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META-ANALYSIS

Head-to-head comparison between ^{18}F-FDG PET/low-dose CT and ^{18}F-FDG PET/contrast-enhanced CT in relapsing ovarian carcinoma: a systematic review and meta-analysis

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Abstract

Introduction Imaging with ^{18}F-FDG PET/CT represents the cornerstone in identifying ovarian cancer (OC) relapse, granting a significantly higher diagnostic accuracy than conventional imaging with CT or MR. Usually, ^{18}F-FDG PET/CT is performed with a low-dose CT (^{18}F-FDG PET/ldCT). In recent years, ^{18}F-FDG PET integration with full-dose diagnostic CT and contrast medium (^{18}F-FDG PET/ceCT) has been proposed. This approach entails a higher absorbed dose, and its clinical benefits are debated. In this study, a systematic review of the literature with a meta-analysis was carried out to compare ^{18}F-FDG PET/ldCT ^{18}F-FDG PET/ceCT in relapsing OC.

Materials and methods We performed a systematic review of the literature through the most relevant databases and web sources. Original articles published before September 2020 and concerning a direct comparison of ^{18}F-FDG PET/ceCT and ^{18}F-FDG PET/ldCT in detecting an OC recurrence were considered. A proportion meta-analysis was then performed using a random-effects model.

Results Out of 111 identified papers, a total of four (296 patients) were selected, all of them representing retrospective analyses. The pooled sensitivity of ^{18}F-FDG PET/ldCT and ^{18}F-FDG PET/ceCT in identifying OC relapse was 84% (95% CI 69–95) and 89% (95% CI 78–97), respectively. The increase of sensitivity when using ^{18}F-FDG PET/ceCT over ^{18}F-FDG PET/ldCT was 6% (95% CI 2–12).

Discussion ^{18}F-FDG PET/CT showed an excellent diagnostic performance in suspected OC recurrence. Given the similar performance between PET/ldCT and PET/ceCT, the low-dose variant could be preferred to reduce absorbed dose and the patients' discomfort during the examination.

The contrast-enhanced addition could be reserved in the case of PET/ldCT doubtful findings, which could affect the therapeutic management.

Keywords Ovarian cancer · Relapse · ^{18}F-FDG · Contrast-enhanced · PET/CT · Meta-analysis

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Introduction

Ovarian carcinoma (OC), often diagnosed at an advanced stage, has a high likelihood of recurrence, even in case of a complete response after first-line treatment [1, 2], and most patients will relapse within the first two years after diagnosis [3]. OC relapse is often characterized by a peculiar peritoneal spreading associated with lymphatic and hematogenous metastatization [4–6]. Peritoneal involvement is the most common sign of disease diffusion, and its identification is particularly specific to confirm disease relapse, regardless of tumor markers (i.e., Ca-125). Although the effectiveness of an early versus delayed treatment of relapse is still under debate [3], the correct diagnosis of a peritoneal recurrence can identify those patients at higher risk of adverse outcome [7]. In this setting, imaging plays an essential role in the detection and quantification of peritoneal carcinomatosis, as well in the identification of lymph node and distant metastases, representing the most reliable and solid evidence on which the therapeutic decision-making is based [8, 9].

^{18}F-FDG positron emission tomography/computed tomography (PET/CT) is a highly accurate imaging procedure in restaging OC. Indeed, ^{18}F-FDG PET/CT has a high sensitivity for detection of OC relapse with a reported pooled sensitivity of 72% when surgical findings have been used as the reference standard [10] and reaching 80–100% when imaging follow-up has been considering the standard of truth [11–14].

Although CT and magnetic resonance imaging (MRI) are commonly used to identify recurrent ovarian cancer, their reliability is limited, especially in detecting small lesions or metastatic deposits on the visceral surfaces [15]. In particular, CT is burdened by very low sensitivity (25–50%) in detecting peritoneal metastases smaller than 1 cm [12, 16].

^{18}F-FDG PET/CT is commonly performed using a "low-dose" CT (^{18}F-FDG PET/ldCT) without contrast enhancement (Ce). This method grants an adequate CT-based attenuation correction of the PET data and allows the reader to pinpoint the sites of ^{18}F-FDG accumulation while avoiding the high radiation burden that would be associated with a full-dose diagnostic CT [17].

