ORIGINAL ARTICLE

The IASLC Lung Cancer Staging Project: Background Data and Proposed Criteria to Distinguish Separate Primary Lung Cancers from Metastatic Foci in Patients with Two Lung Tumors in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer

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ABSTRACT

Introduction: It can be difficult to distinguish between a second primary and a metastasis in patients with lung cancer who have more than one pulmonary site of cancer.

Methods: A systematic review of the literature was conducted by a subcommittee of the International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee to develop recommendations to identify second primary lung cancers. The process entailed review of knowledge relating to the mechanism of metastasis, determination of clonality, and outcomes of patients with resected tumors.

Results: It is easier to determine that two tumors are different than that they are the same; finding similarities does not establish that they are the same. For example, most second primary lung cancers are of the same histotype. Few criteria are reliable by themselves; these include different histologic cancer types or matching DNA breakpoints by sequencing and a comprehensive histologic assessment of resected specimens. Characteristics that are suggestive but

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**See Appendix for the members of the IASLC Staging and Prognostic Factors Committee, Advisory Boards, and the Multiple Pulmonary Sites Workgroup.*

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associated with potential misclassification include the presence or absence of biomarkers, imaging characteristics, and the presence or absence of nodal involvement.

Conclusions: Clinical and pathologic (i.e., after resection) criteria are presented to identify two foci as separate primary lung cancers versus a metastasis. Few features are definitive; many commonly used characteristics are suggestive but associated with a substantial rate of misclassification. Careful review by a multidisciplinary tumor board, considering all available information, is recommended.

Keywords: Lung cancer; Non–small cell lung cancer; TNM classification; Lung cancer staging; Multiple tumors

Introduction

An increasing number of lung cancers exhibit two (or more) malignant pulmonary lesions (15% of surgical patients in a recent large series).[1,2] There is ambiguity in the stage classification of such tumors, and interpretation of how to classify them varies markedly.[3,4] More importantly, it is unclear how to think conceptually about the nature of these lesions, and how to manage the patients.

This article is a review of pertinent data addressing this scenario to establish a basis for classification of such tumors in the eighth edition of the stage classification system. How to manage these patients is beyond the scope of this article.

To address how to distinguish a second primary lung cancer from a pulmonary (oligo)metastasis, three approaches were chosen. First, we examined current data on the mechanism of metastasis. Second, we reviewed data regarding identification of a single or separate lineage (clonality)—whatever the mechanism of metastasis might be. Finally, we examined outcomes—specifically, which scenarios are associated with high cure rates (or subsequent disseminated metastases) after definitive local therapy. Considering everything together, we formulated criteria to classify two synchronous malignant pulmonary lesions as separate primary cancers or as metastatic from one another.

Methods

The International Association for the Study of Lung Cancer (IASLC) Staging and Prognostic Factors Committee (SPFC) is charged with developing proposals for revision of the stage classification of lung cancer. To provide greater clarity and consistency in classification of patients with more than one malignant pulmonary lesion, the SPFC appointed an international multidisciplinary subcommittee (the authors of this article). The full scope of this effort is reported elsewhere[5–7]; however, a fundamental issue is to distinguish whether tumors are separate or related to each other. This specific topic is the focus of this article.

The multiple lesions subcommittee carried out a systematic search with a methodologist's help for relevant literature from 1995 to 2015, building on a prior systematic review of patients with multiple tumor lesions conducted by the American College of Chest Physicians (ACCP) for the Lung Cancer Guidelines (third edition).[8,9] Reference lists of identified articles were also examined, and each article in the ACCP review was revisited to ensure appropriate categorization and data abstraction. For the process of metastasis, articles were limited to review articles from 2000 to 2015. The population, intervention, comparator and outcomes questions, search, results, and inclusion and exclusion criteria are available on request.

The identified evidence was reviewed, interpreted, and summarized by the subcommittee through an iterative process. Successive drafts were discussed and circulated for revision. The article was then sent for critical review to an extended workgroup of individuals with particular interest and expertise in this topic (see the Appendix). The refined article then underwent further review and eventual endorsement by the entire SPFC.

