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Relevance of an extensive follow-up after surgery for non-small cell lung cancer

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Abstract

Background: There are no international guidelines for an appropriate and cost-effective follow-up for resected non-small cell lung cancer (NSCLC).

Methods: We retrospectively reviewed the outcome of NSCLC patients after curative surgery. Follow-up included physical examination and chest X-Ray every 3 months, chest CT-scan, bronchoscopy, abdominal ultrasound, brain CT-scan and bone-scan every 6 months for 3 years then every year during 2 years. Prognostic factors and costs were analysed.

Results: Median overall survival (OS) following surgery for NSCLC in 162 patients was 38.5 months. Recurrence occurred in 85 patients (52.5%) including 41 symptomatic subjects (48%). Disease-free survival was similar between patients with asymptomatic recurrence vs symptomatic patients (11.4 vs. 12 months; p=0.41). Recurrence was detected by physical examination or chest X-ray in 47 patients (55.3%). Curative-intent therapy was provided in 18/44 (41%) patients with asymptomatic recurrence and in 4/41 (10%) symptomatic cases (p=0.001). Median OS from time of recurrence was higher in asymptomatic patients than in symptomatic patients (15.5 vs. 7.2 months; p=0.001). The cost per year of gained life was 32,700 USD (22,397€).

Conclusions: An extensive follow-up, with acceptable cost, may improve the outcome of patients with resected NSCLC through detection of asymptomatic recurrences; validation by prospective studies is required.

Introduction

In current guidelines, surgery is the most appropriate treatment for early stage non-small cell lung cancer (NSCLC). However, only 50% to 60% of these patients will survive more than 5 years after surgery. A recurrence may occur in about 50% of patients [1]. There are no internationally validated guidelines for an appropriate and cost-effective follow-up after surgery for NSCLC. Wide variations in follow-up modalities are observed in Europe and in the USA [2, 3]. On the basis of retrospective studies [4-7], it is usually considered that there is no rationale for other procedure than physical examination and chest X-ray in patients with resected lung cancer. Only one prospective study [8] has evaluated the feasibility and the impact of a standardized intensive post-surgery follow-up; it showed a significant survival advantage in patients with asymptomatic relapses, compared to symptomatic patients. To confirm the potential value of an extensive follow-up of resected NSCLC, a randomized trial should be undertaken as it was already done in breast cancer or colorectal cancer patients [9, 10]. Though, it still remains unclear whether follow-up in these patients is cost-effective and whether it can improve the outcome due to an early detection of relapse.

We performed a retrospective study including a cost effectiveness analysis to assess the feasibility and the impact of a standardized intensive follow-up on outcome of NSCLC patients following curative surgery in our institution.

Patients and methods

Patients

The records of all patients from the Pulmonary and Thoracic Oncology Department of the Lille University Hospital who underwent resection for NSCLC between January 1990 and December 2002 were retrospectively reviewed. Inclusion criteria included a definitive diagnosis of NSCLC, a complete follow-up performed in our department during at least 5 years after surgery, no previous malignancy in the 5 years before NSCLC surgery, a complete surgical resection. Patients having complete resection of synchronous brain metastasis before NSCLC surgery were eligible. Patients who died within 30 days after surgery were excluded from the study. The design of the study was approved by the local ethical committee of our institution.

Follow-up procedures

During the first 3 years after surgery, the patients follow-up included the following procedures: physical examination and chest X-ray every 3 months; chest CT scan, fiberoptic bronchoscopy, abdominal ultrasound, brain CT scan, and bone scan every 6 months.

During the next two years, physical examination and chest X-ray were performed every 3 months, and chest CT scan, fiberoptic bronchoscopy, abdominal ultrasound, brain CT scan, and bone scan were performed once a year.

Compliance with follow-up procedures

The number of chest X-ray, chest CT scan, fiberoptic bronchoscopy, abdominal ultrasound, brain CT scan and bone scan performed until recurrence, death or last date of follow-up in patients without disease recurrence was calculated and compared with the number of scheduled procedures. The frequency of physical examinations was the same as the frequency of chest X-ray, as they were performed at the same time.

