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Randomized Trial Comparing a Web-Mediated Follow-up With Routine Surveillance in Lung Cancer Patients

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Abstract

Background: The use of web-based monitoring for lung cancer patients is growing in interest because of promising recent results suggesting improvement in cancer and resource utilization outcomes. It remains an open question whether the overall survival (OS) in these patients could be improved by using a web-mediated follow-up rather than classical scheduled follow-up and imaging.

Methods: Advanced-stage lung cancer patients without evidence of disease progression after or during initial treatment were randomly assigned in a multicenter phase III trial to compare a web-mediated follow-up algorithm (experimental arm), based on weekly self-scored patient symptoms, with routine follow-up with CT scans scheduled every three to six months according to the disease stage (control arm). In the experimental arm, an alert email was automatically sent to the oncologist when self-scored symptoms matched predefined criteria. The primary outcome was OS.

Results: From June 2014 to January 2016, 133 patients were enrolled and 121 were retained in the intent-to-treat analysis; 12 deemed ineligible after random assignment were not subsequently followed. Most of the patients (95.1%) had stage III or IV disease. The median follow-up was nine months. The median OS was 19.0 months (95% confidence interval [CI] = 12.5 to non-calculable) in the experimental and 12.0 months (95% CI = 8.6 to 16.4) in the control arm (one-sided $P = .001$) (hazard ratio = 0.32, 95% CI = 0.15 to 0.67, one-sided $P = .002$). The performance status at first detected relapse was 0 to 1 for 75.9% of the patients in the experimental arm and for 32.5% of those in the control arm (two-sided $P < .001$). Optimal treatment was initiated in 72.4% of the patients in the experimental arm and in 32.5% of those in the control arm (two-sided $P < .001$).

Conclusions: A web-mediated follow-up algorithm based on self-reported symptoms improved OS due to early relapse detection and better performance status at relapse.

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Although there is substantial variation in acceptable surveillance regimens for locally advanced lung cancer patients after therapy completion or during maintenance therapy, routine follow-up commonly consists of regular clinical assessments with (or without) routine imaging with the purpose of detecting development of recurrent tumors. Such a nonpersonalized approach is a source of anxiety for patients, which can last for several weeks before the planned imaging. Moreover, routine follow-up can delay diagnosis and treatment if recurrence occurs between planned visits. Additionally, numerous sequential imaging is expensive and has low yield in detecting asymptomatic recurrence (1,2). For these reasons, health-related quality of life (QoL) and/or survival have been improved in patients whose symptoms were frequently monitored during routine cancer care (3,4). Because at least 75% of lung cancer relapses are symptomatic and some symptoms have prognostic value in determining the clinical course and survival, patient self-reported symptoms have recently received a growing interest in oncology for their potential to improve the efficiency of follow-up and of clinical care (5,7–10).

A novel personalized follow-up strategy for lung cancer patients based on 12 symptoms self-scored weekly and transmitted to the oncologist via an “e-follow-up application” (e-FAP) was therefore developed with a specific algorithm for detecting lung cancer relapse. The e-FAP was designed to provide an individualized schedule for imaging based on patient symptoms. Two prospective studies have shown that this e-FAP is highly reliable and that relapses were detected (on average) five weeks earlier than with routine scheduled imaging (11,12). A pilot study suggested a better survival rate (86.6%, 95% confidence interval [CI] = 72.0 to 93.8) at one year in the web application arm than in a retrospective control arm (59.1%, 95% CI = 44.1 to 71.4) (13). In the current study, we tested the hypothesis that our web-mediated follow-up improves the survival in lung cancer patients with a high risk of relapse or progression compared with patients with a routine follow-up.

Methods

Study Design

In this prospective multicenter phase III trial, patients with advanced lung cancer were randomly assigned to be followed with either a web-mediated prompting of follow-up imaging or scheduled interval imaging. All patients provided their written informed consent. The study was conducted by the Integrated Center for Oncology (ICO, Angers, France), which gathered the data using an electronic case report form. Internal review board approval was granted by the institution.

