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Detection of lung cancer relapse using self-reported symptoms transmitted via an Internet Web-application: pilot study of the sentinel follow-up

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Abstract

Purpose We aimed to investigate whether patient self-evaluated symptoms transmitted via Internet can be used between planned visits to provide an early indication of disease relapse in lung cancer.

Methods Between 2/2013 and 8/2013, 42 patients with lung cancer having access to Internet were prospectively recruited to weekly fill a form of 11 self-assessed symptoms called “sentinel follow-up”. Data were sent to the oncologist in real-time between planned visits. An alert email was sent to oncologist when self-scored symptoms matched some predefined criteria. Follow-up visit and imaging were then organized after a phone call for confirming suspect symptoms. Weekly and monthly compliances, easiness with which patients used the web-application and the accuracy of the sentinel follow-up for relapse detection were assessed and compared to a routine visit and imaging follow-up.

Results Median follow-up duration was 18 weeks (8–32). Weekly and monthly average compliances were 79 and 94 %, respectively. Sixty percents of patients declared to be less anxious during the few days before planned visit and imaging with the sentinel follow-up than without. Sensitivity, specificity, positive, and negative predictive values provided by the sentinel (planned imaging) follow-up were 100 % (84 %), 89 % (96 %), 81 % (91 %), and 100 % (93 %), respectively and well correlated with relapse ($p\chi^2 < 0.001$). On average, relapses were detectable 5 weeks earlier with sentinel than planned visit.

Conclusion An individualized cancer follow-up that schedule visit and imaging according to the patient status based on weekly self-reported symptoms transmitted via Internet is feasible with high compliance. It may even provide earlier detection of lung cancer relapse and care.

Keywords Lung cancer · Follow-up · Supportive care · Personalized medicine · Early relapse detection · M-health

Introduction

Patient self-reported outcomes in oncology has recently received interest by health care providers for its potential to improve the follow-up of symptoms and, consequently, the efficiency of clinical cares [1, 2].

At least 75 % of lung cancer relapses are symptomatic and some of the symptoms have a prognostic value in determining clinical course and survival [3–5]. Nevertheless, there is no standard follow-up after therapy completion or during maintenance therapy and very few relapses are concerned by curative treatment [6]. Up to now, one of the most common strategies for a routine follow-up is to track the evolution of possible tumors by performing regular clinical assessments with (or without) routine imaging at a few months of interval. This non-personalized approach is a source of anxiety for patients sometimes for many weeks before the planned imaging. Moreover, routine follow-up can leave relapsing symptomatic patients without specific treatment during many weeks between planned visits. Our purpose is therefore to implement a “personalized” scheduling of imaging by using some symptoms weekly evaluated. We thus developed a procedure (called sentinel) based on a weekly self-evaluation of six criteria (weight change, cough, dyspnea, asthenia, pain, and anorexia) for detecting cancer relapse and showed in a

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cohort of 43 consecutive patients that this follow-up has high sensitivity, and specificity. These results were not significantly different ($p=ns$) than those obtained with routine imaging (CT-scan). Detection using the sentinel follow-up was highly significantly correlated to cancer relapse ($p\chi^2<0,001$), which were detected 6 weeks earlier than planned visit [7]. In the present study, we aimed to assess if patients-reported symptoms between planned visits can be used to provide an early indication of disease recurrence or progression in lung cancer and, consequently, to plan an imaging according to the patient status. Compliance, easiness, and anxiety were assessed and performances of this web-application for detecting cancer relapse were compared to those obtained with a routine planned visit and imaging follow-up.

Patients and methods

Study design and patient population

We designed a web-application allowing patient between planned visits to send weekly their self-evaluated symptoms to the oncologist via Internet using Smartphone or a personal computer. Patients with surgical excision, complete response, or detectable but non-progressive lung carcinoma were eligible if they had Internet familiarity and prior email experience. The physician performed a 5-min demonstration of the use of software and an email with instructions and password was then sent to patients. Patient informed consent was required before the enrollment. Patients receiving chemotherapy were excluded except if they received well-tolerated bevacizumab and/or pemetrexed or EGFR tyrosine kinase inhibitor maintenance.

