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Review

A meta-analysis exploring the role of PET and PET-CT in the management of potentially resectable colorectal cancer liver metastases

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ABSTRACT

Background: Positron emission tomography (PET), alone or combined with computed tomography (CT), potentially enhances detection of occult metastatic colorectal cancer.
Methods: We compared the impact of PET/PET-CT with conventional imaging, versus conventional imaging alone, in patients with potentially resectable colorectal cancer liver metastases. MEDLINE, EMBASE, and CENTRAL were searched for studies investigating PET/PET-CT to determine resectability. Outcomes included overall (OS), disease-free survival (DFS), change in surgical management, and futile laparotomy. Evidence quality was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. A pre-specified protocol was registered in PROSPERO.
Results: Of 4034 articles, two randomized trials (n = 554), and 11 non-randomized studies (n = 2251) were included. PET/PET-CT did not improve OS (hazard ratio [HR] 0.94, 95% CI 0.69–1.26, moderate quality) or DFS (HR 1.01, 95% CI 0.82–1.26, moderate quality). In the two trials, PET/PET-CT changed surgical management in 8% of cases (95% CI 5–11%, high quality), and did not significantly reduce futile laparotomies (risk ratio 0.59, 95% CI 0.24–1.47, low quality). Among non-randomized studies, PET/PET-CT changed surgical management in 20% of cases (95% CI 17–22%, very low quality) and reduced futile laparotomies (odds ratio 0.51, 95% CI 0.32–0.81, very low quality).
Conclusions: Moderate-quality evidence suggests that preoperative PET/PET-CT does not improve OS or DFS in patients with colorectal cancer liver metastases. These results do not support routine use of PET/PET-CT in patients with potentially resectable disease. The main limitation of this study was the lack of randomized studies.

1. Introduction

The extent of intra- and extra-hepatic disease guides treatment of patients with liver metastases from colorectal cancer. Conventional imaging to stage metastatic disease consists of contrast-enhanced computed tomography (CT) and/or magnetic resonance imaging (MRI). Despite ongoing advances in surgical planning, 1 of every 20 patients are deemed unresectable at the time of surgery [1]. Of the patients who undergo a curative resection, more than 10% have disease recurrence within 6 months of surgery [2]. Inaccurate staging may account for these recurrences in patients who might have benefited from more extensive resections

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or early initiation of non-surgical treatment.

More accurate tools are needed to identify and localize metastatic disease. There is some evidence that positron emission tomography (PET) with 18F-fluorodeoxyglucose (^{18}F-FDG) alone or combined with CT detects occult metastatic disease that is not identified on conventional imaging [3,4]. PET imaging relies on the functional assessment of tumour activity in the form of ^{18}F-FDG uptake, which can potentially distinguish sites of metastases from residual scar or necrotic tissue more accurately. A number of observational studies [5,6] and one randomized controlled trial (RCT) [7] suggest that PET significantly reduces the number of futile laparotomies. However, a recent Canadian multi-institutional trial found the added benefit of routine PET-CT to be non-clinically relevant on decision-making, futile laparotomy, or survival rates [8]. These results have led to varying preoperative imaging practices in patients with colorectal cancer metastases. For instance, the National Comprehensive Cancer Network continues to endorse routine PET in this setting [9].

The purpose of this systematic review was to evaluate the role of PET and PET-CT in the preoperative management of patients with colorectal cancer liver metastases that are deemed resectable on conventional imaging. The main objective of this study was to evaluate differences in overall survival (OS) and disease-free survival (DFS) when compared to conventional imaging alone. Secondary objectives were to evaluate changes in surgical management and rates of futile laparotomy with routine PET/PET-CT.

2. Methods

This study was written following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline [10]. A protocol was registered in PROSPERO *a priori* (CRD 42017069461).

2.1. Literature search

The following databases were searched for published articles and abstracts from 2000 until July 2018: MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials. The search strategy consisted of MESH terms and key words specific to each database and without language or study design restrictions (see Appendix). The references of relevant studies and previous systematic reviews on this topic were reviewed individually. We also performed manual searches of the references of included articles, conference proceedings, and clinical trial registries.

2.2. Inclusion and exclusion criteria

Studies were eligible if they took place in an adult population ($\geq$18 years old) with colorectal cancer liver metastases deemed surgically resectable on conventional imaging (i.e. CT and/or MRI). The intervention of interest was PET or PET-CT in addition to conventional imaging (i.e. CT, MRI or both). The control was conventional imaging alone. Randomized trials and observational studies were included. Studies were excluded if any participants received chemotherapy less than two weeks prior to PET/PET-CT, or radiotherapy less than six weeks prior to PET/PET-CT. Studies that used PET/PET-CT for surveillance following colorectal cancer surgery, or to diagnose metastatic disease when there was a clinical suspicion, were also excluded.

2.3. Study selection and data extraction

Two independent reviewers performed every step of the screening process independently and in duplicate, with a third party resolving disagreements. Primary outcomes were OS and DFS. Secondary outcomes were change in surgical management (such as less extensive surgery, more extensive surgery, or cancelled surgery) and futile laparotomy, defined as an operation that was aborted upon identifying unresectable or widespread disease.

