Original Investigation

Effect of PET Before Liver Resection on Surgical Management for Colorectal Adenocarcinoma Metastases
A Randomized Clinical Trial

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IMPORTANCE Patients with colorectal cancer with liver metastases undergo hepatic resection with curative intent. Positron emission tomography combined with computed tomography (PET-CT) could help avoid noncurative surgery by identifying patients with occult metastases.

OBJECTIVES To determine the effect of preoperative PET-CT vs no PET-CT (control) on the surgical management of patients with resectable metastases and to investigate the effect of PET-CT on survival and the association between the standardized uptake value (ratio of tissue radioactivity to injected radioactivity adjusted by weight) and survival.

DESIGN, SETTING, AND PARTICIPANTS A randomized trial of patients older than 18 years with colorectal cancer treated by surgery, with resectable metastases based on CT scans of the chest, abdomen, and pelvis within the previous 30 days, and with a clear colonoscopy within the previous 18 months was conducted between 2005 and 2013, involving 21 surgeons at 9 hospitals in Ontario, Canada, with PET-CT scanners at 5 academic institutions.

INTERVENTIONS Patients were randomized using a 2 to 1 ratio to PET-CT or control.

MAIN OUTCOMES AND MEASURES The primary outcome was a change in surgical management defined as canceled hepatic surgery, more extensive hepatic surgery, or additional organ surgery based on the PET-CT. Survival was a secondary outcome.

RESULTS Of the 263 patients who underwent PET-CT, 21 had a change in surgical management (8.0%; 95% CI, 5.0%-11.9%). Specifically, 7 patients (2.7%) did not undergo laparotomy, 4 (1.5%) had more extensive hepatic surgery, 9 (3.4%) had additional organ surgery (8 of whom had hepatic resection), and the abdominal cavity was opened in 1 patient but hepatic surgery was not performed and the cavity was closed. Liver resection was performed in 91% of patients in the PET-CT group and 92% of the control group. After a median follow-up of 36 months, the estimated mortality rate was 11.13 (95% CI, 8.95-13.68) events/1000 person-months for the PET-CT group and 12.71 (95% CI, 9.40-16.80) events/1000 person-months for the control group. Survival did not differ between the 2 groups (hazard ratio, 0.86 [95% CI, 0.60-1.21]; $P = .38$). The standardized uptake value was associated with survival (hazard ratio, 1.11 [90% CI, 1.07-1.15] per unit increase; $P < .001$). The C statistic for the model including the standardized uptake value was 0.62 (95% CI, 0.56-0.68) and without it was 0.50 (95% CI, 0.44-0.56). The difference in C statistics is 0.12 (95% CI, 0.04-0.21). The low C statistic suggests that the standard uptake value is not a strong predictor of overall survival.

CONCLUSIONS AND RELEVANCE Among patients with potentially resectable hepatic metastases of colorectal adenocarcinoma, the use of PET-CT compared with CT alone did not result in frequent change in surgical management. These findings raise questions about the value of PET-CT scans in this setting.

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Colorectal cancer is a leading cause of cancer mortality. Approximately 50% of patients present with or subsequently develop liver metastases.[1] Patients with liver metastases are candidates for potentially curative surgery.[2] However, unidentified occult metastases at the time of surgery can render the operation noncurative. Thus, long-term survival following surgical resection for colorectal cancer liver metastases is only about 50%.[3-5]

A standard workup prior to liver resection includes computed tomography (CT) of the chest, abdomen, and pelvis to accurately define hepatic metastases and to exclude extrahepatic disease, and colonoscopy to rule out local recurrence, detect polyps, or both.[6] Positron emission tomography (PET) is attractive in oncology because tumors preferentially take up ^{18}F-fluorodeoxyglucose and PET can be used to detect occult metastases and lesions that are suspicious for metastases but indeterminate with conventional radiological imaging.[7,8] When PET is combined with CT (PET-CT), functional and anatomical information are provided simultaneously.

In 2004, when we were planning our trial, staging with PET-CT prior to surgery for colorectal liver metastases was being adopted based on the results from small, uncontrolled studies.[9-11] Furthermore, some investigators advocated the use of preoperative PET-CT to identify patients with the highest likelihood of long-term survival after surgery based on the results from small studies.[12] We believed that the evidence to support the routine adoption of PET-CT for staging prior to hepatic surgery in patients with colorectal liver metastases was insufficient to inform policy for the Ontario Ministry of Health. Therefore, a multicenter randomized trial was designed to determine the effect of preoperative PET-CT vs no PET-CT (control) on the surgical management of patients with resectable liver metastases. Secondary objectives were to investigate the effects of PET-CT on overall survival for all patients and for those undergoing curative-intent surgeries, and the relationship between the standardized uptake value and overall survival.

