

AN OVERVIEW ON THE ROLE OF SURGERY IN RESECTABLE PANCREATIC TUMORS

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ABSTRACT

One of the most fatal cancers, making it the seventh-highest rate of cancer-related death globally is pancreatic cancer. Most individuals with pancreatic cancer are asymptomatic until the disease has progressed to an advanced stage where surgery cannot be a potentially curative intervention. The modality of treatment (especially surgery) is usually chosen based on the stage and resectability of the tumor. Provide a proper review of the effect of surgery in the resectable pancreatic cancer treatment. For articles selection the PubMed database was used, and the following keys were utilized in the mesh ("pancreatic cancer"[Mesh]) AND ("resectable" [Mesh]) OR ("surgery"[Mesh]). To improve the rate of curative resection, patients with borderline resectable cancers can benefit from chemoradiation or preoperative (neoadjuvant) chemotherapy alone. Moreover, even in patients with resectable tumors, neoadjuvant chemotherapy has been recommended to ensure that systemic treatment is completed. Nevertheless, the only current potentially curative treatment option is surgical excision with an aggressive purpose. Depending on the location and type of tumor, a pancreatoduodenectomy, distal pancreatectomy, or complete pancreatectomy is done routinely.

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Introduction

Pancreatic cancer is one of the most fatal cancers, accounting for the seventh-highest rate of cancer-related death globally. The 5-year survival for individuals with pancreatic cancer in the United States, is as low as 9% [1-3].

Despite advancements in multimodality treatment with adjuvant therapy and surgery, the death rate of pancreatic cancer continues to rise over time [4, 5]. The illness's poor prognosis is partly due to its late detection, as most individuals with pancreatic cancer are asymptomatic until the disease has progressed to an advanced stage. Early on, only non-specific symptoms may present, although there are currently no screening systems in place available [6, 7].

Furthermore, pancreatic tumor biology may have a role in early metastasis. Early metastasis can be detected even when there is no main tumor in the pancreas, according to a preclinical study utilizing a mouse model of pancreatic cancer [8]. It is related to epithelial-to-mesenchymal transition and localized inflammation. As a result, pancreatic cancer is thought to be a systemic illness, similar to many other forms of malignancies, and multidisciplinary care of this disease is crucial. Surgery, chemotherapy, radiation treatment, and palliative care are all options for treating pancreatic malignancies, and they are chosen

based on the stage of the illness [1]. In this article, we aim to cover the surgical aspects in the published literature and provide an adequate review of the effect of surgery in the resectable pancreatic cancer treatment.

Materials and Methods

For articles selection, PubMed database was utilized, and the following keys were used in the mesh (“pancreatic cancer”[Mesh]) AND (“resectable”[Mesh]) OR (“surgery”[Mesh]).

The articles were selected based on the inclusion of one of the following topics: resectable pancreatic tumor and surgical management. The exclusion criteria were all other articles without these topics as their primary endpoint.

Around 110 publications were chosen as the most clinically relevant out of 3,761 articles indexed in the last decade, and their full texts were evaluated. A total of 33 of the 110 were included after a thorough examination. Additional research and publications were found using reference lists from the recognized and linked studies. Expert consensus recommendations and commentary were added where relevant to help practicing physicians assess cirrhosis most simply and practically possible.

Results and Discussion

90% of all pancreatic carcinomas are pancreatic adenocarcinoma and its variations [9]. The head of the pancreas accounts for 60-70% of pancreatic adenocarcinomas, with the body (15%) and tail (15%) accounting for the rest (15%). At the time of diagnosis, most pancreatic adenocarcinomas have already progressed beyond the pancreas, and nodal metastases are prevalent [10]. Pancreatic adenocarcinoma morphological variations have distinct histological properties than traditional pancreatic adenocarcinomas. These variations may also have distinct prognoses and a different molecular profile [11].

Clinical Features

Early-stage pancreatic cancer is frequently clinically quiet, with symptoms appearing only after the tumor has invaded nearby tissues or spread to distant organs. The majority of persons who appear with pancreatic cancer symptoms have an advanced illness [12]. Patients with pancreatic cancer who had abdominal CT scans before their diagnosis for other reasons, frequently exhibited modest abnormalities suggestive of pancreatic cancer up to a year before developing symptoms, implying a wasted chance for early identification [13].

