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Synopsis: The current study compared the overall survival and progression free survival of a cohort of patients with colorectal liver metastases who underwent neoadjuvant chemotherapy prior to liver resection, based on their structural and metabolic imaging response to neoadjuvant chemotherapy.

Data Availability Statement:

Data available on request due to privacy/ethical restrictions. The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Association Between Imaging Response and Survival Following Neoadjuvant Chemotherapy in Patients with Resectable Colorectal Liver Metastases: A Cohort Study

Behrenbruch C, Prabhakaran S, Udayasiri D, Michael M, Hollande F, Hayes I, Heriot S, Knowles B, Thomson B

ABSTRACT

Background: The association between the imaging response (structural or metabolic) to neoadjuvant chemotherapy (neoCT) prior to colorectal liver metastasis (CRLM) and survival is unclear.

Method: 201 patients underwent their first CRLM resection. 94 (47%) patients were treated with neoCT. A multivariable, Cox proportional hazard regression analysis was performed to compare overall survival (OS) and progression free survival (PFS) between response groups.

Results: Multivariable regression analysis of the CT/MRI (n=94) group showed no difference in survival (OS and PFS) in patients who had stable disease/partial response (SD/PR) or complete response (CR) versus patients who had progressive disease (PD) (OS: HR 0.36 (95%CI 0.11-1.19) p=0.094, HR 0.78 (95%CI 0.13-4.50) p=0.780 respectively), (PFS: HR 0.70 (95% CI 0.36-1.35) p=0.284, HR 0.51 (0.18-1.45) p=0.203 respectively). In the FDG-PET group (n=60) there was no difference in the hazard of death for patients with SD/PR or CR versus patients with PD for OS or PFS except for the PFS in the small CR subgroup (OS: HR 0.75 (95%CI 0.11-4.88) p=0.759, HR 1.21 (95%CI 0.15-9.43) p=0.857), (PFS: HR 0.34% (95% CI 0.09-1.22), p=0.097, HR 0.17 (95%CI 0.04-0.62) p=0.008 respectively).

Conclusion: There was no convincing evidence of association between imaging response to neoCT and survival following CRLM resection.

Introduction

In patients with oligometastatic disease to the liver, resection of colorectal liver metastases (CRLM) offers the only chance of cure, with 5-year survival rates for patients undergoing CRLM resection between 33-55%, compared with 13% if all sites of disease cannot be resected[1-3]. Approximately 10-20% of patients of who present with CRLM have disease amenable to curative resection[4,5]. The use of neoadjuvant chemotherapy (neoCT) to downstage patients with potentially resectable disease, as well as improved surgical and radiological techniques, has resulted in more patients undergoing potentially curative resection[3,6-9]. Unfortunately, recurrence rates following CRLM resection remain unacceptably high (47%-91%)[10-14]. There is continual effort to try to improve selection criteria to more accurately identify patients who will benefit from liver resection to avoid futile surgery.

A number of clinical risk scores have been developed to identify patients at risk of recurrence following CRLM, the most widely accepted being the Memorial Sloane-Kettering Cancer Centre Clinical Score (MSKCC-CS)[15-18]. This score has not been shown to be predictive in patients who have received neoCT prior to resection of CRLM[15,19]. The use of pre-treatment FDG-PET/CT (^{18}F-fluordeoxyglucose positron emission tomography/computed tomography) has been shown to identify previously occult metastases that may prevent futile surgery, although the magnitude of benefit is variably reported[20-24]. Unfortunately, the FDG-PET response following neoCT has not been shown to correlate with recurrence or survival following CRLM resection[25]. A meta-analysis by Xia *et al*. showed that FDG-PET was predictive of event-free survival and OS in the pre-treatment group, but not in the post-treatment group. The

analysis lacked power due to the small number of patients (n=55) included in the post-treatment group[25].

Two additional cohort studies were not included in the meta-analysis. Chiu et al (n=40) showed that patients who achieved a complete metabolic response had better OS than patients who had progressive disease, with no difference between those achieving partial and complete response[26]. Adam *et al*. (n=131) showed that the 5-year survival was significantly worse in patients who progressed on FDG-PET scan compared with those having stable disease or partial response[10]. These studies did not include the final pathology of the resected CRLM. A complete response on FDG-PET has not been shown to correlate with tumour viability, with persistent viable tumour reported in 80-85% of tumours[27,28]. Structural imaging (CT(computerised tomography)) response has similarly been shown to correlate poorly with histopathology, although large studies are lacking. In one study, out of 7 lesions that were deemed to have had a complete CT response, viable tumour was detected in 6/7 (86%) of the resected lesions[27].

Patients with resectable CRLM, but with high risk features such as ≥ 4 liver lesions, are often subjected to neoCT prior to CRLM, to allow tumours with worse " biology" to declare themselves, avoiding potentially futile surgery [29,30]. In patients who progress while on treatment, it has been suggested that tumour control *before* surgery is crucial to offer a chance of prolonged remission in patients with multiple metastases, however the evidence to support this strategy only includes small patient numbers[10]. The current study aimed to determine if there was an association between overall (OS) and progression free survival (PFS) and the post-treatment imaging

response (structural and metabolic) in a cohort of patients receiving neoCT prior to CRLM.

Materials and Methods

This was a retrospective cohort study. Patients were identified from a consecutive database of all CRLM resections performed by two surgeons, across two tertiary referral hospitals, from 2003-2018. Two of the authors independently reviewed and collected data from available electronic and hard copy medical records. Patients were included in the study if: 1) colorectal adenocarcinoma was confirmed on histologically 2) it was their first CRLM resection 3) they received neoCT prior to liver resection, 4) pre-treatment and post-treatment imaging was performed 5) there was macroscopic resection of all sites of disease. Neoadjuvant chemotherapy prior to liver resection was defined as long course chemotherapy given with a view to downstaging or assessing the biology of the CRLM. Patients were excluded if they had radiofrequency or microwave ablation prior to liver resection. Patients were not excluded if there were additional sites of extrahepatic disease such as peritoneum, lung, adrenals or ovaries, as long as all sites of disease were resected. The study was performed according to ethical standards of World Medical Association Declaration of Helsinki of 2013 and ethics approval was obtained for both hospital sites (QA2018007 and 18/84R).

All patients were discussed at a multidisciplinary meeting prior to and following neoCT, to discuss treatment response. There were no standardised criteria used to determine what type of chemotherapy regimen was used. Patients were categorised by response into complete responders (CR), stable/partial responders (SD/PR) and patients who had progressive disease (PD) of their CRLM. Response was determined

on the basis of the formal comparative radiology report stating the response. Patients who had a mixed response were categorised into the least favourable response group. Response was documented and analysed separately for FDG-PET and structural imaging which included either CT or MRI (whichever was the last structural imaging modality prior to CRLM resection). Synoptic histopathology reporting was not standard at either institution, therefore pathology reports were reviewed and the presence of viable tumour, mucin and necrosis recorded as a binary result. Follow-up assessment was performed every 3 months and included carcinoembryonic antigen (CEA) levels and CT or MRI. The primary endpoint was overall survival (OS) and the secondary endpoint progression free survival (PFS).

Statistics

Baseline data were presented as absolute numbers and percentages. Continuous variables were presented as median and interquartile range (IQR). For survival analysis, the start date was defined as date of diagnosis of CRLM, due to the inclusion of both metachronous and synchronous CRLM. Date of last follow up was defined as date of last clinic visit, imaging or pathology test. For OS, patients were censored by date of last follow up or death date. For PFS, patients were censored by date of recurrence or date of last follow up or death. Date of recurrence was defined as the date on which there was imaging confirmation of recurrence or the date of recurrence found at colonoscopy or laparoscopy/laparotomy.

