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Review

Gastric Cancer Invading the Pancreas: A Review of the Role of Pancreatectomy

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Abstract. *Gastric cancer is quite a common type of cancer, with significant associated mortality. Traditionally, combined resections of affected organs have been advocated in cases of locally advanced gastric cancer, in order to achieve an R0 resection. The purpose of the present study was to evaluate the role of pancreatectomy in the treatment of gastric cancer invading the pancreas by reviewing the relevant literature. The oncological benefits to survival rates of multivisceral resection are not always obvious from the relevant survival charts, especially when the pancreas is the organ invaded by the gastric cancer and gastrectomy needs to be combined with a pancreatectomy, an operation with high morbidity rates. In conclusion, careful patient selection is essential to achieving optimal results, balancing the oncological benefits in these properly selected patients against the associated morbidity of extensive resection.*

According to the GLOBOCAN data, more than a million new cases of gastric cancer are diagnosed globally each year, with an estimated 738,000 deaths in 2018 (1). Based on these data, it becomes clear that the prognosis of gastric cancer remains poor. The cumulative 5-year survival rate for gastric cancer is 31% in the United States, although, 5-year survival rates of 67% have been reported for patients with pre-metastatic lesions (1). This obvious variability of gastric cancer prognosis can be explained by the differences of gastric cancer stage upon surgical intervention. In general, only a minority of patients with gastric cancer are diagnosed early in the course of their disease, mainly because small tumors are not usually associated with symptoms specific enough to dictate a tailored diagnostic workup. The result is that at diagnosis, 65% of patients already have advanced cancer (T3, T4), 85% have lymph node involvement, and 40% have metastatic disease (2).

A gastrectomy, either total or subtotal, combined with proper D2 lymph node dissection is the only curative treatment for gastric cancer. Aiming to improve survival rates, the surgical resection is usually supplemented with chemotherapy (3). The prognosis of gastric cancer is negatively influenced as soon as the tumor perforates the serosal layer of the stomach or extends to adjacent organs (T4 tumors). Perioperative chemotherapy or upfront surgery combined with adjuvant chemoradiotherapy has been advocated for the treatment of T4 gastric cancer (3). However, despite these multimodality treatment approaches, the 5-year overall survival rates for this group of patients are still disappointing, *i.e.*, <20% (4).

With the intent of achieving an R0 resection, these patients with locally advanced gastric cancer (T4b) require radical gastrectomy with concomitant resection of other affected organs. Increased perioperative morbidity associated with these multivisceral resections is the cost of achieving negative resection margins. As the oncological benefits of such multivisceral resections on survival rates are not always obvious from the relevant survival charts, proper patient selection appears to be extremely important. The situation becomes even more complex when the pancreas is the organ invaded by the gastric cancer and gastrectomy needs to be combined with a pancreatectomy, a procedure associated with high morbidity. The purpose of the present study was to evaluate the role of pancreatectomy in the treatment of gastric cancer invading the pancreas by reviewing the relevant literature.

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Staging

Careful staging of patients with gastric cancer is of paramount importance for selecting their proper treatment. The TNM staging system of the American Joint Committee on Cancer/Union for International Cancer Control is currently the most utilized system (5). According to this system, a T4 tumor is a tumor that invades the serosa (T4a) or adjacent structures (T4b). Adjacent structures include the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine and retro-peritoneum. Thus, by definition a gastric tumor invading the pancreas is a T4b tumor. In regard to the stage, depending on the lymph node status, such tumors are categorized as stage IIIa (N0), IIIb (N1 or N2) or IIIc (N3) (5).

Surgery represents the key part in the treatment algorithm, with the exception of early gastric cancer with favorable characteristics *i.e.*, those clearly confined to the mucosa, well-differentiated, ≤2 cm in diameter and non-ulcerated, where an endoscopic resection in the form of endoscopic sub-mucosal dissection can be the standalone curative intervention (6). Thus, for patients with stage Ib to III gastric cancer, a radical gastrectomy plus a D2 lymphadenectomy is indicated. Following the results of the MAGIC trial, perioperative chemotherapy has become the standard of care, as well (7).

Defining Patients With T4b Disease

The treatment of T4b gastric cancer *i.e.*, gastric cancer invading adjacent organs, is challenging. Firstly, the diagnosis in the preoperative setting is a rather difficult task, bearing in mind the limitations of conventional imaging (8). Computed tomography and endoscopic ultrasound are routinely used in order to accurately stage gastric cancer, with a reported accuracy in determining T4 disease of 80% and 79%, respectively (8, 9).