However, some reports suggested that performing a ^{18}F-FDG PET with a diagnostic CT and contrast medium (^{18}F-FDG PET/CeCT) may provide better accuracy when compared with ^{18}F-FDG PET with low-dose CT (^{18}F-FDG PET/CT) [18–20]. On the other hand, more recent data, while still confirming the superiority of ^{18}F-FDG PET/CT over CT, could not confirm the diagnostic superiority of ^{18}F-FDG PET/ceCT over ^{18}F-FDG PET/ldCT [21, 22].

The clarification of the usefulness of adding ceCT to the ^{18}F-FDG PET would require a head-to-head comparison between these two PET/CT techniques. Therefore, this study aimed to conduct a systematic review of the literature to find original papers reporting a direct comparison of ^{18}F-FDG PET/CT with ^{18}F-FDG PET/CeCT to detect recurrent OC in the same patient population. Furthermore, a meta-analysis of available data was performed.

Materials and methods

The systematic review was performed in accordance with the PRISMA DTA statement [23].

Search strategy

A four-step search strategy was adopted and the literature search was performed by two authors independently (MM and AP). First, sentinel studies were sought in PubMed using the combinations of the following keywords: ^{18}F-FDG PET/contrast-enhanced CT, ^{18}F FDG PET/CT, contrast-enhanced CT, and ovarian cancer relapse; second, keywords and MeSH terms were identified in PubMed. Third, PubMed, CENTRAL, Scopus, and Web of Science were searched. Fourth, we sought studies evaluating the comparison between ^{18}F-FDG PET/ldCT and ^{18}F-FDG PET/CeCT in identifying relapse in patients with suspected OC recurrence (i.e., PubMed/MEDLINE, Embase and Web of Science). Papers published until August 31st, 2020 were considered. To identify additional studies and expand our search, the references of the articles retrieved were also screened. Furthermore, studies based on preclinical data, phantom studies, case series, case reports, studies including OC patients at the time of first diagnosis and studies with overlapping data were excluded. All remaining articles were screened, and only those reporting a head-to-head comparison between ^{18}F-FDG PET/ldCT and ^{18}F-FDG PET/CeCT in patients with suspected OC relapse were included.

Data extraction

The following information was extracted independently and in duplicate by two investigators (AP, MM) in a piloted form: (1) general information on the study (author, year of publication, country, study type, number of patients); and (2) sensitivity; (3) specificity, (4) accuracy, (5) standard of reference (SOR). For the extraction of data, full papers and supplementary data were searched; if data were missing, the authors were contacted via email. Data were cross-checked and any discrepancy was discussed.

Study quality assessment

The risk of bias of the studies included was assessed independently by two reviewers (AP, PT), according to

QUADAS-2. According to the QUADAS-2 recommendations [24], the risk of bias was rated as low, high, or unclear.

Statistical analysis

A proportion meta-analysis was performed using a random-effects model. Pooled data were presented with 95% confidence interval (95% CI). Heterogeneity among studies was assessed utilizing I^2, with 50% or higher being regarded as high. Publication bias was evaluated by means of Egger's test [25].

The StatsDirect statistical software (StatsDirect Ltd.; Altrincham, UK) was used for the statistical analysis.

Results

Literature search

A total of 97 papers were identified after duplicate removal, and their titles and abstracts were analyzed.

Ten articles were excluded because they were case series or did not analyze or mention at least one of the following issues: ^{18}F-FDG PET/CT, ovarian cancer, and relapse. Among the remaining eighty-seven papers, eighty-three had to be excluded because they did not fit the inclusion criteria (see Fig. 1 for details). Therefore, four articles were selected,

