French Editorial Commentary from the ACHBPT

Surgical techniques and tumor dissemination: a critical review of the CETUPANC trial on the superior mesenteric artery *vs.* no-touch approaches

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The CETUPANC study is a Spanish multicenter randomized trial conducted in 10 pancreatic surgery centers. It compares two surgical approaches to pancreaticoduodenectomy (PD) for pancreatic ductal adenocarcinoma (PDAC): the superior mesenteric artery (SMA)-first approach and the "no-touch" (NT) approach, which aims to achieve tumor resection after complete interruption of venous tumor drainage in the portal vein, without tumor mobilization. The authors hypothesize that this approach may limit the intraoperative dissemination of circulating tumor cells (CTCs) and cellular clusters, thereby reducing the risk of metastasis (1).

After screening 881 patients with pancreatic head lesions, the authors included 101 patients with periampullary lesions that were radiologically resectable according to the National Comprehensive Cancer Network (NCCN) classification. Cancer antigen 19-9 (CA19-9) levels and Eastern Cooperative Oncology Group (ECOG) status were not taken into account. Neoadjuvant therapy was an exclusion criterion. Patients were randomized intraoperatively into two groups after confirmation of the absence of metastases or peritoneal carcinomatosis, into two groups: SMA first (n=51) and NT (n=50). Histologic confirmation of PDAC was obtained only postoperatively, and unresectable cases were excluded. As a result, only 63 patients were included in the final analyses: 34 in the SMA-first group and 29 in the NT group.

For each patient, portal venous blood samples were collected at different surgical time points to measure CTC levels and cluster mobilization: S0 at the beginning of the procedure, S1 after control/ligation in the NT group and after extended dissection of the SMA in the SMA-first group, S2 after tumor resection, and S3 before abdominal wall closure.

The results show that the two techniques had similar CTC and cluster mobilization rates at all surgical time points, except for the NT group, which showed a significant peak in cluster mobilization at S2, after tumor resection (P=0.04). No significant differences in metastasis-free survival or overall survival were observed between the groups (12 *vs.* 18 months and 19 *vs.* 23 months in the SMA-first and NT groups, respectively). Multivariate analysis revealed that significant intraoperative cluster mobilization (delta >14 clusters/mL between the beginning and end of the procedure) was significantly associated with the occurrence of metastases within one year of surgery

(P=0.02).

PDAC accounts for 90% of all pancreatic cancers (2). It is one of the most aggressive cancers, with a poor prognosis, and is predicted to become the second leading cause of cancer-related death in Europe by 2030 (3). The 5-year survival rate is extremely low, estimated at 11% across all stages (4). PDAC is often diagnosed at an advanced stage due to the lack of specific symptoms in its early stages, with approximately 50% of patients presenting with metastases at diagnosis (5).

In localized stages, surgery remains the only potentially curative treatment. However, even after complete (R0) surgical resection, outcomes are disappointing. The median postoperative overall survival is approximately 15 months, with a high rate of metastatic recurrence, often within the first year after surgery. This phenomenon could be attributed to the presence of undetected metastases at diagnosis or to intraoperative dissemination of tumor cells.

The "no-touch" technique aims to reduce the risk of intraoperative dissemination by minimizing tumor manipulation prior to venous ligation (6). This approach could potentially limit the release of tumor cells into the bloodstream and, ultimately, prevent early postoperative metastases.

Recent studies indicate that liquid biopsies, particularly CTCs and cellular clusters detectable in the blood, particularly in the portal vein, are often associated with an increased risk of metastasis and may serve as prognostic biomarkers for postoperative outcomes (7,8). In a pilot study reported in 2021, the MD Anderson team demonstrated that the presence of intraoperatively detected CTCs in portal venous blood significantly impacted survival compared to CTCs isolated in peripheral venous blood (9). These biomarkers were therefore used to compare the two surgical approaches. However, no differences CTC rates or cluster mobilization were observed between the techniques.

While previous studies have suggested lower CTC rates with minimal tumor handling (NT approach), none have demonstrated its impact on recurrence-free or overall survival (10). Thus, the NT technique has not yet demonstrated clinical utility. The rationale for greater tumor mobilization with the SMA-first approach remains highly controversial.

Of particular interest is the dynamic study of tumor dissemination performed in this study. Portal vein sampling at different surgical time points allowed for an evaluation of tumor dissemination throughout the procedure. Notably, a peak in tumor cell release was observed after tumor resection, indicating a tendency for cell shedding during surgical specimen extraction, regardless of the technique used. In addition, patients with significant mobilization of cellular cluster during surgery—defined as a delta >14 clusters/mL between the beginning and the end of the procedure—had a tendency to develop early metastases within the first postoperative year. This phenomenon was particularly pronounced in cases requiring venous resection. However, this observation was no longer evident after 2 or 3 years of follow-up. While isolated CTCs did show a correlation with metastatic development, cellular clusters appear to be a promising biomarker for metastatic risk that warrants further large-scale studies.

The generalizability of these results is limited by the relatively small sample size, with only 63 patients included in the final analysis. Although patients with pancreatic head lesions were screened, only 101 were randomized and only 63 were analysed after histological confirmation (modified intention-to-treat analysis).

Another consideration is the significant number of exclusions due to postoperative histologic findings inconsistent with PDAC. These included 8 ampullary carcinomas, 2 neuroendocrine tumors, and 1 case of chronic pancreatitis in the SMA-first group, and 15 ampullary carcinomas and 1 case of chronic pancreatitis in the NT group. Endoscopic ultrasound-guided histologic confirmation would have been beneficial in cases of diagnostic uncertainty, especially for small tumors (<2 cm) or iso-dense lesions poorly visualized on computed tomography (CT) scans (11).

Future advances will rely on improved patient selection and better identification of biologically borderline disease (12). A tumor is considered biologically borderline if it is anatomically resectable but has suspicious features suggestive of distant spread, such as elevated CA19-9 levels (>500 IU/mL) or the presence of positive regional lymph nodes, without confirmed distant metastases (13). To better identify such cases, the use of more robust biomarkers from peripheral blood and portal venous sampling under endoscopic ultrasound guidance appears promising (14). In addition, neoadjuvant chemotherapy—currently not validated for upfront resectable PDAC (15)—may be warranted in these high-risk cases to reduce the likelihood of early recurrence.

The CETUPANC trial provides valuable insights into the importance of tumor dissemination in PDAC. While

the choice of surgical technique did not show a significant impact on early metastasis or overall survival, tumor clusters appear to stand out as markers of dissemination. The addition of neoadjuvant chemotherapy could potentially reduce the tumor burden in the preoperative setting, provided that accurate and robust preoperative biomarkers are available.

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