2.4. Risk of bias and quality of evidence

Two independent reviewers independently evaluated the risk of bias for each study. The Cochrane Risk of Bias tool was used to appraise randomized studies. This tool uses seven criteria to summarize risk of bias as low risk, high risk, or unclear risk [11]. The Methodological Index for Non-Randomized Studies (MINORS) scale was used to appraise observational studies. This tool appraises studies based on 12 individual items, and rates each item out of 3 as follows: 0 if not reported, 1 if reported but performed inadequately, or 2 if both reported and adequately performed [12].

The quality of the evidence was assessed for each outcome using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach [13]. In the GRADE framework, data from randomized controlled trials starts as high-quality evidence but can be downgraded for study limitations (risk of bias), inconsistency (heterogeneity), indirectness, imprecision and reporting bias. Meanwhile, observational data starts as low-quality evidence but can be upgraded if the treatment effect is large, if there is a dose-response, or if potential biases might decrease the apparent treatment effect. Likewise, observational data can be downgraded to very low-quality, similar to randomized studies.

2.5. Statistical analysis

Randomized and non-randomized studies were analysed separately given distinct differences in study designs. Meta-analyses were performed using a random-effects model, and weights of included studies were estimated using the inverse variance method. A pooled hazard ratio (HR) was estimated for OS and DFS. When necessary, a HR was calculated directly from survival curves using a previously established method [14]. A pooled odds ratio (OR) was used to estimate futile laparotomy among non-randomized studies, as these included a combination of prospective and retrospective designs. A pooled risk ratio (RR) was used to estimate futile laparotomy among randomized studies. Finally, a pooled proportion was estimated for change in surgical management for randomized and non-randomized studies separately. All estimates of effect are reported with corresponding 95% confidence intervals (CI). Between-study heterogeneity was assessed visually using forest plots, while statistical heterogeneity was assessed using Cochran's Q test and quantified using the I^2 statistic with I^2 <25% considered low, 25–75% moderate, and >75% high. Moderate to high heterogeneity was explored via pre-specified subgroup analyses. Statistical analyses were performed using Review Manager version 5.3 (www.community.cochrane.org). For all analyses, $p < 0.05$ was considered significant.

3. Results

The initial search yielded 4432 articles, of which 343 were duplicates. A subsequent update of the search strategy identified 394 articles, of which 47 were duplicates. In the end, 4436 titles and abstracts were screened including articles identified via hand-searching. Following this, full-text screening of 299 articles was performed, yielding a total of 13 included articles (Fig. 1).

3.1. Characteristics of included studies

The study designs included RCTs (N = 2), prospective cohorts

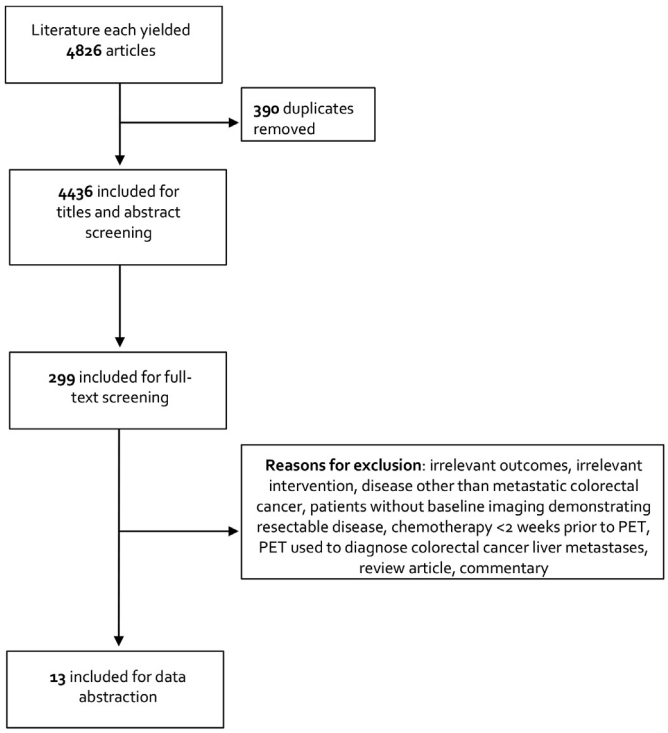

Fig. 1. Flow diagram.

(N = 1), retrospective cohorts (N = 4), and single-arm observational studies (N = 6). The interventions of interest were PET (N = 7), PET-CT (N = 4), or both (N = 2). See Table 1 for relevant study characteristics.

3.2. Risk of bias

For single-arm observational studies [15–20], MINORS scores ranged from 7 to 12 on a scale of 16. For comparative observational studies [5,6,21–23], MINORS scores ranged from 13 to 17 on a scale of 24. Most studies either did not report or had inadequate assessment of outcomes in an unbiased fashion. Additionally, most of the comparative observational studies had inadequate baseline equivalence of comparison groups. Both randomized trials [7,8] demonstrated an overall low-risk of bias based on the criteria of the Cochrane Risk of Bias tool. See Table 1.

