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^{18}F-fluorodeoxyglucose positron-emission tomography-computed tomography to diagnose recurrent cancer

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Background: Sometimes the diagnosis of recurrent cancer in patients with a previous malignancy can be challenging. This prospective cohort study assessed the clinical utility of ^{18}F-fluorodeoxyglucose positron-emission tomography-computed tomography (^{18}F-FDG PET-CT) in the diagnosis of clinically suspected recurrence of cancer.

Methods: Patients were eligible if cancer recurrence (non-small-cell lung (NSCL), breast, head and neck, ovarian, oesophageal, Hodgkin's or non-Hodgkin's lymphoma) was suspected clinically, and if conventional imaging was non-diagnostic. Clinicians were asked to indicate their management plan before and after ^{18}F-FDG PET-CT scanning. The primary outcome was change in planned management after ^{18}F-FDG PET-CT.

Results: Between April 2009 and June 2011, 101 patients (age, median 65 years; 55% female) were enroled from four cancer centres in Ontario, Canada. Distribution by primary tumour type was: NSCL (55%), breast (19%), ovarian (10%), oesophageal (6%), lymphoma (6%), and head and neck (4%). Of the 99 subjects who underwent ^{18}F-FDG PET-CT, planned management changed after ^{18}F-FDG PET-CT in 52 subjects (53%, 95% confidence interval (CI), 42–63%); a major change in plan from no treatment to treatment was observed in 38 subjects (38%, 95% CI, 29–49%), and was typically associated with ^{18}F-FDG PET-CT findings that were positive for recurrent cancer (37 subjects). After 3 months, the stated post-^{18}F-FDG PET-CT management plan was actually completed in 88 subjects (89%, 95% CI, 81–94%).

Conclusion: In patients with suspected cancer recurrence and conventional imaging that is non-diagnostic, ^{18}F-FDG PET-CT often provides new information that leads to important changes in patient management.

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Rising cancer incidence and advances in cancer therapy have resulted in a high prevalence of patients who have no apparent residual disease after initial treatment (Edwards *et al*, 2002; Canadian Cancer Society's Steering Committee on Cancer Statistics, 2011). When such patients have new symptoms or physical findings, the possibility of recurrence is raised. Imaging with X-ray, computed tomography (CT), magnetic resonance imaging (MRI) or nuclear scanning is often performed to diagnose recurrence. However, even after conventional imaging, the diagnosis of recurrence may remain elusive.

^{18}F-fluorodeoxyglucose positron-emission tomography-CT (^{18}F-FDG PET-CT) may be helpful in the diagnosis of recurrent cancer. However, most studies addressing ^{18}F-FDG PET-CT for this purpose have been small, retrospective, single-centre case series (Dittmann *et al*, 2001; Jerusalem *et al*, 2003; Vansteenkiste *et al*, 2004; Isasi *et al*, 2005; Hauth *et al*, 2005; Yen *et al*, 2005; Zimmer *et al*, 2005; Bjurberg *et al*, 2006; Guo *et al*, 2007; Israel and Kuten, 2007; Thrall *et al*, 2007; Roedl *et al*, 2008). Moreover, while these studies generally reported sensitivity and specificity of ^{18}F-FDG PET-CT, they rarely reported on the impact of ^{18}F-FDG PET-CT on clinical management decisions. In the US National Oncologic PET Registry (NOPR), PET was reported to have led to changes in planned management for 39% of patients who had received PET for suspected cancer recurrence (Hillner *et al*, 2008). However, there was no prospective follow-up of patients after PET. Whether the intended post-PET management plans were actually carried out is unclear and was only verified through linkage to administrative billing data (Hillner *et al*, 2013). Furthermore, many patients in the study may not have been fully investigated with conventional imaging before PET; therefore, the impact of ^{18}F-FDG PET-CT beyond conventional imaging in the diagnosis of patients with suspected cancer remains unclear.