Methods

Eligible participants were older than 18 years and had histological proof of colorectal cancer treated by R0 resection, had resectable colorectal liver metastases based on contrast-enhanced CT scans of the chest, abdomen, and pelvis within the previous 30 days, and had a clear colonoscopy within the previous 18 months. Resectable colorectal liver metastases were defined as the potential to obtain negative margins with the removal of all known disease, leaving sufficient future liver remnant. Patients who required a 2-stage resection, or who had undergone a downsized chemotherapy regimen, as well as patients who had specified extrahepatic disease, were eligible if all affected sites were considered resectable at the same time, or shortly thereafter. Patients with eligible sites of extrahepatic disease were included to avoid potential bias of selecting patients in a better prognostic group and to reflect current surgical practice.[13]

Patients were excluded for any of the following: extrahepatic disease not specified as above, prior liver resection, previous radiofrequency ablation of liver lesion, systemic chemotherapy within 3 weeks or radiotherapy within 2 months prior to randomization, were medically unfit for surgery, pregnant or lactating, unable to lie supine, had previously treated cancer other than nonmelanotic skin cancer or carcinoma in situ of the cervix unless disease-free for 5 years or longer, prior resections of colorectal liver metastases, intravenous contrast dye allergy, or a PET scan within 6 months.

Patients were recruited by 21 experienced hepatobiliary/pancreatic surgeons at 9 hospitals in Ontario, Canada, where such surgery is regionalized. The PET-CT scanners were located at 5 academic institutions (Princess Margaret, Toronto, Ontario, Canada; St Joseph's Hospital, Hamilton, Ontario; St Joseph's Health Care, London, Ontario; Sunnybrook Odette Cancer Centre, Toronto, Ontario; Ottawa Hospital, Ottawa, Ontario). Institutional review boards of each center and Health Canada approved the study protocol. All patients provided written informed consent.

To ensure adequate baseline CT imaging, a study radiologist assessed all CT examinations prior to randomization, which were repeated if quality was determined to be inadequate (eMethods 1 in Supplement). Surgeons completed a case report form for every patient and were asked to select the planned operation from a list of possible liver operations prior to randomization.

Randomization was performed centrally through the Ontario Clinical Oncology Group Coordinating and Methods Center located in Hamilton, Ontario. A computer-generated randomization schedule using fixed-size blocks assigned patients within treatment center to either the PET-CT or control group using a 2 to 1 ratio.

PET-CT Imaging

Patients in the PET-CT group underwent the scan within 2 weeks after randomization. Details of imaging procedures have been published previously.[14] Data were shown in attenuation-corrected and non–attenuation-corrected formats for interpretation in a 128 × 128 matrix on a nuclear medicine workstation. Before the trial began, a quality assurance program was established to standardize the scanners and isotopes across the 5 imaging centers and for the reading of the PET-CT scans by nuclear medicine physicians.[14,15] Each hot spot on the PET-CT image was interpreted by the PET physician reader at the study site using a 5-point ordinal scale (0 = normal; 1 = probably normal; 2 = equivocal; 3 = probably abnormal; 4 = definitely abnormal).[16] The standardized uptake value, which is the ratio of tissue radioactivity to injected radioactivity adjusted by weight, was used to help grade identified abnormalities. A specific uptake value cutoff for the determination of cancer was not provided. The PET reader compared the lesion-specific findings of the PET-CT scan with the baseline CT and classified whether PET-CT provided no new information or additional diagnostic information according to 1 or more of the following: abnormal lesions identified on PET-CT scan that were not identified with CT; suspicious lesions identified on PET-CT scan that were seen and not considered to be malignant with CT; and negative PET-CT scan with lesions seen with CT and considered malignant but not identified on PET-CT.

Pathological (ie, biopsy) or clinical (ie, serial diagnostic imaging examinations) confirmation was required if PET-CT suggested the presence of additional disease. This decision was made

by the surgeon. The patients with confirmed extrahepatic disease received therapy at the discretion of the treating oncologist.

