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FDG-PET in colorectal cancer

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Abstract

[^{18}F]Fluorodeoxyglucose (FDG) positron emission tomography (PET) is a useful imaging tool in the evolving management of patients with colorectal carcinoma. This technique is able to measure and visualize metabolic changes in cancer cells. This feature results in the ability to distinguish viable tumor from scar tissue, in the detection of tumor foci at an earlier stage than possible by conventional anatomic imaging and in the measurement of alterations in tumor metabolism, indicative of tumor response to therapy. Nowadays, FDG-PET plays a pivotal role in staging patients before surgical resection of recurrence and metastases, in the localization of recurrence in patients with an unexplained rise in serum carcinoembryonic antigen and in assessment of residual masses after treatment. In the presurgical evaluation, FDG-PET may be best used in conjunction with anatomic imaging in order to combine the benefits of both anatomical (CT) and functional (PET) information, which leads to significant improvements in preoperative liver staging and preoperative judgment on the feasibility of resection. Integration of FDG-PET into the management algorithm of these categories of patients alters and improves therapeutic management, reduces morbidity due to futile surgery, leads to substantial cost savings and probably also to a better patient outcome. FDG-PET also appears to have great potential in monitoring the success of local ablative therapies soon after intervention and in the prediction and evaluation of response to radiotherapy, systemic therapy, and combinations thereof. This review aims to outline the current and future role of FDG-PET in the field of colorectal cancer.

Keywords: *FDG; PET; colorectal cancer; recurrent disease; unexplained CEA rise; liver metastases; unresactable disease; response monitoring.*

Introduction

Colorectal cancer is the second leading cause of cancer-related deaths in the Western world and continues to be a major health problem worldwide. The cumulative lifetime risk is approximately 5%, the incidence in the Western world is 50/100,000 and the 5-year survival rate nowadays is approximately 55%[1]. The prognosis of this disease has improved substantially with the introduction of hepatic resection for treatment of isolated liver involvement and with the introduction of effective chemotherapeutic agents[2–4]. [^{18}F]Fluorodeoxyglucose (FDG) positron emission tomography (PET) is a useful imaging tool in the evolving management of patients with colorectal cancer. FDG-PET localizes tumors by identifying cells in the body that have increased glucose uptake and metabolism. FDG is transported into cells analogous 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. Although the optimal use of FDG-PET in colorectal cancer continues to emerge, this comprehensive review aims to discuss its current and potential future applications in the management of patients with colorectal cancer. The literature is reviewed on the established role of FDG-

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PET in distinguishing fibrosis and scar tissue from viable tumor in residual masses of rectal cancer, localization of recurrence in patients with an unexplained rise in serum carcinoembryonic antigen (CEA), staging before surgical resection of recurrence and/or metastases, and on its emerging role in the prediction and evaluation of treatment response, such as monitoring of radiotherapy and multimodality treatment response in primary rectal cancer, response after local ablative therapy of liver metastases and chemotherapy response in advanced colorectal cancer. FDG-PET in the initial preoperative staging of newly diagnosed colorectal cancer is not discussed, since there is no established role for the systematic use of PET in this part of the management process, due to its poor sensitivity regarding detection of early tumor spread to regional lymph nodes[5].

Detection of recurrent disease

Recurrent rectal cancer in residual masses

Surgery is the key to cure for patients with rectal cancer. In the past, local recurrence rates after conventional surgery averaged 30% and varied considerably between institutions from 15% to 45%[6–8]. Recently, total mesorectal excision with or without preoperative radiotherapy has played a major role in reducing the rates of local recurrence to 5–11%[9–11]. One reason for this is the higher frequency of complete resection of the tumor together with its lymphatic and venous drainage that is achieved by complete removal of the mesorectum[12,13]. During the past decades a broad spectrum of treatment modalities have been examined such as postoperative chemoradiotherapy with different 5-fluorouracil (5FU) based schedules, short-term preoperative radiotherapy (5 G/day in 5 days), prolonged preoperative radiotherapy (alone or in combination with 5FU based regimens or with new drugs), and intraoperative radiotherapy in primary disease, and combinations of drugs in patients with metastatic disease; all aiming at improvement in standards of care, ameliorating quality of life with better local control, fewer complications, and improved survival[14].