Due to the intrinsic heterogeneity of the cohort, a univariable Cox proportional hazard (PH) regression analysis assessing hazard of death was performed for each baseline variable for OS and PFS. Multivariable Cox PH regression analysis was then performed to adjust for potentially confounding variables, with response to neoCT as the principal exposure of interest. Co-variables from the univariable analysis which

were associated with a greater than 10% change in hazard ratio and had less than 20% missing data were included in the multivariable Cox PH regression analysis. The proportional hazard assumption was tested using Schoenfeld residuals complemented by visual assessment of cumulative hazard graphs. The analysis was completed separately for metabolic (FDG-PET group) and structural imaging (CT/MRI group). Sample size was not calculated for this study as the database was a fixed available sample. Data was analysed using Stata version 15.0 (College Station, Texas, USA) statistical software.

Results

Patients

A total of 201 consecutive patients who underwent their first CRLM resection and achieved macroscopic resection of all sites of disease were identified from a larger database of all CRLM resections. Resections were performed by two hepatobiliary surgeons, between 2003-2018. Of these patients 94/201 (46%) received neoadjuvant chemotherapy. Most patients had an ASA (American Society of Anaesthesiologists) score of 2 (78/94, 83%) and none of the patients had a score of 4. With respect to the primary tumour, 30/94 (32%) of patients had rectal tumours, 36/94 (38%) patients had positive nodal disease (pathological) and 32/94 (34%) had T4 disease (pathological). Only 11/94 (12%) were previously treated with adjuvant, post primary resection (PrR) chemotherapy, all of whom had metachronous CRLM (17/94 (18%)) **(Table 1)**.

The majority of patients were administered either FOLFOX (5-Fluorouracil, Oxaliplatin, Leucovorin) or FOLFOX/Bevacizumab prior to CRLM resection, (76/94 (81%)) with minor regimens including 5-Fluorouracil alone, FOLFOX/panitumimab,

FOLFIRI/cetuximab, FOLFIRI/bevacizumab, and FOLFOXIRI/bevacizumab **(Table 2)**. To try to account for time delays in treating rectal tumours (due to the need for neoadjuvant radiotherapy), the time difference between the date of diagnosis of the CRLM and the final staging scan was included as a variable in the regression analysis. A total of 22/94 (23%) had more than 6 months between diagnosis of their CRLM and definitive re-staging scan. Approximately half of the patients had bilobar and half unilobar disease on pre-treatment imaging and 71/94 (76%) had less than or equal to 3 tumours on definitive pathology result. The majority of patients had an R0 resection (microscopically negative), with only 18/94 (19%) having an R1 resection (microscopically positive) **(Table 2)**. Details of the mutational status of patients were not included in the study due to low numbers, as not all patients were routinely tested.

Imaging Results

All 94 patients had pre and post treatment structural imaging (CT or MRI). A total of 60 patients had pre and post treatment imaging with FDG-PET. In the CT/MRI group there were 23/94 (24%) patients with PD, 61/94 (65%) with SD/PR and only 10/94 (11%) had a complete structural response. In the FDG-PET group 10/60 (17%) patients had PD, 27/60 **(**45%) had SD/PR and 23/60 (38%) had a complete metabolic response. The number of patients who had the same response on both structural and metabolic imaging was 39/60 (65%) **(Table 2)**.

Pathological Response

Within the structural imaging group, viable tumour was present in the final pathology specimen in 22/23 (95.6%) patients with PD, 58/61 (95%) with SD/PR disease and 9/10 (90%) of those who had a complete response. In the FDG-PET group, viable

tumour was found on histopathology in 10/10 (100%) of patients with PD, 26/27 (96.3%) with SD/PR and 19/23 (82.6%) of those who had a complete response group. The presence of mucin was documented in 13/94 (14%) patients in the structural group and 8/60 (13%) in the FDG-PET group. Necrosis was identified in 79/94 (84%) patients in the structural group and 50/60 (83%) in the FDG-PET group. Fibrosis and inflammatory infiltrate were not consistently reported **(Table 2)**.

Overall Survival

For OS, the median follow-up time for the CT/MRI group was 3.54 years (3.30-4.56) in the PD group, 3.72 years (2.65-6.80) in the SD/PR group and in the CR group 4.87 years (4.17-5.68). In the FDG-PET group the median follow-up time was 3.28 years (2.11-7.13) in the PD group, 3.43 (2.80-6.67) in the SD/PR group and 4.17 (2.70-5.68) in the CR group. At the end of the study period 59/94 (62.8%) in the CT/MRI group and 39/61 (63.9%) in the FDG-PET group were alive **(Table 2)**. Raw data for OS is displayed in the Kaplan Meier curves in **Figure 1.** Variables adjusted for in the multivariable analysis included age, sex, ASA score, primary tumour staging (site of primary, nodal status, differentiation, T stage, adjuvant chemotherapy), synchronous/metachronous liver metastases, distribution of CRLM, presence of extrahepatic metastases, the time between diagnosis and post treatment imaging, complexity of the liver operation (major/minor), the size and number of CRLM, resection margin and adjuvant therapy post CRLM resection. In the CT/MRI group, although the univariable analysis showed a 33% decrease in hazard of death from all causes in the SD/PR compared to the PD (HR 0.67 (0.31-1.43), p=0.298), on multivariable analysis there was no difference (HR 0.36 (95%CI 0.11-1.19), p=0.094). There was no difference between CR and PD on either univariable (HR

0.97 (95%CI 0.33-2.86, p=0.950) or multivariable analysis (HR 0.78 (95%CI 0.13-4.50), p=0.780) **(Table 3)**.

For the FDG-PET group, the same variables listed above were adjusted for in the multivariable analysis. There was no difference in the univariable or multivariable analysis between the SD/PR or CR and the PD group (HR 0.75 (95%CI 0.11-4.88) p=0.759, HR 1.21 (95%CI 0.15-9.43) p=0.857 respectively) **(Table 4).**

Progression Free Survival

At the end of the follow up period 75/94 (79.8%) patients in the CT/MRI group had recurred and 51/61 (83%) in the FDG-PET group. A total of 22/94 (23.4%) patients in the CT/MRI group had liver only recurrence as had 12/61 (19.7%) in the FDG-PET group. Repeat resection of recurrence (including sites other than liver) was possible for 31/94 (33%) patients in the CT/MRI group and 18/61 (29.5%) in the FDG-PET group **(Table 2)**. The raw data for PFS is shown in the Kaplan Meier curves in **Figure 1**. In the CT/MRI group, multivariable analysis did not show any difference in PFS between those with SD/PR or CR compared with those with PD ((HR 0.70 (95% CI 0.36-1.35),p=0.284), (HR 0.51 (0.18-1.45), p=0.203), respectively) **(Table 5)**. In the FDG-PET group there was no difference in PFS between the patients in the CR and the PD group on the multivariable analysis (HR 0.34% (95% CI 0.09-1.22), p=0.097). In the SD/PR group compared with the PD group there was an 83% decrease in hazard of death from all causes, however the number of patients involved was small and confidence intervals were wide (HR 0.17 (95%CI 0.04-0.62), p=0.008) **(Table 6)**.

Discussion

The results of our study show that survival was not associated with metabolic or structural imaging response to neoCT prior to resection of CRLM. Specifically, there was no difference in OS or PFS between partial or complete responders and those that progressed while on treatment, except for PFS in the SD/PR FDG-PET subgroup. Additionally, we demonstrated poor correlation between complete response on imaging and pathological response, as well as poor concordance between structural and metabolic imaging.

