MARCELO ARAÚJO QUEIROZ

Uso da tomografia por emissão de pósitrons/ressonância magnética (PET/RM) para o estadiamento de pacientes portadores de câncer retal

Tese apresentada à Faculdade de Medicina da Universidade de São Paulo para obtenção do título de Doutor em Ciências

Programa de Radiologia

Orientador: Prof. Dr. Carlos Alberto Buchpiguel

São Paulo
2020

Dados Internacionais de Catalogação na Publicação (CIP)

Preparada pela Biblioteca da
Faculdade de Medicina da Universidade de São Paulo

Queiroz, Marcelo Araujo
Uso da tomografia por emissão de pósitrons/ressonância magnética (PET/RM) para o estadiamento de pacientes portadores de câncer retal / Marcelo Araujo Queiroz. -- São Paulo, 2020.
Tese(doutorado)--Faculdade de Medicina da Universidade de São Paulo.
Programa de Radiologia.
Orientador: Carlos Alberto Buchpiguel.

Descritores: 1.Estadiamento de neoplasias 2.Neoplasias retais 3.Imagem por ressonância magnética 4.Tomografia computarizada multidetectores 5.Tomografia por emissão de pósitrons

USP/FM/DBD-232/20

Responsável: Erinalva da Conceição Batista, CRB-8 6755

Use of positron emission tomography/magnetic resonance (PET/MR) for primary staging of rectal cancer patients

Report submitted to the Medical School of the University of São Paulo for the title of Doctor of Science.

Program of Radiology

Supervisor: Prof. Dr. Carlos Alberto Buchpiguel

São Paulo
2020

DEDICATION

Dedicated to my kids, Isadora and Gustavo, you have been my inspiration.

ACKNOWLEDGMENT

To Prof. Dr. Carlos Buchpiguel, for supervising and supporting this research study.

To Prof. Dr. Giovanni Cerri, for trusting me and opening opportunities at the University of Sao Paulo.

To Prof. Dr. Gustav von Schulthess, my mentor, my friend and a personal advisor, who introduced me to the academic world.

To Prof. Marcelo Tatit and other members of the Post-Graduation Program of Radiology at the University of Sao Paulo, who taught me to see between the lines of research during my years as student representative.

To Lia, our tireless secretary, always helpful and available.

“A persistência supera o que os fracos consideram impossível” (in free translation means “Persistence overcomes what weak people see as impossible”)

Minha mãe (My mother)

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND ACRONYMS

%	-	Percentage
<	-	Less than
=	-	Equal to
>	-	Greater than
±	-	Plus or minus
≤	-	Less than or equal to
≥	-	Greater than or equal to
ADCmax	-	Maximun apparent difussion coeficient
ADCmean	-	Mean apparent difussion coeficient
ADCmin	-	Minnimal apparent difussion coeficient
AJCC	-	*American Joint Committee on Cancer*
CEA	-	Carcinoembryonic antigen
cm	-	Centimeters
DWI	-	Diffusion-weighted imaging
EANM	-	*European Association on Nuclear Medicine*
ESMO	-	*European Society for Medical Oncology*
FDG	-	Fluorodeoxyglucose
EMVI	-	Extramural vascular invasion
LN	-	Lymph node
M	-	Metastatic disease
mL	-	Mililiters
mm	-	Milimeters
CRM	-	Circumferential resection margin
MTV	-	Metabolic tumor volume
N	-	Nodal disease
NCCN	-	*National Comprehensive Cancer Network*
NNT	-	Number needed to treat

OR	-	*Odds ratio*
PET	-	Positron emission tomography
MR	-	Magnetic Resonance
STARD	-	*Standards for reporting studies of diagnostic accuracy iniatiative requirements*
SUVmax	-	Maximum standard uptake value
SUVmean	-	Mean standard uptake value
T	-	Primary tumor
TC	-	Computed Tomography
TLG	-	Total lesion glycolysis
VOI	-	Volume of interest
NPV	-	Negative predictive value
PPV	-	Positive predictive value

RESUMO

Queiroz MA. *Uso da tomografia por emissão de pósitrons/ressonância magnética (PET/RM) para o estadiamento de pacientes portadores de câncer retal* [tese]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2019.

Introdução: o tumor de reto é estadiado com ressonância magnética (RM) da pelve e tomografia computadorizada (TC) de tórax e abdome com contraste. O escaneamento por tomografia por emissão de pósitrons demonstrou elevada taxa de detecção de lesões metastáticas secundárias a tumores colorretais. O uso do PET/RM com fluorodeoxiglicose (FDG) para estadiamento do câncer de reto pode apresentar maior detecção de metástases que o estadiamento convencional (EC). **Métodos:** estudo prospectivo incluindo 101 pacientes com adenocarcinoma de reto comprovado por biópsia e que foram submetidos a estudo de PET/RM com FDG de corpo inteiro em adição ao EC para estadiamento primários. Diferentes leitores analisaram os exames de imagem, sendo um para a RM da pelve, um para a TC de tórax e abdome com contraste e um para o FDG-PET/RM. A presença, número e localização da doença metastática for registrada de acordo com o órgão envolvido (linfonodos não regionais, fígado, pulmões ou outros). Parâmetros do PET e RM do tumor primário foram registrados, incluindo dos componentes mucinoso e não mucinoso, a saber: valor de captação padronizado máximo (SUVmax), valor de captação padronizado médio (SUVmean), volume metabólico tumoral (MTV) e glicólise lesional total (TLG) e estádio tumoral (T) e nodal N, *status* da margem de ressecção circunferencial (MRC) e invasão vascular extramural (IVEM). Os dados foram coletados utilizando-se o REDCap. A análise estatística foi realizada no R Studio e no SPSS. Teste de McNemar foi usado para comparação da acurácia diagnóstica em todos os pacientes (baseado em pacientes e baseado em lesões) e naqueles com e sem IVEM. Para comparação dos parâmetros de PET e RM, foram utilizados os testes t de student, Kruskal-Wallis e qui-quadrado. Para a medida da associação do risco dos parâmetros de PET e RM com presença de metástases, uma regressão logística binária uni e multivariada for realizada. **Resultados:** a acurácia do FDG-PET/RM foi superior ao EC em todos os pacientes (88,4% *vs*. 82,5%, p = 0,003) e naqueles pacientes com IVEM, mas não entre os pacientes sem IVEM. Na análise baseada em lesões, a taxa de detecção do FDG-PET/RM foi superior para todas as lesões (84% *vs*. 69%) e para linfonodos não regionais (90% *vs*. 37%). IVEM foi um fator de risco independente para metástases sincrônicas [*odds ratio* (OR) = 6,4]. Alguns parâmetros de PET (MTV e TLG, mas não SUVmax ou mean) e da RM (estádios T e N e MRC positiva) foram diferentes entre pacientes metastáticos e não metastáticos. O componente mucinoso do tumor primário apresentou menor grau de captação de FDG que o componente não mucinoso (SUVmax = 7,4 *vs*. 16,7, p = 0,001), porém a celularidade não foi diferente entre os dois grupos [coeficiente aparente de difusão médio (ADCmean) = 1,6 *vs*. 1,4, p = 0,36].**Conclusão:** o FDG-PET/RM apresenta maior acurácia que o EC para detecção

de lesões metastáticas, especialmente em paciente com IVEM. A taxa de detecção do FDG-PET/RM foi superior ao EC para todas as lesões e para linfonodos não regionais. Alguns parâmetros do PET e da RM permitem a distinção de pacientes metastáticos e não metastáticos. O componente mucinoso do tumor primário do reto apresenta menor metabolismo glicolítico que o componente não mucinoso.

Descritores: estadiamento de neoplasias; neoplasias retais; imagem por ressonância magnética; tomografía computarizada multidetector; tomografia por emissão de pósitrons.

ABSTRACT

Queiroz MA. *Use of positron emission tomography/magnetic resonance for rectal cancer staging* [thesis]. São Paulo: "Faculdade de Medicina, Universidade de São Paulo"; 2019.

Background: Primary rectal cancer is staged with pelvic magnetic resonance (MR) and contrast-enhanced computed tomography (ceCT) of thorax and abdomen. PET imaging has shown increased detection rate for metastatic lesions of colorectal cancer. The use of PET/MR for primary rectal staging might present higher accuracy for detection of distant metastases compared to conventional staging (CS). **Methods:** Prospective study including 101 patients with biopsy proven adenocarcinoma of the rectum underwent a whole-body FDG-PET/MR in addition of pelvic MR and ceCT of thorax and abdomen for primary staging. Different imaging readers analyzed the pelvic MR, the ceCT of thorax and abdomen and the FDG-PET/MR for primary tumor, nodal and metastatic staging. The presence, number and location of metastatic disease was recorded according to the organ involved (non-regional lymph node, liver, lungs or others). PET and MR parameters of the primary tumor were recorded both for the mucinous and non-mucinous component, namely SUVmax, SUVmean, MTV and TLG and T- and N-stage, status of CRM and EMVI. Data was recorded using REDCap. Statistical analysis was performed using R Studio and SPSS. McNemar test was used to compare accuracies of FDG-PET/MR in all patients (both patient- and lesion-based) and in those with and without EMVI. For comparison of PET and MR parameters between metastatic and non metastatic patients, there were used student t test, Kruskal-Wallis and chi-squared. For the measure of risk association between PET and MR parameters and the presence of metastasis, a uni and multivariate binary logistic regression was used. **Key Results:** The accuracy of FDG-PET/MR was superior to CS in all patients (88.4% vs. 82.5%, p = 0,003) and in those with EMVI, but not among patients without EMVI. In a lesion-based analysis, the detection rate of FDG-PET/MR was superior to CS (84% vs. 69%) for all lesions and for non-regional lymph nodes (90% vs. 37%). EMVI was an independent risk factor for synchronous metastases (OR = 6.4). Some PET (MTV and TLG, but not SUVmax or mean) and MR parameters (T- and N-stage and positive CRM) were able to distinguish metastatic from non-metastatic patients. The mucinous component of the primary tumor presents significantly lower FDG uptake than non-mucinous component (SUVmax = 7.4 vs. 16.7, p = 0.001), but tumor cellularity was not different (ADC mean = 1.4 vs. 1.6, p = 0.36). **Conclusion:** FDG-PET/MR presents higher accuracy than CS for detection of metastatic lesions, especially in patients with EMVI. The detection rate of FDG-PET/MR is superior to CS for all lesion and for non-regional lymph nodes. Some PET and MR parameters are able to distinguish metastatic from non-metastatic

patients. Mucinous component of primary rectal cancer presents lower glucose metabolism than the non-mucinous component.

Descriptors: neoplasm staging; rectal neoplasms; magnetic resonance imaging; multidetector computed tomography; positron-emission tomography.

1 INTRODUCTION

1.1 Epidemiology of Rectal Cancer

Colorectal neoplasms represent the third most diagnosed and the fourth leading cause of cancer death in the world, with increasing incidence and mortality rates in recent years, especially in countries in Eastern Europe, Asia and South America (including Brazil)[1]. For the 2018-2019 biennium in Brazil, there are an estimated 36,360 new cases among men and women[2]. Mortality from colorectal neoplasms is 64.4% in 5 years, with a significant difference according to the stage of the disease at diagnosis, ranging from 89.9% for localized disease, 71.3% for regional disease and 14.2% for systemic disease[3]. Based on current diagnostic methods, about 22% of patients with colorectal neoplasia have distant metastases3. Rectal cancer specifically represents about 35% of colorectal neoplasms and has different etiological characteristics from colon cancer and with some peculiarities, including the pattern of spread of the disease[4,5]. The importance of a thorough pre-treatment staging is evident for the prognostic definition of these patients.

1.2 Pre-Treatment Staging of Rectal Cancer

The evaluation of rectal cancer before treatment requires a multidisciplinary team including radiologists, nuclear medicine physicians, surgeons, radiotherapists, oncologists and pathologists for a better therapeutic definition. The primary pre-treatment stage of rectal cancer consists of an evaluation of the clinical history, physical examination with a digital rectal examination, measurement of carcinoembryonic antigen (CEA) and computed tomography (CT) of the chest and abdomen to define the functional status and the presence of metastases[4]. Positron emission tomography / computed tomography (PET / CT) can be an alternative for this purpose and its role in comparison with the other methods will be discussed below. For the exclusion of synchronous tumors in the colon, a colonoscopy is recommended (which can be virtual by CT in obstructive cases). For early lesions, endoscopic rectal ultrasound is recommended to determine whether the lesion is limited to the mucosa or submucosa. For locally advanced injuries, magnetic resonance imaging (MRI) is recommended to define locoregional staging[4,6]. Then, the roles of imaging exams in the staging of rectal cancer, namely MRI of the pelvis for locoregional staging, CT of the chest and abdomen for systemic staging and PET / CT for locoregional and systemic staging, will be addressed.

1.2.1 Locoregional staging by Pelvic MRI

Anatomically, the proximal rectum begins with the end of the sigmoid at the level of the sacral promontory and extends to the puborectal ring (palpable on rectal examination), from 12 cm to 16 cm in length. MRI is the method of choice for locoregional staging of locally advanced rectal cancer because of its ability to determine the degree of tumor infiltration through the mesorectum[7], in addition to predicting the risk of local recurrence[8] by measuring the distance from the circumferential resection margin, and synchronic metastases[9], through the detection of extramural vascular invasion (EMVI) of medium and large vessels.

Thus, MRI of the pelvis for locoregional staging aims to: 1) select the patient with locally advanced rectal cancer; 2) guide the surgical planning; and 3) to identify factors of poor prognosis, such as EMVI, the presence of mucinous content and involvement of the mesorectal fascia[10].

The MR imaging findings of rectal cancer that are essential for management are: a) location (high, medium or low), morphology (polypoid, ulcerated, circumferential or semi-circumferential) and content (mucinous or not); b) stage T (depth of infiltration of the *muscularis propria*, mesorectum, peritoneal reflection and adjacent organs); c) involvement of anal sphincters in lesions of the lower rectum (internal and / or external); d) status of the circumferential resection margin (compromised if less than 1 mm between the lesion and the mesorectal fascia or at risk if between 1 mm - 2 mm); e) EMVI status (negative or positive in small, medium and thick vessels); and f) lymph node involvement (mesorectal, extra-rectal - including lateral pelvic and distant sides)[10,11].

1.2.2 Systemic staging by contrast-enhanced chest and abdominal CT

Rectal tumor metastases occur, in order of prevalence, to the liver, lungs, bones and peritoneum[5]. The staging of metastatic disease (M) according to the 8th edition Cancer staging manual of the American Joint Committee on Cancer (AJCC) is divided into three: M1a, metastases to a single site (even if multiple in the same organ); M1b, metastases to multiple sites, excluding peritoneal carcinomatosis; and M1c, peritoneal carcinomatosis with or without visceral metastases[12]. For the management decision, it is essential to define the M stage, since patients may still be amenable to treatment with curative intent. The choice of treatment is based on the characteristics related to the tumor and the disease (such as clinical presentation and tumor biology), the patient (such as comorbidities, socioeconomic factors and life expectancy) and the treatment itself (such as toxicity)[13].

Contrast-enhanced CT of the chest and abdomen is the most widely used exam for detection of metastasis in patients with rectal cancer. It is a multiplanar method with excellent diagnostic performance for detecting liver, pulmonary / pleural, peritoneal and bone lesions. However, CT has a limited role in identifying lesions smaller than 1.0 cm, with sensitivity less than 50%[14] and has a lower sensitivity than MRI for detecting liver lesions (83.4% vs. 70.9%)[15]. MR represents an alternative to CT to characterize indetermined liver lesions on tomography, especially with the use of highly sensitive sequences such as diffusion-weigthed imaging and with the use of hepatobiliary-specific contrast medium (gadoxetic acid - Primovist®), exhibiting an accuracy greater than 90%[16].

1.2.3 Systemic staging by PET/CT

According to the American guidelines of the National Comprehensice Cancer Network (NCCN)[6] and *European Society of Medical Oncology* (ESMO)[4], PET/CT is indicated for preoperative staging of rectal cancer in three situations: 1) characterization of indeterminate lesions on contrast-enhanced tomography (or contraindication to the use of intravenous iodinated contrast); 2) evaluation of patients with potentially resectable M1 disease (to exclude occult sites of metastases); and 3) evaluation of patients at high risk for metastases (such as with extensive EMVI or high levels of CEA).

PET/CT represents an alternative for the detection of metastases related to colorectal neoplasms, with diagnostic accuracy greater than 95% and a potential impact on the change of treatment plan in up to 30% of patients[17,18].

Specifically on the use of PET/CT for the preoperative staging of rectal cancer, a prospective study with 97 patients showed a higher rate of detection of metastases in PET/CT compared to CT (24% vs. 14%), with changes in the management of 14.4% of patients[19]. However, to date, there are no prospective studies demonstrating that this higher detection rate with potential impact on conduct has a prognostic difference for the patient outcome.

1.3 PET/MR

Recently, a new diagnostic imaging modality became clinically available, positron emission tomography / magnetic resonance (PET/MR). It is the fusion of a molecular imaging method (the PET) with another of high spatial resolution, high soft-tissue contrast and with functional information capacity (the MRI). Over the past few years, PET/MR has been shown to be effective in the evaluation of some pelvic tumors.

Compared to PET/CT, PET/MR has some immediate advantages, such as: a) higher soft-tissue contrast (allowing evaluation of the T stage); b) simultaneous (and not sequential) acquisition, allowing for better co-registration of molecular, functional and morphological images; c) reduction of exposure to ionizing radiation; and d) lower dose of radiopharmaceuticals, given the higher sensitivity of PET/MR[20-22]. However, there are some relevant disadvantages of PET/RM compared to PET/CT, mainly related to the higher cost (and consequently less availability), longer examination time and limitation in pulmonary evaluation[23].

To perform a PET/MRI examination, it is necessary to define a clinical *workflow* from the time the patient enters the nuclear medicine department until the end of the examination. Just like PET/CT, critical steps such as a restricted carbohydrate diet in the 24 hours prior to the exam and glycemic control (especially for diabetics) are essential. Specifically for PET/MR exams, the definition of a protocol and choice of appropriate MRI sequences are primordial to achieve cost-effective examination times (ideally not exceeding 60 minutes) and for reproducibility.

1.3.1 Role of PET/MR in pre-treatment staging of rectal cancer

The rationale for performing PET/MR for rectal cancer assessment consists of combining MRI to characterize the primary tumor (T) with PET for detection of metastatic disease (M) and both (PET and MR) for a more accuarte evaluation of regional nodal spread (N).

The PET/MR protocol for the evaluation of rectal cancer can thus be divided into three parts: 1) Dedicated PET/MR of the pelvis, with T2-weighted high resolution sequences for the evaluation of the primary tumor, which may include the diffusion sequences and/or perfusion; 2) whole-body PET/MR, including T1 and T2-weighted sequences for anatomical correlation and morphological characterization; and 3) PET/MRI of the liver, with dedicated sequences for hepatic assessment, such as diffusion, which may include post-contrast sequences, with or withour hepatobiliary-specific contrast medium[24].

Few studies have evaluated the use of PET/MR for colorectal neoplasms, both in comparison with CT[25] such as with PET/CT[26-28]. All of them have limitations regarding the low number of patients (between 12 and 51 individuals), the heterogeneity of the population (patients with colon and rectal cancer undergoing staging and restaging) and the design of the study (predominantly retrospective). The conclusions, however, favor the use of PET/MR for staging colorectal neoplasms, showing an additional value to CT and a potential clinical impact on patient management[25], as well as a diagnostic performance similar or even superior to that of PET/CT[26-28].

1.4 Research justification

Pre-treatment staging of rectal cancer requires an MRI assessment of the pelvis to define the T and N stages, as well as a contrast-enhanced CT of the chest and abdomen to determine the M stage[4,6]. In parallel, some studies have shown a higher rate of metastasis detection with abdominal MRI and PET / CT compared with chest and abdomen CT[29]. In addition, it is known that the patient's prognosis changes with the stage of the disease at diagnosis, ranging from 89.9% for localized disease to 14.2% for systemic disease[3]. Moreover, there are no studies demonstrating the use of PET/MR in the population of patients with rectal cancer, with a prospective designd and a sufficient sample size. Thus, the study is justified to evaluate a new imaging method, PET/MR, in the pre-treatment staging of rectal cancer. The hypothesis to be tested in this study is that the use of PET/MR in the staging of patients with rectal cancer would present a higher diagnostic accuracy in detecting metastatic lesions in comparison with conventional staging (CS) by chest and abdominal CT and pelvic MRI.

2 OBJECTIVES

2.1 Primary objective

a) To compare the diagnostic accuracy in detecting synchronic metastases of rectal cancer between FDG-PET/RM and conventional staging (pelvic MRI plus contrast-enhanced CT of the chest and abdomen).

2.2 Secondary objectives

a) To verify the detection rate of metastatic lesions by organ in the FDG-PET/RM and in the CS.

b) To compare the diagnostic accuracy in the detection of synchronic metastases of rectal neoplasia between FDG-PET/MR and CS in patients with and without EMVI.

c) To correlate the FDG-PET/MR parameters between the mucinous and non-mucinous components of the primary rectal tumor.

d) To verify the association between the imaging parameters of the FDG-PET/MR and the presence of synchronous metastases.

3 SYSTEMATIZED TEXT

3.1 The systematized text refers to the following publications grouped by according to the objectives of the thesis:

a) Publication 1

a. Title: Diagnostic accuracy of FDG-PET/MRI versus pelvic MRI and thoracic and abdominal CT for detecting synchronous distant metastases in rectal cancer patients

b. Objectives covered: to compare the diagnostic accuracy in detecting synchronic metastases of rectal cancer between FDG-PET/RM and conventional staging (pelvic MRI plus contrast-enhanced CT of the chest and abdomen). To verify the detection rate of metastatic lesions by organ in the FDG-PET/RM and in the CS. To compare the diagnostic accuracy in the detection of synchronic metastases of rectal neoplasia between FDG-PET/MR and CS in patients with and without EMVI.

c. Journal: European Journal of Nuclear Medicine and Molecular Imaging

d. Status: published on 20 June 2020 (doi: https://doi.org/10.1007/s00259-020-04911-x)

Diagnostic accuracy of FDG-PET/MRI versus pelvic MRI and thoracic and abdominal CT for detecting synchronous distant metastases in rectal cancer patients

Marcelo A Queiroz[1] MD, Cinthia D Ortega[2] MD, PhD, Felipe R Ferreira[2] MD, Sergio C Nahas[3] MD, PhD, Giovanni G Cerri[2] MD, PhD, Carlos A Buchpiguel[1] MD, PhD

[1]Nuclear Medicine Division, Department of Radiology and Oncology, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, BR.

[2]Department of Radiology and Oncology, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, BR.

[3]Department of Surgery, Division of Colorectal Surgery, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, BR.

Corresponding author:

Marcelo A Queiroz, MD – ORCID 0000-0003-0052-0682

Address: Rua Doutor Ovidio Pires de Campos, 872 – Zip Code: 05403-010

City/State/Country: São Paulo/SP/Brazil – Phone/Fax: +55 11 2661 8137

E-mail: marcelo.queiroz@hc.fm.usp.br

ABSTRACT

Purpose: We compared the diagnostic accuracy of detecting distant metastases for baseline rectal cancer staging between PET/MRI and conventional staging (CS).

Materials and Methods: This prospective study from November 2016 to April 2018 included 101 rectal adenocarcinoma patients for primary staging. These patients underwent whole-body PET/MRI in addition to CS (pelvic MRI and thoracic and abdominal contrast-enhanced CT). Different readers analyzed CS and PET/MRI findings for primary tumor, nodal, and metastatic staging. The presence, number, and location of metastases were recorded according to the organ involved (non-regional lymph nodes (LNs), liver, lungs, or others). Lesions were defined as positive, negative, or indeterminate. The number of lesions per organ was limited to 10. The McNemar test was used to compare the accuracies.

Results: PET/MRI exhibited a higher accuracy in detecting metastatic disease than CS in all patients (88.4% vs. 82.6%, p = 0.003) and in patients with extramural vascular invasion (EMVI) (88.9% vs. 85.5%, p = 0.013). The detection rate of PET/MRI was superior to that of CS for all lesions [84.1% vs. 68.9%, p = 0.001], as well as those in the liver (89.2% vs. 84.2%), non-regional LNs (90.0% vs. 36.7%), and lungs (76.4% vs. 66.9%). PET/MRI correctly classified 19/33 (57.5%) patients with indeterminate lesions on CS.

Conclusion: PET/MRI yields higher accuracy than CS for detecting distant synchronous metastases in the baseline staging of patients with rectal cancer and EMVI. PET/MRI exhibited a higher detection rate than CS for identifying non-regional LNs, hepatic lesions, and pulmonary lesions as well as correctly classifying patients with indeterminate lesions.

Keywords: Fluorodeoxyglucose F18; Neoplasm Staging; Positron-Emission Tomography; Magnetic Resonance Imaging; Rectal Neoplasms.

Trial registration: NCT02537340

Introduction

Baseline staging of rectal cancer requires a multidisciplinary team to define the best treatment approach. The imaging work-up for the primary staging of rectal cancer consists of pelvic magnetic resonance imaging (MRI) for locoregional evaluation and thoracic and abdominal contrast-enhanced computed tomography (ceCT) for detection of distant metastases, as recommended by ESMO and NCCN guidelines [1,2]. Alternatively, positron emission tomography/CT (PET/CT) can be used, especially for the following: 1) to characterize indeterminate lesions on ceCT, 2) to evaluate potentially curable metastatic disease (and exclude occult sites of metastases), and 3) to stage patients at high risk for metastases, i.e., with extensive EMVI or high levels of carcinoembryonic antigen [1,2]. Additionally, a liver MRI might be considered to assess indeterminate liver lesions on ceCT [1,2]. The T and N stages of primary rectal tumors are defined according to pelvic MRI, which identifies locally advanced rectal tumors and facilitates in guiding the treatment plan [3]. The M stage is defined according to thoracic and abdominal ceCT, which might be followed by complementary PET/CT and liver MRI to clarify indeterminate lesions, as both methods exhibit higher accuracy for the detection of distant metastases [4,5]. Moreover, the prognosis of patients with rectal cancer depends on the stage of the disease at the time of diagnosis, with overall survival in 5 years decreasing from 89.9% for localized tumors to 14.2% for systemic disease [6].

In this context, the use of PET/MRI for primary rectal cancer staging combines the standard imaging modality for the T and N stages with PET as well as both PET and liver MRI for the M stage. To date, data comparing PET/MRI with other imaging modalities for colorectal cancer is scarce and limited due to small patient numbers, heterogeneous populations (including both colon and rectal cancer patients for primary staging and restaging), and study designs that are mostly retrospective [7–

11]. Nevertheless, these studies suggest that PET/MRI yields a diagnostic performance that is superior to both CT and PET/CT, which could have a robust clinical impact on patient management.

