Assessment of Metabolic Response to Pre-operative Treatment of Rectal Cancer

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Abstract:

In the era of targeted therapy and high precision radiotherapy for patients with cancer, tailoring and individualization of treatment is needed more and more. In part to avoid ineffective administration of a toxic treatment to a patient that unlikely to get any benefit of it. And also to decrease the expenses of treatment and saving the drugs and resources to patients that deserve. Many predictive factors and markers are searched and well-known in many malignancies, but still rectal cancer lacks such predictors. As the pre-operative chemoradiotherapy is becoming the standard of care of treating patients with locally advanced rectal carcinoma, a predictive factor, or at least an early indicator, of patient's response to treatment is needed. First, it may help to modulate the pre-operative treatment by employing another chemotherapeutic or targeted agent e.g. oxaloplatin or cetuximab instead of the standard fluorouracil compounds. It may also help to avoid continuation of unnecessary protracted course of radiotherapy for 5—6 weeks for a patient who is unlikely to achieve a satisfactory response. This will help to avoid the definite toxicity of pelvic irradiation and avoid wasting time before going to surgery. Here comes the role of imaging techniques in predicting the metabolic response such as functional computerized tomography (CT) and magnetic resonance imaging (MRI) or positron-emission tomography (PET) scan. In this review we will go through the principles, indications and benefits of employing such techniques in the assessment of response to pre-operative chemoradiotherapy of rectal cancer.

Key words

Rectal cancer, chemoradiotherapy, metabolic response, predictor

Introduction

During the last decade, sequential 18F-fluorodeoxy-glucose positron-emission-tomography (FDG PET) imaging has been increasingly studied to monitor the metabolic response of the tumor to multimodality treatment of rectal cancer[1–12]. In 15–30% of the patients pre-operatively treated with chemoradiotherapy (CRT), complete tumor regression was observed 6–8 weeks after finishing the pre-operative treatment[3-4-12]. Many studies have been published reporting metabolic treatment response of rectal carcinomas using different imaging modalities e.g. dual time PET-imaging, both before and after therapy, which presents a significant reduction of FDG uptake with neo-adjuvant CRT[1-3–7-10-12]. However, in contrast to response evaluations based on PET-imaging before and after treatment, monitoring the tumor response early during pre-operative treatment enables response guided modifications of the treatment protocol on the basis of early changes, possibly strengthened by additional clinical or biological factors. A significant reduction of the FDG uptake within rectal carcinomas was observed already after 2 weeks of pre-operative CRT, with the reduction of the FDG uptake being a good predictor of pathological treatment response[2-8-11].

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Pre-operative CRT in rectal cancer

Pre-operative CRT followed by total mesorectal excision (TME) has been widely adopted for the management of locally advanced rectal cancers because of its ability to increase the probability of anal sphincter preservation

and, more significantly, to decrease the local recurrence rate[13-14]. The use of CRT also enables consideration to be given to unconventional treatment options such as local excision or no surgery in highly selected patients who show a good or complete clinical tumor response[15-17].

Assessment of response to pre-operative CRT

The various means of clinical restaging of rectal cancer after pre-operative CRT include digital rectal examination, rigid sigmoidoscopy, transrectal ultrasonography (TRUS), computed tomography (CT), magnetic resonance imaging (MRI), functional CT and MRI, and positron emission tomography (PET). There is no consensus as to which method is the best for this purpose. At one end of the spectrum, digital rectal examination is a rather subjective but convenient method of determining volume reduction and tumor mobility. Although the milestone in evaluation of therapeutic effect of cancer treatment, current morphological imaging techniques such as CT have limitations in reliably distinguishing necrotic tumor or post-radiation fibrosis from residual viable tumor tissue. At the other end of the spectrum, three-dimensional magnetic resonance (3D MR) volumetry can accurately and objectively determine the actual tumor shape and volume. Besides a lack of agreement on the relationship between the clinical tumor response and the histopathologic tumor response[18-19], 3D MR volumetry has not been sufficiently evaluated in patients undergoing pre-operative CRT to determine whether the 3D MR findings also correlate with the histopathologic response[20].