The limitations of this study include its retrospective methodology and small patient numbers, however other studies assessing the prognostic accuracy of imaging response are of a similar size, particularly those with corresponding histopathology[10,27,28,31]. The cohort is heterogenous with respect to primary tumour location, the neoCT regimens administered and the structural imaging that was used to assess tumour response. Some variables not included in the regression analysis may have contributed to confounding, such as the sequence of treatment in the case of synchronous CRLM and development of complications from either the primary operation or CRLM resection. In this study histopathology results following resection were included as well as imaging results. Therefore, the results can only be generalised to patients who went on to successful resection of CRLM following neoCT, not all patients who received neoCT. Finally, although RECIST criteria was used by radiologists when reporting imaging, the response to neoCT in our study was determined by the radiologist's formal comparative report rather than an independent assessment of the imaging. These radiologist's reports however, were used to guide

treatment decisions during multidisciplinary meetings and therefore considered 'real-world' imaging results.

The results of our study are in keeping with current evidence that the post-treatment response on FDG-PET following neoCT has poor prognostic accuracy for patients with resectable CRLM, unlike the situation in chemo-naïve patients where higher levels of standard uptake values (SUV) correlate with worse median survival[19,25,27,28,32,33]. The National Comprehensive Cancer Network (NCCN) currently discourages the use of FDG-PET to monitor response to neoCT due to high false negative rates and low sensitivity (as low as 13.3%) when performed within 4 weeks of neoCT[30,33-36]. A meta-analysis by van Kessel *et al*. (n= 223) showed that MRI had the highest pooled sensitivity estimate followed by contrast CT. Again, FDG-PET and PET-CT performed well in chemo- naïve liver metastases, but had low diagnostic accuracy in the neoadjuvant setting[37]. Proposed reasons for false negatives in FDG-PET include the presence of necrosis, the size of the CRLM following treatment, temporary metabolic shutdown from neoCT, contribution of background liver signal due to steatohepatitis, and the presence of mucinous tumours [30,36,38]. One study showed that the sensitivity of FDG-PET went from 100% in tumours about 2cm to 17% in tumours below 2cm[38]. In our cohort of patients with complete response on FDG-PET, 14/23 (60%) of the patients had lesions less than 2cm.

Unlike response on imaging, histological tumour response has been shown to correlate with an improved OS following neoCT[39,40]. Although FDG-PET is highly sensitive for tumour necrosis, tumour regression in CRLM is determined by the proportion of viable tumour and fibrosis present, not necrosis[31,39,41]. Due to synoptic reporting not being performed routinely at our institutions, tumour regression grade of

the CRLM was not formally documented[39,40]. Peri-tumoural lymphocytic infiltrate was also not consistently reported, a finding that has also been shown to be prognostic following neoCT[42]. Therefore, we were unable to accurately calculate sensitivity, specificity or a false negative rate (particularly in the SD/PR group). However, in the CR group, viable tumour was still seen in 19/23 (93%) patients in FDG-PET group and 9/10 (92%) in the structural imaging group. This said, it is not known what proportion of viable tumour results in clonogenic potential[43].

In an attempt to improve identification of "true complete responders", clinicopathological parameters such as normalisation of CEA (carcinoembryonic antigen) levels and more detailed, morphological imaging features have been utilised with some positive results[31,44]. Other groups have tried to determine a mutational signature to predict which patients may benefit from tailored treatment. Mutations of TP53, BRAF, KRAS, SMAD4, PIK3CA have been examined but none are currently used clinically as predictive biomarkers [45-50]. Although FDG-PET avidity generally reflects the biological activity of the tumour, a comprehensive understanding of how that activity translates to survival is lacking[20,35]. It is necessary to move beyond unimodal, clinicopathological or quantitative/topographic imaging techniques when trying to predict which patients will benefit most from CRLM resection following neoCT. Emerging as promising tools are more advanced hybrid imaging/bioinformatic techniques in the form of structural and metabolic imaging-based radiomics and radiogenomics[51,52]. These techniques harness all of the available information that can be gathered about a patient and their tumour, combining numerous quantitative images with the mutational signature, gene expression and proteomic profile of the tumour to generate a statistical model that could reflect the

true "biology" of the tumour and aid in better patient selection for CRLM following neoCT[51,52].

Conclusion

This study has demonstrated no evidence of association between response on structural or metabolic imaging and overall survival or progression free survival following neoCT for resectable CRLM. Based on these results, response on imaging following neoCT cannot be used to reliably determine which patients will benefit from subsequent CRLM resection. Further studies are required to improve interpretation of imaging results and to better understand the biological mechanisms that drive post-treatment imaging responses. This is important not only to ensure avoidance of futile surgery but also to prevent patients who achieve a complete response from being managed conservatively until "true" complete responders can be identified with certainty.

REFERENCES

1. Australia C. Relative survival by stage at diagnosis (colorectal cancer). 2019; https://ncci.canceraustralia.gov.au/outcomes/relative-survival-rate/relative-survival-stage-diagnosis-colorectal-cancer. Accessed 16th August, 2020.

2. Rawla P, Sunkara T, Barsouk A. Epidemiology of colorectal cancer: incidence, mortality, survival, and risk factors. *Prz Gastroenterol.* 2019;14(2):89-103.

3. Adam R, Kitano Y. Multidisciplinary approach of liver metastases from colorectal cancer. *Annals of Gastroenterological Surgery.* 2019;3(1):50-56.

4. Nordlinger B, Van Cutsem E, Rougier P, et al. Does chemotherapy prior to liver resection increase the potential for cure in patients with metastatic colorectal cancer? A report from the European Colorectal Metastases Treatment Group. *European journal of cancer (Oxford, England: 1990).* 2007;43(14):2037-2045.

5. Adams RA, Meade AM, Madi A, et al. Toxicity associated with combination oxaliplatin plus fluoropyrimidine with or without cetuximab in the MRC COIN trial experience. *British Journal of Cancer.* 2009;100(2):251-258.

6. Wen F, Li Q. Treatment dilemmas of cetuximab combined with chemotherapy for metastatic colorectal cancer. *World journal of gastroenterology.* 2016;22(23):5332-5341.

7. Primrose JN. Surgery for colorectal liver metastases. *British journal of cancer.* 2010;102(9):1313-1318.

8. Kron P, Linecker M, Jones RP, Toogood GJ, Clavien P-A, Lodge JPA. Ablation or Resection for Colorectal Liver Metastases? A Systematic Review of the Literature. *Front Oncol.* 2019;9:1052-1052.

9. Pawlik TM, Schulick RD, Choti MA. Expanding Criteria for Resectability of Colorectal Liver Metastases. *The oncologist.* 2008;13(1):51-64.

10. Adam R, Pascal G, Castaing D, et al. Tumor progression while on chemotherapy: a contraindication to liver resection for multiple colorectal metastases? *Annals of surgery.* 2004;240(6):1052-1064.

11. Bismuth H, Adam R, Lévi F, et al. Resection of nonresectable liver metastases from colorectal cancer after neoadjuvant chemotherapy. *Annals of surgery.* 1996;224(4):509-522.

12. Adam R, Delvart V, Pascal G, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. *Annals of surgery.* 2004;240(4):644-658.

13. Capussotti L, Muratore A, Mulas MM, Massucco P, Aglietta M. Neoadjuvant chemotherapy and resection for initially irresectable colorectal liver metastases. *Br J Surg.* 2006;93(8):1001-1006.

14. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. *The Lancet Oncology.* 2013;14(12):1208-1215.

15. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg.* 1999;230(3):309-318; discussion 318-321.

16. Nordlinger B, Guiguet M, Vaillant JC, et al. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Française de Chirurgie. *Cancer.* 1996;77(7):1254-1262.

