Predictors of Extra-Pulmonary Metastatic Disease in Patients with Recurrent Lung Cancer

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Abstract

**Background**: Lung cancer is one of the leading causes of cancer-related mortality worldwide. Its poor prognosis is associated with late detection and high recurrence rates. We aimed to determine if certain imaging characteristics of lung cancer recurrence were predictors of extra-pulmonary metastatic disease.

**Methods**: We conducted a retrospective study of all patients at our institution with lung cancer recurrence detected on post-treatment imaging between January 2014-October 2019. Research ethics board approval was obtained. Included patients underwent pre-treatment imaging, surgical resection, and post-treatment imaging. Imaging characteristics and pathological findings of the pulmonary lesions were analyzed. Univariate logistic regression was performed to assess for potential predictors of extra-pulmonary metastatic disease. The variables evaluated were age, gender, original and recurrent lesion size and imaging characteristics, recurrence location, presence of chest wall or mediastinal invasion, lymphadenopathy, and malignancy subtype.

**Results**: 76 patients were included (33 males; mean age 70.9, standard deviation [SD] 7.7). The primary lesions were adenocarcinoma (N=50), squamous cell carcinoma (N=21), and other (N=5). The mean time to recurrence was 24.3 months (SD=18.8) from date of surgical excision. The two significant predictors of extra-pulmonary metastatic disease were: having >1 recurrent lesion (odds ratio [OR], 8.1; p=0.004), and the presence of suspicious lymphadenopathy at the time of recurrence (OR, 14.1; p<0.001).

**Conclusion**: In lung cancer recurrence, the presence of >1 recurrent lesion and suspicious lymphadenopathy at the time of recurrence were significant predictors of extra-pulmonary metastatic disease. These findings may help guide the risk stratification and management of patients with recurrent lung cancer.

Introduction

Lung cancer is an aggressive malignancy that is one of the major causes of cancer-related deaths in the United States [1, 2]. It is the second most common cancer in men and women, after prostate and breast, respectively [3]. However, despite it being the second most common, it is still the leading cause of death in both men and women [3]. Its poor prognosis has been associated with late detection and high rates of recurrence [4]. Observational studies have demonstrated a risk of recurrence ranging between 6–10% in the first four years following resection, with a decline to 2% thereafter [4]. Additionally, they showed the risk of metachronous tumors to be 3–6%, which did not diminish with time [4].

Although these risks are well documented, guidelines for proper routine follow-up vary internationally [5]. Currently, patients are routinely undergoing radiologic imaging follow-up, including chest radiographs and computed tomography (CT), for which the protocol varies between different institutions. Some international guidelines suggest radiographic follow-up biannually for the first 2 years and annually thereafter [5]. However, since differences exist in recommended guidelines, it is clear that the most beneficial regime for routine follow-up is less clear [5–8]. These investigations expose the patient to
radiation and are costly in terms of time, money, and resources [9]. We believe that having a better understanding of the risks of recurrence could potentially save money, time, and radiation exposure. We hope that examining pre- and post-treatment PET/CT imaging and pathological tissue diagnoses will unveil common factors that could predict the risk of recurrence of lung cancer and/or development of extra-pulmonary metastatic disease following treatment.

Previous researchers have outlined how differing morphological characteristics of different lung cancers can predict post-operative prognosis [10–15]. For example, Iwano et al. [10] demonstrated that patients with non-small cell lung cancer (NSCLC) with solid nodules had a significantly worse prognosis than those with subsolid nodules (those containing mixed solid and ground-glass opacity [GGO] characteristics). Whereas, Hattori et al. [11] demonstrated that a NSCLC tumor with a GGO component had a more favorable prognosis. Meanwhile, other researchers have examined peritumoral characteristics, such as lymphovascular invasion (LVI), and how its presence is associated with tumor recurrence in lung adenocarcinoma (most common histological type of NSCLC) [12]. Another study demonstrated that patients with higher preoperative $^{18}$F-fluorodeoxyglucose (FDG) standardized uptake values (SUV) on positron emission tomography (PET) had higher recurrence rates [13, 14]. All of these studies [10–14] examined only pre-treatment PET/CT imaging to assess for predictors of pulmonary recurrence. Whereas, Sung et al. [15] examined pre-treatment CT imaging to demonstrate that the presence of LVI was a significant predictor of extra-pulmonary metastatic disease. Otherwise, the literature examining pre-treatment PET/CT imaging to predict extra-pulmonary metastatic disease with lung cancer recurrence is scarce.

