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PANCREATIC ADENOCARCINOMA WITH SYNCHRONOUS LIVER METASTASES – IS THERE A ROLE FOR SURGERY?

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ABSTRACT

Pancreatic cancer remains one of the most aggressive neoplasms affecting people worldwide, with lower than one year rates of survival, especially if metastatic disease is encountered. In such cases palliative chemotherapy has been proposed, but the overall prognostic remains extremely poor. Meanwhile, in certain cases, spectacular response to chemotherapy has been observed, with significant reduction and even disappearance of the liver lesions. In this respect, attention was focused on establishing whether surgery might improve the outcomes in such cases. This is a literature review of the largest studies conducted on this issue.

Keywords: pancreatic adenocarcinoma, liver metastases, resection

Abbreviations
CA 19-9 = Carbohydrate antigen 19-9

INTRODUCTION

Pancreatic adenocarcinoma represents one of the most aggressive digestive malignancies affective people worldwide due to its biological aggressiveness; meanwhile, a significant number of patients will present metastatic lesions from the moment of the initial diagnostic, the liver being one of the most commonly affected viscera [1]. In such cases the overall prognostic remains very poor even if chemotherapy is associated. In order to increase the lifespan of these patients, recent studies of medical oncology recommended association between gemcitabine and other chemotherapeutic agents

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such as capecitabine, epirubicin, cisplatin, docetaxel, fluorouracil, oxaliplatin, irinotecan or epirubicin; therefore, after the administration of combined regimens of chemotherapy, the one year overall survival increased from 20% to 35-48%, bringing in this way a new hope for this subset of patients [2,3]. Meanwhile, metastatic to liver cases reported in certain cases significant remission of the disease, hepatic metastases being significantly reduced and even disappearing after the administration of these combinations of chemotherapeutic drugs [4]. In this respect, attention was focused on studying whether surgery might improve the outcomes of these patients.

STUDIES CONDUCTED ON THE ISSUE OF LIVER RESECTION FOR SYNCHRONOUS PANCREATIC CANCER WITH HEPATIC METASTASES

Initially it has been stated that synchronous resection of pancreatic carcinoma and liver metastases is not recommended in the international guidelines for pancreatic cancer patients [5]. However, isolated reports came to demonstrate that in certain cases significant benefit in terms of survival might be achieved [5-8]. In this respect, the issue of resection for liver metastases in pancreatic cancer was further widely investigated [9].

The first study which investigated the benefit of survival in patients submitted to neoadjuvant chemotherapy followed by resection was conducted by Crippa et al. and published in 2016 [4]; in this study the authors included 127 patients with pancreatic adenocarcinoma and liver metastases submitted to neoadjuvant chemotherapy followed by resection; the main inclusion criteria were represented by resectable or borderline resectable pancreatic tumor in association with a significant biochemical response and complete or major response in regard to liver metastases; according to these authors major biochemical response was defined by a serum level decrease of CA 19-9 with more than 90% when compared to the values reported before chemotherapy while major imagistic response was defined by the presence of a single liver metastasis at the end of chemotherapy. Preoperatively, only 10% of cases were diagnosed with unique liver metastases. After ending the neoadjuvant chemotherapy, 19 cases were considered as candidates for surgical resection, 9 cases presenting complete response and the other 10 cases being considered as having partial radiologic response (a single liver metastasis being found at the time of restaging); meanwhile, 7 out of the 19 cases were further excluded due to the evidence of additional peritoneal or hepatic metastases at magnetic resonance imaging or at positron emission tomography or due to the rapid increase of serum CA19-9 during the first month after ending the neoadjuvant chemotherapy. Finally, among the 12 cases submitted to surgery, in one case intraoperatively peritoneal metastases were found and therefore resection was no longer tempted while in the remaining 11 cases surgery with curative intent was considered as feasible. The median overall survival rate of the cohort of 127 patients was of 11 months, being significantly influenced by the type of neoadjuvant chemotherapy (single agent versus multiple chemotherapeutic agents), and association of surgical resection, biochemical response and by the number of liver metastases. Meanwhile, the authors underlined the fact that surgically treated patients reported a median overall survival of 39 months versus 11 months in the remaining 116 patients ($p = 0.0001$) [4].