17. Nagashima I, Takada T, Adachi M, Nagawa H, Muto T, Okinaga K. Proposal of criteria to select candidates with colorectal liver metastases for hepatic

resection: comparison of our scoring system to the positive number of risk factors. *World journal of gastroenterology.* 2006;12(39):6305-6309.

18. Konopke R, Kersting S, Distler M, et al. Prognostic factors and evaluation of a clinical score for predicting survival after resection of colorectal liver metastases. *Liver international: official journal of the International Association for the Study of the Liver.* 2009;29(1):89-102.

19. Small RM, Lubezky N, Shmueli E, et al. Response to chemotherapy predicts survival following resection of hepatic colo-rectal metastases in patients treated with neoadjuvant therapy. *Journal of Surgical Oncology.* 2009;99(2):93-98.

20. Riedl CC, Akhurst T, Larson S, et al. 18F-FDG PET scanning correlates with tissue markers of poor prognosis and predicts mortality for patients after liver resection for colorectal metastases. *J Nucl Med.* 2007;48(5):771-775.

21. Strasberg SM, Dehdashti F, Siegel BA, Drebin JA, Linehan D. Survival of patients evaluated by FDG-PET before hepatic resection for metastatic colorectal carcinoma: a prospective database study. *Ann Surg.* 2001;233(3):293-299.

22. Ruers TJ, Wiering B, van der Sijp JR, et al. Improved selection of patients for hepatic surgery of colorectal liver metastases with (18)F-FDG PET: a randomized study. *J Nucl Med.* 2009;50(7):1036-1041.

23. Moulton C-A, Gu C-S, Law CH, et al. Effect of PET Before Liver Resection on Surgical Management for Colorectal Adenocarcinoma Metastases: A Randomized Clinical Trial. *JAMA.* 2014;311(18):1863-1869.

24. 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):152-163.

25. Xia Q, Liu J, Wu C, et al. Prognostic significance of (18)FDG PET/CT in colorectal cancer patients with liver metastases: a meta-analysis. *Cancer Imaging.* 2015;15:19-19.

26. Chiu KWH, Lam K-O, An H, et al. Long-term outcomes and recurrence pattern of 18F-FDG PET-CT complete metabolic response in the first-line treatment of metastatic colorectal cancer: a lesion-based and patient-based analysis. *BMC cancer.* 2018;18(1):776-776.

27. Tan MCB, Linehan DC, Hawkins WG, Siegel BA, Strasberg SM. Chemotherapy-Induced Normalization of FDG Uptake by Colorectal Liver Metastases Does Not Usually Indicate Complete Pathologic Response. *Journal of Gastrointestinal Surgery.* 2007;11(9):1112-1119.

28. Benoist S, Brouquet A, Penna C, et al. Complete Response of Colorectal Liver Metastases After Chemotherapy: Does It Mean Cure? *Journal of Clinical Oncology.* 2006;24(24):3939-3945.

29. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Annals of oncology: official journal of the European Society for Medical Oncology.* 2016;27(8):1386-1422.

30. Network NCC. NCCN Guidelines Version 4.2020 Colon Cancer. 2020; https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed 15/08/2020, 2020.

31. Goshen E, Davidson T, Zwas ST, Aderka D. PET/CT in the evaluation of response to treatment of liver metastases from colorectal cancer with bevacizumab and irinotecan. *Technol Cancer Res Treat.* 2006;5(1):37-43.

32. Xia Q, Liu J, Wu C, et al. Prognostic significance of 18FDG PET/CT in colorectal cancer patients with liver metastases: a meta-analysis. *Cancer Imaging.* 2015;15(1):19.

33. Byström P, Berglund A, Garske U, et al. Early prediction of response to first-line chemotherapy by sequential [18F]-2-fluoro-2-deoxy-D-glucose positron emission tomography in patients with advanced colorectal cancer. *Annals of oncology: official journal of the European Society for Medical Oncology.* 2009;20(6):1057-1061.

34. Glazer ES, Beaty K, Abdalla EK, Vauthey JN, Curley SA. Effectiveness of positron emission tomography for predicting chemotherapy response in colorectal cancer liver metastases. *Archives of surgery (Chicago, Ill: 1960).* 2010;145(4):340-345; discussion 345.

35. Akhurst T, Kates TJ, Mazumdar M, et al. Recent Chemotherapy Reduces the Sensitivity of [18F]Fluorodeoxyglucose Positron Emission Tomography in the Detection of Colorectal Metastases. *Journal of Clinical Oncology.* 2005;23(34):8713-8716.

36. García Vicente AM, Domínguez Ferreras E, Sánchez Pérez V, et al. Response assessment of colorectal liver metastases with contrast enhanced CT/18F-FDG PET. *Eur J Radiol.* 2013;82(6):e255-261.

37. van Kessel CS, Buckens CF, van den Bosch MA, van Leeuwen MS, van Hillegersberg R, Verkooijen HM. Preoperative imaging of colorectal liver metastases after neoadjuvant chemotherapy: a meta-analysis. *Annals of surgical oncology.* 2012;19(9):2805-2813.

38. Takahashi S, Kuroki Y, Nasu K, et al. Positron emission tomography with F-18 fluorodeoxyglucose in evaluating colorectal hepatic metastasis down-staged by chemotherapy. *Anticancer research.* 2006;26(6c):4705-4711.

39. Rubbia-Brandt L, Giostra E, Brezault C, et al. Importance of histological tumor response assessment in predicting the outcome in patients with colorectal liver metastases treated with neo-adjuvant chemotherapy followed by liver surgery. *Annals of oncology: official journal of the European Society for Medical Oncology.* 2007;18(2):299-304.

40. Blazer DG, 3rd, Kishi Y, Maru DM, et al. Pathologic response to preoperative chemotherapy: a new outcome end point after resection of hepatic colorectal metastases. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology.* 2008;26(33):5344-5351.

41. Moreno Prats M, Sasatomi E, Stevenson HL. Colorectal Liver Metastases: A Pathologist's Guide to Creating an Informative Report and Improving Patient Care. *Archives of Pathology & Laboratory Medicine.* 2018;143(2):251-257.

42. Cai Y, Lu X, Zhu X, Ju H, Sun W, Wu W. Histological tumor response assessment in colorectal liver metastases after neoadjuvant chemotherapy: impact of the variation in tumor regression grading and peritumoral lymphocytic infiltration. *J Cancer.* 2019;10(23):5852-5861.

43. Ware RE, Matthews JP, Hicks RJ, et al. Usefulness of fluorine-18 fluorodeoxyglucose positron emission tomography in patients with a residual structural abnormality after definitive treatment for squamous cell carcinoma of the head and neck. *Head Neck.* 2004;26(12):1008-1017.

44. Chun YS, Vauthey JN, Boonsirikamchai P, et al. Association of computed tomography morphologic criteria with pathologic response and survival in patients treated with bevacizumab for colorectal liver metastases. *Jama.* 2009;302(21):2338-2344.

45. Kawaguchi Y, Kopetz S, Newhook TE, et al. Mutation Status of RAS, TP53, and SMAD4 is Superior to Mutation Status of RAS Alone for Predicting Prognosis after Resection of Colorectal Liver Metastases. *Clinical Cancer Research.* 2019;25(19):5843-5851.

46. Teng H-W, Huang Y-C, Lin J-K, et al. BRAF mutation is a prognostic biomarker for colorectal liver metastasectomy. *Journal of Surgical Oncology.* 2012;106(2):123-129.

47. Tsilimigras DI, Ntanasis-Stathopoulos I, Bagante F, et al. Clinical significance and prognostic relevance of KRAS, BRAF, PI3K and TP53 genetic mutation analysis for resectable and unresectable colorectal liver metastases: A systematic review of the current evidence. *Surg Oncol.* 2018;27(2):280-288.

