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Gastroesophageal junction cancer – current topic and treatment dilemmas

Карцином гастроезофагеалног споја – актуелна тема и дилеме у лечењу

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Gastroesophageal junction cancer – current topic and treatment dilemmas

Карцином гастроезофагеалног споја – актуелна тема и дилеме у лечењу

SUMMARY
Treatment of gastroesophageal junction carcinomas have been debated for many years. This type of carcinomas has been classified as either gastric or esophageal carcinomas until Siewert's classification was established and they were defined as a distinct entity. Risk factors for development of these cancers are gastroesophageal reflux and Barrett's esophagus, obesity, *Helycobacter pylori* infection, smoking, and alcohol. Symptoms of this disease include retrosternal pain, dysphagia to aphagia and weight loss. Esophagogastroduodenoscopy with biopsy and pathohistological verification as well as CT of the chest and abdomen are crucial in establishing the diagnosis. Adenocarcinoma is predominant histological type of these tumors. The stage of the disease is defined by the TNM classification. Treatment of gastroesophageal junction cancer is complex, multidisciplinary and multimodal, and involves the use of surgery, chemotherapy and radiotherapy, alone or in different combinations. Surgery is the major treatment modality for these tumors, especially in local stages. Radiotherapy is used in the treatment of these tumors in all stages of the disease, and especially in the multimodal treatment of locally advanced gastroesophageal junction cancer, both preoperatively and postoperatively, usually in combination with chemotherapy. Chemotherapy is used in the treatment of these cancers as preoperative, postoperative and systemic. Immunotherapy and target therapy, as new promising therapy is usually applied in a systemic and postoperative approach. Future directions in the treatment of these cancers are directed towards new surgical procedures, new types of immunotherapy, as well as new radiotherapy techniques.
Keywords: gastroesophageal junction cancer; surgery; radiotherapy

САЖЕТАК
Карциноми гастроезофагеалног споја су дуго били подручје дилема и класификовани су или као карциноми желуца или једњака све до *Siewert*-ове класификације када су дефинисани као посебан ентитет. Фактори ризика за развој карцинома гастроезофагеалног споја су гастроезофагеални рефлукс и Баретов једњак, гојазност, инфекција *Helycobacter pylori*, пушење и алкохол. Симптоми ове болести укључују ретростернални бол, дисфагију до афагије, регургитацију желудачног садржаја и губитак тежине. Езофагогастродуоденоскопија са биопсијом и патохистолошком верификацијом, као и *CT* грудног коша и абдомена су кључни у постављању дијагнозе. Аденокарцином је доминантни хистолошки тип ових тумора. Стадијум болести се дефинише *TNM* класификацијом. Лечење карцинома гастроезофагеалног споја је комплексно, мултидисциплинарно и мултимодално и подразумева примену хирургије, хемиотерапије и радиотерапије, самостално или у различитим комбинацијама. У мултимодалном лечењу локално узнапредовалог карцинома гастроезофагеалног споја постоје дилеме као што су оптималан хируршки приступ и терапијски редослед. Хирургија је главни модалитет лечења ових тумора, посебно у локалним стадијумима. Радиотерапија се користи у лечењу ових тумора у свим стадијумима болести, а посебно у мултимодалном лечењу локално узнапредовалог карцинома гастроезофагеалног споја, преоперативно и постоперативно, најчешће у комбинацији са хемиотерапијом. Хемиотерапија се користи у свим облицима у лечењу ових карцинома као преоперативна, постоперативна и системска. Имунотерапија и циљна терапија, као најновији облици лечења, до сада је испитивана њихова примена у системском и постоперативном приступу. Будући правци у лечењу ових карцинома су усмерени ка новим хируршким процедурама, новим типовима имунотерапије, као и новим техникама радиотерапије.
Кључне речи: карцином гастроезофагеалног прелаза; хирургија; радиотерапија

INTRODUCTION

Gastroesophageal junction (GEJ) carcinomas are relatively rare and aggressive tumors with an increase in the incidence rate in recent decades [1].