This study aimed to compare the diagnostic accuracy of PET/MRI compared to conventional staging (CS) (that consists of pelvic MRI and thoracic and abdominal ceCT) for the detection of distant metastases during the primary staging of rectal cancer patients. We hypothesized that, compared to combined MRI and CT, PET/MRI might exhibit higher accuracy with a lower prevalence of indeterminate lesions in detecting metastatic disease.

Materials and Methods

Study population

This prospective study was conducted from November 2016 to April 2018 and recruited 203 consecutive patients with biopsy-proven rectal adenocarcinomas (assessed by rigid proctoscopy to be up to 15 cm from the anal verge) to undergo [^{18}F]fluorodeoxyglucose (FDG) PET/MRI. The inclusion criteria were as follows: 1) age more than 18 years, 2) ready to sign the informed consent form, and 3) able to undergo the staging examinations (PET/MRI and ceCT) at a maximum interval of 2 weeks. The exclusion criteria were as follows: 1) previous treatment for rectal cancer, including endoscopic resection, and diagnosed synchronous non-colorectal neoplasia and 2) PET/MRI contraindications. The patients' selection flowchart is presented in Fig. 1. The institutional review board approval was obtained and this study was registered at clinicaltrial.gov under the identification number NCT02537340.

Imaging procedures

- Thoracic and abdominal ceCT

The CT scans were performed within 2 weeks before or after PET/MRI was performed. Thoracic and abdominal CT scans were obtained from the lung apices to the superior iliac crest with a 16−256-multidetector CT (Brilliance CT, Philips, Netherlands). The scans were acquired during a breath hold after intravenous injection of contrast media (Iopamiron 300, Bracco, Italy) based on body weight (1.2 mL/kg) at a rate between 2−3 mL/s during the portal venous phase (70 s after injection). CT parameters were as follows: field of view of 300 mm, 90−120 kV (depending on patient body mass index), variable mAs, rotation between 0.5−0.75 s, pitch between 0.7−1.2, matrix of 512 x 512, slice thickness of 2 mm, and increment of 1 mm.

- Whole-body PET/MRI (including pelvic and liver MRI)

Whole-body FDG-PET/MRI followed the guidelines of the European Association of Nuclear Medicine for oncological imaging in adults [12], adapted for a PET/MRI workflow. The injected activity of FDG was calculated according to the patient's weight (4.5 MBq/kg, mean radiotracer dose of 296 MBq, and range of 197–414 MBq). After FDG injection, the patient rested for 20 min and was then transferred to the PET/MRI scanner for positioning and hyoscine butylbromide injection (20 mg, intravenous). The scanning was initiated 30 min after FDG injection and comprised three parts: 1) dedicated pelvic MRI (without PET acquisition), which was performed for locoregional staging of primary rectal cancer and followed the guidelines of the European Society of Gastroenterology and Abdominal Radiology [13]; 2) whole-body PET/MRI (acquisition started 60 minutes after FDG injection, mean uptake time of 64 minutes), which included 3−5 bed positions per patient and used a 3 min/bed position acquisition time under 3D image acquisition and standard reconstruction protocols; and 3) dedicated abbreviated (5 min) liver MRI (without PET acquisition). The MRI sequences and parameters are shown in Table 1.

Imaging analysis

The imaging readers were only aware of the indication of the examination (primary staging of rectal cancer), but blinded to other clinical data and imaging modalities. A step-by-step read was performed for each imaging modality.

- Conventional staging (CS)
    - Pelvic MRI

A radiologist with 10 years of experience in reading MRI (C.D.O.) analyzed the dedicated pelvic MRI for locoregional staging. The following parameters were

assessed for the primary tumor: a) morphology (annular, semi-annular, ulcerated, or polypoid); b) longitudinal (distance in cm from anal verge) and circumferential (clockwise) location; c) extension (in cm); d) presence of mucinous component (positive high signal within the tumor in the T2w sequence); e) mesorectal fascia status (positive or negative if the circumferential resection margin was ≤ 1 mm or > 1 mm from the tumor, EMVI, or deposit, respectively; for low rectal tumors, a positive margin was considered if the distance between the tumor and the levator ani muscle was ≤ 1 mm or the intersphincteric plane was compromised); f) the presence of EMVI (positive if medium and large vessels were involved, according to Smith et al. [11]). For regional nodal staging, a positive lymph node (LN) was considered when at least one of the morphologically suspicious characteristics (irregular border and/or heterogeneous signal) were present.

- Thoracic and abdominal ceCT

Another radiologist with 5 years of experience in reading CT (F.R.F.) analyzed the thoracic and abdominal ceCT for systemic staging and detection of distant metastases. The metastases were categorized as positive, negative, or indeterminate and listed according to the involved organ, i.e., non-regional nodes, liver, lungs, and others. Malignant criteria were defined based on size and morphology. A positive lesion was defined by: a) a short axis diameter of ≥ 10 mm and/or b) ≥ 2 morphologically suspicious characteristics (round shape, irregular border, and/or hypovascular in the portal venous phase). An indeterminate lesion was defined by: a) a short axis diameter of < 10 mm and b) only one morphologically suspicious characteristic (round shape, irregular border, and/or hypovascular in the portal venous phase). The maximum number of lesions per organ was 10.

- Whole-body PET/MRI

A board-certified radiologist with 8 years of experience in reading MRI and PET (M.A.Q.) and a nuclear medicine physician with 16 years of experience in reading

PET (C.A.B.) analyzed the PET/MRI images by using a dedicated workstation (Advantage Workstation version 4.6, GE Healthcare). The readers were kept blinded as the MRI component of the PET/MRI (comprised by the axial T2w of the pelvis, axial T1 DIXON and coronal T2 SSFSE) did not include the dedicated pelvic MRI (high-resolution T2w sequences oriented to the tumor). For the primary tumor, PET semi-quantitative data was obtained by semi-automatically drawing a volume of interest over the primary tumor using the application PETVCAR (GE Healthcare), which was supported by a visual adaptation of the isocontouring to avoid the inclusion of structures not related to the tumor, such as the bladder. Maximum standard uptake value (SUVmax), Mean SUV (SUVmean), metabolic tumor volume, and total lesion glycolysis (defined as the product of metabolic tumor volume and SUVmean) were recorded. For regional nodal staging, in addition to the MRI criteria, the following metabolic criterion was applied: all LNs with FDG uptake > 2.5 were considered positive, regardless of size or morphology. For metastatic disease staging, a combination of morphology and metabolism was used and varied depending on the organ (retroperitoneal LNs, lungs, liver, and others). For retroperitoneal LNs, a positive lesion was defined by one of the following criteria: a) a short axis diameter of ≥ 10 mm, b) ≥ 2 morphologically suspicious characteristics (round shape, irregular border, and/or heterogeneous signal), c) all mucinous LNs (any size);, and d) the LN was FDG-positive (SUVmax > 2.5). For the lungs, a positive lesion was defined by one of the following criteria: a) a size of > 1 cm and b) focal FDG uptake higher than surrounding parenchyma with or without a morphological correlation. For the liver and other organs (peritoneum, ovaries, and adrenal organs), a positive lesion presented at least two of the following three criteria: a) intermediate intensity on T2w images, b) high signal intensity impeding diffusion on images acquired with a high b value, and c) focal FDG uptake higher than the liver parenchyma. A maximum of 10 lesions per organ was also defined.

Standard of reference

The standard of reference (SOR) for metastatic disease consisted of clinical/imaging follow-ups performed at 3, 6, and 12 months after initial staging and/or histopathological confirmation (when discrepancy between PET/MRI findings and other imaging modalities was present). A lesion was considered positive if it exhibited progression or a response after chemotherapy or if at least one new lesion appeared within 6 months after initial evaluation. Lesions that were stable under treatment were considered negative.

Statistical analysis

IBM SPSS Statistics (version 25) and RStudio (version 1.1.463) were used for statistical analysis. A two-tailed P value of < 0.05 was considered statistically significant. For the calculation of diagnostic accuracy, the indeterminate lesions were considered negative and the McNemar test was applied. The McNemar test was also used to calculate the diagnostic accuracy according to the status of EMVI detected by MRI. The numbers needed to treat were also calculated, i.e., the count of how many people need to be scanned in order for one person to benefit. The primary outcome was the presence of metastases and the comparison was between the metastatic patients observed with CS and the metastatic patients observed with PET/MRI.

Results

Patient characteristics

This study included 101 patients (mean age: 62 y; range: 33–87 y; male-to-female ratio: 51:50). SOR detected 334 synchronous metastases in 36 patients (35.6%), predominantly in the liver (69.4%, 25/36 patients), followed by the lungs (47.2%, 17/36 patients) and non-regional LNs (41.2%, 15/36 patients). Of the 36 metastatic patients, 17 (47.2%) patients exhibited progressive or responsive lesions at imaging follow-up, 16 (44.4%) patients had histopathological confirmation, and 3 (8.3%) patients presented new lesions at imaging follow-up, all of which were confirmed negative on PET/MRI after a second analysis.

According to the dedicated pelvic MRI, most patients exhibited locally advanced rectal cancer, with 80.2% (81/101) of patients exhibiting at least T3b and 50.5% (51/101) of patients exhibiting positive regional LNs. A positive EMVI was observed in 62.7% (63/101) of patients, and an involved mesorectal fascia was observed in 49.5% (50/101) of patients. Table 2 summarizes the patients' characteristics.

Diagnostic accuracy of PET/MRI vs. CS

From the 36 metastatic patients, CS and PET/MRI classified 23 and 31 patients as metastatic, respectively. With this difference, the calculated numbers needed to treat were 5 for the metastatic patients and 12 for all the rectal cancer patients. This indicates that for every 5 metastatic or 12 rectal cancer patients, one presents metastases only on PET/MRI. The patient-based analysis revealed that PET/MRI exhibited a significantly higher accuracy (88.4% vs. 82.6%, $p = 0.003$) and an especially higher specificity in detecting metastatic disease than CS (Table 3). The diagnostic accuracy of PET/MRI for detecting distant metastases was also significantly higher than CS (88.9% vs. 85.5%, $p = 0.013$) in patients with EMVI, but

was not different (85.4% vs. 68.5%, p = 0.22) among patients without EMVI (Table 4; Figs. 2 and 3).

From all of the 334 metastatic lesions, PET/MRI detected 281 in 31 patients, while CS detected 230 lesions in 23 patients (84.1% vs. 68.9%, p = 0.001). The organ-based analysis revealed that the detection rate of PET/MRI was significantly superior to CS for liver (89.2% (124/139 in 23 patients) vs. 84.2% (117/139 in 20 patients), p = 0.023), non-regional LNs (90.0% (54/60 in 18 patients) vs. 36.7% (22/60 in 8 patients), p = 0.001), and lungs (76.4% (97/127 in 13 patients) vs. 66.9% (85/127 in 13 patients), p = 0.019). No difference was observed for other lesions, and both methods presented a diagnostic rate of 75% (6/8 in 6 patients) (Figs. 4 and 5).

On a patient-based analysis, PET/MRI and CS were congruent in 23 metastatic patients and PET/MRI alone identified 8 more patients. There was any metastatic patient positive on CS only. Five patients were considered positive for metastases during imaging follow-up and were considered false negative on both methods. On a lesion-based comparison, PET/MRI and CS detected 223/334 metastatic lesions (66.8%), PET/MR alone detected 58/334 lesions (17,4%), mainly non-regional lymph nodes, and CS alone detected 7/334 lesions (2.1%), especially lung lesions. Both methods missed 46/334 lesions (13.8%), especially lung and liver nodules. See Fig. 6.

Characterization of indeterminate lesions

Both PET/MRI and CS were indeterminate in six patients, of which all proved to be negative for metastases on imaging follow-up. PET/MRI detected five more indeterminate patients (accounting for 16 lesions – 11 non-regional LNs, 0 in the liver, 1 in the lungs, and 4 in other sites), of which CS was negative in four (one false negative and three true negatives) and positive in one (a false positive). On the other

hand, CS detected twenty-seven more indeterminate patients (accounting for 68 lesions – 20 non-regional LNs, 29 in the liver, 16 in the lungs, and 3 in other sites), of which PET/MRI was negative in 18 (4 false negative and 14 true negative) and positive in 9 (4 false positive and 5 true positive). PET/MRI correctly classified 19/33 (57.5%) patients with indeterminate lesions on CS, while CS correctly classified 3/11 (27.2%) patients with indeterminate lesions on PET/MRI (Fig. 7).”

Discussion

Our study demonstrated that PET/MRI has a higher accuracy than CS for the detection of distant synchronous metastases in baseline staging of patients with rectal cancer and of patients that presented EMVI within primary tumors. PET/MRI exhibited a higher detection rate than CS for detecting non-regional LNs as well as hepatic and pulmonary lesions. Moreover, PET/MRI exhibited a more correct classification of patients with indeterminate lesions than CS.

The accuracy for detecting metastatic disease was higher for PET/MRI than pelvic MRI and thoracic and abdominal CT. Recently, a Swedish study assessed the additional value of PET/MRI (and PET/CT) over CS of rectal cancer. Although only 24 patients were included, the PET-component presented a disease upstaging from M0 to M1 in 3 out of 24 patients (12.5%) [11]. In our study, PET/MRI also enabled upstaging from M0 to M1 in eight patients. A meta-analysis of the role of PET and PET/CT in the primary staging of both colon and rectal cancer demonstrated a sensitivity and specificity of 91% and 95%, respectively, compared to a diagnostic accuracy of 80% for CT [14]. This is consistent with the results of our study in which we demonstrated a sensitivity of 90.8% and a specificity of 86.1% for PET/MRI and an accuracy of 82.6% for CS.

The distribution of the distant metastases of this study was more prevalent in the liver and lungs, consistent with the spreading pattern of rectal tumors [15]. Additionally, our study demonstrated a high incidence (15%) of non-regional LNs, similar to a study that performed retroperitoneal lymphadenectomy (17%) [16]. The characterization of metastatic LNs is a limitation of CT and MRI that rely on morphology (especially size and borders), whereas PET/MRI contributes a metabolic aspect, enhancing the sensitivity and specificity of this technique.

PET/MRI exhibited a superior detection of liver metastases compared to CS, in line with the literature that demonstrates that PET/CT and especially MRI exhibit a higher sensitivity than ceCT [17,18]. Sivesgaard et al. [19] compared the diagnostic accuracy of ceCT, MRI, and FDG-PET/CT for the detection of liver metastases and, by analyzing 260 lesions, demonstrated that the sensitivity of MRI was superior to FDG-PET/CT, which was superior to ceCT (85.9% vs. 72.0% vs. 62.3%). Thus, we postulated that the combination of FDG-PET and MRI presents a diagnostic performance superior to CT for the detection of rectal liver metastases. Our study employed T2-weighted MRI sequence and diffusion-weighted imaging for assessment of liver lesions, but not contrast-enhanced sequences (e.g., gadolinium or Primovist). This was due to a time limitation, as our protocol was set to last 60 minutes without the dynamic phase of MRI. Lee et al. [20] demonstrated that the diagnostic performance of PET/MRI was superior to that of multidetector CT or PET for the detection of colorectal cancer liver metastases; however, PET/MRI did not differ from liver-specific contrast-enhanced MRI. Reiner et al. [21] also demonstrated similar diagnostic accuracies for the detection of liver metastases when PET/MRI was read with DWI (99%), contrast-enhanced MRI (98%), and both (99%). This reinforces the idea that the use of contrast in the context of PET/MRI may not be essential.

For lung lesions, however, it was expected that thoracic CT would exhibit a higher detection rate than PET/MRI, as MRI is limited to identifying lung nodules smaller than 1 cm [22]. Nevertheless, in our study, PET/MRI was superior to CT in detecting pulmonary metastases. This might be related to the defined criteria of malignancy with CT (a size > 1.0 cm) compared to the metabolic criteria with PET/MRI (focal FDG uptake higher than surrounding background). Thus, several small lesions (< 1.0 cm) that were considered indeterminate on CT were considered suspicious on PET/MRI due to the focal FDG uptake. Only few papers have compared PET/MRI and CT for

the detection of pulmonary metastases. Rauscher et al. [23] demonstrated that PET/MRI exhibited an inferior detection rate for small lung lesions compared to PET/CT with diagnostic chest CT. Another study that included 51 patients with colorectal lung metastases demonstrated that PET/MRI exhibited a superior diagnostic rate (90%) compared to CT when evaluating lesions larger than 0.5 cm [7].

We also compared the accuracy of PET/MRI and CS in patients with and without EMVI, and PET/MRI exhibited superior detection of metastatic lesions only for EMVI within the primary tumor. Patients with EMVI exhibit an increased risk (OR: 5.68) of metastatic disease [24], which suggests that PET/MRI would detect lesions at a higher rate. So, a patient with positive EMVI and negative conventional staging could benefit for a more carefully investigation. Nevertheless, these results should be interpreted with caution, as the number of metastatic patients without EMVI was too low (5 out of 38 patients) and thus cannot yield significant statistical results.

PET/MRI reduced the number of indeterminate findings observed on CS in more than half of our patient population. As demonstrated by Fraum et al. [25], PET/MRI facilitates better tumor staging, FDG activity localization, and lesion characterization. Other studies have shown that PET imaging may better characterize both lung [26] and liver lesions [27] in colorectal cancer patients.

A limitation of our study is that histological confirmation was not available for all distant metastases; nevertheless, almost half of our patient population was biopsied and all others had imaging follow-ups for at least 6 months. Second, despite the prospective study design, case selection bias might have been present, as most of the included patients presented advanced tumors and a high number of recruited patients was not included, especially because almost half of them had promptly initiated the treatment before performing the PET/MRI; however, this is a particular characteristic of our

tertiary public cancer center. Third, only one radiologist assessed the pelvic MRI and thoracic and abdominal ceCT, which might have influenced the findings. Fourth, reaching a common interpretation of the PET/MRI results could have presented another limitation; therefore, we included both a nuclear physician and radiologist in this study.

This study has demonstrated that PET/MRI yields a higher accuracy than CS for the detection of distant synchronous metastases in patients undergoing rectal cancer staging. The diagnostic performance of PET/MRI was superior to CS in patients with EMVI within primary rectal tumors as well as for detecting non-regional LNs, hepatic lesions, and pulmonary lesions. Furthermore, PET/MRI reduced the number of indeterminate findings observed on CS. These results indicate that PET/MRI is a more appropriate diagnostic method for staging rectal cancer, but future studies should evaluate whether this incremental value of PET/MRI may change patient management and especially outcome.

References

1. Glynne-Jones R, Wyrwicz L, Tiret E, Brown G, Rödel C, Cervantes A, et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Ann Oncol. 2017;28:iv22–40.

2. Benson AB, Venook AP, Bekaii-Saab T, Chan E, Chen Y-J, Cooper HS, et al. Rectal Cancer, Version 2.2015. J Natl Compr Cancer Netw. 2015;13:719–28.

3. Horvat N, Carlos Tavares Rocha C, Clemente Oliveira B, Petkovska I, Gollub MJ. MRI of Rectal Cancer: Tumor Staging, Imaging Techniques, and Management. RadioGraphics. 2019;39:367–87.

4. Seo HJ, Kim M, Lee JD, Chung W, Kim Y-E. Gadoxetate disodium-enhanced magnetic resonance imaging versus contrast-enhanced 18F-fluorodeoxyglucose positron emission tomography/computed tomography for the detection of colorectal liver metastases. Invest Radiol. 2011;46:548–55.

5. Ozis SE, Soydal C, Akyol C, Can N, Kucuk ON, Yagcı C, et al. The role of 18F-fluorodeoxyglucose positron emission tomography/computed tomography in the primary staging of rectal cancer. World J Surg Oncol. 2014;12:26.

6. Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ CK (eds). SEER Cancer Statistics Review, 1975-2016, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2016/, based on November 2018 SEER data submission, posted to the SEER web site, April 2019. [Internet]. 2019. Available from: https://seer.cancer.gov/statfacts/html/colorect.html

7. Kang B, Lee JM, Song YS, Woo S, Hur BY, Jeon JH, et al. Added Value of Integrated Whole-Body PET/MRI for Evaluation of Colorectal Cancer: Comparison With Contrast-Enhanced MDCT. Am J Roentgenol. 2016;206:W10–20.

8. Brendle C, Schwenzer NF, Rempp H, Schmidt H, Pfannenberg C, la Fougère C, et al. Assessment of metastatic colorectal cancer with hybrid imaging: comparison of reading performance using different combinations of anatomical and functional imaging techniques in PET/MRI and PET/CT in a short case series. Eur J Nucl Med Mol Imaging. 2016;43:123–32.

9. Paspulati RM, Partovi S, Herrmann K a., Krishnamurthi S, Delaney CP, Nguyen NC. Comparison of hybrid FDG PET/MRI compared with PET/CT in colorectal cancer staging and restaging: a pilot study. Abdom Imaging. 2015;40:1415–25.

10. Catalano OA, Coutinho AM, Sahani D V., Vangel MG, Gee MS, Hahn PF, et al. Colorectal cancer staging: comparison of whole-body PET/CT and PET/MR. Abdom Radiol. 2017;42:1141–51.

11. Rutegård MK, Båtsman M, Axelsson J, Brynolfsson P, Brännström F, Rutegård J, et al. PET/MRI and PET/CT hybrid imaging of rectal cancer – description and initial observations from the RECTOPET (REctal Cancer trial on PET/MRI/CT) study. Cancer Imaging. 2019;19:1–9.

12. Boellaard R, Delgado-Bolton R, Oyen WJG, Giammarile F, Tatsch K, Eschner W, et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0.

Eur J Nucl Med Mol Imaging. 2014;

13. Beets-Tan RGH, Lambregts DMJ, Maas M, Bipat S, Barbaro B, Curvo-Semedo L, et al. Magnetic resonance imaging for clinical management of rectal cancer: Updated recommendations from the 2016 European Society of Gastrointestinal and Abdominal Radiology (ESGAR) consensus meeting. Eur Radiol. 2018;28:1465–75.

14. Ye Y, Liu T, Lu L, Wang G, Wang M, Li J, et al. F-FDG PET-CT or PET: a meta-analysis including 2283 patients. Int J Clin Exp Med. 2015;8:21773–85.

15. Riihimäki M, Hemminki A, Sundquist J, Hemminki K. Patterns of metastasis in colon and rectal cancer. Sci Rep. Nature Publishing Group; 2016;6:29765.

16. Quadros CA, Falcão MF, Carvalho ME, Ladeia PA, Lopes A. Metastases to retroperitoneal or lateral pelvic lymph nodes indicated unfavorable survival and high pelvic recurrence rates in a cohort of 102 patients with low rectal adenocarcinoma. J Surg Oncol. 2012;106:653–8.

17. Niekel MC, Bipat S, Stoker J. Diagnostic Imaging of Colorectal Liver Metastases with CT, MR Imaging, FDG PET, and/or FDG PET/CT: A Meta-Analysis of Prospective Studies Including Patients Who Have Not Previously Undergone Treatment. Radiology. 2010;257:674–84.

18. Maffione AM, Lopci E, Bluemel C, Giammarile F, Herrmann K, Rubello D. Diagnostic accuracy and impact on management of 18F-FDG PET and PET/CT in colorectal liver metastasis: a meta-analysis and systematic review. Eur J Nucl Med Mol Imaging. 2015;42:152–63.

19. Sivesgaard K, Larsen LP, Sørensen M, Kramer S, Schlander S, Amanavicius N, et al. Diagnostic accuracy of CE-CT, MRI and FDG PET/CT for detecting colorectal cancer liver metastases in patients considered eligible for hepatic resection and/or local ablation. Eur Radiol. 2018;28:4735–47.

20. Lee DH, Lee JM, Hur BY, Joo I, Yi N-J, Suh K-S, et al. Colorectal Cancer Liver Metastases: Diagnostic Performance and Prognostic Value of PET/MR Imaging. Radiology. 2016;280:782–92.

21. Reiner CS, Stolzmann P, Husmann L, Burger IA, Hüllner MW, Schaefer NG, et al. Protocol requirements and diagnostic value of PET/MR imaging for liver metastasis detection. Eur J Nucl Med Mol Imaging. 2014;41:649–58.

22. Heye T, Ley S, Heussel CP, Dienemann H, Kauczor HU, Hosch W, et al. Detection and size of pulmonary lesions: how accurate is MRI? A prospective comparison of CT and MRI. Acta Radiol. 2012/01/31. 2012;53:153–60.

23. Rauscher I, Eiber M, Furst S, Souvatzoglou M, Nekolla SG, Ziegler SI, et al. PET/MR Imaging in the Detection and Characterization of Pulmonary Lesions: Technical and Diagnostic Evaluation in Comparison to PET/CT. J Nucl Med. 2014;55:724–9.

24. Siddiqui MRS, Simillis C, Hunter C, Chand M, Bhoday J, Garant A, et al. A meta-analysis comparing the risk of metastases in patients with rectal cancer and MRI-detected extramural vascular invasion (mrEMVI) vs mrEMVI-negative cases. Br J Cancer. 2017;116:1513–9.

25. Fraum TJ, Fowler KJ, McConathy J, Dehdashti F. Indeterminate Findings on Oncologic PET/CT: What Difference Does PET/MRI Make? Nucl Med Mol Imaging (2010). 2016;50:292–9.

26. Jess P, Seiersen M, Ovesen H, Sandstrøm H, Maltbæk N, Buhl AA, et al. Has PET/CT a role in the characterization of indeterminate lung lesions on staging CT in colorectal cancer? A prospective study. Eur J Surg Oncol. 2014;40:719–22.

27. Parsai A, Miquel ME, Jan H, Kastler A, Szyszko T, Zerizer I. Improving liver lesion characterisation using retrospective fusion of FDG PET/CT and MRI. Clin Imaging. 2019;55:23–8.

