Original Article

Clinical and pathologic staging accuracy in patients with synchronous multiple primary lung cancers

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Background: The incidence of synchronous multiple primary lung cancer (SMPLC) is increasing, occurring in up to 20% of lung cancer patients. Accurately identifying SMPLC can be challenging, and failure to recognize SMPLC results in poor outcomes. We sought to assess the staging accuracy of patients with SMPLC at our tertiary institution.

Methods: We retrospectively reviewed all patients who were evaluated for lung cancer resection between January 2018 to September 2019. Patients with SMPLC were identified using the modified Martini-Melamed criteria. Preoperative imaging, clinical assessment, and pathologic interpretation were reviewed and compared to the final staging assigned by a multidisciplinary lung cancer tumor board to determine accuracy.

Results: Out of 227 patients presenting for lung cancer resection, 47 patients with 119 SMPLC were identified, of which 38 (80.9%) were incorrectly staged by at least one report. Incorrect staging was most common by computed tomography (CT) reports (n=33/47, 70.2%), followed by positron emission tomography-CT (PET-CT) reports (n=28/45, 62.2%), surgeons' clinical assessment (n=10/47, 21.3%), and histopathology reports (n=8/47, 17.0%). CT reports, when incorrect, under-staged 97.0% (n=32) of patients. PET-CT reports, when incorrect, over-staged 25.0% (n=7) of patients by reporting the second primary nodule to be "consistent with metastasis". Histopathology reports, when incorrect, over-staged 87.5% (n=7) of patients despite lack of lymph node involvement.

Conclusions: Patients with SMPLC are at risk of receiving incorrect treatment based on radiographic and histopathologic staging reports alone. The observed staging inaccuracies are concerning, necessitating increased awareness among physicians caring for lung cancer patients.

Keywords: Synchronous multiple primary tumor; lung cancer staging; computed tomography (CT); positron emission tomography (PET); intrapulmonary metastasis (IPM)

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Introduction

Synchronous multiple primary lung cancers (SMPLC) are defined as multiple unrelated primary lung malignancies occurring at the same time (1). Martini and Melamed [1975] were first to establish a criterion to distinguish SMPLC from intrapulmonary metastasis (IPM) (2). Over the years, these criteria have been modified to improve identification of SMPLC (3).

When accurately diagnosed and managed, survival in patients with SMPLC is promising. According to a meta-analysis by Nie *et al.* [2021], 5-year overall survival in patients with SMPLC is approximately 62%, a significant improvement from 5-year overall survival in patients with IPM (4). Thus, failure to recognize SMPLC among patients with multiple pulmonary lung cancers results in suboptimal staging which leads to inappropriate management and poor outcomes.

The incidence of SMPLC has steadily risen (5). A large retrospective study [2023] of patients presenting for lung cancer resection reported a significant rise in the incidence of SMPLC, from 1.35% in 2015 to 15.4% in 2021 (6). In our latest study [2020], we reported an incidence of 20.5% among a contemporary cohort of patients who underwent lung cancer resection (1). However, the incidence of SMPLC widely varies in the literature, reported as low as 0.5% by Zuin *et al.* [2013] (7). We suspect that a lack of understanding, awareness, and application of diagnostic criteria likely results in a lower reported incidence of SMPLC.

To date, no studies have evaluated the accuracy of preoperative staging in patients with SMPLC. We sought to evaluate perioperative staging by computed tomography (CT) scans, positron emission tomography-CT (PET-CT) scans, clinician assessments, and postoperative histopathologic results in patients with SMPLCs at our single tertiary institution. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1383/rc).

Highlight box

Key findings

- In cohort of patients with synchronous multiple primary lung cancer (SMPLC), as assessed by the Modified Martini-Melamed criteria, 80.9% patients were incorrectly staged by at least one modality and 73.6% were incorrectly staged by two or more modalities.

What is known and what is new?

- SMPLC may represent one fifth of patients presenting for lung cancer resection.
- Patients with SMPLC are at risk of being incorrectly staged in this center by preoperative radiographic imaging reports, clinician assessments, and/or histopathology reports.

What is the implication, and what should change now?