Despite these uncertainties, ^{18}F-FDG PET-CT scanning has been adopted in many jurisdictions for the evaluation of patients with suspected cancer recurrence, and the rapid uptake and diffusion of ^{18}F-FDG PET-CT has outpaced efforts to rigorously evaluate its clinical utility (Israel and Kuten, 2007). We conducted a multi-centre, prospective cohort study to assess the impact of ^{18}F-FDG PET-CT on the clinical management of patients with suspected cancer recurrence and inconclusive findings on conventional imaging. This study was part of a field evaluation programme in the province of Ontario, Canada to assess the clinical utility of PET in oncology (Evans *et al*, 2009). We hypothesised that, in patients with suspected recurrence of cancer and non-diagnostic conventional imaging, ^{18}F-FDG PET-CT would provide new information that could lead to important changes in planned management.

MATERIALS AND METHODS

Design. We conducted a prospective, multi-centre, cohort study.

Participants. Patients with a history of cancer presenting with a clinical suspicion of recurrence in which conventional imaging (e.g., X-ray, ultrasound, CT, MRI and nuclear medicine bone scan) was non-diagnostic were eligible. Decisions about eligibility were made locally by the treating physicians: to be eligible for entry into the study, there needed to be a clinical suspicion of recurrent cancer. Clinical suspicion was often based on a constellation of symptoms, signs and blood tests. Then conventional imaging tests would have been performed and read by expert radiologists. If the treating physician was still uncertain about the diagnosis of recurrence, the patient was eligible for enrolment. Sometimes patients with previous malignancies are followed with regular surveillance after surgery, for example, CT scans for non-small-cell lung (NSCL) cancer or colorectal cancer. Occasionally, a new abnormality would appear on the CT scan, which was considered too small or nonspecific to be diagnostic for recurrence. These patients were also eligible. Eligible cancer types were NSCL, breast, head and neck (not thyroid), ovarian, oesophageal or lymphoma (Hodgkin's or non-Hodgkin's). Patients were excluded if: they were <18 years of age, had an established diagnosis of recurrent cancer, had undergone ^{18}F-FDG PET-CT in the 6 months prior to registration, were unable to lie supine for ^{18}F-FDG PET-CT, were pregnant or lactating, had significant medical problems making the patient unfit for further cancer therapy or were unable to give informed consent. Patients were recruited from four regional cancer centres in Ontario. The study was approved by the Ontario Cancer Research Ethics Board and patients provided written informed consent. The study was registered with ClinicalTrials.gov (NCT00686465).

Procedures. At enrolment, baseline clinical data were collected and, before the ^{18}F-FDG PET-CT scan was performed, the treating physician was required to indicate their intended management had ^{18}F-FDG PET-CT not been available (clinical follow-up, additional imaging after a period of time, tissue biopsy or treatment for recurrence).

Subjects then underwent ^{18}F-FDG PET-CT. After ^{18}F-FDG PET-CT, treating physicians were asked to indicate their management plan after considering the ^{18}F-FDG PET-CT findings. The study protocol left decisions about management after ^{18}F-FDG PET-CT to the discretion of the treating physician and the patient.

Subjects underwent a follow-up visit at 3 months post-registration to record data about further testing, biopsies, and treatments since registration. The principal aim of the follow-up visit was to confirm whether the physician's post-^{18}F-FDG PET-CT management plan had been carried out.

^{18}F-FDG PET-CT imaging. ^{18}F-FDG PET-CT scanners had to meet specified performance criteria and underwent quality control evaluation on each day imaging was performed. The ^{18}F-FDG PET-CT scanners, with full-ring bismuth germanate detectors, were: a Discovery ST 64 (General Electric, Waukesha, WI, USA) in London, Ontario, Canada, a Biograph Duo (CTI/Siemens, Knoxville, TN, USA) at Princess Margaret Hospital, a Biograph 16 (Siemens, Knoxville, TN, USA) at St Joseph's Healthcare Hamilton and a 64 slice Gemini TF with lutetium-yttrium orthosilicate detectors (Philips Electronics NV, Eindhoven, Netherlands) in Thunder Bay. To ensure consistent exam quality across all sites, studies were performed using the NEMA NU2-2001 phantom (Data Spectrum Corporation, Hillsborough, NC, USA) to verify calibration inaccuracy, to verify reconstructed image resolution <10 mm full width half maximum and to qualify reconstruction methods at each site. Acquisition protocols were developed at each site to meet a minimum patient noise equivalent counts of >30 Mcounts per m ($\pm 10\%$). Compliance was assured by monthly monitoring and quarterly review by a Quality Assurance Subcommittee. Quality assurance procedures included independent second reading by a nuclear medicine physician of a randomly selected subset of 12 ^{18}F-FDG PET-CT scans.

