ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 29: 931–937, 2018
doi:10.1093/annonc/mdy031
Published online 22 January 2018

ORIGINAL ARTICLE

Colorectal cancer (CRC) monitoring by 6-monthly ^{18}FDG-PET/CT: an open-label multicentre randomised trial

I. Sobhani[1,2*], E. Itti[3], A. Luciani[4], I. Baumgaertner[1], R. Layese[5,6], T. André[7], M. Ducreux[8], J.-M. Gornet[9], G. Goujon[10], T. Aparicio[11], J. Taieb[12], J.-B. Bachet[13], F. Hemery[14], A. Retbi[7], M. Mons[8], R. Flicoteaux[9], B. Rhein[15], S. Baron[11], I. Cherrak[12], P. Rufat[13], P. Le Corvoisier[16], N. de'Angelis[1], P.-A. Natella[5], H. Maoulida[17], C. Tournigand[1], I. Durand Zaleski[17] & S. Bastuji-Garin[5,6]

[1]EA7375 (EC2M3 Research Team), Université Paris-Est Créteil (UPEC)-Val de Marne, Créteil; Departments of [2]Gastroenterology; [3]Nuclear Medicine; [4]Medical Imaging; [5]Public Health, Unité de Recherche Clinique (URC Mondor), APHP-Hôpital Henri Mondor, Créteil; [6]CEpiA Clinical Epidemiology and Ageing Unit, EA7376, Université Paris-Est (UPEC), A-TVB DHU, IMRB, Créteil; [7]Sorbonnes University and Department of Medical Oncology, APHP-Hôpital St Antoine, Paris; [8]Department of Gastrointestinal Oncology, Institut Gustave Roussy, Villejuif; [9]Department of Gastroenterology, APHP-Hôpital St Louis, Paris; [10]Department of Gastroenterology, APHP-Hôpital Bichat, Paris; [11]Department of Gastroenterology, APHP-Hôpital Avicenne, Paris; [12]Department of Gastrointestinal Oncology, APHP-Hôpital Européen Georges Pompidou, Paris; [13]Department of Gastroenterology and Medical Informatics, APHP-Hôpital Pitié-Salpêtrière, Paris; [14]Department of Medical Informatics, APHP-Hôpital Henri Mondor, Créteil; [15]Department of Medical Informatics, Centre Hospitalier d'Intercommunal de Créteil, Créteil; [16]Clinical Investigations Centre, APHP-Hôpital Henri Mondor, Créteil; [17]Healthcare Economics Research Unit, APHP, Paris, France

Correspondence to: Prof. Iradj Sobhani, Service de Gastroentérologie, Hôpital Henri Mondor, 51 Av Mal de Lattre de Tassigny, 94010 Créteil, France.
Tel: +33-149-814-358/812-362; Fax: +33-149-812-352; E-mail: iradj.sobhani@aphp.fr

Background: [^{18}F]2-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (^{18}FDG-PET/CT) has high sensitivity for detecting recurrences of colorectal cancer (CRC). Our objective was to determine whether adding routine 6-monthly ^{18}FDG-PET/CT to our usual monitoring strategy improved patient outcomes and to assess the effect on costs.

Patients and methods: In this open-label multicentre trial, patients in remission of CRC (stage II perforated, stage III, or stage IV) after curative surgery were randomly assigned (1 : 1) to usual monitoring alone (3-monthly physical and tumour marker assays, 6-monthly liver ultrasound and chest radiograph, and 6-monthly whole-body computed tomography) or with 6-monthly ^{18}FDG-PET/CT, for 3 years. A multidisciplinary committee reviewed each patient's data every 3 months and classified the recurrence status as yes/no/doubtful. Recurrences were treated with curative surgery alone if feasible and with chemotherapy otherwise. The primary end point was treatment failure defined as unresectable recurrence or death. Relative risks were estimated, and survival was analysed using the Kaplan–Meier method, log-rank test, and Cox models. Direct costs were compared.

Results: Of the 239 enrolled patients, 120 were in the intervention arm and 119 in the control arm. The failure rate was 29.2% (31 unresectable recurrences and 4 deaths) in the intervention group and 23.7% (27 unresectable recurrences and 1 death) in the control group (relative risk = 1.23; 95% confidence interval, 0.80–1.88; $P = 0.34$). The multivariate analysis also showed no significant difference (hazards ratio, 1.33; 95% confidence interval, 0.8–2.19; $P = 0.27$). Median time to diagnosis of unresectable recurrence (months) was significantly shorter in the intervention group [7 (3–20) versus 14.3 (7.3–27), $P = 0.016$]. Mean cost/patient was higher in the intervention group (18 192 ± 27 679 € versus 11 131 ± 13 €, $P < 0.033$).

Conclusion: ^{18}FDG-PET/CT, when added every 6 months, increased costs without decreasing treatment failure rates in patients in remission of CRC. The control group had very close follow-up, and any additional improvement (if present) would be small and hard to detect.