Figure Captions

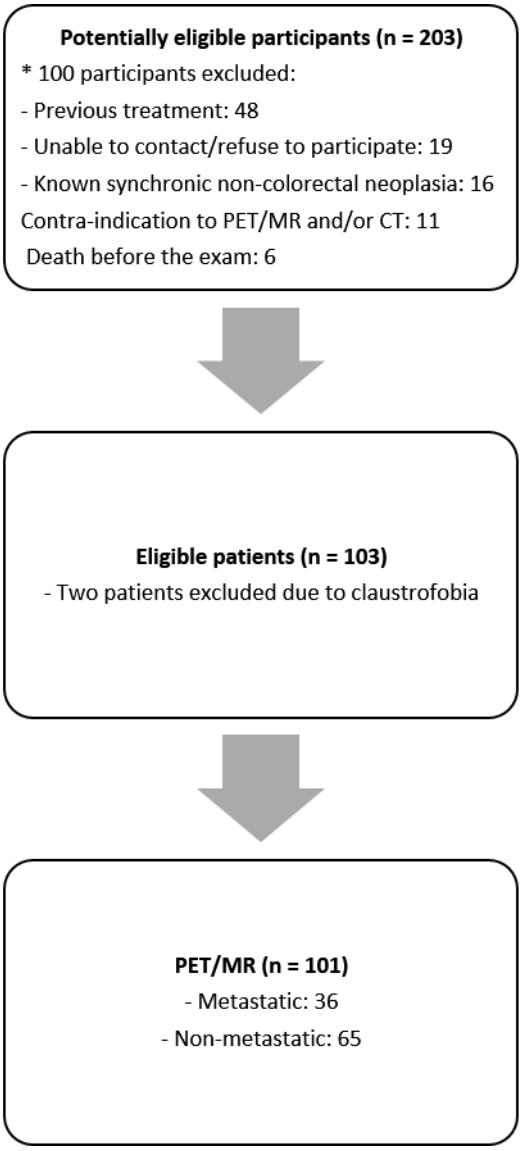

Fig. 1. Flowchart of the participants of the study.

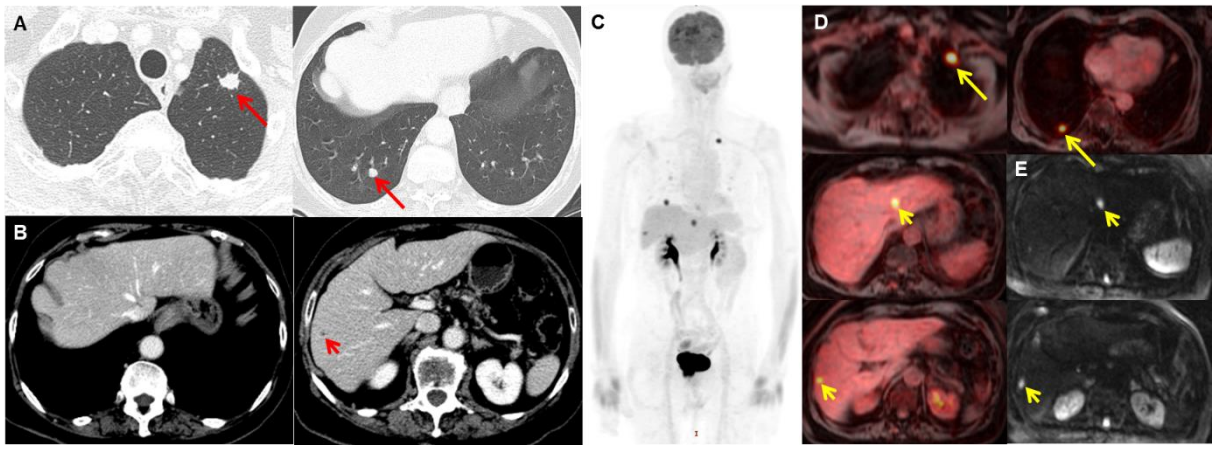

Fig. 2. PET/MRI is superior to CS for staging primary rectal cancer with EMVI. The patient was an 85-year-old woman. Thoracic CT (A; long red arrows) and PET/MRI (D; long yellow arrows) revealed lung metastases. Abdominal CT (B) detected an indeterminate liver nodule (short red arrow). The PET/MRI findings (E) indicated that this nodule was suspicious (restricted diffusion and focal FDG uptake) and additionally revealed liver metastases (yellow short arrows). These lesions were confirmed by imaging follow-up.

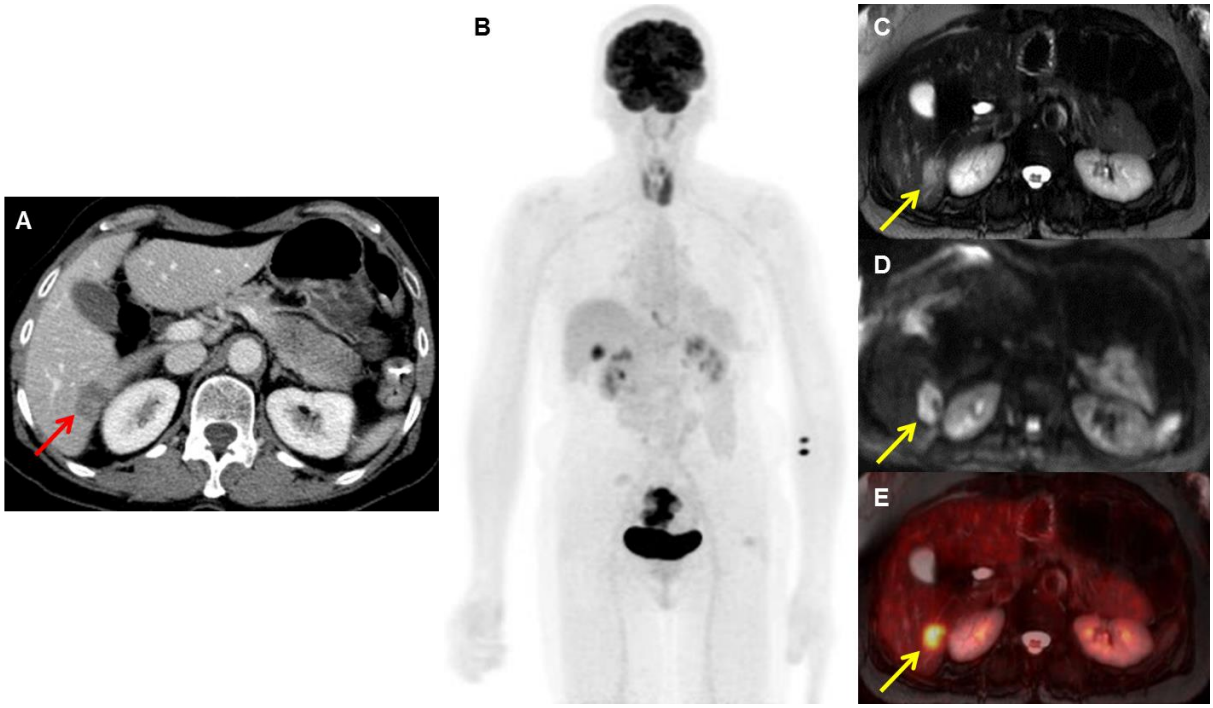

Fig. 3. PET/MRI is similar to CS in a 63-year-old female patient with primary rectal cancer without EMVI. A single metastasis was observed on abdominal ceCT (A; red arrow) as well as PET/MRI with intermediate T2 signal (C), restricted diffusion (D), and high FDG uptake (E). No additional lesions were observed on PET/MRI. This lesion was confirmed by histology.

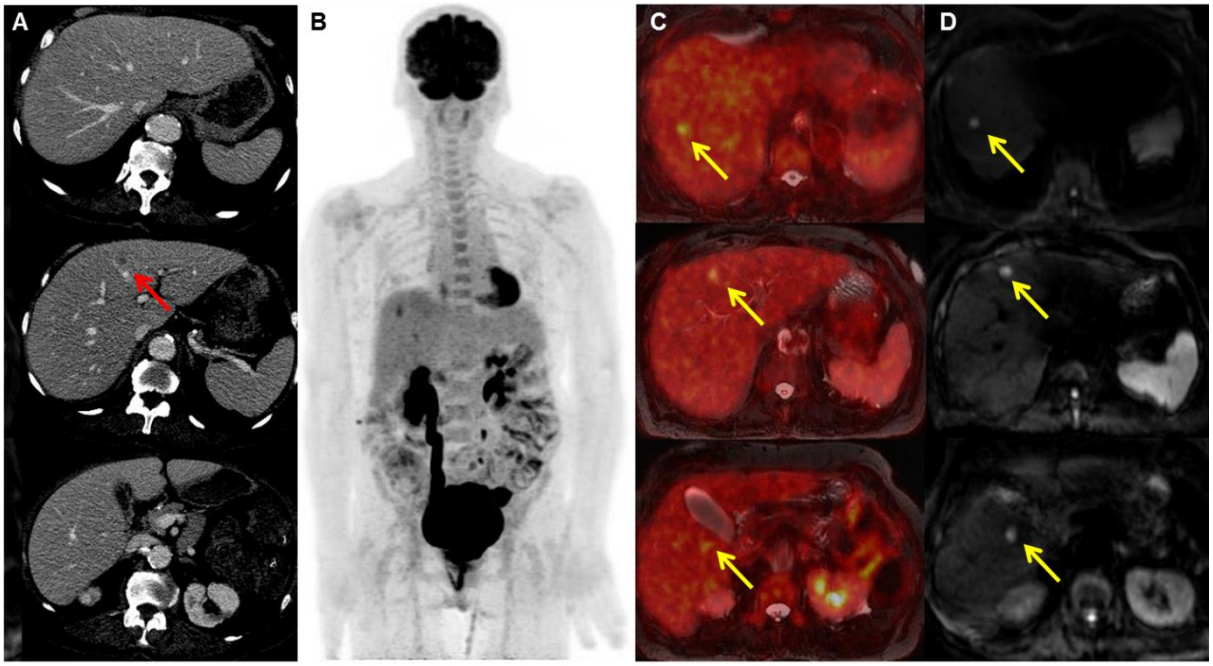

Fig. 4. PET/MRI is superior to CS for upstaging from M0 to M1 in the liver and for clarifying indeterminate lesions detected by CS. The patient was a 61-year-old woman, and abdominal ceCT revealed one indeterminate liver lesion (A; red arrow). PET/MRI revealed that this lesion was positive with restricted diffusion and high FDG uptake (C−D; yellow arrows). PET/MRI also revealed two other liver lesions with similar characteristics (C−D; yellow arrows). These lesions were confirmed by imaging follow-up.

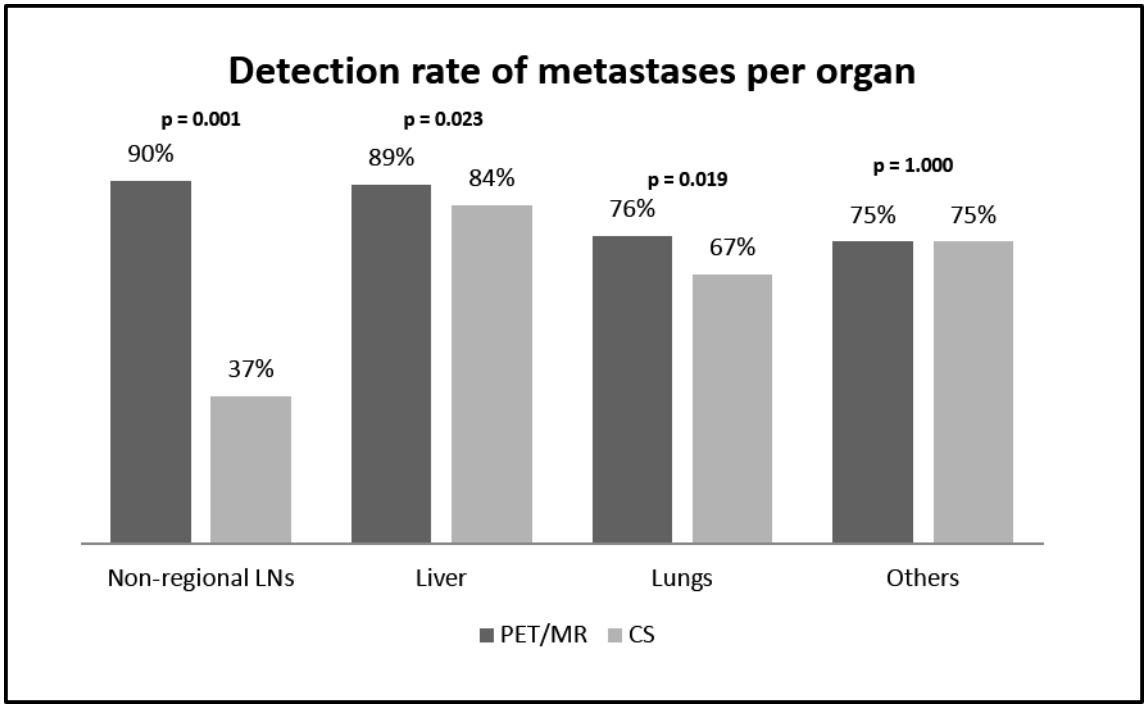

Fig. 5. Comparison of the detection rate of metastases per organ between positron emission tomography/magnetic resonance imaging (PET/MRI) and conventional staging (CS). LN: lymph node.

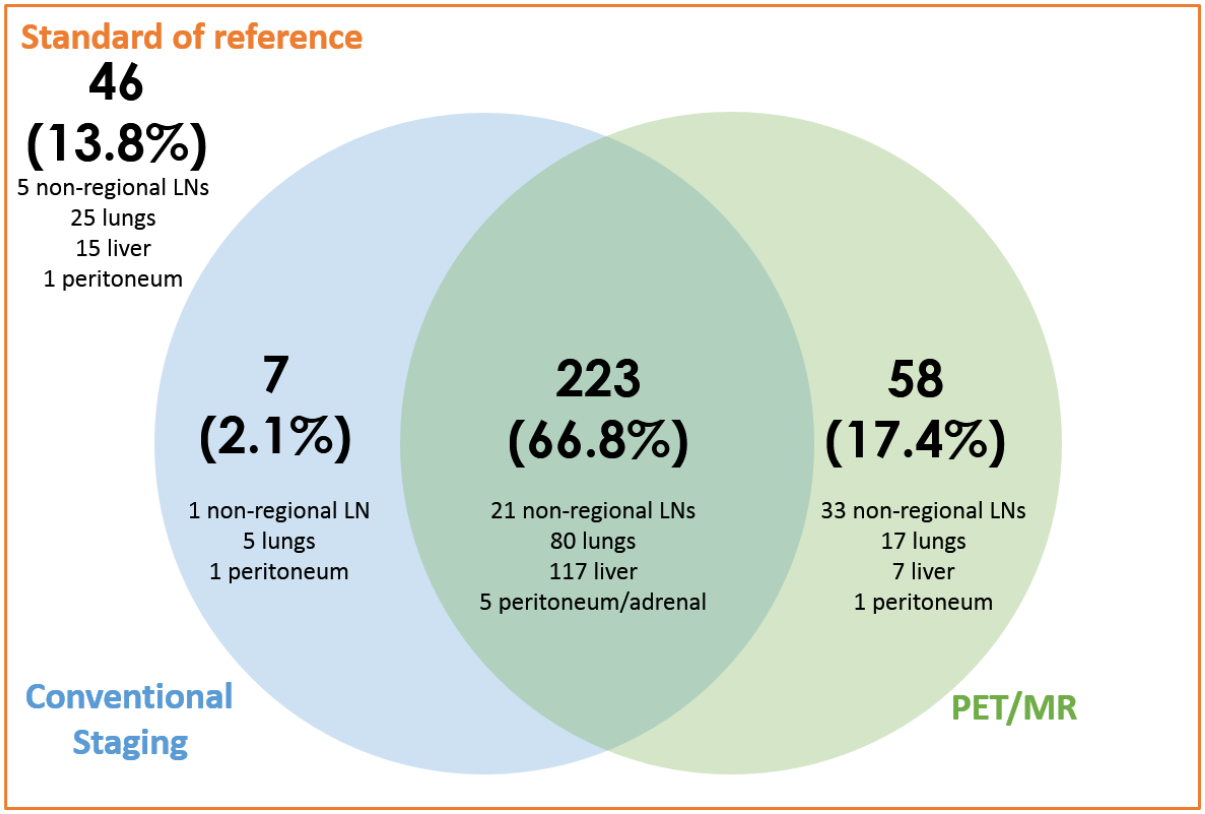

Fig. 6. A comparison of the number of metastatic lesions detected by both PET/MRI and CS, PET/MRI alone, CS alone, and by standard of reference represented in a Venn diagram.

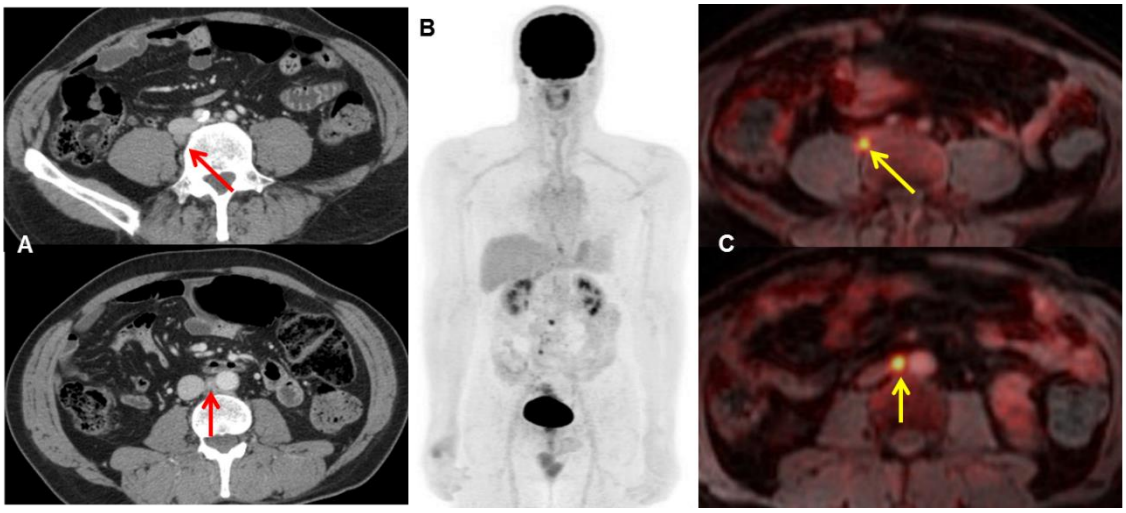

Fig. 7. PET/MRI is superior to CS for upstaging from M0 to M1 in non-regional lymph nodes and for clarifying indeterminate lesions detected by CS. The patient was a 64-year-old man, and PET/MRI revealed two small (< 1 cm) indeterminate retroperitoneal lymph nodes (A; red arrows) that were considered positive due to high FDG uptake. The interaortocaval lesion was biopsied and confirmed as metastatic adenocarcinoma.

Tables

	MR Sequence	Orientation	FOV (mm)	Matrix	Slice thickness (mm)	TE/TR
Dedicated pelvic MRI	T2 FSE (tumor) T2 FSE (tumor) DWI Focus[a] T2 (pelvis) DWI[b]	Saggital Oblique Axial Axial Axial	160 x 160 160 x 160 160 x 160 300 x 300 350 x 350	256 x 256 256 x 256 80 x 50 352 x 352 130 x 130	3.0 3.0 3.0 5.0 5.0	120/4800 120/5600 60/2100 120/8000 68/2800
Whole-body PET/MRI	T1 Dixon T2 SSFSE	Axial Coronal	500 x 500 500 x 500	288 x 192 288 x 192	5.0 5.0	1680/4560 120/3500
Abbreviated liver MRI	T2w SSFSE DWI[c]	Axial Axial	380 x 380 420 x 420	288 x 224 160 x 160	5.0 5.0	120/2100 64/16600

[a]: b-values, 100 e 1000; [b]: b-values, 100 e 1100; [c]: b-values, 50 e 800.
SSFSE: single-shot fast spin-echo; FSE: fast spin echo; DWI: diffusion-weighted imaging/diffusion; MRI: magnetic resonance imaging; PET: positron emission tomography; FOV: field of view; TE: echo time; TR: repetition time.

Table 1. Technical parameters of MRI sequences acquired with PET/MRI.

	All patients (n = 101)
Age (median [IQR])	62 [55-70]
Sex (M:F)	51:50
Quantitative parameters on PET/MRI	
SUVmax (median [IQR])	19,1 [15,1-25,10]
SUVmean (median [IQR])	9,5 [7,9-12,8]
TLG (median [IQR])	276,8 [154,4-502,2]
MTV (median [IQR])	44,8 +- 65,02
Qualitative parameters on PET/MRI	
mrT stage (%)	
Tx	1 (1,0)
T2	19 (18,8)
T3	48 (47,5)
T4	33 (32,7)
mrN stage (%)	
N0	50 (49,5)
N1	44 (43,6)
N2	7 (6,9)
Mesorectal LN on PET (%)	
Negative	57 (56,4)
Positive	44 (43,6)
Mesorectal LN on MRI (%)	
Negative	60 (59,4)
Positive	41 (40,6)
Lateral pelvic LN on PET (%)	
Negative	87 (86,1)
Positive	14 (13,9)
Lateral pelvic LN on MRI (%)	
Negative	80 (79,2)
Positive	21 (20,8)
EMVI	
Negative	38 (37,6)
Positive	63 (62,4)
CRM	
Negative	51 (50,5)
Positive	50 (49,5)
Mucinous component	
No	82 (81,2)
Yes	19 (18,8)
Location	
Low	41 (40,6)
Middle/High	60 (59,4)

IQR: interquartile range; PET: positron emission tomography; MRI: magnetic resonance imaging; SUVmax: maximum standard uptake value; SUVmean: mean standard uptake value; TLG: total lesion glycolisis; MTV: metabolic tumor volume; LN: lymph node; EMVI: extramural vascular invasion; CRM: circumferential resection margin.

Table 2. Characteristics of patient population.

	PET/MRI	CS

Sensitivity	90.8%	98.5%
Specificity	86.1%	66.7%
Positive Likelihood Ratio	6,53	2,96
Negative Likelihood Ratio	0,11	0.02
Accuracy	88.4%	82.6%
	p = 0.003	

Table 3. Diagnostic accuracy of positron emission tomography/magnetic resonance imaging (PET/MRI) vs. conventional staging (CS) in all patients.

	Patients with EMVI (n = 63)		Patients without EMVI (n = 38)	
	PET/MRI	**CS**	**PET/MRI**	**CS**
Sensitivity	90.6%	100%	90.9%	97.0%
Specificity	87.1%	71.0%	80.0%	40.0%
Positive Predictive Value	87.9%	78.1%	96.8%	91.4%
Negative Predictive Value	90.0%	100%	57.1%	66.7%
Accuracy	88.9%	85.5%	85.4%	68.5%
	p = 0.01		p > 0.05	

Table 4. Diagnostic accuracy of positron emission tomography/magnetic resonance imaging (PET/MRI) vs. conventional staging (CS) in patients with and without extramural vascular invasion (EMVI).

Supplementary Material

All patients (n = 101)		Standard of Reference		
		Positive	Negative	Total
PET/MRI	Positive	59	5	64
	Negative	6	31	37
	Total	65	36	101
All patients (n = 101)		**Standard of Reference**		
		Positive	Negative	Total
CS	Positive	64	12	76
	Negative	1	24	25
	Total	65	36	101

Table SM1. Table 2 x 2 of diagnostic accuracies of all patients (n = 101).

Patients with EMVI (n = 63)		Standard of Reference		
		Positive	Negative	Total
PET/MRI	Positive	29	4	33
	Negative	3	27	30
	Total	32	31	63
Patients with EMVI (n = 63)		**Standard of Reference**		
		Positive	Negative	Total
CS	Positive	32	9	41
	Negative	0	22	22
	Total	32	31	63

Table SM2. Table 2 x 2 of diagnostic accuracies of patients with extramural vascular invasion (EMVI) (n = 63).

Patients without EMVI (n = 38)		Standard of Reference		
		Positive	Negative	Total
PET/MRI	Positive	30	1	31
	Negative	3	4	7
	Total	33	5	38
Patients without EMVI (n = 38)		**Standard of Reference**		
		Positive	Negative	Total
CS	Positive	32	3	35
	Negative	1	2	3
	Total	33	5	38

Table SM3. Table 2 x 2 of diagnostic accuracies of patients without extramural vascular invasion (EMVI) (n = 38).

b) Publication 2

a. Title: PET/MR Characterization of Mucinous versus Non-mucinous Components of Rectal Adenocarcinoma: A Comparison of Tumor Metabolism and Cellularity

b. Objectives covered: to correlate the FDG-PET/MR parameters between the mucinous and non-mucinous components of the primary rectal tumor.

c. Journal: American Journal of Roentgenology

d. Status: accepted on 05 May 2020 (doi: https://doi.org/10.2214/AJR.19.22627)

PET/MR Characterization of Mucinous versus Non-mucinous Components of Rectal Adenocarcinoma: A Comparison of Tumor Metabolism and Cellularity

Abstract

Purpose: evaluate if PET/MR using FDG can separate the mucinous from the non mucinous component of the primary rectal tumor, and compare the glycolytic metabolism on PET and tumor cellularity on RM/DWI in both components.

Methods: ninety-nine patients that underwent FDG-PET/MR for primary rectal cancer staging were included in this prospective analysis. MRI defined the mucin component (MC) through the tumor volume. Separate VOIs were drawn on both MC and NMC and propagated to PET and ADC maps. SUVmax, SUVmean, ADCmax, ADCmean and ADCmin were recorded and compared between areas with MC and NMC. Whole-body PET/MR was also evaluated for the presence of distant metastases. Non-parametric testing was used to compare both groups. Logistic regression was performed to calculate the association risk of MC and metastatic disease.

Results: Seventeen patients (17.2%) presented MC within the tumor on T2w images of MR. Most of these patients presented advanced disease, with MC tumor presenting significantly higher T stages than non-mucinous tumors (88.2% vs. 61.0%, p = 0.032). SUVmax (7.4 vs. 16.7, p=0.002) and SUVmean (5.4 vs. 13.4, p=0.001) were significantly lower in MC than in NMC. Tumor ADC measurements were not different between MC and NMC (ADCmean 1.4 vs. 1.6, p=0.361). There was no association regarding the presence of MC within the primary rectal tumor and the presence of synchronous metastases (OR: 1.1 [0.4-3.0], p = 0.904). Moreover, the occurrence of metastases in patients with mucinous tumors was not different from patients with NMC tumors (7/17, 41.2% vs. 32/82, 34.1%, p = 0.887).

Conclusion: PET/MR enables distinguishing the MC and NMC within primary rectal adenocarcinoma based on the metabolic status, with a significantly lower FDG uptake in the MC, but not by tumor cellularity based on MR/DWI. Despite of being associated with higher T stage in the present sample of patients, the presence of MC seems not to be associated with increased risk of synchronous metastases.

Trial registration: NCT02537340

Key words: Fluorodeoxyglucose F18; Positron-Emission Tomography; Magnetic Resonance Imaging; Rectal Neoplasms; Mucinous Adenocarcinoma.

