We thank the reviewers for the critical assessment of our manuscript. Here are our point-to-point responses to the reviewers' comments.

Reviewer 1:

In terms of ideas and content，this article has Insufficient innovation.

Our response: As for the innovation, in this study, we evaluated the prognostic relevance of the 8th edition AJCC TNM staging manual in a large US cohort of distal pancreatic cancer through a multicentric collaboration. Our study provides evidence that the AJCC 8th edition TNM staging system does not improve risk stratification when compared to previous staging system for resectable distal pancreatic cancers. Our finding will provide basis for future AJCC staging system for distal pancreatic cancer. Our study also demonstrates the significant difference of clinical outcome and risk stratification between invasive IPMN and non-IPMN associated PDAC.

Reviewer 2:

This is an interesting clinical study with large sample size to validate the American Joint Committee on Cancer (AJCC) 8th edition of TNM staging in distal pancreatic ductal adenocarcinoma (PDAC). Some issues remain to be clarified.

1. Did all patients receive adjuvant chemotherapy after surgery? Are the same chemotherapy treatments, or not?

Our response: Thank you for the comments. Our study is a multicentric large scale study with a 13-year period involving different clinical guidelines and practice patterns. A total of 454 patients with resected distal pancreatic cancer were enrolled in my study. Among these patients, 303 patients (66.7%) received post-operative adjuvant chemotherapy, 84 patients (18.5%) did not receive post-operative adjuvant chemotherapy, and this specific clinical information was not available on 67 patients (14.8%).

The neoadjuvant regimens have been quite different among centers and during the study period even for the same center. Therefore, for those 303 patients receiving adjuvant chemotherapy after surgery, the chemotherapy treatments were not the same. But more detailed information is not available due to retrospective and multicentric nature of the study.

2. In Table 1, the authors did not provide the information of the treatments after surgery?

Our response: Thank you for the comments. Due to the reason we specified for the first question, as well as the main goal for this study is to validation of AJCC 8th Edition of TNM Staging in resected distal pancreatic cancer, we were not able to provide specific information about post-operative neoadjuvant treatment in Table 1.

3. There are some similar reports (Br J Cancer. 2017 Dec 5;117(12):1874-1882.), the authors should discuss the difference between these report and this paper.

Our response: Thank you for the comments. I have discussed this report in our revised manuscript (Discussion section). Due to the rarity of the cases with resected distal PDAC, majority of the

validation studies, including the above-mentioned study, was performed in patients with predominantly PDAC in the head of pancreas. Specifically, we stated that "*The prognostic value of lymph node involvement has also been reported in a recent large scaled multi-institutional study. Morales-Oyarvide et al. demonstrated that the AJCC 8th edition staging system was a practical classification of lymph node involvement [20]. Similar to other related validation studies [5, 12-16], predominant patient population in this study (74%) had PDAC in the head of pancreas, and only 14% of the patients had PDAC in the tail of pancreas. Notably, the prognostic value of lymph node involvement was weaker in patients with resected distal pancreatic cancer [20]*.**"**

Reviewer 3:

It is a well-designed study and quite a lot of cases from different centers were recruited, associating both distribution and risk stratification of the TNM staging system in the 8th edition of AJCC for invasive IPMN and non-IPMN associated PDAC. I have to say it was from a good angle. However, there are a few questions:

1. Since this is a multicenter study, and it is based on the postoperative pathology, there should be an common surgery to be applied among these centers, which however, is not easy to be realized as an inborn drawback for such studies.

Our response: Thank you for the comments. As a multicentered large-scale study designed to validate the major changes in the newer AJCC TNM staging system for resected distal pancreatic cancers, our study provides important insights for future revision of the AJCC staging system, and this is one of the major strengths of our study. Meanwhile this is also the "inborn drawback for such studies", considering the diverse practice guidelines and practice patterns among different institutions over more than one decade of clinical practice. But overall, the surgery for resectable distal pancreatic cancer remains relatively constant and uniform over time and among institutions in the US. In terms of pathology, 3 previous editions of AJCC have been used, but all cases were re-staged using the new AJCC8th edition. As specified in our discussion, "*Our study also has some limitations. First, all cases were collected from major academic cancer centers that might have introduced selection bias. Second, the cases were collected from a 13-year period of time (2005-2018) during which multiple different AJCC staging editions (5th to 7th edition) had been applied for pancreatic cancer staging. However, all cases in this study were re-staged according to the 7th and 8th AJCC editions.* **"**

2. As for the chemotherapy, which in this study is applied in the None-IMPN group, the chemotherapy protocol should have been well described, should they be identical or what is the evidence for the decision of a certain protocol, eg, the vascular involvement, or the lymph node.

Our response: Thank you for the comments. The main goal for this study is to evaluate the prognostic relevance of the 8th edition AJCC TNM staging manual in a large US cohort of distal pancreatic cancer. We have excluded the cases with pre-operative chemotherapy to avoid it as a potential confounding variant due to its "tumor downstage" effect. As for the post-operative chemotherapy, please refer to our response to Item One from Reviewer 2.

3. As the for the group of the invasive IPMN, one specific character of this type of pancreatic carcinoma in pathology is that the lesions sometimes tend to skip, meaning there might have been some benign

lesions in between the malignancies, leaving a challenge for ruling them out in the remnant pancreatic tissue. Also, under such circumstance, the determination of the diameter of the lesion, ie, the "T" value as in TNM remains to specifically addressed in this study.

Our response: Thank you for the comments. The specific character of invasive IPMN with skip lesion is probably one of the underlying reasons for its aggressive clinical behavior. This issue is well known during our routine surgical pathology practice, given its pivotal role in determining the tumor stage (pT), and usually handled with great efforts among these major US academic centers in our study. However, we agree that this is one limitation of our study due to the retrospectively nature. In the discussion, we have added that "*The size of invasive IPMN was recorded from the surgical pathology report as this parameter is difficult to generate as it depends on the combination of macroscopic examination, sampling, and histology; histology review with measurement on slide alone does not provide an accurate assessment of this parameter.*"