Assessment of Diffusion-Weighted MRI and $^{18}$F-Fluoro-Deoxyglucose PET/CT in Monitoring Early Response to Neoadjuvant Chemotherapy in Adenocarcinoma of the Esophagogastric Junction

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INTRODUCTION

Neoadjuvant (radio)chemotherapy is an accepted choice for the treatment of locally advanced adenocarcinoma of the esophagus and the esophagogastric junction (AEG) [1-4]. Response to preoperative treatment has been an accepted prognostic factor for more than 10 years now [5]. Until today it remains unclear [6] whether patients, who do not respond to preoperative treatment, would profit from a discontinuation of the applied treatment regimen after a short period [7] or if a primary resection would be the treatment of choice for this subgroup [6]. Theoretically, inefficient neoadjuvant treatment increases toxicity, allows tumor progression during...
chemotherapy, costs time, and finally increases health expenses. Therefore, the ability to detect response early in the course of treatment or even better to predict response to chemotherapy pre-therapeutically is of utmost interest. Positron emission tomography (PET) with \(^{18}\)F-fluorodeoxyglucose (FDG) has shown its ability to help selection of treatment schemes and to assess pathohistological tumor response to neoadjuvant chemotherapy [8, 9]. In AEG type I and II, two prospective clinical studies from a single academic center exist, in which therapy was modified early after two weeks of chemotherapy based on metabolic response [7, 10]. The FDG uptake into the tumor was quantified by the calculation of the standardized uptake value (SUV) in static PET scans initiated 60 min post injection. Early metabolic response defined as a decrease of the SUV\(_{\text{max}}\) ≥ 35% in static \(^{18}\)F-FDG-PET two weeks after the start of neoadjuvant chemotherapy was predictive of histopathological response and survival in several consecutive studies including the MUNICON phase I and II trial [7], but this cut-off was never confirmed in randomized prospective multicenter trials or after other treatment regimen than preoperative chemotherapy. A recent meta-analysis demonstrated that these early metabolic tumor changes reflected by relative changes in FDG-uptake are good prognosticators [11].

Currently, MRI is not preferred over CT for the work-up of esophageal cancer except for staging infiltration of mediastinal organs in extensive disease [12, 13]. However, with the advent of respiratory and cardiac gating and fast morphological and functional imaging sequences, the role of MRI should clearly increase [14]. Using high-resolution T2-weighted sequences, 1.5 Tesla MRI can meanwhile correctly assess the three main layers of the esophageal wall, as well as infiltration of periesophageal fat tissue [15]. However, the same study could not detect any changes after chemotherapy by analyzing the tumor signal intensity on T2-weighted images. For this purpose, diffusion-weighted imaging (DWI) is a promising tool, because DWI can assess alterations of tumor cellularity shortly after initiation of chemotherapy that correlate with clinical outcome before morphological sequences can detect any changes in tumor volume [16]. In addition, although results of recent DWI MRI studies suggest that DWI might increase the role of MRI in staging and treatment monitoring of gastrointestinal cancer, such as rectal cancer [9, 17, 18] and gastric cancer [19] by demonstrating superiority over contrast-enhanced CT in TNM staging, studies on DWI in esophageal cancer are lacking.

Thus, this study aims to evaluate the potential of DWI MRI in comparison to static \(^{18}\)F-FDG PET in assessing treatment response in AEG patients. Study objectives are to answer the following questions: 1. Do changes in ADC and SUV correlate with histological regression under neoadjuvant chemotherapy and prognosis? 2. Do changes in tumor apparent diffusion coefficient (ADC) values derived from DWI correlate with those of tumor SUV in static PET scans? 3. Is MRI advantageous over PET/CT in staging local lymph nodes?