Surgery

Surgeons completed the surgery case report form (in which they were asked to select the planned operation from a list of possible liver operations) a second time after receiving the results of the PET-CT and a third time (or a second time for the control group) immediately after surgery to document the operation. An explanation was provided by the surgeon if the operation deviated from the documented plan.

Surgery was performed as soon as possible after PET-CT imaging. Information from the PET-CT was relayed to the surgeon prior to surgery. Start-up meetings prior to the commencement of the study obtained consensus among surgeons that lesions identified outside the inclusion criteria would not be considered for resection. The final decision remained with the individual surgeon. At laparotomy, the abdominal cavity was thoroughly inspected for extrahepatic disease and intraoperative liver ultrasound was routine.

Follow-up

After surgery, patients were seen every 4 months for the first 2 years, and then every 6 months for a total of 3 years. At each visit, a history and physical examination, carcinoembryonic antigen measurement, and a contrast-enhanced CT of the chest, abdomen, and pelvis were obtained.

Outcomes

The primary outcome was change in surgical management in the PET-CT group only based on the PET-CT findings defined by canceled hepatic surgery, more extensive hepatic surgery, or additional organ surgery. All cases suspected of having achieved the primary outcome were reviewed independently by 2 surgical oncologists, who were members of the central adjudication committee. In cases of discrepancy, a third adjudicator was consulted and a decision was reached by consensus. Secondary outcomes included overall survival and disease-free survival defined as local or distant recurrence or death, which was added as an outcome prior to database lock.

Statistical Analysis

The sample size of 400 patients (267 in the PET-CT group and 133 in the control group) was chosen primarily based on the need to have precise estimates (±5%) of the rates for change, which were expected to be 25% for management and 15% for avoidance of surgery in the PET-CT group (details appear in eMethods 2 of Supplement).

The confidence limits for all proportions were calculated using the exact binomial method. Survival and disease-free survival were described in the 2 treatment groups (for all patients and for those undergoing surgery) using the Kaplan-Meier method and compared with a log-rank test. All *P* values are 2-sided and values of less than .05 were considered statistically significant. The treatment effect was summarized by the hazard ratio (HR) with its associated 95% confidence intervals for the PET-CT group relative to the control group, and estimated from an unadjusted Cox proportional hazards model.

In the PET-CT group, the relationship between the standard uptake value of the largest colorectal metastatic lesion and survival was assessed in a similar fashion but with an α level of .10 (patients who did not undergo PET-CT were excluded). For cases with undetectable standard uptake values (<2.0), we imputed standardized uptake values between 0 and 2.0 (the assumed detection limit) using a truncated log-normal distribution. For any missing baseline data, multiple imputation was used in the modeling. All analyses were conducted using SAS version 9.2 (SAS Institute Inc).