Siewert's classification defines them as tumors located within 5 cm of the anatomical cardia (distal or proximal) like:

1) type I - adenocarcinoma of the distal esophagus with tumor epicenter 1 to 5 cm above the GEJ,

2) type II - adenocarcinoma of the cardia with the epicenter of the tumor 1 cm to 2 cm below the GEJ and

3) type III - subcardial gastric carcinoma with the epicenter of the tumor from 2 to 5 cm below the GEJ.

Risk factors for GEJ cancers are gastroesophageal reflux and Barrett's esophagus, obesity, *Helicobacter pylori* infection and smoking [2]. The most common symptoms include retrosternal pain, dysphagia to aphagia, regurgitation of stomach contents and weight loss. The key methods for diagnosis of GEJ cancer esophagogastroduodenoscopy with biopsy and thoracic and abdominal computed tomography (CT). Histopathology with immunohistochemical staining is used for definitive diagnosis and the majority of GEJ cancers are adenocarcinomas, less often they are squamous type. The genome of gastroesophageal carcinoma is complex and includes mutation of the most common genes (especially TP53), high microsatellite instability (MSI) and mutation of oncogenic kinases (EGFR, HER2 and MET). TNM classification is used in stage determination an according to the TNM staging GEJ carcinomas can be divided into:

1) local (early) stage (Tis-T1, N0, M0),

2) locally advanced stage (T2-T4, N1-N3, M0) and

3) metastatic stage (T1-T4, N1-N3, M1).

TREATMENT

The multimodality and multidisciplinarity are necessary in the treatment of GEJ cancer. Surgery, radiotherapy and chemotherapy are treatment modalities. The basic principles of treatment are that early GEJ cancers are treated only with surgery, locally advanced with a combination of surgery, chemotherapy (CT) and radiotherapy (RT), and metastatic with chemotherapy or radiotherapy. Most widely used recommendations for the treatment algorithm are the National comprehensive cancer network (NCCN) and the European society of medical oncology (ESMO).

Early stage

Local (early) GEJ carcinomas includes Tis and T1a-b N0 stage of disease.

The primary approach in early stage of disease is radical surgery and includes endoscopic techniques such as endoscopic mucosal resection (EMR) and endoscopic submucosa dissection (ESD) and classical surgical techniques such as esophagectomy with gastrectomy and lymphadenectomy.

EMR is an option for T1a lesions smaller than 10 - 15 mm and ESD may be considered in T1a lesions larger than 15 mm [3]. If after endoscopic resection histopathology parameters shows poor differentiation, lymphovascular invasion or positive margins further steps may include adjuvant radiochemotherapy (RCT).

For T1b GEJ cancers esophagectomy is indicated, but for T1b cancers with favorable histopathological pattern (well-differentiated, smaller than 2 cm and without LVI) ESD may be a good alternative to esophagectomy. Two types of esophagectomy are used, transthoracic (*Ivor-Lewis* procedure) and transhiatal. The radicality of surgery is imperative due to the significant deep and per continuitatem spread of these tumors (significantly more in type I and II than in type III) [4]. The consensus in surgical treatment of GEJ type I cancer is esophagectomy with transthoracic approach [5]. GEJ type II carcinomas are true junctional tumors, so the choice of surgical approach is very controversial. Two types of surgery are used, total gastrectomy with transhiatal distal esophagectomy and transmediastinal esophagectomy with proximal gastrectomy [6]. Total gastrectomy with distal esophagectomy is needed for GEJ type III carcinomas [6]. Lymphadenectomy implies a dissection of mediastinal and abdominal lymph nodes ("two-field"). Recommendations for lymphadenectomy in GEJ type I cancer are upper, middle and lower mediastinal and abdominal dissection, in type II are upper, middle and lower mediastinal and abdominal dissection and in type III are lower mediastinal and abdominal dissection [7].

In recent years, newer surgical procedures in treatment of GEJ carcinoma such as robot-assisted, hybrid, and minimally invasive esophagectomies (MIE) are promissing to achieve better results comparing to conventionally accepted surgical techniques [8].

Locally advanced stage

Locally advanced GEJ carcinomas includes T2-T4 N0-3 stage of disease.

