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Case report

METASTATIC ESOPHAGOGASTRIC JUNCTION CANCER: CASE REPORT OF A COMPLETE LONG-TERM RESPONSE AFTER COMBINED CHEMORADIOTHERAPY.

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ABSTRACT

This paper presents our experience in the treatment of a patient affected by metastatic esophagogastric junction cancer with a high tumor burden and an incipient visceral crisis. The patient was treated with a combination of induction taxane-based chemotherapy, local radiotherapy and microwave ablation of residual liver metastases. The patient experienced a complete and durable response with long-term survival of more than 3 years, without any relevant acute or late side effects.

1. Introduction

The esophagogastric junction (EGJ) cancer is a rare tumor and its incidence has grown rapidly over the recent decades.
The most frequent histological type is adenocarcinoma, while incidence rates for esophageal squamous cell carcinoma and distal gastric carcinoma have been decreasing.
Prognosis for this disease remains low, because of its elevated tendency to spread through the lymphatic network, increasing the risk of metastasis.
Management of metastatic disease remains dismal with poor prognosis, with a median survival of 8 months. Chemotherapy is the only treatment accepted in this setting, while no role exists for curative surgery or radiotherapy, except in case of obstruction or bleeding.
This paper presents our experience in the treatment of metastatic EGJ cancer with a combination of taxane-based chemotherapy and intensity-modulated radiotherapy (IMRT) in a patient affected by EGJ cancer with a very high tumor burden and incipient visceral crisis.

2. Clinical case

A 64-year-old man was referred to our attention in May 2014 diagnosed with esophagogastric junction adenocarcinoma, HER2 negative.

The EGDS showed that the vegetating and infiltrating neoplasia was located on the lower third of the esophagus (32 cm from the tooth) and it extended beyond the cardia. The lesion had an eroded mucous membrane and was bleeding spontaneously. The brain-thorax-abdomen staging CT (Figure 1) showed a complete alteration of hepatic architecture by multiple metastases, the largest of which measured about 8 cm in diameter.
Multiple lymph node metastases were detected in the perigastric space. In addition, neoplastic thrombosis of both splenic and left renal veins were seen.
Moreover, multiple lymph nodes metastases were detected in periesophageal region and along the small gastric curvature.
From June to September 2014 the patient received six neoadjuvant chemotherapy cycles according to a modified DCF protocol: Docetaxel 75 mg/mq on day 1, Cisplatin 40 mg/mq on day 1-3 and 5-Fluorouracil 600 mg/mq on day 1-3, with granulocyte colony-stimulating factor prophylaxis every 3 weeks.
An interval PET-CT scan showed an absence of FDG uptake in the liver and a persistent uptake in the EGJ. For these reasons, considering the impressive good response in the liver, a local treatment in the primary tumor had to be done.
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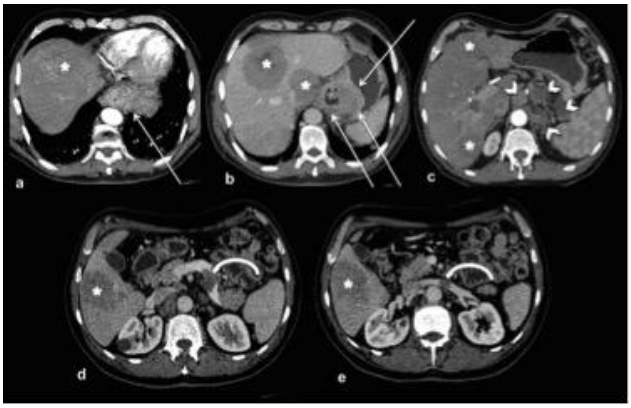

Figure 1. The axial post-contrast CT images showed a huge mass extended from the lower third of the esophagus, through the cardia, to the gastric fundus and body (arrows in a and b).
Hepatic parenchyma was destroyed by several large metastases (asterisks) and many necrotic lymphadenopathies were recognizable in the perigastric space (arrowheads in c).
Neoplastic thrombosis was also detected in both splenic and left renal veins (curved arrows in d and e).

From November 2014 to January 2015 the patient was considered unsuitable for surgery, therefore he was subjected to concomitant radical chemoradiotherapy (CRT) on the esophagogastric junction with weekly Cisplatin 40 mg/mq. Radiation treatment was performed using an intensity-modulated radiotherapy (IMRT) with a simultaneous integrated boost (SIB) on the site of the primitive tumor. Target volumes were defined based on the International Commission on Radiation Units (ICRU) definitions of clinical target volume (CTV) and planning target volume (PTV), as is usually the case in modern radiotherapy practice.
An initial elective large CTV1 including the whole GEJ region with nodal basins at risk of harboring metastatic disease (periesophageal, perigastric, celiac axis, porta hepatis and splenic hilar nodes) received 5040 cGy in 28 fractions of 180 cGy. The SIB volume (CTV2) covered the primary disease and any bulky adenopathy and received an additional 35 cGy daily for a total dose in this region of 6020 cGy.
The dose was prescribed so at least 95% of the CTV received 99% of prescription dose, and that the 95% isodose covered at least 99% of the CTV. The volume was treated using a static step-and-shoot IMRT technique, with 5 fields at different gantry angles, according to our institutional protocol [1-2].
The Elekta XiO treatment planning system was used to develop a case-specific dose distribution (Elekta AB, Stockholm, Sweden).
The calculation plan was based on the Quantitative analyses of normal tissue effects in the clinic (QUANTEC) guidelines[3] and organs at risk (OAR) doses are reported in table 1.
The patient tolerated the treatment well: acute grade III or higher gastrointestinal and hematological adverse events were not observed. He experienced only grade II radiation-induced nausea and vomiting (RINV) during the last 2 weeks of radiotherapy.
Both CT and MRI examinations performed in March 2015 confirmed an almost complete response in the liver, there was only a single residual lesion with a 2 cm diameter.
The EGDS proved that the tumor of the esophagogastric junction had histologically complete response.
To confirm the response obtained, the patient received "adjuvant" chemotherapy (3 cycles till March 2015) with the same modified DCF protocol and a microwave ablation (MWA) of the residual liver lesion.
After three months, in June 2015, the re-staging CT showed a complete response, with only a residual liver cavity in the site of MWA (Figure 2).