Pancreatic cancer commonly presents with mid-back or stomach pain, obstructive jaundice, and weight loss. Anorexia, cachexia, and maldigestion due to pancreatic ductal blockage can all cause weight loss. Pancreatitis attacks can occur when the pancreatic duct is obstructed. Venous thrombosis, both deep and superficial, is common and can be a warning indication of cancer. With more advanced illnesses, a gastric-outlet blockage might cause nausea and vomiting. Panniculitis and sadness are two less prevalent symptoms. About 25% of pancreatic cancer patients had diabetes, and another 40% have damaged glucose tolerance, upon diagnosis [14].

The reason for the diabetogenic condition is unknown, however pancreatic cancer excision can sometimes cure diabetes. Researchers are looking at whether early-stage pancreatic cancer may be detected in elderly people who have recently developed diabetes. The majority of individuals with newly diagnosed diabetes, on the other hand, do not develop pancreatic cancer [15]. Aside from weight loss, there are few clinical indicators to suspect pancreatic cancer in those who have just developed diabetes. As a result, additional screening tests would be required to screen older people with new-onset diabetes for pancreatic cancer [12].

Diagnosis

A triphasic pancreatic-protocol CT scan is the best first diagnostic test for pancreatic cancer. It is also the most accurate way to stage disease, with optimal CT scans—including 3-dimensional reconstruction—providing roughly 80% accuracy in predicting resectability. CT scans quality varies, and imaging technology is improving all the time. The amount of needless laparotomies and staging laparoscopies has decreased dramatically because locally progressed and metastatic disease can be consistently detected by high-quality pancreatic-protocol CT scans [16]. Also, for diagnosing pancreatic cancer, Endoscopic ultrasound is quite accurate, and cytology collection can be done at the same time as the endoscopic ultrasound. MRI can be employed for staging in individuals who cannot bear intravenous contrast for CT.

Patients are classified as borderline resectable, resectable, locally advanced, or metastatic according to clinical staging. It determines the best course of action for the initial therapy. To detect pulmonary metastases, chest imaging (CT or chest radiography) is indicated. PET CT is not currently used in normal staging, although it can be useful if metastases are suspected like ambiguous lesions that cannot be diagnosed by CT, and it may be superior at detecting metastatic illness. Although laparoscopy can detect peritoneal metastases, it is not performed regularly before pancreatic resection. CA19-9 (carbohydrate antigen 19-9) concentrations of greater than 100–200 U/mL predict unresectability and survival before surgery [17].

Although imaging can strongly suggest pancreatic cancer when a pancreatic mass invades adjacent organs, tissue biopsy is necessary for confirming the diagnosis and ruling out benign illnesses such as autoimmune pancreatitis, which manifest with obstructive jaundice and pancreatic enlargement. Endoscopic ultrasonography or CT-guided fine-needle aspiration are commonly used to make a cytological diagnosis. Pancreatic masses’ endoscopic ultrasound-guided fine-needle aspiration is indicated to have about 80% sensitivity [18].

Brushings for cytological diagnosis and Endoscopic Retrograde Cholangiopancreatography (ERCP) may be required to determine the source of biliary or pancreatic duct strictures. Because of the limited sample size and sometimes minor distinctions between non-neoplastic reactive and malignant cells, the cell yield from endoscopic brushings is modest (about 20%). Molecular markers might be used to fine-needle aspirate cytological and supplement brush diagnosis, but further research is needed [19].

For surgical resection, a biopsy specimen is not required when there is a high suspicion of malignancy; in most cases, therapeutic efficacy is resulted by the resection, and significantly delay surgery to ensure that a detection might delay the start of effective therapy [12].

The Definition of Resectability

In pancreatic cancer patients, several researchers have defined borderline resectable, resectable, and unresectable tumors. According to clinical evidence, patients with borderline resectable cancers can benefit from preoperative (neoadjuvant) chemotherapy alone or chemoradiation to improve the rate of therapeutic resection [20-22]. Preoperative radiological imaging of high quality is utilized to specify tumor resectability. The presence of peritoneal or hepatic metastasis, involvement of the portal vein or superior mesenteric vein, and the relationship between the superior mesenteric artery and hepatic artery, celiac artery and the tumor, and the vascular relationship with any anomalous anatomy traditionally used to evaluate the pancreas cancer resectability. The existence of vascular involvement is the most critical determinant in assessing resectability [23].