Recurrences

The criteria reported by Martini et al [11] were used to differentiate second primary lung cancers and recurrences of lung cancer. Patients having tumour recurrence were recorded as being either symptomatic (symptoms or abnormal physical examination) or asymptomatic at the time of diagnosis of the recurrence. The method leading to the diagnosis of recurrence was reported. Treatment of recurrence was considered as curative if the patient had complete surgical resection or irradiation for a local recurrence or a second primary lung cancer, or if he had complete surgical resection of a brain solitary metastasis with a controlled local disease. Chemotherapy for advanced disease, brain radiotherapy and palliative surgery were considered as palliative treatments.

Cost Analysis

The cost analysis was performed as described by Westeel et al [8]. The cost per years of life potentially gained by extra procedures (chest CT scan, fiberoptic bronchoscopy, abdominal ultrasound, brain CT scan and bone scan) was estimated by dividing the cost of "extra investigation" during the median disease-free survival duration for the whole population (A) by the numbers of years gained (B).

- Cost per years of life gained = A / B

Cost of extra procedures (A): The cost was calculated per patient for the median disease-free survival duration for the whole population (=studied period). Reimbursement prices are determined for each procedure by the French health-care system. French health-care system repayment rates and money exchange rate 2007 (1€ = 1.46 $) were used (Table 1). For one patient, the cost of the follow-up program was the total of the costs for each procedure during the studied period, multiplied by the number of times (=a); this procedure was supposed to be performed during the studied period.

- A= (a x Chest CT scan + a x fiberoptic bronchoscopy + a x abdominal ultrasound + a x brain CT scan + a x bone scan) x N (=numbers of patients)

Number of years of life gained by "extra investigations" (B) was the number of asymptomatic patients alive 3 years after recurrence (X) multiplied by 3 among asymptomatic patients who had recurrence detected by "extra investigations" and treated with curative intent, as the benefit of an intensive follow-up is mostly for the patients whose recurrences would'nt have been found by a clinical follow-up.

- B= 3X

Table 1: Costs of procedures

	Cost (USD)	Cost (euros)
Chest CT scan	187	128.4
Abdominal ultrasound	82	56.7
Fiberoptic bronchoscopy	140	96
Bone scan	280	193
Head CT scan	187	128.4

Survival and Statistical Analysis

The date of first treatment (surgery or neo-adjuvant chemotherapy) was considered as day 1. The time from first treatment to death or last observation was defined as the overall survival. The disease-free interval was defined as the time from first treatment to the detection of recurrence (or date of death or last observation in patients without recurrence). Survival from time of recurrence was also analyzed. Survival curves were calculated using the method of Kaplan-Meier. Survival differences between groups were evaluated by the log-rank test. Factors analysed for prognostic significance included sex, age at first treatment, histology (squamous cell carcinoma versus other type), disease free survival from surgery, mode of presentation (asymptomatic versus symptomatic patients), diagnostic procedure (physical examination or chest X-ray versus extra-procedures), site of recurrence (thorax only versus extra-thoracic or both thoracic and extra-thoracic). Multivariate analysis of variables with statistical significance was performed using Cox regression. For the survival analyses, hazard ratio (HR) and the corresponding 95% confidence interval (95% CI) were assessed. Statistically significant differences are indicated by $p<0.05$. All statistical analyses were performed using SAS® 9.1.3.

Results

Patients' characteristics

Between January 1990 and December 2007, 197 patients have been followed in our Department after curative-intent resection of a NSCLC. Thirty five patients were excluded from the study due to incomplete resection (n =4), previous malignancy within 5 years before surgery (n = 14), death within 30 days following surgery (n =17). The remaining 162 patients were included in this study.

Baseline characteristics of the patients included in the study are detailed in Table 2. Median age was 59 year-old (range: 31-81 year-old). Most of the patients were males (90.7%) and had squamous cell carcinoma (57%). Two patients had stage IV disease and had resection of both primary tumor and solitary brain metastasis. The median follow-up period was 38.2 months (range: 1.5-213 months).