Problems might arise even when the assessment of T4 disease is made intra-operatively. Misjudging as a direct invasion what the actual pathology report diagnoses as a desmoplastic reaction is not a rare scenario (10). Studies show that up to 55% of cases treated as direct tumor invasion at laparotomy proved to be an inflammatory reaction on pathology (10, 11). The rate of this false-positive clinical judgment seems to be further unrinsed when the pancreas is the organ invaded by the gastric cancer. Piso *et al*. showed that pathology-documented pancreatic invasion was found in only 39% of gastric cancer cases submitted to a simultaneous gastrectomy and pancreatectomy (12).

Morbidity and Mortality

The paradigm of how the increased morbidity and mortality of an extended procedure, *i.e.*, a lymphadenectomy with splenectomy and partial pancreatectomy, can counterbalance and even outweigh the possible oncological benefits is a lesson learned in the field of gastric cancer. The short-term outcomes of multivisceral resections, *i.e.*, perioperative morbidity and mortality, should be assessed and evaluated appropriately as their effect on the desired long-term oncological results, namely survival, might be more than profound. In general, pancreatic resections, whether combined with a gastrectomy, in the setting of locally advanced gastric cancer, or as standalone procedure for primary pancreatic cancer, are associated with high postoperative morbidity and mortality (13, 14). Literature reports the incidence of complications in to up to 60% of patients, and Clavien–Dindo grade III and higher complications in approximately 40% (13, 15). Interestingly, this increased morbidity is not reflected in a corresponding notable increase in perioperative mortality.

Resection Margins

Traditionally, the actual goal of the surgical treatment of locally advanced gastric cancer is to achieve an R0 resection margin. Kim *et al*. divided 132 patients undergoing surgery for locally advanced gastric cancer (T4) into three subgroups. The first group was submitted to a multivisceral resection, the second underwent a gastrectomy only, while the patients of the third group were not submitted to any kind of resection only to a palliative procedure. Despite the quite notable heterogeneity between the three groups, resection margin status *i.e.*, R0 *vs*. R1 *vs*. R2 had a significant impact on survival. In addition, 5-year survival rates were statistically better in the group submitted to multivisceral resection compared to the gastrectomy-only group (16). Similar findings were reported by Onate-Ocana *et al*., where R0 multivisceral resections were associated with a survival benefit (17).

A recent pooled analysis of studies, including patients submitted specifically to pancreatoduodenectomy, reported 5-year overall survival rates of 39.3% and a median survival of 26 months (18). The results of the Dutch Upper GI cancer audit showed that an R0 gastrectomy with partial pancreatectomy was achieved in 82% of patients undergoing these kinds of resections. The median overall survival of patients after R0 and R1 resection was 20 and 5 months, respectively. The postoperative morbidity was increased when an extensive resection strategy was adopted. The authors concluded that such extensive operations should only be performed if an R0 resection is feasible (19).

The only study showing that negative resection margins did not translate into an oncological benefit, in terms of prolonged survival, was a recent one by Chang *et al*. (20). In their study, patients undergoing multivisceral resections performed for locally advanced but still resectable gastric cancer were stratified into four groups according to the

affected organ, *i.e*., pancreas or other organs, and the distal duodenal margin status. According to the results of this study, patients submitted to a Whipple's procedure in order to obtain a negative duodenal margin did not have a better survival than patients with a positive distal duodenal resection margin who did not undergo Whipple's operation. The authors attributed this unexpected finding to the increased complication rate in the Whipple's operation arm of the study and the resulting immune suppression which promotes cancer growth and metastasis. In addition, they highlighted the stage of the disease and its biological behavior as the most important determinants affecting outcomes in patients with pancreatic head invasion.

Affected Organ Resected

An important part of the equation of the treatment of patients with T4b gastric cancer appears to be the organ invaded directly by the primary tumor on the gastric wall. Survival seems to be higher when the affected organ is the liver and gastrectomy is supplemented by a partial hepatectomy, compared to when surgery for the pancreas, colon or spleen and gastrectomy needs to be supplemented by respective resection of the affected organ *i.e*., pancreatectomy, colectomy, or splenectomy (21).