Distant metastases, circumferential encasement of the celiac axis, or lengthy segmental superior mesenteric or portal vein thrombosis, or proximal hepatic artery, or superior mesenteric artery are all clear contraindications to resection. However, perspectives on whether or not there is more restricted arterial involvement or whether or not the portal/superior mesenteric vein confluence is involved, or how severe it differs widely (vein occlusion vs. patent) [23, 24]. It was previously considered venous attachment and encasement (without occlusion) as resectable if the tumor did not extend to the superior mesenteric or celiac arteries. That concept considered that the superior mesenteric-portal vein confluence was anatomically resectable and that the superior mesenteric-portal vein junction could be resected and rebuilt if needed [25]. Resectable tumors had no distant metastases, no indication of the portal vein or superior mesenteric vein involvement, and a clear fat plane surrounding the celiac artery, superior mesenteric artery, and hepatic artery. Borderline resectable tumors had a severe unilateral superior mesenteric vein/portal impingement, a short superior mesenteric vein occlusion with an open vein distally and proximally (but these were considered unresectable if the proximal superior mesenteric vein was obstructed up to the portal vein branches), abutment to the superior mesenteric artery, gastroduodenal artery encasement up to the origin at the hepatic artery. Tumors that met more than one of these criteria were labeled "locally advanced unresectable tumors."

More aggressive and specified resectability criteria were released by the M.D. Anderson Cancer Center Pancreas Cancer Group [20]. They discovered three categories of borderline resectable tumors: one based on anatomy, the patient's physical condition, or the other two based on illness uncertainty. They intended to identify borderline resectable tumors and also guide treatment strategies using neoadjuvant chemotherapy to achieve enhanced survival outcomes and a high incidence of R0 resection. Borderline resectable tumors were characterized as those with a superior mesenteric vein or an abutment on the portal vein with or without venous deformity, and minimal mesenteric vein and portal vein encasement (short segment occlusion with an appropriate vessel for anastomosis below and above) [20, 23].

Although the goal of resectional surgery is to remove the tumor completely (R0 resection), the difference between R1 status (residual microscopic disease) is debatable. The first issue is that there are two alternative R0 definitions: a 0 mm tumor-free margin and a 1 mm tumor-free margin [26-28]. Second, even though a defined methodology for the assessment of pancreaticoduodenectomy specimens was explicitly outlined previously, there is considerable variation in pathology specimen examination [27]. In addition, tumor development is diffused in pancreatic cancer, and morphological heterogeneity in pancreatic cancer contributes to unequal R0 rates among surgical facilities [29, 30].

As a result, the rate of R0 resection is an unsuitable endpoint in clinical trials, especially following neoadjuvant treatment. There is no clear definition of R0 status following neoadjuvant chemotherapy, and the tumor does not always diminish from the periphery but spot-wise. Another criterion that should not be used as an objective in the assessment of potential treatment benefit is the rate of surgical resection following neoadjuvant therapy. After neoadjuvant chemotherapy, the rate of resection in patients with a resectable tumor drops, since some individuals become unresectable due to advancing illness. However, even if the resection rate does not provide fundamental information on therapeutic importance, it is expected to rise in patients with borderline resectable or locally advanced cancers following neoadjuvant therapy [26, 31].

Resectable Tumors Treatment

In patients with resectable tumors, neoadjuvant chemotherapy has been recommended to ensure that systemic treatment is completed, which may be hampered by postoperative difficulties or early disease progression following upfront surgery. Patients with good tumor biology are selected for future resection as a result of neoadjuvant treatment. Patients with resectable malignancies should have surgery first and then adjuvant treatment, according to a widely held opinion [32]. However, neoadjuvant chemotherapy is becoming more popular in the United States, but upfront surgery is more common in Europe [33]. This is now the standard of therapy, but ongoing trials are evaluating even more powerful anticancer regimens, and a model with second-line treatment as an alternative in the event of persistent illness postoperatively appears to be in the process. Even though adjuvant immunotherapy is not now standard of treatment, its therapeutic benefits are likely to have an important

effect on the future. In this case, however, removing the main tumor is critical to avoid the inhibitory regulatory T-cell impact. This viewpoint favors upfront surgery [26].

Nevertheless, the only current potentially curative treatment option is surgical excision with an aggressive purpose. Depending on the location and type of tumor, a complete pancreatectomy, a distal pancreatectomy, or pancreatoduodenectomy is done routinely. After surgical resection, the hospital fatality rate can be as low as 2%, while total morbidity might be as high as 60%. It should be underlined that a smooth surgical recovery is linked to a higher long-term survival rate [34-36].

