Int. J. Radiation Oncology Biol. Phys., Vol. 77, No. 2, pp. 392–399, 2010

0360-3016/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2009.04.030

CLINICAL INVESTIGATION **Rectum**

ACCURATE PREDICTION OF PATHOLOGICAL RECTAL TUMOR RESPONSE AFTER TWO WEEKS OF PREOPERATIVE RADIOCHEMOTHERAPY USING ^{18}F-FLUORODEOXYGLUCOSE-POSITRON EMISSION TOMOGRAPHY-COMPUTED TOMOGRAPHY IMAGING

Marco H. M. Janssen, M.Sc.,* Michel C. Öllers, M.Sc., Ph.D.,* Robert G. Riedl, M.D.,† Jørgen van den Bogaard, M.A.,* Jeroen Buijsen, M.D.,* Ruud G. P. M. van Stiphout, M.Sc.,* Hugo J. W. L. Aerts, M.Sc.,* Philippe Lambin, M.D., Ph.D.,* and Guido Lammering, M.D., Ph.D.*

*Department of Radiation Oncology (MAASTRO), GROW Research Institute, University Medical Centre Maastricht, Maastricht, The Netherlands; and †Department of Pathology, University Medical Centre Maastricht, Maastricht, The Netherlands

Purpose: To determine the optimal time point for repeated ^{18}F-fluorodeoxyglucose-positron emission tomography (PET)-CT imaging during preoperative radiochemotherapy (RCT) and the best predictive factor for the prediction of pathological treatment response in patients with locally advanced rectal cancer.

Methods and Materials: A total of 30 patients referred for preoperative RCT treatment were included in this prospective study. All patients underwent sequential PET-CT imaging at four time points: prior to therapy, at day 8 and 15 during RCT, and shortly before surgery. Tumor metabolic treatment responses were correlated with the pathological responses by evaluation of the tumor regression grade (TRG) and the pathological TN (ypT) stage of the resected specimen.

Results: Based on their TRG evaluations, 13 patients were classified as pathological responders, whereas 17 patients were classified as pathological nonresponders. The response index (RI) for the maximum standardized uptake value (SUV_{max}) on day 15 of RCT was found to be the best predictive factor for the pathological response (area under the curve [AUC] = 0.87) compared to the RI on day 8 (AUC = 0.78) or the RI of presurgical PET imaging (AUC = 0.66). A cutoff value of 43% for the reduction of SUV_{max} resulted in a sensitivity of 77% and a specificity of 93%.

Conclusions: The SUV_{max}-based RI calculated after the first 2 weeks of RCT provided the best predictor of pathological treatment response, reaching AUCs of 0.87 and 0.84 for the TRG and the ypT stage, respectively. However, a few patients presented with peritumoral inflammatory reactions, which led to mispredictions. Exclusion of these patients further enhanced the predictive accuracy of PET imaging to AUCs of 0.97 and 0.89 for TRG and ypT, respectively. © 2010 Elsevier Inc.

Rectal cancer, Preoperative radiochemotherapy, Repeated PET-CT imaging, Pathological response prediction, TRG.

INTRODUCTION

For patients diagnosed with locally advanced rectal cancer (LARC), preoperative radiochemotherapy (RCT) has become a standard procedure (1–3). Importantly, however, preoperative RCT has been shown to not only reduce the risk for local recurrence but also to induce a significant tumor downsizing and downstaging (4–6). Consequently, in 15 to 30% of these patients, even a pathologically complete tumor regression has been observed (4–7). Interestingly, correlations between the reduction of the uptake of ^{18}F-fluorodeoxyglucose (FDG) within the tumor and the pathological tumor response after RCT have been reported by some groups (5–14). Most of these studies performed positron emission tomography (PET)-CT scans before the start and after the finish of preoperative RCT, correlating semiquantitative measurements of FDG uptake with the tumor regression grade (TRG) (5–12). For the clinical practice, however, an earlier prediction of

Reprint requests to: M. H. M. Janssen, M.Sc., MAASTRO Clinic, Dr. Tanslaan 12, 6202 NA Maastricht, Box 3035, The Netherlands, Tel: (+31) 884455779; Fax: (+31) 884455667; E-mail: marco.janssen@maastro.nl

Philippe Lambin and Guido Lammering contributed equally to this work.

This work was supported by Siemens MI and by The Netherlands Organization for Health Research and Development (by ZonMw clinical fellowship awarded to GL).

Conflict of interest: none.

Acknowledgment—We thank Siemens MI for technical support. Also, we acknowledge efforts of the pathology departments of all participating hospitals for providing patients' pathological specimens.

Received March 30, 2009, and in revised form April 24, 2009. Accepted for publication April 24, 2009.

the pathological tumor response would be even more attractive because it could enable response-guided modifications of the treatment protocol based on changes in FDG uptake, possibly strengthened by clinical or biological factors (13–15). Until now, only two studies have reported an early prediction of the pathological tumor response based on PET-CT imaging during preoperative RCT (13, 14). Cascini *et al*. showed that early changes in the metabolic activity of the tumor, measured 12 days after the start of preoperative treatment with RCT, were predictive for the pathological treatment response in rectal cancer (13). Rosenberg *et al*. presented a correlation of both the early metabolic response evaluation and the late metabolic response evaluation with the histopathological tumor response, of which the accuracy of the late metabolic response was marginally superior (14). Both studies used a protocol in which the second PET-CT scan was performed at the end of the second week during RCT (13, 14). However, no studies have yet examined other time points of PET imaging during preoperative RCT in order to define the best prediction of pathological tumor response as advised by Hindie *et al*. (15). Thus, we initiated this study, in which we performed PET-CT scans at two different time points during preoperative RCT and a presurgical PET-CT scan, in order to determine the optimal time point of PET imaging during preoperative RCT and to define the PET criteria that would result in the best prediction of pathological tumor response.

