of TRAE

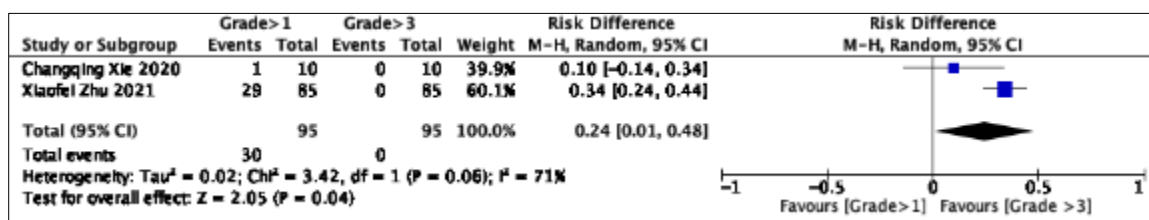### Any Grade versus Grade >3
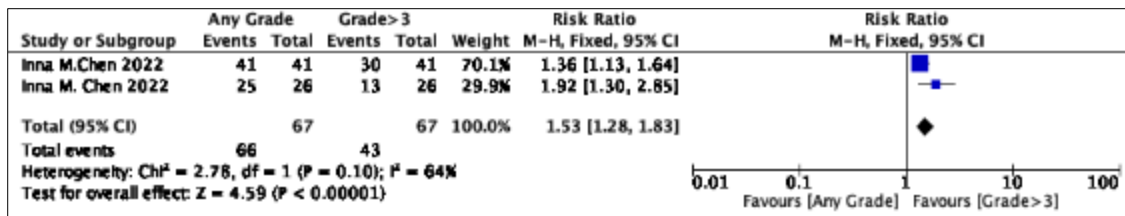
Fatigue (Grade>1 versus Grade >3)
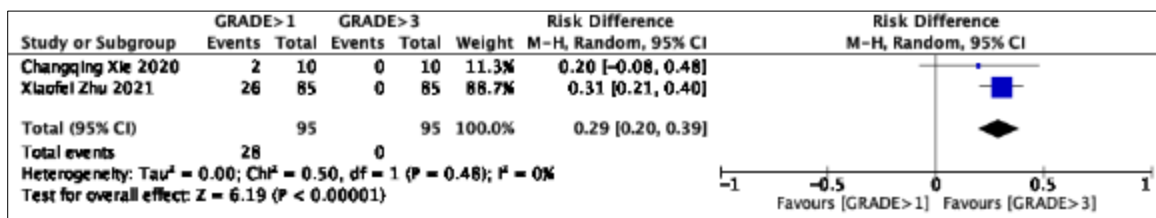
Nausea (Grade>1 versus Grade >3)
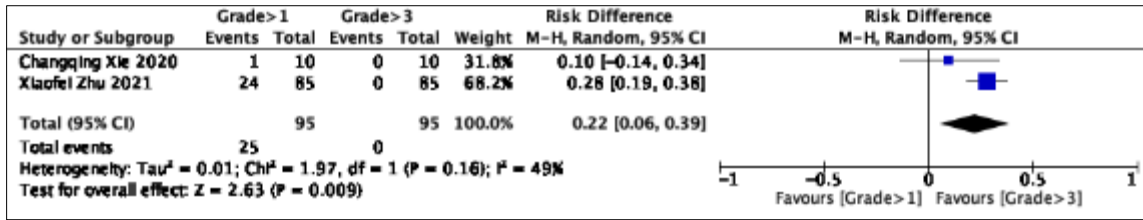

Fever (Grade>1 versus Grade >3)