3.3. Overall survival

Based on two RCTs [7,8] combining 554 patients, OS did not significantly improve in patients who underwent preoperative PET/PET-CT (HR 0.94, 95% CI 0.69 to 1.26, $I^2 = 0$). The quality of the evidence was moderate due to an imprecise pooled estimate See Table 2.

Only one RCT [8] reported on the subset of patients who underwent surgery, and demonstrated no significant difference in OS when patients underwent preoperative PET-CT (HR 0.81, 95% CI 0.56 to 1.18). Similarly, four observational studies [6,21–23] combining 1099 patients demonstrated no significant improvement in OS with PET/PET-CT in patients who underwent surgery (HR 0.87, 95% CI 0.62 to 1.20, $I^2 = 52\%$). The quality of the evidence for this outcome was very low due to lack of randomization, imprecision, and selection bias in the contributing studies. Upon subgroup analysis, the type of intervention in each study (ie. PET versus PET-CT) could explain the heterogeneity found in this

Table 1
Characteristics of included studies.

Study	Single or Multi-Center	Country	Study Design	Time frame	Follow-up (median)	Intervention	Control	Number of Patients		Neoadjuvant Chemotherapy		Risk of Bias
								PET/PET-CT	Control	PET/PET-CT	Control	
Ruers 2009	Multi-center	Netherlands	RCT	2002–2006	At least 36 months	PET	CT of abdomen, pelvis, and chest	75	75	0	0	Low-risk
Moulton 2014	Multi-center	Canada	RCT	2005–2010	36 months	PET-CT	CT of abdomen, pelvis, and chest	270	134	nr	nr	Low-risk
Wiering 2007	Single-center	Netherlands	Prospective cohort	1995–2003	53 months	PET	CT of liver, abdomen and chest; and colon visualization	103	100	nr	nr	15
Abbadi 2014	Single-center	England	Retrospective cohort	1998–2008	At least 5–10 years	PET	CT of chest, abdomen, pelvis and liver MRI	131	57	nr	nr	15
Ayez 2014	Multi-center	Netherlands	Retrospective cohort	2000–2009	36 months	PET	Liver CT or MRI, abdominal imaging and chest CT	206	407	32%		15
Hiraide 2017 (a)	Single-center	Japan	Retrospective cohort	2002–2008	48 months	PET	CT of abdomen and chest, colonoscopy ± MRI	25	25	56%	40%	15
Hiraide 2017 (b)	Single-center	Japan	Retrospective cohort	2009–2013	40 months	PET-CT	CT and MRI of abdomen	30	15	57%	0	17
Pawlik 2009	Single-center	USA	Retrospective cohort	1994–2005	nr	PET	CT of abdomen	230	231	44%		13
Georgakopoulos 2013	Single-center	Greece	Single-arm prospective	2008–2012	nr	PET-CT	na	19	na	nr	na	8
Joyce 2006	Single-center	USA	Single-arm prospective	2000–2002	nr	PET or PET-CT	na	71	na	38%	na	12
Ruers 2002	Single-center	Netherlands	Single-arm prospective	1998–1999	nr	PET	na	51	na	2%	na	8
Strasberg 2001	Single-center	USA	Single-arm prospective	1995–1999	24 months	PET	na	43	na	nr	na	9
Vigano 2017	Single-center	Italy	Single-arm retrospective	2005–2014	nr	PET-CT	na	74	na	nr	na	12
Yip 2014	Single-center	England	Single-arm retrospective	2008–2011	nr	PET-CT	na	433	na	75.60%	na	7

*Risk of Bias was calculated using the Cochrane Risk of Bias tool in randomized studies and MINORS in non-randomized studies.
**Hiraide et al. (2017) reported stratified data. Both strata are reported separately.

pooled estimate (test for subgroup differences, P = 0.02). See Fig. 2.

3.4. Disease-free survival

Based on two RCTs [7,8] (554 patients), DFS did not improve in patients who underwent preoperative PET/PET-CT (HR 1.01, 95% CI 0.82 to 1.26, $I^2 = 0$). The quality of the evidence for this outcome was moderate due to an imprecise pooled estimate. See Table 2.

In the subset of patients who underwent surgery, one RCT [8] demonstrated no difference in DFS when patients had a PET-CT (HR 1.03, 95% CI 0.79 to 1.33). Three observational studies [6,21,22] combining 911 patients also demonstrated no significant difference in DFS with PET/PET-CT in this same subset of patients (HR 0.90, 95% CI 0.76 to 1.06). Heterogeneity in this latter comparison was moderate ($I^2 = 49\%$), and the quality of the evidence was very low due to lack of randomization, inconsistency across point estimates, imprecision, and a significant risk of bias from contributing studies. In subgroup analyses, differences in diagnostic modality (PET versus PET-CT) could explain heterogeneity (test for subgroup differences, P = 0.02). See Fig. 2.

3.5. Change in surgical management

Based on two RCTs [7,8] combining 345 patients, the addition of PET/PET-CT to conventional imaging changed surgical management in 8% of cases (95% CI 5–11%, $I^2 = 0$) and the quality of the evidence was high. In eight observational studies [15–20,22,23] (877 patients), the addition of PET/PET-CT to conventional imaging changed surgical management in 20% of cases (95% CI 17–22%, $I^2 = 0$), but the quality of the evidence was low due to study design. See Fig. 3.