Perfusion computed tomography (pCT) and dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) are noninvasive clinical imaging techniques that are increasingly applied to assess the micro-vascular status of tumor tissue [21-23]. In clinical cancer research, regression of tumor microvasculature is considered an important early surrogate marker for treatment response, even before reductions in tumor volume become apparent. To date, both pCT and DCE-MRI are increasingly used for the prediction and evaluation of treatment response[24-25], as indicators of tumor angiogenesis[26-27], and sometimes for primary tumor staging[28]. CT scan has the advantage of generally being more easily accessible compared with MRI. Moreover, the majority of patients with solid tumors receive radiotherapy for which CT or PET–CT examinations are applied. Therefore, the use of pCT in the assessment of tumor microcirculation could lead to important logistical advantages.

PET and PET-CT

FDG-PET is a molecular imaging technique that visualizes and quantifies metabolic processes in cancer cells. Currently, FDG–PET has an established role in staging patients with colorectal cancer before surgical resection in cases of metastatic disease[29-31], in the localization of recurrence in patients with an unexplained rise of serum carcinoembryonic antigen (CEA)[32], and in the discrimination of a residual mass after treatment[33]. FDG–PET has a great impact on improving patient management, reduces futile surgery, leads to substantial cost savings and probably also leads to a better patient outcome[34-35].

There is an increasing interest in the role of FDG–PET beyond staging, for prediction of tumor response to treatment[2-5-6-36-38-39]. The positron emitter FDG is transported into cells analogously to glucose and is converted to FDG-6-phosphate. This metabolite is trapped in the cell, as it will not be processed in the glycolytic pathway and hence will accumulate preferentially in those cells with high glucose uptake, such as tumor cells[38]. FDG–PET can not only distinguish active disease from residual fibrotic tissue[33] but also quantify FDG uptake to distinguish metabolically highly active from less active tumor tissues. This last criterion may be used to deliver inhomegnous doses of radiotherapy to the tumor itself, according to its activity using intensity modulated radiotherapy technique (IMRT). Furthermore, metabolic alterations in tumor cells, indicative of tumor response to therapy, may occur early before alterations in tumor size.

The molecular basis of this early response is attributed mainly to the destruction of a kinase enzyme called hexokinase. Hexokinase is an enzyme known to phosphorylate six-carbon

sugars, including FDG, making it unable to move or be transported out of the cell[39]. A reduction of the hexokinase concentration leads to a decreased amount of FDG trapped within the cells resulting in decreased standardized uptake values (SUVs)[39].

The degree of chemotherapy-induced changes in metabolic activity of colorectal tumors was shown to be highly predictive for patient outcome[40]. Such FDG uptake measurements provide a valuable surrogate for the intratumoral bio-distribution of the drug within solid tumors and thereby also for the intratumoral effectiveness. For example, a homogeneous intratumoral bio-distribution of the drug capecitabine is an important prerequisite for its effectiveness as a radiosensitizer of cancer cells[41].

Guillem et al.[46], in a study of 15 patients with rectal cancer treated with pre-operative CRT, compared the ability of FDG PET and CT to estimate tumor response to the neoadjuvant regimen. Evidence of response was detected by FDG PET and CT in 100% and 78% of patients, respectively. PET also accurately estimated the extent of response in 60% of patients, whereas the accuracy of the CT was 22%. In another study, 22 patients with locally advanced rectal cancer were submitted to FDG PET scan before and after CRT. FDG uptake reduction was considered as evidence of tumoral response, and this data was compared with endorectal ultrasound (EUS) and histopathological findings[5]. FDG PET was superior to EUS in evaluating tumor response to CRT. Sensitivity was 100% (vs 33% for EUS), with a specificity of 86% (80% EUS). PET positive and negative predictive values were 93% and 100%, respectively, whereas EUS values were 89% and 33%, respectively[5].

In a prospective study, the value of FDG–PET for this indication was also investigated, by measuring tumor glucose metabolism before and after 2 and 6 months of chemotherapeutic treatment. It showed that there was an increase in the rates of death and progression associated with worse response as assessed by PET on Cox proportional regression analysis (Figure 1). The overall survival and progression free survival analysis showed a significant predictive value at