We aim to further investigate the role of pre- and post-treatment imaging, as well as other variables, such as age, pathologic tissue diagnosis, and appearance on PET/CT to attempt to predict the risk of lung cancer recurrence in patients imaged at our institution. Specifically, our objective is to examine pre-treatment PET/CT and post-treatment CT imaging to assess for predictors of lung cancer recurrence, as well as predictors of extra-pulmonary metastatic disease in patients with recurrent lung cancer.

**Methods**

We conducted a retrospective study of all patients at our institution with lung cancer recurrence detected on post-treatment surveillance imaging from January 1, 2014 to October 31, 2019. Research ethics board approval was obtained. Eligible patients underwent pre-treatment PET/CT imaging, surgical resection, and follow-up CT imaging. Inclusion criteria was defined as the following: patients over the age of 18, tissue diagnosis available following lung cancer resection, and evidence of local or metastatic disease recurrence on post-treatment imaging. Patients without tissue diagnosis or pre- and post-treatment imaging at our institution were excluded.

A control group of patients who underwent pre- and post-treatment imaging and surgical resection during the same study period, who were over the age of 18, and had tissue diagnosis available following lung cancer resection, but did not demonstrate lung cancer recurrence, were included. The minimum length of
follow-up imaging to ensure adequate time for detecting recurrence was 24 months. This cut-off was chosen because the mean time to recurrence in the experimental group was 24 months (Table 3).

Data on pre-treatment PET/CT and post-treatment CT imaging characteristics of the pulmonary lesions, as well as pathological findings was collected for each patient. Data for the following variables was obtained: age, gender, size and imaging characteristics (solid, subsolid, GGO, or solid and cystic) of the original and recurrent lesion, location of recurrence (at the surgical margin or distant from the surgical bed but within the lung parenchyma), presence of chest wall or mediastinal invasion, presence of lymphadenopathy, and malignancy subtype (SCC, adenocarcinoma, neuroendocrine, and other). Routine CT chest studies as part of the routine post-treatment follow-up were analyzed for these CT imaging characteristics. CT exams for the abdomen/pelvis and brain were also analyzed, if available, to assess for extra-pulmonary disease. Lymphadenopathy was considered suspicious when the nodes measured ≥1.0 cm or demonstrated avid SUV uptake on PET/CT. All CT studies were reported by the staff radiologists at our institution (2-20 years of radiology experience) and reports were retrospectively analyzed to populate the dataset.

Univariate logistic regression was performed (STATA version 11.2; Texas, United States) for two separate analyses: 1) for assessment of clinical and/or imaging predictors of lung cancer recurrence in patients undergoing imaging follow-up for treated lung cancer (for the recurrence and control groups) and 2) for assessment of clinical and/or imaging predictors of extra-pulmonary metastatic disease in patients with pulmonary recurrence of disease (recurrence group only). Corresponding odds ratios (OR) and p-values were calculated. Two-tailed t-tests (for patient age and size of lesion) and Fisher’s exact tests (for gender, lesion characteristics, mediastinal/chest wall invasion, presence of suspicious lymphadenopathy, and malignancy subtype) were performed to compare patient and lung cancer characteristics on pre-treatment CT imaging between the recurrence and control group, and corresponding p-values were calculated. A p-value of ≤0.05 was considered statistically significant.

