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Entitled "Comparison of Efficacy Between Adjuvant Chemotherapy and Chemoradiation Therapy for Pancreatic Cancer After R0 Resection: AJCC Stage-based Approach"

April 27th, 2020

Hiten RH Patel,

Editor-in-Chief, *World Journal of Clinical Oncology*

Dear Professor Hiten RH Patel,

Thank you for your careful review of our manuscript entitled "Comparison of Efficacy Between Adjuvant Chemotherapy and Chemoradiation Therapy for Pancreatic Cancer After R0 Resection: AJCC Stage-based Approach" and all the helpful comments and suggestions. We have revised our manuscript taking into account all the comments. Changes have been made by changing the color to RED in the revised manuscript to avoid any confusion. We hope that we have addressed all the comments and the changes will be considered satisfactory.

Yours sincerely,

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Point-by-Point Responses to the Reviewer's comments

Reviewer #1

Comment 1. The adjuvant SCT and/or CRT regimen was determined by multidisciplinary discussions with each patient. Since the decision to undergo CRT, SCT or CRT-SCT was undertaken in an "off-protocol" setting in the study hospital, some information about the selection criterias for the three different adjuvant regimens in the authors institution should be presented in the Methods section.

RESPONSE: Thank you for the precious comment. Decisions regarding the type of treatment were discussed in a multidisciplinary team, where clinic-pathological characteristics including age, comorbidity, recovery from surgery, primary tumor extent, lymph node involvement, and surgical margin status were comprehensively reviewed. Since there have been conflicting results regarding CRT as adjuvant treatment, there was no standardized selection criteria to determine the treatment regimens. Due to the retrospective nature of the study, there were limited data regarding treatment decision. We additionally described this information in **"MATERIALS AND METHODS"** part as follows:

Before: In page 5, "Adjuvant treatment" of MATERIALS AND METHODS

The adjuvant SCT and/or CRT regimen was determined by multidisciplinary discussions with each patient.

After: In page 6, "Surgical procedure and adjuvant treatment" of MATERIALS AND METHODS

Decisions regarding the type of treatment were discussed in a multidisciplinary team, where clinic-pathological characteristics including age, comorbidity, recovery from surgery, primary tumor extent, lymph node involvement and surgical margin

status were comprehensively reviewed.

Comment 2. Please define R0 resection. 1 mm rule? How many patients underwent R1 resection at the study centre during the study period? In the Results section it s stated that 126 (37.6%) patients had a safety margin of less than or equal to 0.1 cm=R1 according to current definitons. Thus the title of the manuscript is misleading. Isn`t this paper actually describing both R0 and R1 resections?

RESPONSE: Thank you for your important comment. We defined R0 resection as microscopic absence of tumor cells at definite resection margin. We agree that the title is misleading since we did not use the definition of R0 resection according to AJCC 8th guideline (1mm rule). Therefore, we changed the title of the manuscript and additionally described the definition of R0 resection in the methods part.

Before: In page 2, METHODS of ABSTRACT

A total of 335 patients who underwent resection and adjuvant treatment for PC were included

After: In page 2, METHODS of ABSTRACT

A total of 335 patients who underwent R0 resection and adjuvant treatment for PC were included. R0 resection was defined as microscopic absence of tumor cells at definite resection margin.

Before: In page 5, "Study population" of MATERIALS AND METHODS

Medical records of patients who underwent complete microscopic resection for pancreatic ductal adenocarcinoma (PDAC) at Seoul National University Hospital from September 2005 to December 2017 were reviewed.

After: In page 6, "Study population" of MATERIALS AND METHODS

Medical records of patients who underwent complete microscopic resection for pancreatic ductal adenocarcinoma (PDAC) at Seoul National University Hospital from September 2005 to December 2017 were reviewed. R0 resection was defined as microscopic absence of tumor cells at definite resection margin.

Comment 3. In the discussion the authors state that adjuvant treatment for pancreatic cancer is not yet standardized. mFOLFIRINOX is now the preferred adjuvant regimen in fit patients in current international guidelines from NCCN, European Society for Medical Oncology, and American Society of Clinical Oncology (ASCO). Alternatively, doublet therapy with gemcitabine and capecitabine or monotherapy with gemcitabine or 5-fluorouracil plus leucovorin can be offered. Patients given CRT-SCT in the current study were younger and had better performance status than the other two groups. In light of the recent PRODIGE study would mFOLFIRINOX be considered as adjuvant regimen in the study hospital for these patients?