ClinicalTrials.gov identifier: NCT00624260

Key words: colorectal cancer, monitoring, cost effectiveness, ^{18}FDG-PET/CT

Introduction

Colorectal cancer (CRC) is the second most common cause of cancer-related mortality. The mainstay of treatment is surgery with curative intent, which is feasible in nearly all patients with stages I–III disease and in 15% of those with stage IV disease. However, recurrences are diagnosed after surgery in half the patients, usually within the first 2 years [1–3]. When feasible, the preferred treatment of recurrent disease is surgical resection [4–7].

Early detection of recurrences has been reported to improve patient outcomes [4, 8]. Post-operative monitoring to detect recurrences is therefore mandatory [5–9]. However, intensive follow-up to ensure the early detection of recurrences significantly diminished mortality in some studies [3, 8, 9] but not in others [1, 2, 6]. Thus, the optimal monitoring strategy remains in doubt.

French and international guidelines [10–13] for early recurrence detection after surgery for CRC recommend intensive monitoring with 3-monthly visits for a medical interview, physical examination, laboratory tests, chest X-ray, and liver ultrasound combined. The same guidelines also recognise that highly sensitive imaging procedures such as whole-body computed tomography (wbCT), [^{18}F]2-fluoro-2-deoxy-D-glucose positron emission tomography (^{18}FDG-PET), and/or abdominal magnetic resonance imaging (MRI) may be advisable after potentially curative resection of liver and/or lung metastases [12, 14, 15].

Previous studies have used a variety of intensive monitoring strategies [1–4, 14–17]. A Cochrane review suggests that using highly sensitive investigations may decrease the time to recurrence detection, thereby increasing the proportion of recurrences amenable to potentially curative surgery and expected improving overall survival (OS) [15]. In a previous randomised trial, we showed that adding routine ^{118}FDG-PET to the standard monitoring strategy ensured the earlier detection of recurrences [4]. However, although a meta-analysis of randomised trials suggested that intensive monitoring improved OS, whether this effect was related to earlier treatment of recurrences remained controversial [4–6]. Finally, no studies have evaluated whether adding highly sensitive imaging studies to the CRC monitoring strategy is cost-effective.

We hypothesised that adding routine 6-monthly ^{18}FDG-PET/computed tomography (CT) to the monitoring strategy used routinely increased the frequency of potentially curative surgery for recurrences, thereby decreasing the treatment failure rate and the overall cost of management.

Methods

The study protocol was approved by the appropriate ethics committee and patients provided written informed consent before study inclusion.

We prospectively enrolled patients aged at least 18 years with histologically proven CRC at risk for recurrence after surgery and/or chemotherapy in an open-label multicentre randomised trial. All centres applied the above-mentioned recommendations for the standard monitoring of CRC [10–13].

High risk was defined as stage II CRC with tumour perforation or stage III or IV CRC with complete resection of all synchronous and metachronous metastases. To be eligible for the present study, patients had to be in remission at entry (supplementary Figure S1, available at *Annals of Oncology* online).

After inclusion, patients were randomly allocated in a 1 : 1 ratio to standard monitoring alone (control arm) or with ^{18}FDG-PET/CT (intervention arm).

For each patient, all study data except costs were entered into an electronic case-report form.

The evaluation done to confirm the remission was performed 4–5 months after curative-intent surgery and was based on a physical examination and blood tests (blood cell counts, liver function tests, and tumour markers), as well as wbCT routinely and liver MRI as appropriate and performed less than 1 month before the evaluation date. The first study follow-up visit was planned 6 months after the curative-intent surgery. At this first visit, all patients underwent wbCT and those in the intervention arm also underwent ^{18}FDG-PET/CT.

In both groups, patients were evaluated every 3 months with a physical examination and laboratory tests. Every 6 months, they had wbCT, and intervention-arm patients also had ^{18}FDG-PET/CT. Follow-up duration for the trial was 3 years. Liver ultrasound and chest radiography were performed in all patients in both arms at the visits without wbCT (with or without ^{18}FDG-PET/CT). Follow-up colonoscopy was performed routinely 1 and 3 years following primary CRC resection, as recommended [10].

Imaging studies

The standardised wbCT protocol involved scanning from the neck to the pelvic cavity, after the injection of 1.5 ml/kg of Xenetix 350 or Iomeron 350. All acquisitions were carried out using a multi-slice CT machine (Toshiba or Philips) to obtain slices 2.5 mm in thickness for image analysis.

Whole-body ^{18}FDG-PET/CT was performed after an at least 6-hour fast, as checked by a blood glucose test showing a level no higher than 2 g/l. Scanning was started 60 min after an intravenous injection of 4–5 MBq/kg of ^{18}FDG. PET from the neck to the pelvis was carried out in 9–11 steps. Reformations were obtained with and without attenuation correction using iterative algorithms to compute standardised uptake values.

A senior nuclear medicine specialist and a senior radiologist classified the recurrence status of each ^{18}FDG-PET/CT and wbCT, respectively, as yes, no, or doubtful. The images were reviewed without blinding during the multidisciplinary meetings described in the following.

