

# Routine Follow-Up After Surgical Treatment of Lung Cancer: is Chest CT Useful?

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## 1. Abstract

### 1.1. Objective

To report the experience of a routine follow-up program based on medical visits and chest CT.

### 1.2. Methods

This was a retrospective study involving patients followed after complete surgical resection of non-small cell lung cancer between April of 2007 and December of 2015. The follow-up program consisted of clinical examination and chest CT. Each follow-up visit was classified as a routine or non-routine consultation, and patients were considered symptomatic or asymptomatic. The outcomes of the follow-up program were no evidence of cancer, recurrence, or second primary lung cancer. Results: The sample comprised 148 patients. The median time of follow-up was 40.1 months, and 74.3% of the patients underwent fewer chest CTs than those recommended in our follow-up program. Recurrence and second primary lung cancer were found in 17.6% and 11.5% of the patients, respectively. Recurrence was diagnosed in a routine medical consultation in 69.2% of the cases, 57.7% of the patients being asymptomatic. Second primary lung cancer was diagnosed in a routine medical appointment in 94.1% of the cases, 88.2% of the patients being asymptomatic. Of the 53 patients who presented with abnormalities on chest CT, 41 (77.3%) were diagnosed with cancer. Conclusion: Most of the cases of recurrence, especially those of second primary lung cancer, were confirmed by chest CT in asymptomatic patients, indicating the importance of a strict follow-up program that includes chest CTs after surgical resection of lung cancer.

## 2. Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide. In Brazil, lung cancer is the fourth most incident type, with an estimated 30,200 new cases in 2020 [1]. Only 20% of the new cases present with localized disease amenable to surgical resection, and half of the patients will recur even after complete surgical resection [2]. Another concern is the risk of second primary lung cancer in lung cancer survivors; previous studies reported a rate of 1-3% per patient-year [3]. Diagnosis of recurrence and second primary lung cancer justify the organization of a follow-up program. Some authors reported that 60-75% of recurrence cases were found on routine chest CT scans in asymptomatic patients [4]. Unfortunately, most recurrences occur at a distant site where curative treatment is impossible, and even the majority of the local recurrences are not resectable and have dismal prognosis [5]. However, early diagnosis of lung cancer during a screening program has led to a 20% reduction in cancer-specific mortality [6]. The high risk of a second primary lung cancer justifies the inclusion of such patients in a screening program based on annual low-dose CT. Other reasons that justify follow-up are identifying and treating early and late effects of oncologic treatment;

and caring for other primary cancers that are amenable to primary and secondary prevention; and managing patient anxiety and fear of recurrence [7].

Although the risks of recurrence and second primary lung cancer are well known, an optimal follow-up strategy has yet to be well defined and remains controversial in different guidelines [8-10]. There is no consensus regarding the modality, examinations, frequency, and follow-up period. Various studies have recommended chest CT as the imaging test for follow-up [9,10]. However, it has no influence on overall survival apparently. Moreover, little is known about the optimal time intervals for evaluating patients in a follow-up program [11-15].

The aim of the present study was to report the experience of a routine follow-up program based on chest CT.

## 3. Methods

This was a retrospective review of non-small cell lung cancer patients who were submitted to complete surgical resection between April of 2007 and December of 2015 at the A.C. Camargo Cancer Center, located in the city of São Paulo, Brazil. This study was approved by the local institutional review board (Reference no. 1980/14).

The inclusion criteria were undergoing complete surgical resection of non-small cell lung cancer and participating in the follow-up program at our institution. Age was considered at the date of surgical treatment. Histological types were classified according to pathological reports. Clinical and pathological stages were defined in accordance with the American Joint Committee on Cancer staging manual [16]. All patients underwent PET/ CT and brain MRI for staging.

Surgical treatment included parenchymal resection (segmentectomy, lobectomy, or pneumonectomy) and mediastinal lymphadenectomy. Adjuvant treatments were indicated at the discretion of the clinical oncologist and/or radiotherapist. We defined the end of treatment as the date of surgical resection or the date of the end of adjuvant treatment.

## 4. Follow-up

The institutional routine was based on medical consultations and chest CTs in all cases, and ancillary tests were ordered according to initial assessment. The intervals between follow-up evaluations were as follows: every three months in the first and second year in the program; every six months between the third and fifth years; and every year after five years. Routine follow-up evaluation was defined as a visit scheduled according to our routine evaluation. Non-routine follow-up evaluation was defined as a medical appointment scheduled on a different date motivated by some clinical manifestation at the outpatient clinic or ER.