3.6. Futile laparotomy

When two RCTs [7,8] (554 patients) were combined, PET/PET-CT did not significantly reduce futile laparotomies (RR 0.59, 95% CI

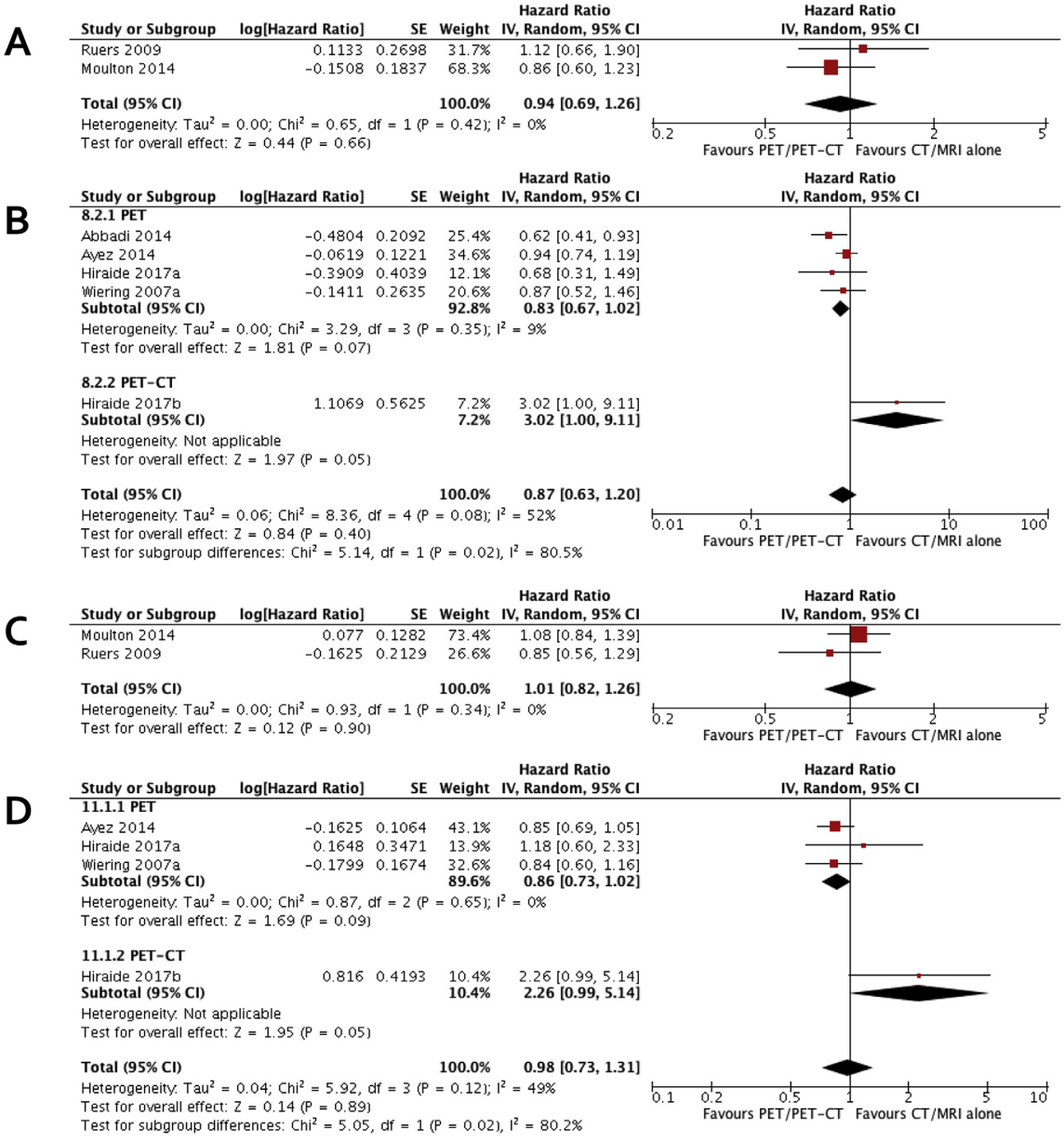

Fig. 2. Primary Outcomes. OS in all patients (A) and in patients who underwent surgery (B). DFS in all patients (C) and in patients who underwent surgery (D).

Table 2
Summary of findings.