Introduction

Rectal adenocarcinomas with mucinous component are characterized by the presence of pools of extracellular mucin in more than 50% of the tumor volume (1), and can be considered as a specific morphological subtype of this cancer,. Mucinous tumors (MT) arising in the rectum are less common than in the colon (9% vs. 16%) (2) and are usually associated to poor prognosis when compared to non-mucinous tumors (NMT) (more advanced T and N stages, poor response to neoadjuvant chemoradiotherapy and higher rates of metastases) (3–5). Magnetic resonance imaging (MRI) is an important method to evaluate the primary rectal tumor, with a more limited role for positron emission tomography (PET) imaging(6). On MRI, the MT present high signal intensity on T2-weighted images, mild or only peripheral enhancement on DCE images and lower signal intensity on DWI (1). The accuracy of MRI in predicting the mucinous histologic component within the rectal tumor volume is 97% (7). Interestingly, MRI is diagnostically even superior to biopsy in the preoperative detection of mucinous component (MC) in rectal cancer (5). In turn, the evaluation of MC in primary rectal cancer by PET imaging is controversial, with the potential of seeing more false-negative results due to the low cellularity and consequently low or absent glycolytic metabolism. Contrary to other MT (8), some studies using PET/CT haven't showed any difference in FDG uptake of rectal mucinous adenocarcinomas compared to non-mucinous ones (9,10). The advent of PET/MRI allows a more thorough evaluation of the primary rectal tumor, enabling the distinction of the different tissue components within the same tumor.

This study aims to compare the glycolytic metabolism on PET and tumor cellularity on MR/DWI in mucinous and non-mucinous components of primary rectal tumors assessed by FDG-PET/MR.

Methods

Patients

This study retrospectively evaluated 99 patients who underwent a whole-body [^{18}F]fluorodeoxyglicose (FDG)-PET/MRI in the Department of Radiology and Oncology, University of São Paulo between November 2016 and December 2018, for primary rectal cancer staging.. Clinical data was obtained from a database originating from a previous study approved by the local institutional review board, for which all patients signed an informed consent. Inclusion criteria consisted of presence of mucinous component (MC) within the primary tumor, defined as tumors presenting at least 50% of high signal intensity on T2-weighted imaging, which was termed mucinous tumors (MT). Patients with non-mucinous component (NMC) only or MC smaller than 50% were called non-mucinous tumors (NMT).

All PET/MR scans were performed on a time-of-flight simultaneous PET/MR (Signa PET/MR, GE Healthcare). Patient preparation included at least 4 h of fasting and a plasma glucose level lower than 200 mg/dL. The injected activity of FDG was calculated according the patient weight (4.5 MBq/ Kg; mean radiotracer dose of 296 MBq; range 197 – 414 MBq). After the FDG and hyoscine butylbromide (Buscopan®, 20 mg, intravenous) injections, a dedicated MRI of the pelvis was performed for the evaluation of the primary rectal cancer. The protocol included for the primary tumor: a) sagittal T2w (Slice thickness 3 mm, Matrix 256 x 256, FOV 160 mm, TE/TR 120/4800); b) tumor-oriented HR T2w (Slice thickness 3 mm, Matrix 256 x 256, FOV 160 mm, TE/TR 120/5600); and c) DWI Focus (Slice thickness 3 mm, Matrix 80 x 50, FOV 160 mm, TE/TR 60/2100), and for the pelvis: a) axial T2w (Slice thickness 5 mm, Matrix 352 x 352, FOV 300 mm, TE/TR 120/8000); b) DWI (Slice thickness 5 mm, Matrix 130 x 130, FOV 300 mm, TE/TR 68/2800); c) 3D isotropic T2w (Slice thickness 0.8 mm, Matrix 512 x 512, FOV 500 mm, TE/TR 120/2800). A whole-body PET/MR was then acquired, including 3 to 5 bed positions per patient, using a 3 minutes/bed

position acquisition time, under 3D image acquisition and standard reconstruction protocols. All scans were obtained without gadolinium contrast agent, as recommended by ESGAR guidelines for primary staging of rectal cancer (11).

Image analysis

A radiologist with 10 years of experience in reading MRI analyzed the dedicated pelvic MR assessing the presence of MC within the tumor, blinded to the PET findings. Then, a board certified radiologist with 8 years of experience in reading MR and PET and a nuclear medicine physician with 16 years of experience in reading PET analyzed the PET/MR images in consensus. For systemic staging, a combination of morphology and metabolism was used and varied according to the organ (retroperitoneal lymph nodes, lungs, liver and others). For retroperitoneal lymph nodes, a positive lesion was defined when: a) short axis diameter ≥ 10 mm; b) lymph nodes with two or more morphologically suspicious characteristics (round shape, irregular border and/or heterogeneous signal); d) all mucinous lymph nodes (any size); and e) all FDG positive (SUVmax > 2.5) lymph nodes. For the lungs, a positive lesion was defined when: a) size larger than 1.0 cm; b) focal FDG uptake higher than surrounding parenchyma with or without a morphological correlation. For the liver and other organs (peritoneum, ovaries, adrenal), three criteria have been defined: 1. intermediate intensity on T2w images; 2. high signal intensity impeding diffusion on images acquired with a high b value; 3. focal FDG uptake higher than the liver parenchyma. A positive lesion presented at least two of these 3 criteria. A maximum of ten lesions per organ was defined. The reference standard for metastatic disease consisted of clinical/imaging follow-up performed at 3, 6 and 12 months after initial staging and/or by histopathological confirmation (when discrepancy between PET/MR findings and other imaging modalities). Additionally, two nuclear medicine physicians analyzed in consensus the pelvic part of the PET/MR of the patients with MC in the primary tumor (n = 17). The largest MC and NMC were identified on axial T2w image

and a VOI was drawn covering at least 50% of their diameter (blinded to PET and DWI of the pelvis). This VOI was then automatically propagated to PET, DWI and ADC images (acquired with the same FOV of the axial T2w) using a dedicated workstation (Advantage Workstation version 4,6, GE Healthcare), as shown of Figure 1. These steps were consistently repeated in the NMC of MT. PET (SUVmax and SUVmean) and DWI (ADCmax, ADCmean and ADCmin) parameters were then recorded.

Additionally, the FDG uptake of the whole MT and NMT was measured by semi-automatically drawing a VOI over the primary tumor using the application PETVCAR (GE Healthcare), which was supported by a visual adaptation of the isocontouring. The SUVmax and SUVmean of the whole MT (wSUVmaxMT and wSUVmeanMT) and NMT (wSUVmaxNMT and wSUVmeanNMT) was annotated.

Statistical analysis

IBM SPSS Statistics, version 25 (IBM Corp. Armonk, NY) was used for statistical analysis. A two-tailed P value of less than 0.05 was considered significant. The PET and DWI parameters of MC and NMC were compared using the independent samples Mann-Whitney U test. MR features such as positive EMVI, compromised CRM, T stage, N-positive, low rectal tumors and synchronous metastasis were compared for the MC and NMC patients. Uni and multivariate regression analysis was performed to test the association between including the presence of MC on MR and synchronic metastatic disease.

Results

Patient characteristics

Among all patients, 17 (17.2%) presented at least 50% of MC within the tumor on T2w images of MR. Most of these patients presented advanced primary staging, being at least T3c in 88.2% (significantly different from the frequency of advanced tumors in NMC patients, 61.0%, p = 0.032). No difference was observed between MC and NMC patients regarding the other features, but the majority of patients in both groups presented with advanced disease. For instance, the involvement of MRF, positive EMVI and N positive was present in 70.6% of MC patients. Patient data is summarized on Table 1.

Comparison of PET and MR data

PET semiquantitative parameters, namely SUVmax (7.4 vs. 16.7, p=0.002) and SUVmean (5.4 vs. 13.4, p=0.001) were significantly lower in MC than in NMC of primary rectal tumors. See Figs. 1 and 2. On the other hand, tumor ADC measurements were not different between MC and NMC (Mean ADC 1.4 vs. 1.6, p=0.361). See Fig. 3. Interestingly, the FDG uptake of the whole volume of the primary tumor was not different between MT and NMT (wSUVmaxMT vs. wSUVmaxNMT (24.0 vs. 20.5, p = 0.264) and wSUVmeanMT vs. wSUVmeanNMT (11.6 vs. 10.6, p = 0.525).

Additionally, a comparison of the FDG uptake between the NMC of MT (17 patients) and NMT (82 patients) was performed and showed no difference between SUVmax (16.1 vs. 20.5, p = 0.051) or SUVmean (13.1 vs. 10.6, p = 0.439).

Risk association of MC and synchronous metastases

There was no association between the presence of MC within the primary rectal tumor and the presence of synchronous metastases (OR: 1.1 [0.4-3.0], p = 0.904) in a uni or a multivariate regression analysis. Moreover, the prevalence of metastatic patients in the group of MC tumors was not different from patients with

NMC tumors (7/17, 41.2% vs. 32/82, 34.1%, p = 0.887), as presented on Table 1. The only feature that persisted significantly associated with the presence of synchronous metastases after multivariate analysis was EMVI of medium and large vessels detected by MR (OR: 6.4 [2.2 – 18.5, p = 0.04]).

Discussion

Our study has shown that PET/MR allows the differentiation of mucinous and non-mucinous components based on the glycolytic metabolism by PET, but not based on tumor cellularity by DWI. Although patients with MC tumors presented more advanced disease (especially with higher T stage), the occurrence of metastases was not higher among patients with MC in comparison to patients with only NMC tumors. The presence of MC within primary rectal tumor was also not associated to higher risk of synchronous distant metastases.

The clinical assumption that MT usually present low FDG uptake is supported in the literature for different abdominal tumors, especially ovarian (12) and gastrointestinal cancers (13). For rectal tumors, however, there are reports that did not show any difference in FDG uptake between tumors with and without MC (9,10), as also shown by the measurement of the SUVmax and SUVmean of the whole primary tumor in our patient population, which was not different between MT and NMT. The method of measurement performed in these studies, however, justifies this incongruence. Previous studies using PET/CT alone or PET/CT and a separate MR were not capable of measuring the FDG uptake in the exact mucinous and non-mucinous components of the tumor, which usually coexist, especially because CT does not allow this differentiation and the visual coregistration between PET and a separate MRI is not sufficient. So, the measurement of MT included the whole tumor volume, comprising both MC and NMC and the SUVmax calculated by these studies included the measurement of the NMC of a mucinous tumor. With the combination of PET and MR in a simultaneous acquisition, it was possible to clearly prove the difference seen in the daily practice. Interestingly, the FDG uptake of the NMC of MT was not different from the one of NMT, reinforcing the reproducibility of our measurement of SUVmax and SUVmean. This is important for image readers since both metastatic regional nodes and distant lesions usually follow the pattern of the

primary tumor and these could be misinterpreted as false-negative disease if you rely only on PET. The most accepted explanation for the lower FDG uptake is that MT have low cellularity due to the presence of both intra and extracellular mucin, which decrease the proportion of viable tumor cells that promote FDG uptake (14).

On the other hand, PET/MR was not able to show the difference in tumor cellularity based on DWI. It is well know that the presence of extracellular mucin results in higher ADC values. However, the measurement of ADC values on MR is not very reproducible. First, because the size and positioning of the ROI have strong influence in calculating this value and that yields a high variability among reads (15). And second, because the ADC values suffer from imaging acquisition parameters and post-processing techniques (16). These reasons taken together might justify the lack of difference in tumor cellularity between MC and NMC observed in our study.

The importance in recognizing the MC of rectal cancers relies on the more aggressive behavior of these tumors that yield a poor prognosis (5,17). The prevalence of MC in rectal tumors is up to 20% (18), similar to the proportion found in our patient population. Mucinous rectal tumors are frequently associated with more advanced T stage, which although not clearly understood, might be related to molecular and genetic factors, such as microsatellite instability and mismatch repair deficiency (3,18). Similarly, our patient population with MC tumors had significantly higher T stages than the patients without MC.

MT were associated to higher risk of distant metastases, especially in colorectal cancers (10,19). These studies, however, point to a higher risk of development of metachronous metastases. The most frequent and independent risk factor for synchronous metastases is the presence of EMVI detected by MR (20), as shown by our study.

This study has some limitations. First, the presence of MC was based on MR only and not confirmed by histopathology. This, however, might have not

compromised our analysis. Although sometimes it is difficult to differentiate the presence of mucinous component from cysts, fluid collections and necrotic tumors, MR has the accuracy of 97% to characterize the MC within primary rectal tumors (7). And besides, the performance of histopathology after neoadjuvant chemotherapy in detecting the proportion of mucinous component does not necessarily reflect the same proportion of seen in the preoperative exam. A second limitation is the high prevalence of advanced tumors in our patient population both among patients with MC and NMC tumors, one particular characteristic of our tertiary public cancer center.

PET/MR enabled distinguishing the MC and NMC within the primary rectal adenocarcinoma volume based on the difference of glycolytic metabolism, significantly lower in the MC. Conversely, tumor cellularity based on the diffusion restriction was not able to differentiate MC and NMC tumors. The presence of MC was not associated with increased risk of synchronous metastases.

Compliance with Ethical Standards

Funding: This study was partially funded by GE Healthcare.

Conflict of Interest: The authors declare that they have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

References

1. Horvat N, Hope TA, Pickhardt PJ, Petkovska I. Mucinous rectal cancer: concepts and imaging challenges. Abdom Radiol. 2019 Nov;44(11):3569–80.
2. Hugen N, Brown G, Glynne-Jones R, de Wilt JHW, Nagtegaal ID. Advances in the care of patients with mucinous colorectal cancer. Nat Rev Clin Oncol. 2016;13(6):361–9.
3. Tarantino I, Hüttner FJ, Warschkow R, Schmied BM, Diener MK, Ulrich A. Prognostic Relevance of Mucinous Subtype in a Population-based Propensity Score Analysis of 40,083 Rectal Cancer Patients. Ann Surg Oncol. 2016;23(5):1576–86.
4. McCawley N, Clancy C, O'Neill BDP, Deasy J, McNamara DA, Burke JP. Mucinous Rectal Adenocarcinoma Is Associated with a Poor Response to Neoadjuvant Chemoradiotherapy: A Systematic Review and Meta-analysis. Dis Colon Rectum. 2016;59(12):1200–8.
5. Yu SKT, Chand M, Tait DM, Brown G. Magnetic resonance imaging defined mucinous rectal carcinoma is an independent imaging biomarker for poor prognosis and poor response to preoperative chemoradiotherapy. Eur J Cancer. 2014;50(5):920–7.
6. Wnorowski AM, Menias CO, Pickhardt PJ, Kim DH, Hara AK, Lubner MG. Mucin-Containing Rectal Carcinomas: Overview of Unique Clinical and Imaging Features. AJR Am J Roentgenol. 2019 Apr 17;(July):1–9.
7. Kim M-J, Park JS, Park S Il, Kim NK, Kim JH, Moon HJ, et al. Accuracy in differentiation of mucinous and nonmucinous rectal carcinoma on MR imaging. J Comput Assist Tomogr. 2003;27(1):48–55.
8. Berger KL, Nicholson SA, Dehdashti F, Siegel BA. FDG PET Evaluation of Mucinous Neoplasms. Am J Roentgenol. 2000 Apr;174(4):1005–8.
9. dos Anjos DA, Habr-Gama A, Vailati BB, Rossi CB, Coturel AE, Perez RO, et al. 18F-FDG uptake by rectal cancer is similar in mucinous and nonmucinous histological subtypes. Ann Nucl Med. 2016;30(8):513–7.
10. Barbaro B, Leccisotti L, Vecchio FM, Di Matteo M, Serra T, Salsano M, et al. The potential predictive value of MRI and PET-CT in mucinous and nonmucinous rectal cancer to identify patients at high risk of metastatic disease. Br J Radiol. 2017 Jan;90(1069):20150836.
11. Beets-Tan RGH, Lambregts DMJ, Maas M, Bipat S, Barbaro B, Curvo-Semedo L, et al. Magnetic resonance imaging for clinical management of rectal cancer: Updated recommendations from the 2016 European Society of Gastrointestinal and Abdominal Radiology (ESGAR) consensus meeting. Eur Radiol. 2018 Apr;28(4):1465–75.
12. Tanizaki Y, Kobayashi A, Shiro M, Ota N, Takano R, Mabuchi Y, et al. Diagnostic value of preoperative SUVmax on FDG-PET/CT for the detection of ovarian cancer. Int J Gynecol Cancer. 2014 Mar 1;24(3):454–60.
13. Berger KL, Nicholson SA, Dehdashti F, Siegel BA. FDG PET evaluation of mucinous neoplasms: Correlation of FDG uptake with histopathologic features. Am J Roentgenol. 2000 Apr;174(4):1005–8.
14. Lakhani A, Khan SR, Bharwani N, Stewart V, Rockall AG, Khan S, et al. FDG PET/CT Pitfalls in Gynecologic and Genitourinary Oncologic Imaging. RadioGraphics. 2017;37(2):577–94.
15. Lambregts DMJ, Beets GL, Maas M, Curvo-Semedo L, Kessels AGH, Thywissen T, et al. Tumour ADC measurements in rectal cancer: Effect of ROI methods on ADC values and interobserver variability. Eur Radiol. 2011;21(12):2567–74.
16. Chen L, Shen F, Li Z, Lu H, Chen Y, Wang Z, et al. Diffusion-weighted

imaging of rectal cancer on repeatability and cancer characterization: An effect of b-value distribution study. Cancer Imaging. 2018;18(1):1–9.
17. Kaneko K, Kawai K, Kazama S, Murono K, Sasaki K, Yasuda K, et al. Clinical significance of mucinous components in rectal cancer after preoperative chemoradiotherapy. Surg Today. 2017;47(6):697–704.
18. Chand M, Yu S, Swift RI, Brown G. Mucinous carcinoma of the rectum: A distinct clinicopathological entity. Tech Coloproctol. 2014;18(4):335–44.
19. Hugen N, Van de Velde CJH, De Wilt JHW, Nagtegaal ID. Metastatic pattern in colorectal cancer is strongly influenced by histological subtype. Ann Oncol. 2014;25(3):651–7.
20. Siddiqui MRS, Simillis C, Hunter C, Chand M, Bhoday J, Garant A, et al. A meta-analysis comparing the risk of metastases in patients with rectal cancer and MRI-detected extramural vascular invasion (mrEMVI) vs mrEMVI-negative cases. Br J Cancer. 2017;116(12):1513–9.

Tables

Patient clinical characteristics			
	Mucinous Tumors	**Non-mucinous Tumors**	***p-value***
Number of patients (n = 99)	17 (17.2%)	82 (82.8%)	
Mean age (years) (SD)	59 (13)	63 (10)	p = 0.138
Sex (%)			
Male	7 (41.2%)	39 (47.6%)	p = 0.400
Female	10 (58.6%)	43 (52.4%)	
T stage			
< T3b	2 (11.8%)	32 (39.0%)	p = 0.032
> T3c	15 (88.2%)	50 (61.0%)	
Mesorectal fascia involvement			
No	5 (29.4%)	44 (53.7%)	p = 0.070
Yes	12 (70.6%)	38 (46.3%)	
EMVI			
No	5 (29.4%)	32 (39.0%)	p = 0.458
Yes	12 (70.6%)	50 (61.0%)	
N status			
N0	5 (29.4%)	44 (53.7%)	p = 0.070
N1	9 (52.9%)	34 (41.5%)	
N2	3 (17.3%)	4 (4.9%)	
M status			
M0	10 (58.8%)	54 (65.9%)	p = 0.887
M1	7 (41.2%)	28 (34.1%)	
Tumor height (%)			
Lower rectum	8 (47.1%)	32 (39.0%)	p = 0.541
Middle rectum	9 (52.9%)	50 (61.0%)	

Table 1. Patient clinical characteristics comparing patients with MC and NMC. MC, mucinous component; NMC, non-mucinous component; EMVI, extramural vascular invasion; T, tumor; N, nodal; M, metastases.

Comparison of PET and DWI (ADC) data of MT			
n = 17 patients	**MC**	**NMC**	***p-value***
ADCmin (x 10^{-3})	0.67	0.53	0.468
ADCmean (x 10-3)	1.4	1.6	0.361
ADCmax (x 10-3)	2.2	1.8	0.056
SUVmax	7.4	16.7	0.002*
SUVmean	5.4	13.4	0.001*

Table 2. PET parameters comparison between MC and NMC in the 17 patients with MT. P-values of less than 0.05 were considered significant. Significant findings are highlighted with *. MT, mucinous tumors; MC, mucinous component; NMC, non-mucinous component; PET, positron emission tomography; DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient; SUV, standard uptake value.

Figures with legends

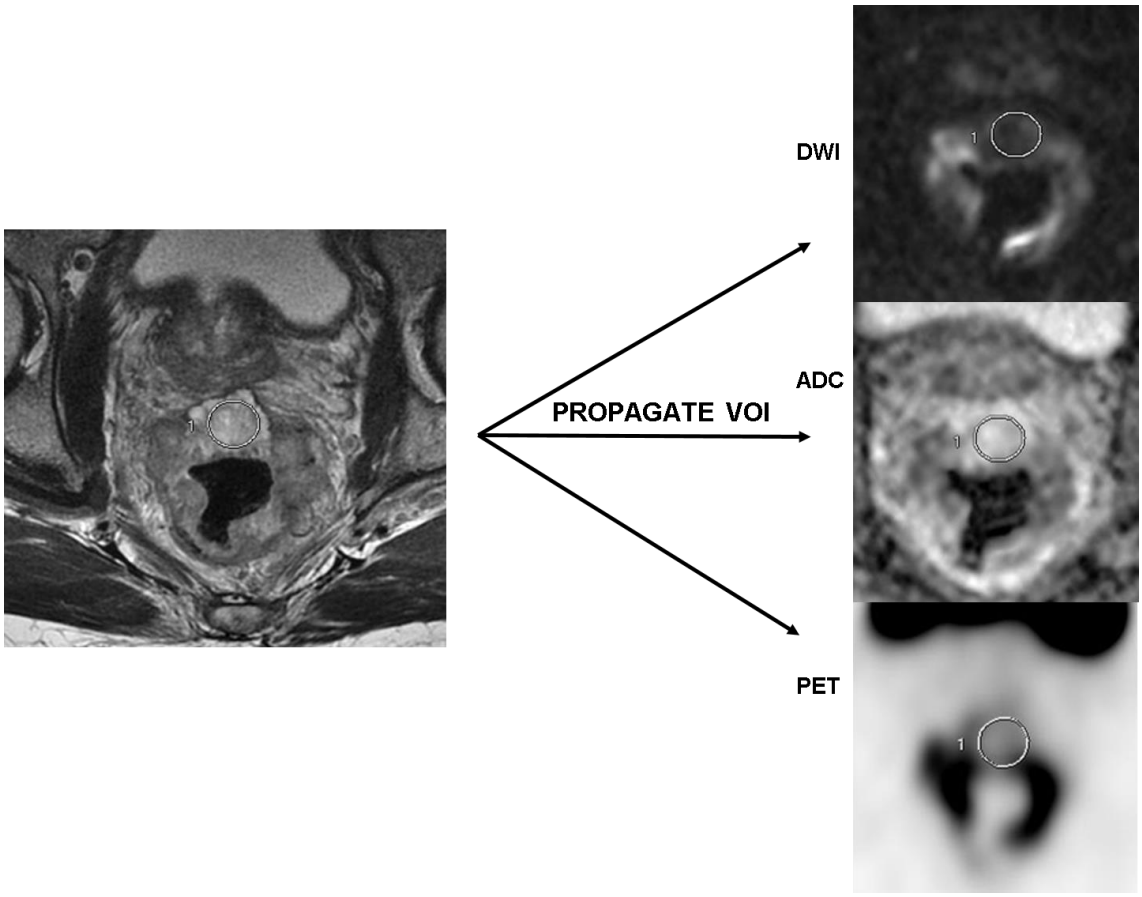

Figure 1. Diagram showing the method of measurement of VOI on PET/MR.

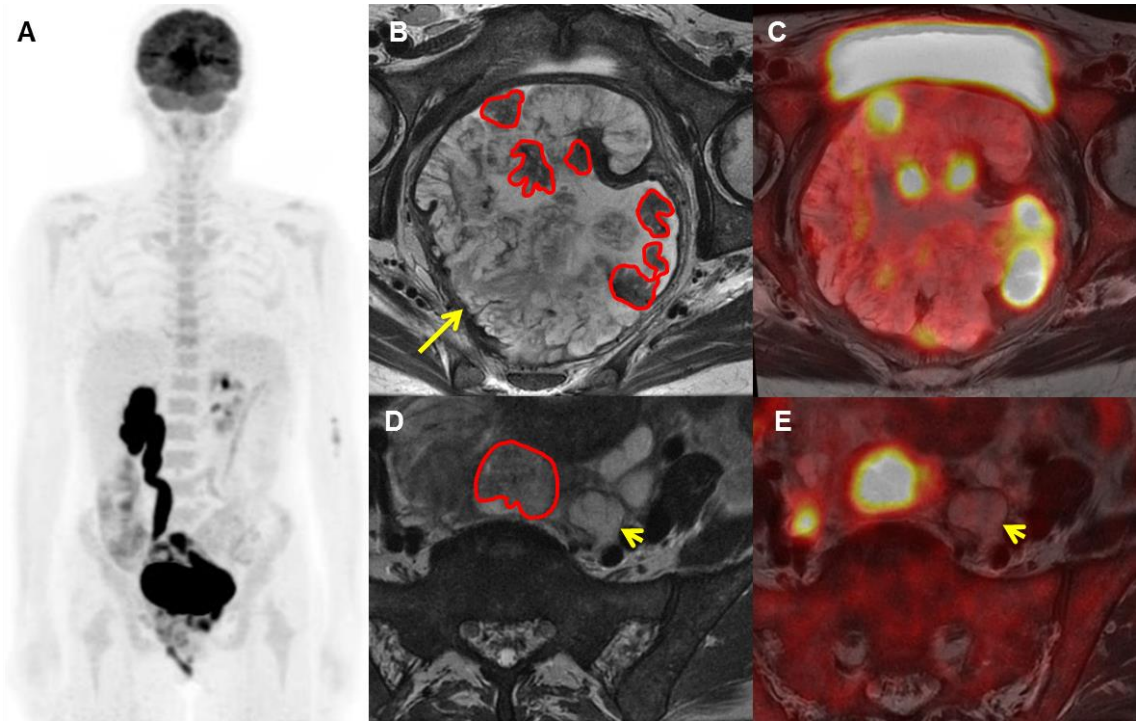

Figure 2. Difference between tumor metabolism between MC and NMC within primary rectal tumor and nodal metastasis. Female, 49 years old, presenting an extensive primary rectal tumor predominantly with MC (yellow arrow on B) with minimum FDG uptake (C) and a small part of NMC (curved red circles on B) with intense FDG uptake (C). Note that the metastatic retroperitoneal enlarged lymph node presents almost exclusive MC (short yellow arrow on D) without FDG uptake on fused images (E). Conversely, the MC in the upper part of the primary lesion (curved circle on D) present a high FDG uptake (E).