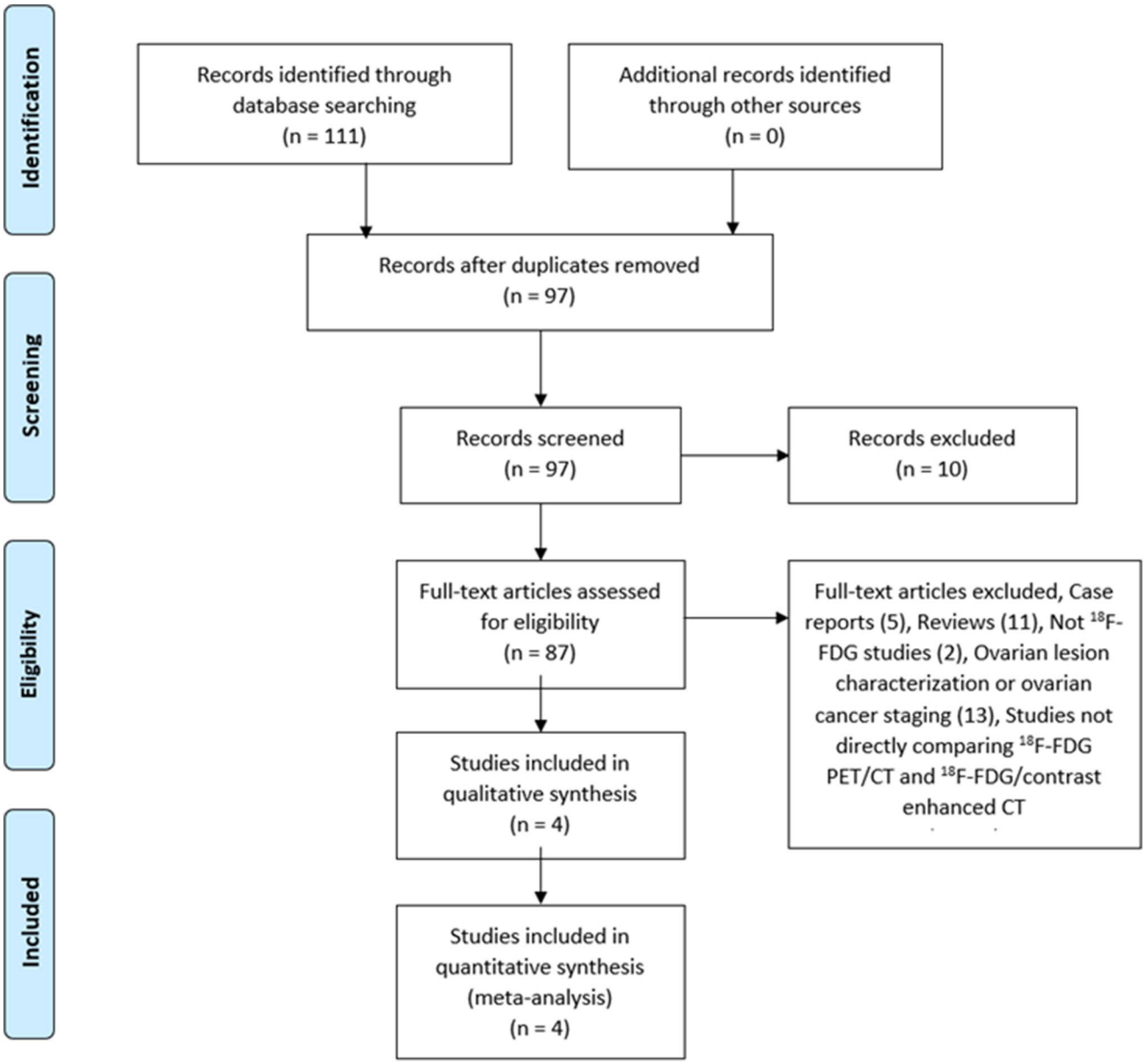

Fig. 1 PRISMA flow diagram of the studies

and 296 patients were finally included (Fig. 1) [26–29]. These articles were published between 2008 and 2020, had sample sizes ranging from 24 to 132 patients treated with primary debulking surgery and platinum-based first-line chemotherapy.

Qualitative analysis (Systematic review)

All studies had a retrospective design. Two studies were carried out in Japan, one in Austria and one in Italy. The characteristics of the studies, patients and methods are summarized in Tables 1, 2 and 3.

Quality assessment of the studies

The risk of bias was assessed based on four study characteristics; these results are reported in Table 4. In general, the risk of bias ranged from low to non-evaluable. Specifically, in 2 out of 4 studies, the patient selection was unclear. The standard of reference applied in two studies was particularly appropriate to evaluate the sensitivity (i.e., surgical and histological findings), thus limiting the reliability of the diagnostic specificity.

Quantitative analysis (Meta-analysis)

The pooled sensitivity of ^{18}F-FDG PET/ldCT and ^{18}F-FDG PET/CeCT in identifying OC relapse was 84% (95% CI 69–95) and 89% (95% CI 78–97), respectively (Fig. 2). Heterogeneity was found (I2 78.1% and 71.8, respectively), and publication bias was absent (Egger test: $p=0.301$ and $p=0.49$).