Study Population

Patients were recruited from five hospitals and clinics in France. Approval was obtained from the ethics review board at the University Hospital at Angers (France). Eligible patients had nonprogressive small cell (SCLC) or non-small cell lung cancer (NSCLC) staged as at least cTxN1/pTxpN1 to TxNxM+ cancer (American Joint Committee on Cancer 2009 classification) (14,15) before their last treatment. Nonprogressive disease was determined by an imaging procedure less than one month before enrollment with last treatment (surgery, adjuvant chemotherapy, combined chemotherapy, conventional or stereotactic radiotherapy, first- or second-line chemotherapy) less than

Table 1. The five different symptoms scored to obtain the initial score*

Symptom	Initial score for symptoms			
	None	Low	Medium	High
Fatigue	0	1	2	3
Appetite loss	0	1	2	3
Cough	0	1	2	3
Breathlessness	0	1	2	3
Pain	0	1	2	3

*Eligibility required a score of less than 7 because our algorithm for relapse detection is not sufficiently discriminant in highly symptomatic patients. The score is the sum of the five scores.

three months before random assignment. Patients with metastatic lung cancer not progressing on tyrosine kinase inhibitor (TKI) treatment or maintenance chemotherapy were also eligible. All included patients had to have a performance status (PS) according to the World Health Organization classification between 0 and 2 and an initial symptom score of less than 7. This score was obtained by the sum of five self-assessed symptoms (appetite loss, fatigue [asthenia], pain, cough, and breathlessness), which were scored from 0 (no symptom) to 3 (major symptoms), as reported in Table 1. We validated this score and this threshold value with the two pilot prospective studies that assessed sensitivity and specificity of the algorithm (11,12). A threshold value equal to 7 was chosen because it was found to be associated with a clinically significant degradation of the general health status (11,12). Each patient or one of his close relatives had internet access and prior email experience.

Through a minimization program produced by Clinsight software (Cenon, France), patients were randomly assigned 1:1 to the two arms. The stratification was carried out according to sex, PS, stage of disease, and type of ongoing treatment (maintenance chemotherapy, TKI treatment, or none). The study was conducted by the Integrated Center for Oncology, which generated the random allocation sequence, enrolled participants, and assigned participants to interventions (16).

Routine and Web-Mediated Follow-up

Clinical follow-up in both arms included oncology visits at least every three months. Systematic CT scans were performed as reported in Table 2 and were more frequent in routine follow-up (control arm) than in the web-mediated follow-up (experimental arm) because our web application was found to be reliable to detect patient relapse by using weekly self-evaluated symptoms (11,12). In both arms, additional CT scans could be performed at the investigator's discretion. Patients undergoing maintenance chemotherapy or TKI were seen before each treatment administration (every three or four weeks).

In the control arm, patients were encouraged to call their family doctor or oncologist between visits if they had new or progressive symptoms. After random assignment, the study staff provided the patients enrolled in the experimental arm with a five-minute presentation on how to use the e-FAP. An e-mail with instructions and password was then sent to them. Details of e-FAP use are in the Supplementary Materials (available online). Twelve items were reported weekly by patients in an electronic form and sent immediately to the medical team after completion. The item scores were sent to the oncologist

Table 2. Frequency of CT scans in the two arms depending on the cancer stage*

Study arm and cancer stage	3 mo	6 mo	9 mo	12 mo	15 mo	18 mo	21 mo	24 mo
Control arm								
Stage II–III A	—	CT scan	—	CT scan	—	CT scan	—	CT scan
Stage III B–IV	CT scan	CT scan	CT scan	CT scan	CT scan	CT scan	CT scan	CT scan
Experimental arm								
Stage II–III A	—	CT scan	—	CT scan	—	—	—	CT scan
Stage III B–IV	—	—	—	CT scan	—	—	—	CT scan

*Routine visits were organized every three months for all patients. In both arms, additional visits and CT scans could be performed at the investigator's discretion. Patients undergoing maintenance chemotherapy or TKI were seen before each treatment administration (every three or four weeks).

