Chest CT scan plus x-ray versus chest x-ray for the follow-up of completely resected non-small-cell lung cancer (IFCT-0302): a multicentre, open-label, randomised, phase 3 trial

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Summary

Background Even after resection of early-stage non-small-cell lung cancer (NSCLC), patients have a high risk of developing recurrence and second primary lung cancer. We aimed to assess efficacy of a follow-up approach including clinic visits, chest x-rays, chest CT scans, and fibre-optic bronchoscopy versus clinical visits and chest x-rays after surgery for resectable NSCLC.

Methods In this multicentre, open-label, randomised, phase 3 trial (IFCT-0302), patients aged 18 years or older and after complete resection of pathological stage I–IIIA NSCLC according to the sixth edition of the TNM classification were enrolled within 8 weeks of resection from 122 hospitals and tertiary centres in France. Patients were randomly assigned (1:1) to CT-based follow-up (clinic visits, chest x-rays, thoraco-abdominal CT scans, and fibre-optic bronchoscopy for non-adenocarcinoma histology) or minimal follow-up (visits and chest x-rays) after surgery for NSCLC, by means of a computer-generated sequence using the minimisation method. Procedures were repeated every 6 months for the first 2 years and yearly until 5 years. The primary endpoint was overall survival analysed in the intention-to-treat population. Secondary endpoints, also analysed in the intention-to-treat population, included disease-free survival. This trial is registered with ClinicalTrials.gov, NCT00198341, and is active, but not enrolling.

Findings Between Jan 3, 2005, and Nov 30, 2012, 1775 patients were enrolled and randomly assigned to a follow-up group (888 patients to the minimal follow-up group; 887 patients to the CT-based follow-up group). Median overall survival was not significantly different between follow-up groups (8·5 years [95% CI 7·4–9·6] in the minimal follow-up group *vs* 10·3 years [8·1–not reached] in the CT-based follow-up group; adjusted hazard ratio [HR] 0·95, 95% CI 0·83–1·10; log-rank p=0·49). Disease-free survival was not significantly different between follow-up groups (median not reached [95% CI not estimable–not estimable] in the minimal follow-up group *vs* 4·9 [4·3–not reached] in the CT-based follow-up group; adjusted HR 1·14, 95% CI 0·99–1·30; log-rank p=0·063). Recurrence was detected in 246 (27·7%) of 888 patients in the minimal follow-up group and in 289 (32·6%) patients of 887 in the CT-based follow-up group. Second primary lung cancer was diagnosed in 27 (3·0%) patients in the minimal follow-up group and 40 patients (4·5%) in the CT-based follow-up group. No serious adverse events related to the trial procedures were reported.

Interpretation The addition of thoracic CT scans during follow-up, which included clinic visits and chest x-rays after surgery, did not result in longer survival among patients with NSCLC. However, it did enable the detection of more cases of early recurrence and second primary lung cancer, which are more amenable to curative-intent treatment, supporting the use of CT-based follow-up, especially in countries where lung cancer screening is already implemented, alongside with other supportive measures.

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For the French translation of the abstrract see **Online** for appendix 1

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Introduction

Approximately 40% of patients with non-small-cell lung cancer (NSCLC) have early stage disease.[1] The standard of care for patients with a good performance status and adequate cardiopulmonary function is surgery with or without perioperative systemic therapy and radiotherapy according to stage. 5-year survival rates after resection range from 41 to 90% according to the pathological stage.[2] The primary cause of death in these patients is lung cancer.[1] They have a risk of developing recurrent disease, increasing with stage and reaching 40% during the first postoperative year in stage IIIA NSCLC,[3] and a

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Research in context

Evidence before this study

After the resection of non-small-cell lung cancer (NSCLC), the relevance of postoperative follow-up and surveillance modalities for patients with lung cancer is still debated. We searched PubMed on Oct 21, 2021, using the search terms "surveillance or follow-up", "lung cancer or NSCLC", and "resection or curative-intent or postoperative or surgery or resected or post-treatment" for full manuscripts published with no language restrictions since 1965. To our knowledge, no published randomised controlled trials to date have attempted to define the role of CT-based patient surveillance after surgery for NSCLC. A recently published systematic review and meta-analysis identified 13 studies involving 5759 patients with stage I–IIIA NSCLC. The benefit of adding chest CT scans could only be evaluated in three studies, showing only that CT scans were associated with the detection of more asymptomatic patients who had developed recurrence.

Added value of this study

To our knowledge, the IFCT-0302 trial is the first phase 3 study to evaluate the effect of chest CT scans on patient survival after complete resection of stage I–IIIA NSCLC. The primary endpoint of overall survival was not met, but this trial shows that CT-based follow-up, including clinic visits, chest x-rays, thoraco-abdominal CT scans, and fibre-optic bronchoscopy for non-adenocarcinoma histology repeated every 6 months for the first 2 years and yearly until 5 years, enables the detection of more cases of early recurrence and second primary lung cancer, which can be treated with curative-intent surgery or radiotherapy, compared with follow-up consisting of only history, physical examination, and chest x-rays.