According to the information recorded in the medical charts, patients were classified as symptomatic or asymptomatic. Symptomatic patients reported any symptoms (spontaneously or stimulated by direct medical questioning) or presented with any findings on physical examination. Patients classified as asymptomatic had neither symptoms nor abnormal findings on physical examination.

The endpoint of each follow-up visit was classified into four categories: 1. no evidence of cancer; 2. recurrence of previous lung cancer; 3. second primary lung cancer; and 4. second primary extrapulmonary cancer. Recurrence was defined preferentially by biopsy. In cases in which biopsy was judged to be unnecessary or difficult to perform, recurrence was determined by clinical and radiological evaluations according to the characteristics of imaging examinations (CT, MRI, or PET/CT) and evolution in sequential assessments. Local recurrence was defined as a tumor occurring at the resection margins, regional recurrence was defined as a tumor in mediastinal lymph nodes, and distant recurrence was defined as a tumor in other organs outside the ipsilateral hemithorax. Recurrence in the ipsilateral pleura and in multiple nodules in the ipsilateral lung was also classified as distant recurrence. However, differentiation between systemic recurrence and second primary lung cancer was very controversial in the cases of a single nodule in the ipsilateral remnant lung. A new pulmonary neoplasm identified during a follow-up evaluation was classified as second primary lung cancer when the histological type was different from the primary one. In patients presenting with the same histological type, second primary lung cancer was defined in accordance with the criteria defined by Martini and Melamed [13]: a) different localization from the primary tumor, preferentially in the contralateral lung; b) disease-free interval greater than two years; and c) absence of involvement of a common lymph node chain between the former and the current primary tumor. Second primary extrapulmonary cancer was defined by anatomopathological examination and classified according to the anatomic site.

**5. Statistical analysis**

Continuous variables were expressed as medians and minimum-maximum variations, and categorical variables were expressed as absolute and relative frequencies. Time to recurrence and time to the diagnosis of second primary lung cancer were calculated from the date of cancer treatment completion to the date of confirmation of recurrence or second primary lung cancer by biopsy or clinical diagnosis. Correlations were determined by the chi-square test or Fisher’s exact test. The level of significance was set at  $p < 0.05$ .

**6. Results**

Between 2007 and 2015, 148 lung cancer patients were included in the study. The median age was 67 years (range, 25-86 years). The characteristics of the patients are described in (Table 1).

Pulmonary lobectomy was the most common type of surgical resection (67.6%), and most of the patients (53.4%) were classified as pathological stage IA (Table 2). In this sample, 41 patients (27.7%) received adjuvant treatment: chemotherapy, in 31 (21.1%); radiotherapy, in 2 (1.3%); and chemoradiation, in 8 (5.4%).

The median time of follow-up was 40.1 months (range, 0.6-123.2 months). The median number of consultations per patient was 9 (range, 1-22), and the median number of chest CTs per patient was 7 (range, 0-18). In the first year of follow-up, the median number of chest CTs was 3 (range, 0-5), whereas this was only 1.5 (range, 0-4) in the second year of follow-up.

We assessed patients according to their adherence to the routine follow-up program of our institution. Regarding the number of chest CTs during the follow-up program, only 21 patients (14.2%) completed it properly, whereas 110 (74.3%) and 17 (11.5%), respectively, underwent fewer and more chest CTs than it was recommended.

In our sample, 95 (64.2%) of the patients were classified as showing no evidence of cancer in the last follow-up visit. Recurrence

was identified in 26 patients (17.6%): locoregional recurrence, in 13 (8.8%), and distant recurrence, in 13 (8.8%). Recurrence was confirmed by biopsy and based on imaging assessment in 16 and 10 patients, respectively. The median time to recurrence was 15.1 months (range, 1.2-59.3 months).

Seventeen patients (11.5%) had the diagnosis of second primary lung cancer: confirmed by biopsy, in 16, and by imaging assessment, in 1. The median time to recurrence was 33.3 months (range, 1.2-75.1 months). Second primary lung cancer was contralateral in 14 (82.4%) of the patients. Adenocarcinoma was the most common histological type, in 10 patients (58.8%), followed by squamous cell carcinoma, in 3 (17.6%); large cell carcinoma, in 2 (11.8%); and unspecific non-small cell lung cancer, in 2 (11.8%). Distribution according to clinical stage was as follows: I (n = 8; 47%); II (n = 1; 5.9%); IIIA (n = 4; 23.5%); IIIB (n = 1; 5.9%), and IVA (n = 2; 11.8%). Figure 1 depicts that most recurrence cases were identified in the first 20 months of follow-up, whereas second primary lung cancer was more commonly identified after 30 months of follow-up.