When considering the pooled discrepancy in sensitivity between these two imaging procedures, the sensitivity increased by 6% (95%CI 2–12) using ^{18}F-FDG PET/CeCT (I^2 29.1% and Egger test $p=0.415$) (Fig. 3).

Table 2 Patients characteristics

First author (year)	Age	Histology	Stage
Kitajima (2008)	56 years (mean)	-Papillary serous adenocarcinoma (49.2%) -Mucinous cystadenocarcinoma (13.6%) -Clear cell carcinoma (12.8%) -Serous cystadenocarcinoma (8.2%) -Undifferentiated adenocarcinoma (6.8%)	I = 15.1% II = 7.5% III = 61.3% IV = 15.9%
Dirisamer (2009)	62 years (mean)	Not reported	Not reported
Kitajima (2012)	59 years (mean)	-Papillary serous adenocarcinoma (10.8%), -Mucinous cystadenocarcinoma (15) -Clear cell carcinoma (15.8%) -Serous cystadenocarcinoma (35%) -Undifferentiated adenocarcinoma (7.5%) -Endometrioid carcinoma (15.8%)	I = 16.6% II = 9.1% III = 58.3% IV = 15.8%
Gaducci (2020)	58 (mean)	Not reported	Not reported

Table 1 Characteristics of included studies

First author and year	Country	Study design	No of pts	Selection criteria	Standard of reference (SOR)
Kitajima (2008)	Japan	Retrospective	132	Suspected ovarian recurrence	Multidisciplinary SOR including histology, clinical and imaging follow-up)
Dirisamer (2009)	Austria	Retrospective	20	Suspected ovarian carcinomatosis	Surgical and pathological findings
Kitajima (2012)	Japan	Retrospective	120	Suspected ovarian recurrence	Multidisciplinary SOR including histology, clinical and imaging follow-up)
Gaducci (2020)	Italy	Retrospective	24	Suspected ovarian cancer	Surgical and pathological findings

Discussion

Table 3 PET/CT scanner and acquisition methods

First author and year	PET/CT scanner	Injected activity	Time from injection to acquisition	Time for bed position	Contrast agent/ rate	Contrast phases
Kitajima (2008)	Biograph, Sensation 16 PET/CT system, Siemens AG, Erlangen, Germany	4 MBq/kg	50 min	3 min	2 ml/kg of Iomeprole 300, Eisai, Japan/2.5 ml/s	Late portal venous phase (90 s after injection)
Dirisamer (2009)	Discovery LS, GE Medical Systems, Milwaukee	370 MBq	50 min	4 min	100 ml of Iopentol 300 mg/ml; Imagopaque GE Healthcare/3 ml/s	Not Reported
Kitajima (2012)	Discovery ST Elite-Performance, GE Healthcare, Waukesha, WI, US	3.3 MBq/Kg	50 min	2 min	80–100 mL of (Iopamiron Inj, Syringe, Bayer Schering Pharma, Berlin, Germany)/2.0–2.5 ml/s	Late portal venous phase (100 s after injection)
Gaducci (2020)	Discovery ST, GE Medical Systems, Milwaukee	3.7 MB/Kg	60 min	Not reported	Not reported/3 ml/s	Not reported

