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Increased risk of thromboembolism in esophageal cancer patients treated with neoadjuvant chemoradiotherapy

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Abstract

BACKGROUND: Neoadjuvant chemoradiotherapy (CRT) in esophageal cancer (EC) patients may increase the formation of thromboembolic events (TEEs). We analyzed the incidence and impact of TEEs in EC patients treated with platinum-based CRT.

METHODS: A total of 336 patients with EC underwent an esophagectomy, of which 110 patients received neoadjuvant CRT (41.4 Gy with concurrent Carboplatin/Paclitaxel). Patients were matched based on pre- and perioperative characteristics.

RESULTS: Preoperatively, 9 (8.2%) patients with neoadjuvant CRT ($P = .004$) were diagnosed with TEEs. Despite delay until surgery ($P = .021$), the postoperative course did not differ. In multivariate analysis, a history of deep vein thrombosis ($P = .005$) and neoadjuvant CRT ($P = .004$) were identified as risk factors. Postoperatively, there were no differences in TEEs ($P = .560$) observed. In multivariate analysis, a history of pulmonary embolism ($P = .012$) was identified as a risk factor for postoperative TEEs.

CONCLUSIONS: Preoperatively, EC patients treated with neoadjuvant CRT have an increased risk to develop a TEE, especially those with a previous history of TEE. After surgery no increased incidence was observed. We recommend secondary prophylaxis during neoadjuvant treatment in this high-risk group.

Neoadjuvant chemoradiotherapy (CRT) followed by surgical resection is a widely accepted curative-intended treatment in patients with esophageal cancer (EC). Depending on oncological and conditional criteria, patients receive, in our center, radiotherapy (41.4 Gy/5 weeks) and concurrent chemotherapy (Carboplatin and Paclitaxel) according to the Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) regimen. This platinum-based neoadjuvant CRT improves locoregional control and overall survival with 13% at 5 years.[1]

As distinct from this benefit, neoadjuvant CRT may subsequently be accompanied by an increased risk for adverse pre- and postoperative complications.[2] It is known that cancer patients, especially those with gastroesophageal cancer, generally have a high risk of venous thrombosis.[3,4] Moreover, the use of CRT seems to be associated with a further enhanced risk of developing thromboembolic events (TEEs), including deep vein thrombosis (DVT) and pulmonary embolism (PE).[5–9]

The authors declare no conflicts of interest.

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In the mid-19th century, Virchow and Trousseau described the pathophysiology of TEEs in cancer patients. However, there still exist significant gaps in the understanding of cancer-associated TEEs in patients treated with chemotherapy alone or combined with radiotherapy. Reported incidences of TEEs during chemotherapy for EC are approximately 10% to 12%, and partly depend on the type of chemotherapy.[9] The risk of TEEs in currently used neoadjuvant CROSS regimen is, according to our knowledge, not previously described. The hypothesis in this study was that neoadjuvant platinum-based CRT in EC patients is accompanied with an increased incidence of TEEs.

Patients and Methods

Patient's characteristics

In this study, we included all 336 patients who underwent a transthoracic esophagectomy with curative intent between January 2000 and December 2012. Of these patients, 110 (32.7%) received neoadjuvant CRT followed by surgery between January 2006 and December 2012. Patients with unforeseen progression of their disease were excluded ($n = 5$). All data were collected prospectively, including demographic and tumor characteristics, comorbidity, therapeutic information, details about neoadjuvant treatment, medication, pre- and postoperative complications, and survival data.

To reduce bias in selection criteria and interfering factors in developing TEEs, we created statistically comparable groups by propensity matching. The propensity score is used to balance covariates allowing 2 study subjects with the same propensity score to be appreciably similar in observed dimensions (implemented in our SPSS [SPSS, Inc, Chicago IL] package[10]). Patients treated with neoadjuvant CRT ($n = 110$) were matched with 95 patients who were treated between 2000 and 2012 with surgery alone. Patients were matched for sex, medical history of DVT, PE, myocardial infarction, and transient ischemic attack/cerebrovascular accident, American Society of Anesthesiology (ASA) classification, and preoperative clinical T stage.

Neoadjuvant chemoradiotherapy

Patients who were eligible for neoadjuvant CRT received Carboplatin, which was administered weekly with a targeted area under the curve of 2 mg/mL/minute and Paclitaxel of 50 mg/m^2 for 5 weeks. Concurrent radiotherapy, which consisted of 41.4 Gy in 23 fractions of 1.8 Gy, was administered 5 times per week. Radiotherapy target volumes were delineated on a planning computed tomography (CT) scan by an experienced radiation oncologist. Oncologic criteria consisted of a clinical tumor stage of T1N1-3 or T2-T4aN0-3 without distant metastases (M0). Conditional requirements were based on the judgment of the surgeon and both the medical and radiation oncologists and were comparable to the eligibility criteria of the national CROSS study.[1]

Preoperative evaluation and comorbidity

All patients were staged with an endoscopic ultrasonography (US) including fine needle aspiration and 16-slice and 64-slice spiral multidetector computed tomography (MDCT) with intravenous and oral contrast of the neck, chest, and abdomen. In locally advanced tumors (T3-4a or N1-3), an 18F-fluoro-2-deoxy-D-glucose positron emission tomography was performed. For the final analysis, the available reports of every EC patient were reviewed and discussed in a multidisciplinary tumor-specific board to assess appropriate management. Patients treated with surgery alone underwent an esophageal resection within 4 to 8 weeks after staging. In patients treated with neoadjuvant CRT, a restaging MDCT with intravenous contrast of the neck, chest, and abdomen was performed to exclude progressive disease in assessing resectability.

Comorbidity was classified according to the ASA score varying from ASA 1 (very good condition) to ASA 5 (moribund patient). The ASA score is a readily available and widely accepted method to stratify surgical patients according to their preoperative risk.

Surgery

All patients underwent, usually within 4 to 8 weeks after (re)staging, a transthoracic esophagectomy with 2-field lymphadenectomy by 2 experienced surgeons. Distal tumors and those around the gastroesophageal junction were approached through a left thoracolaparotomy and intrathoracic anastomoses by gastric tube reconstruction. More cranial-located esophageal tumors were approached through a right thoracolaparotomy with cervical anastomoses.

Thromboembolic event prevention

Patients using preoperative anticoagulation and those diagnosed with a TEE during neoadjuvant CRT were instructed to use a therapeutic dosage (1,1400 U/day) of low molecular weight heparin (LMWH), which was adjusted to a prophylactic dose (2,850 U/day) 5 days before surgery. This was administered by specialized home care nurses. In all patients, LMWH was started perioperatively and continued until discharge. Dosage was dependent on patient's weight and risk factors and varied between 2,850 and 1,1400 U/day. In addition, all patients received compression stockings for the first 24 hours after surgery.

Definition of outcome

The primary outcome was based on the occurrence of TEEs pre- and/or postoperative. Venous, arterial, symptomatic, and idiopathic TEEs were included. In patients