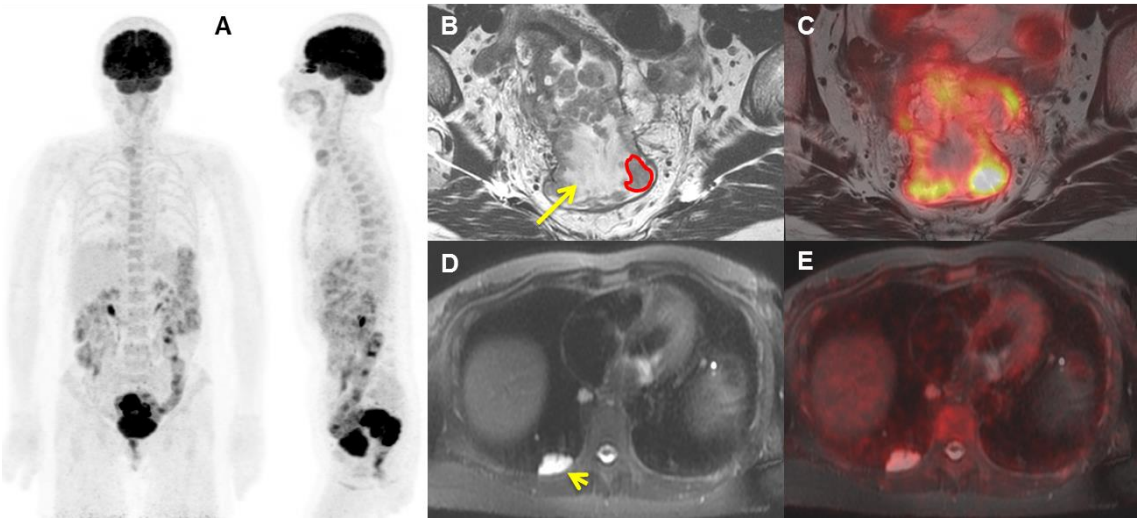

Figure 3. Difference between tumor metabolism between MC and NMC within primary rectal tumor and distant metastasis. Female, 68 years old, presenting a primary rectal tumor with part of MC (yellow arrow on B) with minimum FDG uptake (C) and a part of NMC (curved red circle on B) with high FDG uptake (C). Note a lung metastasis with high signal on T2-weighted image reflecting predominance MC (short yellow arrow on D) without FDG uptake on fused images (E).

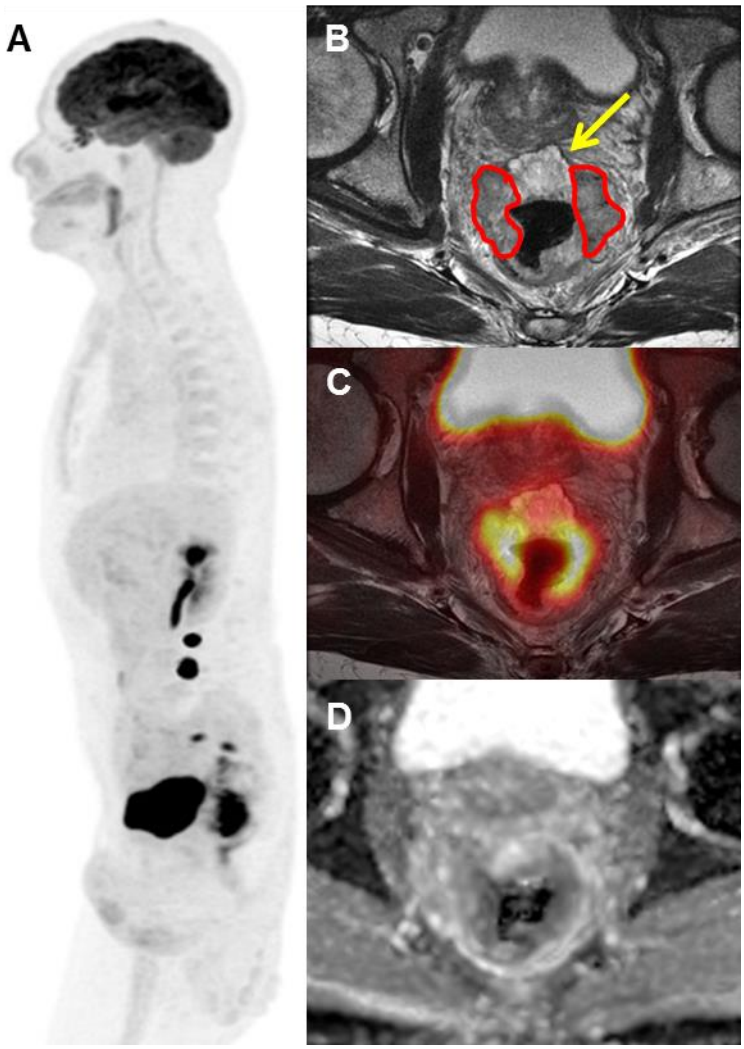

Figure 4. Difference between tumor metabolism and cellularity between MC and NMC within primary rectal tumor. Male, 64 years old, presenting an anterior primary rectal tumor presenting a central MC (yellow arrow on B) with minimum FDG uptake (C) and lateral NMC (curved red circles on B) with intense FDG uptake (C). Note that the difference on restriction diffusion (D) between the MC and NMC is not as intense as the glycolytic metabolism.

c) Publication 3

a. Title: Predictive value of PET/MR in detection of synchronous metastasis of primary rectal cancer

b. Objectives covered: to verify the association between the imaging parameters of the FDG-PET/MR and the presence of synchronous metastases.

c. Journal: Radiology: Imaging Cancer

d. Status: returned from editorial board requiring major revision on 10 September 2020

Predictive value of PET/MR in detection of synchronous metastases of primary rectal cancer

Abstract

Purpose: Analyze the association between PET/MR features and the presence of synchronous metastases of primary rectal cancer.

Methods: From November 2016 to April 2018, 203 participants with rectal adenocarcinoma were recruited in this prospective study (NCT02537340) to undergo to whole-body PET/MR for baseline staging. Two readers analyzed the PET/MR, measuring semiquantitative PET parameters of the primary tumour and also N- and M-stages. Another reader analyzed the MR for loco-regional staging. The standard of reference was biopsy or imaging follow-up. Non-parametric tests were used to compare PET/MR parameters between M0 and M1 participants. Binary logistic regression was used to evaluate the associations between PET/MR parameters and M1 disease.

Results: A hundred and one participants (median 62 y; range: 33 – 87 y) were included. Synchronous metastases were detected in 36/101 (35.6%) participants. Among PET parameters, TLG and MTV of the primary tumor and the presence of PET-positive mesorectal LN were significantly different between M0 and M1 participants. For MR, a significant difference between metastatic and non-metastatic participants was found for mrT stage, positive MR-EMVI and MRF and MR-positive mesorectal LN. On logistic regression, MR-EMVI was the only the significant predictor after a multivariate analysis (6.4 [2.2 - 18.5], p = 0.001).

Conclusion: PET/MR enables the identification of patients at higher risk for metastatic disease based mainly on the MR component. TLG and MTV (but not SUVmax) are different between metastatic and non-metastatic patients.

Key words: Fluorodeoxyglucose F18; Neoplasm Staging; Positron-Emission Tomography; Magnetic Resonance Imaging; Rectal Neoplasms; Predictive value.

Key Points

1. PET/MR for rectal cancer staging shows a high incidence of synchronous metastasis (35.6%) and imaging features of primary tumor are associated with higher risk of M1 disease.

2. MR detected extramural vascular invasion is an independent risk factor for synchronous metastasis (OR = 6.4, p =0.001).

3. PET parameters might complement the MR characteristics of the primary tumor, identifying patients at higher risk for distant metastasis.

Introduction

Improvements in oncologic outcomes in rectal cancer rely both on local disease control and systemic treatment. Accurate baseline staging is pivotal in selecting the best management approach to patients by distinguishing: metastatic patients, who should be sent to chemotherapy or to palliative care; patients bearing early, with no high-risk features for local recurrence rectal cancer, to whom upfront surgery offers good local control; and locally advanced rectal cancer patients, who might benefit from neoadjuvant treatment.

Current guidelines for rectal cancer imaging staging recommend pelvic magnetic resonance (MR) for selecting local recurrence high risk features and chest/abdominal/pelvic contrast-enhanced computed tomography (ceCT) for systemic spread[1–3]. Previous studies have shown potential benefits on staging colorectal cancers with PET/CT when compared to ceCT, presenting a higher detection rate of metastatic lesions, impacting clinical management in up to 30% of cases[4–6]. Additionally, Several PET semiquantitative parameters have been associated to the nodal status[7], response to neoadjuvant treatment[8], local recurrence and overall survival[9] in surgically resected rectal cancer.

With the advent of the simultaneous PET/MR, a possible framework of optimally evaluating not only metastatic disease, but also the primary lesion and the risk of pelvic spread, became possible. PET/MR could be capable of accurately predicting, on the basis of primary tumor imaging, which patients should be at higher risk for distant metastatic disease.

The purpose of this study is to assess whether PET/MR imaging features of the primary tumor and loco-regional lymph nodes can be used to predict the presence of synchronous metastases.

Methods

Study participants

From November 2016 to April 2018, 203 consecutive participants (median 62 y; range: 33 – 87 y) with biopsy-proven rectal adenocarcinoma (up to 15 cm from the anal verge assessed by rigid proctoscopy) were recruited in this prospective study and underwent a whole-body ^{18}F-FDG PET/MR (Signa PET/MR, GE Healthcare) in a referral cancer center. Inclusion criteria were participants older than 18 years old that signed the informed consent form and performed the staging exams (PET/MR and ceCT) at a maximum interval of two weeks. Exclusion criteria were previous treatment for the rectal cancer, including endoscopy resection, known synchronous non-colorectal neoplasia, specific PET (pregnancy or severe uncontrolled diabetes) and MR contraindications (claustrophobia, pacemaker, neurostimulators, cochlear implants, insulin pumps or other paramagnetic devices). The flowchart of participants is represented on Fig. 1. The institutional review board approved the study, and all subjects signed an informed consent form. This study is registered on clinicaltrial.gov under the identification NCT02537340. GE Healthcare partially financed this study, covering the costs of the PET/MR, including the dose of FDG. The authors had control of the data and information submitted for publication.

^{18}F-FDG PET/MR

Patient preparation included at least 4 h of fasting and a plasma glucose level lower than 200 mg/dL. The FDG activity was injected at a rate of 4.5 MBq (0.12mCi)/ Kg - mean radiotracer dose of 296 MBq (8.0 mCi); range 197 MBq (5.3 mCi) – 414 MBq (11.2mCi). After 20 minutes of FDG injection, the patient was transferred to the PET/MR for positioning and hyoscine butylbromide injection (Buscopan®, 20 mg, intravenous). The imaging acquisition was started by a dedicated pelvic MRI for rectal cancer evaluation, which included the following protocol: sagittal T2w, tumor-oriented HR T2w and DWI Focus, and axial T2w, DWI, 3D isotropic T2w of the pelvis. At 60 minutes (mean uptake time of 64 minutes; range 52 – 90 minutes) after FDG injection,

the whole-body PET acquisition started, including 3 to 5 bed positions per patient (depending on the individual body height), using a 3 minutes/bed position acquisition time, under 3D image acquisition and reconstruction protocols. Axial T1 DIXON and a coronal T2 SSFSE were obtained simultaneously to whole-body PET acquisition. Then, two sequences dedicated to the liver were performed: axial T2w SSFSE and axial DWI (mean total acquisition time of 69 minutes, ranging from 53 to 90 minutes). All scans were obtained without gadolinium or liver-specific contrast agent. The MR features are represented on Table 1. The PET/MR workflow is summarized on Fig. 2.

Image analysis

All the imaging readers were aware only of the indication of the exam (primary staging of rectal cancer), but blinded to other clinical data and imaging modalities. A step-by-step read was performed for each imaging modality.

- *Pelvic MR*

A radiologist with 10 years of experience in reading MRI (CDO) analyzed the dedicated pelvic MR for loco-regional staging. The following parameters were assessed for the primary tumor: a) morphology (annular, semi-annular, ulcerated or polypoid); b) longitudinal (distance in cm from anal verge) and circumferential (clockwise) location; c) extension (in cm); d) presence of mucinous component (positive high signal within the tumor in T2w sequence); e) mesorectal fascia (MRF) status (positive if the circumferential resection margin was less or equal than 1mm from the tumor, mesorectal node or deposit; and negative, if the distance was higher than 1mm. For low rectal tumors, a positive margin was considered if the distance of tumor to the levator ani muscle was less or equal than 1mm or the interesphincetic plan was compromised) f) the presence of extramural vascular invasion (MR-EMVI, positive if involvement of medium and large vessels, according to Smith et. al [10]. For regional nodal staging (mesorectal and internal iliac), the malignant criteria

followed the ESGAR guidelines [11] and were based on size and morphology (round shape, irregular border and/or heterogeneous signal). A positive lymph node was considered when: a) short axis diameter ≥ 9 mm; b) short axis diameter 5–8 mm AND ≥ 2 morphologically suspicious characteristics; c) short axis diameter < 5 mm AND 3 morphologically suspicous characteristics; and d) all mucinous lymph nodes (any size).

- *Whole-body PET/MR*

A board certified radiologist with 8 years of experience in reading MR and PET (MAQ) and a nuclear medicine physician with 16 years of experience in reading PET (CAB) analyzed the PET/MR images in consensus by using dedicated software (Advantage Workstation Workstation version 4.6, GE Healthcare). The reading of MR component of PET/MR did not include the dedicated pelvic MR, keeping the readers blinded. For the primary tumor, PET semi-quantitative data was obtained by drawing a volume of interest (VOI) over the primary tumor supported by a visual adaptive algorithm of the isocontouring to avoid the inclusion of structures not related to the tumor, such as the bladder. No fixed threshold was used. SUVmax, SUVmean, metabolic tumor volume (MTV) and total lesion glycolysis (TLG), defined as the product of MTV and SUVmean were recorded. For regional nodal staging, a metabolic criterion was applied, being positive all lymph nodes with an increased FDG uptake from the surrounding background activity on PET regardless size or morphology on MRI. The SUVmax and SUVmean of the liver were measured to ensure homogenous FDG uptake in all patients. For metastatic disease staging, a combination of morphology and metabolism has been used and varied according to the organ (retroperitoneal lymph nodes, lungs, liver and others). For retroperitoneal lymph nodes, a positive lesion was defined when presented at least one of these criteria: a) short axis diameter ≥ 10 mm; b) lymph nodes with two or more morphologically

suspicious characteristics (round shape, irregular border and/or heterogeneous signal); d) all mucinous lymph nodes (any size); and e) all FDG positive (SUVmax > 2.5) lymph nodes. For the lungs, a positive lesion was defined when: a) size larger than 1.0 cm; b) focal FDG uptake higher than surrounding parenchyma with or without a morphological correlation. For the liver and others organs (peritoneum, ovaries, adrenal), three criteria have been defined: 1. intermediate intensity on T2w images; 2. high signal intensity impeding diffusion on images acquired with a high b value; 3. focal FDG uptake higher than the liver parenchyma. A positive lesion presented at least two of these 3 criteria. A maximum of ten lesions per organ was defined.

Standard of reference

The standard of reference for metastatic disease consisted of clinical/imaging follow-up performed at 3, 6 and 12 months after initial staging. and/or histopathological confirmation (when discrepancy between PET/MR findings and other imaging modalities). Imaging follow-up comprised ceCT, abdominal MRI with gadolinium and liver-specific contrast. A positive lesion was determined when presenting progression or response after chemotherapy, or appearance of one or more new lesions in up to 6 months after initial evaluation. Stable lesions under treatment were considered negative. Thirty-six patients were considered metastatic based on these criteria: 17 (47.2%) patients had progressive or responsive lesions at imaging follow-up 16 (44.4%) patients had histopathological confirmation, and 4 (8.3%) patients presented new lesions at imaging follow-up (all confirmed negative on PET/MR at a second-look analysis, and all with positive EMVI).

Statistical analysis

IBM SPSS Statistics, version 25 and RStudio, version 1.1.463 were used for statistical analysis. A two-tailed P value of less than 0.05 was considered significant. The comparison of PET and MR parameters between M0 and M1 participants was performed using student t, Kruskal-Wallis, and chi-squared tests. Uni and multivariate

binary logistic regression was used to evaluate the association of PET and MR parameters with M1 disease.

Results

Patient characteristics

Of the 203 eligible participants, 101 were included. Thirty-six patients presented synchronous metastatic disease by reference standard, mainly in the liver (69.4%, 25/36 patients), lungs (47.2%, 17/36 patients) and non-regional LN (41.2%, 15/36 patients). Based on MR, the majority of patients presented advanced local tumor, being T3b-d or T4 in 80.2% (81/101) and half of patients with regional LN (50.5%, 51/101). Positive MR-EMVI was present in 62.7% (63/101) of the patients and a positive MRF in 49.5 of the patients (50/101). Patient data is summarized in Table 2.

Performance of PET/MR in distinguishing M0 and M1 disease

There was a significant difference in PET and MR parameters of the primary tumor between metastatic and non-metastatic patients. PET-volumetric parameters TLG (352.9 vs. 242.7, p=0.046) and MTV (36.1 vs. 26.2, p=0.028) were significantly higher in metastatic patients. SUVmax (18.9 vs. 19.1, p=0.56) and SUVmean (9.7 vs. 9.3, p=0.98), on the other hand, were not significantly different. See Figs. 3a and 3b. Other parameters also different were mrT stage, presence of MR- or PET-positive mesorectal LNs, and positive MR-EMVI and MRF. All parameters were summarized in Table 3.

Association of synchronous metastasis by PET/MR

On the univariable logistic regression, MR-EMVI presented the highest OR for prediction of metastatic disease (6.4 [2.2 - 18.5], p = 0.001) and it was the only parameter that persisted significant after multivariable analysis (p = 0.042). Other MR parameters also present high OR values on univariable analysis for predicting M1 disease. The mrT and mrN stages and involvement of MRF. For PET, the volumetric parameters (MTV and TLG) and the presence of mesorectal LNs were associated

with higher risk of metastasis. See Fig. 4. These results were summarized on Table 3.

Discussion

PET/MR for staging rectal cancer offers the possibility to assess the loco-regional characteristics of the primary tumor by MR, as recommended by different studies [1,12,13], and the N- and especially M-staging by whole-body PET/MR. The PET/MR parameters of the primary rectal tumor were associated with the presence of synchronous metastasis, especially on MR such as a positive MR-EMVI, but also TLG and MTV on PET. Additionally, semiquantiative data from PET performed well to identify rectal cancer patients at higher risk for synchronous metastasis on MR-EMVI negative patients. This opens the perspective to stratify patients based not only on MR findings but also on PET data.

The distribution of metastatic lesions in our study follows the pattern of rectal cancer spread presented in the literature[14], in which hepatic lesion are by far the most frequent, followed by the lungs. Interestingly, however, it was the high incidence of metastatic LN (14.9% of patients), which was similar to the rate observed after retroperitoneal lymphadenectomy (17% of patients) that was related to worse prognosis[15]. Metastatic retroperitoneal LN is a stated limitation of CT and MRI that rely mainly on size; the use of PET/MR, on the other hand, combines morphology and metabolism, which showed a substantial detection rate that might impact clinical management.

Our study identified some MR features as predictors of synchronous metastasis, such as positive MR-EMVI, mrT and mrN stages. Baseline rectal MR has been used to identify high-risk for metastatic disease patients for treatment stratification that would benefit from more intensive staging[16–18]. The MERCURY study identified some MR findings associated to local recurrence and survival, namely mesorectal fascia involvement, a compromised intersphincteric plane groove (for low rectal tumors), T3c-d or T4 tumors and presence of extramural vascular invasion [19].

MR-EMVI was the most reliable parameter to identify patients with M1 disease, increasing more than 6 times the risk of distant metastasis. This prognostic impact of EMVI has already been shown by several other studies, with an odds ratio varying from 3.0 to 5.7[20,21]. Almost half of patients with positive MR-EMVI presented synchronous metastasis, while only 13% of patients without MR-EMVI were metastatic. The high incidence of positive MR-EMVI is possibly inherent to the characteristics of our Institution, a tertiary high-complex reference cancer center that receives patients from different regions of the state of São Paulo and Brazil. Another study that included more advanced rectal tumors had equivalent incidence rate of positive MR-EMVI (from 50 to 53% of patients)[22,23].

PET-volumetric parameters, namely MTV and TLG allowed for a better distinction of metastastic patients. These parameters have already been associated to rectal tumor risk, including prediction of advanced T stage[24], pathological nodal status[7], response to neoadjuvant therapy[25], cancer recurrence and overall survival[9]. Bundschuh et. al have recently reported that TLG and metabolic tumor volume performed better than SUVmax on pretherapy PET/CT to predict histopathologic response to neadjuvant therapy[26]. Similar findings were observed by Bazan et. al for anal carcinoma, in which MTV yielded prognostic information on progression-free and event-free survival and SUVmax was not prognostic for any clinical outcome[27].

Our study has some limitations. First, there was only one reader for pelvic MR and the findings could depend on the reader experience. Some baseline staging parameters such as lymph node staging had no histopathological confirmation if neoadjuvant treatment had been offered. Moreover, not all lesions detected by PET/MR had histopathological confirmation, but they had correlation with standard contrast-enhanced CT scan and imaging follow-up. Our study used a relatively lengthy protocol, as some authors state that a clinical effective exam should not

exceed 60 minutes. This might be explained by the design of our PET/MR protocol, which was proposed to offer a state-of-art MR of the rectum for primary staging, including HR and isotropic T2w and DWI, and highly sensible MR sequences for the liver with DWI and T2w. This approach, however, might not be the ideal in a clinical setting and some MR sequences could be omitted. Only a few studies have addressed a PET/MR protocol for the evaluation of colorectal cancer (and not rectal exclusively)[28,29] and the average scan time when performing dedicated MR sequences for the pelvis and for the liver (including liver-specific contrast agent) was 85.2 minutes[29]. Lastly, a proper comparison on the detection rate of metastatic lesions and of the potential clinical impact of PET/MR over conventional staging was not performed, which is required to justify management changes and it is the subject of an ongoing trial from our department.

PET/MR enables the identification of patients at higher risk for metastatic disease based mainly on the MR component. TLG and MTV (but not SUVmax) are different between metastatic and non-metastatic patients.

References

1. Engstrom PF, Arnoletti JP, Iii ABB, et al. Rectal Cancer. JNCCN J Natl Compr Cancer Netw. 2009;7:838–881.
2. van de Velde CJH, Boelens PG, Borras JM, et al. EURECCA colorectal: multidisciplinary management: European consensus conference colon & rectum. Eur J Cancer. 2014;50:1.e1-1.e34.
3. Schmoll HJ, Van Cutsem E, Stein A, et al. ESMO Consensus Guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision making. Ann Oncol. Oxford University Press; 2012;23:2479–2516.
4. Ozis SE, Soydal C, Akyol C, et al. The role of 18F-fluorodeoxyglucose positron emission tomography/computed tomography in the primary staging of rectal cancer. World J Surg Oncol. 2014;12:26.
5. Eglinton T, Luck A, Bartholomeusz D, et al. Positron-emission tomography/computed tomography (PET/CT) in the initial staging of primary rectal cancer. Colorectal Dis. 2010;12:667–673.
6. Whaley JT, Fernandes AT, Sackmann R, et al. Clinical utility of integrated positron emission tomography/computed tomography imaging in the clinical management and radiation treatment planning of locally advanced rectal cancer. Pract Radiat Oncol. 2014;4:226–232.
7. Jo HJ, Kim S-J, Kim IJ, et al. Predictive value of volumetric parameters measured by F-18 FDG PET/CT for lymph node status in patients with surgically resected rectal cancer. Ann Nucl Med. 2014;28:196–202.
8. Li Q-W, Zheng R-L, Ling Y-H, et al. Prediction of tumor response after neoadjuvant chemoradiotherapy in rectal cancer using (18)fluorine-2-deoxy-D-glucose positron emission tomography-computed tomography and serum carcinoembryonic antigen: a prospective study. Abdom Radiol (New York). 2016;41:1448–1455.
9. Jo HJ, Kim S-J, Lee HY, et al. Prediction of survival and cancer recurrence using metabolic volumetric parameters measured by 18F-FDG PET/CT in patients with surgically resected rectal cancer. Clin Nucl Med. 2014;39:493–497.
10. Smith NJ, Barbachano Y, Norman AR, et al. Prognostic significance of magnetic resonance imaging-detected extramural vascular invasion in rectal cancer. Br J Surg. 2008;95:229–236.
11. Beets-Tan RGH, Lambregts DMJ, Maas M, et al. Magnetic resonance imaging for clinical management of rectal cancer: Updated recommendations from the 2016 European Society of Gastrointestinal and Abdominal Radiology (ESGAR) consensus meeting. Eur Radiol. 2018;28:1465–1475.
12. Tudyka V, Blomqvist L, Beets-Tan RGH, et al. EURECCA consensus conference highlights about colon & rectal cancer multidisciplinary management: the radiology experts review. Eur J Surg Oncol. Elsevier Ltd; 2014;40:469–475.
13. Dewhurst C, Rosen MP, Blake MA, et al. ACR Appropriateness Criteria pretreatment staging of colorectal cancer. J Am Coll Radiol. 2012;9:775–781.
14. Riihimäki M, Hemminki A, Sundquist J, et al. Patterns of metastasis in colon and rectal cancer. Sci Rep. Nature Publishing Group; 2016;6:29765.
15. Quadros CA, Falcão MF, Carvalho ME, et al. Metastases to retroperitoneal or lateral pelvic lymph nodes indicated unfavorable survival and high pelvic recurrence rates in a cohort of 102 patients with low rectal adenocarcinoma. J Surg Oncol. 2012;106:653–658.
16. MERCURY Study Group. Diagnostic accuracy of preoperative magnetic

resonance imaging in predicting curative resection of rectal cancer: prospective observational study. BMJ. 2006;333:779.
17. Hunter CJ, Garant A, Vuong T, et al. Adverse features on rectal MRI identify a high-risk group that may benefit from more intensive preoperative staging and treatment. Ann Surg Oncol. 2012;19:1199–1205.
18. Chang GJ, You YN, Park IJ, et al. Pretreatment high-resolution rectal MRI and treatment response to neoadjuvant chemoradiation. Dis Colon Rectum. 2012;55:371–377.
19. Taylor FGM, Quirke P, Heald RJ, et al. Preoperative high-resolution magnetic resonance imaging can identify good prognosis stage I, II, and III rectal cancer best managed by surgery alone: a prospective, multicenter, European study. Ann Surg. 2011;253:711–719.
20. Siddiqui MRS, Simillis C, Hunter C, et al. A meta-analysis comparing the risk of metastases in patients with rectal cancer and MRI-detected extramural vascular invasion (mrEMVI) vs mrEMVI-negative cases. Br J Cancer. 2017;116:1513–1519.
21. Kim H, Kim M-J, Kim NK, et al. MRI-detected extramural vascular invasion is an independent prognostic factor for synchronous metastasis in patients with rectal cancer. Eur Radiol. 2014;25:1347–1355.
22. Chand M, Evans J, Swift RI, et al. The prognostic significance of postchemoradiotherapy high-resolution MRI and histopathology detected extramural venous invasion in rectal cancer. Ann Surg. 2015;261:473–479.
23. Zhang X-Y, Wang S, Li X-T, et al. MRI of Extramural Venous Invasion in Locally Advanced Rectal Cancer: Relationship to Tumor Recurrence and Overall Survival. Radiology. 2018;289:677–685.
24. Liao CY, Chen SW, Wu YC, et al. Correlations between 18F-FDG PET/CT parameters and pathological findings in patients with rectal cancer. Clin Nucl Med. 2014;39.
25. Dos Anjos DA, Perez RO, Habr-Gama A, et al. Semiquantitative Volumetry by Sequential PET/CT May Improve Prediction of Complete Response to Neoadjuvant Chemoradiation in Patients With Distal Rectal Cancer. Dis Colon Rectum. 2016;59:805–812.
26. Bundschuh RA, Dinges J, Neumann L, et al. Textural Parameters of Tumor Heterogeneity in 18F-FDG PET/CT for Therapy Response Assessment and Prognosis in Patients with Locally Advanced Rectal Cancer. J Nucl Med. 2014;55:891–897.
27. Bazan JG, Koong AC, Kapp DS, et al. Metabolic Tumor Volume Predicts Disease Progression and Survival in Patients with Squamous Cell Carcinoma of the Anal Canal. J Nucl Med. 2013;54:27–32.
28. Catalano OA, Coutinho AM, Sahani D V., et al. Colorectal cancer staging: comparison of whole-body PET/CT and PET/MR. Abdom Radiol. 2017;42:1141–1151.
29. Kang B, Lee JM, Song YS, et al. Added Value of Integrated Whole-Body PET/MRI for Evaluation of Colorectal Cancer: Comparison With Contrast-Enhanced MDCT. Am J Roentgenol. 2016;206:W10–W20.

