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EDITORIAL

Positron emission tomography as predictor of rectal cancer response during or following neoadjuvant chemoradiation

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Abstract

Positron emission tomography (PET) shows great promise as a tool to evaluate the effectiveness of rectal cancer neoadjuvant therapy as it has demonstrated high predictive value in several studies. Creating a standardized method of using PET has the potential to reduce ineffective treatments. However, relevant studies have been heterogenous in approach, making any unified standard difficult to establish. PET related parameters used to assess treatment response include magnitude and change of standard uptake value, total lesion glycolysis, and visual response. Finding the best evaluation interval and parameters to use for interpreting PET results in the neoadjuvant treatment of rectal cancer needs additional study.

Key words: Positron emission tomography; Rectal cancer; Neoadjuvant therapy

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Colorectal cancer was the third most common cancer in 2009 with 75 590 new cases in men and 71 380 new cases in women in the U.S. in spite of the fact that its incidence has been decreasing over recent years. It is also the second leading cause of cancer deaths in United States, and survival at 5 years is around 66%[1]. New chemotherapeutics and improved screening (earlier detection) have contributed to the improving outcomes and survival[2]. With improved detection and treatment, the presence and change of metabolic characteristics prior to, during, and subsequent to local and systemic therapy is of increasing importance in assessing disease status and making management decisions. For this reason, 18F-deoxyglucose (FDG) positron emission tomography (PET) imaging is increasingly used in the staging and management of colorectal cancers.

PET imaging holds great potential value as a diagnostic and management tool. Unfortunately, PET imaging has limitations in terms of image resolution and image noise created by non-malignant metabolic processes such as treatment-related inflammation. While a number of studies support the idea that PET imaging can be predictive of chemoradiation treatment response, the timing of PET imaging as well as the specific image parameters used for interpretation widely differ in the literature. Here we will examine these issues to review PET's role in the clinical management of colorectal cancer, particularly in relation to preoperative radiotherapy and multimodality therapy response evaluation.

The RECIST criteria (response evaluation criteria in solid tumors) have been widely used to characterize tumor response to therapy[3]. These criteria are based on tumor

size change; specifically, tumor response is designated as a decrease in the sum of the largest diameters of target tumor lesions of at least 30%. However, viability of tumor tissues and cellular reproductive integrity are not necessarily associated with changes in tumor size, and the correlation between size response and patient outcome has been shown to be weak. For example, angiogenesis inhibitors may change the micro-environment of the tumor in a manner that does not immediately or dramatically change size, but effectively decreases tumor viability. In such a case, a metabolic imaging tool such as PET may help in early response assessment where other assessment tools may be inadequate. This may prevent additional futile therapy or allow for a timely change to an alternative therapy.

PET is most valuable when interpreted with morphologic imaging such as computed tomography (CT), magnetic resonance imaging (MRI), or ultrasound. PET scans are frequently obtained with a registered CT scan; in this way, both imaging sets can be obtained with the patient in the same position, and image registration makes the combined functional and morphological information of the scans more readily apparent. However, CT scans are obtained within a shorter time period than PET scans, and registration accuracy may suffer[4]. The longer period of image acquisition associated with PET is partly responsible for the modality's lower resolution with time-averaging of normal internal organ motion.

PET's utility in colorectal cancer has already been demonstrated in a number of ways. Pre-hepatectomy assessment is better performed and residual masses are well identified with PET imaging. PET is useful for localizing recurrences in patients with an unexpected rise in carcinoembryonic antigen levels after surgery[5]. There is some indication that therapy can be tailored to patients with PET-based stratification. However, appropriate usage of PET for post-treatment evaluation of neoadjuvant chemotherapy or radiation is still being defined. A number of studies demonstrate that the modality holds promise, although there is nothing that would constitute a clear foundational guideline for PET application to clinical decision making in that setting.

Perhaps one reason a unified guideline for PET interpretation has not been created is that the quantitative analysis of PET imaging can vary widely, with several markers such as standardized uptake value (SUV) max, SUV mean, dTLG (total lesion glycolysis), metabolism rate of glucose, visual response, *etc*. as possible candidates for interpretational dividers. Each discrete marker can also be compared between sequential scans, adding additional parameters that may be best for interpretation. Uptake values are by their nature relative values and depend on the manner of administrating the test. Attenuation and other correction factors are applied to account for institution-specific equipment and circumstances, and this prevents direct comparisons to imaging from other institutions. Because of the nature of correction algorithms, SUV and other values are not fully amenable to absolute comparisons between and within institutions. Additionally, patient metabolism and health history also affect the uptake and vary depending on the circumstances of an individual test's administration.

