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Comparison of 18FDG-PET/CT and Conventional Follow-up Methods in Colorectal Cancer: A Randomised Prospective Study

Running title: PET/CT and colorectal cancer follow-up

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Conflict of interest

The authors declare that they have no competing interests.

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ABSTRACT

Background: A surveillance program was performed in colorectal cancer (CRC) patients after surgery, to diagnose asymptomatic recurrence.

Aims: To assess whether 18-FDG positron emission tomography/CT (PET/CT) improved the detection of recurrence during a 3-year follow-up.

Methods: A multicentre, two-arm randomised prospective trial comparing different 36-month follow-up strategies. Complete colonoscopy was performed at baseline and after 3 years and clinical exams with imaging every 3 months. The conventional treatment arm (A) received carcinoembryonic antigen, liver echography, and alternated between lung radiography and computed tomography (CT) scans. The experimental treatment arm (B) received PET/CT.

Results: A total of 365 patients with colon (79.4%) or rectal cancer (20.6%), stages II (48.2%) or III (50.8%), were enrolled in this study. At 36 months, intention-to-treat analysis revealed recurrence in 31 (17.2%) patients in arm A and 47 (25.4%) in arm B ($p = 0.063$). At 3 years, 7 of 31 relapses (22.5%) in arm A were surgically treated with curative intent, compared to 17 of 47 (36.2%) in arm B ($p = 0.25$). The rates of recurrence and new cancers were higher in arm B than arm A ($p = 0.038$).

Conclusions: PET/CT follow-up every 6 months did not increase the rate of recurrence at 3 years or the rate of surgically treated recurrence compared with conventional follow-up.

KEYWORDS: colorectal cancer; 18FDG-PET/CT, follow-up study.

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer in the Western world. One-third of the CRC patients experience recurrence with a poor prognosis. Postoperative surveillance after curative surgery for CRC can detect asymptomatic recurrence and identify new metachronous neoplasms that are eligible for curative resection, thereby improving overall survival (OS).

Despite treatment with surgery and chemotherapy, disease recurrence is observed in 30–50% of patients with approximately 90% of recurrence being diagnosed within the first 3 years after curative surgery.¹⁻³ The clinical benefit of postoperative surveillance is contradictory. In 2016, two meta-analyses concluded that intensive surveillance of patients with CRC did not improve survival.^{4, 5} Using data from recent trials,⁶⁻⁸ a meta-analysis by Zhao *et al.*⁹ that included data from 17 trials and 8039 patients concluded that intensive follow-up was associated with improved OS. Positron emission tomography/computed tomography (PET/CT) imaging is widely used in CRC imaging and may be useful for postoperative surveillance due to its high sensitivity and specificity. For detecting the recurrence of colorectal disease, a meta-analysis using data from 487 patients showed that PET/CT provided sensitivity and specificity of 91% and 91%, respectively.¹⁰ However, PET/CT is not used in clinical practice for routine follow-up of cancer patients.^{11 11} This study aimed to assess the clinical relevance (rate of cancer recurrence at 3 years) of 18-FDG PET/CT in CRC follow-up compared to conventional surveillance.

MATERIALS AND METHODS

Patient population and study settings

We included patients in 15 French clinical centres and eight nuclear medicine departments from 2004 to 2009. All patients provided written informed consent. The study was approved

by the Ethics Committee of Limoges Hospital (no.03-024) (France) and registered in ClinicalTrials.gov.fr (NCT00199654).

The study included patients who had undergone curative surgery for stage II or III colorectal cancer with or without adjuvant chemotherapy. Patients who did not provide informed consent, patients with palliative resection (R1 or R2 resection), stage IV cancer, WHO Performance status ≥ 2 , cancer other than CRC, or poorly controlled diabetes, were excluded from the study. Data regarding patient demographics, initial tumour characteristics, treatments, dates, and results of surveillance investigations were collected. Recurrence demographics and management for up to 36 months, as well as survival outcomes for up to 60 months, were also recorded. Disease recurrence was identified by histological samples (obtained via biopsy or surgery) except in patients with disseminated recurrence or clinically evident pathology. Recurrence was defined as local, locoregional (including lymph node involvement), or colorectal metastasis (including distant lymph nodes, the liver, the peritoneum, and the lungs).