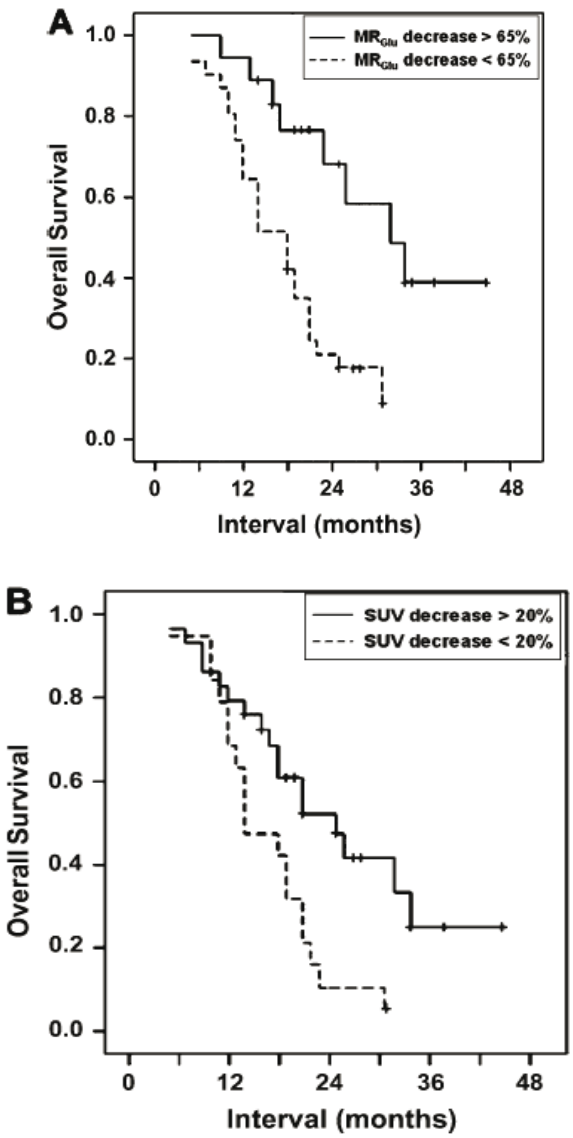

Fig. 1 : Kaplan–Meier estimates for overall survival (OS). Kaplan–Meier analysis of the relationship between OS and (A) Metabolic rate of glucose (MRGlu) between the first and second (FDG–PET) (dichotomized using a cut-off value of 265%, P = 0.009) and (B) Standardized uptake value (SUV) between the first and the second FDG–PET (dichotomized using a cut-off value of 220%, P = 0.021)[5].

broad ranges of SUV cut-off levels. The authors concluded that the degree of chemotherapy-induced changes in tumor glucose metabolism is highly predictive for patient outcome. This means the use of FDG–PET for therapy monitoring seems clinically feasible since simplified methods (SUV) are sufficiently reliable[40].

Another prospective study was initiated to compare early metabolic treatment response in rectal cancer undergoing either concomitant CRT or RT alone during treatment, as there

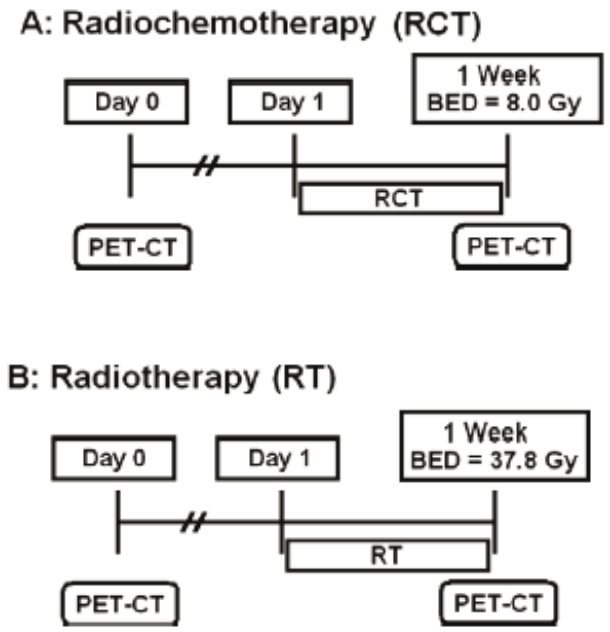

Fig. 2 : PET-CT study scheme for the assessment of the early metabolic treatment response during treatment of rectal cancer. (A) Study scheme for the patients treated with pre-operative CRT. (B) Scheme for the patients treated with only pre-operative short-course hypofractionated (RT)[42]

was a lack of such comparative studies[42]. (Figure 2) In this study Janssen et al showed that for the patients referred for pre-operative CRT, significant reductions of SUVmean ($p < 0.001$) and SUVmax ($p < 0.001$) within the tumor were found already after the first week of treatment (8 Gy biological equivalent dose, (BED). In contrast, 1 week of treatment with RT alone did not result in significant changes in the metabolic activity of the tumor ($p = 0.767$, $p = 0.434$), despite the higher applied RT dose of 38.7 Gy BED. They concluded that the chemotherapeutic agent Capecitabine might be responsible for the early metabolic treatment responses during CRT in rectal cancer (Figure 3 and 4).