METHODS AND MATERIALS

Patient characteristics

A cohort of 30 patients diagnosed with nonmetastasized LARC were included in this study, for whom clinical TN staging was evaluated with a pretreatment magnetic resonance (MR) scan (Table 1). All patients were preoperatively treated with radiotherapy (28 fractions of 1.8 Gy, 5 fractions/week) and concomitant chemotherapy (capecitabine, 825 mg/m^2, twice daily), followed by a total mesorectal excision. As a part of the study, all patients underwent sequential FDG-PET-CT imaging at four different time points: once prior to therapy, on days 8 and 15 of RCT, and once shortly before surgery. Due to technical problems or patient incompliance, not all PET-CTs could be performed as planned. Three patients refused PET-CT imaging on day 15, and for one patient, no FDG could be injected on the second PET-CT scan. For 7 patients, no PET-CT scan could be performed prior to surgery. According to Dutch law, the medical ethics committee approved the trial. All patients gave written informed consent before entering the study.

Table 1. Comparison of predictive factors during the first 15 days of preoperative RCT*

Patient	cTNM	ypTN	TRG	RI of SUV_{max} 0–15
1	T3N1M0	T3N0	3	
2	T2N1M0	T0N0	1	51.9
3	T3N2M0	T3N1	3	41.7
4	T3N2M0	T2N0	2	69.4
5	T3N1M0	T3N0	3	
6	T4N2M0	T3N0	2	38.9
7	T3N1M0	T2N0	2	64.8
8	T3N2M0	T2N0	2	−2.4
9	T3N2M0	T2N0	3	31.5
10	T3N2M0	T4N0	3	−11.8
11	T3N2M0	T3N0	3	47.6
12	T3N2M0	T3N1	4	14.4
13	T3N1M0	T0N0	1	70.4
14	T3N2M0	T3N0	4	28.8
15	T3N1M0	T2N0	3	39.7
16	T3N0M0	T2N0	3	5.1
17	T3N2M0	T3N1	3	35.9
18	T3N1M0	T1N0	2	9.7
19	T3N2M0	T3N2	3	33.4
20	T3N2M0	T3N2	4	28.6
21	T3N2M0	T0N0	1	54.6
22	T3N2M0	T3N1	2	45.5
23	T3N0M0	T3N1	4	5.2
24	T3N1M0	T3N2	3	−8.2
25	T4N1M0	T4N0	4	−15.7
26	T3N1M0	T2N0	2	48.6
27	T3N0M0	T0N0	1	68.4
28	T3N2M0	T2N2	2	45.6
29	T3N2M0	T2N0	2	46.7
30	T3N1M0	T3N1	4	−7.1

* Overview of the clinical (c) and pathological (yp) staging (TN(M)), the tumor-regression-grade (TRG) and the reduction of SUV_{max} during the first 15 days of pre-operative radiochemotherapy.

PET-CT imaging and processing

All PET-CT scans were performed by use of a dedicated Siemens Biograph 40 TruePoint PET-CT simulator (Siemens Medical, Erlangen, Germany) with an axial field of view of 16.2 cm, a slice thickness of 3 mm, and a pixel spacing of 5.3456 mm in both directions. The scanner is equipped with ultrafast detector electronics (Pico3D) and has a spatial resolution of approximately 6 mm at full-width-at-half-maximum. PET imaging was done in three dimensions, requiring a proper scatter correction. CT-based attenuation and decay correction were performed. PET images were reconstructed from the acquired list mode data, using Fourier rebinning and ordered subset expectation maximization reconstruction (two dimensional) with four iterations and eight subsets. After a fasting period of at least 6 hours prior to FDG injection, patients received an intravenous injection of FDG, with the activity normalized for the weight of the patient (where weight [kg] · 4 + 20) [MBq]), followed by an injection of physiologic saline (10 ml). After an uptake period of 60 minutes, the patient was positioned on a flat tabletop, using a movable laser alignment system in a ''head-first supine'' position with the arms crossed above the chest. A PET-CT scan of the abdominal region was performed using an acquisition time of 5 minutes per bed position. Additionally, all PET data were normalized for the blood glucose level measured shortly before FDG administration (16).

PET analysis

For each of the PET scans, a tumor contour was generated using automated standardized uptake values (SUV) that reached threshold levels in which the threshold value (percentage of SUV_{max} within the tumor) was dependent on the tumor-to-background signal ratio, with the gluteus muscle selected as the relevant background (17, 18). Dedicated software (TrueD; Siemens Medical, Erlangen, Germany) was used to calculate the SUV_{mean} and SUV_{max} within the tumor. Subsequently, the response indices (RIs), indicating the percent reduction relative to the pretreatment measured value, were calculated and correlated to the pathological tumor response. If no residual metabolic activity was present on the presurgical PET-CT scan, the patient's tumor was classified as a metabolic complete responder