After resection of the primary tumor most patients will develop a fibrotic mass in the presacral surgical bed, and external beam radiation therapy causes an inflammatory reaction in the pelvic tissues which induces thickening of the perirectal fascia[15,16]. These changes might complicate the detection of pelvic recurrence with ultrasound, CT or MRI, since these techniques have limited ability to distinguish scar from viable tumor. It appears that FDG-PET does not demonstrate this limitation. The first reports on the clinical application of FDG-PET in colorectal cancer addressed the differentiation between scar tissue and local recurrence in rectal cancer[17,18]. There is evidence that FDG-PET is superior to CT scanning for assessing disease activity. FDG-PET has been noted to have a sensitivity of 84–100% and a specificity of 80–100% in the detection of local recurrence and the accuracy ranges from 74% to 96%[16,19–29]. The required interval for postradiotherapy evaluation with FDG-PET has not been studied systematically. It is, however, generally accepted that FDG activity at 6 months after completion of radiation therapy most likely represents tumor recurrence. Increased FDG uptake immediately after radiotherapy may be due to inflammatory changes and is not always associated with residual tumor[19,30,31]. Approximately 25% of FDG uptake can accumulate in non-tumor tissues such as macrophages, neutrophils, fibroblasts, and granulation tissue[32]. Obviously, a true radiation-induced reduction in glucose utilization occurs due to tumor cell loss[33]. However, a short-lived reversible decrease in glucose metabolism may also occur just after radiotherapy, due to the so-called stunning of tumor cells[34]. This phenomenon can mimic actual cytotoxic therapy effects, although only temporarily. As early as 1991, Haberkorn *et al.* showed that it is not possible to distinguish between proliferation, repair, inflammation, and residual viable tumor cells shortly after radiotherapy. In this study, a significant decrease in FDG uptake was not observed in 50% of patients despite good palliative effects[30]. This was confirmed by another study performed in the same institute, and the authors postulated that FDG-PET evaluation is not reliable within 3 months after radiotherapy[31]. This hypothesis was also supported by a retrospective case-controlled study performed by Moore *et al.*[19]. They reviewed the records of 60 surgically resected rectal cancer patients who underwent FDG-PET at least 6 months after radiotherapy. A sensitivity of 84%, a specificity of 88%, an overall accuracy of 87%, a positive predictive value of 76% and a negative predictive value of 92% were observed for the detection of local recurrence. The positive predictive value and accuracy improved in scans performed more than 12 months after radiotherapy. They postulated that the reliability of FDG-PET improves with time, probably due to resolution of early postradiation inflammation.

Accurate detection of locoregional recurrence may be hindered by a marked distortion of the normal pelvic anatomy[21,25]. After abdominoperineal resection, the empty rectal fossa may result in displacement of other pelvic organs. For instance, the urinary bladder tends to move backwards to a presacral or precoccygeal location. Furthermore, the empty fossa may be occupied by the seminal vesicles, uterus, or the small bowel. This altered pelvic anatomy may influence the interpretation of FDG-PET images, especially in the differentiation between tumoral and physiologic FDG uptake in the gastrointestinal or genitourinary tract. Even-Sapir *et al.*[25] reported that physiologic FDG uptake in displaced pelvic organs was the most common cause for false-positive interpretation of FDG-PET findings. Keogan *et al.*[21] suggested appropriate hydration and prescan voiding, bladder catheterization, and registration of anatomic and

metabolic images as ways to overcome this problem. Therefore, there may be an important role for integrated PET/CT, which combines the benefits of the two imaging modalities and provides the clinician with simultaneous metabolic and anatomic imaging information[25]. Even-Sapir *et al.*[25] studied 62 patients and found presacral CT abnormalities in 30 patients (48%). Of these, seven (23%) abnormalities appeared to be malignant. For detection of malignancy in presacral residual masses with PET/CT, they reported a sensitivity, specificity, positive predictive value, and negative predictive value of 100%, 96%, 88%, and 100%, respectively. In this study PET/CT images also provided information concerning the involvement of pelvic structures, which was clinically relevant in selecting an appropriate surgically approach.