Symptom tracking

Patients were asked to weekly report their weight and ten symptoms as appetite loss (anorexia), fatigue (asthenia), pain, cough, and breathlessness (dyspnea). Words that were used for patients self-assessment were “weakness” (“faiblesse” in French) to describe asthenia and “breathlessness” (“essoufflement” in French) to describe dyspnea. All terms were clearly explained by the physician during the visit for initiating the sentinel enrollment. The previously mentioned five symptoms had to be graded the same day as the weight was recorded. Each patient self-assessed the severity of these five symptoms by grading them from 0 (no symptom) to 3 (major symptoms). Five other symptoms (graded “yes” or “no”) were also used: fever superior to 38.2 (only measured if patient felt fever), sudden swelling of the face (to detect superior cave syndrome), appearance of a lump under the skin (to detect sub-cutaneous metastasis), voice changing (to detect potential mediastinal involvement),

and appearance or blood increase in sputum. The 11 items were reported in an electronic form during the study. Weight loss was automatically graded by the software as follows: Grade 0 for no weight loss, grade 1 for 1 kg loss, grade 2 for 2 kg loss, and grade 3 for 3 kg loss or more. Weight loss variation related to the weight measured at sentinel initiation was weekly computed. Data collection was prospectively performed. There was also a possibility for spontaneous additional comments if patient wished to report other symptoms or incident. Filling this window automatically triggered an alert email to the oncologist but did not necessary induce a phone call (Fig. 1).

Routine physical examination and planned imaging were performed during the sentinel follow-up every 2 to 6 months according to disease stage or treatment. PET-CT was systematically used when CT-scan was positive and biopsy/cytology was performed when needed. PET-CT or other modalities were also used in symptomatic patients without CT-scan abnormalities. Due to the lack of a gold standard to follow-up patients with lung cancer, we choose to combine all examinations to serve as a reference for relapse/progression confirmation. We thus compared the efficiency of the common follow-up in our center to the sentinel follow-up. The global score computed from the six clinical parameters and the five “yes-

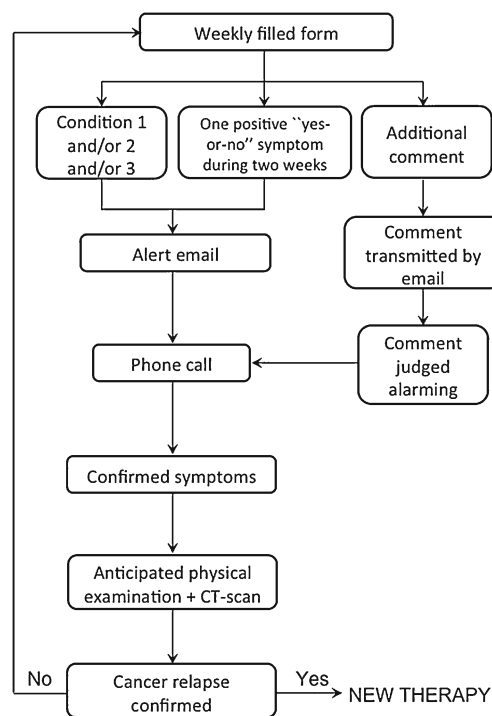


Fig. 1 Decisional tree of the sentinel follow-up. Patient weekly reports 11 self-evaluated symptoms then transmitted via Internet. A score is automatically computed and the software sends alert email to the oncologist if some conditions are verified. The oncologist then calls the patient to confirm that there is no input error and to assess clinical symptoms accuracy. Visit and imaging are brought forward when relapse is suspected

or-no” symptoms of each patient were recorded each week (see Fig. 2, for example). A previous study showed that our global score returns a positive relapse with the highest sensitivity (93 %) when at least one of the three following conditions was verified:

- Condition 1 Three-kilogram weight loss during at least 2 weeks;
- Condition 2 Two symptoms simultaneously equal to grade 3 during at least 1 week;
- Condition 3 A global score greater than 6 during at least two consecutive weeks.

These conditions were tested for detecting relapse only once the global score was less than 7 during 1 week. For instance, a patient returned a global score greater than 6 during the first 3 weeks after inclusion, and less than 7 at the fourth week: this procedure was thus only applied starting from week 4.