**MATERIAL AND METHODS**

**Patients and treatment scheme**

Fifteen patients (13 male, 2 female; median age, 64 years) with biopsy-proven untreated adenocarcinoma of AEG type I (distal esophageal adenocarcinoma) or type II (gastric cardia adenocarcinoma) and locally advanced defined by endoscopic ultrasound and CT were prospectively included in this open, non-randomized, monocentric diagnostic study. The study was approved by the local review board and conducted according to the declaration of Helsinki in the present form. Written informed consent was obtained from all participants.

Figure 1 gives an overview of the treatment scheme. Neoadjuvant EOX chemotherapy started on day 1. Response evaluation using \(^{18}\)F-FDG-PET took place on day 14. Patients were subdivided in two groups upon the early metabolic PET-response of their AEG tumors: Group A (PET-responders, SUV-decrease ≥ 35%) and group B (PET-non-responders, SUV-decrease < 35%). PET-responders continued to receive neoadjuvant chemotherapy for 12 days (weeks 15–16) and then proceeded to surgery (resection 22-36 days after administration of last chemotherapy). In metabolic PET-non-responders, EOX chemotherapy was discontinued after the 2-week evaluation period and these patients proceeded to radiochemotherapy as recommended by the HICON trial [20] with surgical resection 28-42 days after the end of the radiochemotherapy. In this treatment plan, at the same day both at baseline (days -7 till -1) and – to assess early response following induction EOX chemotherapy – at days 14-15 both a PET/CT and MRI examination with DWI were incorporated (Fig. 1).

**Patient examination protocol**

Histological response was assessed in surgical specimens by a senior pathologist. The histopathologic tumor regression was graded according to the Becker Score [21, 22] as 1 = marked (1a: no, 1b: less than 10% viable tumor cells), 2 = partial (regression to 10-50% remaining viable tumor cells), 3 = no/minor response (more than 50% viable tumor remaining). Progression free survival after surgery and overall survival after tumor diagnosis were analyzed. Clinical response was assessed by a senior surgeon in consensus with a senior radiologist as responder and non-responder upon clinical examination and CT scans performed prior to surgery. Response included the CT-response criteria according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) [23] complete remission and partial remission, while non-response included the criteria stable disease and progressive disease.

**MR imaging protocol and image analysis**

All MRI examinations were performed on a clinical 1.5 Tesla scanner (MAGNETOM Avanto, Siemens Healthcare, Erlangen/Germany). Hypotonia of the esophagus was ensured by application of 20 mg of intravenous scopolamine as recommended [24]. The imaging protocol comprised the following sequences: breath hold T2-weighted Half-Fourier-Acquisition Single-Shot Turbo-Spin-Echo (HASTE) in axial (repetition time (TR)/echo time (TE)=801/68 ms, slice thickness (ST), 6 mm) and coronal orientation (TR/TE=1.000/120 ms, ST: 6 mm), respiratory and ECG-triggered T2-weighted axial SPACE (Sampling-Perfection with Application-optimized Contrasts using different flip-angle Evolution; TR/TE=3973/99 ms, ST: 4 mm), respiratory and ECG-triggered sagittal T2-weighted TSE ([15]; TR/TE=3.515/88 ms, voxel size: 0.9×0.9×4 mm\(^3\)), respiratory
triggered diffusion-weighted two-dimensional echo-planar-imaging (TR/TE=3.100/82 ms, voxel size: $1.6\times1.6\times5$ mm$^3$) with 15 slices, a 3-scan Trace diffusion mode and b-values of 50, 400, and 800 s/mm$^2$. The protocol was finished by an axial breath hold T1-weighted Volumetric-Interpolated Breath-hold Examination (VIBE) (TR/TE=3.05/1.12 ms, ST: 4 mm) and a breath hold fat-saturated VIBE (TR/TE=7.07/4.76 ms, ST: 3 mm) performed both before and after i.v. administration of gadobutrol (Bayer Vital, Leverkusen/Germany, 0.1 mmol/kg body weight).