RESPONSE: Thank you for the precious comment. We totally agree that mFOLFIRINOX is the preferred adjuvant regimen in fit patients and doublelet therapy with gemcitabine and capecitabine is also a good alternative treatment option. Unfortunately, they have not been approved for reimbursement by the Korean healthcare system. We modified the DISCUSSION part as follows:

Before: In page 12, Discussion

Third, this study involved heterogeneous chemotherapeutic regimens. However, only the chemotherapeutic agents that have proven efficacy in previous studies were included in this study. In addition, there was no significant difference in OS between the regimens in this study.

After: In page 13, Discussion

Third, this study excluded patients treated with adjuvant chemotherapy with regimens other than FL or gemcitabine. involved heterogeneous chemotherapeutic regimens. Recently, mFOLFIRINOX showed its superiority compared to gemcitabine alone in the adjuvant settings and is preferred in fit patients. However, the use of mFOLFIRINOX as an adjuvant treatment is limited in Korea because it has not been approved for reimbursement by the Korean healthcare system.

Comment 4. ESPAC-1 (reference 22, RCT) showed that adjuvant chemotherapy had a significant survival benefit in patients with resected pancreatic cancer, whereas adjuvant chemoradiotherapy had a deleterious effect on survival when radiotherapy is given before chemotherapy. Of note, the two studies cited in favor of adjuvant CRT (reference 13 and 24) are not randomized clinical trials as ESPAC-1.

RESPONSE: Thank you for your important comment. We agree that the two studies (reference 13 and 24) are not randomized clinical trials and inherently biased. We modified the manuscript to as follows:

Before: In page 11, Discussion

On the other hand, recent studies showed that CRT was superior to SCT. However, the previous study was limited by heterogeneous chemotherapy regimens and various proportion of gemcitabine based-chemotherapy between groups.

After: In page 12, Discussion

On the other hand, recent population-based studies using national cancer registry database showed that CRT gave better survival than SCT. However, they were limited by potential inherent biases and the findings should be carefully interpreted.

Reviewer #2

Comment 1. Authors should better clarify the difference between Chemoradiation (CRT) and Radiotherapy plus systemic Chemotherapy since it appear to be the same thing. By reading through the text one may argue that CRT plus SCT means that patients received CT either during RT or as mantainance treatment after the iniztial one. This sound a bit confusing after all and needs to be clarified. Of course groups need to be renamed according to the treatment (i guess) as RT alone, CT alone and CRT. Furthermore, authors should clarify wich were the issues that addressed the choice of giving RT 45 - 55 Gy 6 to 8 weeks or 20 Gy for 10 consecutive days repeateddly. As written in the section "mats and Meths" it sounds somewhat arbitrary.

Comment 2. Chemotherapics administration associated to RT should be clarified for doses and treatment scheme

RESPONSE for Comment 1 and 2: Thank you for your accurate comment. We modified the manuscript to clarify the definitions of each group and additionally described the treatment schemes as follows:

Before: In page 5, "Adjuvant treatment" of MATERIALS AND METHODS

Patients were evaluated for recurrence at 1 month after R0 resection. If not recurred, adjuvant treatment initiated within 4 months after surgery. The adjuvant SCT and/or CRT regimen was determined by multidisciplinary discussions with each patient. For radiation therapy, a tumor bed, surgical anastomosis sites, and adjacent lymph node basins were applied at 45-55 Gy over 5 to 8 weeks or at 20 Gy for 10 consecutive days 2 times repeatedly.20,21 Chemotherapeutic agents for CRT included 5-fluorouracil, gemcitabine, and capecitabine. Meanwhile, regimens in SCT group included gemcitabine or FL combination therapy; gemcitabine (1000 mg/m2) was administered on days 1, 8, and 15 every 4 weeks or folinic acid (20mg/m2) and

fluorouracil (425 mg/m2) were given intravenously on days 1-5 every 4 weeks. The CRT-SCT group included patients who received CRT with induction and/or maintenance chemotherapy. During the first 2 years after surgery, patients were followed up at 3 to 6 months intervals. In the absence of recurrence in the first two years, patients were evaluated every six months.