Second malignant extrapulmonary neoplasms were diagnosed in 10 patients (6.7%) in the following primary sites: pancreas, in 3; breast, in 2; colon, in 1; prostate, in 1; soft tissue sarcoma, in 1; kidney, in 1, and brain, in 1.

Recurrence was diagnosed in a routine medical consultation in 18 of the 26 patients (69.2%), 15 of whom (57.7%) were asymptomatic, and abnormalities were identified on a routine chest CT: nodule, in 7;

**Table 1:** Clinical characteristics of the patients included in the study (N = 148).

Characteristic	n	%
Gender		
Male	83	56.1
Female	65	43.9
Tobacco use		
Yes	91	61.5
No	57	38.5
Histology		
Adenocarcinoma	99	69.9
Squamous cell carcinoma	34	23
Other	15	10.1
Laterality		
Right	92	61.4
Left	58	38.6
Primary tumor site		
Upper lobe	79	53.3
Middle lobe	11	7.3
Lower lobe	44	30
More than one lobe	14	9.3

**Table 2:** Type of pulmonary resection and pathological stage.

Characteristic	n	%
Type of surgical resection		
Lobectomy	100	67.6
Sublobar resection	29	19.6
Pneumonectomy	10	6.8
Bilobectomy	9	6.1
Pathological stage		
IA	79	53.4
IB	20	13.5
IIA	15	10.1
IIIB	10	6.8
IIIA	20	13.5
IIIB	3	2
IVA	1	0.7

mediastinal lymph nodes, in 3; pleural nodule, in 2; tracheal tumor, in 1; mediastinal tumor, in 1; and pancreatic nodule, in 1. Symptoms related to recurrence were observed in 11 (42.3%) of the patients: pain, in 6; dyspnea, in 2; hemoptysis, in 1; dizziness, in 1; and hoarseness, in 1.

Second primary lung cancer was diagnosed in a routine medical appointment in 16 (94.1%) of the patients, and most of them (88.2%) were asymptomatic. Only 2 patients (11.8%) presented with symptoms of dyspnea (in 1) and hemoptysis (in 1). Of the 15 asymptomatic patients, the most frequent finding on chest CT was pulmonary nodule, in 13 patients, followed by mediastinal lymph node, in 1; and ground glass opacity, in 1.

Table 3 shows that chest CT findings in asymptomatic patients diagnosed second primary lung cancers (88.2%) more frequently than recurrence (57.7%;  $p = 0.04$ ).

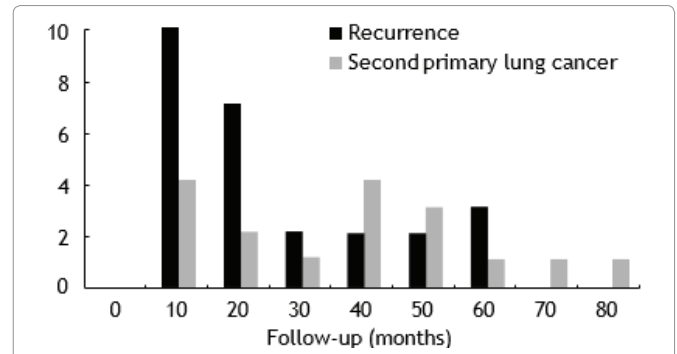
Abnormalities on chest CT were found in 53 patients (35.8%). Figure 2 shows the findings, ancillary examinations performed, presence of symptoms, and endpoints. PET/CT was performed in 34 patients (64.1%). Of the 53 patients, 12 (22.7%) had no cancer despite abnormal CT results. Among these patients, PET/CT and bronchoscopy were performed in 5 and in 1, respectively.

### 7. Discussion

There is controversy in the literature about modality, frequency, and duration of follow-up, as well as type of examinations to be performed, after surgical resection of lung cancer [14]. We analyzed the follow-up program at our institution, with a special focus on the role of chest CT. In the present study, the median follow-up period was 40.1 months. The median number of chest CTs per patient was 3 in the first year of follow-up, but it dropped to 1.5 in the second year. Only 14.2% of the patients underwent the exact number of chest CTs recommended by the current institutional protocol, whereas most of the patients (74.3%) were submitted to fewer chest CTs than what our protocol recommended. Recurrence was observed in 17.6% of the sample (median time to recurrence = 15.1 months). Most recurrence cases were detected in routine consultations (69.2%) and on routine chest CT with abnormal findings in asymptomatic patients (57.7%). Second primary lung cancer was found in 11.5% of the patients, most of them being asymptomatic (88.2%) and having abnormal chest CT findings. We observed that abnormal chest CT findings

in asymptomatic patients diagnosed second primary lung cancers (88.2%) more frequently than recurrence (57.7%;  $p = 0.04$ ).