Implications of all the available evidence

The results of this large, randomised study provide guidance for clinicians and decision makers regarding the follow-up of patients who have undergone surgery for lung cancer. Overall survival was not significantly improved using a CT-based follow-up approach. However, it confirms with a higher level of evidence, the results of non-randomised studies suggesting the detection of more early recurrences or second primary lung cancer with a chest CT follow-up.

cumulative risk of second primary lung cancer of 20% at 10 years.[4,5] Ideally, CT scans can detect cases of early recurrence and second primary lung cancer, whereas curative treatment is still an option and hence might increase the survival rate. However, long-term regular CT scanning is associated with false-positive results and associated consequences, invasive diagnostic procedures and psychological stress, and cumulative radiation risks from repeated CT scans.

Several clinical guidelines for NSCLC patient follow-up recommend regularly scheduled surveillance, including history and physical examination as well as chest CT scanning, every 6 months for the first 2 years after resection and then every year thereafter.[6,7] However, these guidelines are poorly supported by the results of numerous and, at best, prospectively maintained series of surgically treated patients with NSCLC, inconsistently suggesting a potential benefit from thoracic CT scan over chest x-ray.[8–15] Moreover, although non-randomised studies evaluating the effect of postdiagnosis exposures on cancer recurrence, second primary cancer, and survival are crucial, they are also particularly susceptible to multiple biases that might compromise their validity.[16] To our knowledge, there has been no evidence from randomised controlled trials to date that defines the role of CT scan surveillance after surgery for NSCLC.

Here, we report the results of the IFCT-0302 trial, in which we aimed to assess overall survival and follow-up, including clinic visits, chest x-rays and chest CT scans, and fibre-optic bronchoscopy compared with clinical visits and chest x-rays alone, of patients who underwent surgery for stage I–III NSCLC.

Methods

Study design and participants

The IFCT-0302 trial was a multicentre, open-label, randomised, phase 3 trial of follow-up after surgery for NSCLC, conducted in 122 hospitals and tertiary centres in France (appendix 2 pp 14–16). Patients aged 18 years or older with any performance status were eligible for this study within 8 weeks after complete resection of pathological (p) stage I–IIIA NSCLC according to the sixth edition of the TNM classification.[17] Those with pT4 N0–2 NSCLC because of pulmonary nodules located in the same lobe as the primary tumour were also eligible. Anatomical lung resection with microscopical free surgical margins was needed. All perioperative treatments, including preoperative chemotherapy with or without radiotherapy, were permitted. Key exclusion criteria were wedge resection, any formal contra-indication for contrast enhancement including renal insufficiency or allergy, a previous history of breast cancer or melanoma, or another cancer within 5 years (except for basal cell carcinoma of the skin or carcinoma in situ of the uterine cervix). The protocol is available in the appendix 2.

All patients provided written, informed consent. The trial was overseen by an independent data monitoring committee. The study protocol and amendments were approved by the Comité de Protection des Personnes Est II.

Randomisation and masking

Patients were randomly assigned within 8 weeks after surgery (1:1) to the minimal follow-up group (history and

physical examination, and chest x-rays) or the CT-based follow-up group (clinic visits, chest x-rays, thoraco-abdominal contrast-enhanced CT scan, and fibre-optic bronchoscopy). Patients were randomly stratified according to the centre, stage (cI–II *vs* III), histology (adenocarcinomas *vs* others), perioperative chemotherapy (yes *vs* no), and perioperative radiotherapy (yes *vs* no). A randomisation sequence was computer generated by means of the minimisation method, and concealment of group allocation was ensured by use of an automated call centre. This study was open label.

Procedures

In the minimal follow-up group, patients were followed up with clinic visits, including history and physical examination, and chest x-rays. The CT-based follow-up group consisted of clinic visits, chest x-rays, thoraco-abdominal contrast-enhanced CT scan, and fibre-optic bronchoscopy, which was only mandatory in cases of non-adenocarcinoma histology. The choice of the control group was based on the American College of Chest Physicians guidelines, which, at the time of study initiation, recommended surveillance with a medical history, physical examination, and imaging, either chest radiograph or chest CT scan.[18] At the time of study initiation, fibre-optic bronchoscopy was part of the follow-up in many French centres, on the basis of the results of a prospective French series.[8] For both groups, procedures were repeated every 6 months for the first 2 postoperative years and yearly until 5 years or until recurrence or a second primary cancer occurred. In cases involving new symptoms, investigators were allowed to do any procedure as clinically indicated. Additional chest CT scans done in the absence of new symptoms, abnormal physical examination findings, or chest x-ray results were deemed unjustified. Additional chest CT scans for the follow-up of incidental pulmonary nodules were considered as justified.

