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Update on the multidisciplinary management of esophagogastric junction cancer

Evidence in Follow-up and Prognosis of Esophagogastric Junction Cancer☆

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ABSTRACT

Five-year survival of tumors of the esophagogastric junction is 50%, in the most favorable stages and with the most effective adjuvant treatments. More than 40% of patients will have recurrences within a short period, usually the first year after potentially curative surgery. Survival after this recurrence is usually less than 6 months because treatment is not very effective, be it palliative chemotherapy, radiotherapy or surgical excision of single recurrences. As the detection of asymptomatic recurrences allows for earlier and more effective treatments to be used, the type and frequency of follow-up has an influence on survival.

Evidencia en seguimiento y pronóstico del cáncer de unión esofagogástrica

Palabras clave:
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RESUMEN

La supervivencia a cinco años de los tumores de la unión esofagogástrica está en el 50% en los estadios más favorables y con los tratamientos coadyuvantes más eficaces. Más del 40% de los pacientes sufrirá recurrencias en un periodo breve, habitualmente en el primer año tras una cirugía potencialmente curativa y la supervivencia tras esa recurrencia suele ser menor de 6 meses, pues el tratamiento es poco eficaz, sea quimioterapia paliativa, radioterapia o exéresis quirúrgica de las recidivas únicas. El tipo y frecuencia del seguimiento realizado influye en la supervivencia porque la detección de recurrencias asintomáticas permite realizar tratamientos más precoces y efectivos.

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Introduction

The search for prognostic evidence available on esophagogastric junction (EGJ) cancer presents a very important limitation because this entity involves tumors of two different natures, esophageal tumors and gastric tumors, which have different histological/molecular characteristics and prognoses. Using the Siewert classification[1] and the 8th Edition of the TNM classification,[2] EGJ tumors can be differentiated as follows:

a) Distal esophageal adenocarcinomas associated with Barrett's esophagus that have lymph node and metastatic dissemination and a 5-year survival rate of 25%–47%.[3,4]
b) Tumors below the gastric cardia, similar to proximal gastric adenocarcinoma, with a 5-year survival between 18% and 55% and frequent progression in the form of peritoneal carcinomatosis.[5]
c) Anatomical tumors of the cardia (Siewert type II), in which it is not clear whether they are more similar to adenocarcinomas of the esophagus or sub-cardia gastric tumors.

There are few studies that independently evaluate the prognosis and the need for follow-up of EGJ cancer. Most trials include patients with esophageal cancer of other locations and histologies (adenocarcinomas and epidermoid tumors of the middle and proximal thirds) or gastric cancer. Conclusions are drawn according to the proportion of EGJ tumors of the given study, which makes it increasingly difficult to obtain reliable data.

The objective of this article is to review the prognostic evidence on survival in this type of tumors, while determining whether structured follow-up of these patients provides any benefit and defining the most appropriate follow-up studies. Since recurrence is very frequent, knowing the timing and location of these recurrences can guide us in the application of treatments that could lead to longer survival in certain cases.

Survival

EGJ cancer has a poor prognosis because many patients are diagnosed with advanced disease and those treated with curative intent frequently have recurrences. Nevertheless, three facts have improved survival rates in recent decades:

a) Improved staging methods (PET, endoscopic ultrasonography, diagnostic laparoscopy), which select patients who could benefit from a potentially curative treatment.
b) Standardized perioperative care with nutritional support, pre-habilitation and optimization of comorbidities at referral hospitals.
c) Generalized use of coadjuvant treatment in locally advanced tumors.

