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Editorial

DOES ADJUVANT THERAPY ASSOCIATED WITH ESOPHAGECTOMY IMPROVE SURVIVAL IN PATIENTS WITH ESOPHAGOGASTRIC JUNCTION ADENOCARCINOMA?

Terapia adjuvante associada à esofagectomia melhora a sobrevida nos pacientes portadores de adenocarcinoma da junção esofagogástrica?

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In the last ten years several authors have reported progressive increase in the prevalence of adenocarcinoma of the esophagus and the esophagogastric junction in occidental countries[1,2,3,4] and also in some oriental ones[5]. The main factors involved are chronic gastroesophageal reflux, untreated Barrett's esophagus, smoking and obesity[6]. The low intake of fresh fruits, vegetables and cereal fibers may raise this risk[7,8,9,10].

Obesity is associated with the prevalence of various types of tumors and may be an association between patterns of fat distribution and risk of malignant transformation of Barrett's esophagus, for example. Furthermore, altered metabolic profiles in metabolic syndrome may be a key factor in the genetic/cellular changes cycle that mark the progression of Barrett's esophagus to cancer.

Surgery is the primary mode in the treatment of adenocarcinoma of the esophagus. However, the results of surgical treatment alone are limited.

Another aspect to be considered is the fact that in Western countries - where there is no endoscopic surveillance programs - generally adenocarcinomas of the esophagogastric junction are diagnosed in advanced stages, with disease extension to the serosa or to regional lymph nodes at the moment of diagnosis. Thus, adjuvant and neoadjuvant therapies have attracted the interest of several research groups in order to improve survival rates and relatively low cure.

Therefore, the increasing prevalence of this disease in the world, its association with risk factors significant for the population, their surgical treatment - esophagectomy – with important risks and its poor prognosis despite the best surgical techniques, fully justify the need to study new therapeutic strategies.

Adjuvant therapy is generally defined as a treatment that is given after transaction considered "curative" (R0 resection) in order to improve the chances of long term survival. Depending on the type of disease, may be adjuvant chemotherapy, radiotherapy or both.

Adjuvant therapy after surgery has theoretical advantages and disadvantages.

The potential advantages are: a) may or not be based on pathological staging, and in potentially inaccurate clinical staging; b) patients who might benefit from adjuvant therapy can be identified, avoiding toxicity in those who do not need or will not be benefited with this treatment; c) delay, resulting from the neoadjuvant therapy, is prevented and the resection is carried; d) dysphagia is released early in the treatment; e) nutrition can be maintained by jejunostomy performed during the operation; and f) toxicity of neoadjuvant therapy does not affect the operation.

The potential disadvantages are: a) blood flow in the area of resection can be reduced and reducing the amount of chemotherapeutic agents in locoregional tumor bed; b) the therapy target for radiotherapy has been removed in the operation, complicating the definition of the fields to do it; c) postoperative surgical complications may delay adjuvant therapy; d) deaths in the immediate preoperative do not permit completion of adjuvant therapy, causing bias in survival data; and f) the effects of neoadjuvant therapy on tumor resectability are eliminated.

The publication that guides adjuvant treatment is the one of Macdonald et al.[4] in 2001. Was a prospective randomized study involving 556 patients with high risk of recurrence of adenocarcinoma of the stomach and the esophagogastric junction (2/3 with T3 or T4 tumors and 85% with lymph node metastases). The research evaluated the possible benefit of adjuvant chemoradiation. The median overall survival in the surgery group unique was 27 months, whereas in associated with adjuvant chemoradiation was 36 months. The authors concluded that postoperative chemoradiotherapy

should be considered for all patients with high risk of recurrence of gastric adenocarcinoma or esophagogastric junction who underwent to curative resection.

On the other hand, another North American study - also known as Intergroup 0116 - was the first to demonstrate survival benefit with the use of adjuvant therapy in gastric adenocarcinoma and esophagogastric junction, setting a new standard of care in the United States of America to stage II and III UICC. The information relevant to this editorial is the fact that only 20% of the patients included in this study presented adenocarcinomas of the esophagogastric junction, with 80% of distal adenocarcinomas of the stomach. However, the layout of the Intergroup 0116 has recorded high rates of toxicity.

Nevertheless, the same grupo published a summary presented at the American Society of Clinical Oncology in 2009 which reported the results in patients after ten years of follow-up.