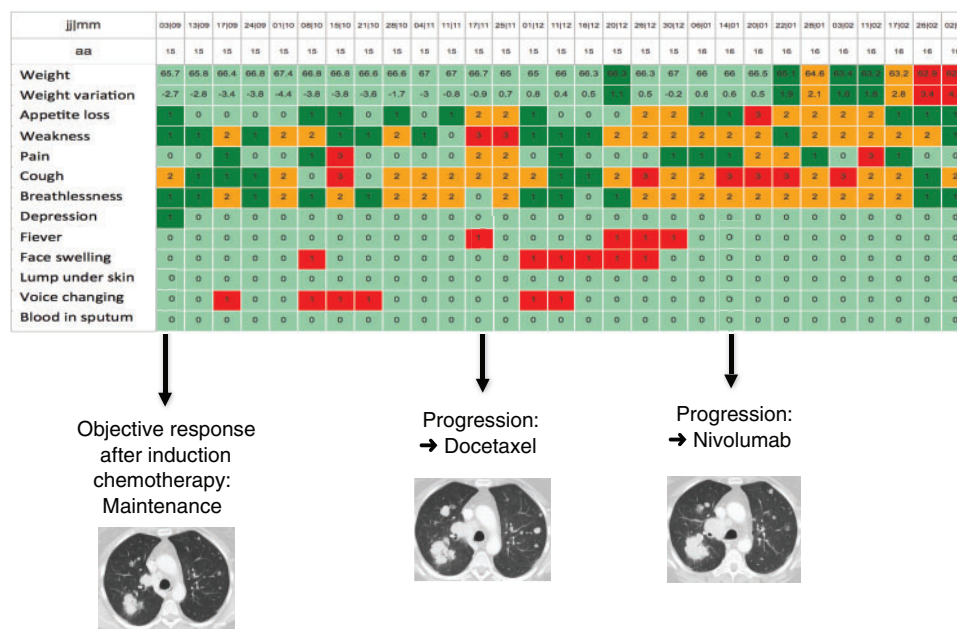


Figure 1. Screenshot of the graphical representation of the evolution of a patient from his weekly completed forms. This patient had stage IV adenocarcinoma, was on maintenance therapy, and was randomly assigned after induction chemotherapy to the experimental arm. Color legend: light green for a score = 0, dark green for a score = 1, yellow for a score = 2, and red for a score = 3. In the present case, the e-FAP triggered an email notification to the medical staff (see the arrow). This patient had two relapses early detected by our e-FAP (performance status = 1), which were confirmed by nonscheduled imaging. A second-line chemotherapy (full dose) followed by an immunotherapy was thus initiated.

and nurse in a graphical format as shown in Figure 1. A dynamic analysis of the weekly self-reported symptoms automatically triggered an alert sent to the oncologist by e-mail when predefined criteria were fulfilled. The use of the e-FAP was maintained during treatment for a relapse to adjust supportive care measures and to detect further progression (Figure 1).

Outcome Assessment

The primary end point was overall survival (OS) defined from random assignment to death or to the last assessment of patient's status when the patient was censored. Secondary end points are detailed in the Supplementary Materials (available online). No change in the trial outcomes was made after study initiation.

Statistical Analysis

Based on the results from our earlier phase II trial (13), we hypothesized that the web-mediated follow-up would improve OS at nine months by 12% compared with standard follow-up

(82% vs 70%). Consequently, with a 1:1 random assignment, we planned to enroll 224 patients for detecting a hazard ratio for the OS equal to 0.55 (corresponding to 73 deaths) with a power of 80% and a one-sided type I error of 5%. An interim OS analysis was planned after the 37th recorded death, allowing cessation of the trial for ethical reasons if the *P* value was less than or equal to .006 (log-rank test) (16). Prespecified patient subgroup analysis for OS was also performed according to sex, PS, ongoing treatment, stage, and histology.

Analyses were performed on an intent-to-treat basis. All patients found to be ineligible after random assignment were excluded from the analysis, as commonly done in intent-to-treat study of disease screening (17). The baseline characteristics of the patients in the two arms were compared using a chi-square test for categorical data and a nonparametric Wilcoxon test for continuous variables (two-sided, 5%). Survival curves in patients from the two arms were plotted using Kaplan-Meier estimates and compared using the stratified log-rank test. To evaluate if different prognostic factors have different effects on OS in patients with and without the web application, hazard