Currently, surgery is considered to be the only potentially curative treatment for adenocarcinomas of the EGJ, but the five-year survival rate of the surgical treatment is between 20% and 34%, regardless of the type of intervention performed.[6,7]

There are many classic factors that influence survival, including advanced age, tumor stage, degree of lymph node involvement, development of postoperative complications, R0 resection, presence of signet ring cells and the degree of cell differentiation.[8–11]

The extension of the lymphadenectomy as a prognostic factor remains a topic of debate, not only in terms of the number of resected lymph nodes[12,13] but also the location of these lymphadenopathies.[14]

Another factor that seems important is the pathological complete response (pCR) to neoadjuvant treatment, which is more frequent in patients treated with neoadjuvant radiochemotherapy than with neoadjuvant chemotherapy alone. Between 20% and 29%[3,8,9] of the tumors present pCR after preoperative radiochemotherapy, reducing the risk of anastomotic and locoregional recurrence and theoretically improving the prognosis. However, between 15% and 40% of patients will develop recurrences, so the influence of pCR on survival is also undefined, and published studies show contradictory results.

Likewise, the ideal chemotherapy regimen has not been defined,[15] and, more recently, the same is true for the preoperative addition of radiotherapy. Even though certain trials have reported 5-year survival rates with this therapy of 40%–56%,[3,8–10,16] the benefit in long-term survival is lost by increasing postoperative mortality. Furthermore, since the majority of recurrence is metastatic, preoperative chemotherapy should be the treatment of choice.

Follow-up

Follow-up after potentially curative treatment of EGJ tumors is controversial. There is no evidence to guide the intervals or studies necessary, nor is there any evidence that takes into account the risks, benefits or cost of said follow-up. A recent study comparing a strict follow-up protocol with a symptoms-based follow-up found that patients with intensive follow-up at a referral center have better survival (85 vs 38 months), especially those with locally advanced tumors (T3-4 y/o N+).[17]

Several organizations have developed guidelines, in which the most frequent recommendation is a clinical follow-up. However, since recurrence manifests itself clinically only in 17% of patients, each surgeon and oncologist perform different studies during follow-up, which may last from 3 to 5 years, including blood tests with tumor markers, CT, PET and endoscopy.[18]

Within these complementary tests, CT is usually used to detect recurrent disease, but it is expensive and produces radiation. The value of PET in the detection of recurrence is limited to the confirmation of suspicions based on the CT image, although some hospitals use it annually.[17] Since half of the recurrences are in the form of liver metastases, abdominal ultrasound may be an adequate tool to alternate with CT, thereby reducing cost and radiation.

Endoscopy is of little value for the detection of local recurrence in asymptomatic patients, so its use is not recommended except in patients at high risk of anastomotic recurrence due to positive or unclear margins.[17] Elevated tumor marker levels (CEA) is the first sign of suspected recurrence in only 5% of

cases, so its use is poorly justified for the detection of recurrence.[19]

In general, an ideal follow-up strategy detects subclinical recurrences so that aggressive treatments can be initiated before the patient's general condition deteriorates or the recurrence becomes untreatable.

However, the latest European Society of Medical Oncology guidelines[20] state that, except for patients who are candidates for endoscopic reoperations or rescue surgeries after insufficient endoscopic treatments or definitive radiochemotherapy with incomplete response or early recurrence, there is no evidence that monitoring improves survival, and follow-ups should focus on psychological support, nutritional advice and symptomatic treatment of the effects of the presumably curative treatment. The type of follow-up of the few patients with complete response to radiochemotherapy should be with endoscopy and CT every 3 months.

On the opposite end are the recommendations of the National Comprehensive Cancer Network for esophageal and esophagogastric junction tumors of 2018[21] in which a close follow-up is advocated according to the tumor stage and the type of treatment applied, using endoscopy more for monitoring tumors treated with radical CRT and CT for the follow-up of patients operated on for 3–6 months up to 5 years.

