

Multiorganic resections in gastric cancer

Ressecções multiorgânicas no câncer gástrico

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Gastric cancer is the fifth most common malignant tumor in the world, surpassed only by malignant neoplasms of the lung, breast, colon/rectum and prostate. About 70% of cases occur in developing countries. It is the third leading cause of cancer death in both genders, behind lung and liver neoplasms¹.

There are expected 12,920 new cases of stomach cancer in men and 7600 in women in Brazil, in the year 2016. Excluding non-melanoma skin tumors, it is the fifth most incident cancer in the country².

Helicobacter pylori infection, consumption of salt and smoked foods, obesity, high alcohol consumption and smoking are the main risk factors for the disease.

Unfortunately, most cases of gastric cancer are unveiled in advanced stages, notably in the West and in developing countries. Japan and South Korea are exceptions, where efficient screening programs have enabled a higher percentage of diagnosis in an early stage.

According to the eighth TNM classification for malignant tumors of the International Union for Cancer Control (UICC), gastric cancer that invades adjacent structures (liver, colon, small intestine, adrenal, diaphragm, pancreas, spleen, kidney) is classified as pT4b. These tumors present a major challenge, since they are usually associated with an important decrease in the patient's general condition and, not infrequently, in peritoneal (microscopic or even macroscopic) dissemination.

The diagnosis of pT4b gastric tumors is not an easy task. The clinical-pathological correlation is very flawed: it is not uncommon that we interpret a computed tomography scan as an invasion of adjacent organ (cT4b) and then confirm a desmoplastic reaction in the

anatomopathological specimen analysis. In a meta-analysis published in 2011, Seevaratnam *et al.*³ studied the role of computed tomography in determining T4 status in gastric cancer: the accuracy of the radiological method was 80%. In another systematic review, Cardoso *et al.*⁴ showed that the accuracy of endoscopic ultrasonography in evaluating T4 gastric tumors (79%) is very similar to that of computed tomography.

Even the intraoperative evaluation is flawed, which eventually leads the surgeon to a multiorganic resection when in fact the structure adjacent to the tumor did not present a real invasion, but rather a desmoplastic reaction. Some Japanese series^{5,6} show that, in up to 55% of cases, what was treated as tumor invasion at laparotomy was, in fact, a desmoplastic reaction confirmed by the pathologist. In particular, the challenge of evaluating tumor invasion is even greater when we deal with a tumor closely related to the pancreas. Piso *et al.*⁷ found pancreatic invasion in only 39% of patients submitted to gastrectomy associated with monobloc pancreatectomy.

Peritoneal dissemination can be assessed by staging laparoscopy. Some studies show that laparoscopy promoted a change in the therapeutic strategy in 20 to 50% of the cases, sparing many patients from an unnecessary laparotomy⁸⁻¹⁰.

In a retrospective study involving 65 patients submitted to radical surgery, Carboni *et al.*¹¹ reached R0 surgery in 40 patients (61.5%). Of these, 80% presented invasion of adjacent organs/structures at the anatomopathological evaluation (pT4b). In the remaining 25 patients the procedure was not radical: in 18 patients the surgical margins were microscopically affected (R1 sur-

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gery) and in the other seven the surgery was R2 (margin macroscopically affected by tumor). On the other hand, Xiao *et al.*¹² reached R0 surgery in 68.2% of the cases of their retrospective series of 63 patients. In only 39.7% of the patients, tumor invasion of the adjacent organ was confirmed by the anatomopathological analysis.

Considering the aggressiveness of the multiorgan surgery, arises the discussion of the real benefit of this procedure when compared to palliative resections or even to the derivative procedures. Kim *et al.*¹³ evaluated 132 patients undergoing surgery for T4 gastric cancer. They compared three subgroups: multiorgan surgery (group 1), isolated gastrectomy (group 2) and surgery without resection, such as gastrojejunostomy and intraperitoneal chemotherapy (group 3). Group 3 included a considerably larger number of patients with Borrmann IV tumor, peritoneal dissemination and distant metastasis. In the multivariate analysis, surgical radicality (R0 vs R1 vs R2) had an impact on survival despite the important disparity between the groups. When groups 1 and 2 were compared, survival at five years was greater in group 1, with statistical significance. In a retrospective series of 169 patients submitted to multiorgan resection, Oñate-Ocaña *et al.*¹⁴ also found different survival rates when compared patients who underwent R0 surgery with those submitted to R1/R2 surgery.

Several studies have sought to evaluate survival after multivisceral resection in gastric cancer according to the associated resected organ. Cheng *et al.*¹⁵ demonstrated a higher median survival in patients with hepatic invasion when compared with invasion of the pancreas, colon and spleen. Min *et al.*¹⁶ evaluated 243 pT4b patients who underwent R0 surgery. Five-year overall survival was 36.8% and median survival was 26 months. In patients with pancreatic invasion, survival at five years was 23.3%, whereas in patients without pancreatic invasion, survival at five years was 42.1%. In patients with pancreatic invasion, there was no survival at five years when resection involved duodenopancreatectomy. In patients who received another type of pancreatic resection (distal pancreatectomy and wedge resection), five-year survival was 27.4%.