Follow-up

Patients were examined between 3-monthly follow-up scheduled visits if their usual physicians felt the symptoms suggested recurrent disease. After each visit, all information regarding patients were reviewed during a multidisciplinary meeting attended by a gastro-enterologist, an oncologist, oncology surgeons, a radiologist, a pathologist, a nuclear medicine specialist, and a geriatric oncology specialist, as well as by additional specialists as dictated by the patient's comorbidity profile. During the review, all findings (physical examination, tumour marker assays, and imaging studies) were assessed. The recurrence status was classified as yes, no, or doubtful. When discrepancies were found among (physical examination, tumour marker, and imaging) findings regarding the presence of a recurrence, additional imaging studies such as liver MRI, bone scintigraphy, and/or ^{18}FDG-PET/CT were considered and additional multidisciplinary review performed.

If the patient had no recurrence, the next 3-monthly visit was scheduled. Patients with one or a few foci of recurrent disease underwent potentially curative surgery. Patients with metastatic dissemination received chemotherapy and/or palliative care. Patients with unresectable disease did not undergo further ^{18}FDG-PET/CT but received standard monitoring until the end of the trial or death. Finally, when the recurrence status was doubtful, a biopsy of the suspected lesion was

considered; the alternative was re-evaluation of the recurrence status at the next 3-monthly visit.

Study end points

The primary end point was treatment failure defined as either unresectable recurrence or death from any cause.

The secondary end points were the mortality rate, incidence of recurrence, incidence of unresectable recurrence, times to resectable and unresectable recurrences, total number of recurrences, OS, and disease-free survival (DFS).

Cost assessment

Costs were assessed in accordance with the Consolidated Health Economic Evaluation Reporting Standards statement for single-trial-based studies. The prospective analysis determined the cost per life-year gained with ^{18}FDG-PET/CT versus the standard of care over the 3-year trial period. Hospital inpatient costs were estimated and average cost for each study group determined with adjustment for the actual length of stay and resources used during the admission including the cost of imaging studies. All outpatient imaging studies were counted separately and both were included in our cost analysis. Discounting was not performed. Total cost was computed both with and without the cost of ^{18}FDG-PET/CT.

A cost-effectiveness analysis was conducted to estimate the incremental costs per additional year of survival. A joint comparison of costs and effects was carried out by non-parametric bootstrapping with 1000 resamples.

Statistical analysis

The required sample size was estimated based on the assumption that 35% of controls would experience an unresectable recurrence during the 3-year follow-up period and that adding ^{18}FDG-PET/CT would decrease this proportion by 15% [1–4]. With alpha set at 0.05, to detect this decrease with 80% power, 240 patients were required in all.

Data analyses were carried out using the intention-to-treat approach. To analyse the primary end point, we first built a multi-level logistic regression model with centre as a random effect, to account for potential clustering [18]. The results showed no centre effect ($P = 1$), indicating that any clustering was negligible. The relative risk (RR) of the primary end point and the absolute risk reduction (ARR) were calculated. Survival was analysed by the Kaplan–Meier method with comparison of the curves using the log-rank test. Multivariate Cox models were fitted to compare the primary end point between the two groups while taking potential confounders into account. Variables associated with P values below 0.20 were entered into a multivariate model, which was used to compute the hazard ratios.

The prevalence of the primary end point and secondary end points was compared between the two groups using the χ^2 test or Fisher's exact test and the Mann–Whitney test when appropriate. Costs were compared between groups using the Wilcoxon test. All statistical tests were two-sided, and P values below 0.05 were considered significant.

The cost analysis was carried out using SAS software, version 9.3 (SAS Institute, Cary, NC) and all other analyses using Stata software version 13.0 (StataCorp, College Station, TX).

Results

From March 2008 to November 2012, 257 potentially eligible patients who underwent curative surgery for CRC were identified (supplementary Figure S1, available at *Annals of Oncology* online). Among them, 239 fulfilled all inclusion and exclusion criteria and were randomly allocated to the control arm ($n = 119$) or intervention arm ($n = 120$). There were no errors in treatment allocation and one patient was lost to follow-up (Figure 1).

The groups appeared well balanced for the main characteristics (supplementary Table S1A–C, available at *Annals of Oncology* online), although the intervention arm had slightly higher proportions of patients with rectal cancer (28.3% versus 16.0%) and neoadjuvant treatment (30.8% versus 23.5%).

Primary end point

The frequency of treatment failure did not differ between arms: 29.2% (35/120, 31 unresectable recurrences and 4 deaths) in the intervention arm and 23.7% (28/118, 27 unresectable recurrences and 1 death) in the control arm [RR, 1.23; 95% confidence interval (95% CI), 0.80–1.88; $P = 0.34$) (Table 1 and Figure 1). Of the 63 patients with unresectable recurrences, 27 (43%) had stage IV disease at baseline. The results were similar when multiple imputation was performed (RR, 1.23; 95% CI, 0.80–1.88, $P = 0.35$).

