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Strategies to improve local control of resected pancreas adenocarcinoma

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ABSTRACT

Background: Only approximately one in ten pancreas cancer patients is a candidate for potentially curative resection of this disease. Even this small fraction of patients has a poor prognosis following pancreatico-duodenectomy. The disease has an anatomic location that makes it difficult for the surgeon to maintain adequate margins of resection and prevent tumor spillage at the time of resection. Also, the disease is biologically aggressive and even with a complete visible resection of the disease, micro-metastases are likely to remain behind.

Methods: A survey of the sites for surgical treatment failure of resected pancreas cancer was performed. Also, the multiple modalities used in an attempt to improve the results of cancer resection are scrutinized.

Results: The surgical treatment failures are regional in nature and occur at the resection site and on peritoneal surfaces, within the liver, and within the regional lymph nodes. These anatomic sites account for nearly 100% of the initial sites of disease progression. Current hypothesis suggests that micro-metastases released from the cancer specimen by the trauma of surgery account for the high incidence of resection site progression and peritoneal metastases. Although surgical trauma may contribute to micrometastases within the liver and lymph nodes, these are most likely present though not detected by preoperative radiologic studies. Adjuvant treatments such as neoadjuvant chemotherapy or combination systemic chemotherapy have not been associated with improved survival. Extended resections such as total pancreatectomy or extended lymphadenectomy have not been associated with benefit. However, resection with a negative margin of excision along with the removal of at least 12 lymph nodes in and around the pancreaticoduodenectomy specimen is associated with superior outcomes. A regional chemotherapy treatment that consists of hyperthermic intraperitoneal chemotherapy (HIPEC) with gemcitabine and long-term normothermic intraperitoneal chemotherapy (NIPEC-LT) gemcitabine for 6 months postoperatively is suggested as a new treatment that has demonstrated decreases in local-regional failure and promises to more adequately target micrometastases in the peritoneal space, in the liver and lymph nodes.

Conclusions: Pancreas cancer surgery should attempt to achieve negative margins of resection with the removal of at least 12 lymph nodes. Hyperthermic intraperitoneal gemcitabine can adequately eradicate malignant cells dislodged from the cancer specimen into the bed of the resection at high density and on distant peritoneal surfaces as peritoneal metastases. Long-term intraperitoneal gemcitabine may act on micrometastases in the liver through absorption into the portal vein blood and the lymph nodes as a result of gemcitabine absorption by subperitoneal lymphatic channels. The use of HIPEC and NIPEC-LT gemcitabine may improve local control of resected pancreas cancer.

1. Introduction

In comparison to other gastrointestinal malignancies, the surgery employed to date for pancreas cancer should be considered a failure. Long term survival following pancreaticoduodenectomy for adenocarcinoma is ten percent or less [1]. The local failure rate with

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a complete resection is at least 50%. Progressive disease at the resection site or on peritoneal surfaces as peritoneal metastases occurs in a large percentage of these patients with profound quality of life consequences. In patients with uninvolved lymph nodes, the risk of a local-only recurrence is increased [2].

The history of surgical oncology tells a consistent story concerning the absolute necessity of local control of a malignancy as first requirement for the testing of systemic adjuvant treatments. The local control of rectal cancer improved through a combined use of preoperative radiotherapy and total mesorectal resection [3]. Similar improvements with low rectal cancer from the extra levator abdominal perineal resection have become a reality [4]. Gastric cancer surgery has moved forward as a result of the D-2 lymph node dissection [5]. In the absence of D-2 resection local post-operative radiochemotherapy has made a difference in survival [6]. However, meaningful improvements in the local control in the surgical management of pancreas cancer are not at present a reality.

2. Patterns of recurrence and cause of death post-resection

When the steps required for a pancreaticoduodenectomy are reviewed, the cause for an absence of long-term survival and high incidence of local-regional failure seems to be obvious. The anatomic position of the pancreas deep in the retroperitoneal part of the upper abdomen causes “no touch cancer resection” to be impossible. Trauma to the resected cancer specimen is often unavoidable. Even more important, because of the surrounding vital structures, the margins of resection are minimal at best and often positive (Fig. 1). A true R-0 cancer resection is unusual; rather than a resection, pancreaticoduodenectomy may be regarded as a debulking procedure. This problematic anatomic location combined with an aggressive tumor biology contribute to the unacceptably high incidence of local-regional treatment failure currently tolerated in the surgical management of pancreas cancer.