Results

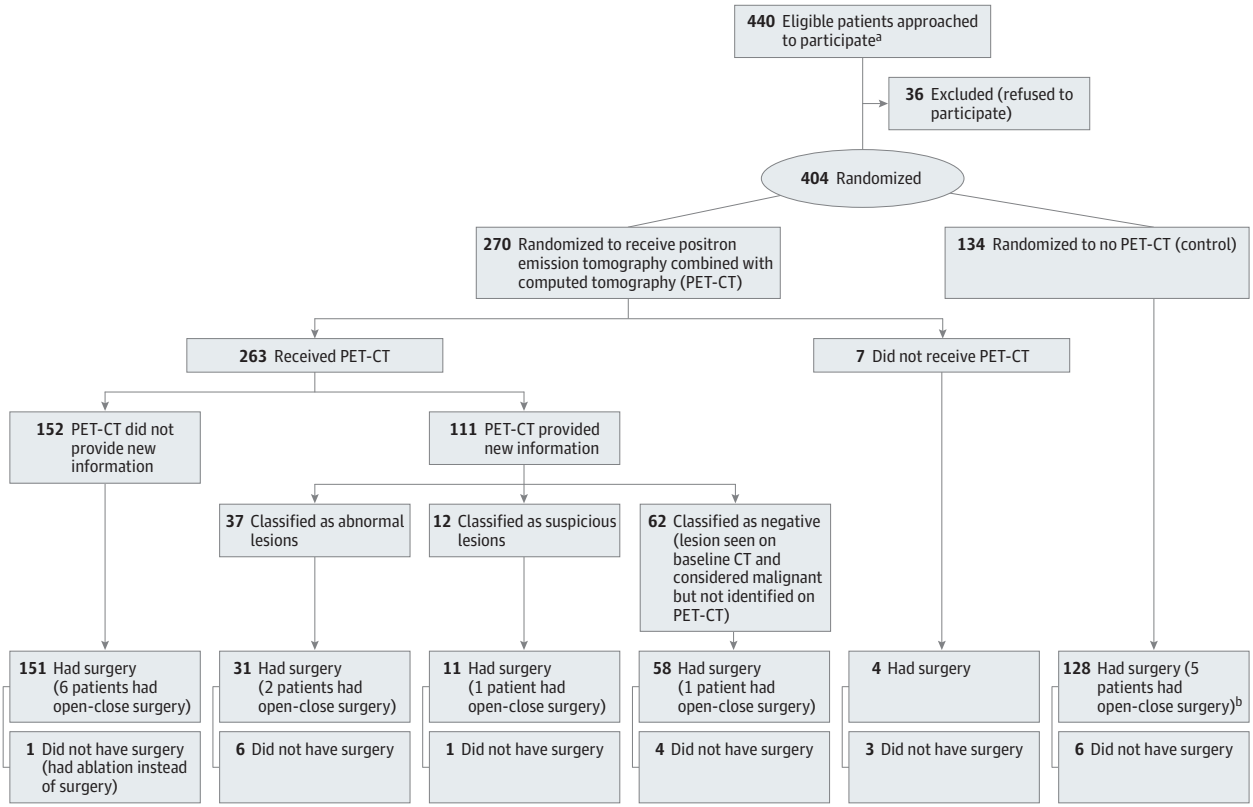
Between November 2005 and April 2010, 440 eligible patients were approached to participate and 404 (92%) provided consent. There were 270 patients randomly assigned to the PET-CT group and 134 patients to the control group (**Figure 1**). The last patient follow-up visit occurred on April 15, 2013. In the PET-CT group, 7 of the 270 patients did not undergo PET-CT (3 withdrew consent, 2 failed to show up for this test, and 2 experienced technical problems with the equipment); 4 of these 7 patients had surgery. Participants within treatment groups were similar at baseline (**Table 1**). The mean number of patients per surgeon was 12.9 (median, 9; range, 2-59) in the PET-CT group and 6.7 (median, 5.5; range, 1-26) in the control group. Twenty surgeons had patients in both study groups and 1 surgeon had 2 patients only in the PET-CT group. The median time between CT and PET-CT was 3.8 weeks. The median time interval between the completion of chemotherapy and the PET-CT imaging was 13 weeks (range, 3.7-685 weeks; interquartile range, 6.5-51.9 weeks).

Change in Management

Of the 263 PET-CT scans, 111 provided new information: 62 were classified as negative (ie, lesions seen on the baseline CT and considered malignant but not identified on PET-CT) and 49 had abnormal or suspicious lesions (37 abnormal, 12 suspicious) as interpreted by the PET-CT reader (Figure 1). The details of the process (eg, biopsy, additional imaging, or follow-up) to confirm the 49 abnormal or suspicious PET-CT scans are described in eTable 1 in Supplement. Twenty-two patients had positive PET-CT scans which, on further investigation or follow-up, were determined not to be cancer.

Surgeons indicated that they would change the surgical plan in 23 patients (8.7%; 95% CI, 5.6%-12.8%) based on the PET-CT. The new plans were: no surgery (9 patients), more extensive surgery (4 patients), further nonhepatic surgery including biopsy (9 patients), and more extensive and further nonhepatic surgery (1 patient). Surgical management was actually changed in 21 patients (8.0%; 95% CI, 5.0%-11.9%); 7 patients (2.7%) did not undergo laparotomy, 4 (1.5%) had more extensive hepatic surgery, 9 (3.4%) had additional organ surgery (8 of whom had hepatic resection), and the abdominal cavity was opened in 1 patient but hepatic surgery was not performed and the cavity was closed (ie, open-close surgery) (**Table 2**). Six patients (4.5%) in the PET-CT group had a change in surgical management.

Figure 1. CONSORT Diagram



There were 270 patients in the PET-CT group and 134 patients in the control group included in the primary analysis. CONSORT indicates Consolidated Standards of Reporting Trials.

[a] A screening log to identify patients who fit inclusion criteria and reasons for exclusion was not collected.