Unexplained carcinoembryonic antigen rise

Although the ideal postoperative follow-up regimen for asymptomatic patients after curative colorectal cancer resection remains undefined, clinicians often use a combination of history, physical examination, imaging, and laboratory tests including measurement of the serum tumor marker carcinoembryonic antigen (CEA)[15]. Elevated serum CEA levels are detected in two-thirds of patients with recurrence of colorectal carcinoma and have been associated with a 3–9-month median lead-time in detection of recurrence over anatomic imaging modalities[5,35–39]. Measurement of serum CEA every 2–3 months for at least 2 years after surgery has been advocated[35,40–42]. Such intensive follow-up after primary curative treatment may detect more cancer relapses that are amenable to curative resection. Two meta-analyses reported that intensive follow-up improves overall survival and reduces absolute mortality by 9–13%[43,44]. Although serum CEA may detect recurrence, it does not identify the site of recurrence. Patients with rising serum CEA levels without detectable disease on morphological imaging pose a clinical challenge. Abnormal serum CEA levels are also observed in a variety of benign conditions, such as liver diseases, bowel diseases, smoking, and renal failure[35]. The problem with false-positive serum CEA elevation is that it may lead to unnecessary imaging or even surgery with associated morbidity. Several studies have demonstrated the value of FDG-PET in patients with rising serum CEA levels and no identifiable lesions on conventional imaging[23,27,45–53]. Fletcher concluded that a serum CEA >10 ng/ml was rarely caused by benign conditions[54]. Liu *et al.*[35] reported that the cumulative survival of patients with an unexplained serum CEA level >25 ng/ml was significantly worse than that of patients with levels <25 ng/ml. They suggested a serum CEA cutoff value of 10 ng/ml as an indication for FDG-PET. An increase in CEA level is also strongly associated with tumor recurrence with a reported specificity of 70–84%. Its sensitivity is approximately 80%, but is not as high for locoregional recurrence and pulmonary metastases as it is for liver metastases[5]. In asymptomatic patients with rising serum CEA levels without abnormal findings of conventional workup, the sensitivity for detection of recurrence with FDG-PET has been reported as 79–100%, specificity as 50–83%, and accuracy as 74–93%[22,35,45–49]. Positive predictive values ranged from 89% to 95% and negative predictive values from 85% to 100%[22,45,47]. In a study of 28 patients with a rising serum CEA, negative imaging and second look laparotomy, the results of FDG-PET and CEA scintigraphy scans (99mTc-labeled arcitumomab) were analyzed as predictors of correct selection of patients for resection[48]. Ninety-four percent of patients had biopsy confirmation of recurrence. Disease was unresectable in 38% of these recurrences. PET correctly predicted unresectable disease in 90% of cases, whereas CEA scintigraphy scan failed to predict any. PET correctly predicted resectable disease in 81% and CEA scintigraphy in only 13%. The impact of FDG-PET on management of patients with a rising serum CEA after primary curative treatment has also been examined[47,55,56]. In a series of 58 patients, 34 (59%) had a management change after FDG-PET, including 18 (31%) who underwent a curative resection and 16 (28%) who were treated with systemic chemotherapy[56]. Similar findings have been reported by Flamen *et al.*[47]. The impact on management in the study of Liu *et al.*[55], however, was even higher (68%). The positive impact of FDG-PET on management decisions in this clinical scenario is evident. FDG-PET is recommended for patients with an otherwise unexplained increase of serum CEA level after primary curative treatment of colorectal carcinoma, provided they are fit to undergo salvage surgery.