Studies in other countries, such as Australia, England, France and Japan, have assessed and published improved survival with neoadjuvant treatment.

Meta-analysis published by the group GASTRIC - Global Advanced / Adjuvant Stomach Tumor Research International Collaboration Group - in 2010 evaluated the impact of adjuvant chemotherapy (mono and politherapies predominantly based on 5-fluorouracil or its derivatives) in overall survival and disease-free survival in operated patients with advanced gastric adenocaracinoma. Included 17 studies with mean follow-up longer than seven years and involving 3838 patients in total. There were 1000 deaths among 1924 patients in the group undergoing adjuvant therapy between 1857, and 1067 deaths in the group submitted to surgical treatment alone. Adjuvant chemotherapy was associated with a statistically significant benefit in overall survival (HR: 0.82, confidence interval 95% from 0.76 to 0.90, p <0.001) and disease-free survival (HR: 0, 82 confidence interval of 95% from 0.75 to 0.90, p <0.001). The overall five-year survival increased from 49.6% to 55.3% with adjuvant chemotherapy. The authors of this meta-analysis concluded that adjuvant chemotherapy based on the use of 5-fluorouracil is associated with decreased risk of death in advanced gastric cancer compared with operation alone.

A good alternative to the treatment protocol of the Intergroup 0116 was suggested in one study led by Cunningham et al.[1] in 2006 that established the utility of the use of epirubicin, cisplatin and infusional 5-fluorouracil in perioperative patients with gastric or esophagogastric adenocarcinoma potentially curable. Two hundred and fifty patients were randomized to perioperative chemotherapy and 253 patients to surgical treatment alone. The authors of this study that became known worldwide as "MAGIC trial" observed chemotherapy in perioperative leads to decrease in tumor size, reduction in tumor staging, improvement in disease-free survival and overall survival, with no increase in postoperative complications. This study resulted in a new standard of care for patients with gastric adenocarcinoma or esophagogastric junction in the UK

Van Hagen et al.[9] in 2012 published the results of "CROSS trial." They assessed the neoadjuvant therapy in esophageal cancer and esophagogastric junction. A total of 368 patients were studied, and 366 actually included in the analysis, of which 275 (75%) with adenocarcinoma. Were administered carboplatin, paclitaxel and radiation therapy preoperatively in 178 patients, with the remaining 188 exclusively treated operatively. The median overall survival in the group undergoing neoadjuvant therapy was 49.4 months and 24.0 months in the group treated with surgery, with statistically significant difference. The authors concluded that neoadjuvant chemoradiotherapy in patients with potentially curable tumors surgically presents improved survival.

Analyzing the recent studies of the benefits of adjuvant treatment, Solomon et al.[6] in a population-based study evaluated chemoradiotherapy in patients operated for adenocarcinoma of the stomach and the esophagogastric junction. Were included 3378 patients who underwent surgery with curative intent, and 636 (18.8%) patients with adenocarcinomas of the esophagogastric junction. These authors found a benefit of adjuvant treatment on survival of those with more advanced stage disease with lymph node invasion or adjacent organs. The authors emphasized the need for careful selection of patients eligible for adjuvant treatment.

Kofoed et al.[2] in 2012 in Denmark evaluated in a retrospective non-randomized study, in the same way as the present study, the possible benefits of adjuvant protocol recommended by Macdonald et al.[4] exclusively in patients with adenocarcinoma of the esophagogastric junction. Were evaluated 211 patients who underwent radical surgery, while 116 patients received adjuvant treatment. The authors concluded that adjuvant protocol could be beneficial in patients with lymph node invasion, finding no significant benefit in the other groups.

The study conducted at Unicamp (State University of Campinas, Campinas, SP, Brazil) including 103 patients with adenocarcinoma of the esophagogastric junction, comparing 78 who underwent to operation exclusively and 25 followed by chemoradiation Macdonald et al.4 protocol, showed no increase in survival at five years follow-up.

After over one hundred years of surgery for esophageal cancer, controversies persist about the

best treatment and should keep for several years due to the difficulties in conducting prospective studies, randomized, multicentre, with rigorous standardization of surgical technique, and same clinicopathological staging in a large number of patients. In addition, there is the continuous development of new drugs and the establishment of new combinations of drugs already used. But the difficulties, if any, should be taken only as a stimulus for constant and relentless search for the best treatment for our patients

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