Table 2: Characteristics of the patients included in the study

	n = 162
Age (year-old)	59, range 31-81
Gender	
Male	147 (90.7%)
Female	15 (9.3%)
Histologic subtypes of NSCLC	
Squamous cell carcinoma	92 (57%)
Adenocarcinoma	61 (37.5%)
Large cell carcinoma	6 (3.5%)
NSCLC N.O.S	3 (2%)
Stage (1997 TNM System)	
Ia/Ib	23/56 (14.2%/34.6%)
IIa/IIb	4/27 (2.5%/16.7%)
IIIa/IIIb	37/13 (22.8%/8%)
IV	2 (1.2%)
Resection	
Pneumonectomy (total//left/right)	36 // 23/13 (22.2% // 14.2%/8%)
Lobectomy/bilobectomy	106/13 (65.4%/8%)
Atypic resection	7 (4.4%)
Perioperative therapy	
Surgery only	89 (55%)
Surgery + perioperative therapy:	73 (45%)
- induction chemotherapy	5 (3.1%)
- consolidation chemotherapy	4 (2.5%)
- consolidation radiotherapy	45 (27.7%)
- induction chemotherapy + radiotherapy	19 (11.7%)

Compliance with follow-up procedures

Most of the procedures were correctly performed in patients at the right time. In fact, 86% of the scheduled physical examination and chest-X ray were performed; 76.5% of chest CT scan, 68% of bronchoscopy, 67.5% of abdominal ultrasound, 52.5% of bone scan, and 24% of brain CT scan were also done as previously planned.

Recurrences

A recurrence occurred in 85 patients (52.5%) and was symptomatic in 41 patients (48%) (Figure 1). Forty patients (47%) had thoracic recurrence, 26 patients (30.5%) had extra-thoracic recurrences and 19 patients (22.5%) had both thoracic and extra-thoracic recurrence.

Patients with thoracic recurrence were significantly more often asymptomatic than symptomatic: 27 (67.5%) vs 13 patients (32.5%), respectively (p=0.006). In contrast, the patients with extra-thoracic ±thoracic recurrence(s) were significantly more often symptomatic than asymptomatic: 28 (62%) vs 17 (38%) patients. The sites of thoracic recurrence were: the pleura (1 patient), pulmonary metastases (6 patients), mediastinum (14 patients), a second primary cancer (13 patients), pulmonary lymphangitis (1 patient), the thoracotomy scar (1 patient), and a combination of several thoracic sites (4 patients).

Recurrence was detected by physical examination or chest X-ray in 47 patients (55.3%), and by another procedure in 38 patients (44.7%). Among the 47 patients whose recurrence was detected by physical examination or chest X-ray, 61 sites of recurrence were detected as some patients may recur in several sites Among the patients whose recurrence was detected by another procedure, recurrence was diagnosed by chest CT scan in 32 patients (52.5%), bronchoscopy in 12 patients (19.5%), abdominal ultrasound in 6 patients (10%), bone scan in 4 patients (6.5%), and brain CT scan in 7 patients (11.5%). As some patients could have several recurrences, several procedures could be positive for the same patient.

Following recurrence, 22 out of 85 patients (26%) were treated with curative intent including surgery in 11 patients (50%), with 5 patients undergoing thoracic surgery and 6 patients undergoing resection of a single metastasis (4 brain metastasis, one adrenal metastasis and one supra-clavicular lymph node

metastasis), radiotherapy in 10 patients (45%) with thoracic irradiation in 7 patients (2 subjects also had curietherapy), thoracic irradiation and curietherapy in 2 patients and curietherapy alone in 1 patient, and local treatment with endobronchial laser therapy in one patient (5%).

Forty four patients (52%) were treated with palliative intent (chemotherapy, radiotherapy). Nineteen patients (22%) received best supportive care only.

Treatment was delivered with curative intent in 18 of the 44 asymptomatic patients (41%) and in 4 of the 41 symptomatic patients (10%) (p=0.001). Twenty asymptomatic patients (45%) and 24 symptomatic patients (58.5%) received palliative therapies (p=0.003). Best supportive care alone was proposed to 6 asymptomatic patients (13.5%) and 13 symptomatic patients (32%) (p=0.003).