Results

A total of 108 patients were included in the study period, of which 76 had lung cancer recurrence, while 32 were followed for a minimum of 24 months with no recurrent disease. Clinical and pre-treatment imaging characteristics for both recurrence and control groups are listed in Table 1. The patient demographics are similar between groups, with 33 (43%) and 14 (44%) males (recurrence group and control group, respectively; p=0.559) and mean age of 70.9±7.7 and 68.4±8.3 years (recurrence group and control group, respectively; p=0.215). The initial pulmonary lesion size was also similar between the recurrence and control group, measuring 3.0±1.7 and 2.9±2.0 cm, respectively (p=0.851). The mean time to recurrence was 24.3±18.8 months. The present study allowed for acceptable follow-up within the control group, with mean time for follow-up of 54.6±25 months. Table 1 displays the distribution of the different lesion characteristics (solid, subsolid, GGO, or solid and cystic), the presence of mediastinal and chest wall invasion, the location of suspicious lymphadenopathy, and the distribution of malignancy subtypes (SCC, adenocarcinoma, neuroendocrine, and other). Information on the TNM (tumor, node, and metastasis)
stage classification (8th Edition) of the recurrence and control groups on pre-treatment PET/CT is provided in Table 2. Table 3 displays characteristics of the recurrent lesion, including: time to recurrence, average number and size of recurrent lesions, and location of recurrence (at the surgical bed, distant to surgical bed, or metastatic). Recurrence distant to the surgical bed refers to recurrence within the lung parenchyma, that is not at the surgical margin. The most common location for extra-pulmonary metastatic disease was in the bones (N=8).

Predictors of pulmonary recurrence in the recurrence and control group are listed in Table 4. Age, gender, malignancy type, lesion size, lesion characteristics, and the presence of suspicious lymphadenopathy on pre-treatment imaging were not statistically significant predictors of local lung cancer recurrence. Predictors of extra-pulmonary metastatic disease in the recurrence group are listed in Table 5. At the time of lung cancer recurrence, the presence of >1 recurrent pulmonary lesion (OR, 8.1; p=0.004), as well as the presence of suspicious lymphadenopathy (OR, 14.1; p<0.001) were statistically significant predictors of extra-pulmonary metastatic disease. Original lesion size, location, and characteristics, as well as chest wall and mediastinal wall invasion on post-treatment CT imaging were not significant predictors of extra-pulmonary metastatic disease.

**Discussion**

The present study retrospectively examined patients at our institution with primary lung cancer, who underwent surgical resection, and had pre-treatment PET/CT and post-treatment CT imaging. Patient and imaging characteristics as well as pathological findings of the pulmonary lesions were analyzed to assess for predictors of lung cancer recurrence and extra-pulmonary metastatic disease. This study demonstrated that the two predictors of extra-pulmonary metastatic lung recurrence were: 1) the presence of >1 recurrent pulmonary lesion and 2) the presence of suspicious lymphadenopathy, on post-treatment CT imaging. Furthermore, lesion size, imaging characteristics, recurrence location relative to surgical bed, or chest wall invasion were not significant predictors of extra-pulmonary metastatic lung cancer recurrence. The reason that the presence of chest wall invasion did not show an association with extra-pulmonary metastatic lung cancer recurrence in this study may have been due to the small number of patients with that characteristic in this cohort.

Many researchers have examined pre-treatment CT imaging to evaluate different factors that may predispose patients to lung cancer recurrence, including CT imaging characteristics and malignancy subtype, to name a couple. However, few researchers have examined post-treatment CT imaging to predict extra-pulmonary metastatic disease with lung cancer recurrence. The current study examined both pre- and post-treatment CT imaging and demonstrated that the presence of >1 recurrent pulmonary lesion and suspicious lymphadenopathy in follow-up CT examinations can predict metastatic recurrence outside of the thoracic cavity. Therefore, in the presence of these two findings on follow-up chest CT, the clinician can predict the likelihood of metastatic recurrence without the additional expended costs (time, resources, money, and radiation) of additional imaging. This additional information may help clinicians
and patients decide on whether or not they wish to undergo further treatment or investigations if the likelihood of extra-pulmonary metastatic disease is higher.