A comparative study, investigating the metabolic activity of the tumor early during chemotherapy alone was unfortunately not feasible, because initial chemotherapy alone is not the standard of care. However, earlier clinical studies have already indicated a prognostic significant differences in FDG uptake as early as one to three weeks after the first cycle of

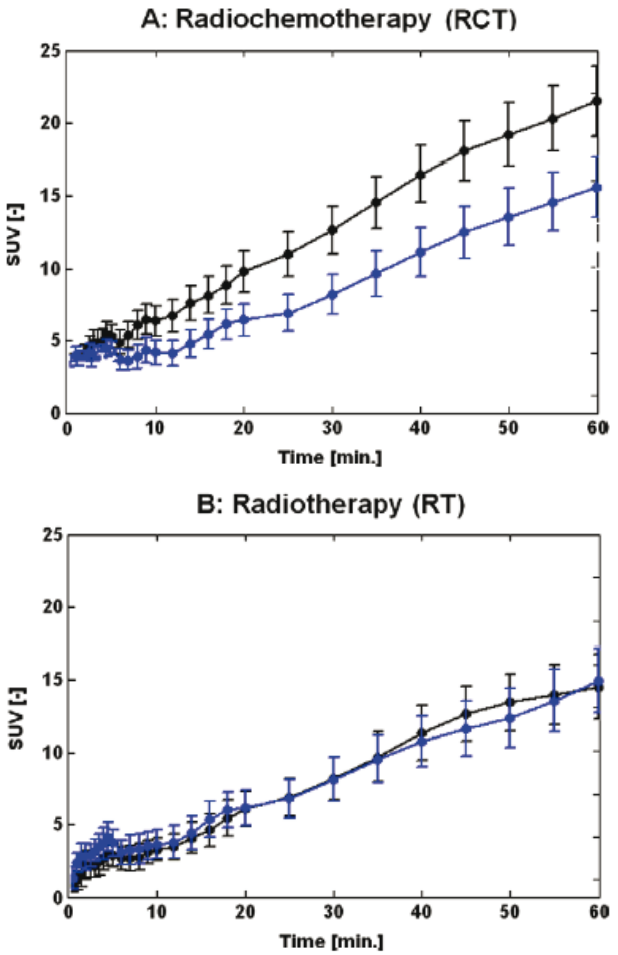

Fig. 3. Mean time-activity-curves (TACs) of the tumor, indicating the amount and rate of FDG uptake over time. (A) Mean TACs at the two imaging time points for the patients treated with CRT, respectively pre-treatment (black) and 1 week (blue) (B) Mean TACs at both time points for the patients treated with short-course RT, respectively pretreatment (black) and after 1 week of treatment (blue), presenting a stable FDG uptake[42].

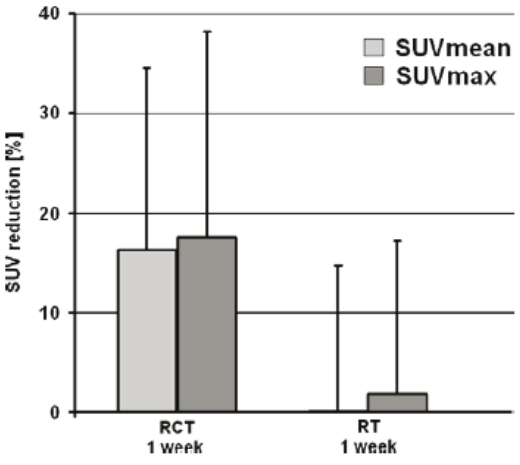

Fig. 4 : Average reductions of both SUVmean and SUVmax within the tumor after 1 week of treatment for the patients treated with respectively CRT and short-course hypofractionated RT[42].

chemotherapy in various cancer types[43-47]. For chemotherapy with 5-FU, a comparable chemotherapeutic drug to capecitabine, a consistent decrease in FDG uptake by 50% was already present as early as 3 days after the start of the chemotherapy[48]. In contrast, chemotherapeutic agents like doxorubicin or paclitaxel increased FDG uptake[48]. Again, the early reduction in FDG uptake under 5-FU treatment might be related to a decreased activity of either the glucose transporter Glut-1 or the phosphorylation enzyme hexokinas[48-50].

