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CLINICAL INVESTIGATION **Esophagus**

INFLUENCE OF IRRADIATED LUNG VOLUMES ON PERIOPERATIVE MORBIDITY AND MORTALITY IN PATIENTS AFTER NEOADJUVANT RADIOCHEMOTHERAPY FOR ESOPHAGEAL CANCER

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Purpose: In some randomized trials, the treatment outcome of locally advanced esophageal cancer has been significantly improved by neoadjuvant radiochemotherapy (RCT). However, increased perioperative pulmonary toxicity in terms of acute respiratory distress syndrome (ARDS) has been linked to radiation exposure of the lungs. In our study we evaluated perioperative morbidity and mortality in patients with cancer Stages IIA–IVA treated with curative intent either with surgery alone (S) or with neoadjuvant RCT followed by surgery (RCTS).
Patients and Methods: Between 1996 and 2003, 55 patients received S, and 98 received RCTS. In the RCTS group, most patients received two cycles of 5-fluorouracil plus cisplatinum simultaneously with normofractionated radiotherapy (40Gy). Four weeks later they underwent surgery. Endpoints were the incidence of acute lung injury (ALI), ARDS, other postoperative complications, and mortality within 31 days.
Results: Between both groups there were no significant differences between the incidence and severity of ALI and ARDS (RCTS: 42.9%, 42.9%; S: 45.5%, 38.2%). Furthermore, there were no significant differences in the incidences of pneumonia, pleural effusion, and pneumothorax (RCTS 29.6% vs. S 16.4%, $p = 0.07$). Perioperative complication rates and mortality did not vary significantly (mortality after RCTS 5.1% vs. S 3.6%). A detailed analysis of 54 RCTS patients according to lung dose–volume histograms did not show any correlation between ARDS and pulmonary exposure. In univariate analysis, only respiratory comorbidity correlated with ARDS.
Conclusion: Neoadjuvant cisplatinum and 5-fluorouracil–based RCT apparently has no detrimental impact on the postoperative course. **© 2010 Elsevier Inc.**

Esophageal carcinoma, Neoadjuvant radiochemotherapy, Dose–volume histogram, Lung toxicity, Acute respiratory distress syndrome.

INTRODUCTION

Surgical therapy of locally advanced esophageal carcinomas results in a 5-year overall survival rate of approximately 20% (1, 2). During the past 20 years, multimodal approaches have been developed and tested to improve therapeutic outcome. In two large randomized studies, induction chemotherapy showed contradictory results (3, 4). To intensify neoadjuvant therapy, radiotherapy was combined with chemotherapy. One prospectively randomized trial showed a significantly higher overall survival rate after neoadjuvant radiochemotherapy (RCT) (5). Another study revealed a significant increase of disease-free survival. (6). A recent meta-analysis of all published trials showed a survival benefit of 12% after neoadjuvant RCT in comparison with surgery alone (7), something that obviously did not depend on the histology of the tumors. However, this approach did not lead to a significant improvement of therapeutic results in all studies (8). This may be due to a possible enhancement of surgical morbidity, especially increased perioperative mortality. A case series of patients with tumors of the distal esophagus resulted in a 25.4% mortality rate within 30 days (9). Interestingly, in this study the diaphragms were included in the target volume definition. This might have caused a high lung exposure to radiotherapy.

These observations on increased perioperative morbidity have been recently linked to radiation exposure of lung volumes during induction therapy. Lee *et al.* (10), Wang *et al.* (11), and Tucker *et al.* (12) analyzed a series of patients regarding irradiated lung volume and the incidence of acute

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respiratory distress syndrome (ARDS). Their research was based on 110 patients who had received combined modality therapy (11). It showed a significant correlation between the volume of lung spared from doses >5 Gy (VS5) and all spared volumes ranging from 5 Gy to 35 Gy. VS5 was interpreted as the volume of ''unexposed'' lung during induction therapy. In conclusion, low irradiation doses were supposed to have detrimental effects on the postoperative clinical course.

The aim of the present study was to evaluate perioperative morbidity and mortality of patients with locally advanced esophageal cancer treated at our institution either with surgery or with neoadjuvant RCT followed by surgery. The possible influences of irradiated lung volumes on perioperative morbidity and mortality were additionally investigated. In contrast to the above-mentioned studies (10–12), we did not find an increased risk of perioperative ARDS after RCT and surgery. This is supported by clinical results of randomized trials.

PATIENTS AND METHODS

The charts of 153 patients treated at our institution between 1996 and 2005 were reviewed. All patients had undergone curative treatment of locally advanced Union international contre le cancer Stages IIA–IVA (13) esophageal carcinoma. They showed no hematogenic metastasis or tracheobronchial fistulae. On first presentation they had been considered anatomically and functionally suitable for surgery. To evaluate the extent of local disease, standard workup of the patients consisted of a barium swallow and an esophagogastroscopy. Endoscopic ultrasound was applied to all patients where feasible. All of them received a chest radiograph and computed tomography scans (CT) of the chest and upper abdomen for staging.