The present study also demonstrated that age, gender, malignancy type, lesion size, lesion CT imaging characteristics, and the presence of suspicious lymphadenopathy on pre-treatment PET/CT imaging were not significant predictors of lung cancer recurrence. Whereas, other researchers have shown a poorer prognosis with solid nodules when compared to subsolid nodules [10, 16], or a more favorable prognosis in nodules with GGO [11, 17]. In regard to predicting prognosis based on lesion size, research groups have found that this comparison should only occur in the pure solid component of nodules [16, 17], with larger size corresponding with worse prognosis [16, 18–22]. The current study was inclusive of all subtypes of NSCLC, whereas other research groups have looked at different subtypes individually [10, 12, 14, 18, 23]. The present study did not find a correlation between malignancy type and disease recurrence, whereas Takei et al. [23] found the poorest prognosis with large cell neuroendocrine carcinoma. Compared to the present study, this disparity may be due to the lack of patients in our experimental group with neuroendocrine histological subtype (Table 1). The reason that lymph node metastasis did not show an association with disease recurrence in this study may have been due to the small number of lymph node metastases in this cohort.

This study had multiple limitations. This was a retrospective, single-center study, and it may not be generalized to other population cohorts. The subject population was small (76 patients) compared to most research groups investigating lung cancer recurrence. The majority of histological diagnoses were adenocarcinoma and SCC (93% of the recurrence group), with few patients with neuroendocrine or other NSCLC tissue diagnoses. Lesion size was measured manually without using computer-aided diagnosis, which lends itself to measurement variabilities [24]. CT exams were read by a single reader and the reports were retrospectively analyzed to populate the dataset. The current study also only included patients who underwent surgical resection. This criterion was used because surgical resection allowed for pathologic correlation as well as to ensure full resection of the lesion. Therefore, the results of the current study would not adequately apply to patients undergoing only chemotherapy and radiotherapy.

**Conclusion**

The two predictors of extra-pulmonary metastatic lung recurrence were: 1) the presence > 1 recurrent pulmonary lesion and 2) the presence of suspicious lymphadenopathy, on post-treatment CT imaging. These findings may help guide clinicians in risk stratification and management of patients with recurrent lung cancer, including the length and frequency of imaging follow-up.

**Declarations**

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Consent for Publication: Not applicable

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Author's Contributions:
- Dr. Tyler Grey: study design, ethics application, data extraction, data analysis, manuscript drafting, article submission, and final approval prior to publishing.
- Dr. Abdullah Alabousi: study design, ethics application, data extraction, data analysis, manuscript editing, article submission, and final approval prior to publishing.
- Dr. Mostafa Alabousi: data analysis, manuscript editing, and final approval prior to publishing.
- Dr. Ehsan Haider: study design, ethics application, manuscript editing, article submission, and final approval prior to publishing.

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Tables

Table 1: Patient and Lung Cancer Characteristics.
PATIENT CHARACTERISTICS

|                                | Recurrence Group | Control Group | p-value |
|--------------------------------|------------------|---------------|---------|
| Number of Subjects             | 76               | 32            | -       |
| Male (%)                       | 33 (43)          | 14 (44)       | 0.559   |
| Female (%)                     | 43 (57)          | 18 (56)       |         |
| Age (years±SD)                 | 70.9±7.7         | 68.4±8.3      | 0.215   |

ORIGINAL LESION

| Characteristics                |                  |               |         |
|--------------------------------|------------------|---------------|---------|
| Size (cm±SD)                   | 3.0±1.7          | 2.9±2.0       | 0.851   |