An email was sent to the physician when the self-evaluated symptoms were matching some criteria (not specified to patient). Email alert was also sent to the oncologist on a dedicated email box when patient had a positive “yes-or-no” symptom for at least two consecutive weeks (except for hemoptysis for which one positive report was enough to induce email alert). If alerted by email, the oncologist called the

patient to check the lack of error in symptom self-assessment. When suspect symptoms were confirmed, a physical examination and a CT scan were anticipated. Self-evaluations of symptoms were stopped when relapse was diagnosed, or when patient was free of relapse for more than 2 years.

Statistical analysis

Sample size was determined according to our previous study [7]. To deserve further development, the sensitivity and specificity had to be greater than 75 %.

To compare the sentinel follow-up to a common visit and imaging follow-up, sensitivity, specificity, positive, and negative predictive values were computed. Youden index and Q Yule coefficients were also computed for all types of relapse (loco-regional or distant failure). Results were then compared to relapse detections obtained with the routine or planned imaging follow-up and with complementary PET-CT, or pathological/cytological assessments if needed. Brain MRI was only performed in the presence of neurologic symptoms and/or signs on physical examination. The fisher exact test was used to compare sensitivity, specificity, positive, and negative predictive values between the “sentinel” and imaging follow-up. Chi² test was used in 2×2 tables to assess statistical association between the disease (relapsing or not) and the “sentinel” or imaging results. All tests were two sided and “p” value was considered significant when less than 0.05.

Longitudinal compliance rates were quantified by calculating the proportion of patients who filled weekly and monthly their forms. Based on previous feasibility studies in related contexts [8–10], the compliance was good enough to deserve further development when the mean monthly (weekly) compliance was greater than 75 % (60 %), that is, for each month (week), at least 75 % (60 %) of patients still in the protocol filled their forms.

A subjective evaluation of the sentinel follow-up was performed during planned visit at the hospital when it occurred after at least 8 weeks in our protocol. Questions were:

- a. “Do you feel better when followed by your oncologist using the sentinel follow-up?”
- b. “Do you feel anxious when you fill the form each week?”
- c. “Do you feel the sentinel web application easy to use?”
- d. “Since you are using this software, do you wait for the results of your routine imaging monitoring with less anxiety?”
- e. “How many times would you be ready to use sentinel before tiring?” Choices were 2, 6, 12, and 24 months, or as long as necessary.
- f. For patients with low compliance (four consecutive weeks without a filled form) “For which reason did you stop to fill the form for more than four consecutive weeks?”

WEEK	1	2	3	4	5	6	7	8
WEIGHT	72	72	72	72	72	72	72	72
Weight loss GRADE	0	0	0	0	0	0	0	0
APPETITE	0	0	0	0	0	0	0	0
WEAKNESS	0	0	0	0	0	0	0	0
PAIN	1	1	1	1	1	1	2	1
COUGH	0	0	0	0	0	0	0	0
BREATHLESSNESS	0	0	0	0	0	0	0	0
Total grade	1	1	1	1	1	1	2	1
FIEVER	N	N	N	N	N	N	N	N
FACE SWELLING	N	N	N	N	N	N	N	N
SUBCUTANEOUS LUMP	N	N	N	N	N	N	N	N
VOICE CHANGE	N	N	N	N	N	N	N	N
HEMOPTYSIS	N	N	N	N	N	N	Y	Y

Fig. 2 Example of a true positive “sentinel” detection. This patient had stage 4 NSCLC and objective response after four cycles of chemotherapy. During the sentinel follow-up, he reported a lump on his right leg 7 weeks after the beginning of the study. A phone call confirmed that the lump was persistent during 1 week. Visit was brought forward by 2 months. PET-CT confirmed the progression and biopsy confirmed metastasis. Second line chemotherapy was then early initiated

Before inclusion, all patients signed written informed consent and “Informatic and Liberty National Commission” form ensuring data deletion upon patient’s request. The study followed guidelines of our institutional ethical committee.

Results

Patient characteristics

Between February 2013 and August 2013, 42 patients were eligible and were enrolled in this prospective study. No patient explicitly cancels his participation to the study, and two patients died during this study. Patient characteristics are reported in Table 1. All patients but one received at least one tumor imaging during the follow-up (after the beginning of this study).