Treatment was delivered with curative intent in 15 of the 40 patients (37.5%) who had thoracic recurrence only and in 7 of the 45 patients (15%) who had an extra-thoracic recurrence or both thoracic and extra-thoracic recurrences (p=0.021).

Survival

Median overall survival following initial surgery was 38.5 months. No significant difference for disease-free period was found between asymptomatic patients and symptomatic patients (11.4 vs. 12 months, p =0.41 HR=1.20 [95% CI: 0.78-1.86]). Median survival from time of recurrence was significantly higher in patients with asymptomatic recurrence than in patients with symptomatic recurrence (15.5 vs. 7.2 months, p=0.001 HR=2.09 [95% CI: 1.33-3.28]) (Figure 2).

The results of univariate analysis of survival are detailed in Table 4. The absence of symptoms at the time of recurrence, the diagnostic procedure (physical examination and chest X-Ray vs other procedures) for the diagnosis of recurrence and gender were found to be significantly associated with a better survival from time of recurrence. Age, site of the recurrence, histology and disease-free period did not significantly affect outcome.

In multivariate analysis, the diagnostic procedure for the diagnosis of recurrence and the absence of symptoms at the time of recurrence were the most significant factors for predicting survival after recurrence (Table 3).

Table 3: Univariate and multivariate analysis of prognostic factors for survival from time of recurrence in patients with resected NSCLC; *median age.

	Median survival following recurrence (months)	Univariate analysis		Multivariate analysis	
		HR [95 % CI]	*p value*	HR [95 % CI]	*p value*
Male/Female	9.2/18	0.48 [0.24-0.96]	*0.04*		*0.22*
Age >59 years/ ≤ 59 years*	10,6/10	0.90 [0.58-1.39]	*0.63*		*Not Done*
Histology: Squamous / Other	8/10.6	0.70 [0.45-1.08]	*0.11*	0.67 [0.43-1.05]	*0.08*
Disease free survival from surgery > 1 year / ≤ 1 year	10.6/9.2	0.91 [0.59-1.41]	*0.68*		*Not Done*
Asymptomatic/Symptomatic recurrence	15.5/7.2	2.09 [1.33-3.28]	*0.001*	2.14 [1.36-3.37]	*0.001*
Site of recurrence: Thoracic only/ extrathoracic ± thoracic	12/7.3	1.44 [0.93-2.24]	*0.10*		*0.84*
Diagnostic procedures: physical examination + Chest X-Ray / Other procedures	6.4/20.2	0.38 [0.24-0.60]	*<0.0001*	0.37 [0.24-0.60]	*<0.0001*

Cost Analysis

For a follow-up period of 32 months (equal to the median disease free survival), the cost per patient was 6660 USD (4561 euros). Eleven patients having an asymptomatic recurrence detected by another procedure than physical examination or chest X-ray were treated with curative intent and were still alive 3 years after recurrence. Therefore, the number of gained years of life was 33. The total cost induced by other procedures than physical examination or chest X-ray (chest CT scan, bronchoscopy, abdominal ultrasound, bone scan, and brain CT scan) was 1,078,920 USD (1,078,920 euros). Thus the cost per year of life gained was 32,700 USD (22,397 euros).

Discussion

In this study, we found that an intensive follow-up of patients with resected NSCLC is feasible, cost-effective and may improve survival by detecting asymptomatic recurrence. Despite the high number of planned procedures in the follow-up program, overall compliance was correct (76% for chest CT scan). However, it was impossible to assess the impact of some exams such as brain CT scan in the follow-up of these patients as the compliance for this procedure was very low (24%). A major limit in our study is the lack of a control group, as it is retrospective and we followed up all of our patients with an intensive program. The second limit is linked at the long duration of the study: we already performed neoadjuvant and adjuvant therapy as it is presently recommended, but the quality of imaging procedures has changed, especially for CT scan. Thus, abdominal ultrasound is not actually the modality recommended for diagnosis of hepatic recurrences because it has less sensitivity than CT scan. *Another limit of the study is that our patients recruited before 2007 were still logically assessed according the 1997 TNM staging system. Due to the limitations of a retrospective study, it was not feasible to reassess our patients' TNM stage according to the most recent (7th) edition of the lung cancer TNM staging system [12], without the risk to approximate or even to provide false data, in particular for the "T" parameter. Therefore we decided to keep the well characterized TNM stage data from the prior TNM classification. Finally, PET-scan was not available at this time in North of France for the follow-up of most of these patients, and thus could not be assessed in this study.*