[b] Indicates that the abdominal cavity was opened but hepatic surgery was not performed and the cavity was closed.

Of the remaining 26 patients with abnormal or suspicious lesions on PET-CT, 3 had known synchronous primary cancer and liver metastases and there was no change in surgical plan; 1 patient had more lesions identified at the time of surgery and underwent a different surgery than planned; and in the remaining 22 patients, the explanation for abnormal scans included another site abnormal (eg, pharynx, thyroid, tonsil, breast, prostate, and rectum); and more liver metastases than found with CT but these did not change the surgical plan (eTable 1 in Supplement). Twenty-one patients went on to have liver resection and 1 had an open-close surgery.

Overall, liver resection was performed on 245 patients (91%) in the PET-CT group (n = 270) and 123 patients (92%) in the control group (n = 134). Open-close surgery was performed in 10 patients (3.7%) in the PET-CT group (6 had negative PET-CT scans and 4 had suspicious findings leading to a targeted approach at time of laparotomy) and in 5 patients (3.7%) in the control group.

Overall Survival

The median follow-up was 36.0 months (maximum, 57 months; interquartile range, 35.5-37.0 months). Thirty-four percent of the 404 patients died (eTable 2 in Supplement). The estimated mortality rate was 11.13 (95% CI, 8.95-13.68) events/1000 person-months in the PET-CT group and 12.71 (95% CI, 9.40-16.80) events/1000 person-months in the control group. There was no statistically significant difference in survival between patients in the PET-CT group vs the control group (HR, 0.86 [95% CI, 0.60-1.21], $P = .38$; **Figure 2**). For the 245 patients in the PET-CT group and 123 patients in the control group who had curative-intent hepatic surgery, the corresponding HR was 0.81 (95% CI, 0.56-1.18, $P = .28$; **Figure 3**). There were no statistically significant differences in disease-free survival for patients in the PET-CT group relative to the control group (HR, 1.08 [95% CI, 0.84-1.39], $P = .56$ in all patients; HR, 1.03 [95% CI, 0.79-1.33], $P = .85$ in those who had surgery). The multivariable models for survival and disease-free survival appear in eTable 3 in Supplement.

In the PET-CT group, the maximum standardized uptake value was not detected in 49 patients (19%). The standardized uptake value was associated with survival (HR, 1.11 [90% CI, 1.07-1.15] per unit increase, $P < .001$). The C statistic for the model including the standardized uptake value was 0.62 (95% CI, 0.56-0.68) and without it was 0.50 (95% CI, 0.44-0.56)

(P = .005). The difference in C statistics was 0.12 (95% CI, 0.04-0.21). The low C statistic suggests that the standard uptake value is not a strong predictor of overall survival.

Post hoc sensitivity analyses were conducted to assess the effect of the inclusion of 25 cases with extrahepatic disease. The results suggest that these cases had little effect on the findings (eTable 4 in Supplement).

Discussion

Surgical resection is an effective treatment for colorectal liver metastases.[17] Unidentified sites of extrahepatic disease at the time of surgery can cause subsequent clinical relapse.[18] Computed tomography has been the standard modality for detection of extrahepatic metastases prior to curative resection. Change in management (canceled, more extensive hepatic surgery, or additional organs resected) as a result of the PET-CT occurred in only 8.7% of cases in our trial and only 2.7% avoided noncurative hepatic surgery. These rates are substantially lower than in previous studies,[9,10,19] which were retrospective, consisted of mixed patient populations, were small in size, and lacked high-quality baseline imaging. In our trial, PET-CT resulted in additional nonhepatic surgery or biopsy in 3.4% of patients and most of them went on to have hepatic resection. There was no difference in the rates of hepatic resection between groups.

No difference in overall survival was detected in the full cohort analysis or among patients who underwent hepatic resection. It is possible that a clinically important difference in survival was not detected due to the size of the trial. In the PET-CT group, the standard uptake value was associated with survival, suggesting that the intrinsic biology of metastases is important in determining the clinical course of these patients, but the C statistic value suggests that it is not strongly predictive.