Figure 2 Forest plot of a; Any grade versus grade>3.b; Fatigue(grade>1versus grade>3).c; Nausea(grade>1versus grade>3). d; Fever(grade>1versus grade>3).
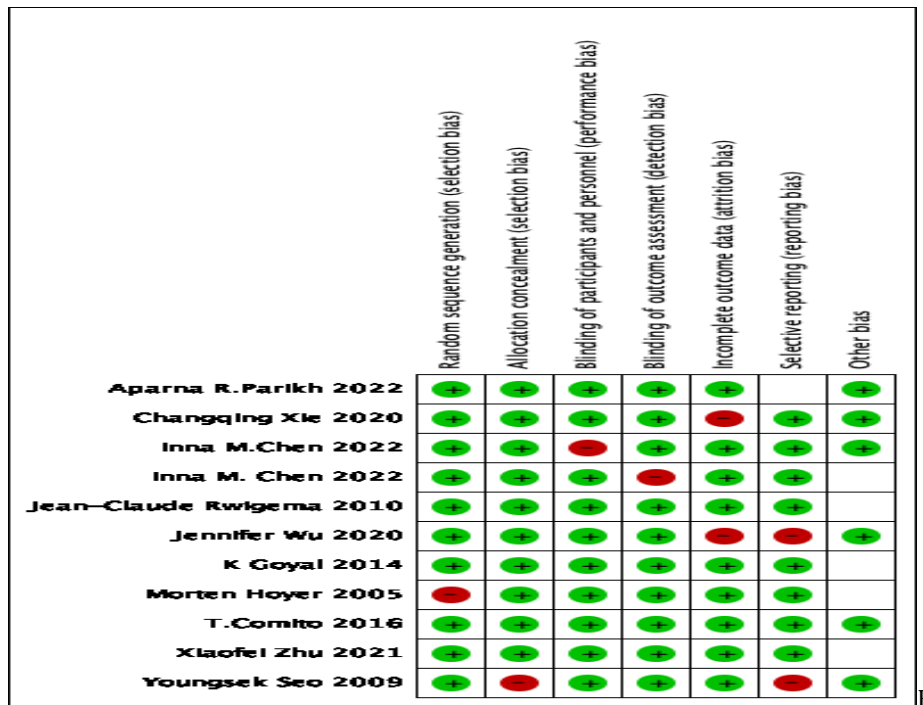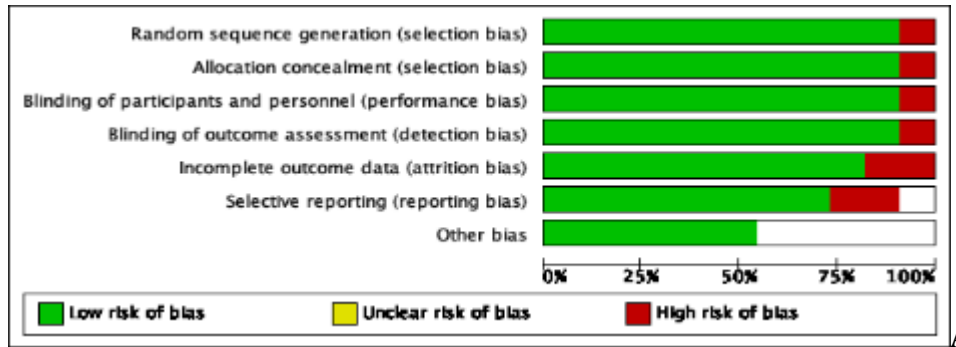

Figure 3 a; Risk of bias graph: review authors judgements about each risk of bias item presented as percentages across all included studies'; Risk of bias summary: review authors judgements about each risk of bias item for each included study ARP(25) ,CX(28) ,IMC(29),JMCR(21),JW(30),KG(22),MH(20),TC(24),YSS(23) ,IMC(26),XZ(27)

4. Discussion

The emphasis of the systematic review and meta-analysis was on the effectiveness and safety of combined SBRT and ICIs (PD-1, PD-L1, and CTLA-4) for treating patients with advanced pancreatic cancer as well as how RT influences the effectiveness of ICIs.

