Review Article

The Role of $^{18}$F-FDG-PET and PET/CT in Patients with Colorectal Liver Metastases Undergoing Selective Internal Radiation Therapy with Yttrium-90: A First Evidence-Based Review

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1. Introduction

Liver is the most frequent site of metastases in patients with colorectal cancer [1]. In the past, only 10% of patients with CRLM were eligible to surgery. New chemotherapy schemes and improvement in surgical techniques allow to treat surgically patients with CRLM in advanced stages of illness [1]. Radioembolization (RE) using yttrium-90 ($^{90}$Y) resin or glass microspheres, also known as selective internal radiation therapy (SIRT), is a palliative treatment [2] which reduces the liver tumour mass, eventually permitting surgical resection.

Clinical evaluation of patients with CRLM needs many different diagnostic tools. Morphological imaging procedures like computed tomography (CT), contrast enhanced CT (CECT), and magnetic resonance imaging (MRI) are useful techniques in staging and treatment evaluation of patients with CRLM, referring to the Response Evaluation Criteria In Solid Tumours (RECIST) [3]. Angiography allows the evaluation of vascular anatomy of the liver before SIRT. Single-photon emission computed tomography (SPECT) with Technetium $^{99m}$Tc albumin aggregated ($^{99m}$Tc-MAA) is used to calculate hepatic shunts to other organs (as lungs) before or after SIRT [4].

Fluorine-18-fluorodeoxyglucose positron emission tomography and positron emission tomography/computed tomography (FDG-PET and PET/CT) are noninvasive functional imaging techniques which have become well established tools in an oncology setting [5]. FDG is a glucose analogue that identifies areas of high-glucose metabolism. Recently published PET response criteria (PERCIST) assessed the usefulness of FDG-PET and PET/CT in treatment evaluation of cancer patients [6].
Until now, several studies have shown the potential role of whole-body FDG-PET or PET/CT in patients with CRLM undergoing SIRT [7–25]. Therefore, the aim of our evidence-based paper is to provide a first evidence-based review of the literature on this topic to confirm known evidence data and to eventually investigate new emerging roles of FDG-PET or PET/CT in patients with CRLM undergoing SIRT.

2. Methods

2.1. Search Strategy. A comprehensive computer literature search of the PubMed/MEDLINE, Scopus, and Embase databases was conducted to find relevant published articles on whole-body FDG-PET or PET/CT in patients with CRLM undergoing SIRT with $^{90}$Y microspheres.

We used a search algorithm that was based on a combination of the terms (a) “SIRT” or “radioembolization” or “yttrium” and (b) “positron emission tomography” or “PET.” No beginning date limit was used; the search was updated until June 18, 2013. To expand our search, references of the retrieved articles were also screened for additional studies.

2.2. Study Selection. Studies or subsets in studies investigating the role of whole-body FDG-PET or PET/CT in patients with CRLM undergoing SIRT with $^{90}$Y were eligible for inclusion. Review articles, editorials or letters, comments, conference proceedings, case reports, and preclinical studies were excluded from this review.

Only those studies or subsets in studies that satisfied all of the following criteria were included: (a) FDG-PET and SIRT with $^{90}$Y performed in patients with CRLM, (b) sample size of at least ten patients with CRLM, and (c) only patients with histologically confirmed CRLM.

The exclusion criteria were (a) FDG-PET or SIRT with $^{90}$Y not performed in patients with CRLM, (b) sample size of less than ten patients with CRLM, and (c) studies with no histologically confirmed CRLM. The studies including patients with both liver metastases from colon-rectum cancer and different primary tumours (or with primary liver cancer) were excluded from this review, if data about CRLM could not be retrieved, to avoid bias in the literature data discussion.

Two researchers (S. Annunziata and G. Treglia) independently reviewed titles and abstracts of the retrieved articles, applying the inclusion and exclusion criteria mentioned above. Articles were rejected if they were clearly ineligible. The same two researchers then independently reviewed the full-text versions of the remaining articles to determine their eligibility for inclusion. Disagreements were resolved in a consensus meeting.