Staging of recurrence irrespective of CEA or tumor site

Several studies have described the additional value of FDG-PET imaging over anatomical imaging in recurrent colorectal cancer[20,22,26–28,57–69]. Metabolically active tumors can be detected before a morphologic change is noted on anatomical imaging. Overall, FDG-PET was more accurate compared to CT scanning. A meta-analysis of 11 clinical reports with 577 patients showed an overall sensitivity of 97% and specificity of 76% for FDG-PET detecting recurrent colorectal cancer[63]. In addition, a comprehensive review of the PET literature (2244 FDG-PET studies) has reported a weighted average for FDG-PET sensitivity and specificity of 94% and 87%, respectively, compared with 79% and 73% for CT scanning[70]. Whiteford *et al.*[26] reported that the sensitivity of FDG-PET imaging for detection of mucinous adenocarcinoma (58%, $n = 16$) was significantly lower than for non-mucinous adenocarcinoma (92%, $n = 93$) ($p = 0.005$). They proposed that this lower sensitivity is due to the

relative hypocellularity of these tumors. Similar findings (sensitivity of 41%) have been reported in a subsequent series of 22 patients[71].

Staging before surgical resection of colorectal liver metastases

Liver metastases are the main cause of death in patients with colorectal cancer. Approximately 20% of patients already have liver metastases at the time of detection of the primary tumor, and another 25% will develop metastatic lesions during the following 4 years[5,72]. Without any treatment, the median survival after the detection of liver metastases is approximately 9 months, depending on the extent of the disease at the time of diagnosis[73]. For patients with recurrent disease confined to the liver, resection of the metastases is the treatment of choice and can result in a 5-year survival of more than 40%, depending on the selection criteria for surgery[74–76]. With the exception of lung metastases, the presence of extrahepatic disease, however, typically precludes surgery as does the involvement of major blood vessels or extensive bilobar liver disease, which would either preclude negative resection margins or would result in inadequate hepatic reserve. Therefore preoperative staging should concentrate on careful evaluation of extrahepatic disease and precise delineation of all liver lesions with regard to number and position to vital anatomic structures. This strongly supports the need for more effective preoperative imaging to improve staging in order to avoid futile surgery. Synchronous metastases, multiple metastases or bilobar disease once considered as absolute contra-indications for resection, currently do not preclude resections with curative intent per se[1]. The selection of patients for surgical resection of colorectal liver metastases, however, still poses a significant clinical problem. A significant number of patients (10–25%) considered suitable for surgical resection of liver metastases appear to have unresectable disease identified during laparotomy[72]. Moreover, 60% of patients will develop recurrent tumor after successful hepatic resection within 3 years, indicating that many of the patients must have harbored unrecognized tumor foci either in the liver or in extrahepatic areas at the time of liver resection[72,77,78].

Whole body survey and analysis of metabolic activity, as performed with FDG-PET has emerged as a pivotal diagnostic tool in patients with suspected recurrent disease in the liver and has proven to be an accurate diagnostic technique for determining whether patients are suitable candidates for curative resection. A meta-analysis of Kinkel *et al.* documented the superiority of FDG-PET over ultrasound, CT, and MRI, and showed that FDG-PET might be the most sensitive imaging modality for detection of hepatic metastases of gastrointestinal cancer[58]. A more recent meta-analysis of 61 studies showed a sensitivity of 95% for FDG-PET on a per-patient basis, which was significantly better compared to CT scanning (65%) and magnetic resonance imaging (MRI) (76%)[57]. Very recently, the meta-analysis of Wiering *et al.*[72] showed a pooled sensitivity and specificity of 88% and 96%, respectively, for hepatic disease, and 92% and 95%, respectively, for extrahepatic disease. For CT scanning, the pooled sensitivity and specificity were 83% and 84%, respectively, for hepatic lesions, and 61% and 91%, respectively, for extrahepatic lesions.