^{18}F-FDG PET-CT was performed after a 6-hour fast; blood glucose was required to be $<10\,\mathrm{mmol\,l^{-1}}$ prior to i.v. administration of ^{18}F-FDG ($5\,\mathrm{MBq\,kg^{-1}}$, not exceeding 550 MBq). PET acquisition was preceded by a low-dose CT, and a whole body ^{18}F-FDG PET-CT scan in supine position was obtained from the base of the skull to the upper half of both femurs. The examination was interpreted by the nuclear medicine physician with knowledge of the clinical history and access to correlative imaging.

Outcomes. The primary outcome was change in planned management after ^{18}F-FDG PET-CT. We further defined a major change in planned management as a change from a pre-^{18}F-FDG PET-CT plan, which did not include treatment to a post-^{18}F-FDG PET-CT

plan which did include treatment. The primary outcome was adjudicated using all available source documents (e.g., clinic notes and imaging reports). Adjudicators also used all available source documents to assess whether, at the 3-month follow-up: (i) planned management was carried out; (ii) further testing or procedures were avoided because of ^{18}F-FDG PET-CT findings and (iii) ^{18}F-FDG PET-CT led to further testing or interventions that were unnecessary. Adjudication was conducted independently and in duplicate by two experienced oncologists (KIP and ISD) not otherwise involved in the conduct of the study. For subjects who terminated the study early, adjudicators used all information available at the time of withdrawal.

Statistical considerations. This study was initially conceived as a pilot to gauge the feasibility of conducting a randomised controlled trial (RCT) of ^{18}F-FDG PET-CT in patients with suspected cancer recurrence. After the pilot was activated at all sites, 35 subjects were enroled in 6 months. Based on this result, the Steering Committee judged that an RCT would be challenging and recruitment of a larger number of patients into the cohort would be prudent. A sample size of 100 subjects would provide a two-sided 95% confidence interval (CI) about an estimated proportion of 0.5 for the primary outcome of ± 0.10, which we judged to be an acceptable level of precision.

For the primary outcome, we calculated the proportion of subjects for whom there was a change in planned management after ^{18}F-FDG PET-CT, and the associated exact binomial 95% CI. Subjects who did not receive ^{18}F-FDG PET-CT were excluded from these analyses.

To evaluate the contribution of ^{18}F-FDG PET-CT to clinical management, we examined the distribution of subjects with a major change, minor change or no change in planned management according to imaging findings on ^{18}F-FDG PET-CT (negative, positive or indeterminate).

RESULTS

Between April 2009 and June 2011, 123 potentially eligible patients were identified. After excluding 2 patients who had undergone ^{18}F-FDG PET-CT in the past 6 months, 17 patients with established recurrence of cancer and 3 patients who did not consent, 101 patients were enroled (Table 1). Subjects had a median age of 65 years, 55% were female and the most common type of cancer (55%) was NSCL cancer. The median number of conventional imaging tests that had been performed to rule out recurrence was 2. Most frequently, CT imaging was non-diagnostic (84 subjects, 83%). Of the 101 subjects enroled, 99 underwent ^{18}F-FDG PET-CT. Of these, 93 subjects completed 3 months of follow-up and the remaining 6 subjects terminated the study early (5 died and 1 was non-adherent) (Figure 1).

Impact of ^{18}F-FDG PET-CT on planned management. Planned management was changed after ^{18}F-FDG PET-CT in 52 subjects (53%, 95% CI, 42–63%); this was a major change in intended management for 38 subjects (38%, 95% CI, 29–49%) and a minor change for 14 subjects (14%, 95% CI, 8–23%) (Table 2). Chance-corrected inter-observer agreement between the adjudicated assessment and the treating physician's assessment of whether ^{18}F-FDG PET-CT changed planned management was high (κ 0.80, 95% CI, 0.68–0.91).