Outcome	Participants (studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other considerations	Overall Quality of Evidence	Pooled Estimate of Effect
OS in all patients	554 (2 RCTs)	Not serious	Not serious	Not serious	Serious[a]	None	Moderate	HR 0.94 (95% CI 0.69–1.26)
OS in patients who undergo surgery	404 (1 RCT)	n/a	n/a	n/a	n/a	n/a	n/a	HR 0.81 (95% CI 0.56 - 1.17)
	1099 (4 observational studies)	Very serious[b]	Not serious	Not serious	Serious[a]	None	Very low	HR 0.87 (95[a] CI 0.63–1.20)
DFS in all patients	554 (2 RCTs)	Not serious	Not serious	Not serious	Serious[a]	None	Moderate	HR 1.01 (95% CI 0.82–1.26)
DFS in patients who undergo surgery	404 (1 RCT)	n/a	n/a	n/a	n/a	n/a	n/a	HR 1.03 (95% CI 0.79–1.34)
	911 (3 observational studies)	Serious[b]	Serious[c]	Not serious	Serious[a]	None	Very low	HR 0.98 (95% CI 0.73–1.31)
Futile laparotomy	554 (2 RCTs)	Not serious	Serious[d]	Not serious	Serious[a]	None	Low	RR 0.59 (95% CI 0.24–1.47)
	728 (2 observational studies)	Very serious[e]	Not serious	Not serious	Not serious	None	Very low	OR 0.51 (95% CI 0.32–0.81)
Change in surgical management	345 (2 RCTs)	Not serious	Not serious	Not serious	Not serious	None	High	8% (95% CI 5–11%)
	877 (8 observational studies)	Not serious	Not serious	Not serious	Not serious	None	Low	20% (95% CI 17–22%)

[a] Confidence intervals vary from significant harm to significant benefit.
[b] Hiraide 2017 offered the intervention exclusively to high risk patients (Clinical Risk Score >3) and at surgeon's discretion, both of which introduced selection bias. Additionally, Ayez 2014 had a higher proportion of patients in the control group that received chemotherapy (ie. more advanced disease).
[c] The point estimates vary widely from one another.
[d] There is moderate heterogeneity (47%) and the two point estimates vary substantially from one another.
[e] There was considerable selection bias in Pawlik 2009, as the intervention was provided at the surgeon's discretion.

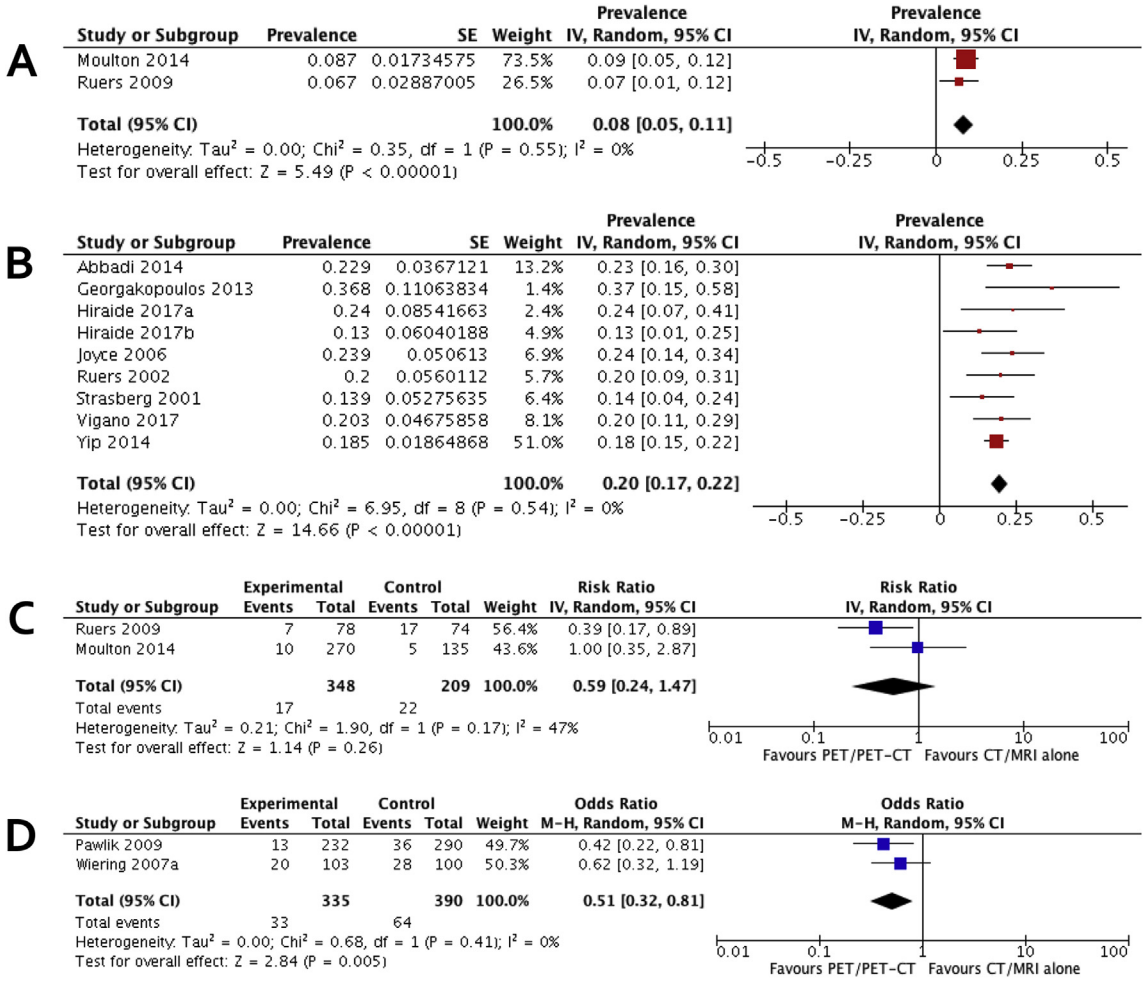

Fig. 3. Secondary Outcomes. Change in surgical management in randomized studies (A) and non-randomized studies (B). Futile laparotomy in randomized-studies (C) and non-randomized studies (D).