The metastatic involvement of regional lymph nodes was assessed in consensus of a senior radiologist and a board-certified nuclear medicine physician separately for the initial MRI and PET/CT examinations. To prevent a reading bias, the MRI and PET/CT examinations were evaluated on separate days and the readers were blinded to the histopathological result and the clinical data. Morphologic criteria for peri-esophageal lymph node involvement were a short-axis diameter of $\geq 6$ mm, a round shape, an eccentric or missing fatty hilum, and a marked or inhomogeneous contrast enhancement [24]. Also, a distinctly reduced ADC compared to the ADC of normal esophagus and an avid FDG uptake were considered as a hint of metastatic lymph node affection.

ADC values were quantified from regions-of-interest (ROIs) placed on the tumor and the healthy appearing adjacent esophagus for each MR examination. The tumor ROIs had a size of at least 80 pixels and avoided necrotic areas. Four ROIs were placed on the tumor and the mean of these 4 ROIs was used for statistical analysis. The ROI placement was performed free hand in consensus of a senior radiologist and a board-certified nuclear medicine physician using the analysis software of our picture-archiving and -communication system (Centricity PACS, version 3.0.4, GE Healthcare, Barrington, IL) that allowed direct comparison and co-registration of anatomic MRI, DWI MRI, and PET/CT data sets on two large-screen high-resolution monitors.

**PET protocol and image analysis**

PET scans were performed using a Biograph 6 PET/CT scanner (Siemens Healthcare, Erlangen/Germany), axial field-of-view of 15.4 cm in 3D mode. Patients fasted at least 6 hours before PET imaging to ensure euglycemic glucose metabolism. Blood glucose levels were measured before each PET scan. Prior to each application, patients were advised to rest and continue to reduce activities for 50 minutes after administration of 250 to 350 MBq $^{18}$F-FDG followed by 500 ml saline solution to increase the distribution volume. A low-dose CT for transmission measurements (30 mAs, 110 KeV) was performed. 60 minutes post injection, a whole-body scan was initiated with 3 min/bed position from head to upper femur. All raw data were reconstructed after dead time, scatter and random correction using an iterative method based on the ordered subsets expectation maximization algorithm of four iterations/eight subsets, using a $256\times256$ matrix with Gaussian smoothing filter applied and 3.5 mm transversal slices at full-width half maximum [20]. After the PET scan, a contrast-enhanced biphasic CT was performed with the following specifications: water as oral contrast media, scan from below liver to cervical vertebra 5 in inspiration, 1 mm slice thickness, 3 mm axial and coronal reconstructions and reformations along the esophagus, arterial and portal phase of biphasic CT after injection of 90 ml iopromide (Ultravist 370, **Fig. 1.** Treatment scheme and time-points of imaging. Responders of neoadjuvant induction EOX chemotherapy (Epirubicin 50mg/m² day 1, Oxaliplatin 130mg/m² day 1, Capecitabin (Xeloda®) 1250mg/m² days 1-21) continued to receive EOX neoadjuvant chemotherapy for 12 weeks and then proceeded to surgery. Metabolic non-responders discontinued EOX chemotherapy after the 2-week evaluation period and proceeded to radiochemotherapy prior to surgery (modified from the HICON trial [20]: one cycle of chemotherapy with Docetaxel (D) 75 mg/m² and Cisplatin (C) 75 mg/m² to allow radiation planning followed by radiochemotherapy starting on day 22 of intensified chemotherapy cycle consisting of radiotherapy (RT) with 1.8 Gy/day and a total dose of 45 Gy and chemotherapy given on a weekly basis with Docetaxel 25 mg/m² on days 1, 8, 15, 22, 29 and Cisplatin 25 mg/m² on days 1, 8, 15, 22, 29 of radiochemotherapy).
Bayer Vital, Leverkusen/Germany) followed by 50 ml saline flush, 4 ml/s flow rate, 25 s delay for the first and 70 s delay for the second scan. The PET image data set was normalized for the injected dose and the patients' body weight, resulting in parametric imaging using SUV on the basis of the formula "SUV = tissue concentration (Bq/g)/(injected dose (Bq)/ body weight (g))". For quantitative evaluation, an automated volume-of-interest derived from generated ROIs using the auto-3D function within the Syngo Software (Siemens Healthcare, Erlangen/Germany) was placed over the tumor in the slice with maximum tumoral FDG uptake in the baseline scan by two experienced nuclear medicine physicians in consensus. In the second PET scan 14 days later, the ROI was placed at the same position as in the baseline PET. The change of FDG-uptake after 14 days of neoadjuvant chemotherapy (PET2) was assessed in relation to the baseline (PET1) [20] (Fig. 1).