2.3. Data Abstraction. For each included study, information was collected concerning basic study (authors, journal, year of publication, country of origin, and type of study), patient characteristics (number of patients with MLT treated with SIRT, sex, mean age, and number of patients performing PET), and technical aspects (PET device, PET tracers, injected FDG activity, acquisition time, type of image analysis, $^{90}$Y device, and injected $^{90}$Y activity). Finally, the main findings of the articles included in this review have been reported and discussed.

3. Results

The comprehensive computer literature search from the PubMed/MEDLINE, Embase, and Scopus databases revealed 268 articles.

Nineteen articles comprising a total sample size of 833 patients with liver metastases were selected applying the inclusion criteria mentioned above [7–25]. Twenty studies involved patients with CRLM and patients with metastases from different primary tumours (or with primary liver cancer); thus they were excluded from this review [26–45].

The 19 included studies were retrieved in their full-text version and included in this review. No additional studies were found after screening the references (Figure 1). The basic and technical characteristics of the studies included are shown in Tables 1 and 2.

3.1. Role of FDG-PET and PET/CT in Treatment Planning of Patients with CRLM Undergoing SIRT. FDG-PET or PET/CT may be used to stage patients with CRLM [46]. Until now, the role of these diagnostic tools in treatment planning of patients with CRLM undergoing SIRT is controversial [11, 12, 19, 23].

About the use of FDG-PET or PET/CT before SIRT, Denecke et al. [11] evaluated a standardized diagnostic approach using different radiological and nuclear medicine imaging procedures. All patients initially underwent chest and abdominal CT. Patients in whom CT revealed no contraindications against RE entered the next diagnostic step, which consisted of MRI of the liver and FDG-PET or PET-CT. This sequential diagnostic algorithm allowed an appropriate patient selection for RE of CRLM and reduced the number of unnecessary examinations and treatments. A recent study [23] included a total of 42 patients planned for SIRT. Patients who underwent both CT and FDG-PET in the diagnostic workup were selected. Findings on CT and FDG-PET matched in 20 patients. In 4 patients, lesions detected on CT were not FDG-avid, and in 18 patients FDG-PET showed significantly more lesions than CT. The same study [23] assessed the value of FDG-PET for preprocedural workup of patients with CRLM referred for RE and found that the use of FDG-PET changed patients’ management in 7 out of 42 patients (17%). Six patients were not treated with RE because of extensive extrahepatic lesions that were only detected with FDG-PET. In one patient, abdominal CT had shown only one liver lesion that would have been treated with SIRT if it had not been for FDG-PET imaging which showed a second lesion in another segment.

In two recent studies FDG-PET or PET/CT was firstly used to validate other triage methods of patients planned for SIRT (as different formula of absorbed dose [12] or $^{90}$Y-PET imaging [19]). An American study group [12] evaluated a patient-specific SPECT-based method of dose calculation for treatment planning of SIRT. Absorbed dose to tumour and normal liver tissue was calculated by partition methods with two different tumour/normal liver vascularity ratios:
268 records identified through database using the terms ("SIRT" or "radioembolization" or "yttrium") and ("positron emission tomography" or "PET"))

268 records screened

229 records excluded (reviews, editorial or letters; case report or case series; no direct link with the main subject)

20 articles excluded due to different primary tumors in the same study

19 full-text articles assessed for eligibility

No additional records identified screening the references

19 studies included in the review

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**Figure 1:** Flow chart of the search for eligible studies on the role of F-FDG-PET or PET/CT in patients with CRLM undergoing SIRT.

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268 records screened

229 records excluded (reviews, editorial or letters; case report or case series; no direct link with the main subject)

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3.2. Role of FDG-PET and PET/CT in Treatment Evaluation of Patients with CRLM Treated with SIRT. Six studies included in this review analysed the role of FDG-PET and PET/CT in treatment evaluation of patients with CRLM treated with SIRT [7–10, 13, 14].

Firstly, FDG-PET or PET/CT was included in a diagnostic algorithm to evaluate feasibility, safety, and tumour response of patients with CRLM undergoing SIRT. These outcomes were investigated in glass microspheres labelled with $^{90}$Y [7, 8] and in different countries (as USA [9, 14] and Europe [10, 13]).