Had ^{18}F-FDG PET-CT not been available, the most common management plan would have been to schedule repeat imaging after waiting a period of time (57 subjects): either as soon as possible ($n=8$), within 1 month ($n=5$), in 3 months ($n=41$), in 6 months ($n=2$) or in 9 months ($n=1$). The next most common management plan, had ^{18}F-FDG PET-CT not been available, was to either pursue a tissue biopsy (28 subjects) or to re-evaluate the patient in clinical follow-up (11 subjects), the latter typically in 3 months ($n=10$). The most frequent change in planned management after ^{18}F-FDG PET-CT was to initiate treatment, rather than pursue additional imaging (Figure 2; Table 3). Of the 38 subjects who had a major change in intended management (i.e., plan changed to treatment after ^{18}F-FDG PET-CT), the plan was to provide palliative treatment in 26 and potentially curative salvage treatment in 12.

Table 1. Characteristics of study cohort ($N=101$)

Characteristic	
Age in years, median (range)	65 (27–90)
Female, *n* (%)	56 (55)
Primary tumour type: *n* (%)	
Non-small-cell lung cancer	56 (55)
Breast cancer	19 (19)
Ovarian cancer	10 (10)
Oesophageal cancer	6 (6)
Lymphoma	6 (6)
Head and neck cancer	4 (4)
Years since primary cancer diagnosis, median (range)	2.1 (0.3–21.4)
Years since last cancer treatment, median (range)	1.3 (0–10.0)
Reason for suspecting recurrence[a]: *n* (%)	
New symptoms	45 (45)
New physical findings	14 (14)
Diagnostic imaging results	95 (94)
Abnormal laboratory test results	9 (9)
Pre-test probability of recurrence[b]: *n* (%)	
0–19%	7 (7)
20–39%	19 (19)
40–59%	51 (51)
60–79%	11 (11)
80–100%	13 (13)

[a]Subjects may fall into more than one category.
[b]According to treating clinician.

Relation of findings on ^{18}F-FDG PET-CT to changes in planned management and biopsy results. Of the 38 subjects whose management plan changed to treatment after ^{18}F-FDG PET-CT, most had findings on ^{18}F-FDG PET-CT imaging that was positive for recurrent cancer (37 subjects); the 1 remaining subject had indeterminate findings on ^{18}F-FDG PET-CT (Figure 2).

Overall, findings of recurrent cancer on ^{18}F-FDG PET-CT were associated with appreciable changes in planned management (Figure 2). In the 57 subjects whose pre-PET management plan was for repeat imaging after a period of time, ^{18}F-FDG PET-CT was positive for recurrent cancer in 35, negative in 12 and indeterminate in 10 subjects. Positive findings on ^{18}F-FDG PET-CT typically led to changes in planned management. Plans were changed for most of the 35 subjects with positive findings on ^{18}F-FDG PET-CT to either initiate treatment (23 subjects) or to pursue tissue biopsy (8 subjects). In contrast, planned management was largely unchanged after ^{18}F-FDG PET-CT for the 22 subjects with negative or indeterminate findings. In the eight subjects with a post-PET plan to pursue tissue biopsy: four had a biopsy positive for malignancy, one had a biopsy negative for malignancy, two declined a biopsy and one ultimately did not receive a biopsy because the surgical consultant felt recurrence was unlikely based on all available clinical information.

In the 28 subjects whose pre-PET management plan was for tissue biopsy, ^{18}F-FDG PET-CT was positive for recurrent cancer in 22, negative in 2 and indeterminate in 4 subjects. Management plans for the 22 subjects with positive findings on ^{18}F-FDG PET-CT changed to initiate treatment in 10 cases. For 11 other subjects with positive findings on ^{18}F-FDG PET-CT, the plan after ^{18}F-FDG PET-CT was unchanged: all 11 subjects went on to receive a biopsy and in all cases results were positive for malignancy.