Tables

	MR sequence	Orientation	FOV (mm)	Matrix	Slice thickness (mm)	TE/TR (ms)
Whole-body	T1w MRAC	Axial	500 x	256 x	5.2	1674/404
	T2w SSFSE	Coronal	500	128	5.0	5
			500 x	320 x		122/1909
Pelvic MR	T2w FSE	Sagittal	500	320	3.0	
	T2w FSE	Oblique			3.0	122/4863
	DWI Focus[a]	Axial	160 x	256 x	3.0	123/5619
	T2w	Axial	160	256	5.0	66/2112
	DWI[b]	Axial	160 x	256 x	5.0	123/8089
	Isotropic	Coronal	160	256	0.8	68/2800
	T2w		160 x	80 x 50		2800/120
Liver MR		Axial	160	352 x	5.0	
	T2w SSFSE	Axial	300 x	352	5.0	120/2100
	DWI[c]		300	130 x		64/16600
			350 x	130		
			350	512 x		
			500 x	512		
			500			
				288 x		
			380 x	224		
			380	160 x		
			420 x	160		
			420			

Table 1. MRI sequences parameters. [a]b-values, 100 and 1000; [b]b-values, 100 and 1100; [c]b-values, 50 and 800. MRAC - Magnetic Resonance Attenuation Correction, SSFSE - single shot fast spin echo, FSE - fast spin echo, DWI - diffusion-weighted imaging, MR - magnetic resonance, FOV - field of view, TE - Echo time, TR - Repetition time).

		Non-Metastatic (n = 65)	Metastatic (n = 36)	p-value
Age (median [IQR])		62.00 [55.00, 71.00]	61.50 [54.00, 69.00]	
Sex (M:F)		32:33	19:17	
Quantitative PET/MR parameters				
SUVmax (median [IQR])		19.1 [14.8, 25.10]	18.85 [15.40, 25.00]	0.560
SUVmean (median [IQR])		9.3 [8.10, 12.10]	9.70 [7.68, 13.00]	0.980
TLG (median [IQR])		242.70 [123.00, 433.50]	352.95 [225.12, 518.48]	0.046
MTV (median [IQR])		26.2 [15.50, 38.20]	36.15 [23.60, 46.60]	0.028
Qualitative PET/MR parameters				
mrT stage				0.008
	Tx	1 (1.5)	0	
	T2	16 (24.6)	3 (8.3)	
	T3	31 (47.6)	17 (47.3)	
	T4	17 (26.1)	16 (44.4)	
mrN stage				0.090
	N0	37 (56.9)	13 (36.1)	
	N1	25 (38.5)	19 (52.8)	
	N2	3 (4.6)	4 (11.1)	
Mesorectal LN on PET (%)				0.009
	Negative	44 (67.7)	13 (36.1)	
	Positive	21 (32.3)	23 (63.9)	
Mesorectal LN on MR (%)				0.026
	Negative	44 (67.7)	16 (44.4)	
	Positive	21 (32.3)	20 (55.6)	
Lateral pelvic LN on PET				1.000
	Negative	56 (86.2)	31 (86.1)	
	Positive	9 (13.8)	5 (13.9)	
Lateral pelvic LN on MR				0.800
	Negative	52 (80.0)	28 (77.8)	
	Positive	13 (20.0)	8 (22.2)	
EMVI				0.0002
	Negative	33 (50.8)	5 (13.9)	
	Positive	32 (49.2)	31 (86.1)	
MRF				0.039
	Negative	38 (58.5)	13 (36.1)	
	Positive	27 (41.5)	23 (63.9)	
Mucinous Component				1.000
	Absent	53 (81.5)	29 (80.6)	
	Present	12 (18.5)	7 (19.4)	
Location				0.830

Low	27 (41.5)	14 (38.9)
Middle or High	38 (58.5)	22 (61.1)

Table 2. Patient baseline characteristics, PET and MR parameters in metastatic and non-metastatic rectal cancer patients. (SUVmax - maximum Standard Uptake Value, SUVmean - mean Standard Uptake Value, FDG - fluorodeoxyglucose, PET/MR - Positron Emission Tomography/Magnetic Resonance, PET - Positron Emission Tomography, MTV - Metabolic tumor volume and TLG - Total lesion glycolysis, MR - Magnetic Resonance).

PET/MR parameters	OR	P2.5	P97.5	p-value
EMVI	6.4	2.2	18.5	0.001*
Mesorectal LN on MR	2.6	1.2	5.9	0.016*
MRF	2.5	1.1	5.8	0.033*
Mesorectal LN on PET	2.4	1.1	5.1	0.022*
mrN stage	2.0	1.0	4.0	0.037*
MTV	1.7	1.0	2.7	0.036*
TLG	1.6	1.0	2.5	0.034*
mrT stage	1.4	1.1	1.9	0.006*
SUVmax	1.2	0.5	2.9	0.740
Lateral pelvic LN on MR	1.1	0.4	3.1	0.792
Mucinous component	1.1	0.4	3.0	0.904
Lateral pelvic LN on PET	1.0	0.3	3.3	0.995
Low tumor	0.9	0.4	2.1	0.795
SUVmean	0.9	0.3	2.4	0.781

Table 3. Associations between PET/MR parameters and the presence of distant metastasis using univariable binary logistic regression (PET/MR - Positron Emission Tomography/Magnetic Resonance, LN - lymph node, MR - magnetic resonance, MRF - mesorectal fascia, PET - Positron Emission Tomography, MTV - Metabolic tumor volume and TLG - Total lesion glycolysis, SUVmax - maximum Standard Uptake Value, SUVmean - mean Standard Uptake Value).

Figure legends

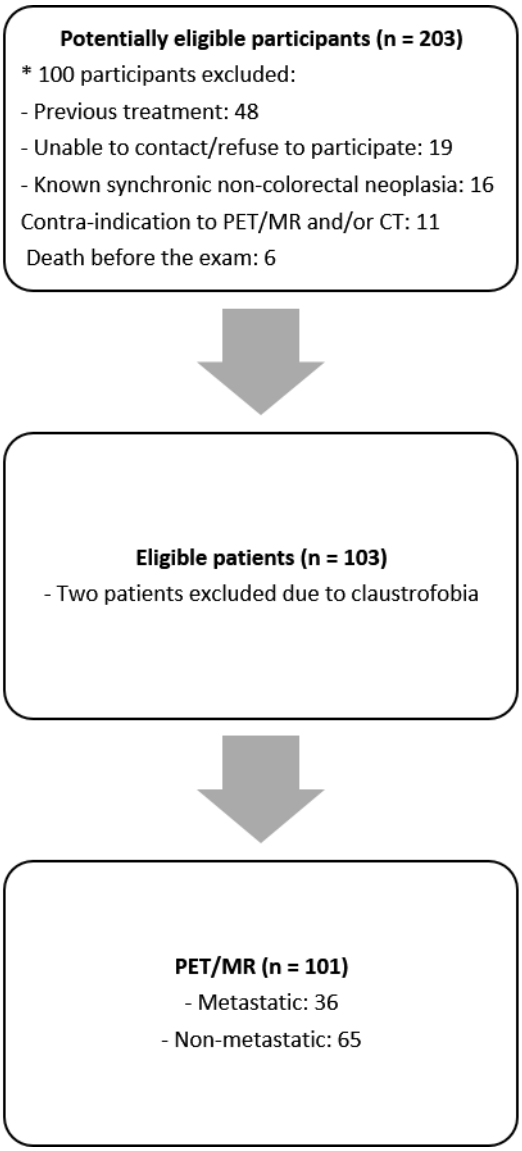

Figure 1. Flowchart of the participants of the study

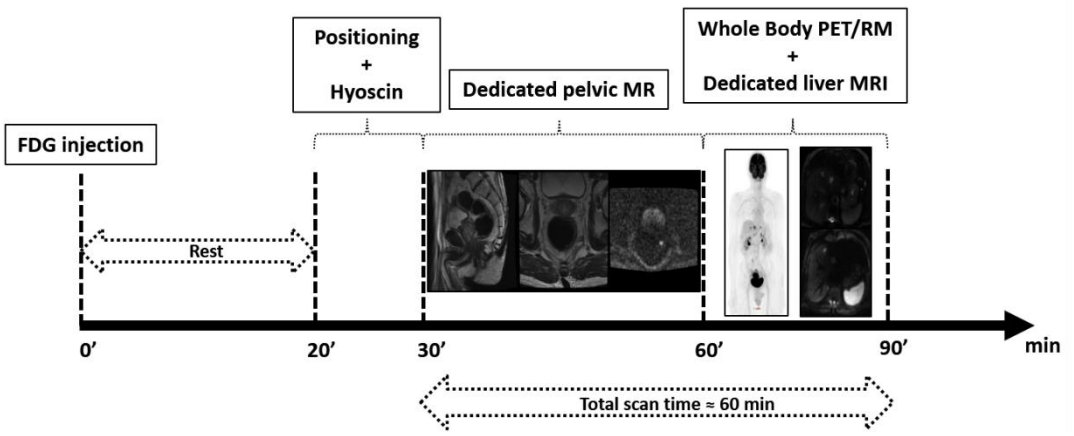

Figure 2. Workflow of FDG-PET/MR for rectal cancer staging (FDG - fluorodeoxyglucose, PET/MR - Positron Emission Tomography/Magnetic Resonance).

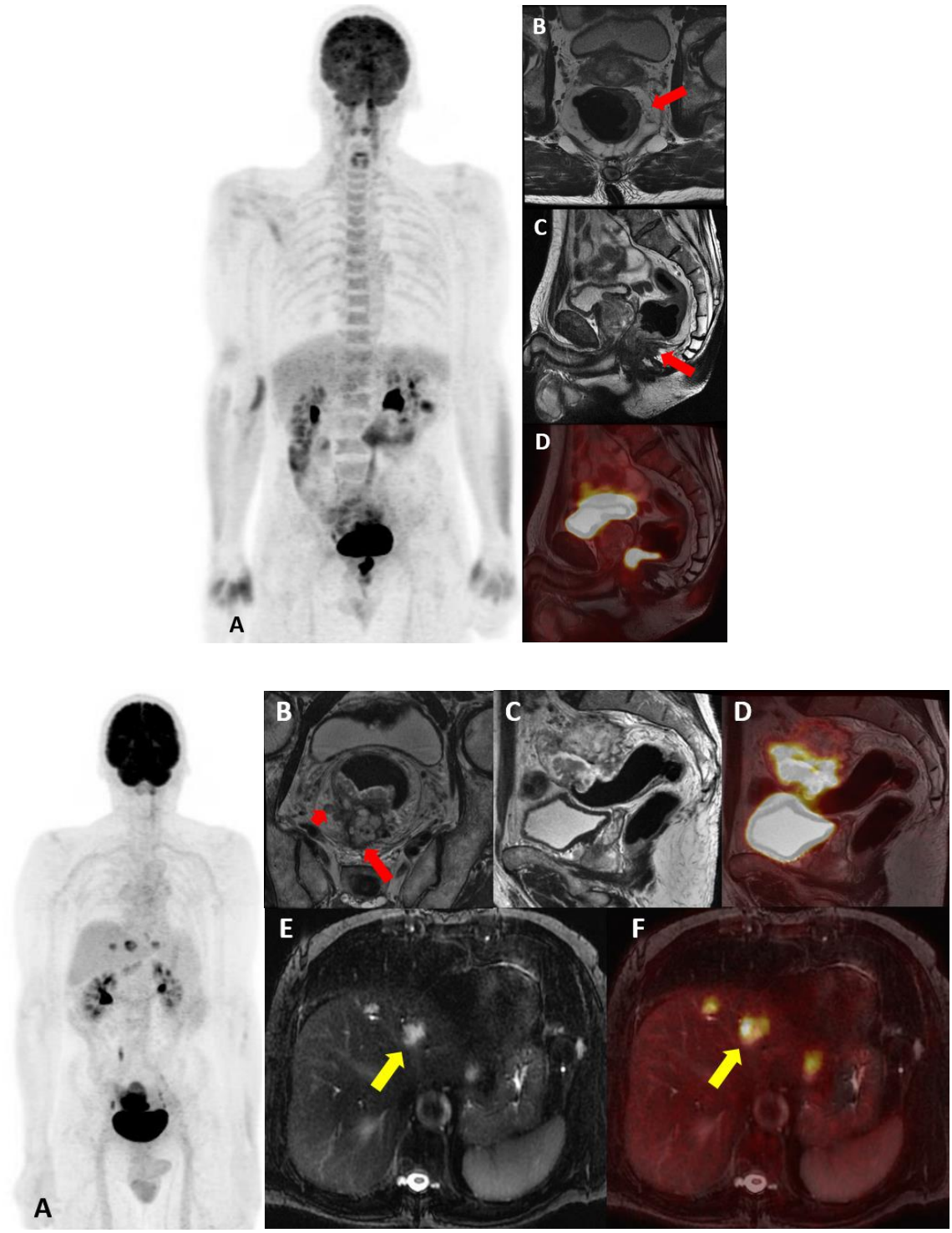

Figure 3. Two patients with high FDG uptake, one non-metastatic (Fig. 2a) and the other metastastic (Fig. 2b). **Fig. 3a.** Seventy-four-year-old man with low-risk rectal adenocarcinoma. Coronal MIP PET (A), axial T2w (B), sagittal T2w (C), and fused PET/MR (D). Although the SUVmax was 25.1, the primary tumor (red arrows)

presented both MR (mrT2N0 without mesorectal fascia involvement or extramural vascular invasion) and PET features of low-risk (MTV of 15.9 and TLG of 133.4). **Fig. 3b.** Sixty-five-year-old man with liver metastases. Coronal MIP PET (A), axial T2w (B, E), sagittal T2w (C), and fused PET/MR (D, F) images of a patient with the primary tumor presenting a SUVmax of 21.4; FDG-PET/MR accurately characterized the features of this primary tumor risk (white long arrows) both on PET (MTV and TLG of 23.3 and 312.6, respectively) and MR - mrT3b with mesorectal fascia involvement (red long arrow), positive extramural vascular invasion and mesorectal lymph nodes (short red arrow). Note TLG and MTV, but not SUVmax, were able to distinguish patients in risk of distant metastasis. (SUVmax - maximum Standard Uptake Value, FDG - fluorodeoxyglucose, PET/MR - Positron Emission Tomography/Magnetic Resonance, PET - Positron Emission Tomography, MTV - Metabolic tumor volume and TLG - Total lesion glycolysis, MR - Magnetic Resonance).

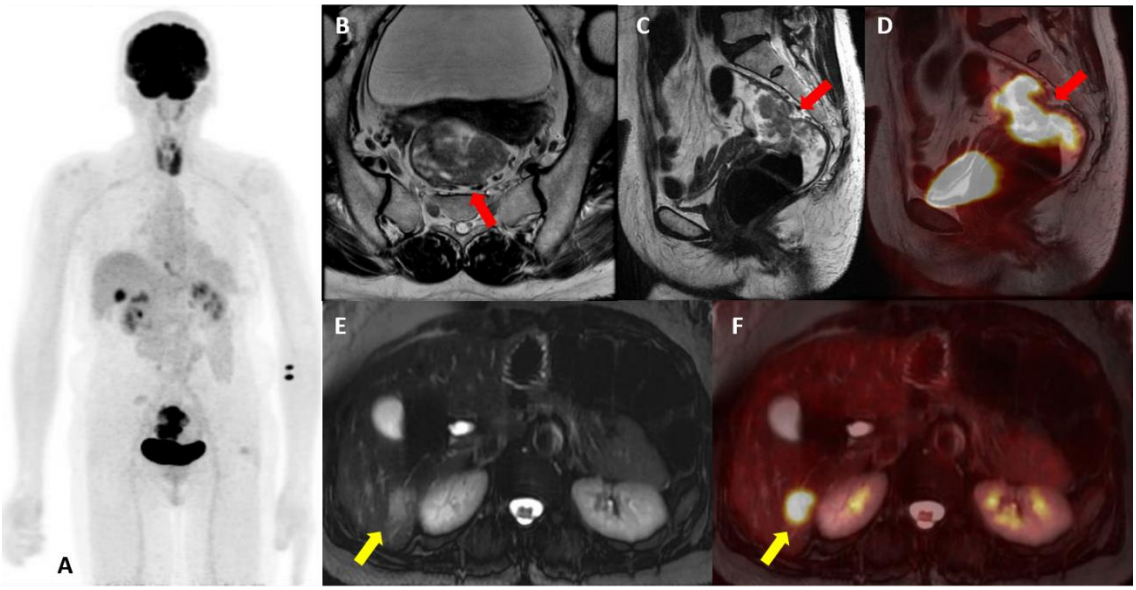

Figure 4. Sixty-three-year-old woman with liver metastasis. Coronal MIP PET (A), axial T2w (B, E), sagittal T2w (C), and fused PET/MR (D, F). On pelvic MR, the primary rectal tumor (red arrows) was characterized as low-risk, presenting as mrT2N0 without mesorectal fascia involvement or extramural vascular invasion. On FDG-PET/MR, however, the primary tumor (white short arrows) presented high-risk values for MTV and TLG (60.8 and 463.5, respectively) and the patient presented a metastatic lesion in the liver on the DWI and fused PET/MR (white arrowheads). (MR - Magnetic Resonance, FDG - fluorodeoxyglucose, PET/MR - Positron Emission Tomography/Magnetic Resonance, MTV - Metabolic tumor volume and TLG - Total lesion glycolysis, DWI - diffusion weighted-imaging)

4 CONCLUSIONS

a) For the detection of distant metastases secondary to rectal adenocarcinoma, the FDG-PET/MR is more accurate than the CS, both in an analysis based on patients and lesions.

b) The detection rate of FDG-PET/MR is higher than that of CS for all metastatic lesions together (non-regional lymph nodes, hepatic, pulmonary and others) and for non-regional metastatic lymph nodes alone.

c) In patients with EMVI in the primary rectal tumor, FDG-PET/MR is more accurate than CS for detecting metastatic lesions; while for patients without EMVI in the primary tumor, FDG-PET/MR and CS did not show statistical difference.

d) FDG-PET/MR allows the distinction between mucinous and non-mucinous components in primary rectal adenocarcinoma due to the difference in glycolytic metabolism on PET, but not due to the difference in cellularity on diffusion-weighted imaging.

e) EMVI detected by MRI in medium and large vessels in the primary rectal tumor is an independent risk factor for synchronous metastases. Some PET parameters, notably the volumetric semi-quantitative data (MTV and TLG), and other MRI parameters, especially the advanced T and N positive stages and CRM impairment, were able to differentiate metastatic from non-metastatic patients.

5 APPENDICES

Appendix A – Published paper on EJNMMI (journal format)

European Journal of Nuclear Medicine and Molecular Imaging
https://doi.org/10.1007/s00259-020-04911-x

ORIGINAL ARTICLE

Diagnostic accuracy of FDG-PET/MRI versus pelvic MRI and thoracic and abdominal CT for detecting synchronous distant metastases in rectal cancer patients

Marcelo A. Queiroz[1] · Cinthia D. Ortega[2] · Felipe R. Ferreira[2] · Sergio C. Nahas[3] · Giovanni G. Cerri[2] · Carlos A. Buchpiguel[1]

Received: 12 December 2019 / Accepted: 7 June 2020

Abstract

Purpose We compared the diagnostic accuracy of detecting distant metastases for baseline rectal cancer staging between PET/MRI and conventional staging (CS).

Materials and methods This prospective study from November 2016 to April 2018 included 101 rectal adenocarcinoma patients for primary staging. These patients underwent whole-body PET/MRI in addition to CS (pelvic MRI and thoracic and abdominal contrast-enhanced CT). Different readers analyzed CS and PET/MRI findings for primary tumor, nodal, and metastatic staging. The presence, number, and location of metastases were recorded according to the organ involved (non-regional lymph nodes (LNs), liver, lungs, or others). Lesions were defined as positive, negative, or indeterminate. The number of lesions per organ was limited to 10. The McNemar test was used to compare the accuracies.

Results PET/MRI exhibited a higher accuracy in detecting metastatic disease than CS in all patients (88.4% vs. 82.6%, $p = 0.003$) and in patients with extramural vascular invasion (EMVI) (88.9% vs. 85.5%, $p = 0.013$). The detection rate of PET/MRI was superior to that of CS for all lesions [84.1% vs. 68.9%, $p = 0.001$], as well as those in the liver (89.2% vs. 84.2%), non-regional LNs (90.0% vs. 36.7%), and lungs (76.4% vs. 66.9%). PET/MRI correctly classified 19/33 (57.5%) patients with indeterminate lesions on CS.

Conclusion PET/MRI yields higher accuracy than CS for detecting distant synchronous metastases in the baseline staging of patients with rectal cancer and EMVI. PET/MRI exhibited a higher detection rate than CS for identifying non-regional LNs, hepatic lesions, and pulmonary lesions as well as correctly classifying patients with indeterminate lesions.

Trial registration NCT02537340

Keywords Fluorodeoxyglucose F18 · Neoplasm staging · Positron-emission tomography · Magnetic resonance imaging · Rectal neoplasms

Introduction

Baseline staging of rectal cancer requires a multidisciplinary team to define the best treatment approach. The imaging work-up for the primary staging of rectal cancer consists of pelvic magnetic resonance imaging (MRI) for locoregional evaluation and thoracic and abdominal contrast-enhanced computed tomography (ceCT) for detection of distant metastases, as

This article is part of the Topical Collection on Oncology - Digestive tract

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00259-020-04911-x) contains supplementary material, which is available to authorized users.

✉ Marcelo A. Queiroz
marcelo.queiroz@hc.fm.usp.br

[1] Nuclear Medicine Division, Department of Radiology and Oncology, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Rua Doutor Ovidio Pires de Campos, 872, Sao Paulo, SP 05403-010, Brazil

[2] Department of Radiology and Oncology, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, Brazil

[3] Department of Surgery, Division of Colorectal Surgery, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, Brazil

Published online: 20 June 2020

recommended by ESMO and NCCN guidelines [1, 2]. Alternatively, positron emission tomography/CT (PET/CT) can be used, especially for the following: (1) to characterize indeterminate lesions on ceCT, (2) to evaluate potentially curable metastatic disease (and exclude occult sites of metastases), and (3) to stage patients at high risk for metastases, i.e., with extensive extramural vascular invasion (EMVI) or high levels of carcinoembryonic antigen [1, 2]. Additionally, a liver MRI might be considered to assess indeterminate liver lesions on ceCT [1, 2]. The T and N stages of primary rectal tumors are defined according to pelvic MRI, which identifies locally advanced rectal tumors and facilitates in guiding the treatment plan [3]. The M stage is defined according to thoracic and abdominal ceCT, which might be followed by complementary PET/CT and liver MRI to clarify indeterminate lesions, as both methods exhibit higher accuracy for the detection of distant metastases [4, 5]. Moreover, the prognosis of patients with rectal cancer depends on the stage of the disease at the time of diagnosis, with overall survival in 5 years decreasing from 89.9% for localized tumors to 14.2% for systemic disease [6].

In this context, the use of PET/MRI for primary rectal cancer staging combines the standard imaging modality for the T and N stages with PET as well as both PET and liver MRI for the M stage. To date, data comparing PET/MRI with other imaging modalities for colorectal cancer is scarce and limited due to small patient numbers, heterogeneous populations (including both colon and rectal cancer patients for primary staging and restaging), and study designs that are mostly retrospective [7–11]. Nevertheless, these studies suggest that PET/MRI yields a diagnostic performance that is superior to both CT and PET/CT, which could have a robust clinical impact on patient management.

This study aimed to compare the diagnostic accuracy of PET/MRI compared to conventional staging (CS) (that consists of pelvic MRI and thoracic and abdominal ceCT) for the detection of distant metastases during the primary staging of rectal cancer patients. We hypothesized that, compared to combined MRI and CT, PET/MRI might exhibit higher accuracy with a lower prevalence of indeterminate lesions in detecting metastatic disease.