Recurrences and second primary lung cancers are presented as reported by investigators, who were requested to use the Martini and Melamed definition.[19] A new pulmonary malignancy was considered a second primary cancer if it fulfilled any of the following criteria: pathological results differing between the new lesion and index tumour; same histology but diagnosed at least 2 years after the resected NSCLC; or same pathological result diagnosed within 2 years of the resected tumour but located in a different lobe or lung, with no positive lymph nodes common to both tumours and no evidence of metastasis.

Sites were required to declare to the French Cooperative Thoracic Intergroup any serious adverse event related to trial procedures, assessed according to Common Terminology Criteria for Adverse Events version 3.0.

Outcomes

The primary endpoint was overall survival, defined as the time between random assignment and death from any cause. Secondary endpoints included disease-free survival, survival from recurrence or a second primary cancer, genetic risk factors for lung cancer, health-related quality of life, and cost-effectiveness. The present Article focuses on overall survival, and disease-free survival. Survival from recurrence or a second primary cancer, genetic risk factors, health-related quality of life, and cost-effectiveness will be reported later. Disease-free survival was defined as the time from randomisation to the date of the first documented event, disease recurrence or a second primary cancer, or death in the absence of recurrence or second primary cancer, if they occurred within 5 years after randomisation.[20] For patients who did not develop recurrence or a second primary cancer and who did not die within 5 years after randomisation, disease-free survival was censored at 5 years.

Statistical analysis

The trial was initially designed to detect a difference of 7·5% in the 3-year survival rate, with a 3-year survival rate of 40% in the minimal follow-up group with a two-sided α level of 5%, a power of 90%, and a follow-up of 5 years. A total of 1744 patients were initially required to observe 984 events. The sample size was re-estimated in February, 2013, keeping an unchanged hazard ratio (HR) of 0·812 with a 3-year survival rate of 68% in the minimal follow-up because, unexpectedly, a large majority of the included patients had stage I or II NSCLC. We aimed to observe 987 events in 1680 patients plus 88 patients (to accommodate an attrition rate of 5%) for a total of 1768 patients, with a minimal follow-up of 4 years.

Analyses were done in the intention-to-treat population, defined as all participants included and analysed in the group to which they were originally assigned.

Two interim analyses were planned when one-third and two-thirds of events had occurred, by means of the alpha spending function, with boundaries established according to the method of O'Brien Fleming at the risk α level of 1‰. The analyses were done in December, 2013, with 388 events (39% of planned), and in December, 2015, with 637 events (65%). The external independent data and safety monitoring committee recommended that the final analysis be done with an endpoint date on Nov 30, 2016, with 747 events (75% of planned) and a planned minimal follow-up of 4 years as further events were deemed unlikely to change the results for the primary endpoint.

We estimated disease-free survival and overall survival by means of the Kaplan-Meier method, with follow-up censored on Nov 30, 2016. The follow-up duration was calculated by means of the reverse Kaplan-Meier method. The HRs and 95% CIs for overall survival and disease-free survival were estimated by means of a Cox model adjusted for stratification factors. Verification of the proportional hazards assumption was based on Schoenfeld residuals. Between-group comparisons were done with a log-rank test.

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For more on **standard of care for NSCLC** see https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1450

See **Online** for appendix 2

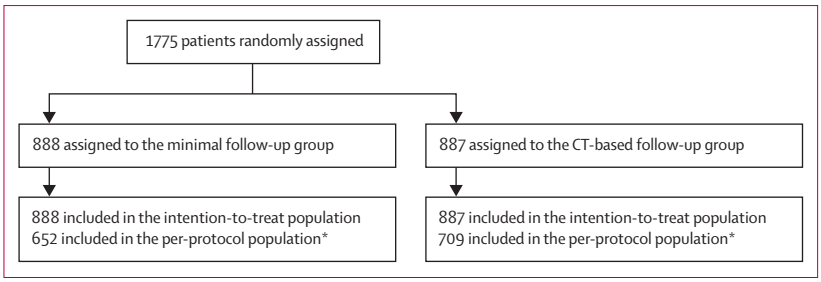

Figure 1: **Trial profile (intention-to-treat population)**
*Patients were excluded from the intention-to-treat population if one or more follow-up visits were missed; patient numbers per timepoint are in the appendix (p 2)