Characteristics

| Characteristics            | Recurrence Group | Control Group | p-value |
|----------------------------|------------------|---------------|---------|
| Solid (%)                  | 59 (78)          | 19 (59)       | 0.322   |
| Subsolid (%)               | 9 (12)           | 5 (16)        |         |
| GGO (%)                    | 2 (3)            | 2 (6)         |         |
| Solid and Cystic (%)       | 6 (8)            | 6 (19)        |         |

Invasion

| Invasion                   |                  |               |         |
|----------------------------|------------------|---------------|---------|
| Mediastinal Invasion       | 0                | 1             | 0.345   |
| Chest Wall Invasion        | 2                | 0             | 0.544   |

Suspicious Lymphadenopathy

| Suspicious Lymphadenopathy |                  |               |         |
|----------------------------|------------------|---------------|---------|
| Ipsilateral Hilar (% of all patients) | 8 (11) | 2 (6) | 0.744 |
| Mediastinal (% of all patients) | 11 (14) | 3 (9) |         |
| Contralateral Hilar (% of all patients) | 1 (1) | 0 (0) |         |
| Supraclavicular (% of all patients) | 5 (7) | 0 (0) |         |
| Total (% of all patients) | 25 (33)          | 5 (16)        |         |

Malignancy

| Malignancy               |                  |               |         |
|--------------------------|------------------|---------------|---------|
| SCC (%)                  | 21 (28)          | 7 (22)        | 0.100   |
| Adenocarcinoma (%)       | 50 (66)          | 23 (72)       |         |
| Neuroendocrine (%)       | 0 (0)            | 2 (6)         |         |
| Other (%)                | 5 (7)            | 0 (0)         |         |

Values are expressed as number ± standard deviation (SD); GGO, ground-glass opacity; SCC, squamous cell carcinoma
Table 2: TNM Classification (8th Edition) for the Recurrence and Control Groups from Pre-Treatment PET/CT Imaging.

| T Stage | Recurrence Group | Control Group | N Stage | Recurrence Group | Control Group | M Stage | Recurrence Group | Control Group |
|---------|------------------|---------------|---------|------------------|---------------|---------|------------------|---------------|
| 1a      | 5                | 1             | 0       | 59               | 29            | 0       | 75               | 32            |
| 1b      | 17               | 13            | 1       | 8                | 0             | 1a      | 1                | 0             |
| 1c      | 21               | 6             | 2       | 5                | 3             | 1b      | 0                | 0             |
| 2a      | 10               | 5             | 3       | 4                | 0             | 1c      | 0                | 0             |
| 2b      | 3                | 2             |         |                  |               |         |                  |               |
| 3       | 13               | 1             |         |                  |               |         |                  |               |
| 4       | 7                | 4             |         |                  |               |         |                  |               |
| **Total:** | **76**         | **32**        | **76**  | **32**           |               | **76**  | **32**           |               |

T (tumor); N (node); M (metastasis).

Table 3: Lung Cancer Characteristics of the Recurrent Lesions.

| LESION CHARACTERISTICS                                      | Recurrence Group |
|-------------------------------------------------------------|------------------|
| Time to Recurrence (months±SD)                              | 24.3±18.8        |
| Average Number of Recurrent Lesions (N±SD)                  | 2.2±2.4          |
| Average Size of Recurrent Lesions (cm±SD)                   | 1.7±1.3          |

Location

| Location                      | Recurrence Group |
|-------------------------------|------------------|
| Recurrence at the Surgical Bed (%) | 23 (30)         |
| Recurrence Distant to the Surgical Bed (%) | 53 (70)         |
| Metastatic Recurrence (%)     | 13 (17)          |

Values are expressed as number ± standard deviation (SD); Recurrence distant to the surgical bed refers to recurrence within the lung parenchyma, that is not at the surgical bed.
Table 4: Predictors of Pulmonary Recurrence on Pre-Treatment Imaging in the Recurrence and Control Groups.

