Title: What is the role of pre-operative PET/PET-CT in the management of patients with potentially resectable colorectal cancer liver metastasis?

Pablo E. Serrano, Julian F. Daza, Natalie M. Solis

June 12, 2017
Need for a review: Problem to be addressed and background

Colorectal cancer is the fourth most prevalent cancer in Canada\(^1\), and 50% of cases metastasize to the liver.\(^2\) Liver resection can be curative in patients with colorectal cancer liver metastasis assuming that there is no disease found elsewhere.\(^3\) In fact, long-term survival for patients who undergo resection is as high as 50%.\(^4\) As part of the pre-operative workup, surgeons typically obtain a computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen and chest, in addition to whole body positron emission tomography/positron emission tomography-computed tomography PET/PET-CT to determine the location and extent of metastatic disease. Successful resection must remove all metastatic disease in the liver while leaving behind sufficient hepatic reserve. The majority of patients with extrahepatic disease are ineligible for surgery. Thus, surgeons heavily rely on pre-operative imaging for planning operations and deciding when to operate. In spite of recent advances in imaging technology, 40% of patients are deemed unresectable at the time of surgery.\(^5\) Of those patients who undergo resection, 50% develop metastatic disease after one year.\(^6\) This calls for improved pre-operative detection of patients who will most benefit from surgery.

It has been proposed that PET with 18F-fluorodeoxyglucose (18F-FDG) alone or combined with CT has overall enhanced detection of extrahepatic disease.\(^7\) However, there remains conflicting evidence on the added benefit of PET/PET-CT for staging purposes.\(^8,9\) Given the additional cost of this imaging test, it is crucial to determine whether or not there is any patient advantage. Thus, we set out to perform a systematic review of literature and meta-analysis to compile the existing knowledge on this topic.

1. **Study Objectives:**
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**Primary objective:** To determine the overall survival in patients with resectable colorectal cancer liver metastases who are staged pre-operatively with PET/PET-CT compared to no PET/PET-CT (e.g. CT, MRI or both).

**Secondary objectives:** 1) To determine disease-free survival between groups. 2) To determine what proportion of surgeries deviate from the initial surgical plan following pre-operative PET-CT or PET. 3) To determine the rate of futile laparotomy (defined as any laparotomy that did not result in complete tumor clearance either intrahepatically or extrahepatically, or that revealed benign disease at laparotomy or histopathologic examination). 4) To determine the sensitivity and specificity of PET-CT or PET. 5) To perform a cost analysis of PET-CT or PET in this setting.

2. **Eligibility criteria / Study sample population:**
Men and women over the age of 18 with histologically confirmed colorectal cancer and liver metastasis (synchronous or metachronous disease). Patients deemed to be resectable candidates based on pre-operative CT abdomen/chest/pelvis, with no extrahepatic disease with the exceptions of lung, colon/rectum, or portal lymph nodes that can be resected at the discretion of the surgeon. Studies that include patients who were initially deemed unresectable and underwent chemotherapy to become resectable are eligible for inclusion.

3. **Intervention:**
Pre-operative PET/PET-CT following standard imaging including CT, MRI, or both.

4. **Comparator:**
Pre-operative CT, MRI or both, exclusively.

5. **Outcomes:**

*Primary outcome:* Overall survival
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Secondary outcomes: 1) Disease-free survival 2) pre-operative change in surgical management (e.g. cancelled surgery, more extensive surgery, additional organ surgery) 3) rate of open-close surgeries 4) sensitivity and specificity. 5) cost-effectiveness.

6. Study questions:

   a. Does pre-operative staging with PET/PET-CT improve overall survival and disease-free survival in patients that are undergoing curative liver resection for colorectal liver metastasis?

   b. Does pre-operative staging with PET/PET-CT change surgical management in patients that are undergoing curative liver resection for colorectal liver metastasis?

   c. Does pre-operative staging with PET/PET-CT decrease the number of open-close surgeries in patients that are undergoing curative liver resection for colorectal liver metastasis?

   d. What is the false positive and the false negative rate of PET/PET-CT in this setting?

   e. Is it cost-effective to use pre-operative PET/PET-CT for staging patients that are undergoing curative liver resection for colorectal liver metastasis?

7. Design:

Randomized controlled trials, prospective and retrospective cohort studies, and single arm observational studies.

8. Exclusion criteria:

Patients with prior (within 2 weeks of PET/PET-CT) chemotherapy and radiation therapy (within 6 weeks of PET/PET-CT).
9. **Selected databases:**

The following databases will be included in our review: Medline, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL). All languages will be searched. (Appendix 1, 2 and 3).

