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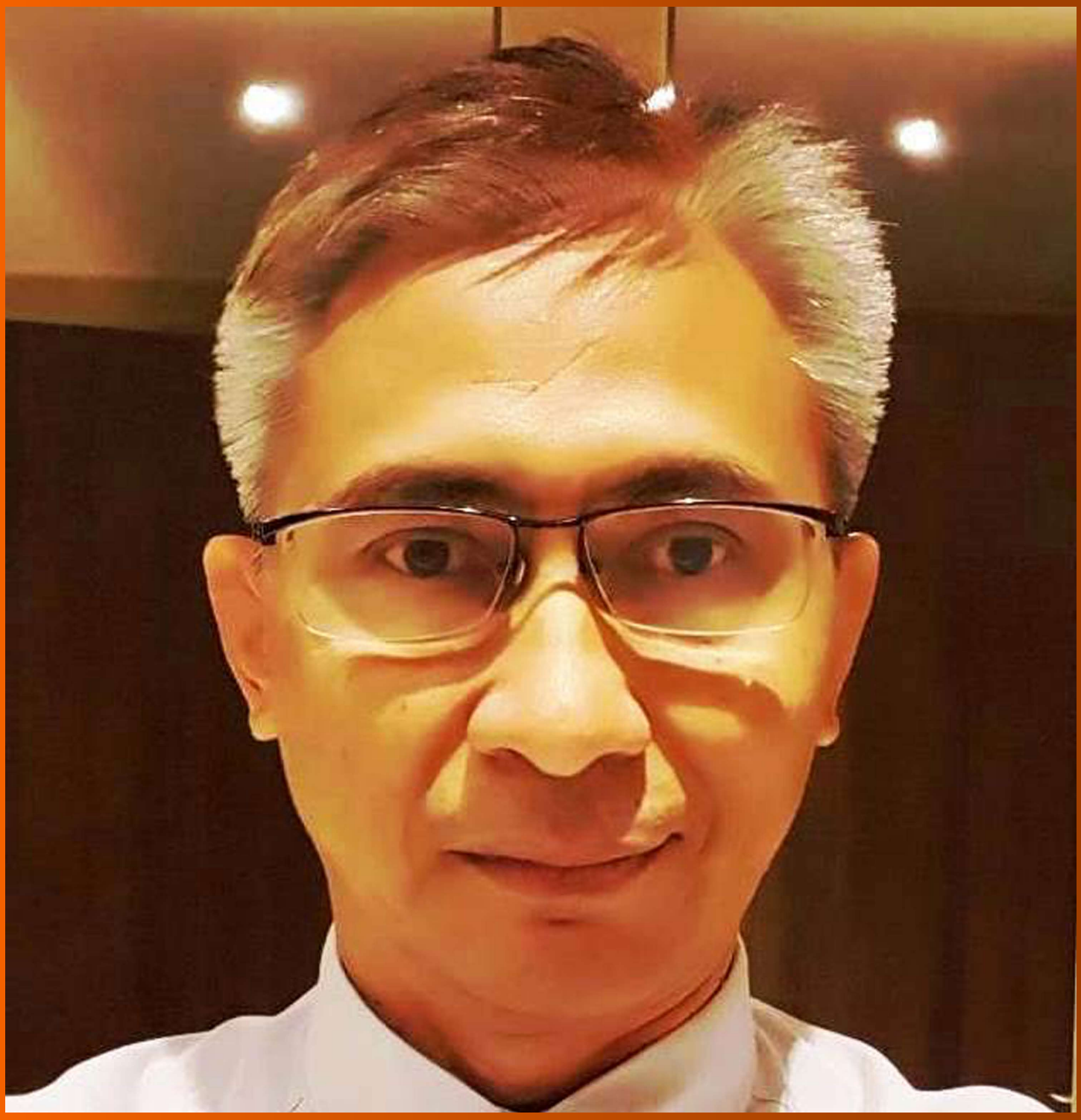

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EDITORIAL

Time to think: Selecting patients who may benefit from synchronous resection of primary pancreatic cancer and liver metastases

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Abstract

Pancreatic cancer remains a lethal disease and is associated with poor prognosis, particularly for patients with distant metastasis at diagnosis. Recently, Oweira reported a retrospective study that included 13233 metastatic pancreatic cancer patients from the Surveillance, Epidemiology and End Results database. They demonstrated that pancreatic cancer patients with isolated liver metastases had worse outcomes than patients with isolated lung metastases or distant nodal metastases. At present, the standard treatment for metastatic pancreatic cancer is chemotherapy. However, improvement in the safety of pancreatic surgery has led to the consideration of more aggressive surgical approaches. Schneitler reported two cases of hepatic metastatic pancreatic cancer in which negative margin (R0) resection and long survival were achieved after effective preoperative chemotherapy. In general, these two studies indicate that although pancreatic cancer patients with liver metastasis have a poor prognosis, surgical approaches may prolong survival for a few of these patients. A strategy to select hepatic metastatic pancreatic cancer patients who may benefit from surgical intervention is urgently needed.

Key words: Liver metastasis; Chemotherapy; Pancreatic cancer; Surgery

Core tip: Pancreatic cancer patients with liver metastasis have worse prognoses than pancreatic cancer patients with metastasis at other sites. Improvement in the safety of pancreatic surgery has led to the consideration of more aggressive approaches. There is increasing agreement that synchronous resection of pancreatic cancer and liver metastases may selectively benefit some patients. A prospective multicenter, randomized, controlled phase three trial has been launched by the Chinese Study Group for Pancreatic Cancer with a goal of establishing such a selection strategy.