With the exception of very early tumors that can be managed with local excision, rectal cancers are managed with radical surgery. Despite improvements in surgical technique with total mesorectal excision, local recurrence rates justify multimodality therapy in appropriate patients[6]. Preoperative chemoradiation improves the local control rate, but distinguishing responders from nonresponders can be difficult prior to the post-operative histopathological analysis. However, accurate restaging prior to surgery is important to help determine the optimal surgical strategy. For example, extent, aggressiveness, and sphincter preservation may all be considered in light of the treatment response. Response assessment during neoadjuvant chemoradiation can also allow for tailored therapy using alternative dosing, fractionation, or agents. Because anatomic imaging modalities can't accurately distinguish between viable and non-viable tissue, the functional approach provided by PET imaging is conceptually an appealing alternative.

In a 1992 report on PET's utility in response assessment, Engenhart *et al*[7] reported a significant small decrease in the SUV of tumor following irradiation of nonresectable pre-sacral recurrent rectal carcinomas and suggested that enhanced glucose uptake is associated with recurrent rectal cancer. Conclusions from the report were conservative stating that the characteristics of normal physiological uptake (including proliferation, repair, and inflammation) needed to be further characterized before PET could reliably distinguish them from residual viable tumor and therefore be useful for radiation treatment monitoring. Table 1 summarizes key studies in evaluating rectal cancer treatment response.

Further work has approached response assessment by evaluating other imaging related parameters with mixed results. Siegel *et al*[8] reported that a significant 40% reduction in SUVmax was observed with PET 17 d after starting radiation for locally advanced rectal cancer, but with no correlation between SUVmax reduction and downstaging or other markers. They did conclude, however, that PET can monitor early effects of short course radiotherapy using post-treatment SUVmax as a surrogate marker for treatment response. Similarly, Oku *et al*[9] used post treatment SUV values as a predictive marker, but in this case of long-term prognosis. They found that neither pre-therapy SUV nor the ratio of post and pre-treatment SUVs had prognostic usefulness. There was a significant difference in recurrence correlated with post-therapy SUVmean. Nakagawa *et al*[10] demonstrated a significant survival benefit in patients with low uptake after preoperative radiotherapy in primary tumors of rectal cancer.

Apart from uptake quantification, visual response has also been tested as a predictive marker. Guillem *et al*[11] prospectively studied several parameters in 21 patients receiving pre-operative chemoradiation, including SUVmean,

Table 1 Relevant studies of PET in evaluating rectal cancer treatment response

Study	*n*	Therapy	Timing	Response criteria	Outcome measure	Result	*P*
Engenhart *et al*[7] (1992)	21	RT	8-9 wk pc	ΔSUV	LC	SUV normalization; PPV 20%; NPV 67%	
Schiepers *et al*[14] (1999)	9	RT	2-3 wk pc	TuGluc	Histo, cell kinetics	Decreased 138 nmol/mL per min after RT	0.008
Guillem *et al*[11] (2000)	15	CRT	4-5 wk pc	ΔSUV, VR, δTLG	Histo	VR PPV 60%	
Oku *et al*[9] (2002)	40	RT	3-5 wk pc	SUV	Recurrence	SUV < 3.2	< 0.05
Amthauer *et al*[15] (2004)	20	CRT + H	2-4 wk pc	ΔSUV	Histo	36% decrease SUV PPV 93%; NPV 100%	0.003
Calvo *et al*[16] (2004)	25	CRT	4-5 wk pc	ΔSUV	Histo	2 *vs* 2.7 decrease SUV	NS
Guillem *et al*[17] (2004)	15	CRT	4-5 wk pc	ΔSUV, VR, δTLG	Recurrence, OS, RFS	63% decrease SUV 70% decrease TLG	0.08 0.03
Denecke *et al*[18] (2005)	23	CRT + H	2-4 wk pc	ΔSUV	Histo	36% decrease SUV PPV 77%; NPV 100%	0.002
Konski *et al*[19] (2005)	20	CRT	3-4 wk pc	ΔSUV	Histo	52% *vs* 75% decrease SUV	NS
Cascini *et al*[20] (2006)	33	CRT	12 d pi	ΔSUV	Histo	22% *vs* 63% decrease SUV	< 0.0001
Capirci *et al*[13] (2006)	88	CRT	5-6 wk pc	Negative PET	5 yr OS and DFS	91% *vs* 72% 81% *vs* 62%	0.024 0.003
Kalff *et al*[12] (2006)	34	CRT	7-43 d pc	VR	OS PFS	100% *vs* 79% 100% *vs* 47%	< 0.0001 < 0.0001
Capirci *et al*[21] (2007)	45	CRT	5-6 wk pc	ΔSUV	Histo	66% decrease SUV PPV 77%; NPV 89%	0.0015
Melton *et al*[22] (2007)	21	CRT	4-5 wk pc	ΔSUV, VR, δTLG	Histo	70% decrease SUV PPV 58%; NPV 100%	< 0.001
Kristiansen *et al*[23] (2008)	30	CRT	7 wk pc	VR	Histo	PPV 83%; NPV 33%	NS
Siegel *et al*[8] (2008)	32	RT (short)	7-8 d pi	ΔSUV	Histo	40% decrease SUV	NS
Nakagawa *et al*[10] (2008)	59	RT	2-3 wk pc	SUV	OS MS	SUV < 5: 95 *vs* 42 mo, 70% *vs* 44%	0.042
Vliegen *et al*[24] (2008)	20	CRT	4-6 wk pc	ΔSUV	Histo	83% *vs* 59% decrease SUV	0.025
Janssen *et al*[25] (2009)	30	CRT	2 wk pc	ΔSUV	Histo	43% decrease SUV PPV 91%; NPV 82%	
Konski *et al*[26] (2009)	53	CRT	3-4 wk pc	ΔSUV	Histo	67% *vs* 55% decrease SUV	NS
Rosenberg *et al*[27] (2009)	30	CRT	pc	ΔSUV	Histo	66% *vs* 48% decrease SUV PPV 83%; NPV 64%	0.040