0.24 to 1.47, $I^2 = 49\%$). The quality of evidence was low due to imprecision and inconsistency. In contrast, when pooling two observational studies [5,6] (728 patients), futile laparotomies were significantly reduced with PET/PET-CT (OR 0.51, 95% CI 0.32 to 0.81, $I^2 = 0$). This corresponded to 7 less futile laparotomies per 100 surgeries (from 3 less to 10 less). The quality of the evidence was very low due to selection bias. See Fig. 3.

4. Discussion

PET, and more recently PET-CT, have gained popularity as staging modalities for malignant diseases such as melanoma, lung

cancer, and lymphoma [24,25]. However, the potential benefits of PET/PET-CT have not yet been elucidated in metastatic colorectal cancer. Previous systematic reviews of observational studies have reported large benefits with PET, quoting changes in surgical management of up to 25% [26,27]. At that time published data were limited, and two major RCTs have since been reported.

We investigated the role of routine PET and PET-CT in patients with potentially resectable liver metastases from colorectal cancer, and evaluated the short- and long-term impacts of these interventions. Results from several non-randomized studies and two randomized trials were pooled separately to inform the question. Among patients with colorectal cancer liver metastases who are deemed resectable on conventional imaging, we found no difference in OS or DFS with the additional use of PET/PET-CT. These results come from an intention-to-treat analysis of all patients undergoing PET/PET-CT prior to planned surgery regardless of whether surgery was actually done. This evidence is of moderate quality largely due to an insufficient sample size despite pooling. There is also very low-quality evidence from observational studies and one randomized study suggesting that PET/PET-CT does not improve OS or DFS in the subset of patients who underwent surgery. With respect to secondary outcomes, low-quality evidence from RCTs suggests that PET/PET-CT does not reduce the number of futile laparotomies. There is also high-quality evidence from RCTs suggesting that PET/PET-CT change surgical management in only 8% of cases. This contrasts with very low-quality evidence from observational studies, which suggests a near 50% reduction in futile laparotomies and a 20% change in surgical management with PET/PET-CT. These findings have major patient and system-level implications. Given the costs associated with PET/PET-CT technologies [28] and the potential delays to curative surgery, the use of these modalities should be reconsidered in this patient population.

Numerous studies have evaluated the diagnostic accuracy of PET and PET-CT in the setting of metastatic colorectal cancer [29–32], but prior to our study, there was no synthesis of the literature on patient outcomes who had been staged with PET/PET-CT. Before broad implementation of a new test, there needs to be evidence that the test has a meaningful impact on decision-making, which in turn enhances healthcare quality and/or efficiency [33]. For instance, the study by Moulton et al. [8] demonstrates that the rate of R0 resections was similar to the control group despite a high frequency of new findings in the PET-CT group, and preoperative staging with PET-CT did not improve the selection of surgical candidates. Part of this can be explained by the fact that PET-CT carries some degree of inaccuracy in the form of both false-positives and false-negatives. In Moulton et al. [8], new findings prompted subsequent investigations that were costly and potentially harmful to patients. Even when PET-CT identified occult disease, it infrequently affected a surgeon's decision to operate, and had no impact on patient outcomes (ie. survival, rate of futile laparotomy). It is possible that the initial CT identifies all moderate-to large-sized metastases with only small metastases left to be detected that do not influence surgical management. Whether or not the size of a metastases versus its metabolic activity measured by SUV is more prognostic remains unclear. Further, it is important to note that the CT in PET-CT is a low contrast CT for anatomic localization of the FDG uptake rather than a diagnostic test itself. Accordingly, the CT component of the PET-CT is not expected to identify many more metastases.

The results presented in this study are only valid for patients with potentially resectable colorectal cancer liver metastases and should not be generalized to other settings. Some authors have suggested that PET/PET-CT should be offered exclusively to patients with a high risk of recurrence; although, no evidence exists to support this claim [21]. This question was beyond the scope of this review. Due to our selection criteria, we also cannot comment on the use of a baseline PET investigation prior to chemotherapy to determine tumour responsiveness to systemic treatment, which is also a topic of debate. Whether or not this additional information would affect surgical management warrants rigorous investigations.

It is important to recognize that PET imaging has been replaced by PET-CT in modern practice. However, a significant portion of the literature, including one randomized study, took place in the setting of PET. Bearing in mind that the CT component of PET-CT is a low contrast CT used for anatomic localization of the FDG uptake, there is a lack of evidence to suggest that PET-CT and PET scans perform differently from one another. Time is also a confounding factor when considering studies with PET versus PET-CT, as there have been improvements in CT, surgical care, and chemotherapy over the last 20 years. For these reasons, both modalities were included in the present study. Respective subgroup analyses were planned *a priori* to evaluate the impact of each modality separately when appropriate. In our survival analyses, the choice of diagnostic modality (PET versus PET-CT) had a similar impact on OS for patients who underwent curative surgery. We cannot comment on the utility of PET versus PET-CT; for this reason, we made general conclusions about both modalities together.