	Minimal follow-up group (n=888)	CT-based follow-up group (n=887)
Sex		
Male	678 (76·4%)	677 (76·3%)
Female	210 (23·6%)	210 (23·7%)
Median age, years (IQR)	63·0 (57·1–70·4)	62·9 (56·2–70·5)
Histological subtype		
Squamous	307 (34·6%)	307 (34·6%)
Adenocarcinoma	520 (58·5%)	522 (58·9%)
Large cell	38 (4·3%)	41 (4·6%)
Others	23 (2·6%)	17 (1·9%)
Smoking status		
Former or current smoker	818 (92·1%)	805 (90·7)
Never smoker	68 (7·7%)	80 (9·0%)
Unknown	2 (0·2%)	2 (0·3%)
Clinical stage		
I	606 (68·2%)	599 (67·5%)
II	119 (13·4%)	125 (14·1%)
III	161 (18·1%)	161 (18·1%)
Unknown	2 (0·2%)	2 (0·3%)
Surgery		
Lobectomy or bilobectomy	758 (85·4%)	775 (87·4%)
Pneumonectomy	111 (12·5%)	95 (10·7%)
Segmentectomy	16 (1·8%)	15 (1·7%)
Unknown	3 (0·3%)	2 (0·2%)
Pathological stage		
I	559 (62·9%)	561 (63·2%)
II	158 (17·8%)	165 (18·6%)
III	163 (18·4%)	152 (17·1%)
Unknown	8 (0·9%)	9 (1·0%)
Preoperative chemotherapy, or preoperative radiotherapy, or both	110 (12·4%)	116 (13·1%)
Postoperative chemotherapy, radiotherapy, or both	342 (38·5%)	350 (39·5%)
Preoperative or postoperative radiotherapy, or both	80 (9·0%)	74 (8·3%)
Preoperative or postoperative chemotherapy, or both	397 (44·7%)	403 (45·4%)

Data are n (%) unless stated otherwise. Data on race or ethnicity were not collected.

Table: **Baseline characteristics (intention-to-treat population)**

Several post-hoc analyses were done, including cancer-specific survival (defined as the time from randomisation to the date of death, with only death from lung cancer being considered as an event) analyses, subgroup overall survival (by sex, age, smoking status, histology, clinical and pathological stage, and perioperative treatment), 3-year and 5-year overall survival, disease-free survival analyses (by clinical and pathological stage, for patients with second primary lung cancers or a distant or intrathoracic recurrence), and an overall survival analysis according to the occurrence of a recurrence or second primary cancer within the first 2 postoperative years. In addition, considering the high proportion of patients with stage I and II NSCLC, who have a lower risk of recurrence, an initially unplanned analysis of overall survival was done by means of a Cox model adjusted for stratification factors but also for recurrence and second primary cancer status (whichever occurred first) as a time-dependent variable. Furthermore, a post-hoc analysis of overall survival and disease-free survival was done in the per-protocol population, which consisted of patients all of whom had planned chest CT scans in the maximal follow-up group and of patients who had no unjustified CT scans in the minimal follow-up group using the Kaplan-Meier method, with follow-up censored on Nov 30, 2016.

All data reported herein are based on the final analysis. For statistical analyses, SAS software (version 9.4) was used, with all p values and CIs being two-sided, with p values of less than 0·05 considered significant. This trial is registered with ClinicalTrials.gov, number NCT00198341.

Role of the funding source

The funding source had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Jan 3, 2005, and Nov 30, 2012, 1775 patients were enrolled and randomly assigned to a follow-up group (minimal follow-up group, 888; CT-based follow-up group, 887; figure 1). 71 patients were ineligible and included in the ITT population (after randomisation) owing to the following: previous history of cancer or synchronous cancer (18 in the minimal follow-up group *vs* 12 in the CT-based follow-up group), incomplete resection (seven *vs* seven), time from surgery greater than 8 weeks (five *vs* six), advanced NSCLC (five *vs* six), and missing written informed consent (four *vs* one).

Patient and treatment characteristics were well balanced between the groups; 1355 (76·3%) of 1775 were men, and the median age was 63·0 years (IQR 56·7–70·5 years); 148 (8·4%) of 1771 were never smokers, 1042 (58·8%) of 1775 had adenocarcinoma, 1205 (68·0%) of 1771 had clinical stage I, 244 (13·8%) of 1771 had clinical stage II, and 322 (18·2%) of 1771 had clinical stage III NSCLC; and 1120 (63·7%) of 1758 had pathological stage I, 323 (18·4%) of 1758 had pathological stage II, and 315 (17·9%) of 1758 had pathological stage III (table). Surgery consisted of lobectomy or bilobectomy in 1533 (86·6%) of 1770 cases,

pneumonectomy in 206 (11·6%), and segmentectomy in 31 (1·8%). Preoperative chemotherapy (plus radiotherapy in 17 patients) was administered in 226 (12·7%) of 1773 patients; postoperative chemotherapy, radiotherapy, or both in 692 (37·2%) of 1772, and postoperative radiotherapy in 138 (7·8%) of 1772. Data on race or ethnicity were not collected.