Study design

The study was an open-label, multicentre, two-arm, randomised, controlled trial. After baseline assessments performed post-surgery, patients were randomly allocated to one of the two experimental groups. Randomisation to one of the two groups at a 1:1 ratio was performed centrally, with a balance based on the cancer staging and location (colon or rectum). All outcome data were entered in a central database, located in the CEBIMER Limoges Hospital, and analysed by research assistants and a biostatistician blinded to participant randomisation. There was no significant amendment to the original protocol during the trial.

The primary outcome was the recurrence rate after 3 years of follow-up (considered early recurrence). The secondary outcomes were the rates of surgically treated recurrence and overall survival.

The two arms were defined as follows:

Arm A involved a 3-year conventional follow-up, including clinical exams, carcinoembryonic antigen (CEA) measurements every 3 months, liver echography every 6 months, and lung radiography or thoracoabdominal CT alternately every 12 months.

Arm B involved a 3-year experimental follow-up, including a clinical exam every 3 months and PET/CT every 6 months over 3 years. In both arms, complete colonoscopies were performed at baseline or after surgery (if not complete before surgery) and after 3 years. For patients who presented symptoms, specialists initiated additional imaging procedures at their convenience, in addition to scheduled visits.

¹⁸F-FDG-PET/CT imaging

Integrated PET/CT was performed in eight different nuclear departments. In one department, patients underwent 20 examinations with PET alone until September 2005. All departments followed the recommendations of the PET/CT guidelines.¹²

After the interpretation of a routine local PET/CT examination, proofreading was performed for all examinations. A multidisciplinary group consisting of four practitioners (two nuclear physicians, one radiologist, and one clinician) validated the interpretation criteria and read the first 525 PET/CT scans. The next 328 scans were re-read by one nuclear physician blinded to the results of the first assessment. In the case of discordance between the two readings, a third one was performed.

Follow-up and outcome events

Locoregional relapse, metastases, and metachronous cancers were confirmed by histology or repeated imaging when possible. The recurrence date was considered to be the date of the first abnormal exam.

Statistical analysis

The quantitative values were expressed as medians and range, while qualitative values were presented as percentages. The primary analysis was an intention-to-treat comparison of the recurrence rate at 3 years in the patients of the two arms. When feasible, crude data were provided. Comparisons were performed between randomised groups; statistical significance was assessed using the χ^2 test for binary or categorical data, Student's *t*-test or analysis of variance for the comparison of group means, and the Kruskal-Wallis test for the comparison of medians. Disease-free survival (DFS) at 3 years was defined as the interval between the beginning of the study and the time of recurrence or last follow-up. Disease-free cancer survival (DFCS) at 3 years was defined as the interval between the beginning of the study and the time of distant recurrence or a second cancer diagnosis or last follow-up. Time to recurrence was analysed by the Kaplan–Meier method to consider both time censoring and the difference in the number of recurrences detected in each group. OS at 5 years was defined as the interval between the beginning of the study and the time of death or last follow-up. The plots of time to recurrence were compared by a log-rank Mantel-Cox statistic. Analyses were performed using SAS V9.3 software (SAS Institute, Cary, NC, USA).

The number of patients to be included in each group was calculated based on the known recurrence rate of mixed patients with colon and rectal cancers at stages II and III at the 3-year follow up. The hypothesis was that PET would increase the diagnostic recurrence rate at 3 years. Sample size calculation was based on a difference in the recurrence detection rate between arm A (37.5%) and arm B (50%) of 12.5%. The α error was set at 5% (one-sided

analysis), while the power was set at 80%. Based on this analysis, 188 patients per group were required.

RESULTS

Population

In total, 376 patients with CRC were prospectively enrolled in this study; however, 11 withdrew (Figure 1). In arm A, 180 patients were subjected to intention-to-treat (ITT) analysis, while 158 to per-protocol (PP) analysis. In arm B, 185 and 172 patients were analysed by ITT and PP analysis, respectively. The characteristics of the 365 patients are summarised in Table 1; no significant differences existed between the two arms. The median follow-up of the patients overall was 5.3 years (range, 0–10.1), with 5.2 years (range, 0–10.1) and 5.4 years (range, 0.6–9.0) in arms A and B, respectively.

Recurrence

By 36 months, 78 participants experienced recurrence: 31 (17.2%) in arm A and 47 (25.4%) in arm B. However, no significant difference was found between the diagnostic performance of PET/CT and conventional follow-up ($p = 0.063$). In PP evaluation at 36 months, 76 of 330 patients had relapsed (23.0%); 30 of 158 (19.0%) in arm A and 46 of 172 (26.7%) in arm B, with no statistically significant difference ($p = 0.073$). The types of recurrence are presented in Table 2. The majority of recurrence cases were metastatic disease.