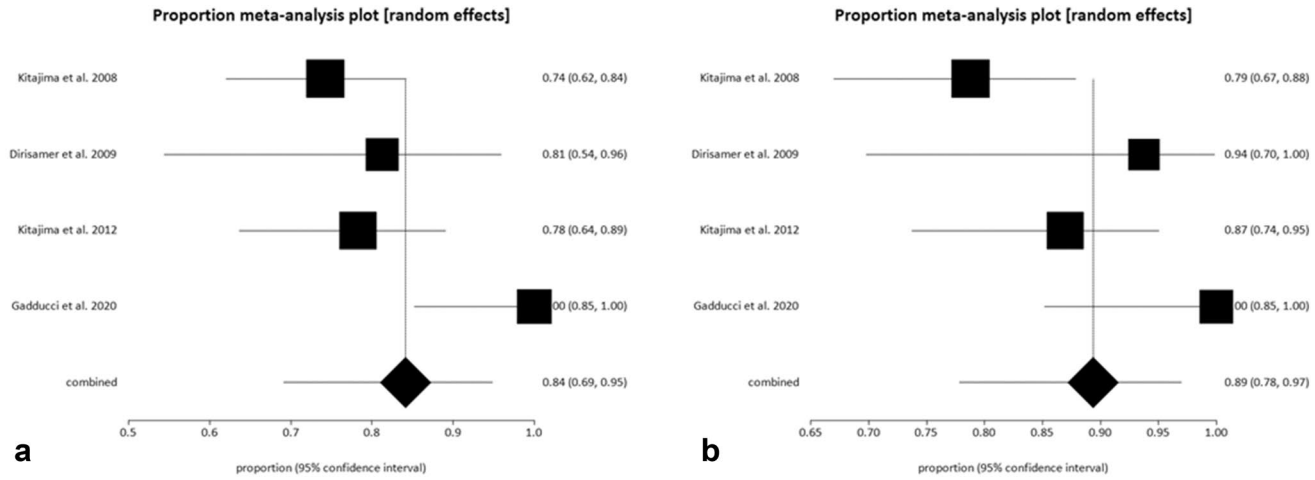

Fig. 2 Diamond represents the pooled sensitivity of ^{18}F-FDG PET/ldCT (**a**) and ^{18}F-FDG PET/CeCT (**b**)

Table 4 Quality assessment of the studies and risk of bias for each study considered

First author	Year	Risk of bias				Feasibility		
		Patient selection	Study test	Reference standard	Timing	Patient selection	Study test	Reference standard
Kitajima	2008	U	U	L	L	U	U	L
Dirisamer	2009	L	U	L	L	L	L	L
Kitajima	2012	L	U	L	L	L	L	L
Gaducci	2020	U	U	L	U	L	L	L

The aim of this systematic review and meta-analysis was to produce evidence-based data on the diagnostic comparison of two important imaging procedures, such as the ^{18}F-FDG PET/ldCT and ^{18}F-FDG PET/CeCT in a particular diagnostic setting as the suspected OC relapse. This issue is of particular interest, considering that the identification

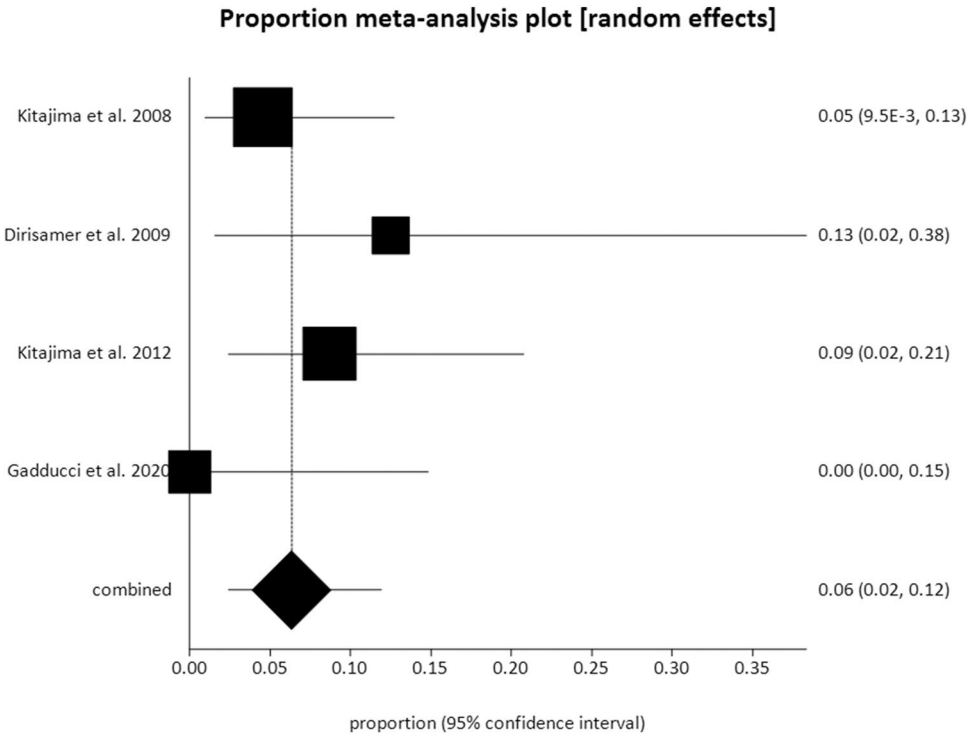

Fig. 3 Pooled discrepancy of patient-based analysis**.** Sensitivity increased by 6% (95% CI from 2 to 12), with I^2 29.1% and Egger test $p = 0.415$

of OC relapse can often be challenging, especially in the case of small-sized peritoneal lesions. On the other hand, the confirmation of recurrence has a relevant implication in the patients' clinical management.