Among the 888 patients randomly assigned to the minimal follow-up group, 250 chest CT scans were considered unjustified, since they were done in patients with no symptoms and no abnormalities noted during the physical examination or on chest x-rays. They included 56 patients (6·6%) of 850 at 6 months, 38 (5·0%) of 764 at 1 year, 37 (5·5%) of 669 at 18 months, 26 (4·2%) of 615 at 2 years, 34 (6·2%) of 547 at 3 years, 30 (6·3%) of 473 at 4 years, and 29 (7·9%) of 369 at 5 years. Among these 250 unjustified chest CT scans done in the minimal follow-up group, recurrence or second primary cancer was detected in 18 cases. 3813 chest CT scans were done in the 887 patients included in the CT-based follow-up group. The numbers of patients who did not undergo the scheduled follow-up thoracic CT scan were 39 (4·6%) of 848 at 6 months, 30 (4·1%) of 722 at 1 year, 24 (3·9%) of 611 at 18 months, 24 (4·3%) of 557 at 2 years, 28 (5·5%) of 508 at 3 years, 28 (6·4%) of 436 at 4 years, and 28 (8·4%) of 332 at 5 years. Reasons for not undergoing the planned follow-up included patient choice or refusal in 763 (71%) of 1074 of cases, non-adherence to the protocol in 236 (22%) of 1074, and intercurrent disease in 75 (7%) of 1074.

The median follow-up time was 7·2 years (IQR 5·7–9·2) for both groups. 399 (44·9%) patients in the minimal follow-up group and 373 (42·0%) in the CT-based follow-up group died. Median overall survival was not significantly different between follow-up groups (8·5 years [95% CI 7·4–9·6] in the minimal follow-up group *vs* 10·3 years [8·1–not reached] in the CT-based follow-up group; adjusted hazard ratio [HR] 0·95, 95% CI 0·83–1·10; log-rank p=0·49; figure 2; appendix 2 p 3). The 3-year overall survival rates (77·2% [95% CI 74·5–80·0] *vs* 76·1% [73·3–78·9]) and 5-year overall survival rates (66·8% [63·7–69·9] *vs* 65·8% [62·6–68·9]) were also not significantly different (post-hoc analysis). There were no differences in overall survival for any of the subgroups analysed (post-hoc analysis; appendix 2 p 9).

The numbers of recurrences, second primary cancers, or deaths were 404 in the minimal follow-up group and 440 in the CT-based follow-up group. Disease-free survival was not significantly different between follow-up groups (median not reached [95% CI not reached–not reached] in the minimal follow-up group *vs* 4·9 [4·3–not reached] in the CT-based follow-up group, adjusted HR 1·14, 95% CI 0·99–1·30; log-rank p=0·063; figure 3). There were no differences in disease-free survival for any of the subgroups analysed (post-hoc analysis; appendix 2 p 10). Post-hoc analyses in the per-protocol population confirmed these results for overall survival and disease-free survival

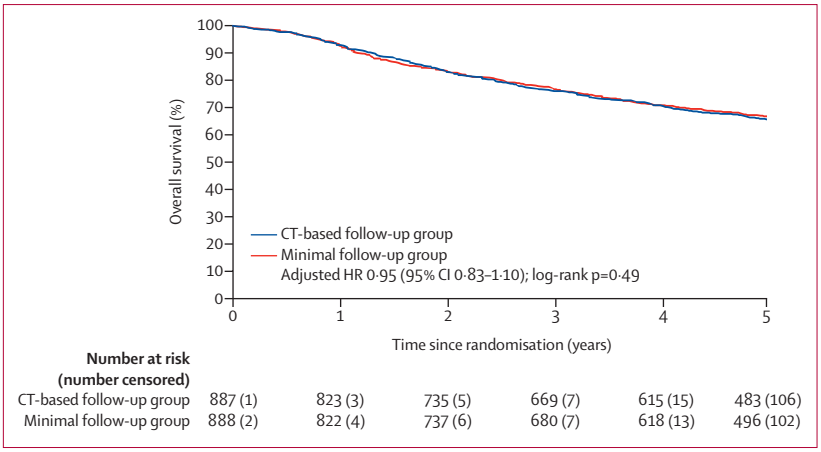

Figure 2: **Kaplan-Meier overall survival curves by follow-up group (intention-to-treat population)**
HR=hazard ratio.