Of the colon cancer patients, 60 of 290 (20.7%) relapsed; 25 in arm A and 35 in arm B with 12 local or locoregional (20.0%) (3 in arm A and 9 in arm B) and 48 metastatic cases of recurrence (80.0%) (22 in arm A and 26 in arm B). Of the rectal cancer patients, 18 of 75 (24.0%) relapsed; 6 in arm A and 12 in arm B with two locoregional relapses (1 in each arm) and 16 metastatic cases of recurrence (5 in arm A and 11 in arm B).

Regarding cancer stages, there were no significant differences between the two arms. In stage II CRC, 25/176 (14.2%) relapses were identified (10 in arm A and 15 in arm B) and in stage III CRC, 51/185 (27.5%) relapses were identified (20 in arm A and 31 in arm B). Among

these 78 recurrences, 81% in arm A and 87% in arm B were detected by a scheduled follow-up investigation.

As shown in Table 3, recurrence detection in arm A was mainly due to an elevation of markers and in arm B to an abnormality in the PET/CT results. In arm A, the follow-up had a sensitivity of 80% (95% CI, 61.4–92.3%) and specificity of 95.9% (CI, 94.7–96.9%). The positive predictive value (PPV) was 30%, the negative predictive value (NPV) was 89.6%, and the accuracy was 95.6%. In arm B, the follow-up had a sensitivity of 88.6% (CI, 75.4–96.2%) and a specificity of 92.1% (CI, 90–93.8%), with a PPV of 37.9%, NPV of 99.3% and an accuracy of 91.9%.

The proofreading of PET/CT scans revealed a change in the recurrence date in 13 patients (12 with a shorter time to recurrence and one with a longer time) and showed discrepancies in peritoneal (3) colon anastomose (2) liver (2) lung (5) abdominal lymph nodes (2) mediastinal (2) and muscle (1) recurrence.

Time to recurrence

The median time to recurrence in the 78 patients who relapsed within 36 months was 14.6 ± 8.9 months globally: 15.5 ± 8.4 months in arm A and 14.1 ± 9.3 months in arm B with no statistically significant difference. ($p = 0.22$).

DFS in ITT analysis

The DFS in the ITT analysis at 36 months was estimated to be 78% (95% CI, 73.3–82%) globally, 82% (CI, 75.4–87.0%) in arm A and 74.2% (CI, 67.2–80.0%) in arm B ($p = 0.063$; Figure 2A). The DFS of colon cancers was estimated to be 78.6% (CI, 73.3–83.0%) for colon cancers and 75.9% (CI, 64.4–84.0%) for rectal cancers with no significant difference ($p = 0.14$ and 0.27 for colon and rectal cancers, respectively).

DFS in PP analysis

The DFS in the PP analysis at 36 months was 76.9% (95% CI, 71.9–81.1%) globally, 81% (CI, 74–86.3%) in arm A, and 73% (CI, 65.7–79.1%) in arm B (Figure 2B). The Kaplan Meier plots in Figure 2A show that PET/CT tended to detect recurrence earlier in arm B than in arm A, yet the difference did not reach statistical significance.

Other cancers diagnosed by imaging

Thirteen additional cancers were detected in the 36-month follow-up; 10 in arm B and 3 in arm A. The locations were lung primary cancer (2), liver lymphoma (1), breast cancer (1), kidney cancer (2), melanoma (1), VADS cancer (1), embryonal cancer (1), prostate cancer (3), and GIST (1). Over the 36-month follow-up, four deaths were attributed to second cancers: one in arm A and three in arm B.

DFCS in ITT analysis at 36 months

The DFCS in ITT analysis at 36 months was 75.2% overall (95% CI, 70.4–79.4%), with 79.6% (CI, 72.3–84.9%) in arm A and 71.0% (CI, 63.9–77.0%) in arm B; this difference reached statistical significance ($p = 0.038$) (Figure 2C).

Curative surgery of recurrence cases

The number of participants with recurrence who were surgically treated with curative intent at 3 years was 24/78 overall (30.7% of recurrences), with 7/31 (22.5%) in arm A and 17/47 (36.2%) in arm B ($p = 0.25$). The other recurrence cases were not surgically treated due to disease diffusion. All cases were discussed in a local multidisciplinary meeting.