Results: The Process of Metastasis

More than 85 years ago James Ewing proposed that metastatic dissemination occurs by purely mechanical factors determined by the anatomical structure of the vascular and lymphatic system.[10] This concept was based on a speculative rationale but was countered by the observation that different primary tumors exhibit a predilection for particular metastatic sites.[11,12] Nevertheless, this simple physical concept of metastasis remains widely pervasive, and terms based on this idea (*hematogenous*, *lymphatic metastases*) are still in common use. "Aerogenous" dissemination via the airways was suggested more than 60 years ago,[13] implying dissemination via airways. The term *intrapulmonary metastasis* has also been used in the context of two or more malignant pulmonary lesions and no other sites of cancer (without clarity regarding how such intrapulmonary dissemination might occur). Recently, the term *spread through air spaces* has been introduced,[14,15] but this describes observing tumor cells under a microscope immediately adjacent to the tumor.

Knowledge of the process of metastasis has progressed dramatically. The data demonstrate this is an intricate multistep process.[16,17] Evidence indicates that key genetic lesions permitting metastasis are an early

event, consistently present in both localized and disseminated tumors.[18] During the process of metastasis the cancer cell is transformed into different phenotypes. Tumor cells exhibit plasticity, meaning that they change, including their morphologic characteristics, as they undergo epithelial to mesenchymal transition during the multistep invasion-dissemination process (invasion, intravasation, migration, and survival in the circulation), and then likely undergo mesenchymal to epithelial redifferentiation as the process of extravasation, colonization, and metastasis formation continues.[16–18]

The various steps are influenced not only by tumor cell–intrinsic genetic and epigenetic determinants but also by a complex array of tumor-host interactions at both the primary and metastatic sites.[16–18] Tumor cells are present simultaneously in many different forms—at the primary site, as circulating tumor cells, and in metastatic sites; furthermore, these various states consist of heterogeneous subpopulations with different gene expression, host-tumor interactions, and potential biologic behavior. Circulating tumor cells can be detected frequently in early-stage lung cancer—in fact, even before evidence of invasion at the primary site; yet the vast majority (99.98%) do not survive to become distant metastases.[17,19] Disseminated tumor cells exist within permissive niches, often remaining for a long time in a dormant state, but then exit this state and actively grow. In addition, there appears to be a complex dynamic flow of tumor cells between the primary site, circulating cells, metastatic niches, and overt metastases and back to the primary site. All of this is influenced by multiple pathways, cell signaling, tissue microenvironment characteristics, and pressures mediated by growth factors and cytokines selecting certain subpopulations (e.g., hypoxia, immune interactions, chemotherapy, etc.).

Additionally, multiple components of the microenvironment steer the metastatic process. Angiogenesis, a major hallmark of cancer, represents activation and proliferation of endothelial cells owing to tumor cell hypoxia.[20] Neovascularization allows recruitment of inflammatory and immune cells in the stroma, as well as the invasion and circulation of tumor cells.[21] However, tumor cells hamper activation of immune response through multiple mechanisms, leading to a failure of immunosurveillance.[22]

The amount of data, as well as the complexity of the process of metastasis, is impressive. Many pieces are still unclear (e.g., the relative impact of various processes and factors governing their rise and fall in importance during the course of the disease). However, the evidence indicates that the process is complex and simple physical transport of a cancer cell through the lymphatics, bloodstream, or airways is a grossly inadequate oversimplification.

Section Summary

The concept that metastasis is determined primarily by physical channels for movement of a malignant cell from one site to another is a historical, speculative hypothesis. Although this concept can explain some observations, it fails to explain others. More importantly, the scientific evidence demonstrates that a purely physical mechanism is not the primary factor determining metastatic behavior. The terms *lymphatic spread* and *hematogenous spread* are an oversimplification that inhibits consideration of the multistep process of metastasis as it is currently understood.

The actual process of metastasis is too complex to be used to identify which lesions are separate tumors and which have arisen from one another. We conclude that a speculative mechanism of metastasis should not be used to categorize two pulmonary lesions.

Results: Establishment of a Single or Separate Lineage

Background

Are there tumor characteristics that define two lesions as having developed separately versus having arisen together and thus being related? This question requires a gold standard that defines separate or related, against which prediction by particular characteristics can be compared; however, no such standard exists.