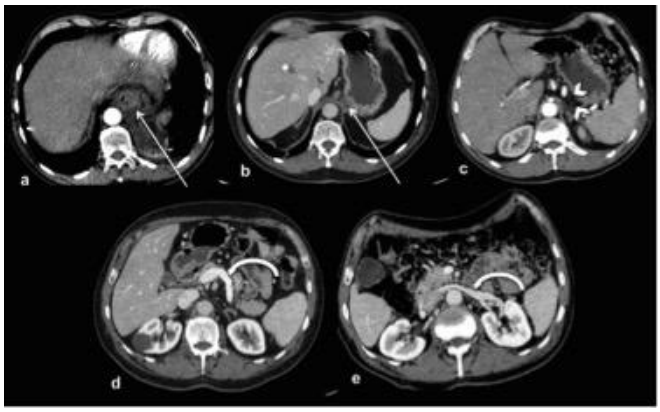

Figure 2. Follow-up CT examination after one year of diagnosis showed drastic reduction of the neoplastic mass at the EGJ (arrows in a and b) and disappearance of hepatic metastases, only with a residual hypodense area in the site of the MWA (asterisk in b). There was no perigastric metastatic lymphadenopathy (arrowheads in c).
Neoplastic thrombosis was resolved in both splenic and left renal veins (curved arrows in d and e).

The patient underwent a thorough follow-up using endoscopy, CT/PET and liver MR, which proved the absence of any disease progression and the maintenance of complete tumor response. Patient is still alive and relapse-free after 32 months from the end of treatment with a survival of 42 months from diagnosis.

3. Discussion

Treatment of locally advanced EGJ adenocarcinoma is still a matter of debate. The management of GEJ adenocarcinoma highlights that surgery only cures 20-30% of patients. This results in the need to implement integrated radio-chemotherapy to increase local control and survival rates. In recent years, the neoadjuvant approach is most widely used in clinical trials and it has led to an increase of long-term survival [4].
Synchronous metastatic EGJ adenocarcinoma is a less frequent clinical presentation. Liver is the most frequent site of metastatic spread. Patients with metastatic EGJ adenocarcinoma have a poor prognosis and a limited life expectancy, with a median survival of 8 months [5].
Exclusive chemotherapy with supportive care is recommended for patients with EGJ cancer, metastatic disease and a good performance status [6].

In metastatic patients, radiotherapy, both external or brachytherapy, with or without chemotherapy, plays only a palliative role in controlling and preventing the mass effect of the tumor and consequent worsening dysphagia, which may cause the patient's death.

With palliative CRT symptomatic improvement can be achieved in 70-75% of patients; about half of patients maintain the benefit over time and OS are significantly higher than patients who only underwent esophageal prosthesis [7].

The role of chemotherapy in the management of GEJ cancer is widely recognized: it is able to improve survival and data from meta-analysis confirms that the therapeutic standard is the three-drug regimens [8].

To date, there is no unanimous consensus on which regimen is preferable to others, but the use of taxane-based chemotherapy is widely increasing. CT which appears to be more relevant in the treatment of EGJ cancer is a schedule with Docetaxel, Cisplatin and 5-Fluorouracil (DCF)[9].

In European countries, Docetaxel-Cisplatin-5Fluorouracil (DCF) is considered a standard first-line three-drug chemotherapy regimen for advanced gastric or gastroesophageal junction adenocarcinoma, but it is associated with significant toxicity. In clinical practice, a modified DCF is currently used to increase safety and maintain efficacy of chemotherapy[10].

Patient treated at our institution had very high tumor burden, with multiple liver metastases with a 8 cm maximum diameter, regional lymph nodes, an obstructive esophago-gastric lesion and a poor life expectancy. The response obtained with the induction taxane-based chemotherapy was impressive and this led to the need for local treatment, with a radical purpose. Radiotherapy was delivered with intensity modulation and SIB technique, in order to reduce the incidence of acute and late side effects, without any grade III toxicity. The complete response obtained was noticeable, both to the primary lesion and to the liver, which is still maintained after 32 months from the end of treatment, in a disease with a median survival of 8 months.

4. Conclusions

The case reported showed that the treatment performed on our patient achieved an impressive response with the complete disappearance of primitive lesion and liver metastases. The use of a modified DCF, with G-CSF prophylaxis before a concomitant radio-chemotherapy treatment with Cisplatin and intensity-modulated RT was highly effective in increasing local control and survival with acceptable toxicity rates. Treatment was well tolerated, without acute grade III or higher gastrointestinal adverse events. After almost three years from diagnosis, disease is well controlled without any evidence of relapse. Patient does not have any treatment or cancer-related disorders.

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