48. Tosi F, Magni E, Amatu A, et al. Effect of KRAS and BRAF Mutations on Survival of Metastatic Colorectal Cancer After Liver Resection: A Systematic Review and Meta-Analysis. *Clinical colorectal cancer.* 2017;16(3):e153-e163.

49. Margonis GA, Buettner S, Andreatos N, et al. Association of BRAF Mutations With Survival and Recurrence in Surgically Treated Patients With Metastatic Colorectal Liver Cancer. *JAMA Surgery.* 2018;153(7):e180996-e180996.

50. Passiglia F, Bronte G, Bazan V, Galvano A, Vincenzi B, Russo A. Can KRAS and BRAF mutations limit the benefit of liver resection in metastatic colorectal cancer patients? A systematic review and meta-analysis. *Crit Rev Oncol Hematol.* 2016;99:150-157.

51. Mainenti PP, Stanzione A, Guarino S, et al. Colorectal cancer: Parametric evaluation of morphological, functional and molecular tomographic imaging. *World journal of gastroenterology.* 2019;25(35):5233-5256.

52. Horvat N, Bates DDB, Petkovska I. Novel imaging techniques of rectal cancer: what do radiomics and radiogenomics have to offer? A literature review. *Abdom Radiol (NY).* 2019;44(11):3764-3774.

Figure

Figure 1. Kaplan Meier Curves for Overall Survival and Progression Free Survival. Structural Imaging: a) Progression Free Survival b) Overall Survival. Metabolic Imaging c) Progression Free Survival d) Overall Survival

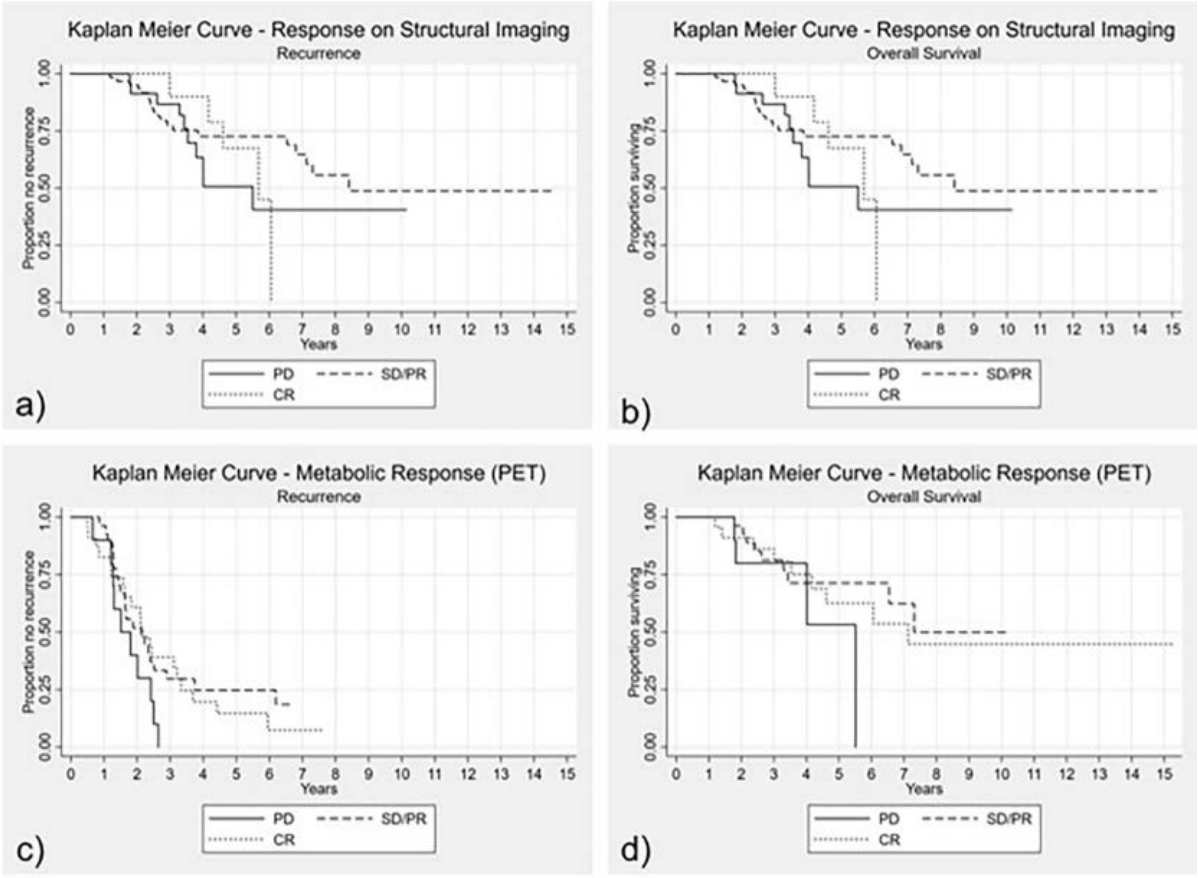

Table 1. Patient Demographics and Primary Tumour Clinical Parameters. PD=Progressive disease, SD/PR=stable disease/partial response, ASA score= American Society of Anesthesiologists,R0=microscopically negative margin, R1=Microscopically positive margin.

		Structural Imaging (CT/MRI)			**Metabolic Imaging (FDG-PET)**		
Variables	**Categories**	**PD n=23**	**SD/PR n=61**	**CR n=10**	**PD n=10**	**SD/PR n=27**	**CR n=23**
Age (years)	**≤55**	11(47.8 %)	20(32.8 %)	1(10.0 %)	5(50.0 %)	13(48.2 %)	5(21.7%)
	>55	12 (52.2%)	41 (67.2%)	9 (90.0%)	5 (50.0%)	14 (51.9%)	18(78.3)
	Median	56 (IQR 49-65)	61 (IQR 51-66)	64 (IQR 56-65)	58 (IQR 51-70)	57 (IQR 49-64)	59 (IQR 56- 66)
Sex	**Male**	12 (52.2%)	36 (59.0%)	7 (70.0%)	7 (70.0%)	14 (51.9%)	17(73.9)
	Female	11 (47.8%)	25 (41.0%)	3 (30.0%)	3 (30.0%)	13 (48.2%)	6 (26.1%)
ASA Score	**2**	21 (91.3%)	49 (80.3%)	8 (80.0%)	8 (80.0%)	22 (81.5%)	19(82.6)
	3	2 (8.7%)	11 (18.0%)	1 (10.0%)	2 (20.0%)	5 (18.5%)	1 (4.4%)
	Missing	0 (0.0%)	1 (1.6%)	1 (10.0%)	0 (0.0%)	0 (0.0%)	3 (13.0%)
Nodal Status of Primary (Pathological)	**Negative**	9 (39.1%)	21 (34.4%)	2 (20.0%)	3 (30.0%)	6 (22.2%)	7 (30.4%)
	Positive	13 (56.5%)	38 (62.3%)	7 (70.0%)	6 (60.0%)	20 (74.1%)	13(56.5)

