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PREDICTION OF RESPONSE TO NEOADJUVANT RADIOTHERAPY IN PATIENTS WITH LOCALLY ADVANCED RECTAL CANCER BY MEANS OF SEQUENTIAL 18FDG-PET

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Purpose: Morphologic imaging techniques perform poorly in assessing the response to preoperative radiotherapy (RT), mainly because of desmoplastic reactions. The aim of this study was to investigate the potential of sequential 18-fluoro-2-deoxy-D-glucose (18FDG-PET) in assessing the response of rectal cancer to neoadjuvant RT and to determine which parameters can be used as surrogate markers for histopathologic response.

Methods and Materials: 18FDG-PET scans were acquired before and during the 5th week after the end of RT. Tracer uptake was assessed semiquantitatively using standardized uptake values (SUV). The percentage differences (%Δ) between pre- and post-RT scans in SUV_{max}, SUV_{mean}, metabolic volume (MV), and total glycolytic volume (tGV) were calculated.

Results: Forty-five consecutive patients with histologically confirmed rectal adenocarcinoma were enrolled. After neoadjuvant RT, 20 of the 45 patients were classified as histopathologic responders and 25 as non-responders. Intense 18F-FDG uptake was seen in all tumors before neoadjuvant RT (average SUV_{max} 12.9 ± 6.0). When patients were classified as histologic responders and nonresponders, significant differences in $\%\Delta SUV_{max}$ (55.8% vs. 37.4%, $p = 0.023$) and $\%\Delta SUV_{mean}$ (40.1% vs. 21.0%, $p = 0.001$) were observed between the two groups. For %ΔMV and %ΔtGV, decreases were more prominent in responders but were not significantly different from those in nonresponders. As demonstrated by receiver operating characteristic analysis, $\%\Delta SUV_{mean}$ was a more powerful discriminator than was $\%\Delta SUV_{max}$. The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value for optimal threshold of $\%\Delta SUV_{mean}$ (24.5%) were 80%, 72%, 76%, 70%, and 82% respectively.

Conclusion: Sequential 18FDG-PET allows assessment of the response to preoperative RT. Both $\%\Delta SUV_{mean}$ and $\%\Delta SUV_{max}$ correlate with histopathologic response and can be used to evaluate and compare the effectiveness of different neoadjuvant treatment strategies. The maximum accuracy figures and the positive predictive value figures for both $\Delta\%SUV_{mean}$ and $\Delta\%SUV_{max}$ are, however, too low to justify modification of the standard treatment protocol of an individual patient.

Rectal cancer, Preoperative radiotherapy, Response evaluation, 18FDG-PET, Histologic regression.

INTRODUCTION

Preoperative (chemo)radiotherapy followed by total mesorectal excision has become the standard of care in locally advanced rectal cancer (1–3). Unfortunately, not all patients benefit equally from neoadjuvant treatment, and an individual assessment of response to neoadjuvant therapy using imaging techniques could be of great value for tailoring the neoadjuvant regimen and the surgical approach to the individual patient. It remains, indeed, a matter of debate whether concomitant chemotherapy should be administered to all patients with T3–4 disease and whether sphincter preservation may be made on the basis of response to the preoperative treatment (4, 5). Additionally, a standardized imaging protocol for assessing tumor response would be of great value for radiobiologic studies, aiming at identifying prognostic markers or evaluating new radiosensitizers.

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Conventional imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), and endorectal ultrasound, although successfully used in the staging of rectal cancer, are known to perform poorly after neoadjuvant therapy. Because of their inability to distinguish desmoplastic reactions and fibrosis from viable tumor cells, these imaging techniques are of limited value in restaging after neoadjuvant treatment (6–8). The potential role of dynamic contrast-enhanced MRI (DCE-MRI) as a noninvasive tool to predict response to treatment in colorectal cancer was reported about 10 years ago. These studies, based on a limited number of patients, concluded that alterations in microcirculation measured by DCE-MRI could be used to monitor tumor response to (chemo)radiotherapy (9, 10). Reports including larger number of patients confirming these initial results are awaited. In contrast to conventional imaging modalities, metabolic imaging with 18FDG-PET allows the discrimination of fibrosis from viable tumor tissue. In addition, there seems to be a rather strong relationship between 18FDG uptake and cancer cell numbers in several studies (11–13). More than a decade ago, 18FDG-PET with quantitative measurement of tracer accumulation was introduced with success to evaluate the effectiveness of breast cancer treatment (14). Since then, therapy-induced modifications in glucose metabolism have been reported and used in a variety of other cancer types, including rectal cancer, to measure the effect of cytotoxic therapies (15–17).