Overall survival (ITT)

OS at 5 years was calculated. Fifty-six patients died: 26 (14%) in arm A and 30 (16%) in arm B, without a statistically significant difference between the two arms ($p = 0.73$). OS was estimated to be 84.6% (95% CI, 80.2–88.0%), with 85.4% (CI, 79.0–90.0%) in arm A, and 83.7% (CI, 77.3–88.5%) in arm B (Figure 2D).

Of those patients who did not reach the median OS, one patient died of pulmonary embolism. For patients surgically treated with curative intent, OS was 52.4 months, with 47.7 months in arm A and 52.4 months in arm B; this difference was not statistically significant ($p = 0.48$).

Adherence to the protocol

In arm A, clinical examination and CEA testing were performed in all patients. The majority of patients received the thorax and abdomen CT scans instead of liver echography. Non-scheduled PET/CT was performed in 29 patients. In arm B, all patients underwent PET/CT scans. Additional CEA testing, CT, and liver echography were required in 93, 75, and 55 patients, respectively, to confirm doubtful PET/CT results. Moreover, one to three additional colonoscopies were performed in 198 patients in the two arms, as shown in Table 4. The planned study of the costs could not be performed so we calculated total cost *a posteriori* by summing the actual costs of exams performed in the two arms. We calculated the per-patient cost of the examinations as 652 € and 2,610 € in arms A and B, respectively.

DISCUSSION

In the present study, using PET/CT in colorectal follow-up did not significantly increase the recurrence detection rate compared to conventional follow-up (and therefore did not provide earlier detection). Data on the follow-up of CRC patients are important for the medical community but take a long time to achieve and require the active participation of many centres. Published trials in CRC are heterogeneous regarding procedures and test frequencies.

Recently, a meta-analysis of Zhao *et al.*⁹ showed that intensive follow-up was associated with improved OS, depending on the frequency of the tests. In our study, conventional follow-up methods (arm A) underwent clinical examination, CEA, liver echography, or CT scan, as recommended by the current surveillance guidelines of the European Society of Medical Oncology.¹³ In this arm, recurrence could be detected by CEA or CT, confirming the ability of CEA to detect asymptomatic recurrence, as reported previously;¹⁴ however, no impact on survival was observed. Moreover, CT could potentially detect resectable asymptomatic distant recurrence.^{15, 16} In fact, in this indication of curative tumour resection, PET/CT has provided better results than CT.¹⁷ In most studies, PET or PET/CT were used to confirm recurrence suspected by clinical, CEA, or CT imaging. The majority of randomised controlled trials did not have sufficient statistical power to confirm PET/CT performance in this follow-up strategy.¹⁸⁻²⁴ We hypothesised that scheduled PET/CT could identify more patients for curative surgery in CRC recurrence compared to conventional follow-up. In our trial, disease recurrence at 3 years occurred in only 20% of patients (18% in arm A and 25.8% in arm B). This low rate of recurrence could be partly explained by the selection of patients with no residual tumour post-surgery. Moreover, the 36-month duration of the study may also have been too short to detect recurrence; however, most cases of recurrence were diagnosed at a median time of 15 months.

In our study, the detection of recurrence by PET/CT tended to be earlier compared to the conventional strategy, yet no statistical significance was observed. However, these results had no impact on OS. Indeed, these results are partly in agreement with those of Sobhani *et al.*²⁵ This trial randomised patients to conventional follow-up, with or without additional PET/CT imaging at 9 and 15 months after primary CRC surgery. Cases of recurrence were detected significantly earlier in the PET group and were surgically treated more frequently, yet without improvement of survival. The difference in results between the two protocols could

be attributable to the inclusion of stage IV CRC (12% of patients) and the addition of PET to the routine follow-up tests in the study of Sobhani *et al.*

Our study highlighted that most cases of recurrence were diagnosed by surveillance in asymptomatic patients, with a metastatic pattern in the majority of cases. Recurrence occurred more often in stage III than in stage II, but with no difference between the two arms. In our study, curative recurrence surgery was performed in 25% of patients in arm A and 36% in arm B. However, we found no statistically significant differences between the two arms in terms of OS at 5 years. The median OS was not reached for the duration of the study. Unexpectedly, detection of a second cancer (10 in arm B and 3 in arm A) permitted a DFCS significantly different from conventional follow-up but did not significantly impact OS.