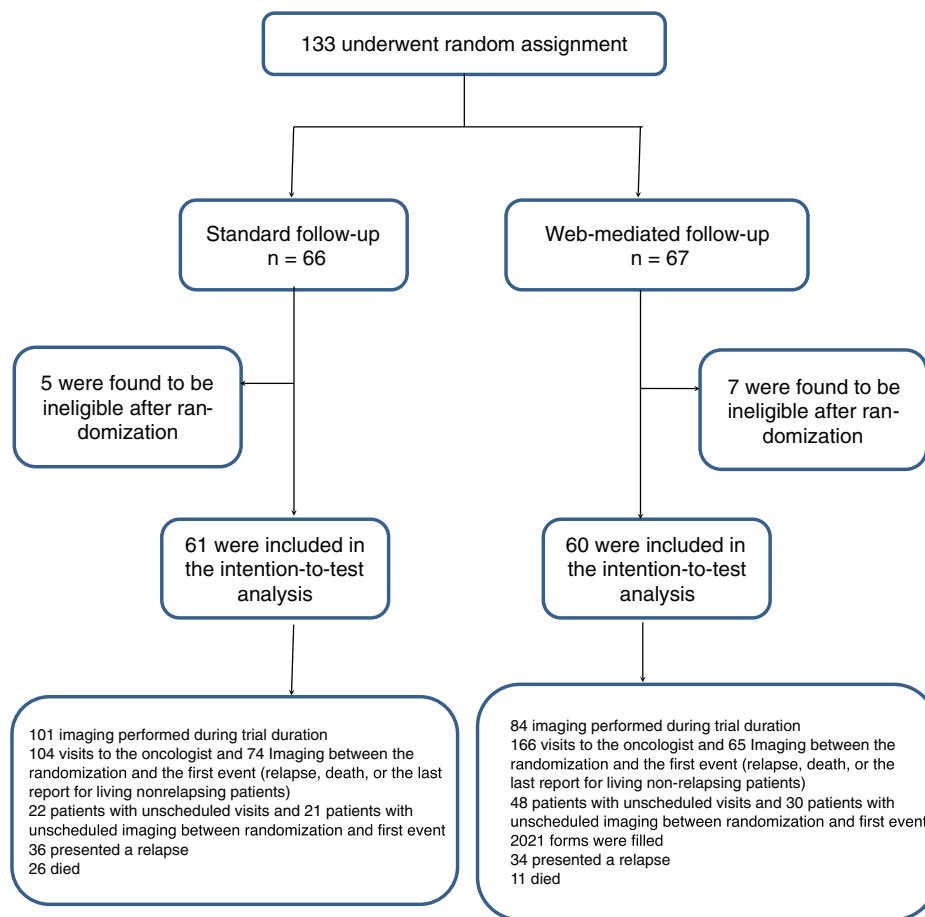


Figure 2. Consort diagram. Random assignment, follow-up, and analysis of the study patients. Population from which the 133 patients were randomly assigned is unknown but is from a base population of lung cancer cases of 850 patients at the centers used.

ratios were calculated using the Cox univariate proportional hazard model stratified for each class of prognostic variable. A plot of the logarithm of the cumulative hazard rates was used to check proportionality of the hazards assumption. Three intermediate models adjusted on each arm were developed. These models highlight the effect of each of the tested variables: one using cancer stage, one using cancer histology, and the last using the FACT baseline QoL score. These are an intermediate step between univariate models and multivariable models with a descending step procedure, and they allowed going beyond a simple univariate analysis by adjusting the relevant variables on each arm. Hazard ratios were presented with their 95% confidence intervals. The comparison of change from baseline QoL to six-month score was performed (chi-square test), and all statistical tests were two-sided except for survival (one-sided only subsequent to pilot trial results that were already strongly in favor of web-mediated follow-up) (18).

An independent data monitoring committee (IDMC) oversaw the study. This study was registered with clinicaltrials.gov (NCT02361099), and the trial protocol is available online (<http://www.cjb72.org/sentinel.pdf>).

Results

From June 1, 2014, to January 9, 2016, 133 patients underwent random assignment in four public recruiting centers and one private

clinic. Twelve patients were deemed ineligible after random assignment and were not subsequently followed. In each arm, two patients had progressive disease, one had a T3N0M0 carcinoma, and one received a nonauthorized maintenance treatment. One patient in the control arm had no confirmed lung carcinoma by histology. In the experimental arm, one patient had symptoms leading to a score greater than 6, and two had neither internet access nor prior e-mail experience. Thus, 121 patients were included in the intent-to-treat analysis (Figure 2). The two groups were well balanced with respect to baseline demographic and disease characteristics, but mean baseline FACT-L score was higher in the experimental arm than in the control arm (99.6, SD = 16.3 and 91.4, SD = 16.2, respectively, $P = .01$) (Table 3). In stage IIIB/IV population, four patients had second-line treatment before inclusion in the control arm (two had weekly paclitaxel stopped for toxicity, and two had TKI) and two in the experimental arm (TKI). Nine patients in the control arm and eight in the experimental arm had epidermal growth factor receptor- or anaplastic lymphoma kinase-positive mutations.