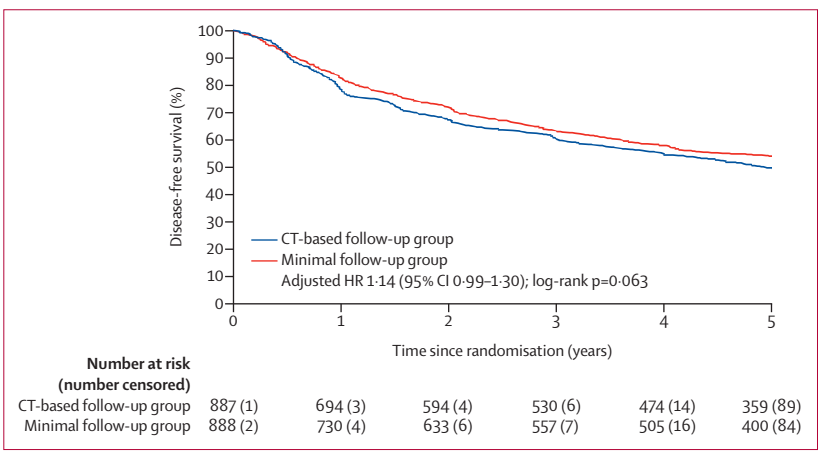

Figure 3: **Kaplan-Meier disease-free survival curves by follow-up group (intention-to-treat population)**
HR=hazard ratio.

(appendix 2 pp 5–6). Verification of the proportional hazards assumption is shown in appendix 2 (p 13).

Recurrence, as reported by investigators, occurred in 246 patients (27·7%) in the minimal follow-up group and in 289 (32·6%) in the CT-based follow-up group; the patients were symptomatic in 203 (82·5%) versus 162 (56·0%) cases, respectively. The most frequent sites of recurrence were the ipsilateral lung, contralateral lung, and brain (appendix 2 p 7). Brain metastases were asymptomatic in five (6·9%) of 72 patients in the minimal follow-up group, and in six (8·8%) of 68 patients in the CT-based follow-up group. 75 (30·5%) recurrences were detected by a planned procedure in the minimal follow-up group, and 162 (56·0%) in the CT-based follow-up group. 195 (67·5%) recurrences were detected by thoracic CT scan, with 162 (83·1%) being detected by planned thoracic CT scan in the CT-based follow-up group. The remaining symptomatic recurrences were detected by history and physical examination. Among these, recurrence was not

detectable on concomitant chest x-ray in 82 cases (42·0%), and no concomitant chest x-ray was done in 73 cases (37·4%). Treatment for recurrence was surgery alone in 14 patients (5·7%) in the minimal follow-up group and 38 patients (13·1%) in the CT-based follow-up group, and it was radiotherapy alone in 30 (12·2%) and 39 (13·4%) patients, respectively.

Second primary cancers were diagnosed in 102 patients (11·5%) in the minimal follow-up group and in 96 (10·8%) in the CT-based follow-up group, and the patients were symptomatic in 64 (63%) and 36 (37%) cases, respectively. The most frequent sites of second primary cancer in the minimal and CT-based follow-up groups were the lung (p=0·028), prostate, and head and neck (appendix 2 p 7). Second primary lung cancers were diagnosed in 27 (3·0%) in the minimal follow-up group and 40 (4·5%) patients in the CT-based follow-up group, were asymptomatic in 13 (48·1%) versus 33 (82·5%) patients, and treated with surgery or radiotherapy alone in eight (29·6%) versus 20 (50·0%) patients, respectively. In the CT-based follow-up group, one second primary lung cancer was treated with cryotherapy and one second primary lung cancer with radiofrequency ablation. Fourteen (52%) of 27 second primary lung cancers in the minimal follow-up group and 35 (87·5%) of 40 in the CT-based follow-up group were detected by a planned procedure (p=0·0029). In the CT-based follow-up group, 34 (85·0%) second primary lung cancers were detected by thoracic CT scan. Among these, second primary lung cancers were not detectable on the concomitant chest x-ray in 27 cases (47%), and no chest x-rays were done in 18 cases (32%). Altogether, treatment of recurrence or second primary lung cancers was surgery or radiotherapy alone in 52 (19·0%) of 273 in the minimal follow-up group and in 97 (29·4%) of 329 patients in the CT-based follow-up group. 166 (48%) of 348 in the minimal follow-up group and 157 (41%) of 385 in the CT-based group, recurrences and second primary cancers were extrathoracic only, and 54 (16%) and 48 (12%) were both intrathoracic and metastatic, respectively.

1762 bronchoscopies were done in the CT-based follow-up group. 13 (3·3%) of the 385 recurrences and second primary cancers in the CT-based follow-up group were only detected by fibre-optic bronchoscopy, and could not be detected by thoracic CT scan.

The overall survival HR adjusted for the stratification factors and for the occurrence of a recurrence or a second primary cancer was (0·77 [95% CI 0·67–0·88]; p=0·0002; post-hoc analysis; appendix 2 p 4). Post-hoc analysis of overall survival by follow-up group in patients with or without recurrence or second primary cancer within the first 2 postoperative years is shown in the appendix 2 (pp 11–12).

