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EDITORIAL – GLOBAL HEALTH SERVICES RESEARCH

Another Potential Benefit of Neoadjuvant Therapy in Pancreatic Cancer: Reduction in Postoperative Readmission Rates

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Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer-related mortality, with an estimated 57,600 new cases and 47,050 deaths in 2020.[1] Most patients present with metastatic or locally advanced unresectable disease, and the overall 5-year overall survival rate remains dismal at 9%.[1] For the small subset of patients who are candidates for upfront surgery, additional treatment with chemotherapy is essential to prolong survival, as survival after surgery alone is relatively poor (approximately 10%),[2] thus suggesting that PDAC is a systemic disease, and multimodal treatment including surgery and chemotherapy is needed even in those with anatomically resectable disease.

Given the critical role of chemotherapy, adjuvant chemotherapy remains the standard of care for resectable PDAC.[3] The PRODIGE 24, phase III, multicenter study of 493 patients reported a median survival of 54.4 months with modified FOLFIRINOX, compared with 35 months in the gemcitabine group.[4] Patients in the trial underwent postsurgical computed tomography (CT) or magnetic resonance imaging (MRI) and did not have metastatic disease, malignant ascites, or pleural effusion. All patients had a performance status of 0 or 1 and carbohydrate antigen (CA) 19-9 of < 180 IU/mL. Therefore, only patients who had undergone complete surgical recovery, did not develop metastatic disease, and had a favorable CA19-9 level were enrolled in the trial. This might explain the long survival in both arms.[4] However, in the real world, almost 50% of patients cannot receive adjuvant therapy due to postoperative complications or a decline in performance status.[5–7]

Neoadjuvant chemotherapy (NAC) has several theoretical advantages over adjuvant therapy.[8] It leads to early initiation of treatment and early treatment of micrometastatic disease. It also helps assess the chemoresponsiveness of tumors and may help spare those who may be at risk of early progression and unnecessary operation. NAC is also associated with increased rates of margin-negative resection and downstaged nodal disease.[9] However, these advantages need to be balanced against toxicities associated with NAC and the risk of progression, which can preclude surgical resection. The randomized phase III PREOPANC trial of neoadjuvant gemcitabine-based chemoradiotherapy versus upfront surgery for resectable and borderline resectable PDAC failed to demonstrated an overall survival advantage, but noted improvement in disease-free survival.[9] Several randomized controlled trials (RCTs) are currently evaluating the role of NAC (FOLFIRINOX or Gem/nab-paclitaxel) in resectable PDAC (SWOG 1505, https://clinicaltrials.gov/ct2/show/NCT02562716; Alliance 021806, https://clinicaltrials.gov/ct2/show/NCT04340141) as its impact on oncologic outcomes needs to be better understood, especially with the modern chemotherapy regimens.

Perioperative outcomes after NAC are of great interest, given the trend towards the increasing use of NAC. The study by Kamarajah et al. is timely.[10] In the current study, the authors performed a retrospective review of patients with PDAC who underwent resection from 2004 to 2016 using the National Cancer Database (NCDB).[10] The

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authors identified 7975 patients (11%) with NAC and 65,338 patients (89%) without NAC (noNAC group). Of patients receiving NAC, 65% (5160/7975) also received neoadjuvant radiotherapy (NART), compared with 0.3% in the noNAC group ($p < 0.001$). The authors used propensity score matching to account for treatment selection bias in patients with or without NAC. There were 2911 patients in each group after propensity score matching. In this matched cohort, NAC was associated with a lower rate of 30-day readmission (univariable 5.5 vs. 7.4%, $p = 0.006$; multivariable odds ratio [OR] 0.74, 95% confidence interval [CI] 0.6–0.92, $p = 0.006$). There was no significant difference in the length of stay (LOS) and 30- or 90-day mortality in the matched cohort. Even though NAC was associated with higher rates of margin-negative resection (83 vs. 80%, $p = 0.004$), there was no difference in overall survival (NAC vs. noNAC: median 27 vs. 26 months, $p = 0.02$). A reduction in readmission rates was noted for both pancreaticoduodenectomy (NAC vs. noNAC: 5.3 vs. 8.2%, $p = 0.045$) and distal pancreatectomy (NAC vs. noNAC: 5.6 vs. 7.1%, $p = 0.046$).