Min *et al*. reported 5-year survival rates of 23.3% in patients with pancreatic invasion by gastric cancer and 42.1% in those with locally advanced gastric cancer where the pancreas was not among the involved organs. In patients with pancreatic invasion, there was no survivors at 5 years when the resection involved a pancreatoduodenectomy. On the other hand, 5-year survival was 27.4% for the patients who underwent another type of pancreatic resection, such as distal pancreatectomy and wedge resection. Therefore, the type of pancreatic resection required also influences the long-term results. Pancreatoduodenectomy was associated with the worst survival, while more favorable outcomes were encountered in patients submitted to other types of pancreatic resection, such as distal pancreatectomy or wedge resection (22).

An audit on the outcomes of multivisceral resections for gastric cancer in seven U.S. academic institutions revealed that multivisceral resections were associated with higher perioperative morbidity but not significantly higher perioperative mortality. A multivisceral resection involving a pancreatectomy was highlighted as an independent predictor of poor survival (13). A recent study by Chang *et al*. revealed that the surgical prognosis for patients with pancreatic involvement was significantly poorer than for those with invasion of other adjacent organs (20).

Nodal Status

A multicenter study evaluated 112 patients undergoing multivisceral resection for gastric cancer (23). In 98 patients (87.5%), there was invasion of adjacent organs (pT4b). An R0 resection was achieved in 43 patients (38.4%), R1 in 30 (26.8%), and R2 in 39 (34.5%). Pathologic N status was: N0 in 12 patients, N1 in 34, N2 in 33 and N3 in 33. There was no homogeneity in the adjuvant chemotherapy regimens used. Survival at 1, 3 and 5 years was 60.7%, 30.3% and 27.2%, respectively. The multivariate analysis showed that the resection margin status (R0 *vs*. R1 *vs*. R2) and the nodal status (N0 *vs*. N1 *vs*. N2 *vs*. N3) were important prognostic factors for survival. More specifically, the 5-year survival was 43.7% in the R0 group, 31.4% in the R1 resection and 0% in patients who had a R2 resection. In regard to the prognostic significance of the nodal status, the 5-year survival of the pN0, pN1, pN2 and pN3 patients was 53.3%, 40.4%, 26.5% and 0%, respectively. The node positivity for the surgical specimen ultimately negatively influenced overall survival. Within the same context, a systematic review of 17 studies, including 1,343 patients in total, designated resection margin status and possible lymph node involvement as the main prognostic factors in multivisceral resections for advanced gastric cancer (24).

Neoadjuvant Chemotherapy

The treatment of gastric cancer has been significantly altered during recent decades (25). Starting from the data yielded from the MAGIC (7) and the FLOT4 (26) trials, there are constantly new reports on the favorable influence of perioperative chemotherapy on the oncological outcomes of gastric cancer treatment. The PRODIGY trial, a recent randomized control trial, showed that neoadjuvant chemotherapy followed by surgery proved superior to up-front surgery in patients with resectable advanced gastric cancer in terms of higher R0 resection rates (96.4% *vs*. 85.8%), lower pathological stage with pathological complete response (10.4% *vs*. 0%) and improved 3-year disease-free survival rates (66.3% *vs*. 60.2%) (27).

The rationale for adopting the strategy of perioperative chemotherapy in locally advanced but resectable gastric cancer is its several advantages over the administration of chemotherapy in the adjuvant setting. First of all, it can be used as a screening tool in order to identify patients with disease of unfavorable biology, thereby avoiding an extensive yet ineffective operation. Higher rates of R0 resection should also be anticipated. Down-staging of a T4b tumor might entirely alter the surgical strategy in regard to the resection of adjacent organs in order to achieve R0 resection margins. Finally, the decline of a patient's performance status as a result of an extensive operation might increase the risk of toxicity of adjuvant chemotherapy. Treating possible occult metastatic foci upfront in a timely manner with neoadjuvant chemotherapy appears to be a justified approach.

Although there is indeed quite solid evidence in the literature regarding the favorable role of neoadjuvant

chemotherapy in gastric cancer treatment, patients with T4b tumors concerning the pancreas are relatively under-represented in relevant trials. Thus, drawing a definite conclusion in regard to the optimal management of such patients is not currently entirely evidence-based. Further studies, preferably focused on this patient group with advanced gastric cancer, are definitely needed.