The rate of asymptomatic recurrences (52%) in our study was higher than previously reported (usually 25 to 30%), which could be due to a more exhaustive follow-up program [5, 8]. Importantly, we found that asymptomatic patients at the time of recurrence had a significantly longer survival from time of recurrence than symptomatic patients. Lead time bias cannot explain this survival advantage since no difference in disease-free survival was found between asymptomatic and symptomatic patients. We found that asymptomatic patients at the time of recurrence were more likely to receive any treatment than symptomatic patients, especially curative-intent therapy (41% vs 10%, p = 0.001).

Westeel et al previously showed that among patients benefiting from an intensive follow-up program including bronchoscopy and chest CT scan with section of the liver and adrenal glands, asymptomatic subjects at the time of recurrence had a better survival from time of recurrence than symptomatic patients [8]. In another study, Walsh et al. retrospectively reviewed the records of 358 resected lung cancer patients [5]. Despite discrepancies in the follow-up plan, they also found that asymptomatic patients at the time of recurrence had a significantly longer survival than symptomatic patients. Thus patients with resected NSCLC may benefit from a follow-up strategy that allows the detection of more asymptomatic recurrences than periodic physical examinations and chest X-ray would do.

A better prognosis of patients with asymptomatic recurrences could also be explained because they may be treated with curative intent, for example in case of rare single (brain or adrenal) metastasis or of unique thoracic recurrence (mediastinal lymph nodes, lung metastasis, or second lung cancer). *In fact, most symptomatic patients did not receive curative-intent treatment. These symptomatic patients had mainly extra-thoracic recurrences that were not accessible usually to curative-intent treatment at this time, and they had poorer PS than patients with intra-thoracic recurrences. However, we were not able to retrospectively collect reliable PS data at the time of recurrence from all patients, allowing us to fully analyze this parameter. Thus this represents a limit of our study. Accordingly, patients with thoracic recurrences were usually asymptomatic, except at a late stage, and could not benefit from a curative-intent treatment.*

Follow-up guidelines for NSCLC patients following resection should take into account benefit on patients' outcome, but also quality of life and cost-effectiveness. Although an intensive follow-up might improve the quality of life by a better diagnosis, the treatment of potential tobacco-related comorbidities and of post-operative symptoms, it might also be deleterious because of potential anxiety generated by repeated procedures. *Physicians should also take account of the radiation exposure risks related to repeated scanning, even limited at low doses similarly to CT-scan procedure proposed for lung cancer screening [13, 14].* There is no published study evaluating follow-up strategies after lung cancer resection that includes a quality-of-life questionnaire. In breast cancer, the

GIVIO study analyzed the psychological impact of the follow-up [9]. The authors concluded that the patients wanted a strict follow-up; there was no impact on their quality of life because the follow-up did not reassure them but was not stressful either.