**Statistical analysis**

MRI was compared with static PET/CT findings. Patients with a decrease in tumor FDG SUV$_{\text{mean}}$ of 35% or more at PET2 compared with PET1 were defined as metabolic PET-responders. Normality for continued variables in both groups (PET-responders and non-responders) was determined both by the tests of Shapiro-Wilk and Kolmogorov-Smirnov. The variables showed normal distribution for all comparisons (p ≥ 0.05). Thus, the unpaired t-test could be performed to test for differences between the metabolic responders' and the non-responders' population. The data of first and second measurements (i.e. before and after 2 weeks of neoadjuvant chemotherapy) were compared using the paired t-test. In all statistical tests, an effect was considered to be significant if the p-value was 0.05 or less. P-values were not adjusted for multiple testing and interpretation of p-values was explorative.

Primary endpoint of the study was overall survival, which was analyzed using the Kaplan-Meier method. The duration of overall survival was calculated from the date of first diagnosis to the date of last clinical presentation or death. Statistical analysis was performed using the Statistical Package for Social Sciences version 21.0 (SPSS for Windows®, SPSS Inc., Chicago/IL). Results were expressed as mean ± standard deviation for quantitative data and as median and range for qualitative data (e.g. the histological tumor regression grade).

**RESULTS**

**Follow-up**

Among the 15 patients in our population, there were 7 PET-responders (6 male, 1 female; median age, 63 years; time from first diagnosis to surgery, 111±23 days; pathological stage ypT3/4: n=4, ypT0/1/2: n=3; clinical response in 2 of 7 (29%)) and 8 PET-non-responders (7 male, 1 female; median age, 65 years; time from first diagnosis to surgery, 126±45 days; ypT3/4: n=3, ypT0/1/2: n=5; clinical response in 1 of 8 (13%)). In 6 of the 8 metabolic non-responders, chemotherapy was changed to radiochemotherapy, while two patients were immediately operated. Median follow-up time was 726 days (range, 89-1482 days). Mean progression free survival was 699±533 days after tumor diagnosis and 588±528 days after surgery in PET-responders compared with 564±411 days and 437±391 days in PET-non-responders (p=0.25 and p=0.22). The median overall survival obtained from the Kaplan-Meier curves was 731 days for the total population (95%-confidence interval (CI) [538, 924]), 757 days for PET-responders (95% CI [690, 824]) and 623 days for PET-non-responders (95% CI [510, 736]) (p=0.138; Fig. 2).

**ADC patterns of AEG tumors, suspicious lymph nodes and normal esophagus**

The ADC within the AEG tumors (n=15, 1.12±0.15 $[\times 10^{-3}$ mm$^2$/s]) was significantly lower than the ADC of the normal esophageal wall (n=6, 1.52±0.22 $[\times 10^{-3}$ mm$^2$/s]; p<0.001). Also, histologically proven lymph node metastases that were covered
by the DWI sequence had lower ADC values (n=3, 1.03±0.15 \([*10^{-3} \text{ mm}^2/\text{s}]\)) than the normal esophageal wall (p=0.011), and the ADC values of lymph node metastases were not different from those of the primary tumors (p=0.345; Fig. 3).