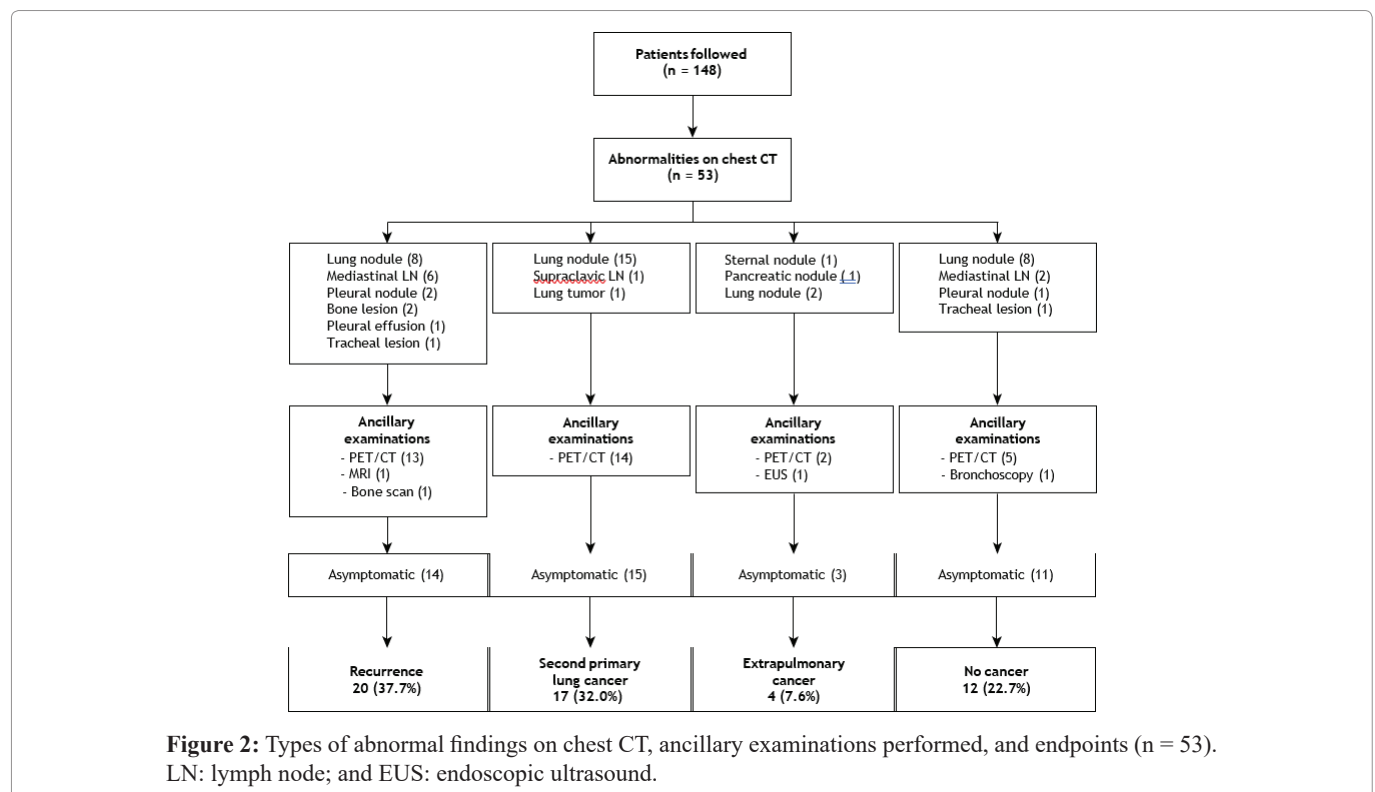
The rate of second primary lung cancer has been reported as high as 1-3% per patient-year in previous studies [3]. Lou et al [4]. reported 7% of cases of second primary lung cancer in a follow-up program. Similarly to our findings, Kent et al [17]. reported a second primary lung cancer rate of 11%. Interestingly, the risk of developing an extrapulmonary primary malignancy in this scenario has been poorly studied. Few authors reported the incidence of additional extrapulmonary malignancy, ranging from 1% to 26% [18-20]. Similarly to our results, Son et al. reported a 4.7% rate of second primary non-pulmonary malignancy during the follow-up of patients submitted to lung cancer resection [20]. The follow-up period is an excellent opportunity for preventing different primary and secondary neoplasms. These aspects should be considered in a comprehensive



**Figure 1:** Number of patients diagnosed with recurrence or second primary lung cancer during the follow-up period.

**Table 3:** Association of the method of diagnosis (symptoms or chest CT in asymptomatic patients) with recurrence or second primary lung malignancy.