There was no difference in cancer-specific survival between follow-up groups (HR 0·91 (95% CI 0·8–1·1; post-hoc analysis; appendix 2 p 8).

No serious adverse events related to the trial procedures were reported.

Discussion

The IFCT-0302 study is a randomised, controlled trial assessing the value of chest CT scans for the surveillance of patients with completely resected NSCLC in terms of overall survival. The results showed that the addition of chest CT scans to a follow-up including clinic visits and chest x-rays did not improve overall survival in the primary stratified analysis. Although diagnoses of recurrences, particularly lung recurrences, and second primary lung cancers were more frequent and more frequently asymptomatic, at an early stage amenable to treatment with surgery or radiotherapy alone in the CT-based follow-up group than in the minimal follow-up group, this finding did not translate into a survival advantage. On the basis of these results, both follow-up strategies might be considered for routine implementation, taking into account the balance between higher costs and supplementary and potentially invasive procedures resulting from more intensive follow-up with CT and the benefit of an earlier diagnosis of recurrence or second primary lung cancer. With 13 (3·3%) recurrences or second primary lung cancer only detected by fibre-optic bronchoscopy, routine implementation of such an invasive procedure is not recommended. Moreover, tumours are likely to remain accessible to curative treatment when they become visible in the CT scan.

The proportions of patients who had an unjustified CT scan and those who did not have a planned CT scan did not exceed 8%. In the minimal intervention group, 18 of the 348 recurrences and second primary cancers were detected by an unjustified CT scan. Both this low figure and the per-protocol analysis, providing similar results to those observed in the intention-to-treat population, suggest that contamination between the two groups cannot entirely explain the lack of an overall survival advantage owing to CT-based follow-up in the IFCT-0302 trial. Nonetheless, CT-based follow-up detected more recurrences (289 second [32·6%] of 887 patients *vs* 246 [27·7%] of 888 patients) and second primary lung cancers (40 [4·5%] patients *vs* 27 [3·0%] patients), which were more frequently asymptomatic and more frequently treated with surgery or radiotherapy alone. Survival results adjusted for recurrence or a primary cancer showed a significant benefit for CT scan follow-up, suggesting that patients who had recurrence or a second primary lung cancer might actually benefit from repeated chest CT scans. Indeed, the cases of recurrence and second primary lung cancers detected early via CT might not have been sufficient to translate into a survival advantage in the primary survival analysis. Conversely, the benefit of CT became apparent in the Cox model when cases of recurrence and second primary cancer were included as time-dependent variables, as methodologically recommended for covariates that vary over time. As the recurrence status is not known upfront, the result of this analysis cannot contribute to adaptation of the surveillance strategy for future patients, but it supports our interpretation.

Exploratory, unplanned analyses suggest the possible benefit of chest CT scans in patients who have had no recurrence or a second primary cancer within the first two postoperative years. According to the definition Martini and Melamed used to differentiate second primary lung cancer from lung recurrence, most lung events after 2 years are second primary lung cancers rather than lung recurrence.[19] Recurrence reflects the aggressiveness of resected disease, yet second primary lung cancers have a greater chance of being localised lung cancers that are amenable to curative treatment.[10] Patients who have undergone surgery for NSCLC have a high risk of developing second primary lung cancers, with an incidence of six cases per 100 person-years at 5 years.[4,10,11,21–25] With 33 asymptomatic second primary lung cancers detected by the 3813 CT scans done in our trial, and 203 (0·9%) lung cancer cases detected by 22 600 CT scans in the Nelson trial, which showed reduced lung-cancer mortality with CT screening, patients with resected NSCLC might benefit from CT scans as much as high-risk smokers recruited to lung cancer screening trials.[26] Such a high incidence might be reflected in the late separation of the overall survival curves. In our study, contrast-enhanced diagnostic standard-dose CT scans were preferred to low-dose CT scans for several reasons, including postoperative changes, and the risk of non-pulmonary recurrences such as mediastinal or liver recurrences. With the decline of the recurrence risk over time, non-contrast-enhanced low-dose CT scan might be used for the late follow-up, aiming at detecting second primary lung cancers, but the IFCT-0302 trial did not address this question.