The interim analysis (January 9, 2016) at the 37th death (median follow-up = 9 months) showed that the median OS was 19.0 months (95% CI = 12.5 to noncalculable) in the experimental arm and 12.0 months (95% CI = 8.6 to 16.4) in the control arm ($P = .001$). The IDMC thus recommended cessation of the study and reporting of the findings. The hazard ratio (HR) for death was equal to 0.32 (95% CI = 0.15 to 0.67, $P = .002$) (Figure 3). The OS

Table 3. Baseline characteristics

Characteristic	Control arm	Experimental arm	Total	P*
Sex, No. (%)				.75
Male	40 (65.6)	41 (68.3)	81 (66.9)	
Female	21 (34.4)	19 (31.7)	40 (33.1)	
Median age (min–max), y	64.3 (42.7–88.1)	65.2 (35.7–86.9)	64.5 (35.7–88.1)	—
Performance status score, No. (%)				.70
0	18 (30.0)	16 (26.2)	34 (28.1)	
1	36 (60.0)	36 (59.0)	72 (59.0)	
2	6 (10.0)	9 (14.8)	15 (12.4)	
Cancer stage, No. (%)				.52
II (TxN1)	3 (4.9)	2 (3.3)	5 (4.1)	
IIIA	16 (26.2)	13 (21.7)	29 (24.0)	
IIIB	2 (3.3)	8 (13.3)	10 (8.3)	
IV	40 (65.6)	37 (61.7)	77 (63.6)	
Histology, No. (%)				.60
Small cell lung cancer	9 (14.8)	11 (18.3)	20 (16.5)	
Non–small cell lung cancer	52 (85.2)	49 (81.7)	101 (83.5)	
Histology of NSCLC, No. (%)				.18
Adenocarcinoma	35 (67.3)	33 (67.3)	68 (67.3)	
Squamous cell carcinoma	10 (19.2)	14 (28.6)	24 (43.8)	
Large cell carcinoma	7 (13.5)	2 (4.1)	9 (8.9)	
Ongoing treatment, No. (%)				.86
No treatment	35 (57.4)	37 (61.7)	72 (59.5)	
Tyrosine Kinase Inhibitors	10 (16.4)	8 (13.3)	18 (14.9)	
Maintenance chemotherapy	16 (26.2)	15 (25.0)	31 (25.6)	
Maintenance chemotherapy, No. (%)				.35
Bevacizumab	6 (37.5)	5 (33.4)	11 (35.4)	
Pemetrexed	8 (50.0)	6 (40.0)	14 (45.2)	
Bevacizumab+pemetrexed	2 (12.5)	2 (13.3)	4 (12.9)	
Gemcitabine	0	2 (13.3)	2 (6.4)	
Patients in each treatment arm with baseline assessment of FACT-L, No. (%)	54 (88.5)	52 (86.7)	106 (87.6)	.82
Mean (SD) baseline FACT score†	99.6 (16.3)	91.4 (16.2)	95.6 (16.7)	.01

*The P value is obtained from the two-sided chi-square or Fisher test. NSCLC = non–small cell lung cancer.

†Baseline quality of life score was measured at baseline after random assignment.

rate at one year was 74.9% (95% CI = 56.6 to 86.4) in the experimental arm and 48.5% (95% CI = 31.9 to 63.2) in the control arm. Prespecified patient subgroup analysis of OS favored the web application in all histologies and in stage IIIB/IV. There was also a positive trend in the rather small population of stage IIIA patients ($P = .05$). In the subgroup of stage IV patients, the median survival was 8.7 months (95% CI = 5.8 to 14.9) in the control arm and noncalculable in the experimental arm (log-rank $P = .01$). OS was not different in patients under maintenance therapy. After adjusting for cancer stage and histology, multivariable analysis still led to a better overall survival in the experimental arm than in the control. All deaths in the experimental arm and all deaths but one (anaphylactic shock) in the control arm were due to cancer. Once median follow-up reached 13 months, OS was re-evaluated: The one-year OS was 78.2% (95% CI = 67.7 to 88.6) in the experimental arm (control arm OS = 58.2%, 95% CI = 45.8 to 70.5, $P = .008$). Adjusted by baseline QoL score, survival remains higher in the experimental arm ($P = .002$), and QoL baseline score was not associated with survival ($P = .53$).

The comparison of change from baseline in QoL to six-month score favored the experimental arm because 80.6% of patients in the experimental arm had stable or improved scores, 58.6% in the control arm ($P = .04$) (Table 4). Eighty-six percent of the patients from the experimental arm had at least one alert that triggered a phone call from the oncologist that led to additional supportive care over the course of the trial.

