



The management strategy of pancreatic cancer in the era of systemic therapy – “Surgery First” or “Surgery Last”?

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With the development of chemotherapy, targeted therapy and immunotherapy, the management of solid tumors has evolved from a single discipline to multi-disciplinary comprehensive treatment in recent years. The outcome of patients with malignant tumors, including several gastrointestinal cancers, has been continuously improved, along with a significant improvement in long-term survival rate. However, as a common malignant tumor of the digestive system, pancreatic cancer (PC) is still correlated with a very poor prognosis, characterized by the close parallel between incidence and mortality, which more than doubled from 1990 to 2017, according to global statistics (1). The finding represents that the clinical diagnosis and management of PC are still extremely challenging.

Establishment of “Surgery First” in PC management

In the era when systemic treatments were absent, surgical resection was the only curative therapy to improve the prognosis of patients with PC. Looking back on the development of pancreatic surgery over the past century, “Surgery First” lead the management of PC for a long time, and “resect all possible malignancies” was the guiding ideology. However, the technical proficiency of surgeons, which determined the safety of pancreatic surgery, was the main basis for successfully implanting this strategy, while the oncological evaluation of the tumor was seriously underestimated. From the regional pancreatectomy proposed by American scholar Fortner (2) in the 1970s to the radical D2 resection of pancreatic cancer suggested

by Japanese scholar Ishikawa (3) in the 1990s, the above-mentioned concepts reflected the ideology of improving the prognosis of PC patients through radically extended surgical resections. After decades of exploration and practice, however, the radically extended resection of PC following the “Surgery First” strategy failed to improve the prognosis of PC patients. On the contrary, the extended surgery increased the incidences of perioperative complications and mortality rate significantly (4). Hence, the above procedures were not universally accepted for the treatment of PC.

Shifts in the “Surgery First” strategy in the context of systemic therapy

Postoperative adjuvant therapy for PC

In 1995, the use of gemcitabine in the adjuvant treatment of PC started the era of systemic therapy. In the following 20 years, with the development of evidence-based medicine and the application of relevant methodology, a series of high-quality randomized controlled trials (RCTs) verified that adjuvant therapy can improve the prognosis of PC patients who undergo surgery. From the CONKO-001 trial using gemcitabine monotherapy to the PRODIGE 24 study using the FOLFIRINOX regimen (a quadruple therapy of fluorouracil, leucovorin, irinotecan and oxaliplatin), adjuvant therapy significantly improved the disease-free survival (DFS) and overall survival (OS) of resected PC patients (5,6). In particular, the adjuvant FOLFIRINOX regimen extended the postoperative OS of PC patients to 54.4 months, proving the important role of adjuvant therapy in the comprehensive treatments of PC (6).

However, not all PC patients have the opportunity to complete postoperative adjuvant therapy. Some patients might fail to start the adjuvant therapy in time, and others might not complete all adjuvant regimen cycles, either due to postoperative complications or poor postoperative physical conditions. Wu *et al.* (7) reported the clinical data of 1,144 PC patients who underwent pancreaticoduodenectomy (PD) in Johns Hopkins Hospital, pointing out that the total postoperative complication rate was 49.1%, with only 54.3% of the patients implemented adjuvant treatment after surgery.

From adjuvant therapy to neoadjuvant therapy

More than 60% of PC patients ultimately encountered recurrence and/or distant metastasis even after radical resection (8). Moreover, nearly 30% of cases developed distant metastasis within one year after surgery (9). Occult metastatic lesions may be missed in preoperative imaging evaluation, which supports the theoretical rationale of preoperative neoadjuvant therapy for PC treatment. In addition, more and more studies have shown that for patients with borderline resectable PC, neoadjuvant chemotherapy could improve the R0 resection rate, reduce the rate of local recurrence and lymph node metastasis, and thus improve the prognosis of patients (10,11). Neoadjuvant therapy was also recommended to be used proactively for resectable PC patients with significantly elevated serum CA19-9, suspicious lymph node metastasis, or large tumor burden (12,13). Recently, scholars proposed the concept of total neoadjuvant therapy (TNT), which extended the duration of preoperative neoadjuvant therapy from 2–3 months to over 5 months, so the neoadjuvant therapy could reach its maximum therapeutic effect (10,14). The regimen of TNT usually started with either the FOLFIRINOX or gemcitabine plus nab-paclitaxel, and the effects should be evaluated after 2–3 months. If no obvious downstage of PC lesion was shown, especially when the serum CA19-9 level did not decrease, the two chemotherapy regimens should be switched, followed by another 2–3 months of continuous treatment with sequential chemoradiotherapy. The concept of TNT expanded the duration and the regimen of the preoperative systemic therapy for PC treatment, which further improved the pathological complete response rate when compared with the traditional short-term neoadjuvant therapy, reflecting the trend of extreme application of neoadjuvant systemic therapy (10,14).