Treatment

Surgery group (S). Depending on the attending surgeon, 55 patients underwent surgery without induction therapy. Of those, 12 patients received transhiatal surgery and 43 patients underwent abdominothoracal resection. Within this group, 44 patients were categorized as R0 (no residual tumor), 10 patients as R1 (microscopic tumor infiltration of resection margin), and 1 as R2 (macroscopic tumor residues).

Preoperative RCT group (RCTS). By applying two different protocols, 98 patients received preoperative RCT during the neoadjuvant setting. Of those, 22 patients with squamous cell carcinoma (SCC) were treated with RCT as described by Stahl *et al.* (14, 15). They received three courses of chemotherapy before radiochemotherapy, consisting of folinic acid 300 mg/m^2, etoposide 100 mg/m^2, 5-fluorouracil (5-FU) 500 mg/m^2, and cisplatinum (CDDP) 30 mg/m^2 on days 1–3 every 3 weeks. After 3 weeks they were irradiated simultaneously with CDDP 50 mg/m^2 on days 2 and 8 and etoposide 80 mg/m^2 on days 4–6.

Because of high toxicity (especially hematologic toxicities), this protocol was substituted in 2001 for patients with SCC by the one proposed by Walsh *et al.* (5) ($n = 30$). All patients with adenocarcinoma received the same RCT ($n = 46$), i.e., two cycles of chemotherapy (5-FU 15 mg/kg on days 1–5, CDDP 75 mg/m^2 on day 7) during the first and sixth weeks of the treatment. Radiotherapy occurred during weeks 1–4. In contrast with the original protocol by Walsh *et al.*, instead of 2.67 Gy per fraction we administered 2 Gy to the target volume.

The primary tumor and enlarged lymph nodes were irradiated with 40 Gy. The planning target volume was defined as the tumor volume plus 5 cm safety margins in proximal and distal directions, 2 cm in the radial direction, and an additional safety margin of 0.5 cm in all directions. Radiation was delivered by a linear accelerator (Varian, Palo Alto, USA) with 20 mV photons. The first course was applied by ventrodorsal fields. After 26 Gy, a three-field technique (anterior, right posterior, and left posterior oblique fields) was used to reduce spinal cord exposure.

Surgery was performed 4 weeks (median, 31 days) after completion of induction therapy. Of patients undergoing surgery, 14 underwent transhiatal resection, 79 abdominothoracal resection, and 5 additional partial lung excision. 85 patients were classified R0, 6 patients R1, and one patient R2. Because of incomplete patient charts, 6 patients could not be allocated.

Risk factors

In our analysis, several factors, such as smoking habits, were evaluated in terms of their impact on pulmonary toxicity and treatment outcome. These were classified as nonsmoker, ex-smoker, and smoker. As to drinking habits, we distinguished between alcohol abuse and no alcohol abuse. Pulmonary comorbidity was defined as anamnestic lung disease such as chronic obstructive pulmonary disease, asthma, or silicosis. Cardiac comorbidity manifested itself as previous myocardial infarction or cardiopathy. Vascular comorbidity included peripheral arterial occlusive disease and hypertension. Diabetes mellitus and other malignant diseases present before the diagnosis of esophageal carcinoma were also registered.

Analysis of dose–volume histograms (DVH)

To determine the influence of treatment-related factors on pulmonary toxicity and pulmonary exposure to irradiation, 54 patients were analyzed in detail by means of DVHs. In the initial planning CT the lungs were drawn. Radiation exposure was calculated and visualized by plotting the dose vs. percentage of the irradiated lung volume (Eclipse, Varian). The V2 (percentage of lung volume receiving at least 2 Gy), V5, V10, V15, V20, V25, V30, and V35 were calculated. During these procedures, the lung was considered as a single organ. With 44 patients a DVH analysis was impossible. They needed a second planning CT before treatment technique was changed after 26 Gy.

Scoring lung injury

Acute side effects and mortality during induction therapy and within 31 days after surgery were documented. According to the criteria of the Centers for Disease Control and Prevention, pneumonia was defined when at least three of the following symptoms were fulfilled: leukocytosis (WBC >10,000/mm^3 or <3,000/mm), abnormal body temperature (>38.5°C or <35°C), purulent sputum, persistent infiltrate on chest radiograph (>48 h), or pathogenic bacteria in endotracheal aspirate (16).

To define pulmonary injury, we used two widely accepted scoring systems. First was the Horovitz Index, which is based on the quotient of the arterial oxygen partial pressure in mm/Hg (PaO_2) to the inspiratory oxygen concentration (FIO_2) without reference to the positive end-expiratory pressure (PEEP) level (17). It serves as an indicator of the transpulmonary oxygen transport and is used in the diagnosis of acute lung injury (ALI) or ARDS. Values above 450 mm/Hg are considered normal; values under 350 mm/Hg as pathologic. An ALI is defined for values below 300 mm/Hg; an ARDS below 200 mm/Hg.