For patients who are medically fit and good performans status (ECOG PS 0-1) with potentially resectable locally advanced disease stage T2-T4a indication is preoperative radiochemotherapy with/without surgery, perioperative chemotherapy with surgery or neoadjuvant/perioperative immune checkpoint inhibitors therapy with/without surgery. T4b tumors with involvement of the surrounding organs are unresectable, so that patients, if they are medically fit with ECOG PS 0-2 are candidates for definitive chemoradiotherapy or chemotherapy.

Today, a standard in the treatment of locally advanced GEJ carcinoma is a multimodal approach (a combination of radiotherapy, chemotherapy and surgery). Even though radiochemotherapy provides higher rates of complete pathologic response and better locoregional control then perioperative chemotherapy, survival in both types of therapy is similar [9]. The ESOPEC-trial [10], which compares these two modalities in neoadjuvant setting in patients with esophageal adenocarcinoma is in progress, and results are expecting. For GEJ adenocarcinomas preoperative radiochemotherapy is generally used in the USA, while perioperative chemotherapy is favored in most European countries, but for GEJ squamous cell carcinomas preoperative RCT is standard of care in general. The most important study that established the benefit of preoperative RCT is the Dutch CROSS trial [11], with over 300 patients that compared the 5-year survival of two groups of patients, treated with surgery alone or a combination of preoperative RCT (CT with paclitaxel/carboplatin and 3D conformal RT with TD 41,4Gy) and surgery. The percentage of R0 resection was 92% vs. 69%, 5-year survival was 43,2 vs. 27,1 months (RCT and surgery group vs. surgery group), pCR was 23%, and grade III toxicity was up to 10%. The most relevant study on the role of perioperative CT in gastric and GEJ cancer is MAGIC trial [12], with 500 patients, which compares two groups of patients treated with surgery alone and patients treated with perioperative CT (epirubicin/CDDP/5-FU) with surgery. The results showed acceptable toxicity (0,3-23,8% of hematological gr III and 2,6-6,4% of non-hematological gr III), and 5-year survival 36% vs. 23% in favor of the CT group.

The combination of radiotherapy and chemotherapy enhances the effect of the therapy. The most modern radiotherapy techniques include intensity modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) [13]. Radiotherapy doses in preoperative RCT are ~ 41,4-50,4Gy in ~ 23-28 fractions.

After preoperative chemoradiotherapy, if there is local disease (partial tumor regression or stable disease), patients are referred for surgery. However, in the case of a complete clinical response (cCR), patients can undergo esophagectomy or continue to follow-up [14].

Perioperative CT with FLOT (5-Fluorouracil, Leucovorin, Oxaliplatin and Docetaxel) has become the gold standard treatment for medically fit patients with operable gastroesophageal adenocarcinoma [15]. In patients who are intolerant to multiple agents, HT with 5FU/CDDP can be used [16]. Perioperative CT is incorporated in guidelines such as ESMO and NCCN, but preoperative RCT is emerging as the standard in the treatment of locally advanced GEJ carcinomas [17, 18]. Preffered regimens combination of cytostatic drugs in preoperative radiochemotherapy are 5-FU/CDDP and paclitaxel/carboplatin.

Definitive radiotherapy is performed less often GEJ cancer patients who are considered medically unfit for surgery, in unrectable disease (cT4b stage) and for patient with resectable disease who declines surgery. Radiotherapy technics and combination of cytostatic drugs are the same as in preoperative RCT, and radiotherapy doses are 45-54Gy in 25-30 fractions.

In postoperative approach after esophagectomy, further therapy depends on previous therapy (preoperative CT/RCT), margin resection status, nodal status, number of exctracted lymphnodes, tumor stage, tumor differentiation and tumor invasion [17, 18].

In general, there is no consensus in adjuvant treatment of GEJ cancers. Although most patients with locally advanced disease receive preoperative therapy, in the USA postoperative chemoradiation remains a standard of care for GEJ/gastric cancers. Postoperative chemotherapy is a standard of care in East [19].