The main limitation of this study was the low rate of recurrence compared with the projected results. The 3-year recurrence rate in our study was only 18% (37.5% anticipated) in arm A and 25.8% (50% projected) in arm B. With such rates, it would be necessary to enrol 886 patients to obtain a power of 80%, with a prohibitive cost. In our study (376 patients), the examinations in arm B were four times as expensive as those in arm A. Another limitation was the impact of additional non-protocolary imaging (including PET) performed by specialists in all centres, reflecting real life of follow-up habits. Furthermore, biological prognostic factors of colon cancer recurrence, as proposed recently by Yamano,²⁶ were not available. We hypothesise that PET/CT follow-up would be more appropriate in selected patients with a poor prognosis for CRC.

The main strength of this trial was the early, post-initial surgery, inclusion of patients. In our study, all PET/CT were reviewed by the nuclear medicine team and showed high sensitivity and specificity of 88.6% and 92.1%, respectively, for the detection of recurrent disease. PET/CT has been previously reported to provide a sensitivity of 89–98% and a specificity of

83–96% for detection of recurrence in patients with CRC.^{27–30} A meta-analysis including 487 patients showed a pooled sensitivity of 91% and specificity of 91% for PET/CT.¹⁰ For detection of locoregional recurrence and lymph node metastases, PET/CT was superior to other imaging modalities.^{31, 32}

CONCLUSION

In conclusion, disease recurrence at the 3-year follow-up occurred in less than 30% of patients after curative surgery. Compared to conventional follow-up, PET/CT detected more cases of recurrence, but the difference was not statistically significant. Furthermore, more indolent second cancers were detected by PET/CT compared to conventional follow-up; however, this did not impact OS. At this time, there is not enough evidence to support the routine use of PET/CT every 6 months as an alternative strategy.

ADDITIONAL INFORMATION

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Ethics approval and consent to participate

Clinical data were collected in accordance with French bioethics laws regarding patient information and consent. The study was performed in accordance with the Declaration of

Helsinki. Data collection and use were approved by the Limoges Hospital Ethics Committee (approval number 03-024).

Consent for publication

Not applicable.

Data availability

The datasets used or analysed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

NTM, JM, JFS, DS, SLD, and OM participated in the conception and design. All authors participated in the data acquisition. AL performed the statistical analysis. NTM, SLD, ED, and JM analysed the data. NTM and JM supervised the work. NTM, JM, SLD, AL, and ED were the major contributors to writing the manuscript. All authors contributed to the manuscript, critically revised it, and approved its final version.