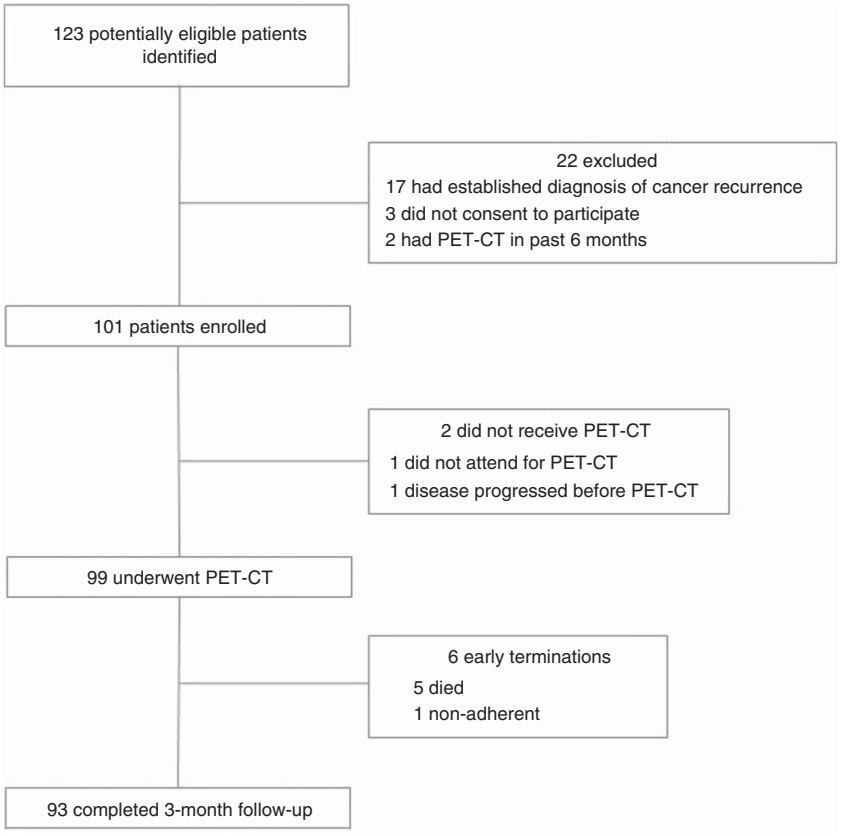


Figure 1. Study flow diagram.

Table 2. Impact of ^{18}F-FDG PET-CT on planned management ($N = 99$)

	Cancer subtype							
	NSCL ($n = 56$)	Breast ($n = 19$)	H&N ($n = 3$)	Ovarian ($n = 10$)	Oesophageal ($n = 5$)	Lymphoma ($n = 6$)	Total ($N = 99$)	
Outcome	*n* (%)						*n* (%)	95% CI
No change	24 (43)	11 (58)	2 (67)	3 (30)	3 (60)	4 (67)	47 (47)	37–58%
Any change	32 (57)	8 (42)	1 (33)	7 (70)	2 (40)	2 (33)	52 (53)	42–63%
Major change[a]	28 (50)	4 (21)	1 (33)	4 (40)	0	1 (17)	38 (38)	29–49%
Minor change:	4 (7)	4 (21)	0	3 (30)	2 (40)	1 (17)	14 (14)	8–23%
Clinical or imaging follow-up to biopsy	2 (4)	2 (11)	0	3 (30)	2 (40)	0	9 (9)	4–17%
Imaging to clinical follow-up	0	2 (11)	0	0	0	0	2 (2)	0–7%
Biopsy to clinical or imaging follow-up	2 (4)	0	0	0	0	1 (17)	3 (3)	1–9%

Abbreviations: CI = confidence interval; H&N = head and neck; NSCL = non-small-cell lung; ^{18}F-FDG PET-CT = ^{18}F-fluorodeoxyglucose positron-emission tomography-computed tomography.
[a]From no treatment to treatment.