In this field, choosing the most appropriate PET/CT procedure is relevant to offer the patients a personalized diagnostic iter to fit with their needs. To our knowledge, this is the first meta-analysis to focus specifically on this issue. An extensive database search was performed without time restrictions, and inclusion criteria were defined "a priori."

In the vast majority of PET/CT scans, the CT component is performed with a low current setting and without intravenous contrast. Its purpose is to allow an attenuation correction of the PET dataset and obtain an anatomical correlation of radiotracer distribution. Indeed, the adoption of a low-dose, contrast-free CT protocol has been guided mostly by practical considerations to decrease radiation burden, reduce patient discomfort, and minimize scanning time. However, given the spatial resolution of 4–6 mm of currently available PET systems, and the fact that ^{18}F-FDG is not a tumor-specific tracer, the detection of microscopic lesions remains challenging. This decrease in sensitivity occurs, especially when the anatomic details are unclear, and the delineation of the surrounding organs is hardly evident. To overcome these limitations, PET/CT with intravenous iodine contrast medium and full radiation dose, called PET/CeCT, has been gradually introduced in the clinical setting and was mainly used to reveal abdominal relapse, especially in case of hostile anatomy. In this setting, this hybrid protocol of PET/CeCT has been applied to colorectal [30, 31], ovarian [26–29], and uterine cancer, showing promising results [32, 33].

However, when the OC relapse was considered, only a few studies investigated this interesting issue; these articles reported conflicting results. Three studies [26, 27, 29] did not find any significant difference between PET/CT and PET/CeCT at the patient level; on the contrary, one [28] showed a significantly higher sensitivity of ^{18}F-FDG PET/CeCT in detecting OC relapse, especially in the case of peritoneal and retrovesical metastases**.** Please see Fig. 4 for an example in which the integration of ceCT did not attain an improvement of the diagnostic accuracy; Fig. 5, on the other hand, highlights an example of more accurate diagnostic procedure through the use of PET/ceCT.

Our study confirmed an irreplaceable role of ^{18}F-FDG PET/CT in the diagnosis of recurrent OC with a pooled sensitivity of 84% that is in line with previous meta-analyses published on this topic [10–14]. In parallel, we found that, although ^{18}F-FDG PET/CeCT is more sensitive than ^{18}F-FDG PET/ldCT, the slight difference in diagnostic performance does not support its routine use in clinical practice.

In light of this evidence, it might be advisable to integrate PET/CT with contrast enhancement on a case-by-case basis in circumstances where an important discrepancy between FDG uptake and low-dose CT findings reduce the interpretation reliability, thus affecting the therapeutic decision-making process. In other words, contrast enhancement could be injected only in the case of doubtful findings on