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TABLE AND FIGURE LEGENDS

Figure 1. Flowchart

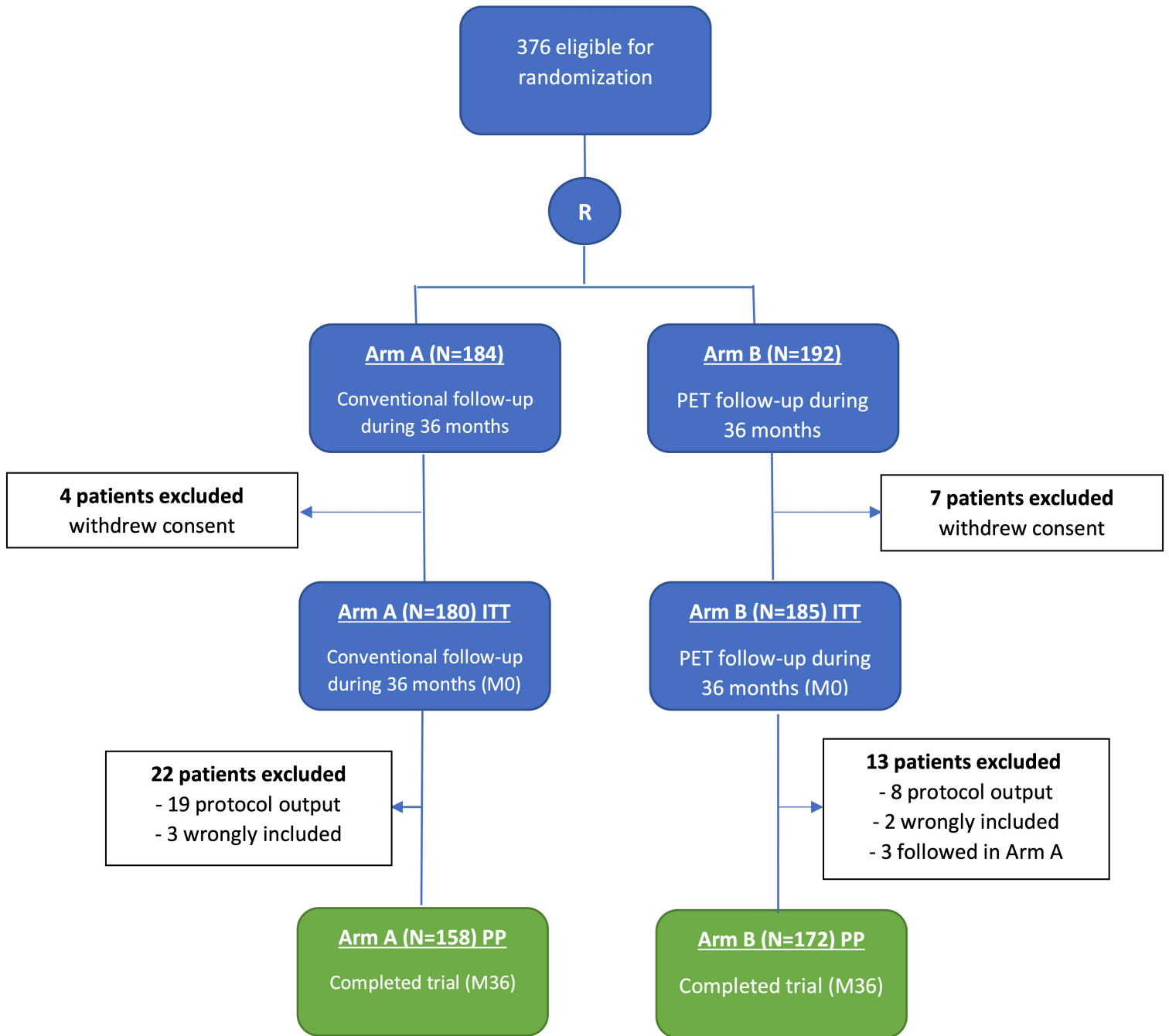
Figure 2. A Disease-free survival (intention-to-treat) at 36 months; B Disease-free survival (per protocol) at 36 months; C Disease-free cancer survival (intention-to-treat) at 36 months; D Overall survival (intention-to-treat) at 60 months

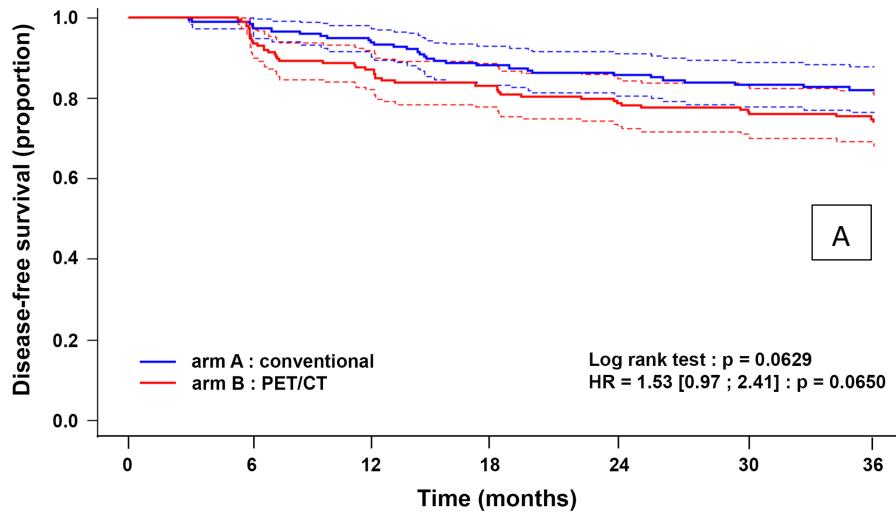
Table 1. Patient characteristics at baseline (N = 365)

Table 2. Diagnosis of recurrences by randomisation group (intention-to-treat)

Table 3. Screening method for recurrence detection (N = 78)