In the only other randomized trial that evaluated PET-CT in patients with colorectal liver metastases, Ruers et al[20] compared the rates of futile laparotomy among 150 patients who

Table 1. Baseline Characteristics by Treatment Group

Characteristic	No. (%) of Patients[a]	
	PET-CT (n = 270)	Control (n = 134)
Age at entry, median (range), y	62 (23-87)	62 (20-84)
Female sex	102 (38)	42 (31)
Rectal primary tumor	69 (26)	42 (31)
Tumor grade at first diagnosis		
Low	71 (26)	29 (22)
Moderate or intermediate	174 (64)	92 (69)
High	18 (7)	9 (7)
Unknown	7 (3)	4 (3)
Margins involved at first surgery	35 (13)	16 (12)
Node stage		
N0	85 (31)	53 (40)
N1	107 (40)	42 (31)
N2	73 (27)	39 (29)
Nx	5 (2)	0
Temporal relationship to primary		
Synchronous	129 (48)	60 (45)
Metachronous	141 (52)	74 (55)
Type of treatment		
Radiotherapy	45 (17)	34 (25)
Chemotherapy	189 (70)	95 (71)
Carcinoembryonic antigen level, median (range), μg/L[b]	6.5 (0.4-6089)	9.5 (0.6-852)
No. of lesions, median (range)	2.0 (0-10)	1.5 (1-7)
Size of largest tumor, median (range), mm	28.0 (0-260)	30.0 (0-460)
Disease-free duration, median (range), mo[c]	11 (0-167)	14 (0-80)
Bilateral tumor[d]	99 (37)	42 (31)
Extrahepatic disease	14 (5)	11 (8)

Abbreviation: PET-CT, positron emission tomography combined with computed tomography.

[a] Unless otherwise indicated.

[b] There were 56 (14%) patients without this measurement.

[c] Defined as disease-free interval from primary diagnosis to metastases.

[d] Bilobar hepatic metastases or liver metastases in both right and left lobes of the liver.

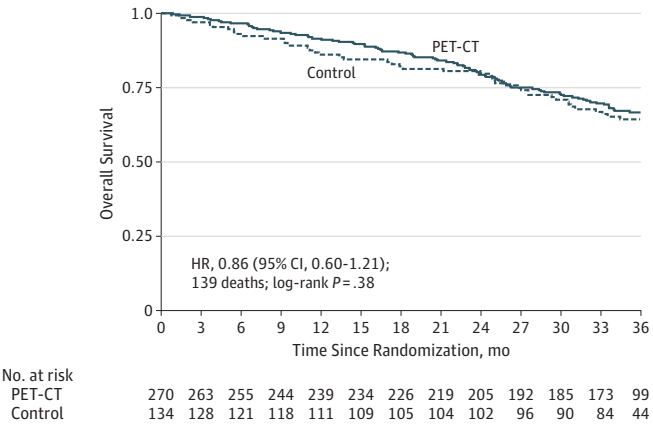
Table 2. Change in Surgical Plan Based on PET-CT Result and Actual Surgery

Revised Plan	No. of Patients	Site	No. of Patients	Actual Hepatic Surgery, No. of Patients		
				Resection	No Resection	Open-Close[a]
No surgery	9	Bone	2	2	7	0
		Peritoneal or omental	3			
		Abdominal nodes	4			
More extensive surgery	4	More segments	4	4	0	0
Nonhepatic surgery	9	Nodes	4	8	0	1
		Local recurrence	1			
		Sigmoid and spleen	1			
		New colonic neoplasm	1			
		Gastroscopy and lymph node biopsy	1			
		Colonoscopy and sigmoid colon cancer resection	1			
More extensive and nonhepatic surgery	1	More segments, laparoscopy planned	1	0	0	1
Total	23		23	14	7	2

Abbreviation: PET-CT, positron emission tomography combined with computed tomography.

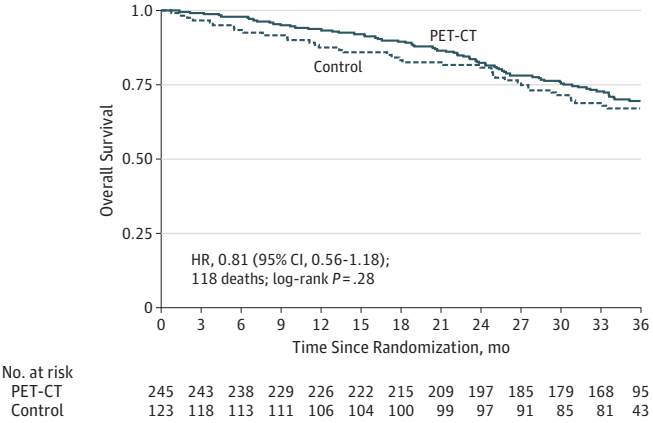
[a] Indicates the abdominal cavity was opened but hepatic surgery was not performed and the cavity was closed.