Integrating 11 including studies (5 SBRT and 6 combination therapy) and data from 363 patients with advanced pancreatic cancer, our pooled data showed that, the incidence of grade>3 TRAE in all studies recorded 75% (104 patients) in the combination therapy studies and as compared to the SBRT studies with 21.5% in 26 patients. A recent advanced in combination approach (RT and nivolumab) on other cancer cancer also recorded grade >3 to be 48% (31).The meta-analysis also reported the risk of having any grade, grade>1 and grade>3 TRAE after the use combination of SBRT and ICIs. The analysis showed that, the risk of grade>3 was decreased after combination therapy than the risk of any grade (Heterogeneity: Chi^2 = 2.78, df = 1 (P = 0.10); I^2 = 64%). In addition, the risk of grade> 3 fatigue, nausea and fever were also decreased as compared to grade>1 with I^2=0%, I^2 =71% and I^2 =49% respectively. Still, upcoming RCTs are essential to modify this conclusion. These outcomes in our studies may signify that dual ICI combined with low fraction dosing has a more substantial immunomodulating effect(28). The reason for the poor results of immunotherapy in the past trials is that pancreatic adenocarcinoma is a cancer with deprived immunogenicity and low tumor mutational burden(13). Therefore, appropriate dosing of SBRT with dual ICI needs to be considered for further studies.

It may be beneficial to investigate combined therapies as an alternative given that the preliminary results from trials investigating the efficacy of immunotherapy as a standalone treatment for pancreatic cancer have not been encouraging(12, 13).In the overall studies, in terms of comparison between the SBRT and SBRT plus ICIs studies, the primary endpoint(OS) was 44% and 42% respectively. The OS at the rate one year saw a mild difference among the two groups. These findings suggest that local control should be a taken seriously. However, studies by Xiaofei Zhu et al, revealed that the combination of RT and IT led to a clinically significant decrease in the risk of death, with an HR of 0.69 (95% CI 0.44-0.95) for overall survival (32).We analyzed PFS between the studies ,the SBRT recorded 46 %(38 patients) and the combination therapy with 74%(86 patients). There was no discernible change in OS between the two concurrent therapy schedules when PD-L1 blockade was added on days 1 and 5 of radiotherapy or seven days after radiotherapy, according to other studies(33). The impact of scheduling RT and ICIs blockade on survival has also been largely inconsistent, with some retrospective studies finding no significant difference in OS between concurrent and nonconcurrent radioimmunotherapy while others found that patients who had ever received RT prior to PD-1 blockade fared significantly better in terms of PFS and OS than those who had not(34, 35, 36).

Of 11 studies evaluable in efficacy analyses, 51 patients in the SBRT studies had a CR of 7.8% and 10 patients in combination of SBRT and ICI had 70%. In the SBRT studies,103 patients recorded an overall PR of 44% and SBRT + ICI involving 67 patients showed PR of 9%. Wanting Huo et al, described combination of SBRT plus ICIs with ORR of 5.1%(37).Therefore, combining dual ICI therapy with SBRT did not yield a better response. Study on 6 (14%) patients in combination with SBRT and ICIs arm attained a PR, which was confirmed in five patients and lasted for a median of 5.4 months, suggesting durable clinical benefit in some patients with metastatic pancreatic cancer(mPC) with the proposed strategy (29). In the SBRT studies, 81 patients reported SD of 29.6% and combination therapy (SBRT+ICI) with a total of 77 patients resulted in 25% .20 patients in the SBRT studies revealed a PD of 15%. Though PD in the combination treatment with SBRT+ICI among 67 patients revealed 54%. These results demonstrate similar clinical outcome compared to previous reports of no response with ICI monotherapy or a 1.5% ORR with dual ICI in advanced pancreatic ductal adenocarcinoma(PDAC)(12, 13, 14, 38).

This current study had several limitations. Firstly, there was a variation in sample size among the studies, which could hinder investigations. Secondly, for the comparison of OS and PFS to be possible, more studies are required in each group. Thirdly, administering different types of immunotherapy can also affect the studies and result in fewer Tshene, more studies are necessary to assess the use of PD-1/PD-L1/CTLA-4 and <u>stereotactic body radiation therapy</u>.

5. Conclusion

In summary, the combination of SBRT and ICIs demonstrate modest treatment efficiency and acceptable safety profile in patients with advanced pancreatic cancer. However, combination trials are fewer, and further studies are warranted. Furthermore, SBRT in combination with ICIs (Nivolumab, ipilimumab, durvalumab, and tremelimumab) can increase antitumor activity and results in comparable rates of adverse event to either modality alone in advanced pancreatic cancer. The dose and sequence of ICIs and radiation therapy will be investigated in forthcoming studies.

Compliance with ethical standards

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