Compliance

Participants filled 564 forms, that is, 82 % of the maximum number (691) of forms, which was expected with our 42 patients. Thirteen patients stopped to fill their forms due to a confirmed relapse (see our decisional tree shown in Fig. 1). Figure 3 shows longitudinal weekly and monthly compliance rates for the cohort. The mean monthly compliance was 94 % and the mean weekly compliance was 79 %. Both are greater than the prespecified compliance threshold (75 and 60 %, respectively) required for positive feasibility. Weekly compliance tended to slightly decrease versus time but monthly compliance remained quite constant. Median duration of the sentinel follow-up was 18 weeks (1–28).

Six patients were not compliant for more than four consecutive weeks. One stopped to fill the forms 3 weeks after his study inclusion and was lost of follow-up, two patients replied that they forgot to fill their forms; two others replied that they were feeling well (implicitly meaning that they did not see the need for filling their forms), and one replied that he was on holiday without Internet access.

Subjective evaluation of the sentinel procedure

During the planned visit, which occurred at least 8 weeks after the first form filled, 25 patients accepted to answer to our questionnaire. All patients replied that they were reassured by knowing that they were followed by their oncologist using the sentinel follow-up.

None was anxious when filling the form. All patients found the sentinel application easy to use. Sixty percents (CI95 41–79 %) expected the results of their planned imaging with less anxiety since they use the sentinel follow-up. Except one patient, all others were ready to use sentinel as long as necessary (96 % CI95, 88–100 %). The remaining patient replied

Table 1 Patient characteristics

Characteristics	N=42
Males/females	36/6
Pathology	
Squamous cell	13
Adenocarcinoma	20
Large cell carcinoma	5
Small cell carcinoma	3
Undifferentiated non-small cell carcinoma	1
Initial stage	
I/II	9
IIIA	15
IIIB	1
IV	17
Detectable disease at the beginning of the study	
Yes	18
No	24
Previous treatment	
Surgery	11
Radiotherapy	1
Concomitant radio-chemotherapy	13
Chemotherapy	17
Disease status at study entry	
Complete response after surgery	11/11
Partial or complete response after radio-chemotherapy	11/13
Stable disease after radio-chemotherapy	2/13
Partial or complete response after palliative chemotherapy	8/17
Stable disease after palliative chemotherapy	9/17
Treatment ongoing	
None	36
Maintenance therapy	6
Planned imaging	
CT-scan	36
PET-CT	6

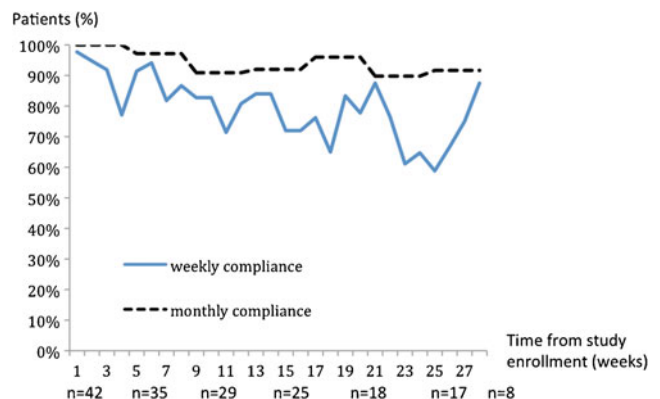


Fig. 3 Rate of filled forms versus time measured using two different compliance definitions: at least one form per week or at least one form per month

that she was ready to use the sentinel application during 24 months.

Accuracy of cancer relapse detection by sentinel

Median duration of form filled was 18 weeks (min 8, max 32). We performed comparison between sentinel and planned/symptoms guided imaging (CT-scan or PET-CT) and/or cytology. All patients but one presented at least one tumor imaging after reference imaging assessment (which was performed at the beginning of the study). One patient stopped to fill his form 3 weeks after his recruitment and, consequently, only the forms of the 41 remaining patients were used for investigating the accuracy of the sentinel follow-up for detecting cancer relapse. The sentinel follow-up provided results as follows. Thirteen patients were true positive, three were false positive, none were false negative, and 25 were true negative ($p\chi^2 < 0.001$). For all true positive “sentinel” patients, symptoms were detectable on average 5 weeks before planned imaging (min 1 week, max 13 weeks).

Sensitivity, specificity, positive, and negative predictive values, Youden index and Q Yule coefficient for evaluating sentinel results versus those obtained with a routine planned imaging are reported in Table 2. Sensitivity and specificity were high and not statistically different ($p=ns$) compared to imaging. None of the three false positive cases according to our sentinel follow-up corresponds to the one found with a routine imaging.