In both arms, 89% of the relapses were symptomatic. The relapse rate was 50.8% in the control arm and 48.3% in the experimental arm. Progression-free survival (PFS) was not statistically significantly different between the two arms ($P = .13$), but the PFS of a subgroup of patients in the control arm with a low baseline physical well-being score (3.5 months, 95% CI = 3.0 to 5.8) was statistically significantly smaller ($P = .01$) than the other pooled subgroups (8.1 months, 95% CI = 5.7 to 11.9). This subgroup performed slightly better ($P = .08$) in the experimental arm (6.1 months, 95% CI = 3.0 to 18.6).

The PS at the first relapse was 0 to 1 in 75.9% of the patients in the experimental arm and 32.5% of those in the control arm ($P < .001$), leading to optimal treatment in 72.4% of the patients from the experimental arm and in 32.5% from the control arm ($P < .001$).

The total number of imaging events (CT scan, PET, or MRI) during the entire trial was smaller in the experimental arm (84) than in the control arm (101). The numbers of visits and imaging between random assignment and the first event are reported in Figure 2. Because of a longer median OS observed in patients included in the experimental arm, the rate of imaging was reduced by 49% per patient per year compared with the control arm. More patients attended unscheduled visits in the experimental arm (58.3%) than in the control arm (24.6%, $P = .008$). One patient from the control arm did not attend all planned visits because of surgery for a nonmalignant etiology.

