Esophageal cancer (EC) is now the 8th most commonly diagnosed malignancy worldwide.\(^1\) Currently, the primary curative treatment for EC consists of neoadjuvant chemoradiotherapy (CRT) followed by surgery. However, the prognosis of patients with locally advanced EC remains poor even after subsequent curative-intended resection, with an overall survival rate of 35% to 38%.\(^2,3\)

A recently performed meta-analysis and outcome of the latest published randomized controlled Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study trial underline the significant positive effect of neoadjuvant CRT on survival and local recurrence rate.\(^4,5\) Even then, only approximately 50% of the patients benefit from neoadjuvant CRT, while 8% to 17% of the patients develop distant metastases in the time interval between CRT and surgery.\(^6-9\) Surgery in these patients is futile and should be avoided. Instead, maintenance of quality of life with palliative support on guidance of complaints should be the principal treatment.

Guidelines regarding restaging after neoadjuvant CRT are lacking. Conventional staging methods, including endoscopic ultrasonography (EUS) and computed tomography (CT), are based on disturbance of anatomical
structures. Limitations of these techniques include difficulty with distinguishing vital tumor tissue from necrotic or fibrotic tissue and the delay between cell death and tumor shrinkage. On the other hand, CT has a low false positivity with a high availability rate and is associated with relatively low costs. Furthermore, the spatial resolution of CT has improved over the last decennium.

Detection of viable tumor tissue with 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) is based on increased metabolic activity of the tumor, leading to a high FDG uptake. Integrated PET-CT scans combine the metabolic information from the PET with the anatomical location found with the CT scan. Three studies showed a better detection of distant metastases with integrated PET-CT (3 out of 4 patients) compared with CT alone (2 out of 4 patients). PET-CT, however, also has a high false positivity rate, which has been reported to be as high as 8%.

In our esophageal center, all patients received a post-CRT CT to assess whether the patient has developed progressive disease during the time interval. In this study, we hypothesize that CT is effective in detecting distant metastasis and clinically relevant lymph node progression to restrict futile surgery after neoadjuvant CRT.

Patients and Methods

Patients

Between 2006 and 2011, 116 patients with potentially resectable locally advanced EC who received a restaging CT within 3 weeks after neoadjuvant CRT were eligible for inclusion. In total, 19 patients were excluded because of missing post-CRT data (n = 7), missing pre-CRT CT data (n = 1), treatment in different medical centers (n = 3), a premature post-CRT CT (n = 6) made during the neoadjuvant treatment, and clinically proven progressive disease during CRT treatment (n = 2). Finally, 97 of the 116 patients could be included in this study. This study was performed in accordance with the guidelines of the national and our own Ethical Board. We created a database containing patient and tumor characteristics, treatment-related data and follow-up data.

Patient characteristics are summarized in Table 1. The male/female ratio is 3.3:1 with a median age of 65 years (interquartile range 60 to 70 years) and tumors staged clinically from stage IIa (T2N0M0) to stage IIIc (T4aN1-2M0/T4bN1-2M0/T4aN3M0) at the time of diagnosis.

Initial staging procedure

Initial staging consisted of EUS with fine needle aspiration on indication and a CT of the chest and abdomen. A full-body FDG-PET or PET/CT was employed in all T2-T4a and/or nodal-positive patients (N+). The outcomes of all staging methods were discussed in a multi-disciplinary meeting participated by at least one of the two experienced radiologist, an oncologist, a radiotherapeutic oncologist, a nuclear medicine physician, pathologist, a gastroenterologist, and a surgical oncologist involved in the treatment of EC patients. All participants of this meeting agreed that the patients included in this study should be treated with neoadjuvant CRT.

Restaging preoperative post-chemoradiotherapy computed tomography

All patients received both pre- and post-CRT 64-multisliced CT scan (PhilipsMX 8000, Philips Medical Systems, Best,
The Netherlands; Siemens Somatom Sensation, Siemens, Erlanger, Germany or GE medical systems, Milwaukee, WI), according to the EC protocol used in our center. The CT includes the cervical, thoracic, and abdominal region and was performed with adequate oral and intravenous contrast. Pretreatment CT images with a maximum slice thickness of 5 mm from other medical centers were allowed. All included patients had their preoperative post-CRT CT within at least 3 to 4 weeks after the end of the neoadjuvant treatment. All post-CRT CT scans were performed in our center, with a Somatom Sensation 64 CT (Siemens, Erlanger, Germany) with slices of 2/1.5 mm. In case of suspicious progressive disease, additional examinations (either PET, magnetic resonance imaging, ultrasonography, cytology, or a combination) were carried out to strengthen or prove progressive disease.