Figure 2. Overall Survival for All Patients



The 2-year survival rate was 0.80 (95% CI, 0.75-0.85) for the PET-CT group and 0.80 (95% CI, 0.73-0.87) for the control group. PET-CT indicates positron emission tomography combined with computed tomography.

Figure 3. Overall Survival for Patients Who Had Surgery



The 2-year survival rate was 0.83 (95% CI, 0.78-0.87) for the PET-CT group and 0.81 (95% CI, 0.74-0.88) for the control group. PET-CT indicates positron emission tomography combined with computed tomography.

had preoperative PET-CT vs those not having PET-CT (28% and 45%, respectively). Based on our trial experience, the noncurative futile laparotomy rate of 45% and the open-close surgery rate of 23% among their control group seems high. There were a number of differences between our trial and theirs (eg, definition of futile laparotomy, eligibility criteria).

To our knowledge, our study is the largest to address the role of PET-CT in the surgical management of colorectal liver metastases. Our study was randomized and based on high-quality baseline imaging. Outcome measures were defined by objective criteria and adjudicated by a panel of experts. A quality assurance program was established to ensure high-quality performance and reading of PET-CT scans.[14-16] Surgeons participating in the trial were experienced in hepatobiliary surgery and were members of the provincial hepatobiliary/pancreatic surgical oncology community, suggesting a uniform surgical approach.

Akhurst et al[21] reported that the standardized uptake values of liver metastases in 13 patients who received chemotherapy within 12 weeks of hepatic surgery were lower than those for 19 patients who did not receive chemotherapy within 12 weeks of surgery. About half the patients received chemotherapy within 12 weeks of surgery in our trial. Thus a potential limitation is that chemotherapy may have resulted in false-negative PET-CT imaging. This needs to be weighed against delaying surgery to accommodate timing of the PET.

Our goal was to address how PET-CT would influence the clinical management of patients who had already undergone CT staging. A randomized design was used both to estimate the observed rate of change in surgical management with precision using the PET-CT cohort and to compare the survival of patients allocated to PET-CT vs control. A limitation of basing the primary outcome on a single-group prospective cohort is that it is necessary to place a value judgment on the clinical importance of the rate. The use of a randomized design to compare the survival of groups in which one intervention deselects patients for curative surgery is complicated. It is possible that such surgery is unlikely to improve cancer survival. Despite this limitation, we chose to conduct an analysis of survival because it had been previously reported that PET-CT resulted in improved survival based on better selection of patients for surgery.[12]

Many countries struggle to maintain quality health care within existing budgets.[22] This is difficult because of increas-

ing health care costs as a result of an aging population and the expense of new therapies and technologies, including diagnostic and functional imaging.[23,24] In 2009, the US Institute of Medicine released a report[25] regarding comparative effectiveness research (CER), which is part of health care reform efforts in the United States. Our trial is part of a program of trials in Ontario evaluating PET imaging in oncology and is a strong example of CER.

Conclusions

Among patients with potentially resectable hepatic metastases of colorectal adenocarcinoma, the use of PET-CT compared with CT alone did not result in frequent change in surgical management. These findings raise questions about the value of PET-CT scans in this setting.

ARTICLE INFORMATION

Author Contributions: Dr Levine had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Moulton, Gu, Law, Hart, Jalink, Husien, Haider, Julian, Levine, Gallinger.
Acquisition, analysis, or interpretation of data: Moulton, Gu, Law, Tandan, Quan, Fairfull Smith, Jalink, Serrano, Hendler, Ruo, Gulenchyn, Finch, Julian, Levine, Gallinger.
Drafting of the manuscript: Moulton, Gu, Law, Julian, Levine, Gallinger.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Gu, Julian.
Obtained funding: Moulton, Levine, Gallinger.
Administrative, technical, or material support: Moulton, Gu, Law, Tandan, Jalink, Husien, Serrano, Hendler, Haider, Ruo, Gulenchyn, Finch, Gallinger.
Study supervision: Moulton, Jalink, Serrano, Julian, Levine, Gallinger.

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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Role of the Sponsor: The Ontario Ministry of Health and Long-term Care had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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