FDG-PET as a complementary staging method has been shown to significantly alter and improve therapeutic management in 14–65% of patients with colorectal liver metastases, especially by detecting unsuspected extrahepatic disease in 13–36%[16,20,22,23,28,45,52,53,59–61,78–86]. A prospective study by Ruers *et al.*[78] demonstrated a change in clinical management in 20% of patients (10 out of 51 patients) being evaluated as candidates for resection of colorectal liver metastases, especially by detecting unsuspected extrahepatic disease. In a another prospective study of 102 patients with suspected or confirmed regional recurrence of colorectal cancer, FDG-PET influenced management decisions in 59% of cases. The high impact on treatment planning in this study was also predominantly due to avoiding surgery in patients with widespread disease[27]. Huebner *et al.* reported in a meta-analysis that the pooled change-in-management was calculated at 29% (95% confidence level, 25–34%)[63]. The pooled change in-management in the meta-analysis of Wiering *et al.* was 32% (range 20–58%)[72]. A comprehensive review of the PET literature has reported a weighted average change of management related to FDG-PET findings in 32% of 915 patients[70]. The results of these numerous studies brought about a broad consensus that FDG-PET has a clear role in the re-staging of recurrent colorectal cancer.

Although survival is not an endpoint for a diagnostic test, Strasberg *et al.*[87] estimated the survival of patients who underwent FDG-PET imaging in their preoperative evaluation for resection of hepatic metastases. The Kaplan–Meier estimate at 3 years was 77% for overall survival and 40% for disease-free survival. Both percentages were higher than those previously reported[88]. Fernandez *et al.* showed that FDG-PET imaging prior to surgical resection improved the 5-year survival rate compared to historical controls[89]. This improvement in survival is certainly mainly due to the so-called Will Rogers phenomenon or the phenomenon of stage migration due to more careful staging of cancer[90].

Although FDG-PET provides highly relevant information for patient management, it does not substitute the excellent anatomical imaging provided by spiral CT scanning. CT scanning provides the detailed anatomic information that is required for an optimal planning of hepatic resection. Resectability of liver metastases is generally determined by the extent of liver involvement and the specific relation of metastases to anatomic

structures, such as the hepatic veins and the biliary tract[1]. Thus, in patients with suspected hepatic metastases from colorectal cancer, FDG-PET may be best used in conjunction with anatomic imaging. Integrated PET/CT modalities, that combine the benefits of both anatomical (CT) and functional (PET) information and allow optimal coregistration of images, may lead to a significant improvement of preoperative liver staging and preoperative judgment on the feasibility of resection[91]. A study of 45 patients[92] reported that PET/CT imaging increases the accuracy and certainty of locating lesions. The frequency of equivocal and probable lesion characterization was reduced by 50% with PET/CT compared with PET alone, the number of definite locations was increased by 25%, and the overall correct staging increased from 78% to 89%.

These advances in imaging technologies bring another challenge to physicians at times when it is also important to provide care at an acceptable cost. Increasing cost-effectiveness and decreasing the number of invasive procedures are currently two of the major trends in health care. Including FDG-PET in the evaluation of patients with recurrent colorectal carcinoma has been shown to be cost-effective in a study using clinical evaluation of effectiveness with modeling of costs and studies using decision tree sensitivity analysis[22,93–95]. Zubeldia *et al.*[94] found an average expected surgical cost per patient of $16,278 when FDG-PET was used, compared to $21,547 for conventional management, a net saving of $5269. In a prospective study involving 115 patients who underwent CT and FDG-PET scanning for diagnosis or staging of recurrent colorectal carcinoma Valk *et al.*[22] found per-patient savings of $3003. Their smaller cost reductions may be explained by the inclusion of pelvic ($12,916) and lung ($15,508) resection in addition to hepatic resection ($20,668). The analysis of Zubeldia considered only hepatic resection[94]. So, integration of FDG-PET into the presurgical evaluation of patients with potential resectable hepatic metastases alters and improves therapeutic management, reduces morbidity due to futile surgery, leads to substantial cost savings and probably also to a better patient outcome. Randomized, controlled clinical trials should be performed to confirm the actual impact of FDG-PET on overall survival, in order to further strengthen the role of FDG-PET in the management of colorectal liver metastases.