Reassessment of progressive disease

Two experienced radiologists, including a senior radiologist specialized in gastroesophageal cancer, reviewed both the pre- and post-CRT CT images and restaged these images according to the 7th tumor node metastasis (TNM) edition. Both radiologists were blinded to the outcome of the CT and further treatments. The primary outcome was treatment change because of progressive disease (yes or no) detected by comparing the pre- and post-CRT CT. Progressive disease was defined as any radiological visible increase in tumor volume, including both nodal progression and distant metastasis. Locoregional progression without signs of invasion in surrounding organs was not included as clinically relevant progressive disease in this study, because it would not alter the course of surgical treatment. As a reference standard, we used either the cytological or histological confirmation of progressive disease detected before and during surgery, or based on pathological examination of the resected specimens. In addition, we considered all suspect lesions that occurred within 3 months after the post-CRT CT as missed with CT. All patients received a PET/CT scan 3 months after surgical treatment for other research purposes, which was also used to detect progressive disease. Patients suspected of progressive disease were discussed in a multidisciplinary board and received additional examinations, such as magnetic resonance imaging, ultrasonography, or EUS-guided fine needle aspiration on indication. In defining true progressive disease, we included all cytologically/histologically proven progressive disease detected before or during surgery and pathological proven or clinical evidence of recurrent/persistent disease found within 3 months after the post neoadjuvant CRT CT.

We determined the sensitivity, specificity, negative predictive value, and positive predictive value of both radiologists in detecting progressive disease by comparing the pre- and post-CRT CT. Patients assessed differently by the 2 radiologists were re-evaluated until agreement was obtained.

Treatment

Neoadjuvant treatment consisted of intravenous Paclitaxel (50 mg/m²) and Carboplatin (area under the curve = 2), administered 5 times during a 4-week radiotherapy period with a total dose of 41.4 Gy given in 23 fractions of 1.8 Gy. As standard surgical procedure, we performed a radical transthoracic esophagectomy through a left or right thoracolaparotomy combined with a 2-field lymphadenectomy of mediastinal and abdominal lymph nodes, including nodes at the celiac trunk and those along the common hepatic and splenic artery at the upper border of the pancreas.

Pathology

Pathological processing of all resected specimens and lymph nodes has been standardized according to a detailed protocol on radicality, including the proximal, the distal, and the circumferential margin. The extension of the primary tumor, localization, number of nodal involvement, and L/N ratio was accurately described.

Statistical analysis

SPSS Version 17 (SPSS, Inc, Chicago, IL) was used to perform statistical analyses. The distribution of all patient characteristics was assessed with a QQ- and PP-plot. Normally distributed variables were reported as mean ± standard deviation, non-normally distributed variables as median [interquartile range], and categorical variables were reported as amount [percentage].

Results

In Table 1, the patient, tumor, and treatment-related characteristics are summarized. Of the 97 patients, 9 (9%) patients had progressive disease after neoadjuvant CRT. The initial post-CRT CT prevented futile surgery in 5 (5/97; 5%) patients: 4 patients developed liver metastases and 1 patient developed lung metastases. Three patients had progressive disease identified during surgery: 1 patient had a previous undetected peritoneal metastasis, 1 patient had a metastatic lesion on the top of the bladder, and 1 patient had both liver and omental metastases. In addition, cervical lymph node metastasis was observed in 1 patient with PET-CT performed because of a suspect vertebral lesion which was assessed as benign on PET-CT. More information on these lesions and the imaging techniques used to strengthen or prove metastatic disease is revealed in Table 2. Pathologic proof of progressive disease was obtained in 6 patients. There were no patients with a metastasis found within 3 months after the post-CRT CT.
Efficacy in detecting progressive disease

Both radiologists detected 4 patients with liver metastases and 1 patient with lung metastases. CT images are depicted in Fig. 1. Progressive disease was missed by the radiologists in 4 patients: 1st patient with a bladder top metastasis, the 2nd had a peritoneal metastasis, the 3rd had a cervical lymph node metastasis, and the 4th had both liver and omental metastases. During reassessment of the CT images of patients with missed progressive disease, the radiologists agreed that the missed cervical node metastasis, which was detected on PET/CT, should have been found on the post-CRT CT. However, because both radiologists missed this cervical node involvement, it was scored as missed progressive disease. Fig. 2 depicts both the CT and PET-CT images in this patient. Resectable nodal progression was detected by both radiologists in 2 patients, but this was not relevant for subsequent treatment. However, one of these patients also had a liver and omental metastasis identified during surgery.

Radiologist 1 falsely suggested 2 metastases – a lung and vertebral metastasis (Fig. 3) – identifying progressive disease with a sensitivity and specificity of 56% and 98% and an negative predictive value (NPV) and Positive Predictive Value (PPV) of 96% and 71%, respectively. Radiologist 2 correctly assessed the vertebral lesion as nonspecific based on the osteoblastic character, identifying progressive disease with a sensitivity and specificity of 58% and 100% and an NPV and PPV of 96% and 100%, respectively.

After the differently assessed CT images were discussed, the radiologists agreed that the vertebral lesion was nonspecific for metastasis and the lung lesion was benign. After agreement, both radiologists detected clinically relevant progressive disease, with a sensitivity and specificity of 56% and 100% and an NPV and PPV of 96% and 100%, respectively.

Retrospectively, with knowledge of the metastases and its location, a suspicious hepatic lesion of approximately 1 cm could be seen in the patients with both liver and omental metastases. Even after re-evaluation, the CT-missed omental metastases could not be detected. The CT-missed bladder top metastasis was located outside of the range of the abdominal CT.