Patients with widespread metastases are a reasonable clinically defined cohort with foci of cancer that are related. How well particular characteristics predict a single lineage in this setting is a surrogate for how well such characteristics might identify single lineage in a patient with two or more malignant pulmonary lesions (and no other distant metastases). A reasonable definition of unrelated lung cancers is metachronous cancers—ideally, widely separated in time (e.g., >5 years). However, such details are not explicitly reported in published studies.

Comparison of Primary and Metastatic Foci in Patients with Obvious Metastatic Dissemination.

Histologic Appearance. It is widely accepted that the histologic appearance of metastases mirrors that of the primary tumor, although sometimes metastases are less well differentiated. Biopsy of a metastasis is considered adequate to establish a diagnosis, and the morphologic appearance is used to define the organ of origin. Although no recent articles address how reliably morphologic appearance is conserved, there are no published reports of a discrepancy. It seems reasonable to accept that the morphologic appearance of metastases matches that of the primary site; this implies that a

morphologically different appearance is reasonable evidence that two tumors are unrelated.

However, our knowledge of mechanisms that control histologic appearance may be rudimentary. Tumors can change their appearance from one histotype to another. For example, after treatment with an epidermal growth factor receptor (EGFR) inhibitor, adenocarcinomas can change their appearance to that of small cell (and back again).[23] In the laboratory, depending on the culture medium used during early propagation, human mammary cells can be transformed into either a squamous cell carcinoma or an adenocarcinoma.[18,24] Nevertheless, the widespread consistent clinical observation is that morphologic appearance is maintained for a given cancer across all sites of growth.

Biomarker Pattern. Genomic analysis of lung cancer led to the identification of, among numerous other molecular alterations, specific mutations that are necessary and sufficient to drive tumor formation and maintenance.[25] These "driver mutations" occur primarily in genes that encode signaling proteins critical for cellular proliferation and survival. Expression of these single mutant oncogenes drives growth, even without other alterations. On the other hand, a hallmark of cancer is genomic instability leading to an increasing number of mutations. However, these "passenger mutations" typically have unknown significance for the growth of tumors, but may indicate a specific developmental lineage within heterogeneous tumors.[26]

In breast cancer, frequent discordance (5%–50%) of common biomarkers (Estrogen Receptor, Progesterone Receptor, and Human Epidermal Growth Factor Receptor 2) between the primary tumor and metastatic sites is reported.[27] In lung cancer, a recent review noted discordance between primary and metastatic sites of 0% to 38% for an epidermal growth factor receptor gene (*EGFR*) mutation, and 23% to 33% for *EGFR* by fluorescence in situ hybridization.[27] Numerous other studies (Fig. 1) report a substantial rate of discordance (~25%, range 12%–45%) between primary and metastatic sites of lung cancer for driver mutations (*EGFR*, *KRAS*, and *p53*)[28–38]; only one study of six patients found no discordance.[39] Similarly, sampling of 50 to 60 different areas in 21 resected *EGFR*-mutated lung cancers found mixtures of *EGFR*-mutated and nonmutated cells in 29% of the samples.[40] However, discordance might be explained by technical variability, assay sensitivity, size of specimens, tumor cell content, storage issues, and variable sensitivity of genotyping methods. A carefully done study using multiple controls found no discordance between primary and metastatic sites in 137 lung adenocarcinomas, and no heterogeneity among three different sampled areas of a tumor in 50 patients and among 100 different areas in five patients.[41] Another detailed analysis using multiplex sequencing found only 7% discordance between primary and metastatic sites for lung cancer driver mutations, but approximately 40% for somatic alterations (i.e., passenger mutations).[42] Discordance in *ALK* rearrangements between primary tumors and metastases has also been reported.[43]

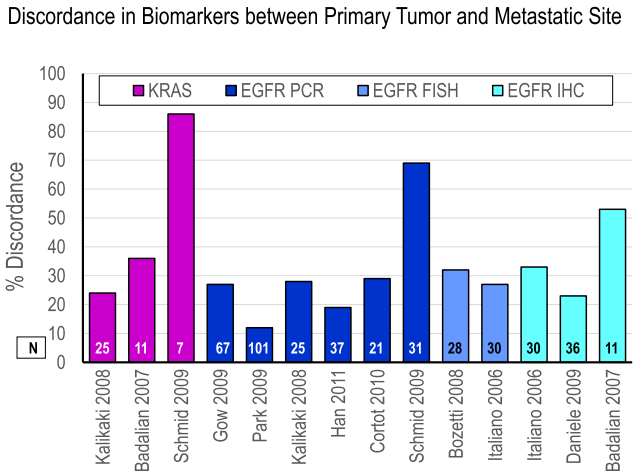

Figure 1. Reported rates of discordance between primary and metastatic sites of lung cancer for various biomarkers. These studies excluded patients who had been treated.