**Metabolic tumor response following neoadjuvant chemotherapy**

Table I illustrates the intratumoral values of ADC and SUV before and after neoadjuvant chemotherapy. Regarding the total patient population, following neoadjuvant EOX chemotherapy there was a mean tumor ADC increase of 16.0±21.1% (p=0.007) and a tumor FDG SUV decrease of 29.1±23.2% (p=0.002). Concordance of ADC increase and PET-response was observed in 73.3% of all patients. The initial ADC and SUV were comparable in responders and non-responders. The ADC within tumor tissue at first MRI and the tumor SUV at first PET/CT were not different in responders and non-responders (Table I). After 14 days of neoadjuvant EOX chemotherapy, the mean ADC increase was significantly higher in PET-responders (26.8±22.2%) than in PET-non-responders (6.5±15.8%, p=0.0298). The FDG uptake of the esophageal tumor tissue was significantly reduced after 14 days of neoadjuvant chemotherapy in PET-responders (mean SUV decrease of 49.3±8.5% in responders vs. 11.3±15.5% in non-responders, p<0.001; Fig. 4). Using the decrease in FDG SUV \(_\text{mean} \geq 35\%\) as reference [7], the ADC increase yielded a sensitivity/specificity of 100%/50% with positive/negative predicting values of 75%/100%, ADC (p=0.13) und SUV (p=0.20) changes did not differ between clinical responders and non-responders (Table II).

**Histopathologic response of AEG tumors following neoadjuvant chemotherapy**

Histopathologic response (grade 1a according to [21, 22], n=2; grade 1b, n=0; grade 2, n=8) following neoadjuvant chemotherapy was observed in 10 of 15 patients (67%). No/

**Table I.** Apparent diffusion coefficient and tumor \(^{18}\)F- fluorodeoxyglucose uptake values in metabolic responders and non-responders.

<table>
<thead>
<tr>
<th>PET Response</th>
<th>ADC ([*10^{-3} \text{ mm}^2/\text{s}])</th>
<th>SUV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responder (n=7)</td>
<td>1.14 ± 0.17</td>
<td>16.0 ± 17.6</td>
</tr>
<tr>
<td>Non-responder (n=8)</td>
<td>1.11 ± 0.13</td>
<td>18.0 ± 15.4</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>After 14 days of neoadjuvant chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responder (n=7)</td>
</tr>
<tr>
<td>Non-responder (n=8)</td>
</tr>
</tbody>
</table>

Note. P-values indicate the differences between responders and non-responders. PET, positron emission tomography. ADC, apparent diffusion coefficient. SUV, standardized uptake value.
A minor histologic response (grade 3) was observed in 3 of 8 PET-non-responders (38%) and 2 of 7 PET-responders (29%); \( p = 0.376 \). AEG tumors with histologic regression grades 1-2 had significantly higher initial ADC values (1.17±0.12 vs. 1.03±0.16, \( p = 0.043 \)) compared to those with grade 3 (no/minor histopathologic regression), but there were non-significant differences of the ADC increase (16.7±25.1% vs. 14.7±11.8%, \( p = 0.436 \)), initial SUV (15.2±14.1 vs. 21.0±20.2, \( p = 0.261 \)), and the SUV decrease (32.9±25.2% vs. 21.4±18.4%, \( p = 0.191 \)). ADC (\( p = 0.30 \)) and SUV (\( p = 0.22 \)) baseline values and their changes following neoadjuvant chemotherapy (ADC increase, \( p = 0.45 \), SUV decrease, \( p = 0.43 \)) were not different between patients with complete response (grade 1a) and the others (grades 2-3).