In terms of endocrine function, disease progression is more important than surgical intervention, and new-onset diabetes mellitus may typically be treated with pancreatic tumor removal. Both surgical and institutional volumes have a substantial correlation with surgical outcomes. Several studies have shown that high-volume facilities had lower death and morbidity rates. Even after adjusting for perioperative mortality, this connection is true for long-term survival. This link between better outcomes and hospital volume is thought to be complex. One theory is that more skilled medical personnel are better able to recognize and manage difficulties at an earlier stage, perhaps improving the result.

Superior surgical performance as a result of more frequent operations might enhance both short- and long-run outcomes. The oncologists' outcomes are expected to improve as their experience and their skills grow because the treatment is multimodal and involves adjuvant therapy. The 2-year survival rate among resected patients has risen by over 10% when centralization was implemented, and it is regarded as a fantastic technique to enhance surgical results.

It is debatable if neoadjuvant treatment is better than adjuvant therapy for a pancreatic tumor. Improved chemotherapeutic invasion due to improved vascularization, decreasing the percentage of positive lymph nodes, potential downstaging of borderline resectable tumors, a higher percentage of accomplished R0 resections, and early treatment of micrometastases are all proposed benefits of neoadjuvant therapy. Patients who get neoadjuvant therapy are also thought to have a greater likelihood of completing the whole multidisciplinary treatment. Another benefit mentioned is the ability to choose and exclude individuals who are developing progressive or metastatic illnesses, thus preventing needless surgery. Histological confirmation is required for neoadjuvant therapy, which may enhance the discovery of individuals who are unlikely to benefit from resection. Neoadjuvant treatment is linked to a delay in resection and, as a result, potential risk of tumor development [36].

The Role of Biliary Drainage before Resection

Jaundice affects a large percentage of people with pancreatic cancer. This might result in coagulopathy and an increase in perioperative infective problems. Patients with obstructive jaundice were traditionally treated for it before undergoing resection. Nevertheless, a recent multi-center randomized research comparing ERCP with drainage to urgent surgery indicated that the drainage group had a greater prevalence of perioperative complications. This shows that for a small set of individuals, accelerated surgery may be preferable for biliary decompression before resection [11, 37].

Anastomotic Method

The leak from the pancreatic anastomosis and pancreatic fistula establishment are two significant causes of morbidity after pancreaticoduodenectomy surgery. Following pancreaticoduodenectomy, the alimentary canal can be rebuilt by anastomosing the pancreatic remnant to the jejunum or stomach. When these two approaches were examined, there was no difference in the result. Also, variations in the anastomotic method have been recorded, although a recent meta-analysis failed to show that the "duct-to-mucosa" anastomosis had a lower risk of pancreatic fistula than the "invagination" procedure [11, 38].

The Debate of Minimally Invasive Surgery

Minimally invasive procedures for pancreatic surgery have risen in popularity, as they have in other fields. The first minimally invasive pancreatic resection was characterized as laparoscopic distal pancreatectomy. It has been shown that open distal pancreatectomy and laparoscopic have similar morbidity and mortality outcomes, although the minimally invasive group had a shorter hospital stay and less blood loss. Moreover, positive resection margins occur at the same rate in both approaches. Laparoscopic distal pancreatectomy is at least non-inferior to open surgery, but that it could not be considered superior due to a lack of level one evidence [39].

Moreover, efforts have been taken to optimize pancreaticoduodenectomy surgery using robotic technology. A retrospective cohort studies meta-analysis indicated that robotic pancreatectomy had a less margin involvement and lower complication rate than open pancreatectomy. However, because these trials are not randomized, they are susceptible to selection bias. Also, Robotic surgery necessitates a large financial commitment, and none of the articles included cost-effectiveness analyses [40].

Conclusion

Patients that have borderline resectable cancers can benefit from chemotherapy or chemoradiation preoperative (neoadjuvant) alone to improve the rate of curative resection. Moreover, even in patients with resectable tumors, neoadjuvant chemotherapy has been recommended to ensure that systemic treatment is completed. Nevertheless, the only current potentially curative treatment option is surgical excision with an aggressive purpose. Depending on the location and type of tumor, a pancreatoduodenectomy, distal pancreatectomy, or complete pancreatectomy is done routinely.

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