PET: Positron emission tomography; RT: Radiation; CRT: Chemoradiation; CRT + H: Chemoradiation with hyperthermia; pc: Post completion; pi: Post induction; δTLG: Change in total lesion glycolysis; TuGluc: Tumor glucose utilization; VR: Visual response; Histo: Histopathology; LC: Local control; OS: Overall survival; MS: Median survival.

SUVmax, PET-derived tumor size, visual response score, and change in total lesion glycolysis. Visual response score showed the most potential, accurately estimating the extent of pathologic response in 60% of cases compared with 22% of cases with CT[11]. Kalff *et al*[12] graded tumor response as complete, partial, or absent, based on visual assessment. At median follow-up of 3.1 years, all 17 patients with a complete visual metabolic response continued free of disease while 6 of the 10 patients with a partial visual metabolic response were disease free and all 3 nonresponders had died.

In a larger study, Capirci *et al*[13] performed PET on 88 patients 6 wk after the completion of chemoradiation, to assess response. Surgery was performed between 8 and 9 wk after completion of chemoradiation. With a median follow-up after surgery of 38 mo, overall survival was 91% in patients with negative post-treatment PET and 72% in those with a positive PET ($P = 0.024$). Disease-free survival was 81% in patients with negative PET and 62% in those with positive findings ($P = 0.003$). Negative PET was defined as "faint and diffuse uptake" while positive PET was defined as "intense, moderate, or mild focal or diffuse uptake" as determined by visual inspection.

While collectively there is fairly persuasive evidence that PET can successfully indicate clinical response, a review of the literature provides little guidance on how precisely to use PET-derived response information. Retrospective data have shown stronger relationships between PET values and response, although these associations have not been strong in prospective studies. Specific SUVmax or SUVmean cutoff values vary between reports and have been determined retrospectively, tailored to the study population. There has also been a change in the technical format of PET delivery as centers switch to PET/CT machines to improve imaging registration. The change to PET/CT has been accompanied by a change in the attenuation correction algorithms used for PET image production, and this may have caused a shift in the magnitude of PET parameters. Finally, normal tissue uptake can be confusing within the pelvis as bowel lumen, uterine cavity or muscular uptake provide increased noise.

Overall, PET shows great promise as a tool to evaluate the effectiveness of rectal cancer neoadjuvant therapy as it has demonstrated high predictive value in several studies.

However, it is important to note that PET cannot be considered as surrogate for complete pathological response because patients with complete PET response often harbor residual microscopic disease. Therefore, appropriate surgical resection should be done even in patients with a complete PET response. Finding the best evaluation interval and parameters to use for interpreting PET results needs additional study. Creating a standardized method of using PET has the potential to reduce ineffective treatments when patients are not responding as well as modify surgical planning to decrease morbidity for those patients who are.

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