- Suboptimal staging of patients with SMPLC is a cause of concern and may lead to poor outcomes. Vigilance of SMPLC among physicians is necessary to optimize the outcomes of this patient population.

Methods

This is a single-center retrospective cohort study that was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethics board of Albany Medical College (No. 5603) and individual consent for this retrospective analysis was waived. From January 2018 to September 2019, consecutive patients who underwent surgical lung cancer resection at our institution were reviewed. A multidisciplinary lung cancer tumor board (MDTB) confirmed patients with SMPLC. The MDTB defined SMPLC using the Modified Melamed-Martini criteria, defined as two or more or more non-small cell lung tumors of: different major histologic types; different histologic subtypes, regardless of nodal status; similar histology arising from *in situ* disease; similar histology without metastatic disease in the intervening regional or mediating lymph nodes; and in the absence of extra-thoracic metastatic disease (1).

Demographics, clinical characteristics, and preoperative clinical staging of radiographic reports, thoracic surgeons, and postoperative histopathology reports were reviewed. Preoperative imaging (CT and PET-CT scan) and surgeons' reports were identified as (I) correct if they identified all malignant nodules, (II) under-staged if they failed to identify all suspicious or malignant nodules, or if they identified all nodules but incorrectly identified one or more nodules as "likely benign" or "not concerning for neoplasm/malignancy", and (III) over-staged if all suspicious nodules were identified but incorrectly reported to be "concerning for metastatic disease", "consistent with metastasis", or "likely metastatic". Histopathology report was compared to the determinations of a MDTB and was

Table 1 Patient characteristics (n=47)

Variables	Values
Age (years)	66.4±8.6
Gender	
Male	20 (42.6)
Female	27 (57.4)
Obesity	7 (14.9)
History of smoking	41 (87.2)
Average pack-year	48.2±18.7
Former smoker	26 (55.3)
Life-long non-smoker	6 (12.8)
Past medical history	
Hypertension	31 (66.0)
Hypercholesterolemia	32 (68.1)
Prediabetes	3 (6.4)
Insulin-independent diabetes	10 (21.3)
Coronary artery disease	14 (29.8)
Peripheral artery disease	7 (14.9)
Chronic obstructive pulmonary disease	22 (46.8)
Emphysema	5 (10.6)
Asbestos exposure	1 (2.1)
Previous extrapulmonary cancer	18 (38.3)

Numbers are presented as n (%) or as mean ± standard deviation.

identified as (I) correct if the results reported the presence of SMPLC, (II) under-staged if the final staging was lower than the current guidelines according to the 8th edition of the American Joint Committee on Cancer (AJCC), and (III) over-staged if it incorrectly identified synchronous tumors as metastatic disease in the absence of intervening lymph nodes (8).

Due to the inherent association between the variables, statistical comparison was deemed inapplicable. Continuous variables are presented as mean ± standard deviation. Categorical variables are presented as n (%). Analyses were performed using the R Version 4.2.2 (R Foundation for statistical computing, Vienna, Austria).

Results

During the 21-month study period, 297 lung cancers were resected with curative intent. Forty-seven patients with 119 tumors met the modified Martini-Melamed criteria for SMPLC: 12 (25.5%) had tumors with distinct histology (Criteria I), 26 (55.3%) had tumors of similar histology but with different histologic subtypes (Criteria II), 6 (12.8%) had tumors with similar histologic subtype in the same lobe, originating from separate foci (Criteria III), and 3 (6.4%) had tumors with similar histologic subtype in different lobes, without any intervening lymph node stations (Criteria IV).

Of these 47 patients, 44 (93.6%) underwent complete surgical resection of all lung tumors. All patients were staged according to the National Comprehensive Cancer Network (NCCN) guidelines (9), including but not limited to preoperative invasive mediastinal staging and intraoperative lymph node sampling or lymphadenectomy.

Patient characteristics

Of 47 patients, 27 (57.4%) patients females, 41 (87.2%) reported present/prior tobacco use, and 18 (38.3%) had a history of previous extrapulmonary cancer. Patient demographics are shown in *Table 1*.

