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Improved survival in pancreatic ductal adenocarcinoma: Exciting promise of multimodal management strategies

Pancreatic ductal adenocarcinoma (PDAC) remains one of the most aggressive and treatment-resistant malignancies. It is characterized by a propensity for metastatic dissemination, a dense immunosuppressive microenvironment exhibiting high interstitial pressures impeding efficient intra-tumoral drug delivery, and resistance to conventional therapies—all contributing to an exceptionally poor prognosis. Over the past decade, multidisciplinary advances, including surgical techniques, chemotherapy regimens, immunotherapy, and other novel treatment approaches, have led to modest but meaningful improvements in patient outcomes. The concept of “Precision medicine” has revolutionized the treatment paradigms for pancreatic cancer [1,2]. Nevertheless, the multimodal management of PDAC remains a formidable challenge, and improving patient survival continues to be a central focus for both clinicians and researchers.

A recent retrospective study led by Tingbo Liang reported a remarkable 5-year survival rate of 23.3 % in PDAC patients treated at the First Affiliated Hospital, Zhejiang University School of Medicine (FAHZU), with a median overall survival of 18.5 months across all disease stages [3]. These outcomes represent the best reported to date, significantly surpassing historical benchmarks, such as the 5-year survival of 12.8 % reported by the U.S. SEER database (2014–2020) and 8.5 % by the Chinese National Cancer Center (2021) [4]. Notably, this retrospective study is based on a cohort of 3268 patients with PDAC treated at a high-volume, high-expertise institution with standardized diagnostic and therapeutic protocols. It provides valuable complementary evidence to multicenter clinical trials, particularly in assessing real-world efficacy of contemporary, guideline-directed PDAC multimodal management.

Liang and colleagues used a modified FOLFIRINOX regimen, consisting of 85 % oxaliplatin, 75 % irinotecan, and zero fluorouracil bolus [5]. This modification significantly improved treatment tolerability while maintaining therapeutic efficacy [6], thereby facilitating the broader adoption of multimodal therapy concepts across the country. The evolving understanding of PDAC as a systemic disease, rather than just a localized malignancy, has become a cornerstone of modern oncologic paradigms. The clinical implications of neoadjuvant therapy for resectable PDAC (RPC) have become a prominent research frontier in recent years. In this study, 16.0 % of total patients with RPC underwent surgery after neoadjuvant therapy, demonstrating significantly improved outcomes in both overall survival (37.5 months vs. 28.9 months, $P < 0.01$) and recurrence-free survival (17.6 months vs. 13.8 months, $P = 0.02$) compared to upfront surgery. Patients who did not proceed to surgery—owing either to adverse effects or disease progression during neoadjuvant therapy were excluded from the analysis,

representing a limitation of this study. Despite the promising retrospective evidence, neoadjuvant therapy has yet to show a significant survival benefit in randomized prospective trials, including NORPACT-1 and PREOPANC-1. To address this gap, Liang has recently led a randomized controlled trial (CISPD-1, NCT03750669), which has completed patient recruitment. CISPD-1 evaluates the efficacy of sequential neoadjuvant therapy using gemcitabine plus nab-paclitaxel (GnP) followed by modified FOLFIRINOX in patients with RPC. The potential synergistic effect of these two regimens may further improve patient outcomes. The findings from CISPD-1 are highly anticipated and may offer an important addition to the therapeutic arsenal for RPC.

Surgery remains the only curative approach for PDAC. With the advancement of systemic therapies, an increasing number of patients who were initially diagnosed with unresectable disease are now becoming eligible for surgical intervention. The improvement on conversion surgery rate has emerged as an important factor contributing to better overall prognosis in PDAC [7]. One notable breakthrough contribution by Liang et al. in this area is the radical resection with intestinal autotransplantation (RRCIA). This innovative approach offers a feasible and safe strategy for patients with locally advanced disease (LAPC) involving extensive invasion of vessels [8]. For LAPC, Liang reported a resection rate of 28.1 %, with a 5-year survival rate of 16.2 %, significantly exceeding outcomes from a multicenter retrospective study in Europe and the U.S., which showed a resection rate of 17.6 % and a 5-year survival rate of 9.5 % among 958 patients with LAPC [9]. Moreover, a R0 resection rate of 94.4 % was achieved for patients with RRCIA, dramatically surpassing the reported 55 % for LAPC with conventional vascular reconstruction surgery after systemic treatment [9]. RRCIA is strongly recommended for patients who achieved normalization of CA19-9 level and completed more than 8 cycles of initial treatment [10]. Patients who underwent RRCIA with all protective factors demonstrate a median overall survival of 34.5 months. However, RRCIA imposes remarkably high demands on institutional capabilities, including response assessment, surgical technique and perioperative management. Therefore, it is only recommended exclusively in high-volume centers. Notably, there is no significant difference on postoperative survival between borderline resectable PDAC (BRPC) and LAPC resected groups (median overall survival 22.9 months vs. 25.4 months). This finding underscores the importance of tumor biology over anatomical classification in guiding surgical decision-making. In patients with metastatic PDAC (MPC), 10.6 % of those treated at FAHZU underwent conversion surgery—a notably higher proportion than previously reported. The subset with surgical treatment demonstrates significantly prolonged median overall survival (20.4 months)

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compared to non-surgically managed patients (11.0 months). Similar survival benefits have been observed in cohorts from other high-volume institutions, including Johns Hopkins Hospital [11]. While the survival benefit of surgery for highly selected MPC patients is well-established, significant heterogeneity exists in patient selection criteria across institutions, and no international consensus has yet been established. Combination therapies hold great promise for the management of PDAC [12].

In addition to aggressive surgical strategies, the implementation of a specialized multidisciplinary team (MDT) is another important factor in improving outcomes by enabling the development of individualized, optimized treatment plan for patients with PDAC [13,14]. At FAHZU, over 50 % of patients with PDAC are managed under MDT guidance, in stark contrast to the national average, where only approximately 5 % of patients with PDAC participated in MDT discussions [15]. As a result of MDT-driven decision-making in this study, 41.5 % and 35.5 % of advanced PDAC patients received modified-FOLFIRINOX and GnP, respectively, as first line regimen in this study. These rates are significantly higher than those from a real-world study involving 5349 patients with advanced PDAC in China, where modified-FOLFIRINOX and GnP were given in only 11.9 % and 18.1 % of patients, respectively [15]. These findings underscore the clinical value and real-world effectiveness of guideline-directed, MDT-informed multimodal management in a high-volume, specialized center.

In summary, PDAC remains one of the most challenging malignancies. Achieving a 5-year survival rate exceeding 20 % represents a significant therapeutic milestone for PDAC. Around 80 % of patients are ineligible for surgery at diagnosis. However, the use of highly effective first-line chemotherapy regimens enables more patients to regain the opportunity of surgery. Routine MDT discussion, increased adoption of guideline-recommended regimens, precise selection of surgical candidates, and the implementation of aggressive surgical procedures collectively contribute to optimal multimodal management of PDAC patients across all stages.

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