The small number of trials included in our meta-analysis is a limitation of our study. This dampened the precision in some of the data, and prevented the exploration of heterogeneity via subgroup analyses. In fact, pooled analyses of OS and DFS continue to be underpowered. Although there were several observational studies included in this review, most posed a high risk of bias and yielded very low-quality evidence. Further, we did not define a minimally important difference for change in surgical management, nor one is defined in the literature. Some may argue that 8% change in surgical management is sufficient to justify routine use PET/PET-CT. It would be interesting to incorporate a change in management of 8% in a cost-effectiveness analysis. Of note, this estimate does not translate in avoidance of laparotomy for 8% of patients; it also includes any more or less extensive resection.

Our study also has a number of strengths. This is the only systematic review on the topic reporting on patient-important outcomes such as OS, DFS, and rates of futile laparotomy that characterize the clinical utility of PET/PET-CT. We performed a broad search strategy and carefully selected studies, eliminating those in which chemotherapy may have been administered within two weeks of PET/PET-CT. We chose to exclude these studies because chemotherapy prior to PET studies reduces metabolic activity at the tumour site, resulting in higher than average false-negatives [34]. To further inform clinical practice on the added benefit of PET/PET-CT after conventional imaging, we limited inclusion to studies where patients were deemed surgical candidates based on conventional imaging. As such, we excluded several studies that used PET/PET-CT as a means of surveillance following colorectal cancer surgery, and also as a means of diagnosing metastatic disease when there was clinical suspicion. Additionally, we evaluated the quality of evidence with GRADE to better inform clinicians on the certainty of our results.

5. Conclusion

The results of this systematic review and meta-analysis will inform future guidelines on the preoperative management of patients with colorectal cancer liver metastases. At this time, our results do not support routine PET/PET-CT when patients are deemed resectable on conventional imaging, as there is no difference in survival or proportion of futile laparotomies. Future studies should focus on identifying select patient populations that may benefit

from additional imaging studies, such as those patients with extrahepatic lesions that have a high-index of suspicion or with lesions that cannot be fully characterized on conventional imaging.

Conflicts of interest

None.

Appendix

Search: 2000–July 2018.

Database(s): Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R).

1.Exp Positron emission tomography/
2.Exp Tomography, x-ray computed/
3.Exp Magnetic resonance imaging/
4.Fluorodeoxyglucose F18/
5.$FDG.ti,ab,kf.
6.FDG*.ti,ab,kf.
7.Fluorodeoxygl*.ti,ab,kf.
8.PET*.ti,ab,kf.
9.CT.ti,ab,kf.
10.MRI.ti,ab,kf.
11.Positron emiss*.ti,ab,kf.
12.Magnetic resonance*.ti,ab,kf.
13.Tomograph*.ti,ab,kf.
14.1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15.Exp Colorectal neoplasms/
16.Colorect*.ti,ab,kf.
17.Colon*.ti,ab,kf.
18.Rectal.ti,ab,kf.
19.Rectum.ti,ab,kf.
20.Recto*.ti,ab,kf.
21.15 or 16 or 17 or 18 or 19 or 20
22.Exp Neoplasm metastasis/
23.Neoplasm Recurrence, Local/
24.Exp Recurrence/
25.Neoplasm, Residual/
26.Recurr*.ti,ab,kf.
27.Metasta*.ti,ab,kf.
28.22 or 23 or 24 or 25 or 26 or 27
29.Exp Liver neoplasms/
30.Liver.ti,ab,kf.
31.Hepat*.ti,ab,kf.
32.Intrahepat*.ti,ab,kf.
33.Extrahepat*.ti,ab,kf.
34.29 or 30 or 31 or 32 or 33
35.Hepatectomy/
36.Metastasectomy/
37.Hepatectomy.ti,ab,kf.
38.Metastasectomy.ti,ab,kf.
39.Resect*.ti,ab,kf.
40.35 or 36 or 37 or 38 or 39
41.14 and 21 and 28 and 34 and 40
42.Limit 41 to (humans and yr = "2000 -Current")

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.03.025.