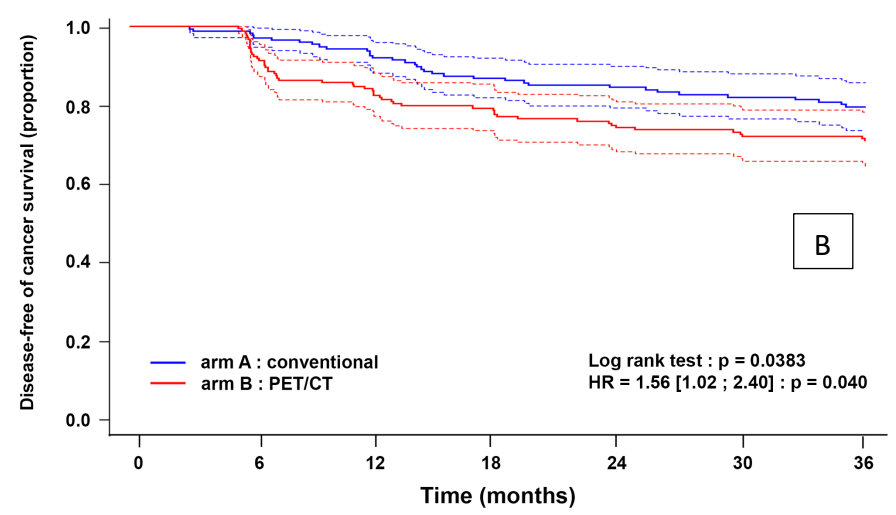
Table 4. Additional colonoscopies





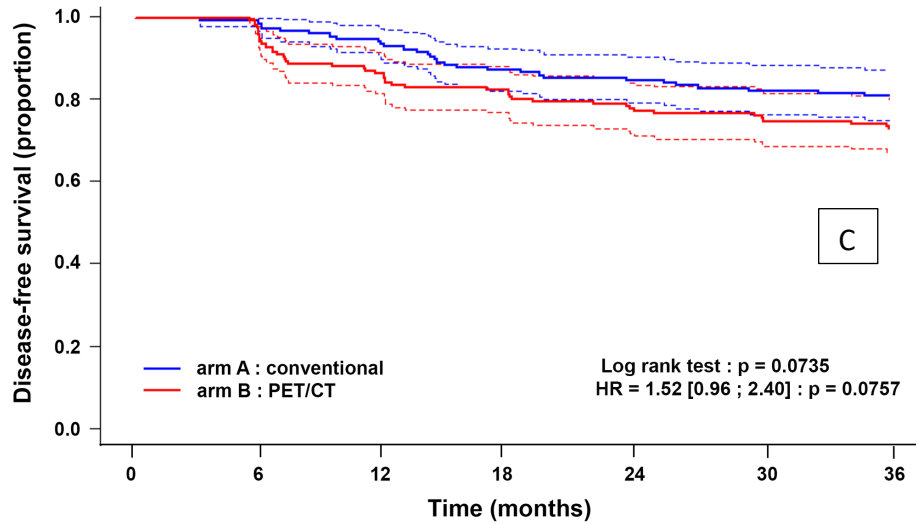
Number at risk

	0	6	12	18	24	30	36
arm A	180	174	164	152	143	135	131
arm B	184	174	156	149	139	135	131



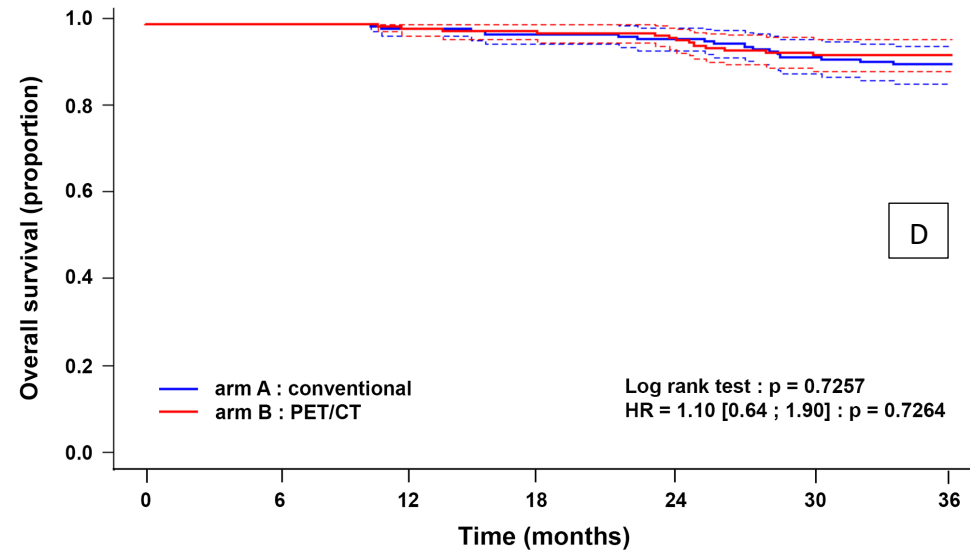
Number at risk

	0	6	12	18	24	30	36
arm A	180	174	162	150	141	133	127
arm B	184	172	152	142	133	130	127