Due to the high morbidity of multivisceral surgery and the high mortality found in some series, several authors tried to stratify the main prognostic factors

in the surgical treatment of pT4b patients. An important multicenter Italian study¹⁷ evaluated 112 cT4b patients undergoing multivisceral resection. In 98 patients (87.5%) there was invasion of adjacent organs (pT4b). They obtained R0 surgery in 43 patients (38.4%), R1 in 30 (26.8%), and R2 in 39 (34.5%). They also assessed nodal status: 12 patients N0, 34 N1, 33 N2 and 33 N3. After surgery, patients received adjuvant chemotherapy. There was no homogeneity in the adjuvant protocols, the ECF scheme (epirubicin, cisplatin and fluorouracil) being the most used. As a result, adjuvant chemotherapy was not considered in the statistical analysis. Survival at one, three and five years was 60.7%, 30.3% and 27.2%, respectively. The multivariate analysis showed that the resection status (R0 vs. R1 vs R2) and the nodal status (N0 vs N1 vs N2 vs N3) are the main prognostic factors in multivisceral resection. The five-year survival was 43.7% in the R0 surgery and 31.4% in the R1 resection. There was no 5-year survival in patients undergoing R2 surgery. For patients pN0, pN1, pN2 and pN3, the survival was 53.3%, 40.4%, 26.5% and 0%, respectively. When comparing N0 and N+ patients, there was a significant impact on survival in five years (pN0=53.3% vs pN+=21.5%, p=0.006). In a systematic review of the literature, which included 17 studies of 1,343 patients, Brar *et al.*¹⁸ also found the resection status and the nodal status as the main prognostic factors in multiorgan resection for advanced gastric cancer. The authors also ponder the morbimortality of multivisceral resection and the difficulty in defining the invasion of adjacent organs before indicating the extended procedure.

More recent studies have attempted to stratify patients so as to achieve maximum benefit with multiorgan resection. Min *et al.*¹⁶ exclude from the multivisceral resection patients with lymph node metastasis in the para-aortic chain and those who would require associated duodenopancreatectomy. There are also trends in the literature¹⁹ that suggest neoadjuvant treatment, either with chemotherapy or with chemotherapy + radiotherapy, in order to promote tumors' downstaging and to evaluate the biological response – in case of disease progression, patients would be spared from extensive surgery without therapeutic benefit. Neoadjuvant therapies (chemotherapy/radiotherapy) and/or adjuvants (chemotherapy/radiotherapy) when associated with multiorga-

nic resection in locally advanced gastric cancer, could also contribute to better cancer outcomes, notably with increased survival.

We lack prospective and randomized studies aimed at patients with T4b tumors to better define the role of (neo) adjuvant therapies. Hyperthermochemotherapy, associated with multivisceral surgery, is another alternative due to the high probability of microscopic peritoneal spread in T4b tumors.

The curative treatment of patients with pT4b gastric cancer requires an experienced multidisciplinary team, as it will involve the surgical-anesthetic team, intensivists, clinical oncologist and even the radiotherapist (the latter two in the scenario of neoadjuvance/adjuvance). Preferably, patients should be referred to referral centers trained and experienced in the treatment of gastric cancer. In practice, most patients will be submitted to palliative treatment, be it surgical, clinical or even palliative care.

Considering the literature published so far on the subject of gastric cancer and multivisceral resection, we can conclude that:

- Gastric cancer is a global public health problem.
- Except for countries like Japan and South Korea, where there are effective programs to track gastric cancer, the disease is most often diagnosed in advanced stages.
- pT4b gastric tumors represent a challenge for

the therapeutic team and, especially, for the surgical one.

- The correct staging of pT4b tumors is still limited by current radiological methods.
- Even during the surgical procedure, the distinction between desmoplastic reaction and actual invasion of the adjacent organ still poses a challenge.
- Surgery is the central pillar of gastric cancer treatment. In tumors pT4b, multiorgan resection represents the radical surgical treatment with curative intent.
- The pT4b tumors with invasion of the head of the pancreas seem to have a worse prognosis when compared to the invasion of other structures adjacent to the stomach.
- A judicious selection of patients is of paramount importance to achieve low morbimortality in multivisceral resection for gastric cancer.
- R0 surgery and the absence of lymph node metastasis (and possibly N1 status) are the main prognostic factors in multiorgan surgery for gastric cancer.
- Neoadjuvant therapies may contribute to the selection of patients who are candidates for multiorgan resection. Neoadjuvant and/or adjuvant therapies may improve oncologic outcomes when associated with multiorgan resection in gastric cancer.
- The literature aimed at patients with T4b gastric tumors consists essentially of retrospective studies. It would be very important to develop prospective, randomized studies to define the optimal therapeutic protocol for such patients.

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