The authors used propensity score matching to minimize the bias and have large numbers in each group.[10] However, the study has some limitations, which the authors have acknowledged. These include coding errors inherent to large databases, and the lack of details regarding the type and extent of chemotherapy, anatomic resectability, and need for vascular reconstructions. Additionally, 13% of patients in the noNAC group had a pathologic complete response, which again highlights some of the coding errors inherent to large databases. Readmission is defined in the NCDB as "readmission to the same hospital, for the same illness, within 30 days of discharge following the index procedure". This may underestimate the readmission rates, as many times readmissions occur at another hospital and the principal diagnosis may also change.

The findings of a decrease in readmission rates after NAT are interesting. As previous studies have shown a reduction in pancreatic fistula rates after NAT (NAC and NART), the authors surmised that a reduction in readmission rates could be because of reduced fistula rates and decreased incidence of organ space infections. Marchegiani et al. analyzed a cohort of 305 pancreaticoduodenectomies and noted a decrease in postoperative pancreatic fistula (POPF) in those who underwent neoadjuvant therapy (NAT) [NAT, $n = 99$; noNAT, $n = 206$; POPF 9.1% vs. 15.6%, $p = 0.05$).[11] However, patients who underwent distal pancreatectomies (DP) after NAT experienced a higher rate of grade C POPF (NAT, $n = 26$; noNAT, $n = 68$; 11.5 vs. 2.9%, $p = 0.01$). In a systematic review and meta-analysis of 24 studies, Kamarajah et al. noted a decrease in POPF after NAT in those undergoing PD (OR 0.57, $p < 0.001$), but not in distal pancreatectomies (OR 0.79, $p = 0.091$).[12] Similarly, the PREOPANC study also noted a decrease in the incidence of POPF in the NAT arm (NAT vs. upfront surgery POPF: 0 vs. 9.2%, $p = 0.011$).[13] However, a perceived decrease in readmission rates could also be a bias induced by the database definition. As only readmissions to the same hospital for the same diagnosis are required for readmission coding in the NCDB, this could lead to underestimation of readmission rates. Studies reporting on the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database observed overall higher readmission rates with no significant difference between the groups (NAT vs. noNAT: 18 vs. 16.5%, $p = 0.29$).[14] Therefore, it remains to be determined if NAT truly leads to a reduction in post-pancreatectomy readmission rates. The current study provides an opportunity for the experts to define readmission after pancreatic surgery. Post-pancreatectomy readmission rates were not reported in the surgical outcomes of the SWOG 1505 trial;[15] however, in the PREOPANC study, readmission rates of 16% were noted in both arms.[13] Ongoing RCTs will also provide further data on the subject.

The negative findings of the current study are also equally important. There was no difference in LOS and 30- or 90-day mortality between the NAC and noNAC groups. Additionally, these data points were not affected by database-specific definitions, thus suggesting that NAC does not lead to worse perioperative outcomes compared with upfront surgery. These findings are also similar to the PREOPANC study where NAT was not associated with an increase in LOS or perioperative mortality.[13]

The major intent/goal of NAT in PDAC is to improve oncologic outcomes and minimize perioperative morbidity and mortality. In the current study, there was no significant difference in the median survival of the matched NAC versus noNAC groups (27 vs. 26 months, $p = 0.2$).[10] The SWOG 1505 trial reported a median survival of 22.4 months in the FOLFIRINOX arm versus 23.6 months for gemcitabine nab-pactlitaxel.[16] These median survivals are not comparable with the 54.4 months and 35 months for adjuvant FOLFIRINOX and gemcitabine alone, respectively, in the adjuvant PRODIGE24 trial;[4] however, both studies had limitations as the SWOG trial did not have an upfront surgery arm and the PRODIGE 24 trial only enrolled the best postoperative candidates. The ongoing Alliance 021806 trial with perioperative chemotherapy (modified FOLFIRINOX) and surgery versus upfront surgery followed by adjuvant chemotherapy (modified FOLFIRINOX) will shed further light on the effectiveness of NAT with regard to oncologic and perioperative outcomes.

Despite the above limitations, this study will add to the body of literature to demonstrate the safety of NAC in the perioperative setting, with comparable median survival with upfront surgery.[10] Although NCDB data suggest a reduction in readmission rates, the definition of readmission in the NCDB may introduce bias in the calculations. Nonetheless, the current manuscript also calls for a standardized definition of readmission rates after pancreatic surgery. Ongoing randomized studies will provide further comparative data on the oncologic effectiveness and perioperative outcomes of NAT compared with upfront surgery for resectable PDAC.

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