Recently, six studies mainly analysed the diagnostic performance of FDG-PET or PET/CT in treatment evaluation of patients with CRLM treated with SIRT [7–9, 13, 14, 22]. Several studies have shown that FDG-PET/CT imaging in liver metastases from different primary tumours performs better than anatomical imaging in evaluating the early tumour response to SIRT [25]. Wong et al. [7] assessed the feasibility of using FDG-PET for quantifying metabolic response of SIRT for CRLM by comparing visual estimates with hepatic lesion standardized uptake values (SUVs). SUVs of the entire axial slices of liver agree well with subjective visual evaluations, so quantitative FDG-PET is a useful technique in the treatment response evaluation of these patients.

Lewandowski et al. [8] treated 27 patients with unresectable CRLM at a targeted absorbed dose of 135–150 Gy. Tumor response measured by FDG-PET imaging exceeded that measured by CT imaging for the first (88% versus 35%) and second (73% versus 36%) treated lobes. Another group [14] performed a baseline CT scan within 4 weeks of treatment. Baseline FDG-PET imaging was encouraged but not mandatory. Improvement was noted in 30 of 39 patients (77%) who had pretreatment and posttreatment FDG-PET studies available. Kennedy et al. [9] performed salvage SIRT for
Table 1: Basic characteristics of the included papers.

| Authors                | Year | Country | Type of study | Number of patients planned for SIRT | Sex (% male) | Mean age (years) | Number of patients undergoing PET |
|------------------------|------|---------|---------------|------------------------------------|-------------|-----------------|----------------------------------|
| Wong et al. [7]         | 2004 | USA     | Prospective   | 27                                 | 56%         | 68              | 27                               |
| Lewandowski et al. [8]  | 2005 | USA     | NR            | 27                                 | 56%         | 68              | 27                               |
| Kennedy et al. [9]      | 2006 | USA     | Retrospective | 208                                | 62%         | 62              | NR                               |
| Mancini et al. [10]     | 2006 | Italy   | Prospective   | 48                                 | NR          | Range 18–75     | NR                               |
| Denecke et al. [11]     | 2008 | Germany | Prospective   | 22                                 | 68%         | 58              | 18                               |
| Campbell et al. [12]    | 2009 | USA     | Retrospective | 12                                 | 58%         | Range 40–69     | 12                               |
| Cianni et al. [13]      | 2009 | Italy   | Retrospective | 41                                 | 73%         | 61              | NR                               |
| Mulcahy et al. [14]     | 2009 | USA     | Prospective   | 72                                 | 65%         | 61              | 39                               |
| Wong et al. [15]        | 2010 | USA     | Retrospective | 48                                 | 58%         | 62              | 48                               |
| Tochetto et al. [16]    | 2010 | USA     | Retrospective | 28                                 | 64%         | 62              | 28                               |
| Gulec et al. [17]       | 2011 | USA     | Prospective   | 20                                 | 65%         | 61              | 20                               |
| Gulec et al. [18]       | 2013 | USA     | Prospective   | 20                                 | 65%         | 61              | 20                               |
| Bagni et al. [19]       | 2012 | Italy   | NR            | 10                                 | 60%         | 63              | 10                               |
| Schonewolf et al. [20]  | 2012 | USA     | Retrospective | 30                                 | 60%         | 61              | 30                               |
| Tochetto et al. [21]    | 2012 | USA     | Retrospective | 38                                 | 65%         | 65              | 20                               |
| Zerizer et al. [22]     | 2012 | UK      | Retrospective | 25                                 | 56%         | 59              | 25                               |
| Rosenbaum et al. [23]   | 2013 | Netherlands | Retrospective | 42                                 | 57%         | 59              | 42                               |
| Fendler et al. [24]     | 2013 | Germany | Prospective   | 80                                 | 73%         | 61              | 80                               |
| Soyda et al. [25]       | 2013 | Turkey  | NR            | 35                                 | 57%         | 62              | NR                               |

NR: not reported.

patients with unresectable CRLM that were refractory to oxaliplatin and irinotecan. A total of 208 patients were treated from April 2002 to April 2005. CT partial response was 35% and FDG-PET response was 91%. An Italian group [13] evaluated the effectiveness of CRLM RE with $^{90}$Y. A CT scan and a FDG-PET were performed to assess liver disease and to evaluate extrahepatic metastatic disease. According to RECIST, a complete response was observed in 2 patients, a partial response in 17 patients, stable disease in 14 patients, and progressive disease in 8 patients. Zerizer et al. [22] evaluated the ability of FDG-PET/CT imaging to predict early response to $^{90}$Y-RE in comparison with CECT using RECIST and lesion density criteria. The patients response to treatment were categorized using PET criteria, tumour density criteria, and RECIST. Early response assessment to $^{90}$Y-RE using FDG-PET/CT was superior to RECIST and tumour density.