The main limitation of the study is its lack of power, resulting from an unexpectedly high proportion of patients with stage I and II NSCLC, which led to fewer overall survival events than anticipated. Accordingly, a long 7·2-year median follow-up was required to observe a sufficient number of events, and standard treatments of NSCLC have changed in both the perioperative setting with the advent of immunotherapy and osimertinib for *EGFR*-mutated NSCLC, and for advanced disease during this period of time. However, although they reduce the risk of recurrence, immune checkpoint inhibitors in the perioperative setting did not seem to significantly alter postoperative recurrence patterns, and the follow-up times of two reported trials were too short to measure the risk of second primary lung cancers.[27,28] *EGFR* mutations are only present in a small proportion of patients with NSCLC from European populations, such as in the IFCT-0302 trial. Therefore, it is very unlikely that adjuvant osimertinib would have affected the results of the trial. With the emergence of local treatments, such as surgery or stereotactic radiotherapy, and 26% of recurrences detected in the brain in the present study, the question of follow-up brain MRI would be relevant. The management of pulmonary nodules also changed over time. This would not alter the proportion of unjustified chest CT scans, because all follow-up CT scans for incidental pulmonary nodules were already considered as justified. Another limitation is that, despite the increasing risk of recurrence with stage, the same follow-up strategies were compared whatever the stage. One could expect a benefit from close CT surveillance by the early detection of recurrences in stage III NSCLC and from the diagnosis of second primary lung cancer (occurring mostly after 2 years) in stage I disease. Stage subgroup analyses were only exploratory and post hoc and no definitive conclusion can be drawn about the benefit of CT-based surveillance within stage subgroups.

Despite these limitations, the randomised design of the trial, the compliance of more than 90% with surveillance procedures, and this long follow-up duration provide robust data on recurrence and second primary lung cancer. Furthermore, in the absence of new methods for both the detection and the treatment of recurrences and second primary lung cancers in routine clinical settings, questions regarding the role of chest CT scans in follow-up remain pertinent.

Innovative approaches for the follow-up of resected cases include the detection of circulating tumour cells or circulating tumour DNA. Technological improvements, greater knowledge of circulating tumour cells and circulating tumour DNA dynamics and profiling and their consequences, in terms of tumour recurrence and treatment indications, need to be addressed before the routine use of liquid biopsies in the postoperative follow-up setting.[29] Web-based symptom monitoring approaches,[30] which have been shown to improve overall survival in metastatic lung cancer, might also be an interesting strategy for following up patients who are resected and to detect recurrence and second primary lung cancer early when symptoms appear. Nevertheless, as more recurrences and second primary lung cancers were asymptomatic in the CT scan-based follow-up group, they should not be considered substitutes, but rather complementary methods to diagnostic tests.

In conclusion, the results of the IFCT-0302 trial indicated that the addition of thoracic CT scans to follow-up, including clinical visits and chest x-rays after surgery for early-stage NSCLC, did not result in significantly longer survival times. However, thoracic CT scans did detect more recurrences and second primary lung cancers, which were more frequently asymptomatic, at an early stage and more frequently treated with surgery or radiotherapy alone. As the incidence of second primary lung cancers in these patients is similar to the incidence of lung cancer cases detected by CT screening in high-risk smokers, these data might still support a CT-based follow-up, especially in countries where lung cancer CT screening is implemented. Routine follow-up should be part of a comprehensive surveillance programme in patients with resected NSCLC, which should also include

patient education, organised prompt management of patients who are symptomatic, smoking cessation measures, and treatment for comorbidities.

Contributors

VW conceptualised the study; all authors participated in data acquisition. VW, AL, FM, and GZ verified the raw data and analysed and interpreted the data. VW, PG, NG, AL, FM, BM, GZ, and FB wrote the original draft. All authors had full access to all the data in the study, critically reviewed and revised the manuscript, approved the final version, and accepted responsibility for the decision to submit for publication.

Declaration of interests

VW reports payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing, or educational events from Amgen, AstraZeneca, Bristol Myers Squibb (BMS), Merck Sharpe and Dohme, Pfizer, and Roche outside the submitted work; support for attending meetings or travel from AstraZeneca, BMS, and Sanofi outside the submitted work; and participation on a data safety monitoring board or advisory board from MSD and Takeda outside the submitted work. JT reports support for attending meetings or travel from Roche and BMS, outside the submitted work. EQ reports payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing, or educational events from Chugai and BMS, outside the submitted work; and support for attending meetings or travel from BMS, Roche, and Takeda, outside the submitted work. GZ reports grants or contracts from Fondation Roche, Takeda, and BMS outside the submitted work; consulting fees from BMS and AstraZeneca, outside the submitted work; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from BMS, AstraZeneca, Pfizer, and MDS, outside the submitted work; support for attending meetings or travel from BMS, AstraZeneca, and AbbVie, outside the submitted work. FB reports payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing, or educational events from AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly Oncology, F Hoffmann–La Roche, Novartis, Merck, MSD, Pierre Fabre, Pfizer, and Takeda, outside the submitted work. All other authors declare no competing interests.

Data sharing

The individual participant data that underlie the results reported in this Article, as well as the study protocol and statistical analysis plan, will be made available after deidentification immediately following publication and for 3 years. Researchers who provide a methodologically sound proposal for any purpose can direct it to contact@ifct.fr. To gain access, data requestors will need to sign a data access agreement that requires approval by the French Cooperative Thoracic Intergroup.

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