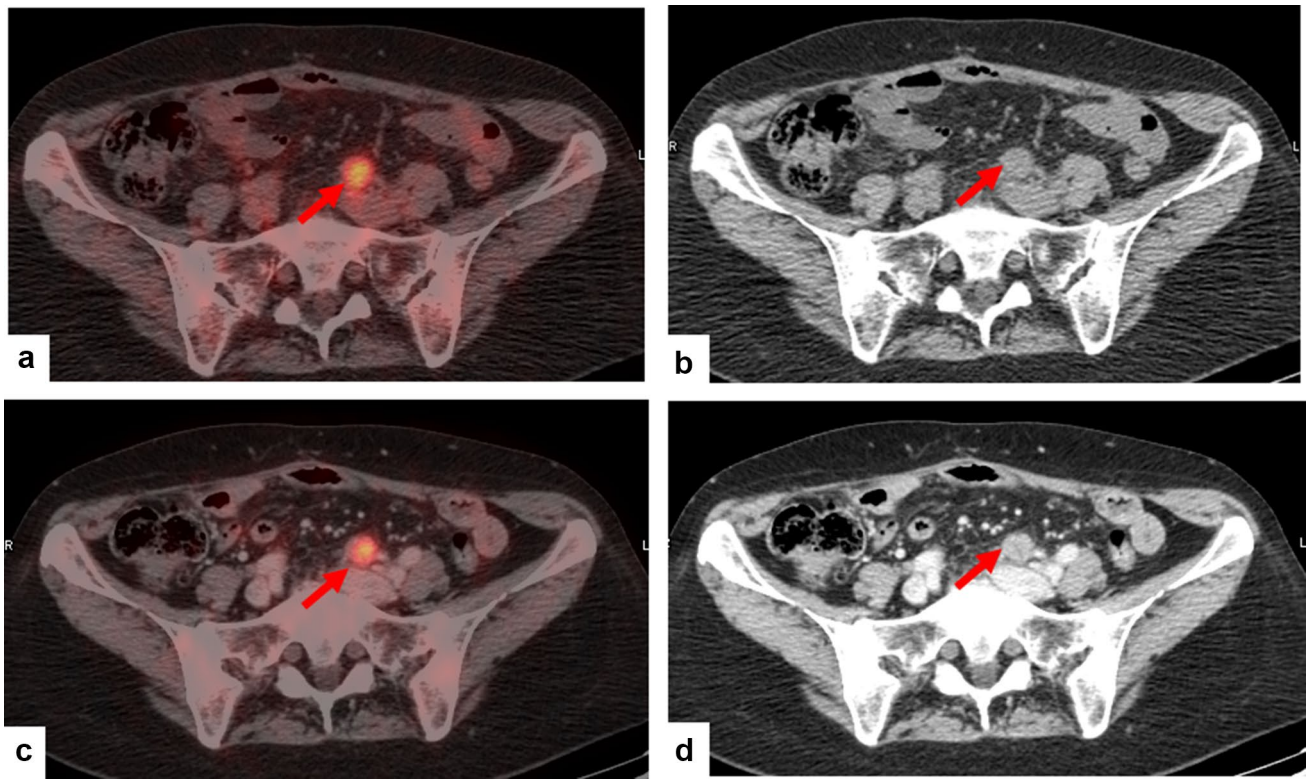

Fig. 4 Sixty-two-year-old female with suspected OC relapse. Both ^{18}F-FDG PET/ld CT (**a**, **b**) and ^{18}F-FDG PET/CeCT (**c**, **d**) clearly detected a focal tracer uptake corresponding to a pathological left iliac lymph node (red arrows)

^{18}F-FDG PET/ldCT (i.e., FDG uptake without any densitometric correlation). This is feasible after a quick evaluation of the images by the on-duty nuclear medicine physician in adequately scheduled hybrid imaging session. Another possibility to manage this tricky imaging interpretation on ^{18}F-FDG PET/ldCT may be to follow, at proper time interval, the patients with ^{18}F-FDG PET/CeCT especially in those for which a consensus is not achieved. This is what is possible to obtain over the years after a profitable collaboration with the radiologists saving cost, time, dose exposure and improving the quality of the PET/CT reports.

This case-by-case approach needs shared acquisition protocols and close cooperation between Nuclear Medicine and Radiology Departments and their Physicians and Technicians.

In all other cases, given the excellent accuracy of PET/CT, the association with contrast medium and diagnostic CT could be discouraged. Indeed, a significant reduction of radiation exposure would be obtained, reducing at the same time the possibility of renal dysfunction, which is not uncommon in ovarian cancer patients [34].

Some limitations, however, should also be mentioned. First, only four papers were included in this meta-analysis with a limited number of patients (i.e., 296 pts). However, this study is based on a direct head-to-head comparison or the two diagnostic procedures performed on the same patient simultaneously. This particular selection of the studies allows a more appropriate interpretation of the data.

A second limitation of our analysis is related to the different truth standards considered in the different studies. Indeed, in the two studies, including most patients, the gold standard was mostly based on follow-up imaging procedures rather than on histopathology. This approach may have overestimated the sensitivity of the PET/CT procedures.

Third, only 3 out of the four studies reported true-negative results. From this point of view, we preferred not to report an unreliable evaluation of the specificity of the two imaging procedures.