In two different studies [16, 21], Tochetto et al. concluded that changes in CT attenuation of CRLM treated with $^{90}$Y-RE correlated highly with metabolic activity at FDG-PET and might be useful as an early surrogate marker for assessing treatment response. In the first study [16], for an attenuation reduction level of 15% or greater, attenuation showed 84% sensitivity and 83% specificity in predicting response at FDG-PET evaluation. In the second study [21], a similar strong association was found between FDG-PET response at 3 months and response based on attenuation criteria.

In another study [18], FDG-PET/CT was used to analyse patients treated with SIRT, in combination with contemporary systemic chemotherapy. Systemic chemotherapy was supplied to both liver lobes, whereas SIRT was administered selectively to the target liver lobe only. Response to treatment was evaluated by serial FDG-PET/CT performed at 4 weeks, 2 to 4 months, and 6 to 8 months. The chemo-SIRT combination produced greater objective responses as compared with chemo-only therapy in a front-line treatment in patients with CRLM.

Finally, in the past FDG-PET and PET/CT helped to assess that SIRT is a safe and feasible treatment for patients with CRLM. Recent studies confirmed that FDG-PET and PET/CT are useful to evaluate treatment response in these patients, in both early and long-term follow-up.

3.3. Prognostic Value of FDG-PET/CT in Patients with CRLM Undergoing SIRT. Five recent studies mainly focused on the prognostic value of FDG-PET/CT in patients with CRLM treated with SIRT [15, 17, 20, 22, 24].

In 2011 Gulec et al. [17] investigated the relationship between functional tumour volume (FTV), total lesion glycolysis (TLG), and clinical outcomes. FTV and TLG seemed to be predictive of clinical outcomes and useful criteria for patient selection and disease prognostication. In a recent study, authors of [25] evaluated tumour response using FDG-PET/CT in similar patients. Calculation of SUV, FTV, and TLG before and at the sixth week after SIRT seemed to play an important role in evaluating early tumour response and survival expectancy in these patients and to decide whether these patients should be referred to other treatment modalities or to follow-up. Another study [15] analysed 48 patients with
Table 2: Technical characteristics of the included papers.

| Authors                | Year | PET device | PET or PET/CT | FDG mean injected activity (MBq) | Time between injection and acquisition (min) | PET image analysis | ⁹⁰Y-SIRT device | ⁹⁰Y mean injected activity (GBq) |
|------------------------|------|------------|---------------|----------------------------------|-----------------------------------------------|-------------------|-----------------|-------------------------------|
| Wong et al. [7]        | 2004 | PET        |               | 370                              | 60                                           | Visual and semiquantitative | Glass microspheres | LM formula               |
| Lewandowski et al. [8]| 2005 | PET        |               | 370                              | 60                                           | Visual                     | Glass microspheres | 2.37                        |
| Kennedy et al. [9]    | 2006 | PET        |               | NR                               | NR                                           | Visual                     | Resin microspheres | 1.75                        |
| Mancini et al. [10]   | 2006 | PET        |               | NR                               | NR                                           | Visual                     | Resin microspheres | BSA method               |
| Denecke et al. [11]   | 2008 | PET or PET/CT | 4-5/kg        | 90                               | Visual                                      | NR                           | NR                       |
| Campbell et al. [12]  | 2009 | PET/CT     |               | 555                              | Range 60–90                                 | Visual and semiquantitative | Resin microspheres | 0.92                        |
| Cianni et al. [13]    | 2009 | PET        |               | NR                               | NR                                           | Visual                     | Resin microspheres | 1.82                        |
| Mulcahy et al. [14]   | 2009 | PET        |               | NR                               | NR                                           | Visual                     | Glass microspheres | NR                           |
| Wong et al. [15]      | 2010 | PET or PET/CT | Range 370–555 | 60                               | Visual and semiquantitative                  | NR                           | NR                           |
| Tochetto et al. [16]  | 2010 | PET        |               | 360                              | 60                                           | Visual and semiquantitative | Glass microspheres | NR                           |
| Gulec et al. [17]     | 2011 | PET/CT     |               | NR                               | NR                                           | Visual and semiquantitative | Resin microspheres | 1.58                        |
| Gulec et al. [18]     | 2013 | PET/CT     |               | NR                               | NR                                           | Visual and semiquantitative | Resin microspheres | 1.58                        |
| Bagni et al. [19]     | 2012 | PET/CT     |               | NR                               | NR                                           | Visual and semiquantitative | Resin microspheres | 1.37                        |
| Schonewolf et al. [20]| 2012 | PET/CT     |               | NR                               | NR                                           | Visual and semiquantitative | Resin microspheres | 1.85                        |
| Tochetto et al. [21]  | 2012 | PET        |               | 360                              | 60                                           | Visual and semiquantitative | Glass microspheres | NR                           |
| Zerizer et al. [22]   | 2012 | PET/CT     |               | 370                              | 60                                           | Visual and semiquantitative | Resin microspheres | BSA method               |
| Rosenbaum et al. [23] | 2013 | PET or PET/CT | 3.7/kg        | 60                               | Visual                                      | NR                           | NR                           |
| Fendler et al. [24]   | 2013 | PET/CT     |               | 300                              | 60                                           | Visual and semiquantitative | Resin microspheres | 1.80                        |
| Soydal et al. [25]    | 2013 | PET/CT     | Range 296–370 | 60                               | Visual and semiquantitative                  | Resin microspheres | BSA method               |