### Table II

<table>
<thead>
<tr>
<th>Clinical response</th>
<th>ADC ([10^{-3} \text{mm}^2/\text{s}])</th>
<th>SUV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responder (n=3)</td>
<td>1.13 ± 0.01</td>
<td>9.7 ± 2.7</td>
</tr>
<tr>
<td>Non-responder (n=12)</td>
<td>1.12 ± 0.17</td>
<td>19.0 ± 17.3</td>
</tr>
<tr>
<td>( p = 0.45 )</td>
<td>( p = 0.19 )</td>
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</table>

After 14 days of neoadjuvant chemotherapy:

<table>
<thead>
<tr>
<th>Clinical response</th>
<th>ADC ([10^{-3} \text{mm}^2/\text{s}])</th>
<th>SUV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responder (n=3)</td>
<td>1.46 ± 0.49</td>
<td>5.8 ± 2.7</td>
</tr>
<tr>
<td>Non-responder (n=12)</td>
<td>1.26 ± 0.19</td>
<td>13.5 ± 11.6</td>
</tr>
<tr>
<td>( p = 0.13 )</td>
<td>( p = 0.14 )</td>
<td></td>
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</tbody>
</table>

Note. P-values indicate the differences between responders and non-responders. ADC, apparent diffusion coefficient. SUV, standardized uptake value.

Fig. 4. 63 year-old man with adenocarcinoma of the esophago-gastric junction. A-F: Status before neoadjuvant EOX chemotherapy, A: axial T2-weighted MRI, B: corresponding ADC parameter map and C: diffusion-weighted image (b-value 50 s/mm\(^2\)), D: contrast-enhanced T1-weighted MRI, E: contrast-enhanced CT and F: FDG PET/CT image. The thickening of the esophageal wall due to the adenocarcinoma is well appreciated (arrows). Note the avid tumoral FDG uptake (open arrow). G-L: Status after 14 days of neoadjuvant EOX chemotherapy. G: axial T2-weighted MRI, H: corresponding ADC parameter map showing a 30% increase in the tumoral ADC value (visible as an increased brightness of the tumor in H compared with B, corresponding diffusion-weighted image (b-value 50 s/mm\(^2\)), J: contrast-enhanced T1-weighted MRI, K: contrast-enhanced CT and L: FDG PET/CT image showing a 53% decrease in tumor FDG uptake which is hardly discernible within the tumor (open arrow).
Lymph node staging

There was concordance of PET/CT and MRI in 15 of 15 cases (100%), but only in 9 of 15 cases (60%) there was concordance between the sincere classification of local lymph node metastases by imaging and histopathology (ypN); subdivided according to metabolic response, there was concordance in 4 of 7 PET-responders (57%) and 5 of 8 PET-non-responders (63%).

DISCUSSION

We could demonstrate that the ADC increased two weeks after initiation of neoadjuvant chemotherapy of AEG tumors and was significantly different between responders and non-responders. ADC increase and metabolic response were concordant in 73% of patients. MRI is less time consuming, more cost-effective and more widely available than PET. Also, MRI examinations of esophageal cancer are covered by the statutory health insurance companies of our country, while PET examinations are not remunerated. Our observation of a significantly higher ADC increase in PET-responders than non-responders is in agreement with the fact that also in other malignant tumors such as breast cancer, primary and metastatic cancers to the liver, primary sarcomas of bone, and gliomas, successful treatment is reflected by increases in ADC values [25]. However, metabolic response was not associated with overall and progression-free survival in our patient population. Our ADC values were in accordance with the ADC values reported within primary esophageal cancer (1.12 vs. 1.06 \( \times 10^{-3} \) mm\(^2\)/s reported by [26]) and slightly lower in normal esophagus (1.52 vs. 2.08 \( \times 10^{-3} \) mm\(^2\)/s [26]). One reason may be that esophagus with normal wall was only covered by our DWI sequence in 6 patients (in contrast to n=47 of [26]). In accordance with [26], ADC values of lymph node metastases were significantly lower than those of normal esophagus. Since ADC inversely correlates to tissue cellularity [16], our findings of significantly lower ADC values within the AEG tumor tissue and in histologically proven lymph node metastases than in normal esophageal wall and an increasing ADC following chemotherapy are plausible, given the fact that chemotherapeutic response leads to decreased tumor cell density at histology [21]. Our finding of higher initial ADC values in those tumors with histopathologic response are in agreement with observations in a rat tumor model treated with a vascular targeting agent that low tumor ADC values still had viable tumor cells on histologic diagnosis after therapy, whereas tumors with higher ADC values had a greater degree of cell kill [27]. Of note, the reason why malignant tumors have lower ADC values is probably related to a combination of higher cellularity, tissue disorganization, and increased extracellular space tortuosity, all contributing to reduced motion of water leading to increased ADC values [25]. Although we used three b-values to accurately calculate the ADC values according to recent recommendations [25], and despite a starting b-value of 50 s/mm\(^2\) to suppress large vessels, especially the aorta, which makes the esophageal adenocarcinoma more conspicuous, the effect of microvascular perfusion or potential temperature effects on the calculated ADC values cannot be completely omitted. This has to be considered, because neoadjuvant chemotherapy leaves the vascular network and thus the blood supply of the tumor intact [21].