After: In page 6, "Surgical procedure and adjuvant treatment" of MATERIALS AND METHODS

All the operations were carried out in accordance with standardized protocols. Lymph node groups that were resected in pancreatoduodenectomy include regional lymph nodes to the right side of the celiac and superior mesenteric artery and all the tissues in the hepatoduodenal ligament, except for the portal vein and hepatic artery. Patients were evaluated for recurrence at 1 month after R0 resection. If not recurred, adjuvant treatment initiated within 4 months after surgery. Decisions regarding the type of treatment were discussed in a multidisciplinary team, where clinic-pathological characteristics including age, comorbidity, recovery from surgery, tumor extent, lymph node involvement, and surgical margin status were comprehensively reviewed. The adjuvant treatment modalities were categorized into 3 groups based on the receipt of adjuvant SCT and/or CRT: CRT group, those receiving adjuvant CRT alone; SCT group, those receiving adjuvant SCT alone; and CRT-SCT group, those receiving both adjuvant CRT and adjuvant SCT. CRT consisted of 45-55 Gy over 5 to 8 weeks or 20 Gy for 10 consecutive days 2 times repeatedly with chemotherapeutic agents: 5-fluorouracil (500mg/m^2 on each first 3 days of radiation therapy), gemcitabine (weekly 300-1000mg/m^2), or capecitabine (1600mg/m^2 daily with weekend breaks).[20,21] Radiotherapy was delivered to tumor bed, surgical anastomosis sites, and adjacent lymph node basins. SCT group received either gemcitabine or FL combination therapy; gemcitabine (1000 mg/m^2) on days 1, 8, and 15 every 4 weeks or folinic acid (20mg/m^2) and fluorouracil (425 mg/m^2) on days 1-5 every 4 weeks. CRT-SCT group included patients who received sequential

treatment (CRT followed by maintenance chemotherapy or induction chemotherapy followed by CRT) and those who received sandwich CRT (SCT followed by CRT, and then by SCT). During the first 2 years after surgery, patients were followed up at 3 to 6 months intervals. In the absence of recurrence in the first two years, patients were evaluated every six months.

Comment 3."the proportion of patients with a free margin of < than 1 mm was highest in the CT alone group". Well this may be a major selection bias since it is well known that RT increases the local recurrence free survival for these patients and, in my opinion, this should be addresed in the discussion. Moreover i think that the issue "stage III local reccurrence should be considered according to the "locally advanced" instead of the N2 condition.

RESPONSE: Thank you for your important comment. We agree with your comment and modified the manuscript as follows:

Before: In page 12, DISCUSSION

The limitations of this study are as follows. First, there can be an inherent selection bias of a single-center retrospective study design.

After: In page 13-14, DISCUSSION

The limitations of this study are as follows. First, there can be an inherent selection bias of a single-center retrospective study design. Due to the nature of the study, the baseline characteristics of the groups were different. Compared with other groups, CRT-SCT group had a higher proportion of young patients and ECOG performance status of zero. Patients with better performance status might have been selected for CRT-SCT, which could potentially bias the results in favor of CRT-SCT. Furthermore, it is now well known that radiation therapy increases the local recurrence free survival in patients with surgical margin≤1mm. However, the proportion of these

patients were lowest in CRT-SCT group and highest in SCT group, which may be a major selection bias.

Minor issues:

Comment 1) in the abstract there is no mention to the secondary endpoints

RESPONSE: Thank you for the comment. We additionally described secondary outcomes in the ABSTRACT.

Comment 2) Introduction is far too long and needs to be shortened and simplyfed.

RESPONSE: Thank you for the comment. We simplified the INTRODUCTION part.

Comment 3) Since you're dealing with cancer staging, the extent of linfadenectomy routinely perfoermed should be described

RESPONSE: Thank you for the precious comment. We additionally described the extent of lymphadenectomy as follows:

After: In page 5, "Surgical procedure and adjuvant treatment" of MATERIALS AND METHODS

All the operations were carried out in accordance with standardized protocols. Lymph node groups that were resected in pancreatoduodenectomy include regional lymph nodes to the right side of the celiac and superior mesenteric artery and all the tissues in the hepatoduodenal ligament, except for the portal vein and hepatic artery.