Prediction and evaluation of treatment response

The current definition of tumor response is based on the measurement of changes in tumor size as determined with morphological imaging methods. According to the response evaluation criteria in solid tumors (RECIST) criteria a tumor is classified as responding when the largest diameter of the tumor decreases by at least 30%[96]. Despite the widely accepted practice of using these criteria, it is important to realize that a 30% decrease of tumor size is an arbitrary convention, and is not based on outcome studies. In fact, the correlation between morphologic tumor response and patient outcome is rather weak[97]. Moreover, morphological imaging techniques have limitations in assessing the therapeutic effect, since changes in tumor size lag behind the biologic response to therapy, which is considered a problem in early response monitoring. Besides, residual non-tumoral masses may persist, despite the fact that disease activity may have completely resolved after successful therapy. Furthermore, the introduction of molecular-targeted agents such as the angiogenesis inhibitor bevacizumab, requires new surrogate end points for monitoring therapeutic effects since they have different biological effects compared to classic cytotoxic chemotherapy. These new agents inhibit the growth of new blood vessels in cancer tissue, which does not immediately result in dissolution of tumor masses, and thus poses new demands on imaging modalities. When anticancer therapy becomes more individualized, it is increasingly important to identify response to therapy as early as possible. Early identification of non-responders may allow physicians to spare these patients the morbidity (and costs) of systemic treatment. Several studies performed on tumors other than colorectal carcinoma have already confirmed the hypothesis that changes in tumor glucose metabolism early in the course of treatment predict therapy outcome and long-term prognosis[98–102]. So far, in colorectal carcinoma only studies in small series of patients have been performed, and the interval between onset of antitumor therapy and FDG-PET evaluation, as well as the method of quantification differ per study. The optimal method for quantification has not yet been defined and the threshold set for response depends on multiple variables such as tumor type, type of therapy and interval after onset of therapy. Therefore, further studies are needed before definite conclusions can be drawn. This section reviews the currently available literature on radiotherapy and/or chemotherapy response monitoring in colorectal carcinoma.

Preoperative multimodality and radiotherapy treatment response evaluation in primary rectal cancer

In rectal cancer, preoperative chemoradiotherapy is used in advanced T3 and T4 tumors in the attempt to downstage the disease, in order to reduce the risk of local recurrence and to allow sphincter preserving tumor resection in selected cases[103,104]. FDG-PET may have a role in preoperative multimodality treatment response evaluation and in a preoperative strategy aimed at identifying patients most suitable for sphincter preserving surgery.

Amthauer *et al.*[34] performed FDG-PET and endorectal ultrasound in 20 consecutive patients with locally advanced primary rectal cancer before and 2–4 weeks after completion of neoadjuvant chemoradiotherapy in combination with regional hyperthermia. Reduction in tumor standardized uptake value (SUV) was significantly greater in (histopathologically confirmed) responders compared to non-responders. Using a minimum posttherapeutic SUV reduction of 36% to define response, FDG-PET revealed a sensitivity of 100% and a specificity of 86%. The corresponding positive and negative predictive values were 93% and 100%, respectively, which was significantly better than for endorectal ultrasound. In a similar study performed in the same institute, 23 patients underwent FDG-PET, as well as CT scanning and MRI[105]. The results suggested that FDG-PET was also superior to both CT and MRI. Guillem *et al.*[106] assessed the response in primary rectal cancer to preoperative radiation and 5-FU-based chemotherapy in 15 patients. FDG-PET was obtained before and at 4–5 weeks after completion of chemoradiotherapy. All patients demonstrated a pathologic response, which was predicted in 100% of cases by PET, compared with 78% by CT. They also demonstrated that estimation of rectal cancer response to preoperative chemoradiotherapy by FDG-PET predicts long-term clinical outcome, a finding that has recently been corroborated by others[107,108]. It is striking that the confounding radiotherapy-induced effects, as discussed earlier, have less impact on the results of FDG-PET if it is combined with chemotherapy and/or regional hyperthermia. This implies that the nature of the combination of treatment modalities for neoadjuvant therapy is important in the timing of FDG-PET evaluation. Further studies are required to ascertain the exact sequence of time-dependent (radio)biological effects during neoadjuvant multimodality treatment.