10. **Grey literature:**

The grey literature will be reviewed as follows: 1) Hand search of abstracts published by the American Society of Clinical Oncology in their journal, Journal of Clinical Oncology, for the following meetings: ASCO-GI, ASCO and ASTRO. Abstracts published in the Annals of Surgical Oncology, as part of the Society of Surgical Oncology (SSO) meeting will also be searched, as well as a hand search of abstracts for the following meetings: European Society of Surgical Oncology (ESSO), European Society of Medical Oncology (ESMO), Japanese Society of Medical Oncology (JSMO), the European Society of Medical Oncology – Asia meeting (ESMO-Asia), the Chinese Society of Clinical Oncology (CSCO) meeting and the Federation of Asian Clinical Oncology (FACO) meeting. 2) Review clinical trials registries for relevant unpublished studies: clinicaltrials.gov, the International Standard Randomized Controlled Trial Number (ISRCTN) Register, and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP). 3) The references of included studies in the meta-analysis will be reviewed to evaluate for potential studies to be included. 4) Experts in the field will be contacted to determine what studies they are aware of that meet the inclusion criteria.

11. **Methods to ensure agreement:**

There will be two independent researchers involved in selecting and reading abstracts and full papers to establish if they meet eligibility criteria for inclusion in the meta-analysis. Detailed screening criteria forms will be utilized. Data abstraction from different sources, including
Medline, Embase, and Cochrane will be exported to a software called “EndNote” in order to perform a duplicate screening of retrieved references’ titles and abstracts. Once the final list has been obtained, it will be distributed to the reviewers via a web-based software called “Distiller SR” (http://www.distillercer.com) in order to start the process of inclusion and exclusion of studies. For excluded references, a justification for the most important reason for exclusion will be documented. The full text of all relevant references will be obtained. For those with discrepancies between viewers, an in depth analysis will take place to determine why one person thought it should or should not be included. After discussion, we expect there will be agreement. If there is not, a third party reviewer will be consulted. We will use a weighted kappa to assess agreement between reviewers on the selection of articles for inclusion, assessment of the certainty of effect and data abstraction.

12. **Risk of bias:**

Each selected study will be assessed by the two independent reviewers using the Cochrane Risk of Bias Tool for randomized and non-randomized studies.

13. **Heterogeneity:**

Heterogeneity will be calculated using a statistical program (P value for Chi-squared for heterogeneity) and will also be informed using the I² statistic, following the recommendations of The Cochrane Collaboration, where a result between 0 to 40% indicates not important heterogeneity, 30 to 60% moderate, 50 to 90% substantial and 75 to 100% high heterogeneity.

14. **A priori hypothesis to explain possible heterogeneity:**

This meta-analysis will pool widely, including randomized control trials versus non-randomized control trials, and prospective versus retrospective studies, outcomes in high volume versus low volume centers, simple versus complex resections, and detection of PET-CT compared to
standard imaging versus PET compared to standard imaging. We expect to have high heterogeneity between studies due to the effect of pooling widely.

**A priori hypothesis to explain clinical sources of heterogeneity:**

- Subgroup analysis of randomized control trials vs. non-randomized studies: we expect that patients who had PET-CT will have better overall survival in retrospective studies because patients are highly selected in retrospective studies compared to prospective studies and randomized control trials. This improvement in survival might be due to loss to follow up, inaccurate data gathering and recall bias in retrospective studies.

- High volume centers will have better outcomes than low volume centers: we expect that PET-CT will not make a difference in overall survival in high volume centers. We expect that PET-CT will result in higher overall survival in low volume centers because high volume centers have better evaluation through the use of other imaging such as CT and MRI that is not involved in low volume centers.

- Simple resections will have better outcomes than complex resections: we expect that PET-CT will have a larger effect on overall survival in studies that have complex resections (multiple liver metastases and extrahepatic disease) because there are more chances of avoiding an operation and therefore patients who had surgery will have better overall survival compared to studies that did not include multiple liver metastases and extrahepatic disease.

- PET-CT detects more disease compared to PET alone: we expect that studies which included PET-CT as opposed to PET alone will have detected more disease and would have avoided more operations as a result, and therefore there would be better overall survival for patients who had surgery.
A priori hypothesis to explain methodological sources of heterogeneity:

- Risk of bias: we will perform sensitivity analysis of studies with high vs. low risk of bias. We expect that studies with a higher risk of bias will show better overall and disease-free survival.
- Missing data: sensitivity analysis will be performed comparing studies with missing data for the primary outcome vs. studies with complete data: we expect studies with missing data will show better overall and disease-free survival.

15. Data collection and missing data:
Two independent reviewers will collect data using pre-defined data collection forms. The corresponding author will be contacted for relevant missing data. If after two weeks the corresponding author does not answer by e-mail, we will contact the last author of the paper. If after two weeks there is no answer, we will call then first author. If they fail to give an answer after two weeks of our last contact, we will acknowledge the missing data.