Peritoneal Cytology Status

Peritoneal metastases of gastric cancer have a dismal effect on prognosis, and such patients are qualified for palliative chemotherapy alone (28). In contrast to macroscopic peritoneal involvement, the prognostic significance of microscopic peritoneal disease as documented by a positive peritoneal cytology sample remains unclear (29). In patients with gastric cancer, the incidence of positive peritoneal cytology ranges from 4% to 41% (30). In general, the stage of the disease has been highlighted as an important determinant of positive peritoneal cytology. While there is virtually no likelihood of a positive cytology result in cases with small tumors *i.e.*, T1/T2, the probability increases when a T3 or T4 tumor (10%) or metastatic disease (59%) is present (31).

The optimal treatment of these patients is under debate and the lack of consensus in the available guidelines further complicates the issue (32). The National Comprehensive Cancer Network gastric cancer guidelines define gastric cancer with positive peritoneal cytology as metastatic (M1) disease and recommend only palliative treatment (33). Similarly, the Japanese Gastric Cancer Association classifies positive peritoneal cytology as M1 disease and excludes surgery from the treatment algorithm (34). In contrast, the European Society for Medical Oncology guidelines avoid characterizing these patients with positive cytology as inoperable (35). Finally, the most recent TNM classification categorizes gastric cancer with positive cytology as a stage IV disease (5).

A recent meta-analysis confirmed that positive peritoneal cytology was a negative prognostic factor for survival in gastric cancer but still of better prognosis compared to macroscopic peritoneal disease (36). However, the authors underlined the modifiable nature of this factor under the influence of chemotherapy. The alteration of the cytology status, from a positive to negative result, following chemotherapy was shown to be associated with a survival benefit (37). An approach of reassessing the results of an initially positive, peritoneal cytology result after chemotherapy would therefore appear to be valid This knowledge justifies reassessment of the presence of positive peritoneal cytology as an absolute indication for palliative treatment without further consideration of changing status following chemotherapy.

Discussion

It becomes obvious that patient selection is the most crucial part in the treatment algorithm of gastric cancer invading the pancreas. An approach of tailoring the indications for multivisceral resections might have a notable, favorable impact on the final outcome. For example, Min *et al.* excluded patients with involvement of the para-aortic lymph nodes, as well as those who would require a pancreatoduodenectomy in addition to gastrectomy, from multivisceral resection (22).

In general, the management of these patients should be decided in multidisciplinary team meetings with close collaboration of all relevant specialties. A detailed staging scheme should be the basis of all treatment decisions. Exhausting the capabilities of the imaging modalities in determining the possible direct involvement of the pancreatic parenchyma in the malignant process of the stomach is imperative. However, the documentation of such occurrence might not be entirely accurate even after a detailed imaging staging.

In general, patients with these locally advanced gastric cancers should receive chemotherapy upfront. Treating possibly systematic disease such as T4 gastric cancer with a systematic treatment upfront, achieving down-staging of the primary tumor thereby enabling a clear resection margin without multivisceral resection, and ultimately selecting patients who would benefit from an extensive multivisceral resection according to their favorable response to the chemotherapeutic regimen, represent the rationale for adopting upfront chemotherapy.

A staging laparoscopy combined with peritoneal cytology testing might further aid in proper patient selection. A positive cytology at this point, after chemotherapy, would be an absolute indication for palliative chemotherapy alone. In the absence of evident macroscopic or microscopic disease, a surgical intervention with an anticipated R0 resection is advocated. Even during laparotomy, there might be problems in accurately determining the presence of direct pancreatic invasion of gastric cancer. Often, the tumor-related desmoplastic reaction can be misdiagnosed as direct invasion. Using frozen section pathology on the resection margin towards the pancreas might avoid an unnecessary pancreatectomy and its high associated morbidity.

In conclusion, the treatment of patients with locally advanced gastric cancer, such as gastric cancer invading the pancreas, requires a multimodality approach. Careful patient selection is essential to achieving optimal results. Balancing the oncological benefits in these properly selected patients against the associated morbidity of extensive resections can ultimately indicate the oncological appropriateness of the procedure.

Conflicts of Interest

The Authors declare no potential conflicts of interest in relation to this study.

Authors' Contributions

Study conception and design: D. Symeonidis and K. Tepetes. Acquisition of data: L. Kissa, A. Samara and E. Bompou. Analysis and interpretation of data: L. Kissa, A. Samara and E. Bompou. Drafting of article: D. Symeonidis and D. Zacharoulis. Critical revision: K. Tepetes and A. Samara.

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