Lastly, a significant statistical heterogeneity was found among the included studies about the pooled sensitivity of ^{18}F-FDG PET/ldCT and ^{18}F-FDG PET/CeCT. This heterogeneity could be explained by the different characteristics of patients, index test and comparison in the included studies (see Tables). Unfortunately, the available data were limited to further explore this heterogeneity by using subgroup analyses or meta-regression analysis. Conversely, we did not find a significant publication bias in our analysis. Overall, based on our systematic review, we suggest performing more studies and in particular randomized and large multicentre prospective studies and cost-effectiveness analyses to

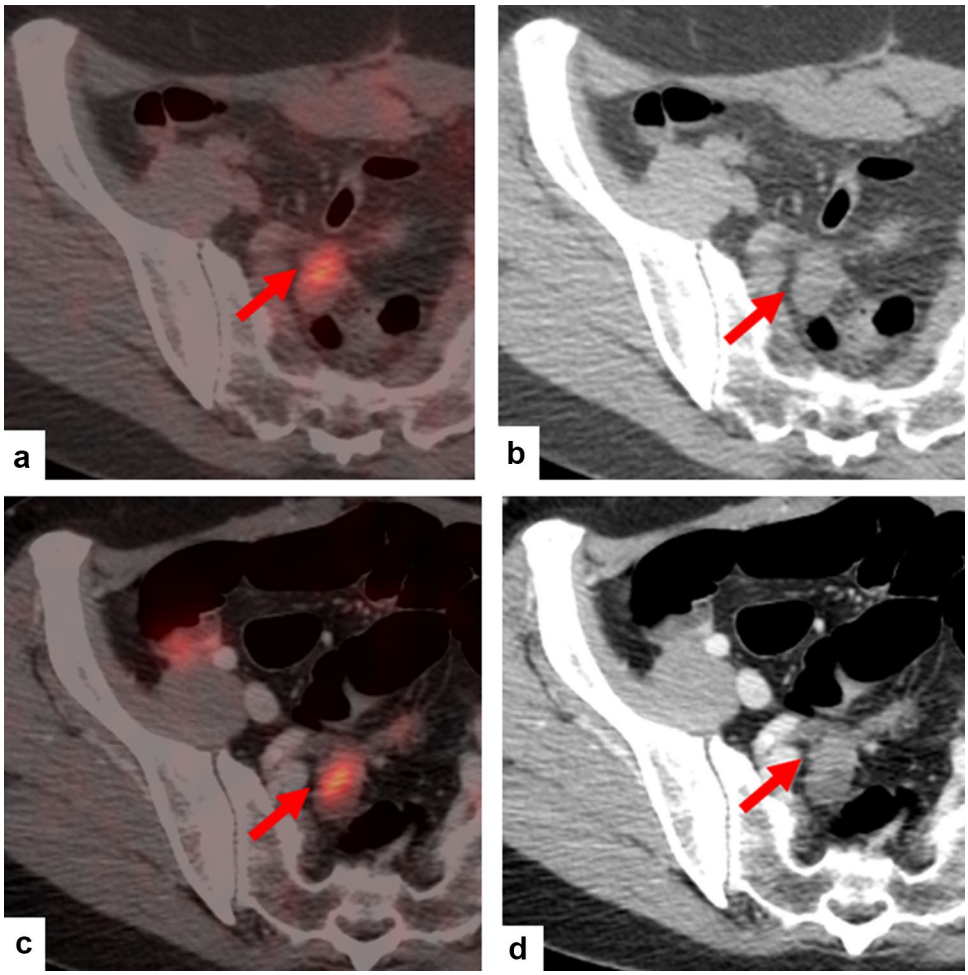

Fig. 5 Fifty-three-year-old female with suspected OC relapse. ^{18}F-FDG PET/ld CT (**a**, **b**) detected a faint but focal tracer uptake with apparent localization on a pelvic portion of the small bowel (red arrows). After injection of contrast enhancement, ^{18}F-FDG PET/CeCT (**c**, **d**) showed that the tracer uptake corresponded to a pathological peritoneal nodule adjacent to small intestine (red arrows)

compare ^{18}F-FDG PET/ldCT and ^{18}F-FDG PET/CeCT in recurrent OC.

Conclusion

^{18}F-FDG PET/ldCT and ^{18}F-FDG PET/CeCT are both sensitive in detecting OC relapse. Furthermore, the discrepancy in sensitivity between the two imaging procedures is 6% in favor of ^{18}F-FDG PET/CeCT. These characteristics should be considered in the clinical context for the management of every patient.

Compliance with ethical standards

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

Informed consent For this type of study, informed consent is not required.

This article does not contain any studies with human or animal subjects performed by the any of the authors.

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