This type of follow-up adapted to the tumor stage is defended in other recent studies, where patients with asymptomatic recurrences (45%) had better survival.[17]

Patients who have received neoadjuvant therapy have early recurrences, which reflects the advanced early stage of the disease and should be followed closely during the first two years. According to some authors, in patients with primary esophagectomies there is a risk of recurrence up to 7 years after surgery, so follow-up should be prolonged up to that point.[22]

Therefore, it seems that the staging of patients with EGJ tumors in different risk categories, depending on the frequency, location and time of recurrence, is necessary to plan adequate follow-up. Therefore, the classification of patients into four risk groups for recurrence is proposed, according to the tumor stage, lymph node involvement and the response of the tumor to the preoperative treatment. According to these groups, an adequate follow-up calendar is established at the maximum risk of recurrence (between 1 and 5 years) with the intention of carrying out rescue treatments as soon as possible.[3]

Thus, while patients with advanced tumors (T3-4 and/or N+) should be followed every 3 months by CT for two years, every 6 months during the third and fourth years and stop after 5 years, patients with T1-2 tumors with negative lymph nodes should have a less intense follow-up, every 6 months for 3 years and every 12 months until the 5th year.[17]

Recurrence

During follow-up, around 40% of patients with a tumor of the EGJ present some type of recurrence of the following three types[16,19,22,23]:

- locoregional (12%–30%): located in the anastomosis or in the regional mediastinal and upper abdominal nodes.
- distant (55%–66%): distant nodes (supraclavicular, paraaortic), peritoneal carcinomatosis or metastases in other organs.
- mixed (10%–22%): a combination of the previous two.

More than half of patients present recurrence in the first year after surgery, more than 80% in the first two years and more than 90% in the three years after surgery.[3,17] Recurrence is earlier (8 vs 12 months) in patients who have received neoadjuvant therapy. More than 90% of recurrences appear within 2 years, while in patients in initial stages they are later (some 3 years)[3,19]; recurrence after 4 years is exceptional.[9]

Recurrence in the form of distant metastasis is also earlier than locoregional recurrence, and the most frequent locations of metastatic disease include the liver (57%), lymph nodes, lung, bone and brain,[10] with subtle differences in the location of metastasis between patients with pCR and those who did not respond.[3] Patients with pCR after neoadjuvant radiochemotherapy also have fewer locoregional recurrences (11% vs 20%).[24]

Factors influencing the development of recurrence include tumor stage, histology grade, lymph node involvement, R0 resection and pCR.[23,25] The latter is also related to disease-free time.

The next step in the selection of treatment should be to identify patients who relapse early after trimodal therapy and who experience the disadvantages of surgery due to postoperative morbidity, mortality and serious impairment of quality of life. In a recent publication[16] a nomogram was developed in order to predict the risk of early recurrence and to operate only on patients with low risk of early recurrence as they significantly improve their five-year survival with trimodal versus bimodal treatment (66% vs 46%). In patients with a high risk of recurrence who do not relapse within a year, rescue esophagectomy/gastrectomy would be indicated. Factors for early recurrence would be: male, histological grade, presence of signet ring cells, positive lymph nodes and maximum SUV on PET > 7.

Survival after recurrence is only 7 months (3–16 months), with no differences between patients with neoadjuvant therapy or primary surgery. Survival is prolonged if the recurrence can be treated (3 vs 9 months).[19]

Since most recurrences are metastatic, postoperative chemotherapy can control them and reduce mortality by up to 30%. It should be offered to patients with residual disease in the primary tumor or lymph nodes.[26,27]

Treatment of Recurrence

The treatment of recurrence by radio or chemotherapy in most cases with palliative intent attempts to control disease symptoms, improve quality of life and increase survival.

In selected cases, if resection of the locoregional recurrence is possible, average survival rates of up to two years have been reported.[17,19] However, in the case of resection of metastasis, the median survival drops to 9 months.[3]

Treatment with systemic chemotherapy for metastatic recurrence can be performed in almost 60% of patients,[17] including associations with fluorouracils and platinums,

epidermal growth factor inhibitors or immunotherapy,[28] which may achieve modest improvements in survival.[29]

A different case is rescue surgery after initial radical radiochemotherapy with complete response, since 15% of these patients will experience only local recurrence in a relatively short time (less than 3 years) and 8% can be successfully resected.[30,31]

The treatment of dysphagia caused by local recurrences is essential, preferably with self-expanding stents compared to other local methods, although the association of brachytherapy can slightly improve survival.[30,32]

Conflict of Interests

The authors have no conflict of interests to declare.

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