	Missing	1 (4.4%)	2 (3.3%)	1 (10.0%)	1 (10.0%)	1 (3.7%)	3 (13.0%)
Grade of Primary (Pathological)	**Other**	17 (73.9%)	38 (62.3%)	4 (40.0%)	8 (80.0%)	17 (63.0%)	15(65.2)
	Poor	0 (0.0%)	9 (14.8%)	2 (20.0%)	0 (0.0%)	4 (14.8%)	3 (13.0%)
	Missing	6 (26.1%)	14 (23.0%)	4 (40.0%)	2 (20.0%)	6 (22.2%)	5 (21.7%)
Site of Primary Tumour	**Colon**	12 (52.2%)	46 (75.4%)	6 (60.0%)	7 (70.0%)	18 (66.7%)	13(56.5)
	Rectum	11 (47.8%)	15 (24.6%)	4 (40.0%)	3 (30.0%)	9 (33.3%)	10(43.5)
Primary resection margin **(Pathological)**	**R0**	14 (60.9%)	41 (67.2%)	5 (50.0%)	7 (70.0%)	18 (66.7%)	14(60.9)
	R1	0 (0.0%)	5 (8.2%)	0 (0.0%)	0 (0.0%)	2 (7.4%)	2 (8.7%)
	Missing	9 (39.1%)	15 (24.6%)	5 (50.0%)	3 (30.0%)	7 (25.9%)	7 (30.4%)
T stage of Primary (Pathological)	**0-3**	12 (52.2%)	33 (54.1%)	6 (60.0%)	5 (50.0%)	11 (40.7%)	14(60.9)
	4	9 (39.1%)	20 (32.8%)	3 (30.0%)	5 (50.0%)	12 (44.4%)	6 (26.1%)
	Missing	2 (8.7%)	8 (13.1%)	1 (10.0%)	0 (0.0%)	4 (14.8%)	3 (13.0%)
Adjuvant Chemotherapy	**No**	19 (82.6%)	54 (88.5%)	9 (90.0%)	10(100.0)	25 (92.6%)	20(87.0)
(Post primary resection)	**Yes**	4 (17.4%)	6 (9.8%)	1 (10.0%)	0 (0.0%)	2 (7.4%)	3 (13.0%)

	Missing	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)	4 (14.8%)	3 (13.0%)

Table 2. Liver Metastases Clinical Parameters and Survival. PD=Progressive disease, SD/PR=stable disease/partial response, NeoCT=neoadjuvant chemotherapy, CRLM=colorectal liver metastasis, LR=liver resection, R0=microscopically negative margin, R1=Microscopically positive margin. [a]Includes FOLFOX/XELOX/CAPEOX/Bevacizumab. [b]Includes 5FU, FOLFOX/panitumimab, FOLFIRI/cetuximab, FOLFIRI/bevacizumab, Irinotecan/bevacizumab→FOLFOX/bevacizumab, FOLFOXIRI/bevacizumab, Trial drugs. [c]Includes nodal, lung, adrenal, ovary, spine, brain, peritoneum. [d]Columns do not equal 100% as can be primary and other sites.

		Structural Imaging (CT/MRI)			**Metabolic Imaging (FDG-PET)**		
Variables	**Categories**	**PD n=23**	**SD/PR n=61**	**CR n=10**	**PD n=10**	**SD/PR n=27**	**CR n=23**
NeoCT regimens	**FOLFOX**	6 (26%)	30 (49.2%)	5 (50.0%)	2 (20.0%)	8 (29.6%)	8 (34.8%)
(Prior to LR)	**FOLFOX/Bev[a]**	12 (52.2%)	19 (31.1%)	4 (40.0%)	7 (70.0%)	11 (40.7%)	10 (43.5%)
	Others[b]	5 (21.7%)	12 (19.7%)	1 (10.0%)	1 (10.0%)	8 (29.6%)	5 (21.7%)
Time Δ diagnosis and	**<6 months**	7 (30.4%)	43 (70.5%)	6 (60.0%)	2 (20.0%)	19 (70.4%)	16 (69.6%)
post-neoCT scan	**>6 months**	16 (69.6%)	18 (29.5%)	4 (40.0%)	8 (80.0%)	8 (29.6%)	7 (30.4%)
Metachronous/	**Metach**	4 (17.4%)	12 (19.7%)	1 (10.0%)	0 (0.0%)	2 (7.4%)	5 (21.7%)
synchronous	**Synch**	19 (82.6%)	49 (80.3%)	9 (90.0%)	10(100.0)	25 (92.6%)	18(78.3)

	missing	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Distribution of CRLM (Imaging)	**Unilobar**	11 (47.8%)	28 (45.9%)	5 (50.0%)	6 (60.0%)	11 (40.7%)	14(60.9)
	Bilobar	12 (52.2%)	33 (54.1%)	4 (40.0%)	4 (40.0%)	16 (59.3%)	9 (39.1%)
	Missing	0 (0.0%)	0 (0.0%)	1 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Number of CRLM (Pathological)	**1-3**	15 (65.2%)	47 (77.1%)	9 (90.0%)	7 (70.0%)	20 (74.1%)	18 (78.3%)
	≥4	8 (34.8%)	14 (23.0%)	1 (10.0%)	3 (30.0%)	7 (25.9%)	5 (21.7%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Size of CRLM (cm) (Pathological)	**0-5**	18 (78.3%)	52 (85.3%)	10 (100.0%)	7 (70.0%)	22 (81.5%)	23 (100.0%)
	≥5	5 (21.7%)	9 (14.8%)	0 (0.0%)	3 (30.0%)	5 (18.5%)	0 (0.0%)
LR margin (Pathological)	**R0**	20 (87.0%)	48 (78.7%)	8 (80.0%)	9 (90.0%)	22 (81.5%)	20 (87.0%)
	R1	3 (13.0%)	13 (21.3%)	2 (20.0%)	1 (10.0%)	5 (18.5%)	3 (13.0%)
CRLM Composition	**Necrosis present**	17 (73.9%)	54 (88.5%)	8 (80.0%)	8 (80.0%)	25 (92.5%)	17 (73.9%)

(Pathology)	**Viable tumour**	22 (95.6%)	58 (95.0%)	9 (90.0%)	10 (100%)	26 (96.3%)	19 (82.6%)
	Mucin present	3 (13.0%)	8 (13.1%)	2 (20.0%)	3 (30.0%)	2 (7.4%)	3 (13.0%)
Adjuvant	**No**	9 (39.1%)	16 (26.2%)	1 (10.0%)	4 (40.0%)	8 (29.6%)	5 (21.7%)
Chemotherapy	**Yes**	11 (47.8%)	42 (68.9%)	9 (90.0%)	6 (60.0%)	18 (66.7%)	17 (73.9%)
(Post liver resection)	**Missing**	3 (13.0%)	3 (4.9%)	0 (0.0%)	0 (0.0%)	1 (3.7%)	1 (4.4%)
Site of Recurrence[d]	**Liver**	5 (21.8%)	13 (21.3%)	4 (40.0%)	1 (10.0%)	4 (14.8%)	7 (30.4%)
	Local recurrence	1 (4.3%)	3 (4.9%)	1 (10.0%)	0 (0.0%)	4 (14.8%)	0 (0%)
	Other distant site[c]	14 (60.9%)	29 (47.5%)	5 (50.0%)	8 (80.0%)	13 (48.1%)	13 (56.5%)
	Peritoneal	4 (17.4)	5 (8.2%)	2 (20.0%)	3 (30.0%)	1 (3.7%)	5 (21.7%)
	Nodal Recurrence	5 (21.7%)	14 (23%)	4 (40.0%)	4 (40.0%)	7 (25.9%)	7 (30.4%)
	Lung Recurrence	5 (21.7%)	14 (23 %)	1 (10.0%)	4 (40.0%)	4 (14.8%)	5 (21.7%)
	No recurrence	2 (8.7%)	16 (26.2%)	1 (10.0%)	1 (10.0%)	6 (22.2%)	3 (13.0%)
	missing	1 (4.3%)	1 (1.63%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Recurrence	**Yes**	9 (39.1%)	21 (34.4%)	1 (10.0%)	3 (40.0%)	9 (33.3%)	6 (26.1%)
Resected	**No**	11 (47.8%)	23 (37.7%)	7 (70.0%)	6 (60.0%)	12 (44.4%)	14 (60.9%)
	Missing	1 (4.3%)	1 (1.6%)	1 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	No recurrence	2 (8.7%)	16 (26.2%)	1 (10.0%)	1 (10.0%)	6 (22.2%)	3 (13.0%)
Death at follow up	**Yes**	10 (43.5%)	20 (32.8%)	5 (50.0%)	4 (40.%)	9 (33.3%)	9 (39.1%)
	No	13 (56.5%)	41 (67.2%)	5 (50.0%)	6 (60.0%)	18 (66.7%)	15 (65.2%)

Table 3. Univariable and Multivariable Analysis for Structural Imaging – Overall Survival. ASA=American Society of Anaesthesiologists, PrR=primary resection, CRLM=colorectal liver metastasis, LR=liver resection, PD=progressive disease SD/PR=stable disease/partial response, CR=complete response, R0=microscopically negative margin, R1= microscopically positive margin, HR= hazard ratio, CI=confidence interval, NC= not calculable due to event number restriction on multivariable regression.

