Let's come together to fight with pancreatic cancer

In this series "Pre- and post-operative treatment for pancreatic cancer", we publish four insightful narrative reviews by the experts from medical oncology, surgical oncology, and pathology (1-4). We respectfully express my gratitude to all authors contributing to this series.

As the authors emphasized, the emergence of FOLFIRINOX (combination of 5-fluorouracio, leucovorin, oxaliplatin, and irinotecan) and GA (gemcitabine plus nab-paclitaxel) regimens with comparable disease control rate each other have enhanced the benefit of multidisciplinary treatment for pancreatic cancer. These regimens used as preoperative chemotherapy improved the resectability rate of initially unresectable or borderline resectable disease compared with previous regimens of mainly the single agent of gemcitabine, and lots of clinical trials showed better survival compared with upfront surgery. On the other hand, as Hyung *et al.* suggested, the effect of radiotherapy remains controversial and further studies are expected (2). In this special series we did not focus on the radiotherapy. Although the data is still limited, recent advance of carbon-iron particle therapy showed encouraging outcomes in the treatment of locally advanced or locally recurrent pancreatic cancer (5,6).

The term "borderline resectable (BR)" has become a globally household word since its first proposal from MD Anderson in 2006 (7). As Hester *et al.* introduced (4), the concept of BR has been updated from solely anatomic one based on the tumor contact with the surrounding vessels to the one including biological factors and patients physical conditions (8). Biologic factor is mainly represented by serum CA19-9 levels. Here we should not ignore certain proportion of do not secrete CA19-9. In such patients serum DUPAN-2 could be an alternative marker as Omiya *et al.* recently showed that DUPNAN-2 >2,000 U/mL corresponded to CA19-9 >500 U/mL (9). The difficulty in the assessment of radiologic response even by high-resolution computed tomography (CT) remains to be a major concern to decide the appropriate timing of surgery. This is because soft-tissue density representing extrapancreatic tumor invasion rarely disappear even after effective treatment, and tumor viability cannot be assessed by the radiologic change of the density. As Hyung *et al.* commented (2), ^{18}F-fluorodoxygrlucose (^{18}F-FDG) positron emission tomography (PET)-CT may compensate this limitation of CT. Our recent study showed that preoperative high FDG uptake value was associated with lower postoperative relapse-free survival rate (10). Several studies showed that the change in decreased FDG uptake after chemotherapy was useful in predicting pathologic tumor response and postoperative prognosis (11-13).

Even after the curative surgical resection and following adjuvant chemotherapy, tumor recurrence rate is not at all low. The figures summarized by Okusaka showing recurrence rate of 50% to 80% after surgery followed by adjuvant therapy (1) were unsatisfactory, but sadly we are used to such poor outcomes. On the other hand, we must not give up hope because the choice of treatment keeps increasing. As a result, patients survival prolongs even after recurrence and may expect increased opportunity of curative resection following a period of disease control for local recurrence or oligometastases.

Difficulty in pathologic evaluation seems a rather new concern in this era of preoperative chemotherapy. In this respect Taherian *et al.* reviewed comprehensively the current issues (3). We should be aware that in the pathologic evaluation of pancreatic cancer specimens following preoperative therapy tumor size and lymph node metastases can potentially be underestimated especially when cancer cells remain only sparsely within the scar or fibrotic tissues. In addition, we must carefully evaluate the excisional margins especially of the extrapancreatic nerve plexus around the superior mesenteric artery, which is the most common site of tumor exposure resulting in R1 resection after pancreaticoduodenectomy (14,15).

The four instructive reviews also presented unsolved issues and future perspectives. Including my own opinion, these could be summarized as the follows. First, development of new drugs is expected to expand the choice of treatment, which still is not sufficient compared with other malignancies. Olaparib or pembrolizumab that has recently become available is effective only in a few patients with *BRCA* germline mutations or high microsatellite instability, respectively, which both accounts for only less than a few percent of the total population with pancreatic cancer. Second is the pursuit of standardization of the regimens and period for pre- and postoperative treatment. It is no doubt that

FOLFIRINOX or GA should be currently the first choice of treatment for preoperative treatment, however, appropriate duration according to the resectability status remains to be fixed. The evidence of their utility themselves are limited in the patients with initially resectable disease Third, the establishment of the methods to predict pathologic response with imaging studies and/or biomarkers is demanded. In addition, the influence of lymph node micro metastases and/or R1 resection only due to sparse residual tumor in the dissection surface on prognosis should be evaluated to investigate the role of adjuvant chemotherapy or radiotherapy. As another minor concern, the influence of adverse events by preoperative treatment on the postoperative morbidity or mortality has not well been evaluated. In contrast to the influence of chemotherapy induced liver injury on the outcomes of hepatectomy including hepatic insufficiency or mortality (16,17), their impact on pancreatectomy may be ignorable. However, pancreaticoduodenectomy is still associated with around 2–3% of in-hospital morality even by the most recent reports (18,19). Therefore, this matter should be explored in large number of cohorts.

I expect this special series help leaning the current standard and future issues in pre-and post-operative treatment for pancreatic cancer and enhancing further cooperation of the multidisciplinary teams to provide the most effective and appropriate treatment.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Chinese Clinical Oncology* for the series "Pre- and Post-operative Treatment for Pancreatic Cancer". The article did not undergo external peer review.

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at https://cco.amegroups.com/article/view/10.21037/cco-23-7/coif). The series "Pre- and Post-operative Treatment for Pancreatic Cancer" was commissioned by the editorial office without any funding or sponsorship. YK serves as an unpaid Guest Editor of the series and serves as an unpaid editorial board member of *Chinese Clinical Oncology* from December 2022 to November 2024. The author has no other conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Keywords: Pancreatic cancer; preoperative chemotherapy, radiotherapy, pathologic response

Submitted Feb 09, 2023. Accepted for publication Feb 19, 2023. Published online Feb 27, 2023.
doi: 10.21037/cco-23-7
View this article at: https://dx.doi.org/10.21037/cco-23-7

Cite this article as: Kishi Y. Let's come together to fight with pancreatic cancer. Chin Clin Oncol 2023;12(1):1. doi: 10.21037/cco-23-7