Materials and methods

Study population

This prospective study was conducted from November 2016 to April 2018 and recruited 203 consecutive patients with biopsy-proven rectal adenocarcinomas (assessed by rigid proctoscopy to be up to 15 cm from the anal verge) to undergo [^{18}F]fluorodeoxyglucose (FDG)-PET/MRI. The inclusion criteria were as follows: (1) age more than 18 years, (2) ready to sign the informed consent form, and (3) able to undergo the staging examinations (PET/MRI and ceCT) at a maximum interval of 2 weeks. The exclusion criteria were as follows: (1) previous treatment for rectal cancer, including endoscopic resection, and diagnosed synchronous non-colorectal neoplasia and (2) PET/MRI contraindications. The patients' selection flowchart is presented in Fig. 1. The institutional review board approval was obtained, and this study was registered at clinicaltrial.gov under the identification number NCT02537340.

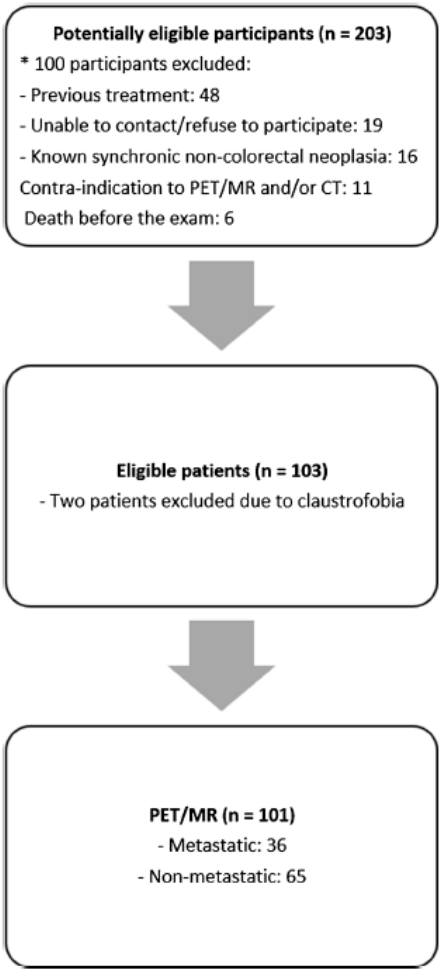

Fig. 1 Flowchart of the participants of the study

Imaging procedures

Thoracic and abdominal ceCT

The CT scans were performed within 2 weeks before or after PET/MRI was performed. Thoracic and abdominal CT scans were obtained from the lung apices to the superior iliac crest with a 16–256-multidetector CT (Brilliance CT, Philips, Netherlands). The scans were acquired during a breath hold after intravenous injection of contrast media (Iopamiron 300, Bracco, Italy) based on body weight (1.2 mL/kg) at a rate between 2 and 3 mL/s during the portal venous phase (70 s after injection). CT parameters were as follows: field of view of 300 mm, 90–120 kV (depending on patient body mass index), variable mAs, rotation between 0.5–0.75 s, pitch between 0.7 and 1.2, matrix of 512 × 512, slice thickness of 2 mm, and increment of 1 mm.

Whole-body PET/MRI (including pelvic and liver MRI)

Whole-body FDG-PET/MRI followed the guidelines of the European Association of Nuclear Medicine for oncological imaging in adults [12], adapted for a PET/MRI workflow. The injected activity of FDG was calculated according to the patient's weight (4.5 MBq/kg, mean radiotracer dose of 296 MBq, and range of 197–414 MBq). After FDG injection, the patient rested for 20 min and was then transferred to the PET/MRI scanner for positioning and hyoscine butylbromide injection (20 mg, intravenous). The scanning was initiated 30 min after FDG injection and comprised three parts: (1) dedicated pelvic MRI (without PET acquisition), which was performed for locoregional staging of primary rectal cancer and followed the guidelines of the European Society of Gastroenterology and Abdominal Radiology [13]; (2) whole-body PET/MRI (acquisition started 60 min after FDG injection, mean uptake time of 64 min), which included 3–5 bed positions per patient and used a 3-min/bed position acquisition time under 3D image acquisition and standard reconstruction protocols; and (3) dedicated abbreviated (5 min) liver MRI (without PET acquisition). The MRI sequences and parameters are shown in Table 1.

Imaging analysis

The imaging readers were only aware of the indication of the examination (primary staging of rectal cancer), but blinded to other clinical data and imaging modalities. A step-by-step read was performed for each imaging modality.

Conventional staging

Pelvic MRI A radiologist with 10 years of experience in reading MRI (C.D.O.) analyzed the dedicated pelvic MRI for locoregional staging. The following parameters were assessed for the primary tumor: (a) morphology (annular, semi-annular, ulcerated, or polypoid); (b) longitudinal (distance in cm from anal verge) and circumferential (clockwise) location; (c) extension (in cm); (d) presence of mucinous component (positive high signal within the tumor in the T2w sequence); (e) mesorectal fascia status (positive or negative if the circumferential resection margin was ≤ 1 mm or > 1 mm from the tumor, EMVI, or deposit, respectively; for low rectal tumors, a positive margin was considered if the distance between the tumor and the levator ani muscle was ≤ 1 mm or the intersphincteric plane was compromised); and (f) the presence of EMVI (positive if medium and large vessels were involved, according to Smith et al. [11]). For regional nodal staging, a positive lymph node (LN) was considered when at least one of the morphologically suspicious characteristics (irregular border and/or heterogeneous signal) was present.

Thoracic and abdominal ceCT Another radiologist with 5 years of experience in reading CT (F.R.F.) analyzed the thoracic and abdominal ceCT for systemic staging and detection of distant metastases. The metastases were categorized as positive, negative, or indeterminate and listed according to the involved organ, i.e., non-regional nodes, liver, lungs, and others. Malignant criteria were defined based on size and morphology. A positive lesion was defined by a) a short axis diameter of ≥10 mm and/or b) ≥ 2 morphologically suspicious characteristics (round shape, irregular border, and/or hypovascular in the portal venous phase). An indeterminate lesion was defined by (a) a short axis diameter of < 10 mm and (b) only one morphologically suspicious characteristic (round shape, irregular border, and/or hypovascular in the portal venous phase). The maximum number of lesions per organ was 10.

Whole-body PET/MRI A board-certified radiologist with 8 years of experience in reading MRI and PET (M.A.Q.) and a nuclear medicine physician with 16 years of experience in reading PET (C.A.B.) analyzed the PET/MRI images by using a dedicated workstation (Advantage Workstation version 4.6, GE Healthcare). The readers were kept blinded as the MRI component of the PET/MRI (comprised of the axial T2w of the pelvis, axial T1 DIXON, and coronal T2 SSFSE) did not include the dedicated pelvic MRI (high-resolution T2w sequences oriented to the tumor). For the primary tumor, PET semi-quantitative data was obtained by semi-automatically drawing a volume of interest over the primary tumor using the application PETVCAR (GE Healthcare), which was supported by a visual adaptation of the isocontouring to avoid the inclusion of structures not related to the tumor, such as the bladder. Maximum standard uptake value (SUVmax), mean SUV (SUVmean), metabolic tumor volume, and total lesion glycolysis (defined as the product of metabolic tumor volume and SUVmean) were recorded. For

Table 1 Technical parameters of MRI sequences acquired with PET/MRI

	MR sequence	Orientation	FOV (mm)	Matrix	Slice thickness (mm)	TE/TR
Dedicated pelvic MRI	T2 FSE (tumor)	Saggital	160 × 160	256 × 256	3.0	120/4800
	T2 FSE (tumor)	Oblique	160 × 160	256 × 256	3.0	120/5600
	DWI focus[a]	Axial	160 × 160	80 × 50	3.0	60/2100
	T2 (pelvis)	Axial	300 × 300	352 × 352	5.0	120/8000
	DWI[b]	Axial	350 × 350	130 × 130	5.0	68/2800
Whole-body PET/MRI	T1 Dixon	Axial	500 × 500	288 × 192	5.0	1680/4560
	T2 SSFSE	Coronal	500 × 500	288 × 192	5.0	120/3500
Abbreviated liver MRI	T2w SSFSE	Axial	380 × 380	288 × 224	5.0	120/2100
	DWI[c]	Axial	420 × 420	160 × 160	5.0	64/16600

SSFSE single-shot fast spin-echo, *FSE* fast spin echo, *DWI* diffusion-weighted imaging/diffusion, *MRI* magnetic resonance imaging, *PET* positron emission tomography, *FOV* field of view, *TE* echo time, *TR* repetition time

[a] *b* values, 100 and 1000

[b] *b* values, 100 and 1100

[c] *b* values, 50 and 800

regional nodal staging, in addition to the MRI criteria, the following metabolic criterion was applied: all LNs with FDG uptake > 2.5 were considered positive, regardless of size or morphology. For metastatic disease staging, a combination of morphology and metabolism was used and varied depending on the organ (retroperitoneal LNs, lungs, liver, and others). For retroperitoneal LNs, a positive lesion was defined by one of the following criteria: (a) a short axis diameter of ≥ 10 mm, (b) ≥ 2 morphologically suspicious characteristics (round shape, irregular border, and/or heterogeneous signal), (c) all mucinous LNs (any size), and (d) the LN was FDG-positive (SUVmax > 2.5). For the lungs, a positive lesion was defined by one of the following criteria: (a) a size of > 1 cm and (b) focal FDG uptake higher than that of the surrounding parenchyma with or without a morphological correlation. For the liver and other organs (peritoneum, ovaries, and adrenal organs), a positive lesion presented at least two of the following three criteria: (a) intermediate intensity on T2w images, (b) high signal intensity impeding diffusion on images acquired with a high *b* value, and (c) focal FDG uptake higher than that of the liver parenchyma. A maximum of 10 lesions per organ was also defined.

Standard of reference

The standard of reference (SOR) for metastatic disease consisted of clinical/imaging follow-ups performed at 3, 6, and 12 months after initial staging and/or histopathological confirmation (when discrepancy between PET/MRI findings and other imaging modalities was present). A lesion was considered positive if it exhibited progression or a response after chemotherapy or if at least one new lesion appeared within 6 months after initial evaluation. Lesions that were stable under treatment were considered negative.

Statistical analysis

IBM SPSS Statistics (version 25) and RStudio (version 1.1.463) were used for statistical analysis. A two-tailed *P* value of < 0.05 was considered statistically significant. For the calculation of diagnostic accuracy, the indeterminate lesions were considered negative and the McNemar test was applied. The McNemar test was also used to calculate the diagnostic accuracy according to the status of EMVI detected by MRI. The numbers needed to treat were also calculated, i.e., the count of how many people need to be scanned in order for one person to benefit. The primary outcome was the presence of metastases, and the comparison was between the metastatic patients observed with CS and the metastatic patients observed with PET/MRI.

Results

Patient characteristics

This study included 101 patients (mean age, 62 years; range, 33–87 years; male-to-female ratio, 51:50). SOR detected 334 synchronous metastases in 36 patients (35.6%), predominantly in the liver (69.4%, 25/36 patients), followed by the lungs (47.2%, 17/36 patients) and non-regional LNs (41.2%, 15/36 patients). Of the 36 metastatic patients, 17 (47.2%) exhibited progressive or responsive lesions at imaging follow-up, 16 (44.4%) had histopathological confirmation, and 3 (8.3%)

presented new lesions at imaging follow-up, all of which were confirmed negative on PET/MRI after a second analysis.

Table 2 Characteristics of patient population

	All patients ($n = 101$)
Age (median [IQR])	62 [55–70]
Sex (M:F)	51:50
Quantitative parameters on PET/MRI	
SUVmax (median [IQR])	19.1 [15.1–25.10]
SUVmean (median [IQR])	9.5 [7.9–12.8]
TLG (median [IQR])	276.8 [154.4–502.2]
MTV (median [IQR])	44.8 ± 65.02
Qualitative parameters on PET/MRI	
mrT stage (%)	
Tx	1 (1.0)
T2	19 (18.8)
T3	48 (47.5)
T4	33 (32.7)
mrN stage (%)	
N0	50 (49.5)
N1	44 (43.6)
N2	7 (6.9)
Mesorectal LN on PET (%)	
Negative	57 (56.4)
Positive	44 (43.6)
Mesorectal LN on MRI (%)	
Negative	60 (59.4)
Positive	41 (40.6)
Lateral pelvic LN on PET (%)	
Negative	87 (86.1)
Positive	14 (13.9)
Lateral pelvic LN on MRI (%)	
Negative	80 (79.2)
Positive	21 (20.8)
EMVI	
Negative	38 (37.6)
Positive	63 (62.4)
CRM	
Negative	51 (50.5)
Positive	50 (49.5)
Mucinous component	
No	82 (81.2)
Yes	19 (18.8)
Location	
Low	41 (40.6)
Middle/high	60 (59.4)

IQR interquartile range, *PET* positron emission tomography, *MRI* magnetic resonance imaging, *SUVmax* maximum standard uptake value, *SUVmean* mean standard uptake value, *TLG* total lesion glycolysis, *MTV* metabolic tumor volume, *LN* lymph node, *EMVI* extramural vascular invasion, *CRM* circumferential resection margin

According to the dedicated pelvic MRI, most patients exhibited locally advanced rectal cancer, with 80.2% (81/101) of patients exhibiting at least T3b and 50.5% (51/101) of patients exhibiting positive regional LNs. A positive EMVI was observed in 62.7% (63/101) of patients, and an involved mesorectal fascia was observed in 49.5% (50/101) of patients. Table 2 summarizes the patients' characteristics.

Diagnostic accuracy of PET/MRI vs. CS

From the 36 metastatic patients, CS and PET/MRI classified 23 and 31 patients as metastatic, respectively. With this difference, the calculated numbers needed to treat were 5 for the metastatic patients and 12 for all the rectal cancer patients. This indicates that for every 5 metastatic or 12 rectal cancer patients, one presents metastases only on PET/MRI. The patient-based analysis revealed that PET/MRI exhibited a significantly higher accuracy (88.4% vs. 82.6%, $p = 0.003$) and an especially higher specificity in detecting metastatic disease than CS (Table 3). The diagnostic accuracy of PET/MRI for detecting distant metastases was also significantly higher than that of CS (88.9% vs. 85.5%, $p = 0.013$) in patients with EMVI, but was not different (85.4% vs. 68.5%, $p = 0.22$) among patients without EMVI (Table 4; Figs. 2 and 3).

From all of the 334 metastatic lesions, PET/MRI detected 281 in 31 patients, while CS detected 230 lesions in 23 patients (84.1% vs. 68.9%, $p = 0.001$). The organ-based analysis revealed that the detection rate of PET/MRI was significantly superior to that of CS for liver (89.2% (124/139 in 23 patients) vs. 84.2% (117/139 in 20 patients), $p = 0.023$), non-regional LNs (90.0% (54/60 in 18 patients) vs. 36.7% (22/60 in 8 patients), $p = 0.001$), and lungs (76.4% (97/127 in 13 patients) vs. 66.9% (85/127 in 13 patients), $p = 0.019$). No difference was observed for other lesions, and both methods presented a diagnostic rate of 75% (6/8 in 6 patients) (Figs. 4 and 5).

On a patient-based analysis, PET/MRI and CS were congruent in 23 metastatic patients and PET/MRI alone identified 8 more patients. There was any metastatic patient positive on CS only. Five patients were considered positive for metastases during imaging follow-up and were considered false negative

Table 3 Diagnostic accuracy of positron emission tomography/magnetic resonance imaging (PET/MRI) vs. conventional staging (CS) in all patients

	PET/MRI	CS
Sensitivity	90.8%	98.5%
Specificity	86.1%	66.7%
Positive likelihood ratio	6.53	2.96
Negative likelihood ratio	0.11	0.02
Accuracy	88.4%	82.6%
	$p = 0.003$	

Table 4 Diagnostic accuracy of positron emission tomography/magnetic resonance imaging (PET/MRI) vs. conventional staging (CS) in patients with and without extramural vascular invasion (EMVI)

	Patients with EMVI ($n = 63$)		Patients without EMVI ($n = 38$)	
	PET/MRI	CS	PET/MRI	CS
Sensitivity	90.6%	100%	90.9%	97.0%
Specificity	87.1%	71.0%	80.0%	40.0%
Positive predictive value	87.9%	78.1%	96.8%	91.4%
Negative predictive value	90.0%	100%	57.1%	66.7%
Accuracy	88.9%	85.5%	85.4%	68.5%
	$p = 0.01$		$p > 0.05$	

on both methods. On a lesion-based comparison, PET/MRI and CS detected 223/334 metastatic lesions (66.8%); PET/MR alone detected 58/334 lesions (17.4%), mainly non-regional lymph nodes; and CS alone detected 7/334 lesions (2.1%), especially lung lesions. Both methods missed 46/334 lesions (13.8%), especially lung and liver nodules. See Fig. 6.

Characterization of indeterminate lesions

Both PET/MRI and CS were indeterminate in six patients, of which all proved to be negative for metastases on imaging follow-up. PET/MRI detected five more indeterminate patients (accounting for 16 lesions—11 non-regional LNs, 0 in the liver, 1 in the lungs, and 4 in other sites), of which CS was negative in four (one false negative and three true negatives) and positive in one (a false positive). On the other hand, CS detected twenty-seven more indeterminate patients (accounting for 68 lesions—20 non-regional LNs, 29 in the liver, 16 in the lungs, and 3 in other sites), of which PET/MRI was negative in 18 (4 false negatives and 14 true negatives) and positive in 9 (4 false positives and 5 true positives). PET/MRI correctly classified 19/33 (57.5%) patients with indeterminate lesions on CS, while CS correctly classified 3/11 (27.2%) patients with indeterminate lesions on PET/MRI (Fig. 7).

Discussion

Our study demonstrated that PET/MRI has a higher accuracy than CS for the detection of distant synchronous metastases in baseline staging of patients with rectal cancer and of patients that presented EMVI within primary tumors. PET/MRI exhibited a higher detection rate than CS for detecting non-regional LNs as well as hepatic and pulmonary lesions. Moreover, PET/MRI exhibited a more correct classification of patients with indeterminate lesions than CS.

The accuracy for detecting metastatic disease was higher for PET/MRI than pelvic MRI and thoracic and abdominal CT. Recently, a Swedish study assessed the additional value

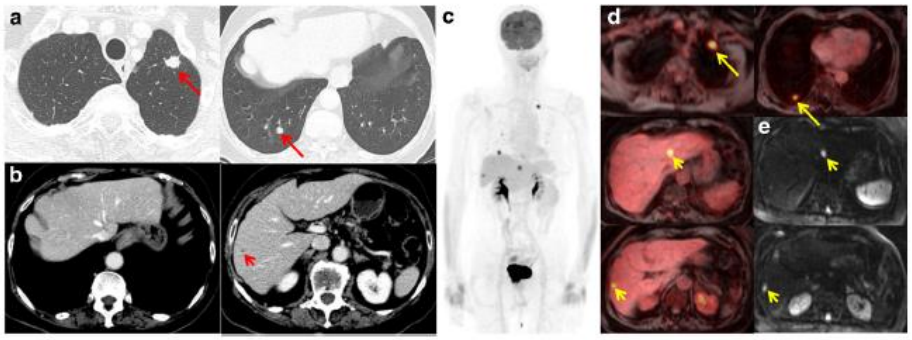

Fig. 2 PET/MRI is superior to CS for staging primary rectal cancer with EMVI. The patient was an 85-year-old woman. Thoracic CT (**a**; long red arrows) and PET/MRI (**d**; long yellow arrows) revealed lung metastases. Abdominal CT (**b**) detected an indeterminate liver nodule (short red arrow). The PET/MRI findings (**e**) indicated that this nodule was suspicious (restricted diffusion and focal FDG uptake) and additionally revealed liver metastases (yellow short arrows). These lesions were confirmed by imaging follow-up

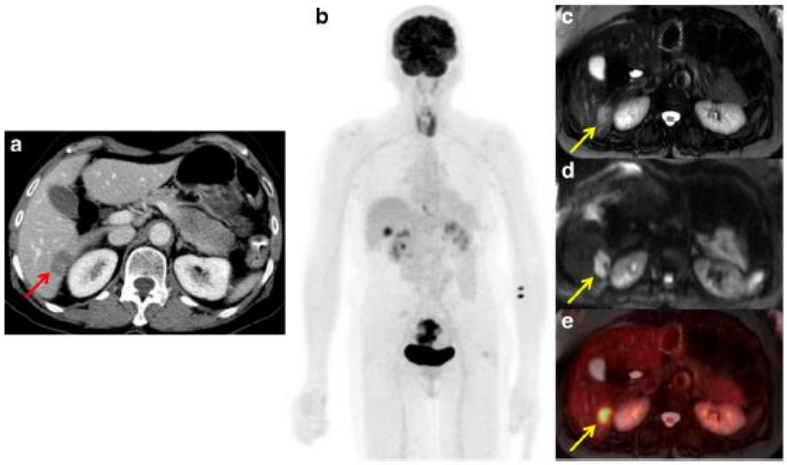

Fig. 3 PET/MRI is similar to CS in a 63-year-old female patient with primary rectal cancer without EMVI. A single metastasis was observed on abdominal ceCT (**a**; red arrow) as well as PET/MRI with intermediate T2 signal (**c**), restricted diffusion (**d**), and high FDG uptake (**e**). No additional lesions were observed on PET/MRI. This lesion was confirmed by histology

of PET/MRI (and PET/CT) over CS of rectal cancer. Although only 24 patients were included, the PET component presented a disease upstaging from M0 to M1 in 3 out of 24 patients (12.5%) [11]. In our study, PET/MRI also enabled upstaging from M0 to M1 in eight patients. A meta-analysis of the role of PET and PET/CT in the primary staging of both colon and

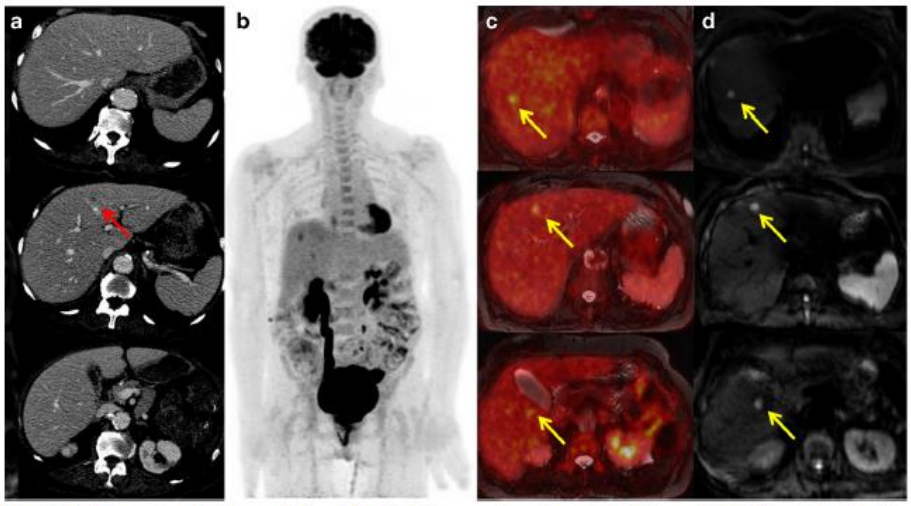

Fig. 4 PET/MRI is superior to CS for upstaging from M0 to M1 in the liver and for clarifying indeterminate lesions detected by CS. The patient was a 61-year-old woman, and abdominal ceCT revealed one indeterminate liver lesion (**a**; red arrow). PET/MRI revealed that this lesion was positive with restricted diffusion and high FDG uptake (**c**, **d**; yellow arrows). PET/MRI also revealed two other liver lesions with similar characteristics (**c**, **d**; yellow arrows). These lesions were confirmed by imaging follow-up

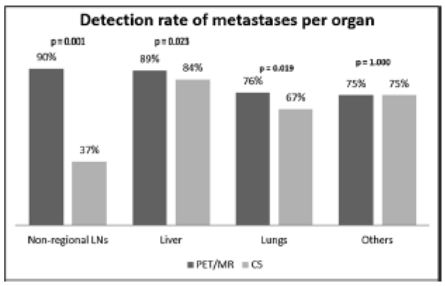

Fig. 5 Comparison of the detection rate of metastases per organ between positron emission tomography/magnetic resonance imaging (PET/MRI) and conventional staging (CS). LN, lymph node

rectal cancer demonstrated a sensitivity and specificity of 91% and 95%, respectively, compared to a diagnostic accuracy of 80% for CT [14]. This is consistent with the results of our study in which we demonstrated a sensitivity of 90.8% and a specificity of 86.1% for PET/MRI and an accuracy of 82.6% for CS.

The distribution of the distant metastases of this study was more prevalent in the liver and lungs, consistent with the spreading pattern of rectal tumors [15]. Additionally, our study demonstrated a high incidence (15%) of non-regional LNs, similar to a study that performed retroperitoneal lymphadenectomy (17%) [16]. The characterization of metastatic LNs is a limitation of CT and MRI that rely on morphology (especially size and borders), whereas PET/MRI contributes a metabolic aspect, enhancing the sensitivity and specificity of this technique.

PET/MRI exhibited a superior detection of liver metastases compared to CS, in line with the literature that demonstrates that PET/CT and especially MRI exhibit a higher sensitivity than ceCT [17, 18]. Sivesgaard et al. [19] compared the diagnostic accuracy of ceCT, MRI, and FDG-PET/CT for the detection of liver metastases and, by analyzing 260 lesions, demonstrated that the sensitivity of MRI was superior to that of FDG-PET/CT, which was superior to ceCT (85.9% vs. 72.0% vs. 62.3%). Thus, we postulated that the combination of FDG-PET and MRI presents a diagnostic performance superior to that of CT for the detection of rectal liver metastases. Our study employed T2-weighted MRI sequence and diffusion-weighted imaging for assessment of liver lesions, but not contrast-enhanced sequences (e.g., gadolinium or Primovist). This was due to a time limitation, as our protocol was set to last 60 min without the dynamic phase of MRI. Lee et al. [20] demonstrated that the diagnostic performance of PET/MRI was superior to that of multidetector CT or PET for the detection of colorectal cancer liver metastases; however, PET/MRI did not differ from liver-specific contrast-enhanced MRI. Reiner et al. [21] also demonstrated similar diagnostic accuracies for the detection of liver metastases when PET/MRI was read with DWI (99%), contrast-enhanced MRI (98%), and both (99%). This reinforces the idea that the use of contrast in the context of PET/MRI may not be essential.