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INTRODUCTION

Pancreatic cancer remains a challenging disease to treat and is associated with a poor prognosis[1,2]. Surgery remains the only curative treatment and provides an opportunity for long-term survival. Unfortunately, however, approximately 50% of pancreatic cancer patients are diagnosed with distant metastases; these patients are then deemed incurable and are generally not considered to be suitable for radical surgeries with curative intent[3]. At present, chemotherapy is the standard treatment for patients with metastatic pancreatic cancer. However, improvement in the safety of pancreatic surgery has led to the consideration of more aggressive approaches. Synchronous resection of primary tumors and metastatic sites continues to be attempted[4-6]. Synchronous pancreas and liver resection procedures account for the largest proportion of these attempts. However, the most relevant studies have only indicated the safety of such operations, which have failed to produce survival benefits. Nevertheless, there are many case reports demonstrating that certain pancreatic cancer patients can achieve long-term survival after resection of both the primary tumor and liver metastases[7,8].

STUDY ANALYSIS

In a recent issue of World Journal of Gastroenterology, Oweira reported a retrospective study performed using data from the Surveillance, Epidemiology and End Results database. A total of 13233 patients with stage IV pancreatic cancer and distant metastases at known sites were included for analysis. Metastatic pancreatic cancer patients were classified according to the site of metastases (liver, lungs, bone, brain or distant lymph nodes). Survival analysis indicated that pancreatic cancer patients with isolated liver metastases had worse outcomes than patients with isolated lung metastases or distant nodal metastases. This research demonstrated that we can reasonably provide different treatment strategies for pancreatic cancer patients with metastases at different sites.

Another interesting study by Schneitler *et al*[9] in *World Journal of Gastroenterology* merits attention. Two cases of hepatic metastatic pancreatic cancer were described in which negative margin (R0) resection and long survival were achieved after a preoperative FOLFIRINOX chemotherapy regimen consisting of Fluorouracil (5-FU), folinic acid, irinotecan and oxaliplatin. This study showed that certain pancreatic cancer patients with liver metastasis would benefit from surgical resection after effective chemotherapy.

Taken together, the results of these two studies indicate that although pancreatic cancer patients with liver metastasis generally have poor prognoses, surgical approaches may prolong survival for a few of these patients. There is increasing agreement that synchronous resection of pancreatic cancer and pancreatic liver metastases should be performed in a highly selective manner in some patients[10,11]. Thus, the determination of how to select for and then treat patients who would benefit from such approaches is urgently required.

PERSPECTIVE

In 1995, Hellman and Weichselbaum first proposed the clinically significant condition of oligometastasis, which is a state between local and systemic disease, and advocated for the potential for curative local treatments[12]. Further studies have identified distinct biological differences between limited metastatic lesions and widely disseminated disease for multiple tumor types, including pancreatic cancer[13-15]. Radical surgery to treat both primary and metastatic sites has been accepted and conducted for an increasing number of tumor types[16-18]. Thus, pancreatic cancer patients with few liver metastases may benefit from aggressive surgical approaches. Zanini *et al*[5] indicated that the number of liver metastases had a detrimental effect on survival after surgical resection. However, the number of liver metastases alone is insufficient to identify patients who are likely to be surgically cured and achieve improved overall survival.

Chemosensitivity is another important factor that could influence long-term survival and should therefore also be considered and evaluated. In previous studies on surgical resection of primary pancreatic cancer, preoperative chemotherapy was more common than direct surgery for three reasons[19,20]. First, recurrence and new metastases were observed within a short time after surgery and were the main causes of surgical failure[5]. Preoperative chemotherapy can inhibit tumor activity

and increase both the R0 and negative lymph node (N0) rates[21]. Second, the preoperative chemotherapy period can provide an opportunity to verify biological characteristics of cancers and select patients with less aggressive tumors[22,23]. Last, tumor burden may be reduced after preoperative chemotherapy, resulting in decreased surgical difficulty and increased safety.

Another important issue is the time at which to conduct surgical intervention. Although Response Evaluation Criteria In Solid Tumors (RECIST) are commonly employed to evaluate the efficacy of chemotherapy, these criteria are not appropriate for determining the optimal time point for an operation. Carbohydrate antigen 19-9 (CA19-9) is the most commonly used serum tumor marker of pancreatic cancer. It has been reported that CA19-9 response could be used to improve the selection of borderline and locally advanced pancreatic cancer patients who can benefit from resection after primary chemotherapy[24]. This conclusion may also be generalized to pancreatic cancer patients with liver metastases. However, approximately five to ten percent of the population are Lewis-negative individuals; it is known that such individuals exhibit little to no CA19-9 secretion (34, 35). Carbohydrate antigen 125 and carcinoembryonic antigen are alternative markers because they are the most common serum tumor markers for pancreatic cancer other than CA19-9. In addition, the capacity for resection of both the primary tumor and liver metastases should be carefully evaluated before surgical intervention.

Based on the above ideas, the Chinese Study Group for Pancreatic Cancer (CSPAC) has launched a prospective multicenter, randomized, controlled phase three trial (NCT03398291) named CSPAC-1. Their goal is to establish a treatment strategy to select patients who can benefit from simultaneous resection of primary pancreatic cancer and liver metastatic sites. The results of this trial are planned to be released in 2025; we are looking forward to their release because they may alter current the treatment modes for pancreatic cancer.

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