Ipsilateral tumors occurred in 24 (51.1%) of 47 patients, of which 14 (58.3%) patients had tumors located in the same lobe and 10 (41.7%) patients had at least 1 tumor in a different lobe. Bilateral tumors were found in 23 (48.9%) patients; 13 (27.7%) patients had 3 or more SMPLC.

Of 47 patients, at least one tumor was composed of adenocarcinoma in 40 (85.1%) patients, followed by squamous cell carcinoma in 10 (21.3%), carcinoid in 7 (14.9%), and large cell carcinoma in 2 (4.3%). Histologically distinct tumors were found in 38 (80.9%) patients, while the same histological subtype was found in 9 (19.1%).

Of the 119 SMPLC, 6 (5.0%) had N1 disease and none had N2. Based on the highest pathologic stage of the tumor, 34 (72.3%) patients were diagnosed with stage IA disease, 7 (14.9%) patients had stage IIB disease, 4 (8.5%) patients had stage IB disease, 1 (2.1%) patient had stage IIA disease, and 1 (2.1%) patient had stage IIIA disease.

Perioperative staging

Two (4.3%) PET-CT scans were not available for review. All other reports were successfully retrieved and reported for all patients. Overall, only 9 (19.1%) of 47 patients were correctly staged by all reports (CT scan, PET-CT scan, surgeon, and pathology). Thirty-eight (80.9%)

Table 2 Staging accuracy in patients with synchronous multiple primary lung cancer (n=47)

Modality	Number of reports	Interpretation of results		Type of error	
		Correct	Incorrect	Over-staged	Under-staged
CT scan	47 (100.0)	14 (29.8)	33 (70.2)	1 (3.0)	32 (97.0)
PET scan	45 (95.7)	17 (37.8)	28 (62.2)	7 (25.0)	21 (75.0)
Surgeon	47 (100.0)	37 (78.7)	10 (21.3)	0	10 (100.0)
Pathology	47 (100.0)	39 (83.0)	8 (17.0)	7 (87.5)	1 (12.5)

Numbers are presented as n (%). CT, computed tomography; PET, positron emission tomography.

patients were incorrectly staged by at least one report and 28 (73.6%) were incorrectly staged by two or more modalities. Two (4.3%) patients were incorrectly staged by all four modalities.

CT interpretations were incorrect in 33 (70.2%) of 47 reports. PET-CT interpretations were incorrect in 28 (62.2%) of 45 reports. Thoracic surgeons were incorrect in 10 (21.3%) of 47 patients. Histopathology reports were incorrect in 8 (17.0%) of 47 patients.

CT reports, when incorrect, most often under-staged in 32 (97.0%) of 33 patients, of which 27 (84.4%) failed to detect the second malignant nodule and 5 (15.6%) described the second primary nodule as benign.

PET-CT reports, when incorrect, under-staged 21 (75.0%) of 28 patients, of which 17 (81.0%) failed to detect the second malignant nodule and 4 (9.0%) described the second primary nodule as benign. PET-CT reports, when incorrect, over-staged 7 (25.0%) patients by reporting metastatic disease.

Overall, four surgeons were involved in the staging and treatment of patients with SMPLC. Surgeons, when incorrect, under-staged all 10 (100.0%) patients, of which 6 (60.0%) patients had an unrecognized second primary lung cancer at the time of initial presentation and 4 (40.0%) had an incidental second primary tumor removed with the primary surgical resection.

Histopathology reports, when incorrect, most often over-staged in 7 (87.5%) of 8 patients, by reporting T4, M1a, or 'likely metastatic disease' in the absence of positive intervening lymph nodes. Histopathology reports under-staged only 1 (12.5%) patient with two primary tumors in the same lobe who was misclassified as T1a instead of T3. Data regarding staging is demonstrated in *Table 2*.

Three patients (6.4%) underwent surgical resection of at least 1 SMPLC but failed to undergo planned resection for subsequent tumors. Of these cases, 1 patient developed hypertensive crisis intraoperatively, thus the case was aborted. The remaining 2 patients denied subsequent contralateral surgical intervention and were included with intention to treat.