Number at risk

	0	6	12	18	24	30	36
arm A	158	156	147	138	134	130	127
arm B	171	162	144	138	132	129	126



Number at risk

	0	6	12	18	24	30	36
arm A	178	175	173	168	162	151	146
arm B	181	181	179	176	170	164	163

Table 1. Patient characteristics at baseline (N=365)

	All patients (n=365)	Arm A (n=180)	Arm B (n=185)
Age, years, median (min-max)	65 (26 – 87)	65 (30 – 87)	64 (26 – 86)
Sex, n (%)			
Male	200 (54.8)	93 (51.7)	107 (57.8)
Female	165 (45.2)	87 (48.3)	78 (42.2)
Stage, n (%)			
I	2 (0.5)	2 (1.1)	0 (0.0)
II	176 (48.2)	86 (47.8)	90 (48.6)
III	185 (50.7)	91 (50.6)	94 (50.8)
IV	2 (0.5)	1 (0.5)	1 (0.6)
Time between cancer diagnosis and protocol inclusion (months), median (min-max)	2.8 (0.5 – 15.6)	2.8 (0.7 – 15.6)	2.7 (0.5 – 8.7)
Tumour location, n (%)			
colon	290 (79.4)	147 (91.7)	143 (77.3)
rectum	75 (20.6)	33 (18.3)	42 (22.7)
Treatment, n (%)			
Adjuvant Chemotherapy	276 (75.6)	133 (73.9)	143 (77.3)
Radiotherapy pre-surgery	51 (14.0)	21 (11.7)	30 (16.2)
Surgery alone	38 (10.4)	26 (14.4)	12 (6.5)

Table 2. Diagnosis of recurrences by randomization group (ITT analysis)

Recurrence type (n=78)	A ARM (n=31)	B ARM (n=47)
Locoregional, n (%)		
• Colon	3 (9.6)	9 (19.1)
• Rectum	1 (3.2)	1 (2.1)
Metastatic, n (%)		
• Colon	22 (70.9)	26 (55.3)
• Rectum	5 (16.1)	11 (23.4)

Table 3. Screening method for recurrences detection (N=78)

PROCEDURE	All patients (n=78)	ARM A (n=31)	Arm B (n=47)
Colonoscopy, n (%)	3 (3.8)	2 (6.4)	1 (2.1)
Echography, n (%)	6 (7.7)	6 (19.3)	0 (0.0)
Clinical exam, n (%)	1 (1.3)	1 (3.2)	0 (0.0)
MRI, n (%)	1 (1.3)	1 (3.2)	0 (0.0)
Markers, n (%)	12 (15.4)	11 (35.5)	1 (2.1)
CT-Scan, n (%)	11 (14.1)	8 (25.8)	3 (6.4)
¹⁸ FDG-PET, n (%)	44 (56.4)	2 (6.4)	42 (89.4)

Table 4. Additional colonoscopies

	ARM A (n=180)	ARM B (n=185)
1 additional colonoscopy,	82 (45.5)	80 (43.2)
For polyps	19 (10.6)	13 (7.0)
Suspicion Recurrence	13 (7.2)	31 (16.8)
CT Toxicities or intercurrent pathology	0 (0.0)	6 (3.2)
Specialist decision	50 (27.7)	30 (16.2)
2 additional colonoscopies	11 (6.1)	18 (9.7)
For polyps	3 (1.6)	6 (3.2)
Suspicion Recurrence	3 (1.6)	8 (4.3)
CT Toxicities or intercurrent pathology	0 (0.0)	2 (1.1)
Specialist decision	5 (2.7)	2 (1.1)
3 additional colonoscopies	1 (0.5)	6 (3.2)
For polyps	1 (0.5)	1 (0.5)
Suspicion Recurrence	0 (0.0)	2 (1.1)
CT Toxicities or intercurrent pathology	0 (0.0)	3 (1.6)