The cost of the intensive follow-up we used (32,700 USD / 22,397 euros) can be considered as acceptable, considering that in the USA, 50,000 USD is regarded as the upper limit of acceptable cost-effectiveness [7, 15]. Without the bone scan that does not diagnose curable recurrences, this cost would even be decreased to 25,800 USD. Our results are consistent with those from Westeel et al who also found an acceptable cost per gained year of life (13,000 USD) in the follow-up of resected NSCLC [8]. The lower cost per gained year of life observed in their study may be due to a less extensive follow-up, and a shorter median disease-free survival (19 months) than in our study (32 months). As our study is more recent than that from Westeel et al, a more accurate staging before surgery due to technological improvements, may explain the low recurrence rate in our study. Younes et al retrospectively compared the cost effectiveness of two different follow-up plans after NSCLC resection in 130 patients: a strict one (frequent visits, chest X-Ray, chest CT scan and liver function test) and another one based on symptoms [16]. The costs of follow-up for the strict plan group were significantly higher than those for the symptoms plan group, with no difference in survival after recurrence between the two groups. However, the follow up only lasted 2 years after resection, and recurrences occurred in 32 patients (24%), 14 patients in the strict group and 18 patients in the symptom group, limiting the statistical analysis of this follow-up role on patients' outcome. In colon cancer, an intensive post-operative follow-up is recommended, and the cost per year of life gained is less than 10,000 USD to be compared with a cost per gained year of life of 64,000$ for hemodialysis [4]. Kent et al. created a decision analysis model in which a hypothetical cohort of patients underwent annual chest CT after resection of a stage IA NSCLC [16]. The incidence of a second primary lung cancer, sensitivity and specificity of chest CT scan, as well as survival after resection of initial primary and second lung cancer were derived from published literature. It showed a cost of surveillance by chest CT scan once a year during five years of 47,676 USD per quality-adjusted life-year gained [16]. However, several factors could explain a cost-ineffective follow-up by chest CT scan in this case: (a)

an age over 65 years when starting the follow-up, (b) a cost of chest CT scan higher than 700 USD, (c) an incidence of second pulmonary lung cancer lower than 1.6% per patient per year of follow-up, and (d) a false positive rate by chest CT-scan higher than 14%.

In the present study, a survival advantage was shown in asymptomatic patients whose recurrence was diagnosed during an intensive follow-up. Our follow-up program could be still effective although less extensive and thus cheaper without bone scan, and if the CT scans were performed every 6 months during the first 2 years instead of the first 3 years of follow-up. We are currently testing this hypothesis in our institution.

An ongoing French prospective randomized trial with cost analysis (IFCT-0302 trial, NCT00198341) aims at comparing a 5 years non-intensive follow-up with an intensive follow-up (2 arms study) in patients with resected NSCLC. The non-intensive follow-up includes a physical examination and a chest X-ray every six months during the first 2 years then every year during three years. The intensive follow-up includes a physical examination, a chest X-ray but also a chest CT scan with sections of the liver and adrenal glands, and a bronchoscopy (depending on the histology of NSCLC) every six months during the first 2 years then every year during three years. The primary endpoint of the study is overall survival. This trial will help determining the appropriate follow-up of patients with resected NSCLC. However the value of FDG-PET scan and brain CT scan, and the surveillance following new treatments such as stereotactic radiosurgery will still need to be assessed in future trials.

In conclusion, our data suggest that asymptomatic recurrence following curative surgery for NSCLC is associated with a better survival than symptomatic recurrence. An intensive follow-up may improve the outcome for patients with resected NSCLC through detection of recurrence at an asymptomatic stage. The results of ongoing randomized trials are urgently awaited to suggest guidelines for the follow-up of these patients.

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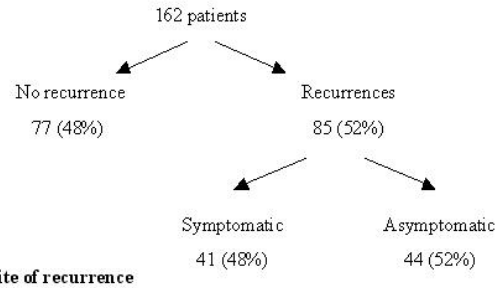
Figure 1 : Symptoms, sites and diagnostic procedures at the time of recurrence



Site of recurrence

thoracic	13	+	27	=	40 (47%)
extrathoracic	19	+	7	=	26 (30.5%)
Thoracic and extrathoracic	9	+	10	=	19 (22.5%)

Diagnostic procedure

Clinical examination or Chest X-Ray	41	+	6	=	47 (55.3%)
Other investigation	0/NA	+	38	=	38 (44.7%)

Figure 2: Survival of resected NSCLC patients from the time or recurrence according to the presence of symptoms or not at the time of recurrence