Discussion

SMPLC is a common clinical scenario in patients presenting with lung cancer. In 2016, the International Association for the Study of Lung Cancer (IASLC) suggested that the incidence of patients presenting with a separate primary nodule has increased from less than 3% [1999–2005] to 10% [2007–2010] (10). Our recently published [2020] incidence of contemporary SMPLC in patients undergoing lung cancer resection is as high as 20.5% (1).

Patients with SMPLC are at risk of incorrect staging by initial imaging studies, physicians, and pathologists. Both clinical and radiographic assessments can result in either over-staging or under-staging of patients. This implies that nearly one-fifth of lung cancer patients are at risk of being incorrectly staged which leads to undertreatment. This leads to significant consequences for overall and cancer-specific survival in this group of patients.

In general, patients with SMPLC can be offered surgical resection with impressive 5-year overall survival. Based on the IASLC database [2016], the overall survival in patients with separate tumors has improved from 43% (2004–2006 cohort) to 71% [2007–2010] in patients with N0 M0 lung cancer (10). In a 2021 metanalysis by Nie *et al.*, the pooled 5-year overall survival of patients with reported SMPLC was 62% which was lower (45%) upon exclusion of multifocal ground glass opacities (4). Our group reported a 69% 5-year cancer-specific survival in patients with SMPLC and excluded nonsolid tumors (11). As a result of these favorable outcomes, we have pursued research in hopes of further optimizing these patients' care. In this pursuit, we

sought to clarify how some of these patients are incorrectly staged by radiographic reports, surgeons, and pathologists.

In solitary nodules of the lung CT scan has a reported sensitivity of 93% and a specificity 76% for detecting solid pulmonary nodules, and a sensitivity of 50–70% and a specificity of 65–85% for detecting nodal involvement (12,13). In this study, CT reports were the most inaccurate and staged patients incorrectly in 70.2% of cases. Among the patients who were incorrectly staged, under-staging was more common and occurred in 97.0% of cases. It appears that in patients with a high index lesion, the report frequently elaborated on the high index lesion, its mediastinal staging, and recommendations, but frequently understated, underestimated, or entirely failed to comment on the additional nodules that eventually proved to represent a second primary lung cancer. Over-staging was uncommon by CT reports. Only 1 (2.1%) of 47 patients with a second primary tumor was interpreted to have a "metastatic lesion".

^{18}F-fluorodeoxy-glucose PET-CT scan is routinely used in staging of lung cancer with a reported sensitivity of 88–96% and a specificity of 70–90% for detecting solitary malignant pulmonary nodules, and a sensitivity of 75–85% and a specificity of 85–90% for detecting nodal involvement (based on the standardized uptake value threshold of 2.5) (12,13). In this study we found that PET-CT reports were incorrect 62.2% of the time. Incorrect staging in this group differed from the CT group with many more reported as metastatic disease (25.0%). PET-CT reports under-staged 75.0% of cases. Once again, in patients who were under-staged, radiographic reports appeared to underreport the secondary less conspicuous lesion(s).

Surgeons' preoperative staging was more accurate than CT and PET-CT reports; 79.7% of secondary malignant nodules were correctly identified preoperatively. Only 21.3% of patients were incorrectly staged by surgeons. All patients who were incorrectly staged by the surgeon were under-staged. Among those, most patients had an unrecognized second primary lung cancer at the time of initial presentation, and the remainder had an incidental second primary tumor removed with the primary surgical resection and subsequently identified by pathology and vetted to be SMPLC according to the MDTB.

As expected, histopathology reports were the most accurate, but not in every case. In fact, 17.0% of patients with SMPLC, when compared/vetted to the MDTB, were incorrectly staged. Among those that were incorrectly staged, 87.5% were over-staged. In these cases, the histopathology report commonly mislabeled SMPLC as T4 or M1a disease, particularly when tumors of the same histology were located in different lobes. According to our MDTB, which used the modified Martini-Melamed classification, these tumors represent SMPLC in the absence of positive intervening lymph nodes. Many of the instances of over-staging pathology reports involved comments about the "potential for SMPLC" or "evidence of *in situ* disease", but in the end still staged them inaccurately as T3, T4, and M1 disease.