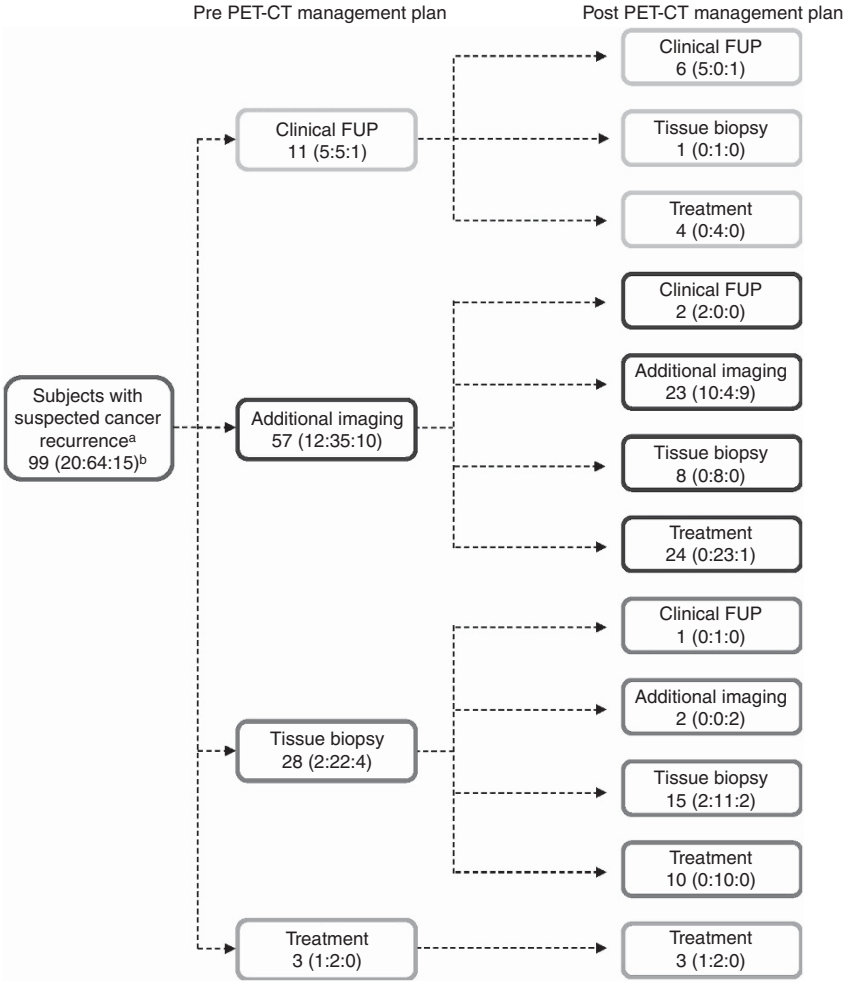
In the 11 subjects whose pre-PET management plan was clinical follow-up after a period of time, ^{18}F-FDG PET-CT was positive for recurrent cancer in 5, negative in 5 and indeterminate in 1. Management plans for the five subjects with positive findings on ^{18}F-FDG PET-CT changed to initiate treatment (four subjects) or to pursue tissue biopsy (one subject). The latter subject ultimately did not receive a biopsy because the lesion was too small to biopsy and the subject declined wedge resection.

Actual management after ^{18}F-FDG PET-CT. After 3 months, the stated post-PET management plan was completed in 88 subjects (89%, 95% CI, 81–94%). There were six subjects who had a change in planned management after ^{18}F-FDG PET-CT but who did not receive the intended treatment during follow-up: one died prior to planned treatment; two declined to proceed with the proposed plan; for one subject, the surgical consultant felt that the planned biopsy was not necessary; for another, the planned biopsy was not feasible and the subject declined to have wedge resection; one subject was non-adherent.

At the 3-month follow-up, findings on ^{18}F-FDG PET-CT were judged to have resulted in the avoidance of further tests for 34 subjects (34%), and resulted in unnecessary testing for 3 subjects (3%).

DISCUSSION

In this multi-centre, prospective cohort study of patients with suspected recurrence of cancer and non-diagnostic conventional imaging, ^{18}F-FDG PET-CT provided new information that led to



[a] This figure excludes the 2 subjects who did not go on to receive PET-CT
[b] PET-CT result (negative: positive: unclear)

Figure 2. Relation of findings on PET-CT to changes in planned management.

Table 3. Comparison of pre- and post-^{18}F-FDG PET-CT management plans

	Pre-^{18}F-FDG PET-CT management plan[a]				
Post-^{18}F-FDG PET-CT management plan[a]	**Clinical follow-up**	**Additional imaging**	**Tissue biopsy**	**Treatment**	**Total**
Clinical follow-up	**6**	2	1	0	9
Additional imaging	0	**23**	2	0	25
Tissue biopsy	1	8	**15**	0	24
Treatment	4	24	10	**3**	41
Total	11	57	28	3	**99**

Abbreviation: ^{18}F-FDG PET-CT = ^{18}F-fluorodeoxyglucose positron-emission tomography-computed tomography. The diagonal bolded numbers (except the total) represent the unchanged cases.
[a]Number of subjects.

major changes in planned management (i.e., from no treatment to treatment) in about one in three patients.