For induction radiotherapy alone, it has not yet been sufficiently investigated whether FDG-PET could play a role in the preoperative radiotherapy response assessment of primary rectal cancer. The generally accepted interval of at least 6 months for FDG-PET evaluation after adjuvant radiotherapy is not applicable in a neoadjuvant setting. Probably due to these expected confounding radiotherapy-induced effects on FDG uptake only one study on this subject has been performed. This study of Schiepers *et al.*[33] investigated nine patients with rectal cancer before and 2–3 weeks after radiotherapy. They observed an overall decrease of glucose utilization with a reduction in SUV after neoadjuvant treatment of 65% in comparison to the pretherapy value, which correlated to reduction of tumor burden and cell death. The authors concluded that they could discriminate as early as 2 weeks after radiotherapy between successfully and unsuccessfully treated tumors with an accuracy of 80%. These surprising results call for systematic investigation of the required interval for postradiotherapy evaluation with FDG-PET.

Monitoring response after local ablative therapy of liver metastases

For patients with colorectal liver metastases surgical resection offers the best chances for cure. In most patients with colorectal liver metastases, however, resection cannot be performed. When this is caused by the number and/or localization of metastases, local ablative techniques such as cryosurgery or radiofrequency ablation may offer an alternative treatment that produces localized intrahepatic tumor destruction and possibly results in a prolongation of survival. A prospective randomized trial on the impact of radiofrequency ablation versus chemotherapy (CLOCC) is on-going.

Different morphological imaging techniques have been used to facilitate the intraoperative localization. However, during the process of local ablation the destruction process cannot easily be ascertained with intraoperative ultrasound imaging because of the hyperechogenicity that is induced within the treated area[109]. Furthermore, evaluation with CT scanning or MRI of residual tumor after the ablation procedure is limited because posttreatment hyperemia or tissue regeneration may result in contrast enhancement in the periphery of the ablative necrosis[110]. This can lead to either a delayed diagnosis of treatment failure or to confusion between incomplete local ablative treatment and the occurrence of new metastases in regions adjacent to the treatment site. Several studies described the feasibility of FDG-PET scanning in the surveillance of these patients[55,111–113]. It appears to have great potential in identifying residual tumor soon after local ablative treatments. In a prospective study of 23 patients with a mean follow-up of 16 months, Langenhoff *et al.*[111] showed that FDG-PET has a positive predictive value of 80% (4/5 lesions) and a negative predictive value for the detection of local treatment failure of 100% (51/51 lesions) when performed less than 3 weeks after the ablative procedure. There was one false-positive FDG-PET caused by abscess formation in a lesion treated with radiofrequency. In all patients the time point of detection of recurrence by FDG-PET was considerably earlier compared to the detection by CT scanning. Donckier *et al.*[113] reported on the value of FDG-PET performed at 1 and 4 weeks after local ablative treatment. Residual hypermetabolism in the periphery of ablated sites detected by FDG-PET correlated well with incomplete tumor destruction in 4/28 lesions. CT imaging performed at the same time failed to demonstrate residual hypervascularized lesions in these patients. After a median follow-up of 11 months, none of the 24 FDG-PET negative postablative lesions had developed a local recurrence. A more recent study[112] performed in 43 patients with 104 ablated lesions, CT scanning after treatment did not predict local treatment failure, whereas FDG-PET within 3 weeks after local ablative treatment

predicted 6/7 local recurrences. One local recurrence was detected on FDG-PET 3 months after treatment. The negative predictive value of FDG-PET at 3 months was 100%. Since FDG-PET showed one false positive result due to focal infection, the positive predictive value was 88%. The data presented here indicate that FDG-PET could play a central role in optimizing the use of local ablative treatment of liver metastases as it recognizes early incomplete tumor ablation that is not detectable by CT scanning. FDG-PET determines the need for further investigations and guides the reading of the CT scan, which on its own appears difficult to interpret in the early period after local ablative therapy. The combined information of FDG-PET and CT scans offers the opportunity to re-treat tumors at an early stage.