Similarly to this study, the Chinese authors conducted by Wei et al. created a prospective randomized multicenter phase III trial; in this trial the authors included oligometastatic pancreatic cancer patients, oligometastatic disease being represented by less than 3 hepatic lesions; according to prior studies the authors expected a 30% conversion rate The study was initialized in July 2018 and is expected to end within five years, the main outcomes being represented by overall survival, quality of life score, postoperative morbidity and mortality [10].

A similar conclusion to Crippa's study was also presented by the Japanese authors conducted by Niguma et al. [11]; in their paper the authors included 64 patients with biliary tract or pancreatic cancers and liver metastases submitted to surgery. Among these cases the authors reported 19 pancreatic adenocarcinoma, 21 intrahepatic cholangiocarcinoma, nine extrahepatic cholangiocarcinomas, 12 gallbladder carcinomas and three ampullary carcinomas. The authors further grouped these patients in two groups – pancreatic carcinoma group and non-pancreatic carcinoma group and demonstrated that the overall survival was of 12.3 months in the first group and 1.6 months in the second group. Meanwhile, in the pancreatic group there were two long survivors (with a reported survival higher than 30 months), both cases reporting a significant response to chemotherapy. Therefore, the authors concluded that in pancreatic adenocarcinoma with

liver metastases surgery should be reserved only for the high responders to chemotherapy patients [11].

Maybe the largest study published so far on this issue was conducted by Andreas Andreou at Campus Charité Mitte and Campus Virchow Klinikum, Charité – Universitätsmedizin Berlin. The study included 76 patients submitted to synchronous pancreatic and liver resection for pancreatic adenocarcinoma with liver metastases. After a median follow-up period of 130 months the authors reported a one year, three year and five year survival rate of 41%, 13% and 7% respectively. In univariate analysis poorer survival was associated with the type of pancreatic resection, the necessity of association of superior mesenteric artery resection, T4 stage, positive resection margins on the liver metastases specimen, positive lymph nodes, poorly differentiated tumors, and the absence of neoadjuvant/adjuvant chemotherapy; meanwhile in multivariate analysis the tumoral degree of differentiation, positive resection margins at the level of the liver metastases and the absence of neoadjuvant/adjuvant chemotherapy. During the follow-up period recurrence was encountered in 57 cases and consisted of new liver metastases (in 42 cases), local recurrences (in 8 cases), lung metastases (in other 8 cases) and probably lymph node metastases (in 4 cases). Meanwhile, among patients experiencing longer than three or five year survival the location of the recurrent disease, if any, was unanimously represented by liver [12]. These data come to demonstrate once again that, in selected cases, a significant benefit in terms of survival might be achieved in pancreatic cancer patients with liver metastases especially if negative resection margins are achieved and if perioperative chemotherapy is associated. In the meantime, the German authors also underlined the necessity of adjuvant chemotherapy in order to eradicate the circulating cells present in the systemic blood flow after resection and which might be responsible for the development of early hepatic recurrence [12].

THE ROLE OF LIVER DIRECTED THERAPIES IN METASTATIC PANCREATIC CANCER

Other authors went further and investigated the effectiveness and safety of liver directed therapies in cases presenting hepatic metastases with pancreatic origin. Among these therapies radiofrequency ablation, transarterial chemoembolization and selective internal radiation therapy were the most widely investigated [13-18]. However, it should not be omitted the fact that in certain cases after performing such conservative therapies for liver metastases from pancreatic adenocarcinoma recurrence might develop after a shorter interval and iterative procedures or systemic chemotherapy might be needed in order to control the disease [18].

CONCLUSIONS

Although data regarding the role of surgery for pancreatic adenocarcinoma liver metastases is scarce, preliminary results presented so far come to sustain the efficacy of the method in selected cases; therefore, it seems that the best results are to be expected among cases with well differentiated tumors and good response to neoadjuvant chemotherapy. In the meantime, association of adjuvant chemotherapy seems to be salutary in order to decrease the risk of early recurrence due to the presence of circulating tumoral cells. However, larger studies are still needed and the results of the ongoing trials are expected in order to establish clear treatment guidelines for pancreatic cancer liver metastases patients.

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