The frequency of treatment failure was significantly associated with TNM stage (Table 2) and showed a trend towards an association with tumour differentiation ($P = 0.14$). The multivariate

Table 1. Primary and secondary end points

	Intervention ($n = 120$)	Control($n = 119$)	P value	RR [95% CI]	ARR (%) [95% CI]
Primary end point (120/118)					
Death or unresectable recurrence	35 (29.2)	28 (23.7)	0.34	1.23 [0.80–1.88]	5.4 [–5.7 to 16.6]
Delay, months, median [Q1–Q3][a]	7.0 [3.4–19.5]	13.8 [6.4–27.2]	0.026		
Secondary end points					
Death	13 (10.8)	7 (5.9)	0.17	1.83 [0.76–4.42]	4.9 [–2.1 to 11.9]
Unresectable recurrence	31 (25.8)	27 (22.9)	0.60	1.13 [0.72–1.77]	3.0 [–7.9 to 13.9]
Delay (31/27), months, median [Q1–Q3][a]	7.0 [3.1–19.7]	14.3 [7.3–27.3]	0.016		
Δ CEA level (27/24), ng/mL	2.4 [0.2–6.0]	7.4 [–0.1 to 25.2]	0.29		
Δ CA 19-9 level (21/19), IU/l	0 [–5.4 to 25.2]	13.1 [0–69]	0.036		

Data are *n* (%) unless specified otherwise.

[a]From randomisation to the first unresectable recurrence.

RR, relative risk; CI, confidence interval; ARR, absolute risk reduction; Δ, absolute difference between values at end point occurrence and baseline; Q1–Q3, interquartile range (25th–75th percentiles); CEA, carcinoembryonic antigen.

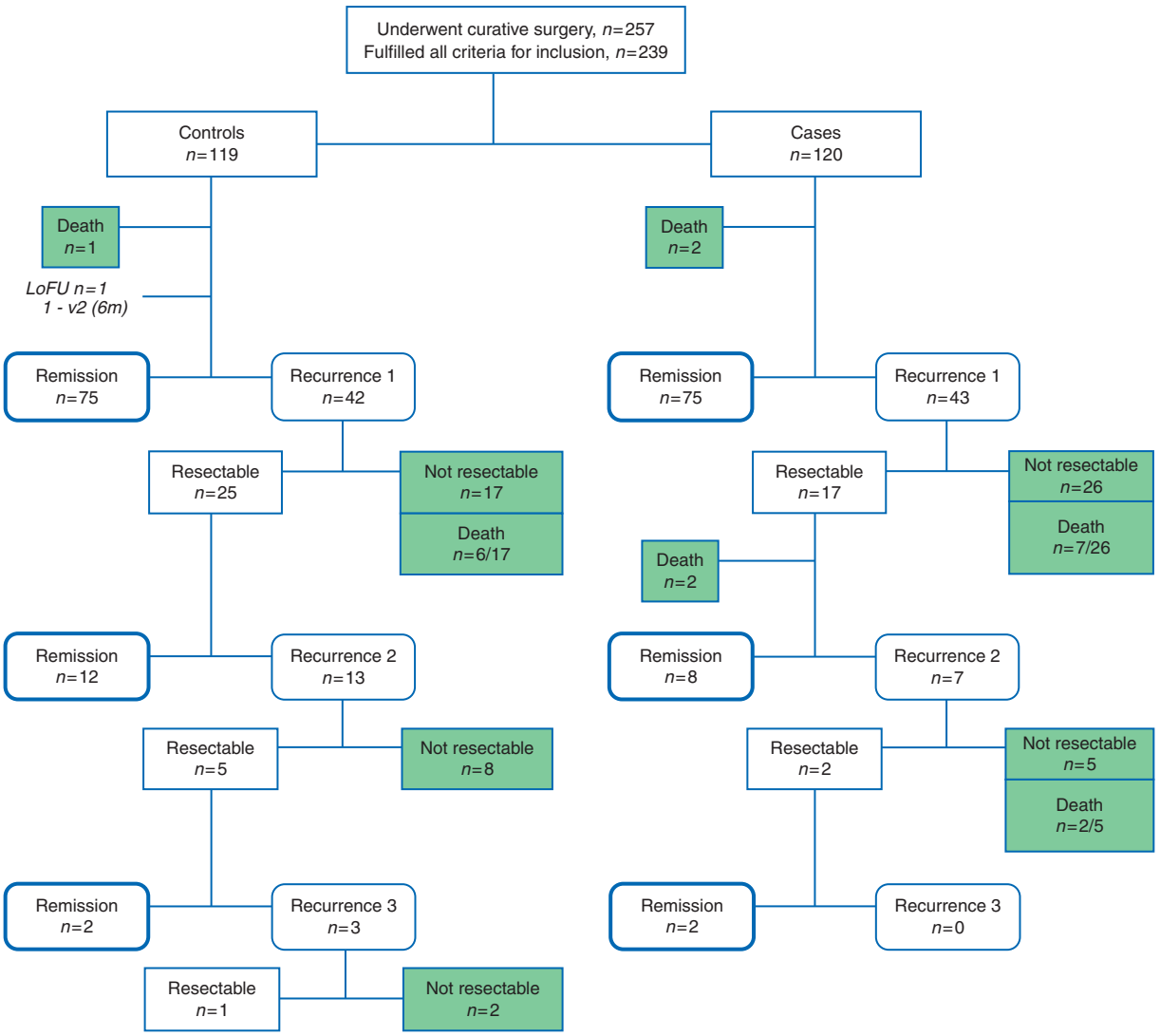

Figure 1. Patient flow diagram. LoFU, lost to follow-up.