Comparison of Foci in Patients with Clearly Separate Tumors.

Histologic Appearance. Most second primary lung cancers are consistently reported as being of the same major histotype (e.g., 2 adenocarcinomas, or 2 squamous cell carcinomas).[9,44–66] Generally good outcomes are observed, suggesting that the assessment as two separate primary cancers was correct. Furthermore, there is no survival difference in second primary cancers with the same versus a different cell type.[9,45–49,55,57–61,63,65–69,70] Rarely has a trend toward better survival been observed when the histotypes are different.[62,71]

Therefore, the finding that two (otherwise seemingly separate) tumors are of the same cell type is not proof that these are a single tumor. Whatever etiologic factors are involved in a patient might be expected to lead to the same histotype, potentially explaining the fact that most often both tumors are the same cell type.

Biomarker Pattern. There are few data regarding how often metachronous second primary lung cancers exhibit the same genetic mutation. One study of 75 evaluable patients found that 33% of metachronous second primary lung cancers had matching EGFR and/or p53 mutations as the first primary lung cancer.[72] Matching mutations could simply reflect the high prevalence of such mutations or the impact of similar etiologic factors.

In addition, several studies have shown that driver mutations are frequently (7%–43%) present in normal lung tissues of patients with lung cancer.[73–75] A germline *EGFR* mutation that confers a predisposition to similar familial lung cancers across multiple generations has also been demonstrated.[76–78] Thus, finding the same gene mutation does not prove that two lung cancers arose from the same clone.

Potential Criteria to Define Lineage of Two Malignant Lung Lesions

Histologic Appearance.

Histologic Type. Because histologic appearance is conserved when widely metastatic, it seems very unlikely that it would not be conserved in an oligometastasis. This rationale argues that we can be confident that lesions of different tumor types have developed independently.

However, two lesions of the same major histotype in a given patient do not prove that they arose from a single source (indeed, it is the most common presentation of separate primary lung cancers). Two lesions being of the same histologic type should be viewed as necessary but not sufficient to establish a single lineage.

A recent systematic review and meta-analysis found an interobserver agreement rate on non–small cell lung cancer (NSCLC) histotype in resected specimens of 67% to 90% (3022 cases in total).[79] A study based on 1032 biopsy specimens noted agreement in 81% of cases (no immunostains were used).[80] Cell type diagnosed by cytologic examination was concordant with histologic examination findings in 87% of 158 cases in another study (excluding inconclusive cases).[81] However, these studies were conducted before the 2015 revisions in the World Health Organization classification.[82]

Histologic Subtype. A more detailed assessment has been proposed; it involves evaluation of the histologic subtype, the relative proportion of subtypes, grade, and cytologic and stromal features (Fig. 2).[83] In an assessment of 20 patients with 42 multiple lesions (both synchronous and metachronous) the comprehensive histologic assessment was concordant with a detailed molecular assessment (a five-gene mutation panel and comparative genomic hybridization [CGH] in 91%). Furthermore, patients classified as having separate cancers by the comprehensive histologic assessment exhibited good survival, and those classified as having similar tumors had poor survival after resection; the detailed histologic assessment predicted survival better than did either molecular or Martini-Melamed (MM) criteria.[83] A study involving a similar approach found 91% concordance of the detailed histologic assessment with a detailed molecular evaluation; survival in the 12