For lung lesions, however, it was expected that thoracic CT would exhibit a higher detection rate than PET/MRI, as MRI is limited to identifying lung nodules smaller than 1 cm [22]. Nevertheless, in our study, PET/MRI was superior to CT in detecting pulmonary metastases. This might be related to the defined criteria of malignancy with CT (a size > 1.0 cm) compared to the metabolic criteria with PET/MRI (focal FDG uptake higher than surrounding background). Thus, several small lesions (< 1.0 cm) that were considered indeterminate on CT were considered suspicious on PET/MRI due to the focal FDG uptake. Only few papers have compared PET/MRI and CT for the detection of pulmonary metastases. Rauscher et al. [23] demonstrated that PET/MRI exhibited

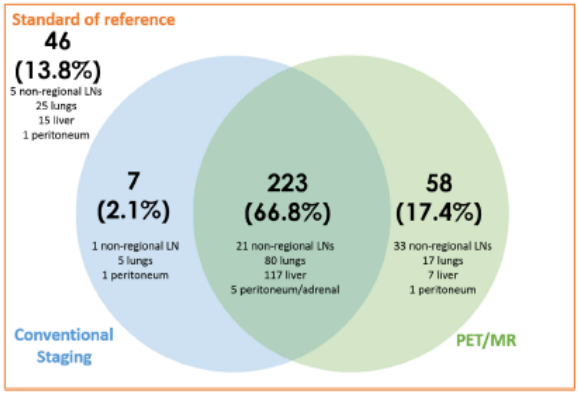

Fig. 6 A comparison of the number of metastatic lesions detected by both PET/MRI and CS, PET/MRI alone, CS alone, and by standard of reference represented in a Venn diagram

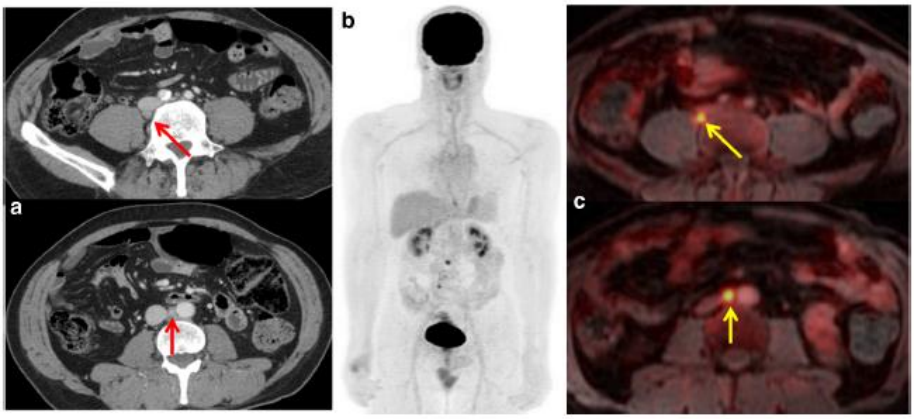

Fig. 7 PET/MRI is superior to CS for upstaging from M0 to M1 in non-regional lymph nodes and for clarifying indeterminate lesions detected by CS. The patient was a 64-year-old man, and PET/MRI revealed two small (< 1 cm) indeterminate retroperitoneal lymph nodes (a; red arrows) that were considered positive due to high FDG uptake. The interaortocaval lesion was biopsied and confirmed as metastatic adenocarcinoma

an inferior detection rate for small lung lesions compared to PET/CT with diagnostic chest CT. Another study that included 51 patients with colorectal lung metastases demonstrated that PET/MRI exhibited a superior diagnostic rate (90%) compared to CT when evaluating lesions larger than 0.5 cm [7].

We also compared the accuracy of PET/MRI and CS in patients with and without EMVI, and PET/MRI exhibited superior detection of metastatic lesions only for EMVI within the primary tumor. Patients with EMVI exhibit an increased risk (OR, 5.68) of metastatic disease [24], which suggests that PET/MRI would detect lesions at a higher rate. So, a patient with positive EMVI and negative conventional staging could benefit from a more careful investigation. Nevertheless, these results should be interpreted with caution, as the number of metastatic patients without EMVI was too low (5 out of 38 patients) and thus cannot yield significant statistical results.

PET/MRI reduced the number of indeterminate findings observed on CS in more than half of our patient population. As demonstrated by Fraum et al. [25], PET/MRI facilitates better tumor staging, FDG activity localization, and lesion characterization. Other studies have shown that PET imaging may better characterize both lung [26] and liver lesions [27] in colorectal cancer patients.

A limitation of our study is that histological confirmation was not available for all distant metastases; nevertheless, almost half of our patient population was biopsied and all others had imaging follow-ups for at least 6 months. Second, despite the prospective study design, case selection bias might have been present, as most of the included patients presented advanced tumors and a high number of recruited patients was not included, especially because almost half of them had promptly initiated the treatment before performing the PET/MRI; however, this is a particular characteristic of our tertiary public cancer center. Third, only one radiologist assessed the pelvic MRI and thoracic and abdominal ceCT, which might have influenced the findings. Fourth, reaching a common interpretation of the PET/MRI results could have presented another limitation; therefore, we included both a nuclear physician and radiologist in this study.

This study has demonstrated that PET/MRI yields a higher accuracy than CS for the detection of distant synchronous metastases in patients undergoing rectal cancer staging. The diagnostic performance of PET/MRI was superior to that of CS in patients with EMVI within primary rectal tumors as well as for detecting non-regional LNs, hepatic lesions, and pulmonary lesions. Furthermore, PET/MRI reduced the number of indeterminate findings observed on CS. These results indicate that PET/MRI is a more appropriate diagnostic method for staging rectal cancer, but future studies should evaluate whether this incremental value of PET/MRI may change patient management and especially outcome.

References

1. Glynne-Jones R, Wyrwicz L, Tiret E, Brown G, Rödel C, Cervantes A, et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Ann Oncol. 2017;28:iv22–40.
2. Benson AB, Venook AP, Bekaii-Saab T, Chan E, Chen Y-J, Cooper HS, et al. Rectal cancer, version 2.2015. J Natl Compr Cancer Netw. 2015;13:719–28.

3. Horvat N, Carlos Tavares Rocha C, Clemente Oliveira B, Petkovska I, Gollub MJ. MRI of rectal cancer: tumor staging, imaging techniques, and management. RadioGraphics. 2019;39:367–87.
4. Seo HJ, Kim M, Lee JD, Chung W, Kim Y-E. Gadoxetate disodium-enhanced magnetic resonance imaging versus contrast-enhanced 18F-fluorodeoxyglucose positron emission tomography/computed tomography for the detection of colorectal liver metastases. Investig Radiol. 2011;46:548–55.
5. Ozis SE, Soydal C, Akyol C, Can N, Kucuk ON, Yagci C, et al. The role of 18F-fluorodeoxyglucose positron emission tomography/computed tomography in the primary staging of rectal cancer. World J Surg Oncol. 2014;12:26.
6. Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ CK (eds). SEER cancer statistics review, 1975–2016, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2016/, based on November 2018 SEER data submission, posted to the SEER web site, April 2019. [Internet]. 2019. Available from: https://seer.cancer.gov/statfacts/html/colorect.html
7. Kang B, Lee JM, Song YS, Woo S, Hur BY, Jeon JH, et al. Added value of integrated whole-body PET/MRI for evaluation of colorectal cancer: comparison with contrast-enhanced MDCT. Am J Roentgenol. 2016;206:W10–20.
8. Brendle C, Schwenzer NF, Rempp H, Schmidt H, Pfannenberg C, la Fougère C, et al. Assessment of metastatic colorectal cancer with hybrid imaging: comparison of reading performance using different combinations of anatomical and functional imaging techniques in PET/MRI and PET/CT in a short case series. Eur J Nucl Med Mol Imaging. 2016;43:123–32.
9. Paspulati RM, Partovi S, Herrmann KA, Krishnamurthi S, Delaney CP, Nguyen NC. Comparison of hybrid FDG PET/MRI compared with PET/CT in colorectal cancer staging and restaging: a pilot study. Abdom Imaging. 2015;40:1415–25.
10. Catalano OA, Coutinho AM, Sahani DV, Vangel MG, Gee MS, Hahn PF, et al. Colorectal cancer staging: comparison of whole-body PET/CT and PET/MR. Abdom Radiol. 2017;42:1141–51.
11. Rutegård MK, Båtsman M, Axelsson J, Brynolfsson P, Brännström F, Rutegård J, et al. PET/MRI and PET/CT hybrid imaging of rectal cancer – description and initial observations from the RECTOPET (REctal Cancer trial on PET/MRI/CT) study. Cancer Imaging. 2019;19:1–9.
12. Boellaard R, Delgado-Bolton R, Oyen WJG, Giammarile F, Tatsch K, Eschner W, et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. Eur J Nucl Med Mol Imaging. 2014.
13. Beets-Tan RGH, Lambregts DMJ, Maas M, Bipat S, Barbaro B, Curvo-Semedo L, et al. Magnetic resonance imaging for clinical management of rectal cancer: updated recommendations from the 2016 European Society of Gastrointestinal and Abdominal Radiology (ESGAR) consensus meeting. Eur Radiol. 2018;28:1465–75.
14. Ye Y, Liu T, Lu L, Wang G, Wang M, Li J, et al. F-FDG PET-CT or PET: a meta-analysis including 2283 patients. Int J Clin Exp Med. 2015;8:21773–85.
15. Riihimäki M, Hemminki A, Sundquist J, Hemminki K. Patterns of metastasis in colon and rectal cancer. Sci Rep. 2016;6:29765 Nature Publishing Group.
16. Quadros CA, Falcão MF, Carvalho ME, Ladeia PA, Lopes A. Metastases to retroperitoneal or lateral pelvic lymph nodes indicated unfavorable survival and high pelvic recurrence rates in a cohort of 102 patients with low rectal adenocarcinoma. J Surg Oncol. 2012;106:653–8.
17. Niekel MC, Bipat S, Stoker J. Diagnostic imaging of colorectal liver metastases with CT, MR imaging, FDG PET, and/or FDG PET/CT: a meta-analysis of prospective studies including patients who have not previously undergone treatment. Radiology. 2010;257:674–84.
18. Maffione AM, Lopci E, Bluemel C, Giammarile F, Herrmann K, Rubello D. Diagnostic accuracy and impact on management of 18F-FDG PET and PET/CT in colorectal liver metastasis: a meta-analysis and systematic review. Eur J Nucl Med Mol Imaging. 2015;42:152–63.
19. Sivesgaard K, Larsen LP, Sørensen M, Kramer S, Schlander S, Amanavicius N, et al. Diagnostic accuracy of CE-CT, MRI and FDG PET/CT for detecting colorectal cancer liver metastases in patients considered eligible for hepatic resection and/or local ablation. Eur Radiol. 2018;28:4735–47.
20. Lee DH, Lee JM, Hur BY, Joo I, Yi N-J, Suh K-S, et al. Colorectal cancer liver metastases: diagnostic performance and prognostic value of PET/MR imaging. Radiology. 2016;280:782–92.
21. Reiner CS, Stolzmann P, Husmann L, Burger IA, Hüllner MW, Schaefer NG, et al. Protocol requirements and diagnostic value of PET/MR imaging for liver metastasis detection. Eur J Nucl Med Mol Imaging. 2014;41:649–58.
22. Heye T, Ley S, Heussel CP, Dienemann H, Kauczor HU, Hosch W, et al. Detection and size of pulmonary lesions: how accurate is MRI? A prospective comparison of CT and MRI. Acta Radiol. 2012;53:153–60.
23. Rauscher I, Eiber M, Furst S, Souvatzoglou M, Nekolla SG, Ziegler SI, et al. PET/MR imaging in the detection and characterization of pulmonary lesions: technical and diagnostic evaluation in comparison to PET/CT. J Nucl Med. 2014;55:724–9.
24. Siddiqui MRS, Simillis C, Hunter C, Chand M, Bhoday J, Garant A, et al. A meta-analysis comparing the risk of metastases in patients with rectal cancer and MRI-detected extramural vascular invasion (mrEMVI) vs mrEMVI-negative cases. Br J Cancer. 2017;116:1513–9.
25. Fraum TJ, Fowler KJ, McConathy J, Dehdashti F. Indeterminate findings on oncologic PET/CT: what difference does PET/MRI make? Nucl Med Mol Imaging. 2016;50:292–9.
26. Jess P, Seiersen M, Ovesen H, Sandstrøm H, Maltbæk N, Buhl AA, et al. Has PET/CT a role in the characterization of indeterminate lung lesions on staging CT in colorectal cancer? A prospective study. Eur J Surg Oncol. 2014;40:719–22.
27. Parsai A, Miquel ME, Jan H, Kastler A, Szyszko T, Zerizer I. Improving liver lesion characterisation using retrospective fusion of FDG PET/CT and MRI. Clin Imaging. 2019;55:23–8.

6 REFERENCES

1. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. *Gut*. 2017;66(4):683-91.

2. Instituto Nacional do Câncer. Estimativa incidência de câncer no Brasil - Biênio 2018-2019. Vol. 1, Inca. 2018.

3. Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ CK (eds). *SEER Cancer Statistics Review*, 1975-2016, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2016/, based on November 2018 SEER data submission, posted to the SEER web site [internet], April 2019. [acesso em 2019 um 20]. Disponível em: https://seer.cancer.gov/statfacts/html/colorect.html.

4. Glynne-Jones R, Wyrwicz L, Tiret E, Brown G, Rödel C, Cervantes A, Arnold D; ESMO Guidelines Committee. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;28(Supl. 4):iv22-iv40.

5. Riihimäki M, Hemminki A, Sundquist J, Hemminki K. Patterns of metastasis in colon and rectal cancer. *Sci Rep*. 2016;6:29765.

6. Benson AB 3rd, Venook AP, Bekaii-Saab T, Chan E, Chen YJ, Cooper HS, Engstrom PF, Enzinger PC, Fenton MJ, Fuchs CS, Grem JL, Grothey A, Hochster HS, Hunt S, Kamel A, Kirilcuk N, Leong LA, Lin E, Messersmith WA, Mulcahy MF, Murphy JD, Nurkin S, Rohren E, Ryan DP, Saltz L, Sharma S, Shibata D, Skibber JM, Sofocleous CT, Stoffel EM, Stotsky-Himelfarb E, Willett CG, Gregory KM, Freedman-Cass D. Rectal Cancer, Version 2.2015. *J Natl Compr Canc Netw*. 2015;13(6):719-28.

7. MERCURY Study Group. Extramural depth of tumor invasion at thin-section mr in patients with rectal cancer: results of the MERCURY Study 1. *Radiology*. 2007;243(1):132-9.

8. MERCURY Study Group. Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study. *BMJ*. 2006;333(7572):779.

9. Siddiqui MRS, Simillis C, Hunter C, Chand M, Bhoday J, Garant A, Vuong T, Artho G, Rasheed S, Tekkis P, Abulafi AM, Brown G. A meta-analysis comparing the risk of metastases in patients with rectal cancer and MRI-detected extramural vascular invasion (mrEMVI) vs mrEMVI-negative cases. *Br J Cancer*. 2017;116(12):1513-9.

10. Horvat N, Carlos Tavares Rocha C, Clemente Oliveira B, Petkovska I, Gollub MJ. MRI of rectal cancer: tumor staging, imaging techniques, and management. *RadioGraphics*. 2019;39(2):367-87.

11. Nougaret S, Reinhold C, Mikhael HW, Rouanet P, Brown G. The use of MR imaging in treatment planning for patients with rectal carcinoma: have you checked the "DISTANCE"?. *Radiology*. 2013;268(2):330-44.

12. American Joint Committee on Cancer. AJCC Cancer Staging Manual. 8th ed. Heidelberg: Springer; 2017.

13. Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, Aranda Aguilar E, Bardelli A, Benson A, Bodoky G, Ciardiello F, D'Hoore A, Diaz-Rubio E, Douillard JY, Ducreux M, Falcone A, Grothey A, Gruenberger T, Haustermans K, Heinemann V, Hoff P, Köhne CH, Labianca R, Laurent-Puig P, Ma B, Maughan T, Muro K, Normanno N, Österlund P, Oyen WJ, Papamichael D, Pentheroudakis G, Pfeiffer P, Price TJ, Punt C, Ricke J, Roth A, Salazar R, Scheithauer W, Schmoll HJ, Tabernero J, Taïeb J, Tejpar S, Wasan H, Yoshino T, Zaanan A, Arnold D. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol*. 2016;27(8):1386-422.

14. Tirumani SH, Kim KW, Nishino M, Howard SA, Krajewski KM, Jagannathan JP, Cleary JM, Ramaiya NH, Shinagare AB. Update on the Role of Imaging in Management of Metastatic Colorectal Cancer. *RadioGraphics*. 2014;34(7):1908-28.

15. Niekel MC, Bipat S, Stoker J. Diagnostic Imaging of colorectal liver metastases with CT, MR imaging, FDG PET, and/or FDG PET/CT: a meta-analysis of prospective studies including patients who have not previously undergone treatment. *Radiology*. 2010;257(3):674-84.

16. Seo HJ, Kim M, Lee JD, Chung W, Kim Y-E. Gadoxetate disodium-enhanced magnetic resonance imaging versus contrast-enhanced 18F-fluorodeoxyglucose positron emission tomography/computed tomography for the detection of colorectal liver metastases. *Invest Radiol*. 2011;46(9):548-55.

17. Ye Y, Liu T, Lu L, Wang G, Wang M, Li J, Han C, Wen J. F-FDG PET-CT or PET: a meta-analysis including 2283 patients. *Int J Clin Exp Med*. 2015;8(11):21773-85.

18. Petersen RK, Hess S, Alavi A, Høilund-Carlsen PF. Clinical impact of FDG-PET/CT on colorectal cancer staging and treatment strategy. *Am J Nucl Med Mol Imaging*. 2014;4(5):471-82.

19. Ozis SE, Soydal C, Akyol C, Can N, Kucuk ON, Yagcı C, Erkek AB, Kuzu MA. The role of 18F-fluorodeoxyglucose positron emission tomography/computed tomography in the primary staging of rectal cancer. *World J Surg Oncol*. 2014;12:26.

20. von Schulthess GK, Schlemmer H-PW. A look ahead: PET/MR versus PET/CT. *Eur J Nucl Med Mol Imaging*. 2009;36(Suppl 1):S3-9.

21. Sekine T, Delso G, Zeimpekis KG, de Galiza Barbosa F, ter Voert EEGW, Huellner M, Veit-Haibach P. Reduction of 18F-FDG Dose in Clinical PET/MR Imaging by Using Silicon Photomultiplier Detectors. *Radiology*. 2018;286(1):249-59.

22. Queiroz MA, Delso G, Wollenweber S, Deller T, Zeimpekis K, Huellner M, de Galiza Barbosa F, von Schulthess G, Veit-Haibach P. Dose optimization in TOF-PET/MR compared to TOF-PET/CT. *PLoS One*. 2015;10(7):e0128842.

23. Czernin J, Ta L, Herrmann K. Does PET/MR Imaging improve cancer assessments? Literature Evidence from more than 900 patients. *J Nucl Med*. 2014;55:59S-62S.

24. Hope TA, Kassam Z, Loening A, McNamara MM, Paspulati R. The use of PET/MRI for imaging rectal cancer. *Abdom Radiol (New York)*. 2019 Jun 14.

25. Kang B, Lee JM, Song YS, Woo S, Hur BY, Jeon JH, Paeng JC. Added value of integrated whole-body PET/MRI for evaluation of colorectal cancer: Comparison with contrast-enhanced MDCT. *Am J Roentgenol.* 2016;206(1):W10-20.

26. Brendle C, Schwenzer NF, Rempp H, Schmidt H, Pfannenberg C, la Fougère C, Nikolaou K, Schraml C. Assessment of metastatic colorectal cancer with hybrid imaging: comparison of reading performance using different combinations of anatomical and functional imaging techniques in PET/MRI and PET/CT in a short case series. *Eur J Nucl Med Mol Imaging*. 2016;43(1):123-32.

27. Paspulati RM, Partovi S, Herrmann K a., Krishnamurthi S, Delaney CP, Nguyen NC. Comparison of hybrid FDG PET/MRI compared with PET/CT in colorectal cancer staging and restaging: a pilot study. *Abdom Imaging*. 2015;40(6):1415-25.

28. Catalano OA, Coutinho AM, Sahani DV, Vangel MG, Gee MS, Hahn PF, Witzel T, Soricelli A, Salvatore M, Catana C, Mahmood U, Rosen BR, Gervais D. Colorectal cancer staging: comparison of whole-body PET/CT and PET/MR. *Abdom Radiol (NY)*. 2017;42(4):1141-51.

29. Hunter C, Brown G. Pre-operative staging of rectal cancer: a review of imaging techniques. *Expert Rev Gastroenterol Hepatol*. 2016;10(9):1011-25.

30. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig L, Lijmer JG, Moher D, Rennie D, de Vet HC, Kressel HY, Rifai N, Golub RM, Altman DG, Hooft L, Korevaar DA, Cohen JF; STARD Group. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. *Radiology*. 2015;277(3):826-32.

31. Boellaard R, Delgado-Bolton R, Oyen WJ, Giammarile F, Tatsch K, Eschner W, Verzijlbergen FJ, Barrington SF, Pike LC, Weber WA, Stroobants S, Delbeke D, Donohoe KJ, Holbrook S, Graham MM, Testanera G, Hoekstra OS, Zijlstra J, Visser E, Hoekstra CJ, Pruim J, Willemsen A, Arends B, Kotzerke J, Bockisch A, Beyer T, Chiti A, Krause BJ; European Association of Nuclear Medicine (EANM). FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. *Eur J Nucl Med Mol Imaging*. 2015;42(2):328-54.

32. Beets-Tan RGH, Lambregts DMJ, Maas M, Bipat S, Barbaro B, Curvo-Semedo L, Fenlon HM, Gollub MJ, Gourtsoyianni S, Halligan S, Hoeffel C, Kim SH, Laghi A, Maier A, Rafaelsen SR, Stoker J, Taylor SA, Torkzad MR, Blomqvist L. Magnetic resonance imaging for clinical management of rectal cancer: Updated recommendations from the 2016 European Society of Gastrointestinal and Abdominal Radiology (ESGAR) consensus meeting. *Eur Radiol*. 2018;28(4):1465–75.

33. Smith NJ, Barbachano Y, Norman AR, Swift RI, Abulafi AM, Brown G. Prognostic significance of magnetic resonance imaging-detected extramural vascular invasion in rectal cancer. *Br J Surg*. 2008;95(2):229-36.

34. Taylor FGM, Quirke P, Heald RJ, Moran BJ, Blomqvist L, Swift IR, Sebag-Montefiore D, Tekkis P, Brown G; Magnetic Resonance Imaging in Rectal Cancer European Equivalence Study Study Group. Preoperative magnetic resonance imaging assessment of circumferential resection margin predicts disease-free survival and local recurrence: 5-year follow-up results of the MERCURY study. *J Clin Oncol*. 2014;32(1):34-43.

35. Rutegård MK, Båtsman M, Axelsson J, Brynolfsson P, Brännström F, Rutegård J, Ljuslinder I, Blomqvist L, Palmqvist R, Rutegård M, Riklund K. PET/MRI and PET/CT hybrid imaging of rectal cancer – description and initial observations from the RECTOPET (REctal Cancer trial on PET/MRI/CT) study. *Cancer Imaging*. 2019;19(1):52.

36. Quadros CA, Falcão MF, Carvalho ME, Ladeia PA, Lopes A. Metastases to retroperitoneal or lateral pelvic lymph nodes indicated unfavorable survival and high pelvic recurrence rates in a cohort of 102 patients with low rectal adenocarcinoma. *J Surg Oncol*. 2012;106(6):653-8.

37. Maffione AM, Lopci E, Bluemel C, Giammarile F, Herrmann K, Rubello D. Diagnostic accuracy and impact on management of 18 F-FDG PET and PET / CT in colorectal liver metastasis: a meta-analysis and systematic review. *Eur J Nucl Med Mol Imaging*. 2015;42(1):152-63.

38. Sivesgaard K, Larsen LP, Sørensen M, Kramer S, Schlander S, Amanavicius N, Bharadwaz A, Tønner Nielsen D, Viborg Mortensen F, Morre Pedersen E. Diagnostic accuracy of CE-CT, MRI and FDG PET/CT for detecting colorectal cancer liver metastases in patients considered eligible for hepatic resection and/or local ablation. *Eur Radiol*. 2018;28(11):4735-47.

39. Lee DH, Lee JM, Hur BY, Joo I, Yi NJ, Suh KS, Kang KW, Han JK. Colorectal cancer liver metastases: diagnostic performance and prognostic value of PET/MR imaging. *Radiology*. 2016;280(3):782-92.

40. Reiner CS, Stolzmann P, Husmann L, Burger IA, Hüllner MW, Schaefer NG, Schneider PM, von Schulthess GK, Veit-Haibach P. Protocol requirements and diagnostic value of PET/MR imaging for liver metastasis detection. *Eur J Nucl Med Mol Imaging*. 2014;41(4):649-58.

41. Sohn B, Lim J seok, Kim H, Myoung S, Choi J, Kim NK, Kim MJ. MRI-detected extramural vascular invasion is an independent prognostic factor for synchronous metastasis in patients with rectal cancer. *Eur Radiol.* 2015;25(5):1347-55.

42. Kim SH, Song B Il, Kim BW, Kim HW, Won KS, Bae SU, Jeong WK, Baek SK. Predictive value of [18F]FDG PET/CT for lymph node metastasis in rectal cancer. *Sci Rep*. 2019;9(1):4979.

43. dos Anjos DA, Habr-Gama A, Vailati BB, Rossi CB, Coturel AE, Perez RO, São Julião GP, de Sousa JB, Buchpiguel CA. 18F-FDG uptake by rectal cancer is similar in mucinous and nonmucinous histological subtypes. *Ann Nucl Med*. 2016;30(8):513-7.

44. Barbaro B, Leccisotti L, Vecchio FM, Di Matteo M, Serra T, Salsano M, Poscia A, Coco C, Persiani R, Alfieri S, Gambacorta MA, Valentini V, Giordano A, Bonomo L. The potential predictive value of MRI and PET-CT in mucinous and nonmucinous rectal cancer to identify patients at high risk of metastatic disease. *Br J Radiol*. 2017;90(1069):20150836.

45. Berger KL, Nicholson SA, Dehdashti F, Siegel BA. FDG PET Evaluation of Mucinous Neoplasms. *Am J Roentgenol*. 2013;174(4):1005-8.

46. Flavell RR, Naeger DM, Aparici CM, Hawkins RA, Pampaloni MH, Behr SC. Malignancies with low fluoro-deoxyglucose uptake at PET/CT: Pitfalls and prognostic importance. *Radiographics*. 2016;36(1):293-4.

47. Horvat N, Hope TA, Pickhardt PJ, Petkovska I. Mucinous rectal cancer: concepts and imaging challenges. *Abdom Radiol (NY).* 2019 Apr 16.

48. Chen L, Shen F, Li Z, Lu H, Chen Y, Wang Z, Lu J. Diffusion-weighted imaging of rectal cancer on repeatability and cancer characterization: An effect of b-value distribution study. C*ancer Imaging*. 2018;18(1):1-9.