References

[1] Dunne DFJ, et al. Routine staging laparoscopy has no place in the management of colorectal liver metastases. Eur J Surg Oncol 2013;39:721–5.
[2] Vigano L, et al. Early recurrence after liver resection for colorectal metastases: risk factors, prognosis, and treatment. A LiverMetSurvey-based study of 6,025 patients. Ann Surg Oncol 2014;21:1276–86.
[3] Flamen P, et al. Additional value of whole-body positron emission tomography with fluorine-18-2-fluoro-2-deoxy-d-glucose in recurrent colorectal cancer. J Clin Oncol 1999;17:894–901.
[4] Valk PE, et al. Whole-body PET imaging with [18F] fluorodeoxyglucose in management of recurrent colorectal cancer. Arch Surg 1999;134:503–11.
[5] Pawlik TM, et al. Trends in nontherapeutic laparotomy rates in patients undergoing surgical therapy for hepatic colorectal metastases. Ann Surg Oncol 2009;16:371–8.
[6] Wiering B, et al. The role of FDG-PET in the selection of patients with colorectal liver metastases. Ann Surg Oncol 2007;14:771–9.
[7] Ruers TJM, et al. Improved selection of patients for hepatic surgery of colorectal liver metastases with (18)F-FDG: a randomized study. J Nucl Med 2009;50:1036–41.
[8] Moulton CA, et al. Effect of PET before liver resection on surgical management for colorectal adenocarcinoma metastases: a randomized clinical trial. J Am Med Assoc 2014;311:1863–9.
[9] National Comprehensive Cancer Network. Colon cancer. Clin pract guidel oncol (NCCN guidelines in oncology. 2015. Version 2, . [Accessed October 2018].
[10] Moher D, et al. Preferred reporting items for systematic reviews and meta-analyses: the Prisma statement. PLoS Med 2009;6. e100097.
[11] Higgins JPT, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:1–9.
[12] Slim K, et al. Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ J Surg 2003;73:712–6.
[13] Guyatt GH, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924–6.
[14] Tierney JF, et al. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007;8.
[15] Ruers BTJM, et al. Value of positron emission tomography with [F-18] fluorodeoxyglucose in patients with colorectal liver metastases: a prospective study. J Clin Oncol 2002;20:388–95.
[16] Georgakopoulos A, et al. Impact of 18F-FDG PET/CT on therapeutic decisions in patients with colorectal cancer and liver metastases. J Clin Imaging 2013;37:536–41.
[17] Joyce DL, et al. Preoperative positron emission tomography to evaluate potentially resectable hepatic colorectal metastases. Arch Surg 2006;141:1220–6.
[18] Strasberg SM, et al. Survival of patients evaluated by FDG-PET before hepatic resection for metastatic colorectal carcinoma: a prospective database study. Ann Surg 2001;233:293–9.
[19] Vigano L, et al. Positron emission tomography-computed tomography for patients with recurrent colorectal liver metastases: impact on restaging and treatment planning. Ann Surg Oncol 2017;24:1029–36.
[20] Yip VS, et al. Optimal imaging sequence for staging in colorectal liver metastases: analysis of three hypothetical imaging strategies. Eur J Cancer 2014;50:937–43.
[21] Ayez N, et al. Preoperative FDG-PET-scan in patients with resectable colorectal liver metastases does not improve overall survival: a retrospective analyses stratified by clinical risk score. Dig Surg 2014;30:451–8.
[22] Hiraide T, et al. The role of positron-emission tomography/computed tomography in patients with colorectal liver metastases who are candidates for liver resection: is it useful? J Surg 2017;5:1–7.
[23] Abbadi RA, et al. Improved long-term survival after resection of colorectal liver metastases following staging with FDG positron emission tomography. J Surg Oncol 2014;110:313–9.
[24] Rigacci L, et al. Positron emission tomography in the staging of patients with Hodgkin's lymphoma. A prospective multicentric study by the Intergruppo Italiano Linfomi. Ann Hematol 2007;86:897–903.
[25] Fischer B, et al. Preoperative staging of lung cancer with combined PET–CT. NEJM 2009;361:32–9.
[26] Maffione AM, et al. 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;42:152–63.
[27] Wiering B, et al. The impact of fluor-18-deoxyglucose-positron emission tomography in the management of colorectal liver metastases - a systematic review and metaanalysis. Cancer 2005;104:2658–70.
[28] Serrano PE, et al. Positron emission tomography–computed tomography (PET-CT) versus No PET-CT in the management of potentially resectable colorectal cancer liver metastases: cost implications of a randomized controlled trial. J Oncol Pract 2016;12:e765–74.
[29] Arulampalam THA, et al. FDG-PET for the pre-operative evaluation of colorectal liver metastases. Eur J Surg Oncol 2004;30:286–91.
[30] Chan VO, et al. Diagnostic performance of MDCT, PET/CT and gadoxetic acid (Primovist®)-enhanced MRI in patients with colorectal liver metastases being considered for hepatic resection: initial experience in a single centre. Ir J Med Sci 2012;181:499–509.

[31] Kochhar R, et al. The role of FDG PET/CT in patients with colorectal cancer metastases. Cancer Biomark 2010;7:235–48.
[32] Takahashi S, et al. Positron emission tomography with F-18 fluorodeoxyglucose in evaluating colorectal hepatic metastasis down-staged by chemotherapy. Anticancer Res 2006;26:4705–11.
[33] Bossuyt PMM, et al. Beyond diagnostic accuracy: the clinical utility of diagnostic tests. Clin Chem 2012;58:1636–43.
[34] Lubezky N, et al. The role and limitations of 18-fluoro-2-deoxy-d-glucose positron emission tomography (FDG-PET) scan and Computerized Tomography (CT) in restaging patients with hepatic colorectal metastases following neoadjuvant chemotherapy: comparison with operative and pathological findings. J Gastrointest Surg 2007;11:472–8.