Table 2. Factors affecting the primary end point of treatment failure defined as death or unresectable recurrence

	Failure		Univariate analysis		Multivariate analysis[a]	
	Yes ($n = 63$)	No ($n = 176$)	HR [95% CI]	*P* value	HR [95% CI]	*P* value
Intervention group	35 (55.6)	85 (48.3)	1.34 [0.81–2.20]	0.25	1.33 [0.80–2.19]	0.27
Age, years, median [Q1–Q3]	63.7 (56.4–67.7)	61.9 (52.7–70.8)	1.01 [0.99–1.03]	0.54	–	
Male gender	39 (61.9)	93 (52.8)	1.32 [0.79–2.19]	0.29	–	
Site of tumour						
Colonic	46 (73.0)	140 (79.6)	1			
Rectal	17 (27.0)	36 (20.4)	1.44 [0.82–2.49]	0.21	–	
TNM stage[b]				<0.001		
Stage II	6 (9.5)	20 (11.4)	1		1	
Stage III	28 (44.5)	124 (70.4)	0.75 [0.31–1.81]	0.52		
Stage IV	29 (46.0)	32 (18.2)	2.31 [0.96–5.57]	0.06	3.01 [1.83–4.97]	<0.001

Data are *n* (%) unless specified otherwise.

[a]The multivariate analysis was adjusted for study arm, TNM [TNM, T (tumour size), N (degree of spread to regional lymph nodes) and M (presence or absence of distant metastasis) as defined by the Union for International Cancer Control (UICC)] stage, and tumour differentiation.

[b]See also supplementary Tables S1 and S2, available at *Annals of Oncology* online for details.

HR, hazard ratio; 95% CI, 95% confidence interval; Q1–Q3, interquartile range (25th–75th percentiles).

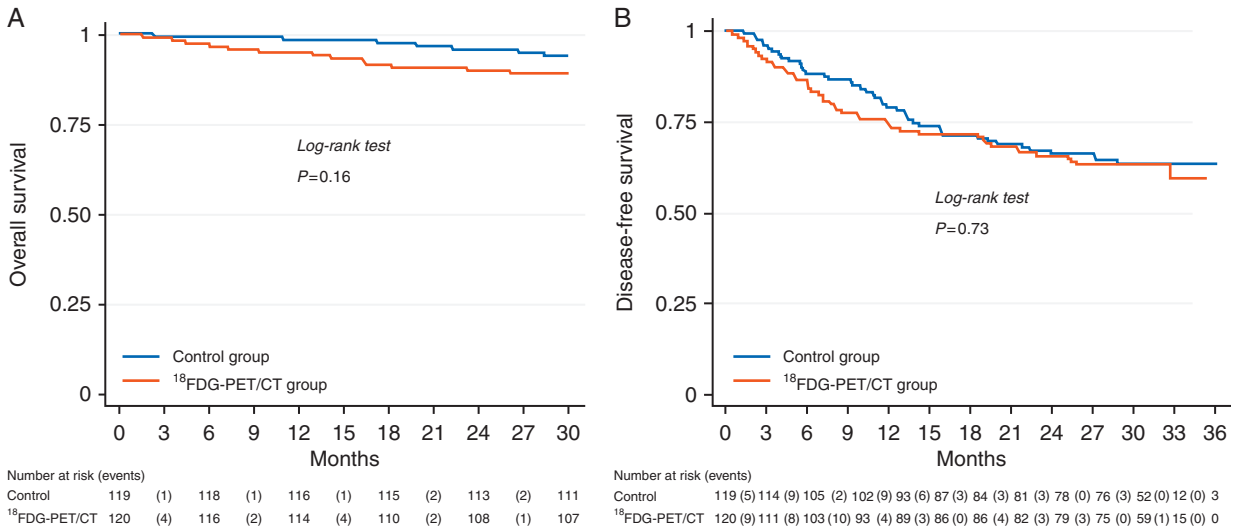

Figure 2. Probability of survival. (A) Probability of overall survival. (B) Probability of unresectable recurrence-free survival. Included patients in remission over follow-up period as well as patients with resectable recurrences.

Cox regression analysis adjusted for these variables showed no significant between-group difference in the treatment failure rate. The only baseline variable independently associated with treatment failure was stage IV disease (supplementary Tables S2 and S3, available at *Annals of Oncology* online).

Secondary end points

Neither OS nor DFS differed significantly between groups (Figure 2 and supplementary Table S3C, available at *Annals of Oncology* online).

Time to the first unresectable recurrence was significantly shorter in the intervention than in the control arm: 7.0 versus 14.3 months (Table 1). Overall, 13 and 7 patients died in the intervention and control arms, respectively ($P = 0.17$).

The CA 19-9 (but not carcinoembryonic antigen) increase versus baseline at the time of the unresectable recurrence was significantly larger in the control arm than in the intervention arm ($P = 0.036$) (Table 1; see also supplementary Table S2 and Figure S2A, available at *Annals of Oncology* online).

The number of patients with at least one recurrence was similar in the intervention [43/120 (35.8%)] and in the control arm [42/119 (35.3%)] ($P = 0.19$) (Figure 1). Neither was any difference found for the proportion of resectable recurrences [17/43 (39.5%) and 25/42 (59.5%), respectively; $P = 0.86$]. A second recurrence was detected in 7/17 intervention-arm patients and 13/25 controls and a third recurrence in three controls.