		Univariable						**Multivariable**				
Structural Imaging – Overall Survival		**n**	**Death**	**HR**	**95% CI**		**P**	**n**	**HR**	**95%CI**		**P**
Primary Exposure	SD/PR v PD	61v23	20v10	0.67	0.31	1.43	0.298	63	0.36	0.11	1.19	0.094
	CR v PD	10v23	5v10	0.97	0.33	2.86	0.950	63	0.78	0.13	4.50	0.780
Age (years)	>55 v ≤55	62v32	24v11	1.00	0.49	2.05	0.997					
Sex	Female v Male	39v55	12v23	0.58	0.29	1.18	0.136	63	0.42	0.12	1.53	0.189

ASA score	3 v 2	14v 78	6v2 7	1. 05	0. 43	2. 56	0.9 10					
Nodal metastasis	Yes v No	58v 32	27v 7	3. 14	1. 36	7. 28	0.0 08	6 3	3. 75	0. 93	15. 07	0.0 63
Tumour grade/differentiation	Yes v No	11v 59	6v1 9	2. 34	0. 92	5. 91	0.0 73	6 3	0. 76	0. 17	3.4 9	0.7 24
Primary resection margin	R1 v R0	5v6 0	1v2 2	0. 85	0. 11	6. 49	0.8 77					
Primary T stage	T4 v T0-3	32v 51	15v 17	1. 26	0. 63	2. 54	0.5 11	6 3	0. 74	0. 18	3.0 4	0.6 75
Adjuvant therapy (post PrR)	Yes v No	11v 82	7v2 8	1. 96	0. 85	4. 52	0.1 15	6 3	N C	N C	NC	NC
Synchronous v metachronous	Synch v metach	77v 17	28v 7	1. 14	0. 49	2. 65	0.7 57	6 3	N C	N C	NC	NC
Distribution of CRLM	Bilobar v Unilobar	49v 44	14v 20	0. 64	0. 32	1. 27	0.1 98	6 3	1. 39	0. 37	5.3 1	0.6 28
Extrahepatic Metastases	Yes v No	15v 79	7v2 8	1. 20	0. 52	2. 76	0.6 66	6 3	0. 61	0. 16	2.3 0	0.4 69
Time Δ diagnosis and post-neoCT scan	> 6 months v < 6 months	38v 56	17v 18	1. 07	0. 55	2. 08	0.8 42					
Complexity of operation	Major v minor	61v 33	21v 14	0. 74	0. 38	1. 46	0.3 92	6 3	0. 33	0. 07	1.4 8	0.1 48
Number of CRLM	≥4 v 1-3	23v 71	5v3 0	0. 58	0. 22	1. 5	0.2 62	6 3	0. 78	0. 22	2.8 2	0.7 05
Size of CRLM (cm)	≥5 v 0-5	14v 80	3v3 2	0. 64	0. 19	2. 11	0.4 64	6 3	1. 57	0. 32	7.8 1	0.5 80
LR margin	R1 v R0	18v 76	9v2 6	1. 32	0. 62	2. 82	0.4 72	6 3	1. 94	0. 55	6.8 8	0.3 04

Adjuvant therapy (post LR)	Yes v No	62v 26	18v 15	0. 51	0. 26	1. 02	0.0 58	6 3	0. 25	0. 04	1.4 6	0.1 24
Site of primary tumour	Rectum v colon	30v 64	12v 23	1. 20	0. 59	2. 41	0.6 15	6 3	1. 83	0. 59	5.6 7	0.2 93

Table 4. Univariable and Multivariable Analysis for Metabolic (FDG-PET) Imaging – Overall Survival., ASA=American Society of Anaesthesiologists, PrR=primary resection, CRLM=colorectal liver metastasis, LR=liver resection, PD=progressive disease SD/PR=stable disease/partial response, CR=complete response, R0=microscopically negative margin, R1= microscopically positive margin, HR= hazard ratio, CI=confidence interval, NC= not calculable due to event number restriction on multivariable regression.

		Univariable						**Multivariable**				
Metabolic Imaging- Overall Survival		**n**	**Death**	**HR**	**95% CI**		**P**	**n**	**HR**	**95%CI**		**P**
Primary Exposure	SD/PR v PD	27v 10	9v4	0. 50	0. 15	1. 69	0.2 66	4 5	0. 75	0. 11	4. 88	0.7 59
	CR v PD	23v 10	9v4	0. 56	0. 17	1. 89	0.3 51	4 5	1. 21	0. 15	9. 43	0.8 57
Age (years)	>55 v ≤55	37v 23	13v 9	0. 72	0. 30	1. 70	0.4 52	4 5	0. 56	0. 13	2. 44	0.4 39
Sex	Female v Male	22v 38	7v1 5	0. 75	0. 30	1. 84	0.5 27	4 5	0. 53	0. 11	2. 52	0.4 21
ASA score	3 v 2	8v4 9	3v1 7	0. 79	0. 23	2. 71	0.7 04	4 5	2. 22	0. 25	19 .5	0.4 70
Nodal metastasis	Yes v No	39v 16	16v 5	1. 78	0. 65	4. 91	0.2 65	4 5	1. 60	0. 34	7. 57	0.5 54
Tumour grade/differentiation	Yes v No	7v4 0	4v1 4	2. 23	0. 72	6. 90	0.1 64	4 5	1. 16	0. 20	6. 75	0.8 69
Primary resection margin	R1 v R0	4v3 9	0v1 5	0. 00	0. 00	.	1.0 00					
Primary T stage		23v	10v	1.	0.	2.	0.8					

		30	10	07	44	59	79					
Adjuvant therapy (post PrR)	Yes v No	5v55	3v19	1.97	0.58	6.69	0.277	45	NC	NC	NC	NC
Synchronous v metachronous	Synch v metach	53v7	19v3	1.10	0.32	3.77	0.876	45	NC	NC	NC	NC
Distribution of CRLM	Bilobar v Unilobar	23v37	11v11	1.42	0.62	3.29	0.409	45	0.98	0.25	3.88	0.977
Extrahepatic Metastases	Yes v No	29v31	9v13	0.82	0.35	1.93	0.650					
Time Δ diagnosis and post-neoCT scan	> 6 months v < 6 months	12v48	4v18	1.07	0.36	3.19	0.902	45	1.88	0.50	7.13	0.354
Complexity of operation	Major v minor	40v20	13v9	0.63	0.27	1.48	0.288	45	0.14	0.02	1.09	0.060
Number of CRLM	≥4 v 1-3	15v45	4v18	0.93	0.31	2.78	0.891					
Size of CRLM (cm)	≥5 v 0-5	8v52	2v20	0.99	0.22	4.44	0.994					
LR margin	R1 v R0	9v51	4v18	1.09	0.37	3.22	0.878	45	0.17	0.02	1.43	0.103
Adjuvant therapy (post LR)	Yes v No	41v17	12v9	0.54	0.23	1.29	0.168					
Site of primary tumour	Rectum v colon	22v38	9v13	1.12	0.48	2.62	0.798	45	1.12	0.29	4.33	0.872

Table 5. Univariable and Multivariable Analysis for Structural Imaging – Progression Free Survival. ASA=American Society of Anaesthesiologists, PrR=primary resection, CRLM=colorectal liver metastasis, LR=liver resection, PR=progressive disease SD/PR=stable disease/partial response, CR=complete response, R0=microscopically negative margin, R1= microscopically positive margin, REC=recurrence, HR=hazard ratio, CI=Confidence Interval, NC= not calculable due to event number restriction on multivariable regression.