Chemotherapy response monitoring in advanced colorectal cancer

There are four reports suggesting that FDG-PET can predict response to chemotherapy in patients with irresectable colorectal cancer liver metastases. Findlay *et al.*[114] studied 18 patients on 5-FU chemotherapy before and at 1–2 and 4–5 weeks. Responding lesions had a greater reduction in FDG uptake compared to the baseline value than non-responding lesions (−33% vs. −1%). The 4–5-week tumor-to-liver ratio was able to discriminate response from non-response in both a lesion-by-lesion assessment as well as in an overall patient response assessment with a sensitivity of 100% and specificities of 90% and 75%, respectively. A clear 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. The authors mention the so-called flare phenomenon that occurs 1–2 weeks after the initiation of chemotherapy, which can be observed as a marked increase in FDG metabolism in lesions that show a response later on. Bender *et al.*[115] studied 10 patients with irresectable liver metastases prior to and 72 h 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. All metastases responding to therapy ($n = 6$) exerted a statistically significant decrease of FDG uptake ($-22 \pm 10\%$). Metastases showing a short-term effect (duration of tumor reduction <3 months, $n = 2$) had a slightly diminished FDG uptake, and in progressing metastases ($n = 3$) an enhanced FDG uptake ($13 \pm 17\%$) was observed. Probably the flare phenomenon does not play a role as early as 72 h after initiation of chemotherapy. These preliminary data indicate that acute changes of glucose utilization following a single application of chemotherapy seem to be indicative for the final therapeutic outcome. More recently, Dimitrakopoulou-Strauss *et al.*[116] 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, and oxaliplatin) at baseline and after the first and second cycle. The clinical response data, according to the WHO classification, served as a standard of reference. Even the first PET study (at baseline) was predictive with respect to therapy outcome. The so-called fractal dimension, a parameter that can be obtained from kinetic analysis and may help to quantify tumor heterogeneity, showed the best results and classified progressive disease correctly in 90% of cases and stable disease in 75% of cases at baseline. Furthermore, metastases with a baseline SUV lower than 4.6 did not respond to chemotherapy. The authors postulate that tumors with a low FDG uptake often reveal an enhanced expression of resistance genes. A low FDG uptake, particularly in pretreated patients, may reflect an enhanced resistance to chemotherapeutic drugs and is therefore associated with a poor outcome of chemotherapy. In another study with 25 patients of similar characteristics Dimitrakopoulou-Strauss *et al.*[117] examined the ability of serial FDG-PET to predict chemotherapy response as reflected by individual survival times. In this study, scans were performed before initiation of therapy and after the first and third cycle. They showed that a combination of kinetic parameters of the first and the third scan provided the best results for classification into a short or long term survival class (defined as survival for less than 1 year or more than 1 year, respectively) and that even an individual prognosis of survival could be achieved. The authors feel that quantitative, dynamic FDG-PET should be used preferentially for chemotherapy response monitoring.

Conclusions

FDG-PET plays a pivotal role in the detection of recurrent disease, the assessment of residual masses after treatment, the localization of recurrence in patients with an unexplained rise of serum CEA, and in staging patients before surgical resection of local recurrence and metastatic disease.

FDG-PET is emerging as a potentially valuable technique in the prediction and evaluation of response to radiotherapy, systemic therapy, and combinations thereof. Correlation between changes in FDG uptake and overall patient survival remains a very worthwhile avenue of research to pursue. The preliminary findings call for systematic inclusion of FDG-PET in therapeutic trials to adequately position FDG-PET in treatment time lines in order to change current therapeutic concepts to individualized treatment of patients with advanced colorectal cancer.

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