16. Plans to summarize results (time-points for pooling data):
We will use the statistical program Review manager (RevMan) to calculate the effect sizes, as the Cochrane Collaboration has endorsed this program. The effect size will be stated along with a 95% confidence interval and presented as well in a graphical representation (i.e., forest plots). The pool estimates of effect will be calculated using random-effects model with Mantel-Haenszel statistics. The results will be presented as relative risk with a 95% confidence interval for dichotomous variables and as mean difference with 95% confidence interval for continuous outcomes. Potential publication bias will be analyzed using Funnel Plot. Subgroup analysis will be performed to assess for clinical and methodological sources of heterogeneity. We expect to
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finish with the different processes of review as follows: article assessment for eligibility: May 2017, Data analysis: June 2017, Manuscript writing: August 2017, Publication: January 2018.

17. **Assessment of confidence in estimates of effect:**
At the end of this meta-analysis, 2 independent reviewers will evaluate the confidence of the estimates of effects using the GRADE approach.

18. **Reporting:**
This protocol will be published in PROSPERO. The final manuscript of the meta-analysis will be published in a peer-reviewed journal.
Appendix 1

MEDLINE search strategy

**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.
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/
17. Colon*.ti,ab,kf.
18. Rectal.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/


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.


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 2

EMBASE search strategy

Database(s): **Embase** 1996 to 2017 April 28

1. computer assisted tomography/
2. exp Computer assisted emission tomography/
3. exp Nuclear magnetic resonance imaging/
4. x-ray computed tomography/
5. fluorodeoxyglucose f 18/
6. SFDG.ti,ab,kw.
7. FDG*.ti,ab,kw.
8. Fluorodeoxygl*.ti,ab,kw.
9. PET*.ti,ab,kw.
10. CT.ti,ab,kw.
11. MRI.ti,ab,kw.
15. 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 or 14
16. exp Colon tumour/
17. exp Rectum tumour/
18. Colorect*.ti,ab,kw.
19. Colon.ti,ab,kw.
20. Rectal.ti,ab,kw.
21. Recto*.ti,ab,kw.

22. Rectum.ti,ab,kw.

23. 16 or 17 or 18 or 19 or 20 or 21 or 22

24. exp Metastasis/

25. tumor recurrence/

26. minimal residual disease/

27. Metasta*.ti,ab,kw.


29. 24 or 25 or 26 or 27 or 28

30. exp Liver tumor/

31. Liver.ti,ab,kw.

32. Hepat*.ti,ab,kw.

33. Intrahepat*.ti,ab,kw.

34. Extrahepat*.ti,ab,kw.

35. 30 or 31 or 32 or 33 or 34

36. exp Liver surgery/

37. exp Metastasis resection/

38. Hepatectomy.ti,ab,kw.


40. Resect*.ti,ab,kw.

41. 36 or 37 or 38 or 39 or 40

42. 15 and 23 and 29 and 35 and 41

43. limit 42 to (human and yr="2000 -Current")
Appendix 3

CENTRAL search strategy

1. MeSH descriptor: [Tomography, Emission-Computed] explode all trees
2. MeSH descriptor: [Tomography, X-Ray Computed] explode all trees
3. MeSH descriptor: [Magnetic Resonance Imaging] explode all trees
4. MeSH descriptor: [Fluorodeoxyglucose F18] this term only
5. FDG
6. Fluorodeoxyglu*
7. PET
8. CT
9. MRI
10. Positron emission
11. Magnetic resonance
12. Tomograph*
13. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 of #12
14. MeSH descriptor: [Colorectal Neoplasms] explode all trees
15. Colorect*
16. Colon
17. Recto*
18. Rectal
19. Rectum
20. #14 or #15 or #16 or #17 or #18 or #19
21. MeSH descriptor: [Neoplasm Metastasis] explode all trees
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22. MeSH descriptor: [Neoplasm Recurrence, Local] this term only

23. MeSH descriptor: [Neoplasm, Residual] this term only

24. Metasta*

25. Recurr*

26. #21 or #22 or #23 or #24 or #25

27. MeSH descriptor: [Liver Neoplasms] explode all trees

28. Liver

29. Hepat*

30. Intrahepat*

31. Extrahepat*

32. #27 or #28 or #29 or #30 or #31

33. MeSH descriptor: [Hepatectomy] this term only

34. Hepatectomy

35. Metastasectomy

36. Resect*

37. #33 or #34 or #35 or #36

38. #13 and #20 and #26 and #32 and #37
References:


2. Al Asfoor A, Resection versus no intervention or other surgical interventions for colorectal cancer liver metastases. Cochrane Database Syst Rev. 2008