Structural Imaging – Progression Free Survival		**n**	**REC**	**HR**	**95% CI**		**P**	**n**	**HR**	**95%CI**		**P**
Primary Exposure	SD/PR v PD	61v23	45v21	0.86	0.51	1.44	0.557	76	0.70	0.36	1.35	0.284
	CR v PD	10v23	9v21	0.76	0.35	1.68	0.503	76	0.51	0.18	1.45	0.203
Age (years)	>55 v ≤55	62v32	50v25	0.97	0.60	1.57	0.901					
Sex	Female v Male	39v55	29v46	0.71	0.44	1.13	0.145	76	0.55	0.32	0.97	0.038
ASA score	3 v 2	14v78	9v64	0.72	0.36	1.45	0.360	76	0.80	0.38	1.70	0.568
Nodal metastasis	Yes v No	58v32	48v23	1.65	1.00	2.72	0.048	76	1.76	1.00	3.08	0.048
Tumour grade/differentiation	Yes v No	11v59	9v45	1.27	0.62	2.61	0.514					
Primary resection margin	R1 v R0	5v60	4v47	1.39	0.50	3.90	0.529					
Primary T stage	T4 v T0-3	32v51	27v41	1.10	0.67	1.79	0.705	76	1.08	0.57	2.02	0.815
Adjuvant therapy (post PR)	Yes v No	11v82	10v64	1.57	0.80	3.05	0.189	76	4.33	0.81	23.15	0.086
Synchronous v metachronous	Synch v metach	77v17	62v13	1.10	0.60	2.00	0.757	76	2.48	0.54	11.46	0.246
Distribution of CRLM	Bilobar v Unilobar	49v44	40v34	1.25	0.79	1.98	0.342	76	1.30	0.74	2.28	0.354

Extrahepatic Metastases	Yes v No	15v 79	14v 61	1. 12	0. 63	2. 01	0.7 00	7 6	1. 52	0. 72	3.1 9	0.2 69
Time Δ diagnosis and post-neoCT scan	> 6 months v < 6 months	38v 56	32v 43	0. 73	0. 46	1. 16	0.1 86	7 6	0. 59	0. 31	1.1 2	0.1 05
Complexity of operation	Major v minor	61v 33	50v 25	0. 94	0. 58	1. 52	0.7 99					
Number of CRLM	≥4 v 1-3	23v 71	18v 57	1. 09	0. 64	1. 86	0.7 40					
Size of CRLM (cm)	≥5 v 0-5	14v 80	10v 65	0. 87	0. 44	1. 69	0.6 73	7 6	1. 70	0. 78	3.6 8	0.1 82
LR margin	R1 v R0	18v 76	14v 61	0. 98	0. 55	1. 75	0.9 39					
Adjuvant therapy (post LR)	Yes v No	62v 26	50v 21	1. 21	0. 73	2. 03	0.4 58	7 6	1. 69	0. 84	3.3 7	0.1 39
Site of primary tumour	Rectum v colon	30v 64	22v 53	0. 64	0. 39	1. 05	0.0 77	7 6	0. 73	0. 39	1.3 7	0.3 21

Table 6. Univariable and Multivariable Analysis for Metabolic (FDG-PET) Imaging – Progression Free Survival. ASA=American Society of Anaesthesiologists, PrR=primary resection, CRLM=colorectal liver metastasis, LR=liver resection, PR=progressive disease SD/PR=stable disease/partial response, CR=complete response, R0=microscopically negative margin, R1= microscopically positive margin, REC=recurrence, HR=hazard ratio, CI=Confidence Interval, NC= not calculable due to event number restriction on multivariable regression.

Metabolic Imaging – Progression Free Survival		**n**	**REC**	**HR**	**95% CI**		**P**	**n**	**HR**	**95%CI**		**P**
Primary Exposure	SD/PR v PD	27v10	21v10	0.46	0.21	1	0.051	45	0.17	0.04	0.62	0.008
	CR v PD	23v10	20v10	0.53	0.24	1.16	0.112	45	0.34	0.09	1.22	0.097
Age (years)	>55 v ≤55	37v23	32v19	1.1	0.62	1.94	0.744	45	2.95	1.17	7.43	0.022
Sex	Female v Male	22v38	18v33	0.95	0.53	1.7	0.867					
ASA score	3 v 2	8v49	5v43	0.53	0.21	1.34	0.177	45	0.25	0.06	1.02	0.053
Nodal metastasis	Yes v No	39v16	34v12	1.92	0.99	3.73	0.053	45	8.41	2.10	33.7	0.003
Tumour grade/differentiation	Yes v No	7v40	5v34	0.87	0.34	2.23	0.772	45	0.25	0.06	1.01	0.052
Primary resection margin	R1 v R0	4v39	3v32	1.06	0.32	3.51	0.918					
Primary T stage		23v30	19v26	0.84	0.46	1.52	0.556	45	0.81	0.34	1.93	0.638
Adjuvant therapy (post PrR)	Yes v No	5v55	5v46	2.18	0.85	5.59	0.104	45	0.64	0.06	6.92	0.710
Synchronous v metachronous	Synch v metach	53v7	44v7	0.65	0.29	1.45	0.291	45	0.49	0.06	3.92	0.503
Distribution of	Bilobar v	29v	24v	1.	0.	2.	0.5	4	2.	0.	6.1	0.08

CRLM	Unilobar	31	27	2	69	09	26	5	32	88	1	9
Extrahepatic Metastases	Yes v No	23v 37	21v 30	0. 9	0. 51	1. 58	0.7 12					
Time Δ diagnosis and post-neoCT scan	> 6 months v < 6 months	12v 48	11v 40	0. 99	0. 51	1. 95	0.9 87	4 5	0. 82	0. 31	2.1 7	0.68 7
Complexity of operation	Major v minor	40v 20	33v 18	0. 71	0. 39	1. 26	0.2 41	4 5	0. 66	0. 22	1.9 5	0.44 8
Number of CRLM	≥4 v 1-3	15v 45	11v 40	0. 95	0. 48	1. 85	0.8 71					
Size of CRLM (cm)	≥5 v 0-5	8v5 2	8v4 3	1. 23	0. 58	2. 62	0.5 93	4 5	5. 11	1. 33	19. 56	0.01 7
LR margin	R1 v R0	9v5 1	7v4 4	0. 75	0. 34	1. 68	0.4 85	4 5	0. 55	0. 16	1.87	0.3 38
Adjuvant therapy (post LR)	Yes v No	41v 17	34v 15	1. 09	0. 59	2. 01	0.7 87					
Site of primary tumour	Rectum v colon	22v 38	17v 34	0. 53	0. 29	0. 97	0.0 4	4 5	1. 82	0. 72	4.64	0.2 06