Cost assessment

Cost data were available for 188 of the 239 patients (92 in the intervention arm and 96 in the control arm; supplementary Table S4, available at *Annals of Oncology* online). Overall cost of management, not counting the imaging studies, was non-significantly higher in the intervention arm (14 573 ± 27 531€/patient) than in the control arm (11 131 ± 13 254€/patient; $P = 0.23$) (supplementary Figure S3, available at *Annals of Oncology* online). Adding the imaging costs to the other management costs increased the total 3-year cost to 18 192 ± 27 679€ in the intervention arm, which was significantly higher than in the control arm ($P < 0.0033$) (Table 3).

Table 3. Mean resource use and costs (2016 Euros) including those of ^{18}FDG-PET/CT over the 3-year follow-up in the two study arms

Mean (SD) unless otherwise specified	Intervention ($n = 92$)	Controls ($n = 96$)	*P* value (*t*-test)
Resource use			
Outpatient admissions	6	7	
Inpatient admissions	2	2	
Total days[a]	12 (23)	13 (14)	
Costs			
Outpatient	2291 (3501)	3102 (2941)	0.33
Inpatient	6444 (12 145)	4535 (6201)	0.14
Chemotherapy	5838 (27 073)	3494 (8755)	0.36
PET	3610 (1900)	–	
Total costs	18 192 (27 679)	11 131 (13 254)	0.033

[a]Provided by the coding system used to obtain reimbursement by the statutory health insurance system.

The probabilistic sensitivity analysis suggested that the intervention strategy increased costs without improving patient outcomes, with a likelihood of 87% for the survival end point (Figure 3).

Discussion

This study was designed under the hypothesis that adding ^{18}FDG-PET/CT to a standard intensive monitoring strategy for patients at high risk for CRC recurrence would diminish the treatment failure rate, defined as death or unresectable recurrence, by detecting recurrences earlier. Although, recurrences were indeed detected earlier in the ^{18}FDG-PET/CT arm, this

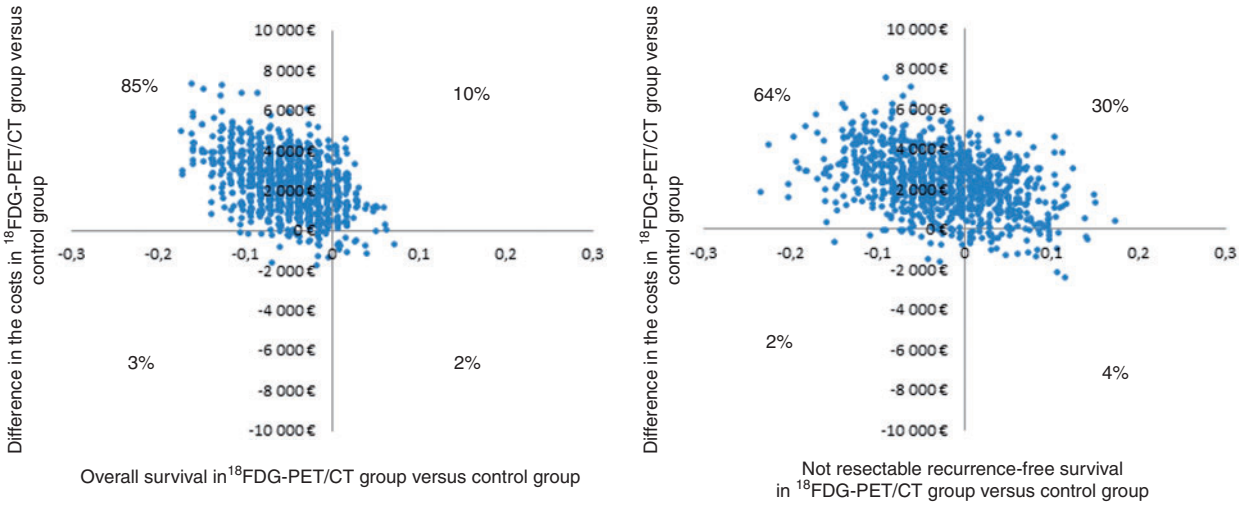

Figure 3. Cost effectiveness. Cost effectiveness of adding ^{18}FDG-PET/CT to standard monitoring, assessed based on overall survival (A) and on death or unresectable metastasis (B). The scatterplots (from bootstrap replications of the initial sample) illustrate the uncertainty regarding costs and outcomes.

earlier detection did not translate into a lower treatment failure rate. Also, neither OS nor DFS was better in the intervention arm. While the study was powered to detect a 15% ARR in the intervention group, a non-significant 5.5% absolute risk increase was found. Therefore, our negative result cannot be ascribed to underpowering. The intervention resulted in higher costs compared with the control strategy. Thus, our findings argue against adding ^{18}FDG-PET/CT to our standard monitoring strategy.

