Editorial

# Neoadjuvant therapy for resectable pancreatic cancers

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Pancreatic cancer (PC) is a potentially systemic disease with more diverse biology than generally considered. At present, surgical resection is the only curative therapy available for patients with PC, and its indications have long been discussed based on anatomical resectability. A recent consensus recommends neoadjuvant therapy (NAT) for anatomically borderline resectable (BR) cancers (1) as well as induction therapy for unresectable locally advanced (UR-LA) or metastatic (UR-M) cancers. Although the primary goal of induction therapy for UR cancers is palliation with slight prolongation of overall survival, conversion surgery can be considered for some patients with a sustained good response and can provide them a chance of cure (2). For anatomically BR cancers, NAT is proposed not only to improve the R0 resection rate (local control) by shrinking the tumor but also to optimize patient selection by excluding those with radiologically occult metastases (ROM) (3,4). Although the rationale and potential benefits of NAT for such advanced PCs are clear and straightforward, the rationale of NAT for resectable PCs is not clear. R0 resection rates of resectable PCs are generally high, the indication for NAT remains controversial for patients with resectable PC, and the evidence to support the routine use of NAT for resectable PC is limited. First, there is no robust evidence that NAT improves the overall survival of patients with resectable PC. Second, routine NAT entails the risk of tumor progression and the loss of a chance of cure. Although a recent phase 2 single-armed prospective trial indicated that NAT for resectable PCs did not decrease the rate of resection (5), we still have to confirm the benefit of NAT for resectable PCs, that is, improvement of R0 resection rate or overall survival.

Birrer *et al.* analyzed pooled data from three randomized controlled trials (RCTs) of resectable PCs (6). Although these RCTs had an advantage in that they were designed to include exclusively pure cohorts of technically resectable PCs, they were discontinued without conclusive recommendations owing to poor patient accrual (7-9). The authors integrated patient data from these three trials and created a set of 130 patients randomized into NAT (n=56) and upfront surgery (n=74) groups. Disease-free survival (DFS) was significantly longer in the NAT group than in the upfront surgery group [hazard ratio (HR), 0.6; 95% confidence interval (CI): 0.4–0.9; P=0.01]. Furthermore, DFS for the subgroup of R0 resection was similarly longer in the neoadjuvant treatment group (HR, 0.6; 95% CI: 0.35–0.9; P=0.045). Overall survival was higher in the neoadjuvant group than in the upfront surgery group (22.9 months; 95% CI: 12–30.7 *vs.* 16.2 months; 95% CI: 11.4–20), although the difference was not statistically significant (P=0.1). The R0 resection rate was not significantly improved by NAT (70.2% *vs.* 53.8%, P=0.1). These results are important because this is the first reliable evidence to support the survival benefit of NAT in patients with technically resectable tumors. The fact that the R0 resection rate was not improved by NAT is somewhat expected, given that the main purpose of NAT for resectable PCs is to control occult metastasis rather than local management. Furthermore, confirmation of these findings needs to be established in other groups and countries. Motoi *et al.* presented the results of large and well-powered Japanese nationwide RCTs, which concluded that NAT had significantly improved overall survival in a large cohort that included mainly resectable patients. Although the study

could receive criticism because patients with portal venous invasion, some of whom were not regarded as technically resectable, were included, BR tumors threatening arterial contact were considered distinct from technically resectable tumors and excluded. This trial included an unprecedented cohort scale (362 patients) and produced reliable and robust indications, even in the subgroup analysis of patients with strictly resectable tumors.

Based on Birrer's analysis, we obtained the conclusions that supports the application of NAT to resectable PCs. In the future, two issues need to be addressed to optimize the treatment of individual patients. First, a cluster of unfavorable biological factors among technically resectable PCs must be considered. Birrer *et al.* focused strictly on anatomical resectability in their analysis of the three previous RCTs. These were designed in an era when biological resectability was not established. Recent consensus on resectability includes taking into account the biological factors of the tumor, even if it is easily resectable (6). Ushida *et al.* reported that technically resectable PCs with elevated carbohydrate antigen 19-9 (CA19-9) levels (>500 U/mL) are associated with similar or worse survival rates compared with anatomically BR PCs (10). In such a cluster, NAT should be modified to include more intensive and long-term contents for controlling micrometastases or excluding patients with ROM. Second, we must identify patients with truly favorable biology or early-stage disease who may experience a similarly favorable survival rate without NAT. Iacobuzio-Donahue *et al.* reported that approximately one-third of patients did not develop widespread systemic metastasis and died of destructive local growth of the tumor (11). This indicated that the delay of surgery due to unnecessary NAT can result in loss of opportunity for curative treatment, rather than in reasonable selection of patients with PC in this type of biology. Moreover, the proportion of such patients is likely to be large enough not to be ignored, as shown in Birrer's report (16.1% of patients with NAT did not reach resection). To avoid non-beneficial delays in definitive surgery, patients should be designated appropriately for NAT or upfront surgery, according to the risk of treatment failure. If we can identify the characteristics of such a favorable cohort, unnecessary interventions can be omitted.

In conclusion, accumulating evidence indicates that NAT has survival benefit for most patients with PC. Detailed indications and optimal neoadjuvant strategies should be determined based on anatomical and biological features.

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