Forty-three email alerts were sent to the oncologist. Twenty-two of them were triggered by additional comments without other positive conditions and were not followed by a

Table 2 2×2 tables and results for evaluable patients (n=41) with the sentinel and the routine imaging (CT-scan or PET-CT) when compared with a relapse/progression detection using all modalities

	Relapse	No relapse
Sentinel positive	13	3
Sentinel negative	0	25
Imaging positive	11	1
Imaging negative	2	27
	Sentinel % (CI 95)	Routine imaging % (CI 95)
Sensitivity	100 %	85 % (66–100)
Specificity	89 % (77–100)	96 % (89–100)
Positive predictive value	81 % (62–100)	92 % (77–100)
Negative predictive value	100 %	93 % (84–100)
Youden Index	0.89	0.81
Q Yule coefficient	1	0.99
$p\chi^2$	<0.001	<0.001

Chi-squared test indicates that there is a significant association between the two forms of assessment and the disease (relapse or no relapse)

phone call. Twenty-three email alerts were caused by positive conditions (condition 1, 2, 3, or “yes-or-no” symptom). Seven alerts were not confirmed by the phone call; two false alerts were caused by weight input errors, one by a dysphonia which was actually an hoarseness, three due to positive condition 3 from patients with regressive acute bronchitis and one due to a patient with a gastro-enteritis and 3 kg weight loss. In this false positive population, phone call led to maintain the visit as initially planned, and which revealed no relapse on planned imaging. For 16 patients, complementary phone calls led to bring forward visit on average by 5 weeks (range 1 to 13). Table 3 reports alerts origins and subsequent oncologist actions.

Thirteen patients presented a tumor relapse/progression as determined by combining clinical, imaging (CT-scan and PET-CT), and cytological/pathological examinations. All patients who relapsed were symptomatic and detected by the sentinel follow-up. Three patients were false positive according to the sentinel follow-up (the oncologist was not able to detect the origin of the symptoms during the phone call and planned a visit). One patient was positive for condition 3 and a “yes-or-no” symptom due to a port-a-cath thrombosis. Another patient was positive for condition 3 and a “yes/no” condition subsequent to severe delayed acute grade 3 esophagitis resulting from a combined radio-chemotherapy. The third patient had appearance of blood in sputum (a “yes-or-no” symptom) subsequent to pneumonia. CT-scan or PET-CT eliminated relapse in all patients and evolutions were favorable.

Table 3 Alerts and subsequent oncologist actions

	Condition 1 and/or 2 and/or 3	Positive “yes-or-no” symptom alone	Condition 1/2/3 AND “yes-or-no” symptom	Additional comments
#email alert	17	4	2	22
#phone call	17	4	2	0
#anticipated visit+CT-scan or TEP-CT	10	4	2	0
#confirmed relapses	10	3	0	0

Condition 1: 3-kg weight loss during at least 2 weeks; condition 2: two symptoms simultaneously equal to grade 3 during at least 1 week; condition 3: a global score greater than 6 during at least two consecutive weeks. “yes-or-no” symptoms are (1) fever superior to 38.2°C, (2) voice changing, (3) one episode of sudden swelling of the face, (4) appearance of a lump under the skin, and (5) blood appearance or increase in sputum. We say that there is a positive “yes-or-no” symptom when at least one of them is reported by the patient for at least two consecutive weeks (except for hemoptysis for which one positive report was enough to induce email alert). Additional comment was free text sent by patient using the sentinel application. For instance, patients could have simultaneously a positive “yes/no” symptom and match one of the other three conditions

Symptoms guided CT-scan and PET-CT did not allow detecting relapse in two patients who were positive according to the sentinel follow-up but had cytologically proven meningeal carcinomatosis.

Discussion

To the best of our knowledge, this study is the first to test a real-time symptom-based follow-up to detect relapse in lung cancer between routine imaging. Such a follow-up presents the advantage to schedule visit and imaging according to the patient status. Visit and imaging for 16 patients was thus brought forward. Thirteen cancer relapse were confirmed and a severe disease was diagnosed for the three other patients. We did not find a single relapse, which was not detected with the sentinel follow-up. It therefore suggests that a follow-up requesting weekly self-scored patient symptoms could be rather reliable. In the present case, the sentinel follow-up was even more efficient than the planned visit and imaging to detect cancer relapse or tumor progression since there are two false negative cases in the routine follow-up. All patients found the sentinel application easy to use and 60 % reported less anxiety with the sentinel follow-up use before planned visit and imaging than without. Moreover, patients filled their forms with a high compliance.