Strategy of PC treatment: “Surgery First” or “Surgery Last”?

Transition of systemic therapy and surgery

Currently, the application of systemic therapy of PC tends to move forward and expand, in terms of treatment timeline and applicable regimens, respectively, from single-drug chemotherapy to combined chemotherapy, from postoperative adjuvant therapy to preoperative neoadjuvant therapy, or even from neoadjuvant to TNT. These progressions reflect that the development of systemic therapy is approaching its ultimate targets. On the contrary, the traditional “Surgery First” strategy is facing more and more challenges. At present, there has been consensus that for borderline resectable and some locally advanced PC, preoperative systemic treatment followed by surgical treatment for effective patients, or called “Surgery Last” strategy, is essential to improve OS (10–15). Meanwhile, this strategy is also recommended for selected resectable PC patients with high risks of recurrence or metastasis. Meanwhile, although the timing of surgical intervention is postponed, the indications and the resection rate are actually expanded (16). Late staged PCs such as locally advanced or distant metastasized PCs which were previously considered unresectable, now have the opportunity to be cured with radical resection following successful systemic therapy, or called conversion therapy. Today’s surgery is not only improved in terms of technical safety and minimally invasive modality, but also adjusted the ideology from “resection as much as possible” to “resection as much as necessary”.

Preparing for necessary surgery, while avoiding unnecessary operation

PC is characteristic of highly heterogeneous. The same treatment strategy could lead to distinct effects among different individuals, resulting in inconsistent conclusions from different clinical studies, which represents the peculiar biological attribute of this disease (17). At present, the molecular classification of PC is still too preliminary to carry out individualized treatment according to the biological characteristics of each case. Whether it is “Surgery First” or “Surgery Last”, there were successes and failures, and either outcome is reasonable for a specific PC patient group. The key is how to make an appropriate decision. Overall, tumor biological behavior plays a more determinant role in the prognosis of PC patients.

For some stage T4 patients with relatively low-grade malignancy of tumor biological behavior, presented with local progression but no distant metastasis, resection after neoadjuvant therapy could still be attempted. However, for some cases with high-grade tumor biological behavior, even if the imaging examinations indicated early-stage resectable manifestations, the possibility of occult distant organ metastases is high. In this scenario, it is rational to carry out systemic therapy first, that is, the “Surgery Last” strategy. In order to determine the appropriate treatment strategy, it is crucial to judge the biological behavior of the tumor. However, nowadays there is still a lack of sensitive biological markers. A comprehensive judgment could be made by combining the assessment of neoadjuvant therapy with the change of CA19-9, PET-CT, and so on (12,13). On the other hand, the effective rate of current chemotherapy is still low, and the survival benefit of neoadjuvant therapy for all resectable PC is limited. So currently surgical treatment is still feasible for most early-staged resectable PC patients.

The gold standard of surgical treatment of PC is R0 resection, regardless of “Surgery First” or “Surgery Last”. The rationality of “Surgery Last” is to create conditions for R0 resection after systemic therapy. However, the molecular mechanisms of PC occurrence and progression are still unclear. The primary and acquired chemoresistance of PC is the major obstacle for systemic treatment strategy in clinical practice, making the therapeutic result uncertain. In conclusion, challenges and opportunities coexist. Drawing the successful experiences from other solid tumors, to improve the long-term survival of PC still relies on the progress of basic research, the development of targeted drugs, and the reversion of the immunosuppression in the tumor microenvironment.

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