The high incidence of local-regional failure from cancer seeding is matched by a high incidence of liver metastases and regional lymph node metastases. The aggressive tumor biology of the primary pancreas lesion causes dissemination into the portal blood and lymphatic channels to occur early in the natural history of the cancer. However, since little or no success with prevention or treatment of disease at systemic sites exists, the focus of this manuscript is on improved local control. Cause of death and disease-free survival may be altered by improved local control.

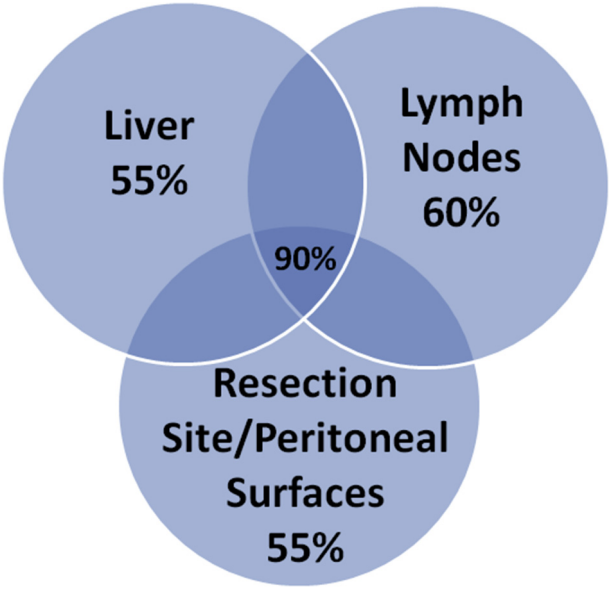

Fig. 1. Sites of initial treatment failure for resected pancreas cancer.

3. Pathophysiology of resection site disease and peritoneal metastases

In patients who have a positive margin of resection of pancreas cancer, the local recurrence can be assumed to be a local progression of small volume residual disease. In distinct contrast, local recurrence and resection site disease in patients with an R-0 resection is considered to have a different causation. In the process of performing the pancreaticoduodenectomy with clear margins, cancer cells may gain access to the peritoneal space and grow out at high density at the resection site. The phenomenon has been called tumor cell entrapment; it has three prominent causes (Fig. 2). Tumor cells may escape the pancreas cancer specimen as lymphatic channels contaminated by malignant tumor emboli are transected. Similarly, venous invasion by the pancreas cancer may result in spillage of malignant tumor emboli as transaction of small vessels from the cancer specimen inevitably occurs. Thirdly, the surgical trauma that inevitably occurs with extirpation of the pancreas cancer specimen can cause a minimal but real disruption of the malignancy. Also, this surgical trauma would increase the number of cancer cells dislodged from transected lymphatic channels. This mechanism for local recurrence of pancreas cancer despite a clear margin of resection has been referred to as the “tumor cell entrapment hypothesis” [7].

These free cancer cells would be expected to implant with high efficiency at the wounded site [8]. The local implantation and then progression of cancer cells within the bed of the resected pancreas cancer would cause a high density of local recurrence. However, not only resection site implants but also distant peritoneal implants would be expected. The former at high density would eventually be detected as a mass progressing within the resection bed; the latter at lower density would eventually be detected at a distance from the resection site as peritoneal metastases. In conclusion, free cancer cells emanating from the trauma of pancreas cancer resection would explain two sources of treatment failure commonly seen following pancreaticoduodenectomy.

Study of the natural history of resected pancreas cancer suggests that peritoneal metastases are most likely the result of cancer cells or multicellular cancer nodules gaining access to the free peritoneal space. Peritoneal metastases occur prior to the pancreatic resection in an estimated 10% of patients. However, after the pancreatectomy in patients who had no peritoneal metastases at the time of resection, 50% or more patients will develop local recurrence and/or peritoneal metastases in follow-up. This observation strongly suggests that cancer cells disseminated at the time of pancreas resection as a result of surgical trauma to a specimen that has minimal margins of resection causes the local resection site recurrence and the peritoneal metastases. These free cancer cells implant and grow not only at a distance from the resection site as peritoneal metastases but also within the resection site as a local recurrence.

4. Pathophysiology of liver and lymph nodal recurrence/progression

The causation of liver metastases and regional lymph nodal metastases detected in follow-up are readily apparent. They result from the progression of micrometastases not imaged by preoperative radiologic studies. Because systemic chemotherapy or chemoradiation therapy is ineffective for these micrometastases, these treatments have little effect on the natural history of this disease.