M-Health based on self-evaluated symptoms transmitted via Internet is of a growing interest for various domains and particularly for oncology for which the compliance is rather high and the benefit of clinical relevance. A study with 286 long-term patients self-reporting toxicities at home during chemotherapy recently showed that the mean monthly compliance equals to 83 % with a mean follow-up duration of 34 weeks [9]. Another study in 44 patients showed that real-time transmission to investigators of 13 self-reported symptomatic adverse events, Karnofsky performance status, semi-automated RECIST measurements, and laboratory data during a phase II lung cancer trial was feasible and may induce earlier clinical decision [10].

Lung carcinomas present a high risk of relapse or progression after treatment. Moreover, relapses are very often symptomatic. Nevertheless, no documented standard for the surveillance of these patients were set in the NCCN, ACCP ASCO, or ESMO guidelines [6, 11, 12]. Although there is rarely an effective therapy against a recurrence, individualized visit and imaging schedule may limit unnecessary anxiety as observed between routine planned imaging and may limit expensive unnecessary imaging for non-symptomatic and non-relapsing patients. Moreover, early detection of relapse is important to avoid degradation of performance status limiting anti-cancer treatment and is relevant for patient comfort; it could be also a prognostic factor for survival in cancer patients undergoing palliative care [13]. In order to do that, we

previously prospectively validated a score based on self-evaluation symptom forms weekly filled at home by patients having lung carcinoma and high risk of relapse [7]. This score was strongly associated with relapse ($p\chi^2 < 0.001$). We then introduced this score into software allowing its use with electronic devices using Internet to monitor 11 symptoms weekly filled at home and to send them to the oncologist in real time. In the present study, we found that the sentinel follow-up was more reliable for some patients as a routing planned imaging follow-up, reproducing similar results as those obtained in our first study [7]. Moreover, on average, relapse detection with the “sentinel” follow-up occurred 5 weeks before planned imaging. In our institution, standard follow-up (without sentinel) was quiet more intensive (a visit and a CT scan every 3–4 months) than recent report ESMO, which suggests annual CT for non-metastatic lung cancer and clinical assessment every 3–6 months. If we had used these recommendations, the sentinel follow-up would have probably been positive by about 3 or 4 months before planned visit. As numerous symptomatic patients do not quickly visit their physician when symptoms appear (even when they are associated with relapse), we think that our sentinel follow-up may avoid that these patient wait for planned visits with relapse-associated symptoms [14].

Moreover, our population was mainly composed by stages 3 and 4 patients. This could explain the very high sensitivity and negative predictive values (100 %), and the lack of curative asymptomatic relapse that are more often observed in early stages using planned CT scan. The small size of the cohort may also explain this result, but χ^2 test and Yule Q coefficient measuring the link between the disease and our results are quite convincing as they were in our previous study [7].

Patients who used the sentinel software for monitoring their condition report that they felt closer to their oncologist due to a better communication (even if this is only by transmitting their own data). Moreover, the effort spent to remember the evolution of their symptoms between two visits at the clinic disappeared because they were aware that sentinel already provided to the oncologist the history of their symptoms and weight. During the visit, such a feature may also reduce the time patient spends describing its problems (unfortunately we did not record visit duration). All these features lead us to believe that patients may prefer this technology to traditional follow-up, but this is yet to prove in a specific study dedicated to such aspect. We did not compare resource utilization between sentinel and traditional cohorts in our study. However, data analysis and phone calls by the oncologist for managing the cohort of this study represents less than 15 min per week for the entire cohort. Once designed, using sentinel as a follow-up only requires secure web-server and the sentinel software.

In conclusion, a weekly follow-up using Internet facility seems feasible to detect relapse or tumor progression with a

high compliance. This approach needs further investigations such as survival, quality of life, cost analysis and accuracy study and a multicenter randomized study to compare the sentinel follow-up to planned visits and imaging, or both for lung carcinoma is in progress. Specific forms are also designed in our center for other types of cancer.

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