Assessment of response to pre-operative chemotherapy in metastatic liver disease

The experience in the assessment of chemotherapy response in metastatic colorectal cancer, however, is limited to four reports in small series of patients with irresectable liver metastases[49-51-53]. Findlay et al.[51] studied 18 patients treated with 5-FU chemotherapy. A correlation was observed between the reduction of tumor metabolism 5 weeks after the initiation of chemotherapy and treatment outcome, which was not observed at 1–2 weeks on treatment. These results show the importance of a correct timing of FDG–PET after the onset of chemotherapy. Bender et al.[52] studied 10 patients with irresectable liver metastases before and 72 hours after a single infusion of 5-FU and folinic acid. SUVs were correlated with therapy outcome, with a follow-up of at least 6 months. More recently, Dimitrakopoulou-Strauss et al.[49-50] examined the ability of serial semiquantitative as well as quantitative dynamic FDG–PET examinations in 28 patients to predict response to second-line FOLFOX (5-FU/folinic acid/ oxaliplatin) at baseline and after the first and second cycle. The authors postulated that quantitative, dynamic FDG–PET should be used preferentially for response monitoring. However, the results of a study, that included almost twice as much patients, showed that semiquantitative analysis is sufficiently reliable[40].

Metabolic response for pre-operative radiotherapy alone

As indicated before, in contrast to chemotherapeutic agents, RT alone on cancer cells does not lead to early changes in its glucose transport or cellular hexokinase activity[41]. Instead, RT induces changes on the cellular cell cycle, the DNA repair and apoptosis, all of which do probably not lead to early changes in the FDG uptake of cancer cells, as seen in a study conducted by Schoder et al[41]. Thus, the metabolic changes in PET images after the first week of CRT in rectal cancer might be more seen as activity changes in the cells ability to incorporate glucose under the influence of the chemotherapeutic drug rather than as RT-induced cytotoxicity.

Another important confounder in the use of PET-imaging is a peritumoral inflammatory reaction, as inflammatory cells are known to avidly consume FDG[11-53]. An increased FDG uptake by inflammatory cells in the direct neighborhood of the tumor can lead to an underestimation of the SUV decrease within the tumor[8-11].

Metabolic response and correlation with pathological and clinical outcomes

Patients who have minimal response to CRT might benefit from alternative therapy, but identifying them in an early phase is a challenge. Based on that, Chessin et al.[54] submitted 21 patients with rectal carcinoma to FDG PET 10–12 days after the first session of CRT and compared this findings with the histopathological specimen. PET identified complete or partial response in 20 of 21 pathologic responders (95%). The authors concluded that PET might allow identification of those patients who would benefit from the proposed scheme.

FDG PET has also been evaluated in its capacity to predict long-term oncologic outcomes in patients with rectal cancer submitted to CRT. Guillem et al.[7] demonstrated that two PET parameters (standard uptake value and total lesion glycolysis) were significant predictors of overall survival and recurrence free survival. Calvo et al.[37], in a similar study, observed that the maximum standardized uptake value correlated with 3-year survival rate.

Future directions

More randomized clinical trials are needed to validate the metabolic response as a surrogate

to pathological response which is established as an indicator of clinical outcome. This will help to take a decision to terminate pre-operative treatment and go directly to surgery. Hence the unpleasant finding of progressive disease after 6 weeks of toxic treatment will be avoided. Also, alteration of the chemotherapeutic agent used in pre-operative setting should be studied. The lack of survival benefits of new agents such as oxaloplatin, irinotecan and targeted therapy in the neoadjuvant setting may be due to their usage in inheritably responsive tumor. Also, high-precision radiotherapy, such as IMRT can be employed to escalate the dose to the non-responding areas of the heterogeneous tumor and saves more normal tissue. All these points can be studied with a benefit of acquiring results early as the end point will be usually the pathological response rate rather than disease-free or over-all survival.

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