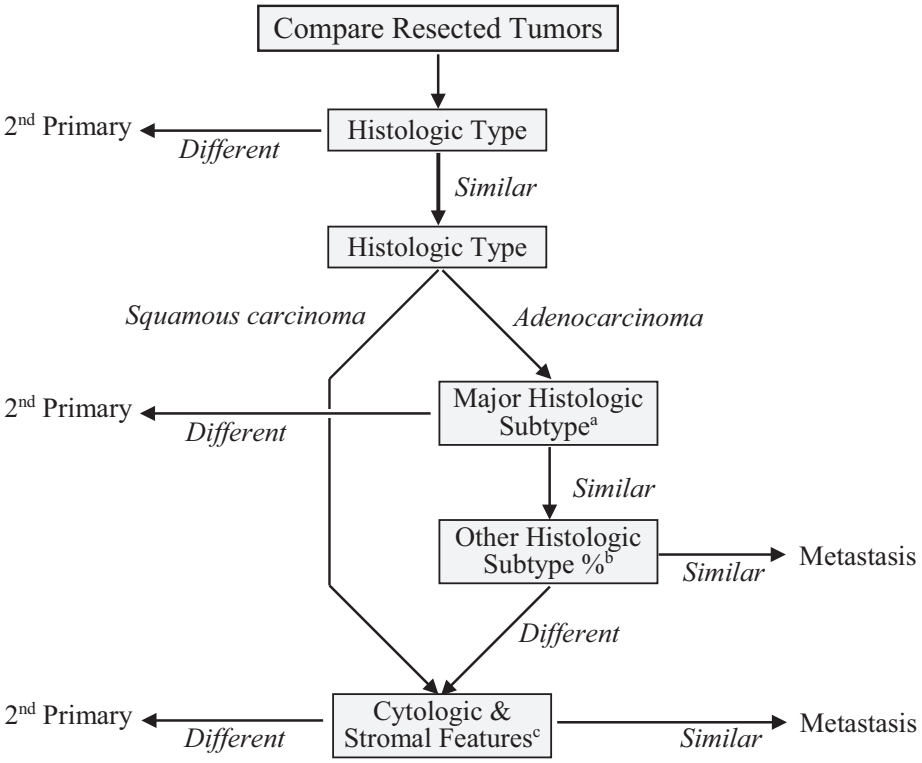

Figure 2. Process of conducting a comprehensive histologic assessment. [a]The predominant subtype is determined. [b]The relative percentage of each histologic subtype is estimated in 10% increments. [c]Cytologic/stromal features include grade, necrosis, inflammation, lymphoid hyperplasia, desmoplasia, and keratinization. Adapted from Girard et al.[83]

study patients was not assessed.[84] Another study[66] observed equal survival for node-negative synchronous adenocarcinomas whether classified as the same or different by histologic subtype assessment (n = 30 versus 48, 5-year overall survival [OS] = 61% versus 69%, $p = 0.5$, respectively). However, no detailed assessment was performed (i.e., percentages of each subtype, stromal, and cytologic or nuclear characteristics). Furthermore, reproducibility in subtyping adenocarcinomas and poorly differentiated NSCLC is moderate, likely due to heterogeneity.[85,86]

Details of how a comprehensive histologic assessment is done may be important: the comprehensive histologic assessment did not perform well in banked frozen tissue samples, being discordant with assessment in paraffin-embedded tissue in 17% of cases and not evaluable in another 8%.[83] This means that the comprehensive histologic assessment is primarily applicable to resected patients (after treatment decisions have been made). It has not been assessed in small biopsy specimens or intraoperative frozen section settings.

Supporting a comprehensive histologic assessment as a way to identify tumors as being separate or the same is the general conservation of appearance between primary tumors and (distant) metastases, the correlation with a detailed genomic assessment, and the correlation with survival in one study.[83] Furthermore, the comprehensive histologic assessment results (when consistently assessed by two reviewers) were concordant with the lineage as assessed by CGH in 89% (nine of 11 patients).[87] Nevertheless, the data on comprehensive histologic assessment are based on a limited number of patients and we lack a gold standard. It may be that a different appearance on detailed assessment is sufficient to define separate primary tumors, but a similar appearance does not necessarily define lesions as metastases.