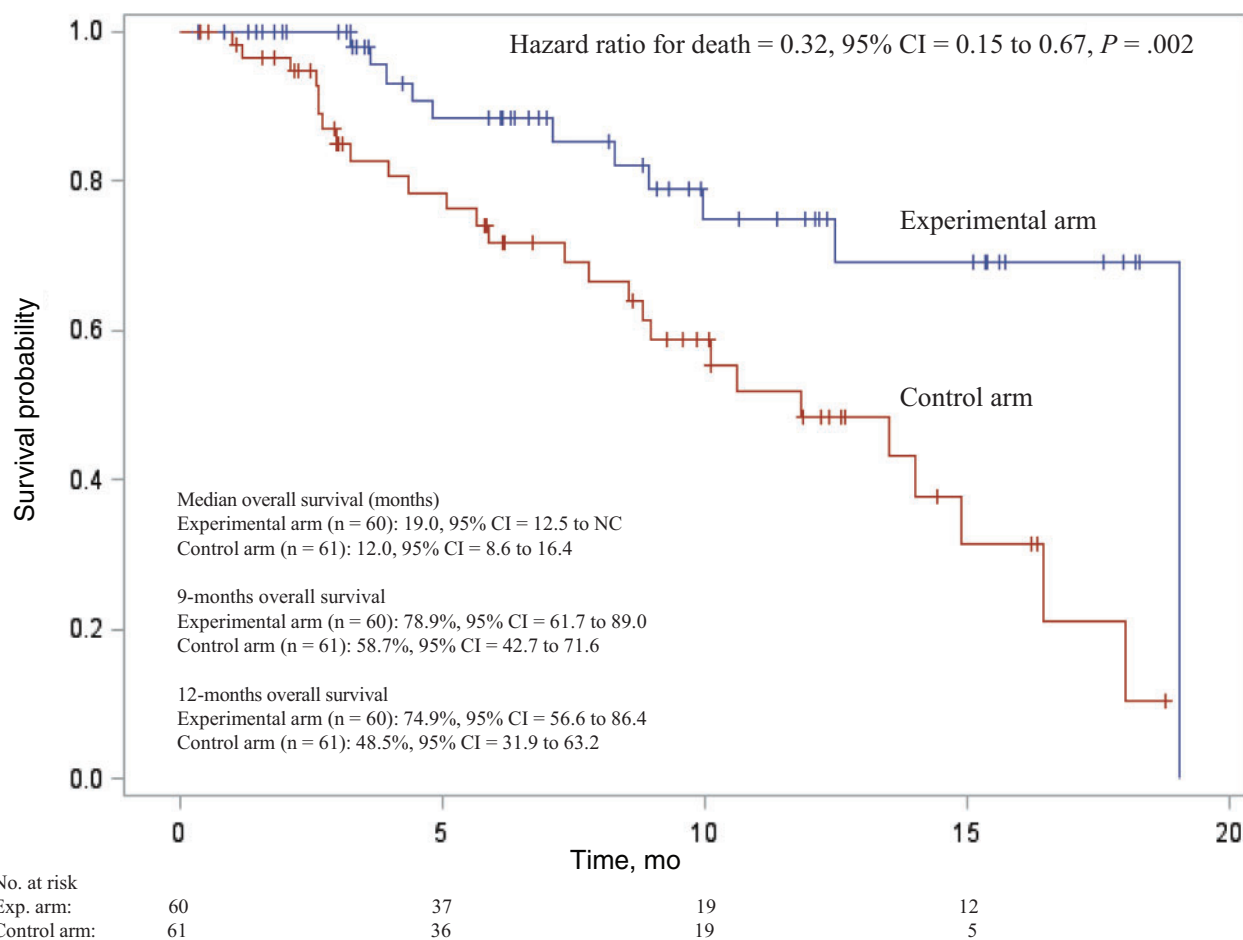


Figure 3. Kaplan-Meier estimates for the survival between the initiation and the end of the trial corresponding to the planned interim analysis. The P value is obtained from the one-sided log-rank test. CI = confidence interval; OR = odds ratio; OS = overall survival.

Table 4. Six-month mean changes of quality of life FACT scores from baseline*

	Control arm No. (%)	Experimental arm No. (%)	Total No. (%)	P †
Mean (SD) baseline FACT score	99.6 (16.3)	91.4 (16.2)	95.6 (16.7)	.01
6-mo evaluation/baseline*				
Improvement or stable	17 (58.6)	25 (80.6)	42 (70.0)	.04
Deterioration	12 (41.4)	6 (19.4)	18 (30.0)	

*Improvement was defined by a six-point increase between the two evaluations. Deterioration was defined by a six-point decrease between the two evaluations; stability is the intermediary situation.

†Two-sided chi-square test.

Any first alert prompted by the e-FAP and confirmed by a phone call from the oncologist led to an unscheduled visit ($n = 35$). In the experimental arm, 72.4% of the first relapses were detected between scheduled visits while only 32.5% of first relapses in the control arm were detected between visits ($P < .001$). The mean duration weekly spent by the oncologist to manage all the web alerts was 15 minutes for 60 simultaneous users.

Discussion

To the best of our knowledge, this is the first multicenter phase III randomized trial with an experimental arm based on a web-

mediated follow-up algorithm with a primary outcome of OS in lung cancer patients. We showed better survival in patients using the e-FAP than in patients with control follow-up including serial imaging. The e-FAP also allowed a decrease of the number of imaging tests.

The prespecified subgroup analysis suggested a survival benefit using the web application in NSCLC as well as in SCLC, mainly in stage IIIB/IV patients. There was also a positive trend in the rather small population of stage IIIA patients. There was no statistically significant survival benefit in the subgroup of patients receiving maintenance therapy. This is probably due to the fact that these patients had more planned visits (every three weeks) compared with those without maintenance therapy

(every three months). However, in maintenance therapy patients, although it was not quantified, the web application helped to manage symptoms and toxicity of the chemotherapy and also reduced the number of CT scans.

The survival benefit observed in patients from the experimental arm is consistent with the results obtained through intensive follow-up. Temel et al. showed that the median survival (from the firstline chemotherapy initiation) in stage IV metastatic lung cancer patients was statistically significantly longer (11.6 months) in patients receiving early supportive care than in patients receiving routine care (8.9 months) (19). In our control arm, the median survival in this type of patient (both small cell and non-small cell histologies) was 8.7 months from random assignment. But because the median duration between the last treatment initiation (four to six cycles of induction chemotherapy) or stage IV diagnosis and random assignment was 5.4 months in both arms, the median survival was thus 14.1 months in the control arm and not calculable in the experimental arms. This relatively high median survival in the control arm suggests that these patients had quality attention and treatments. While maintenance therapy was not performed in patients with squamous cell carcinoma, small cell carcinoma, or PS 2 (77/121 patients) as suggested in the American Society of Clinical Oncology guidelines, among the 44 remaining nonprogressive stage IV patients, 70% were on maintenance therapy at the time of random assignment. This proportion is similar to that reported in the literature (1,20).