Whether intensifying monitoring strategies improves the outcomes of patients with CRC is controversial [3–5, 10, 14, 16]. Considerable heterogeneity across studies may explain the discrepancies in results. An intensive monitoring strategy was compared with less intensive investigations in some studies and to no follow-up at all in others [1, 10, 12]. The investigations used in the intensive and control arms varied widely [1, 2, 15–17]. The absence of benefits from intensified monitoring in older studies may be ascribable to the poorer performance of CT at the time, compared with current performance. Seven studies found earlier detection of recurrences with intensified follow-up but no effect on survival [1, 2, 11, 12, 17], a finding contradicted by a meta-analysis of randomised trials [15]. The four systematic reviews and/or meta-analyses published before our study was designed [3–9, 14] found better survival with intensified follow-up. However, the components of the monitoring strategies varied so considerably that no conclusions could be drawn about which test combination and schedule was optimal [19–26]. A Cochrane review of 15 studies including 5403 participants with stage II or III CRC [15]—despite variability in settings and, follow-up intensity—shows more salvage surgery with curative intent in patients in the group undergoing intensified follow-up. However, in a meta-analysis of 16 randomised controlled trials, including 11 with survival data [2], intensified monitoring was not associated with better survival.

We speculated that the combination of wbCT and ^{18}FDG-PET/CT used in the intervention arm was the most sensitive strategy identified so far for monitoring all high-risk CRC patients. Within the 3-year follow-up period, 35% of patients experienced recurrent disease in the current study. The recurrence was resectable in only half of them (17% of the overall population), in keeping with earlier data [1, 5, 6]. The recurrence rate was not significantly different between the two groups. Neither were there any differences in OS or DFS. Time from randomisation to detection of the first unresectable recurrence was shorter in the intervention group (7 months versus 14 months in the control group). As these recurrences were unresectable, however, detecting them earlier failed to improve survival.

Costs were higher in the intervention arm, in contradiction to our working hypothesis that earlier recurrence detection would offset the cost of additional ^{18}FDG-PET/CT by diminishing treatment costs. Inpatient admissions for conventional chemotherapy or targeted therapy were the main source of costs; they were required chiefly for patients with unresectable recurrences and were similar in the two groups.

Our study has several limitations. We chose a composite primary end point of treatment failure defined as unresectable recurrence or death hindering comparisons of our work to earlier studies, as most of these used only OS or DFS. A well-designed randomisation procedure was followed and despite two groups appeared well balanced at baseline, we cannot be entirely sure that consecutive patients were considered for enrolment in all centres. Blinding was not feasible and reading the imaging studies was not standardised across centres. Follow-up was only 3 years; however, most unresectable recurrences were in patients with stage IV disease at baseline, in whom time to recurrence is usually less than 3 years. Quality of life of the patients was not assessed. Conceivably, the shorter time to detection of unresectable recurrences with no survival benefit in the intervention group might have adversely affected quality of life by shortening the time during which the patients believed they were free of disease. Strengths of our study include the randomised controlled design, careful statistical analysis, appropriate sample size, and complete follow-up for all patients but one.

In summary, adding 6-monthly ^{18}FDG-PET/CT to an intensive 3-year monitoring strategy in patients with CRC failed to

diminish the treatment failure rate and increased costs. ^{18}FDG-PET/CT is not advised routinely although in some selected patients such as those with tumour marker elevation but no other evidence of disease it might be useful.

Acknowledgements

Investigators: Dr E. Assaf, Dr L. Albiges; Drs F. Brunbetti, Prof. A. Laurent, Prof. D. Cherqui, Prof. Ph. Rougier; Dr O. Dubreuil, Dr T.Boussaha, Dr P. Simon; Dr C. Lobry; Dr J. Philip; Prof. R. Benamouzig; Dr. G. Des Guetz; Dr C. Lemarchand; Prof. R. Adam; Prof.D. Castaing; Prof. D. Azoulay; Dr H. Hagege; Dr E. Malaurie Dr R. Henault; Dr I. Ekoume; Dr M. Martin; Dr. P. Afchain; Dr ML. Garcia; Dr L. Bengrine-Lefúvre; Dr P. Staub; Dr H. Gervais; Dr T. Maindrault; Dr C. Chibaudel; Dr O. Bourges; Dr M. Simon; Dr C. Baudry; Dr L. Pacault; Dr. V. Li; Dr A. Tranquart; Dr B. Bedjaoui; Dr D. Dilin; and Dr Ch. Ebenzer. *Clinical research assistants and senior clinical researchers:* S. Balloul; A. Gouja, K. Benzekri; A. Gueye; M. Benallaoua; M. Arfaoui; A. Stana; G. Saber; R. Krimi; G. Landry; and K. Raab. *Data management and statistics:* C. Viallette and C. Thuong.

Funding

French Ministry of Health (grant PHRC 2007AOM07156 and PHRC 2009 AOM11324) and monitored by a clinical research unit (Unité de Recherche Clinique—URC) at the Henri Mondor University Hospital-Assistance Publique-Hôpitaux de Paris (AP-HP, the network of publicly funded university hospitals in the Paris conurbation), where the data were centralised. Supporting for publication fee: Association Charles Debray-ACD.

Disclosure

The authors have declared no conflicts of interest.