The aim of the current study was to investigate whether semiquantitative measurement of 18FDG accumulation at the primary tumor site using (sequential) PET could be applied to assess the effects of neoadjuvant radiotherapy (RT), using histopathology as a gold standard. In addition, we investigated the potential of several parameters, reflecting tumor aggressiveness and/or tumor burden, derived from 18FDG-PET studies in their ability to discriminate responders from nonresponders.

PATIENTS AND METHODS

Preoperative RT

Forty-five consecutive patients (34 male and 11 female, aged 65.4 $\pm$ 12.5 years) with histologically confirmed locally advanced (cT3/T4) rectal adenocarcinoma were enrolled in a Phase II study, evaluating helical tomotherapy and daily megavolt CT positioning (Tomotherapy Hi Art II system.). Staging and treatment have been previously described (18–20). Essentially, a dose of 46 Gy, in daily fractions of 2 Gy, was delivered to the presacral space and the perineum if abdominoperineal resection was deemed necessary. No concomitant chemotherapy was administered, but the dose of radiation was increased by a simultaneous integrated boost to 55.2 Gy when the circumferential resection margin was less than 2 mm.

18FDG-PET or PET/CT acquisition, reconstruction, and quantification

The PET or PET/CT scans were acquired before and during the 5th week after the end of RT using a dedicated PET camera (Ecat Accel, Siemens, Hoffman Estates, IL, USA) in 40 individuals or a PET/CT camera for the remaining five (Gemini TF, Philips Medical Systems, OH, USA). The patients fasted for at least 6 hours. Prescanning glucose levels were systematically checked and ranged from 72 to 185 mg/dL (107 $\pm$ 17 mg/dL).

The activity of 18FDG administered averaged 447 $\pm$ 68 MBq for the Ecat Accel and 317 $\pm$ 48 MBq when the Gemini TF camera was used. Whole body images corrected for attenuation were acquired, starting 60 minutes after tracer administration. The acquisition and reconstruction parameters were as follows: (*1*) For Ecat Accel: 3 minutes emission, 2 minutes transmission per bed position, iterative reconstruction of emission data using OSEM (2 iterations, 16 subsets), scatter correction and postreconstruction filtering (6 mm Gauss), forward projection of attenuation correction factors (obtained with 68Ge sources) for each line of response. The resulting images had a transaxial resolution of 6.0 mm. (*2*) For Gemini TF: 1 minute emission per bed position, iterative reconstruction of emission data using BLOB-OS (3 iterations, 33 subsets), scatter correction, forward projection of CT-derived attenuation correction factors for each line of response. The resulting transaxial resolution of the images was 4.7 mm.

The uptake of 18FDG within the tumor was measured using a three-dimensional volume of interest placed over the lesion, carefully avoiding the urinary bladder. Activity measurements were corrected for dose administered, body weight, and decay and were expressed in standardized uptake values (SUV). No correction for glycemia, lean body mass, or body surface was made.

The following response parameters were acquired before the start of RT and in the 5th week after completion of RT: SUV_{max}, SUV_{mean} (average SUV of tumoral pixels with SUV $\geq$2.5), metabolic volume (MV, sum of tumor pixels with SUV $\geq$2.5) and total glycolytic volume (tGV, MV $\times$ SUV_{mean}). In addition, the response indices (percentage difference (%Δ) between pre- and post-RT scans) for the different parameters were calculated.

Surgery and histologic regression

All patients underwent surgery in the 6th week after completion of RT: standard total mesorectal excision was carried out for tumors of the middle and lower third of the rectum and partial mesorectal excision for tumors of the upper third of the rectum (21). Tumor regression (fraction of tumor replaced by fibrous tissue) was graded by histologic evaluation of the surgical specimens according to the criteria described by Dworak *et al*. (22). Grading of regression was established as follows:

Grade 0: no regression

Grade 1: dominant tumor mass with obvious fibrosis and/or vasculopathy

Grade 2: dominantly fibrotic changes with few tumor cells or groups (easy to find)

Grade 3: very few (difficult to find microscopically) tumor cells in fibrotic tissue with or without mucous substance

Grade 4: no tumor cells, only fibrotic mass (total regression or response)

Statistical analysis

Statistical analysis was performed with GraphPad Prism (GraphPad Software 5.0b, Inc.). The results were expressed in mean and standard deviation. For the comparison of the different response parameters and indices obtained after RT vs. baseline, the Wilcoxon signed rank test (paired, two-tailed) was applied. To evaluate correlations between the different response indices and the stratification of patients according to tumor regression grade, the Kruskal-Wallis test and the Dunn multiple comparison test was used.