Comments

In this study, CT after neoadjuvant CRT (post-CRT CT) showed to be effective in the detection of clinically relevant progressive disease which leads to a change in treatment in these EC patients. Detection of progressive disease before surgery on post-CRT CT prevented futile surgery in 5 (5%) of these patients, but missed progressive disease in 4 (4%) patients. Detection of progressive disease that alters the initial treatment strategy is of great importance, as the majority of these patients is beyond curative treatment and should be refrained from surgery.

In this study, we used only small-slice (2/1.5 mm) post-CRT CT scans for adequate radiological assessment of suspect lymph nodes and/or metastatic lesions by 2 radiologists. Most previously published studies used thicker slice (5/5 mm) CT scans to detect tumor progression. The study by Bruzzi et al6 had distant metastases as primary outcome, comparing CT with PET-CT in the detection of distant metastasis after neoadjuvant CRT. With PET-CT, it was possible to detect distant metastasis in 7 patients (8%) after neoadjuvant CRT, while CT alone detected distant metastasis in 5 (6%) of these patients. Both missed metastases were located outside the range of the routinely performed CT imaging of the chest and abdomen. This was also observed in our study with a bladder top metastasis that was located outside of the range of routine CT imaging.

Cerfolio et al7 compared CT with EUS and PET-CT in restaging patients with EC after neoadjuvant CRT. The additional value of a PET-CT was limited; only one additional metastasis was found and both PET-CT and CT still

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cTNM = clinical tumor node metastasis; CT = computed tomography; PET = positron emission tomography. *Resectable lymph node progression.

Table 2 Characteristics of patients with progressive disease relevant for further treatment
Figure 1  CT images of the patients with progressive disease detected by both radiologists. (A) Pre-CRT CT and (B) post-CRT CT. Images 1 to 4 are of patients with liver metastases, and image 5 is of a patient with lung metastasis.
missed an omental metastasis. PET-CT also falsely suggested one more distant metastasis.

A more recent study, Blom et al,\(^7\) compared CT with PET-CT in detecting distant metastases after neoadjuvant CRT. With PET-CT, 4 out of 5 patients with a distant interval metastasis were identified, while CT alone detected only 2 of these lesions. One of the metastases that were missed with CT was located in the iliac crest, which is usually located outside the range of the CT. The other metastasis missed with CT was located in the right scapula. Both CT and PET-CT missed 1 patient with peritonitis carcinomatosa and PET-CT falsely suggested a pulmonary metastasis.

One of the reasons most studies advise a PET-CT is that EC tends to metastasize to uncommon and unusual distant locations after CRT, such as skeletal muscles, brain, peritoneum, subcutaneous soft tissue, pleura, pancreas, and thyroid gland.\(^{13}\) These distant metastases can be missed with CT, because only thoracic and abdominal CT images are made. PET scans, in contrast, are full-body scans. However, most metastases after neoadjuvant CRT were located in either the liver or the lungs.\(^{5,7,14}\) In our study, 6 out of 9 metastases were located in either the liver or the lungs, of which CT detected 5 metastases. Most of the metastases located in the liver and the lungs can be found with CT.\(^{15}\) In one of the 4 patients with missed tumor progression on CT in this study, re-assessment of a PET-CT for suspected vertebral metastases showed progression of cervical lymph node, which was initially not been detected on post-CRT CT. In addition, after postoperative re-examination of the CT, a suspect lesion could be detected in the liver of the patient with both liver and omental metastases. Omental metastases are generally hardly detected with CT and the missed peritoneal metastases in this study could not be detected even after revision. It is known that CT is inaccurate in detecting peritoneal metastases of \(<1 \text{ cm}.\(^{16,17}\) However, the additional value of PET/CT is also limited in depicting small-volume metastatic lesions of 5 to 7 mm.\(^{18}\) Currently, accurate detection of peritoneal metastasis is only possible by surgical intervention.
including laparoscopy or laparotomy. In our center, we start with a laparotomy at the first phase of the esophagectomy followed by subsequent curative resection through a thoracotomy.

One of the disadvantages of this retrospective study is that we did not compare CT with PET-CT. Future research should compare a thin-slice thickness CT with PET-CT, in the detection of patients with progressive disease after neoadjuvant CRT. According to the retrospective design of our study, we were unable to obtain pathological prove of metastatic disease in 3 patients with distant metastasis. Because of small numbers it was not possible to accurately determine the interobserver variability between both, a skilled and a specialized radiologist on EC in reviewing CT images in this study. The different findings between them, 1 radiologist had 2 false-positive results, might be caused by a difference in experiences.

The potentially extended interval caused by the neoadjuvant treatment and the rate of progression during neoadjuvant treatment emphasizes the importance of imaging after neoadjuvant CRT. Different studies assessed PET-CT to be more effective in the detection of distant metastases. However, compared with CT, PET-CT has a lower availability, is more expensive, and has a high amount of false-positive outcomes. CT is therefore a useful method to detect patients with clinically relevant progressive disease in EC patients treated with neoadjuvant CRT.

References