Research that can serve as a landmark regarding the application of postoperative RCT in GEJ cancers is INT 0116/SWOG 9008 trial [20]. In this trial surgery or surgery plus postoperative RCT have been used in over 500 patients with gastric or GEJ cancer (RT with 45Gy in 25 fractions and CT with 5-fluorouracil/leucovorin). Three-year survival was 50% vs. 41% in favor of the RCT group, and local and regional relapse was reduced in the RCT group (19% vs. 29% and 65% vs. 72%). The radiation techniques used in postoperative RT are also IMRT and VMAT, and the doses are also in the range of 45-50,4Gy in 25-28 fractions.

The use of adjuvant CT after surgery is established after CLASSIC trial [21], which included 1000 patients with gastric and GEJ cancer and showed enhanced five-year survival in patients

who had postoperative CT over the patients who had only surgery. Preferred combination of cytostatic drugs in postoperative CT are also 5-FU/CDDP and paclitaxel/carboplatin.

Advancements in radiotherapy techniques are improving tumor delineation (RT planning based on MRI and PET), reducing interfraction motion (using IGRT and 4DCT) and intrafractional motion (respiratory-gated RT), increasing the dose to the tumor (simultaneous integrated boost (SIB) technique of RT) [22]. Recently, proton therapy has shown promising results especially in sparing of organs at risk.

In the treatment of GEJ cancer, immunotherapy with monoclonal antibodies are used such as trastuzumab and "checkpoint" inhibitors such as pembrolizumab and nivolumab.

Adjuvant Nivolumab after surgery in patients with esophageal and GEJ cancers, who had received neoadjuvant RCT and have evidence of residual pathological disease in the resection specimen (>ypT1 and/or>ypN1) leads to significant improvement in disease-free survival [23].

Metastatic stage

Metastatic GEJ carcinomas includes T1-T4 N1-N3 M1 stage of disease.

Chemotherapy with/without immunotherapy is the standard of treatment in metastatic disease, followed by palliative radiotherapy. Patients with good ECOG PS (0-2) are considered for systemic chemotherapy.

Combination treatments with two drugs (fluoropyrimidines-platinum) are treatment standard, combinations with 3 drugs (5-FU+platinum+docetaxel) are controversial but could be apply in patients with excellent ECOG PS, and monotherapy (fluoropyrimidine, irinotecan, taxane weekly) could be the choice in patients with poor ECOG PS [24]. Adding Transtuzumab to standard CT in the first-line setting led to improved outcomes in patients with HER2-positive, advanced GEJ cancers [25]. Nivolumab in combination with standard first-line CT demonstrate superior results [26]. Both paclitaxel and irinotecan are reasonable second-line treatment options because there is no statistically significant difference between them in overall survival [25].

The first clinical trials on the application of immunotherapy based on human dendritic cells showed good tolerance and prolonged survival time in patients with gastrointestinal tract cancers, but the application is still a great challenge [27].

More than 40% of patients with metastatic cancer receive palliative radiotherapy (PRT) [28]. Indications are local recurrence, bleeding, obstruction, pain, bone and brain metastases, and radiation doses are 8Gy in 1 fraction, 16Gy in 4 fractions, 20Gy in 5 fractions or 30Gy in 10 fractions.

CONCLUSION

Treatment of gastroesophageal junction cancers is complex and applies the use of radiotherapy, chemotherapy, surgery and immunotherapy alone or in different combinations. Surgery is the first choice of GEJ cancer treatment, especially in the localized stage of the disease. Radiotherapy has a significant role in the treatment of these tumors in all stages of the disease, especially in locally advanced cancers in the neoadjuvant approach, usually in combination with chemotherapy, but also in the adjuvant approach. The modern radiotherapy techniques have enabled the application of higher doses of radiation with significant protection of the surrounding healthy tissues in this region, leading to a significant reduction in the toxicity of radiotherapy alone or combination with chemotherapy. Various chemotherapy regimens are unavoidable in the treatment of gastroesophageal junction cancer in a neoadjuvant, adjuvant or systemic approach. Immunotherapy as new promising therapy is being imposed in the treatment of these cancers. The future of treatment of these cancers is directed toward new surgical procedures, wider application of immunotherapy, as well as new radiotherapy techniques.

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Conflict of interest: None declared.

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