Regarding the detection of local lymph node metastases which very much determine the prognosis [14], our study is in accordance with studies reporting only an insufficient detection of locoregional lymph node metastases by PET and MRI [21,28]; especially micro metastases may not be detected [21]. Additionally, the continuation of either chemotherapy or even radiochemotherapy strongly influences the posttherapeutic lymph node involvement. Responders are known to have a significantly lower rate of lymph node metastases [22] and the addition of radiotherapy might increase the histopathological response of initially metabolically non-responding patients [10]. Of note, endosonography is the method of choice for T and local N staging [13,29], but in 30-50% of all esophageal cancers the tumor stenosis cannot be passed by the endoscope [14], which makes MRI and PET/CT in these cases very important to give precise information on both T- and N-stage. Thus, cross-sectional imaging and its further optimization for this issue is mandatory.

Limitations

The limited number of patients has to be acknowledged. Furthermore, the addition of radiotherapy in a subgroup of patients makes the interpretation more difficult. Also, the evaluation of the lymph node metastases is limited, because only data before and two weeks of therapy are compared with the resected specimen after the completion of either chemotherapeutic response leads to decreased tumor cell density at histology [21]. Our finding of higher initial ADC values in those tumors with histopathologic response are in agreement with observations in a rat tumor model treated with a vascular targeting agent that low tumor ADC values still had viable tumor cells on histologic diagnosis after therapy, whereas tumors with higher ADC values had a greater degree of cell kill [27]. Of note, the reason why malignant tumors have lower ADC values is probably related to a combination of higher cellularity, tissue disorganization, and increased extracellular space tortuosity, all contributing to reduced motion of water leading to increased ADC values [25]. Although we used three b-values to accurately calculate the ADC values according to recent recommendations [25], and despite a starting b-value of 50 s/mm\(^2\) to suppress large vessels, especially the aorta, which makes the esophageal adenocarcinoma more conspicuous, the effect of microvascular perfusion or potential temperature effects on the calculated ADC values cannot be completely omitted. This has to be considered, because neoadjuvant chemotherapy leaves the vascular network and thus the blood supply of the tumor intact [21].

Response of AEG tumors to neoadjuvant chemotherapy is reflected by a significantly higher increase in tumor ADC in PET-responders than in PET-non-responders. Although the ADC increase is concordant to PET-response in 73% of all patients with AEG tumors following chemotherapy, neither ADC changes nor PET-response are correlated to prognosis this study. Since a metabolic response was never tested prospectively in a multicenter setting and such a design is more complicated with PET/CT than with MRI, further investigations on DWI as a tool for early response evaluation appear promising.

CONCLUSIONS

Response of AEG tumors to neoadjuvant chemotherapy is reflected by a significantly higher increase in tumor ADC in PET-responders than in PET-non-responders. Although the ADC increase is concordant to PET-response in 73% of all patients with AEG tumors following chemotherapy, neither ADC changes nor PET-response are correlated to prognosis this study. Since a metabolic response was never tested prospectively in a multicenter setting and such a design is more complicated with PET/CT than with MRI, further investigations on DWI as a tool for early response evaluation appear promising.

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