	Symptoms	Chest CT	Total	P
Recurrence	11 (42.3%)	15 (57.7%)	26 (100%)	0.04
Second lung cancer	02 (11.8%)	15 (88.2%)	17 (100%)	



**Figure 2:** Types of abnormal findings on chest CT, ancillary examinations performed, and endpoints (n = 53). LN: lymph node; and EUS: endoscopic ultrasound.



survivorship program after curative treatment of lung cancer.

Although most guidelines have recommended the use of chest CT in follow-up programs after curative surgical resection of lung cancer, there is no consensus about its usefulness in this scenario [21]. Lou et al [4]. reported their vast experience about the role of chest CT in the follow-up of surgically treated lung cancer patients. Similarly to our experience, they found that recurrence and second primary lung cancer were diagnosed in 61% and 93% of asymptomatic patients, respectively, by chest CT and during a routine consultation. Recently published screening studies have affirmed the importance of early diagnosis of lung cancer [6,17]. Therefore, we can extrapolate these results to the early diagnosis of second primary lung cancer during a follow-up program. However, we cannot assume that the early diagnosis of recurrence might impact on overall survival or quality of life. A systematic review and meta-analysis found a trend toward better survival in an intensive follow-up program, and the identification of recurrence in asymptomatic patients was associated with significantly increased survival [22]. Crabtree et al. [23] reported that chest CT resulted in earlier diagnosis of successive malignancy, although no difference in survival was demonstrated when chest CT and chest X-ray were compared. In our experience, chest CT significantly identified more cases of second primary lung cancer than those of recurrence, and time to recurrence was shorter than time to diagnosis of second primary lung cancer.

The optimal interval between surveillance screenings is not well defined, although most of the guidelines recommend surveillance every six months in the first two years, and then annually [10,11]. On the basis of our previous experience, we have recommended a stricter follow-up program than those in most guidelines [15]. However, the present study showed that most of the patients had been submitted to fewer chest CTs than suggested in our guideline. The low adherence rate to our follow-up protocol can be explained by its short time interval, especially in the first two years of follow-up. We also found that most of recurrence cases occurred in the first two years of follow-up, whereas cases of second primary lung cancer occurred more commonly after the third year of follow-up. This suggests that surveillance should be stricter in the first two years of follow-up in order to detect recurrence and should be maintained annually over time. In analogy to screening guidelines [6,17]. conventional chest CT could be replaced by low-dose chest CT after the second year of follow-up. Currently, for initial stages (I and II), we recommend the use of chest CT every six months in the first two years of follow-up, followed by annual exams after the third year.

In our follow-up program, abnormalities on chest CT were found in all cases of recurrence or second primary lung cancer. Korst et al [24]. studied 92 patients with abnormal chest CT findings in a follow-up program and reported that pulmonary nodules and pleural effusion were associated with recurrence. Interestingly, the abnormalities considered as false positives were very similar to those observed in patients who had recurrence or second primary lung cancer. False positive results might lead to unintended consequences, such as performing additional examinations (including risky invasive procedures or greater radiation exposure even if the procedures are noninvasive), decreasing cost-effectiveness, and increasing patient anxiety and fear. Similarly to our results, Lou et al [4]. reported 25% of false-positive findings on chest CT, and additional invasive procedures were performed in only 5% of the cases.

The most important limitation of the present study was its retrospective design. Although our cohort had a long follow-up period, the study reflects the experience of a single institution specializing in cancer care and might not be generalized. The classification of abnormal or suspicious findings on chest CT was determined by clinicians and might have decreased the rate of false-positive results. However, we believe that this is not a problem, because, in practice, the interpretation of the exam is made by the clinician and not by the report of the imaging examination alone. In some cases, it might be difficult to distinguish between pulmonary recurrence and second

primary lung cancer, especially in retrospective studies. The impact on overall survival should be the major endpoint to evaluate the efficacy of a follow-up strategy after surgical resection of lung cancer. Due to the small number of patients and the lack of a control group (patients not enrolled in the follow-up program), we were unable to evaluate overall survival in the present study.

In conclusion, we found that most cases of recurrence, and especially most of the cases of second primary lung cancer, were detected on the basis of abnormal chest CT findings in asymptomatic patients, which suggests the importance of a strict follow-up program that includes chest CT after surgical resection of lung cancer..

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