Strengths of our study include prospective collection of data regarding physicians' intended management; independent, central adjudication of the primary outcome and inclusion of a 3-month follow-up period to validate that post-^{18}F-FDG PET-CT management plans were actually carried out. Our study also has limitations. First, tissue biopsy was not mandated by the study protocol. In some cases, a positive ^{18}F-FDG PET-CT scan may have provided the treating physician with just enough evidence to take an easier pathway, avoid biopsy and institute treatment. Because of this limitation, it is possible that some subjects could have received unnecessary treatment for a false positive finding on ^{18}F-FDG PET-CT. Second, the assessment of eligibility required the local treating physician to make a clinical judgment about the presence of 'non-diagnostic' conventional imaging results. To the extent that local treating physicians enroled patients in whom recurrence was very probable, such entry bias could have resulted in an overestimate of the impact of ^{18}F-FDG PET-CT on planned management. However, our observation that pre-test probability of

disease was 20–79% for the majority of subjects (81%) in our study cohort suggests that there was appreciable uncertainty about the diagnosis of recurrence for most of the study subjects. Third, data on health resource utilisation after ^{18}F-FDG PET-CT were not collected. As a result, we are not able to assess the economic attractiveness of ^{18}F-FDG PET-CT when added to conventional imaging in the diagnostic evaluation of patients with suspected cancer recurrence. However, adjudication of 3-month follow-up data suggests that ^{18}F-FDG PET-CT led to avoidance of further testing rather than triggering unnecessary follow-up testing. Finally, our focus was to assess the impact of ^{18}F-FDG PET-CT on clinical decision making and we did not include a control group, which would have enabled evaluation of the additional potential benefits of ^{18}F-FDG PET-CT other outcomes, such as reduced anxiety for patients if recurrence can be excluded and improvements in overall survival due to earlier initiation of treatment.

The main impact of ^{18}F-FDG PET-CT on clinical decision making in our study was to shift planned management from non-treatment to treatment, typically as a result of positive findings on ^{18}F-FDG PET-CT. It is interesting to note, however, that there were several subjects with positive findings on ^{18}F-FDG PET-CT for whom the post-test management plan was for tissue biopsy rather than treatment. This differential effect of ^{18}F-FDG PET-CT imaging findings on planned management reflects the inherent complexity of clinical decision making when recurrence is suspected. In particular, there are numerous factors that may have influenced treating physicians' and patients' test *vs* treatment thresholds, including anatomical considerations (e.g., technical feasibility of obtaining a biopsy), the burdens or toxicity of biopsy *vs* treatment in each individual case and the physicians' and patients' comfort making decisions to treat under conditions of uncertainty.

Our findings are consistent with the US NOPR study, which reported that PET changed planned management for 39% of the 5388 patients enroled in the study for suspected recurrence of cancer (Hillner *et al*, 2008). Although the NOPR study was large, it also had important limitations. First, no clinical follow-up data were obtained to assess whether post-PET management plans described by treating physicians were actually carried out. A subsequent analysis of NOPR data linked to Medicare claims data, within the subset of patients enroled for initial cancer staging, suggests that stated management plans are carried out in 64–79% of cases at 60 days follow-up (Hillner *et al*, 2013). However, administrative billing data may be incomplete or inaccurate and only provide inferences about subsequent care. Our study addresses this limitation by demonstrating that, based on centrally adjudicated assessment at 3-month follow-up, the majority (89%) of planned management after ^{18}F-FDG PET-CT was carried out. Furthermore, collection of detailed clinical data during follow-up enabled us to understand the reasons planned management was not carried out. Second, many patients enroled in NOPR may not have been fully investigated with conventional imaging before ^{18}F-FDG PET-CT was done. As a result, the true impact of ^{18}F-FDG PET-CT over and above conventional imaging in the evaluation of patients with suspected cancer recurrence was unclear. Our study extends knowledge in this field by demonstrating the incremental value of ^{18}F-FDG PET-CT in this clinical setting. Given these benefits, RCTs directly comparing ^{18}F-FDG PET-CT to conventional imaging are warranted to determine whether ^{18}F-FDG PET-CT can replace conventional imaging in the initial evaluation of patients presenting with suspected cancer recurrence.

In conclusion, our findings indicate that, in patients with suspected cancer recurrence and conventional imaging that is non-diagnostic, ^{18}F-FDG PET-CT often provides new information that leads to important changes in patient management.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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