| Variable                                                      | Recurrence Group | Control Group |
|---------------------------------------------------------------|------------------|---------------|
|                                                               | Odds Ratio       | Standard Error| p-value       | Odds Ratio       | Standard Error| p-value       |
|                                                               | (95% CI)         |                |               | (95% CI)         |                |               |
| Age                                                           | 1.06             | 0.05           | 0.20          | 1.05             | 0.03           | 0.11          |
|                                                               | (0.97-1.15)      |                |               | (0.99-1.10)      |                |               |
| Gender (female; reference: male)                              | 0.47             | 0.30           | 0.24          | 1.05             | 0.45           | 0.92          |
|                                                               | (0.13-1.65)      |                |               | (0.45-2.41)      |                |               |
| **ORIGINAL LESION**                                           |                  |                |               |                  |                |               |
| Type (Adenocarcinoma; reference: SCC)                         | 1.00             | 0.75           | 1.00          | 0.71             | 0.36           | 0.50          |
|                                                               | (0.23-4.31)      |                |               | (0.26-1.91)      |                |               |
| Type (Other; reference: SCC)                                  | 4.00             | 4.42           | 0.21          | 0.833            | 0.79           | 0.85          |
|                                                               | (0.46-34.92)     |                |               | (0.13-5.30)      |                |               |
| Size of Original Lesion                                       | 0.93             | 0.18           | 0.69          | 1.04             | 0.13           | 0.72          |
|                                                               | (0.63-1.35)      |                |               | (0.82-1.32)      |                |               |
| Size of Original Lesion at 3cm cut-off (>3cm; reference: <3cm)| 1.33             | 0.86           | 0.66          | 1.07             | 0.48           | 0.87          |
|                                                               | (0.38-4.69)      |                |               | (0.45-2.56)      |                |               |
| Characteristics of Original Lesion (solid & cystic/GGO; reference: solid) | 0.27             | 0.29           | 0.22          | 0.43             | 0.19           | 0.06          |
|                                                               | (0.03-2.23)      |                |               | (0.18-1.04)      |                |               |
| Lymphadenopathy on PET/CT (yes; reference: no)                | 1.65             | 1.07           | 0.44          | 2.54             | 1.39           | 0.09          |
|                                                               | (0.47-5.88)      |                |               | (0.87-7.41)      |                |               |

CI, confidence interval; SCC, squamous cell carcinoma; GGO, ground-glass opacity
Table 5: Predictors of Extra-Pulmonary Metastatic Disease on Post-Treatment Imaging in the Recurrence Group.

| Variable                                                                 | Odds Ratio (95% CI) | Standard Error | p-value |
|--------------------------------------------------------------------------|---------------------|----------------|---------|
| Recurrent Lesions* (>1; reference: 1)                                     | 8.11 (1.96-33.59)   | 5.88           | 0.004   |
| Size of Dominant Recurrent Lesion                                         | 1.30 (0.86-1.98)    | 0.28           | 0.22    |
| Size of Dominant Recurrent Lesion - 3cm cut-off (>3cm; reference =<3cm)  | 2.29 (0.51-10.30)   | 1.76           | 0.28    |
| Location (distant from surgical bed; reference: at surgical margin)      | 0.52 (0.15-1.85)    | 0.34           | 0.31    |
| Characteristics of Recurrent Lesion (solid & cystic/GGO; reference: solid)| 0.18 (0.02-1.50)    | 0.20           | 0.11    |
| Chest or Mediastinal Wall Invasion (yes; reference: no)                   | 1.34 (0.14-13.16)   | 1.56           | 0.80    |
| Lymphadenopathy on CT* (yes; reference: no)                               | 14.18 (3.30-61.04)  | 10.56          | <0.001  |

CI, confidence interval; GGO, ground-glass opacity; *, significant difference (p≤0.05).

Supplementary Files

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- APPENDIXA.docx