Similar histologic staging does not necessarily indicate the second lesion is an IPM. In fact, our data here supports that IPM may be relatively uncommon and pulmonary metastases in different lobes (T4 and M1a) even less common. This is strongly supported by a study from Memorial Sloan Kettering. Finley *et al.* [2010], which reviewed 34 histologic T3 tumors for subtyping and found that 27 (79.4%) of those tumors were discordant—meaning they represented SMPLC and not IPM (14). The recommendations proposed by Martini and Melamed in 1975 have remained consistent, with the most significant change over the past 45 years being the histologic subtyping of same lobe lesions introduced by Finley *et al.* in 2010 (14). Regardless of Finely's choice to include T3 tumors of different histology is unimportant since present guidelines for T3 same lobe tumors includes surgery. Where we fail to manage these patients properly is in recognizing SMPLC in patients who present with multiple lung cancers in multiple lobes. Great care must be taken to avoid staging SMPLC as IPM, which inevitably eliminates the option for surgery, treatment with curative intent, and results in poor outcomes.

Recommendations for workup of patients with multiple separate and distinct nodules are outside the scope of this paper, although the IASLC [2016] has published their recommendation (10). Preoperative biopsies are frequently unhelpful and can increase confusion. The fundamental problem is that having the same histology does not rule out SMPLC, nor does it guarantee IPM. Preoperative biopsies have several imitations. First, their sensitivity and specificity are not particularly high. Second, biopsy techniques often yield insufficient tissue, making it challenging or even impossible to differentiate histologic subtypes. Third, biopsies frequently fail to sample key tumor components, such as tumors arising from *in situ* disease. Ultimately, the major drawback of relying on biopsies in these patients is that having the same histology does not always entail the presence of IPM.

Improving the accuracy of staging for patients with two or more suspicious lung nodules can be achieved by implementing a MDTB and raising awareness of SMPLC among healthcare professionals, including thoracic oncologists, primary care physicians, radiologists, pathologists, and thoracic surgeons. Radiologists are advised to report all suspicious nodules, rather than solely focusing on the primary high-index lesion, and to refrain from prematurely "labeling" lung nodules as malignant unless there is evidence of extrapulmonary metastasis.

While next-generation sequencing technology shows potential for enhancing the detection of SMPLC (15), this approach is costly and is still in its early stages. Further, it has several limitations including frequent discordance (5) among tumors with the same histology and identical driver genes, recently reported in 7.5% of cases (15). While continued efforts are necessary to determine the role of molecular analysis in the management of patients with multiple suspicious lung nodules, current endeavors should also focus on refining the existing approach for patients with multiple suspicious lung nodules until this technology becomes more widely available.

Perhaps the nomenclature itself is poor and could be modified into a more self-defining language. We propose SMPLC should simply stand for Simultaneous Multiple Primary Lung Cancer, and we will do so in our future publications.

One limitation that holds significance for future investigations is the fate of those who undergo staging but are not subsequently referred to surgeons. The findings presented in this study only pertain to patients who have been referred to thoracic surgeons at a tertiary referral center. Certainly, there are additional patients with SMPLC who receive treatment based on radiographic assessments only that incorrectly stage them as having IPM and referred elsewhere. Unfortunately, those patients are mismanaged. Future prospective studies should explore the factors contributing to inaccurate perioperative staging in patients who present with multiple concerning lung nodules.

Conclusions

This study highlights the crucial role of thoracic surgeons and a MDTB in staging of patients with SMPLC. The high prevalence of under-staging by preoperative imaging is a cause for concern and may be attributed to the radiologists' emphasis on the primary nodule in question, which may be further influenced by their education and experience with lung cancer. The limitation of preoperative imaging mandates the independent auditing of images to accurately stage lung cancer patients. It is crucial for all clinicians involved in the management of patients with primary lung malignancies to be aware of SMPLC and the risk of undertreating potentially curable patients. Future studies should explore factors that contribute to inaccurate staging in patients with simultaneously multiple primary lung cancers.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1383/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1383/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethics board of Albany Medical College (No. 5603) and individual consent for this retrospective analysis was waived.

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