NR: not reported, BSA: body surface area, and LM: liver mass.

pretreatment FDG-PET or PET/CT to find a score named tumour metabolic load index (TMLI), obtained converting SUV by logarithm in equivalent volumes of liver mass. TMLI value seemed to correlate with an increased occurrence of extrahepatic disease in patients with CRLM undergoing SIRT. Fendler et al. [24] confirmed this conclusion, assessing that changes in TLG rate predicted survival in patients with CRLM, whereas changes in SUV and RECIST criteria did not. Similarly, Zerizer et al. [22] evaluated the role of early FDG-PET/CT in predicting liver progression-free survival. Early FDG-PET/CT seemed to be superior to CECT in predicting progression-free survival in patients with liver metastases and tumour marker responses after ⁹⁰Y-RE. To assess by FDG-PET/CT patterns of failure and factors affecting recurrence patterns, another group [20] demonstrated that patients with CRLM treated with SIRT developed a greater proportion of extrahepatic failure, and tumour volumes >300 mL were predictive for hepatic recurrence.

To date, FDG-PET/CT is an emerging prognostic tool in patients with CRLM undergoing SIRT. Semiquantitative factors (as FTV and TLG) seem to correlate with outcome and survival in these patients better than RECIST criteria.
However, further prospective studies are needed to confirm this indication of FDG-PET/CT in patients with CRLM treated with SIRT.

3.4. Limitations of the Studies Included. Some limitations of the included studies in our evidence-based review should be underlined. The most significant ones are the heterogeneity of the patients enrolled, the variability in the sample analysed, the different devices used (PET or PET/CT, resin or glass $^{90}$Y-labelled microspheres), the methodology used to perform the scans (and lack of technical data in some papers), and the frequent retrospective nature of the studies. The most important limitation of this review is the exclusion of the studies including patients with both liver metastases from colon-rectum cancer and different primary tumours, to avoid possible biases in the literature data discussion.

4. Conclusion

From this first evidence-based review of the literature about the role of FDG-PET and PET/CT in patients with CRLM undergoing SIRT we conclude the following:

1. FDG-PET and PET/CT seem to be useful molecular imaging methods in evaluating treatment response of patients with CRLM treated with SIRT.
2. FDG-PET or PET/CT may have a role in treatment planning and patient selection for SIRT, but more studies are needed to confirm this indication.
3. FDG-PET/CT is emerging as an important prognostic tool in patients with CRLM undergoing SIRT, especially referring to PET semiquantitative analysis factors (as FTV and TLG).

Further studies are needed to evaluate the impact of FDG-PET and PET/CT on clinical management of these patients.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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