Our results are in line with previous work utilizing electronic health initiatives. Bakitas et al. observed a greater by 15% one-year survival improvement in cancer patients using a telehealth (phone call) follow-up right after enrollment compared with those who started the tele-health program three months later (3). This study was conducted in a population with various types of cancer (lung, breast, gastrointestinal, etc.) and varying stage. Survival was not their primary outcome. A second report by Basch et al. noted an increase from 6% to 14% in the survival of 766 patients receiving chemotherapy whose symptoms were monitored via tablet computer (4). However, this study was monocentric, in a population with various types of cancer at any stage, again with survival as a secondary outcome.

In our study, the survival benefit is observed in the main subgroups of patients, a result that could be explained by earlier relapse detection and, consequently, in patients with a better performance status at the relapse detection, allowing optimal salvage treatment. Salvage treatments are indeed reserved for patients with a good PS (0–1) because of drug toxicities, and a lack of a survival benefit is observed in patients with a PS equal to 2 to 4 (1). Moreover, other dangerous medical conditions (one pulmonary embolism, two pneumonia, one severe bronchitis, one pericarditis, and one deep venous thrombosis) were also detected and treated earlier in the web-mediated follow-up arm, leading to a reduction in mortality.

Despite earlier detection of progression by using the e-FAP, we found no difference in progression-free survival. This may be explained by the difference in the frequency of tumor assessment between the two groups, the fact that nearly all relapses were symptomatic, and a possible positive effect of the quality of life on the progression-free survival. Although no quantitative analysis was made on the supportive care timing, we guess that it was earlier and more often performed in the experimental arm due to frequent and timely notifications of weight loss, depressive symptoms, pain, or asthenia as provided by our e-FAP to caregivers. Moreover, the web application allows for monitoring the supportive care efficacy by visualization of the

symptom evolution through a novel graphic (Figure 1). This may explain the statistically significantly higher quality of life of patients in the experimental arm at six months. Better quality of life could favor better survival and progression-free survival: Early management of physical and depressive symptoms as well as iatrogenic events may delay patient degradation, while these symptoms may be not necessarily managed as quickly with routine follow-up. As other authors have already suggested, PFS and OS may be improved subsequent to a QoL improvement in lung cancer (19–22).

In the control arm, results of patient visit attendance reassure that substandard attention was not provided to patients in the control arm. We choose to perform less scheduled CT imaging in the experimental arm because our previous trials showed that most relapsing patients were detected by our e-FAP five to six weeks before a scheduled CT scan. We also showed in these studies that symptomatic patients often waited for scheduled imaging and visits, sometimes many weeks with symptoms, leading to a low performance status at the time of relapse detection by scheduled CT scan. We therefore preferred to reduce the routine CT scan imaging schedule in the experimental arm and to perform a CT scan triggered by symptoms of relapse detected by our follow-up before deterioration.

There are limitations to our study. First, the median follow-up and overall patient number are small because the interim analysis led to early trial stoppage due to the large survival benefit we observed in the experimental arm. As recommended by the IDMC, a switch of patient from control to experimental arm started to increase the follow-up duration. The reduction in patient numbers may affect the actual survival benefit and reduce the power of our subgroup analysis. Second, the heterogeneity in patients at random assignment is a study weakness, although 96% had stage III or IV lung cancer. However, the main object of this study was to show that an intensive follow-up of patients with a high risk of relapse is beneficial: Regarding the risk of relapse or death, all our patients had a high risk. Third, it was difficult to propose a uniform follow-up in the control arm because there is no recommendation widely accepted in our country and the access to imaging is not homogenous. Fourth, the extra time the trial staff spent with patients from the experimental arm to explain the list of symptoms may also have stressed the importance of these symptoms and symptom reporting. Finally, baseline QoL data showed a statistically significant difference in QoL favoring the intervention arm. This difference may have been favored because in the experimental arm explanation of the list of symptoms to report by the trial staff was done just before the baseline QoL form was filled by patients. Patients may have felt reassured by these explanations and may have reported higher scores on their baseline QoL forms. We should have provided instruction to all the patients to fill out their forms before (and not after) random assignment to avoid this bias. However, we showed that OS adjusted for baseline QoL remained statistically significantly higher in the experimental arm. These results showed that the imbalanced baseline QoL score did not statistically significantly impact survival and quality of life changes over time in the web-mediated follow-up.

This study is an exploratory analysis that could guide development of larger trials in more specific patient populations, for example, in stage IV cancer or real-life studies. However, earlier detection of symptomatic relapse and management of symptoms through a web-mediated individualized follow-up strategy

can provide an improvement in quality of life and overall survival.

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