References

1. Mant D, Gray A, Pugh S et al. A randomised controlled trial to assess the cost-effectiveness of intensive versus no scheduled follow-up in patients who have undergone resection for colorectal cancer with curative intent. Health Technol Assess 2017; 21(32): 1–86.
2. Mokhles F, Macbeth V, Farewell F et al. Meta-analysis of colorectal cancer followup after potentially curative resection. Br J Surg 2016; 103(10): 1259–1268.
3. Rodriguez-Moranta F, Salo J, Arcusa A et al. Postoperative surveillance in patients with colorectal cancer who have undergone curative resection: a prospective, multicenter, randomized, controlled trial. J Clin Oncol 2006; 24(3): 386–393.
4. Sobhani I, Tiret E, Lebtahi R et al. Early detection of recurrence by 18FDG-PET in the follow-up of patients with colorectal cancer. Br J Cancer 2008; 98(5): 875–880.
5. Figueredo A, Rumble RB, Maroun J et al. Follow-up of patients with curatively resected colorectal cancer: a practice guideline. BMC Cancer 2003; 3(1): 26.
6. Tjandra JJ, Chan MK. Follow-up after curative resection of colorectal cancer: a meta-analysis. Dis Colon Rectum 2007; 50(11): 1783–1799.
7. Sjovall A, Granath F, Cedermark B et al. Loco-regional recurrence from colon cancer: a population-based study. Ann Surg Oncol 2007; 14(2): 432–440.
8. Renehan AG, O'Dwyer ST, Whynes DK. Cost effectiveness analysis of intensive versus conventional follow up after curative resection for colorectal cancer. B Med J 2004; 328 (7431): 81.
9. Secco GB, Fardelli R, Gianquinto D et al. Efficacy and cost of risk-adapted follow-up in patients after colorectal cancer surgery: a prospective, randomized and controlled trial. Eur J Surg Oncol 2002; 28(4): 418–423.
10. Thesaurus national de cancérologie digestive. Chapitre 4. Cancer colorectal métastatiques; http://www.snfge.org/sites/default/files/SNFGE/TNCD/tncd_ccrm_vfinale_22_juin_2016.pdf (14 March 2018, date last accessed).
11. Desch CE, Benson AB, III, Somerfield MR et al. Colorectal cancer surveillance: 2005 update of an American Society of Clinical Oncology practice guideline. J Clin Oncol 2005; 23(33): 8512–8519.
12. Van Cutsem E, Cervantes A, Adam R et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol 2016; 27(8): 1386–1422.
13. Fiorentini G, Sarti D, Aliberti C et al. Multidisciplinary approach of colorectal cancer liver metastases. W J Clin Oncol 2017; 8(3): 190–202.
14. Laubert T, Bader FG, Oevermann E et al. Intensified surveillance after surgery for colorectal cancer significantly improves survival. Eur J Med Res 2010; 15: 25–30.
15. Jeffery M, Hickey BE, Hider PN, See AM. Follow-up strategies for patients treated for non-metastatic colorectal cancer. Cochrane Database of Systematic Reviews 2016; (11): Art. No. CD002200. doi: 10.1002/14651858.CD002200.pub3.
16. Vargas GM, Sheffield KM, Parmar AD et al. Physician follow-up and observation of guidelines in the post treatment surveillance of colorectal cancer. Surgery 2013; 154(2): 244–255.
17. Meyerhardt JA, Mayer RJ. Follow-up strategies after curative resection of colorectal cancer. Semin Oncol 2003; 30(3): 349–360.
18. Kahan BC, Morris TP. Assessing potential sources of clustering in individually randomized trials. BMC Med Res Methodol 2013; 13: 58.
19. Engelmann BE, Loft A, Kjær A et al. Positron emission tomography/computed tomography for optimized colon cancer staging and follow up. Scand J Gastroenterol 2014; 49(2): 191–201.
20. Patel K, Hadar N, Lee J et al. The lack of evidence for PET or PET/CT surveillance of patients with treated lymphoma, colorectal cancer, and head and neck cancer: a systematic review. J Nucl Med 2013; 54(9): 1518–1527.
21. Sanli Y, Kuyumcu S, Ozkan ZG et al. The utility of FDG-PET/CT as an effective tool for detecting recurrent colorectal cancer regardless of serum CEA levels. Ann Nucl Med 2012; 26(7): 551–558.
22. Shyn PB, Madan R, Wu C et al. PET/CT pattern analysis for surgical staple line recurrence in patients with colorectal cancer. AJR Am J Roentgenol 2010; 194(2): 414–421.
23. Ruers TJ, Langenhoff BS, Neeleman N,J et al. Value of positron emission tomography with [F-18]fluorodeoxyglucose in patients with colorectal liver metastases: a prospective study. J Clin Oncol 2002; 20(2): 388–395.
24. van Kessel CS1, Buckens CF, van den Bosch MA et al. Preoperative imaging of colorectal liver metastases after neoadjuvant chemotherapy: a meta-analysis. Ann Surg Oncol 2012; 19(9): 2805–2813.
25. Strasberg SM, Dehdashti F, Siegel BA et al. Survival of patients evaluated by FDG-PET before hepatic resection for metastatic colorectal carcinoma. Ann Surg 2001; 233(3): 293–299.
26. Moulton CA, Gu CS, Law CH et al. Effect of PET before liver resection on surgical management for colorectal adenocarcinoma metastases: a randomized clinical trial. JAMA 2014; 311: 1863–1869.