Genetic Characterization. Many types of genetic characterization are available, each with advantages and limitations. Furthermore, genetic alterations may involve specific mutations, gene amplifications or deletions, and gene fusions or rearrangements. Mutation profiling by polymerase chain reaction (PCR) sequencing (for specific mutations) and fluorescence in situ hybridization (for amplification/deletions and fusion/rearrangements) are inexpensive, widely available, and feasible in small biopsy specimens but have limited sensitivity in heterogeneous specimens (i.e., low tumor content). Multiplex genotyping assays have increased sensitivity and allow for simultaneous detection of multiple mutations but are applicable only to prespecified specific mutations. Multiplex PCR-based massively parallel next-generation sequencing does not require prespecification but is not applicable to amplification or fusion alterations. CGH to detect chromosomal aberrations and focal amplification/deletion has become more widely available but requires a relatively large amount of high-quality DNA. So-called "third-generation" capture-based massively parallel next-generation sequencing has high sensitivity and can rapidly detect all types of genetic alterations, requires less DNA, and is applicable to biopsy specimens. This approach can detect thousands of single-nucleotide variations and rearrangements—and although the same specific single-nucleotide variation mutations (e.g., in *EGFR* and Kirsten rat sarcoma viral homolog gene [*KRAS*]) are often found in different patients, identical breakpoints in genetic rearrangements have not been detected among different patients.[87,88] Finally whole-exome or whole-genome sequencing has been proposed, but it suffers from being expensive, not being applicable for rearrangements, being hard to implement in the clinic, and having limited sensitivity as currently available.

Specific Mutations. Many studies assessed particular mutations to define clonality—assuming that a match of a few (one to five) markers defines a single clone whereas a difference defines separate cancers (Supplementary Table 1, Supplementary Digital Content 1).[73,89–92] However, the heterogeneity of marker detection in clearly related tumor deposits (Fig. 1) calls for caution. OS after resection can serve as a gold standard; it is striking that studies evaluating survival demonstrated no correlation between clonality defined by specific gene mutations and outcomes (Supplementary Table 1, Supplementary Digital Content 1).[73,90,93] Therefore, it is unclear that either a difference in specific mutations identifies separate primary cancers or that mutations in the same gene define a single lineage.

Comparative Genomic Hybridization. Some studies used more sophisticated genomic analysis techniques, often combined with assessment of specific mutations.[1,84] The markedly greater detail assessed suggests these may be a more reliable measure of clonality. When such a detailed genomic assessment is compared with evaluation of specific mutations or with a comprehensive histologic assessment (type, subtype, and various morphologic features), each technique shows a low level of discordance with the other assessments in 0% to 25% of cases in small studies (eight and 12 patients),[1,84] and it is not clear that the more sophisticated techniques are best. The survival of patients classified by CGH plus mutational profiling as having different tumors showed only a nonsignificant trend toward better survival than that of patients classified as having similar tumors (n = 20, p = 0.13).[83] Moreover, CGH is complex to integrate in

a routine clinical practice, especially on small biopsy specimens, given the need for large amounts of high-quality tumor DNA.

Next-Generation Sequencing. Next-generation DNA sequencing identifies breakpoints in gene rearrangements; to date, no duplicate breakpoints have been reported among clearly unrelated tumors (e.g., different patients and tumors with different histologic features), whereas shared breakpoints are common within related tumors (primary and metastatic sites or in multiple biopsy specimens from one site).[87] This technique appears promising to identify lineage;[87] however, there is no gold standard with which to compare, and the evaluation is limited to 11 patients.[87] Furthermore, the analysis involves complex management of a bioinformatics algorithm (e.g., to minimize false positives, false negatives, and other errors) and a probability statistic (to estimate the probability of relatedness based on the number of shared breakpoints).[87]

Section Summary

In the setting of obvious metastatic dissemination, histologic appearance is generally conserved. Thus, it is reasonable to conclude that lesions of different histotypes are two separate primary cancers. A more detailed histologic assessment (Fig. 2) appears to be useful, although only reported in a few small studies and without a gold standard that would permit robust assessment. Nevertheless, it seems reasonable to define lesions that are different by a comprehensive histologic assessment as separate primary cancers. This is based on the general conservation of histologic appearance between primary and metastatic sites, and on the correlation with survival and with a detailed genomic assessment.

Establishing that two lesions are not just similar but actually the same tumor is more difficult. Simple demonstration of the same histotype is not sufficient. It is appealing to consider a comprehensive histologic assessment, but the data regarding this are limited and probably apply primarily to resected specimens (after a management decision has been made). At this point we conclude that a matching appearance by detailed histologic assessment is best viewed as strongly suggestive that lesions are of a single lineage.

Demonstration of specific driver mutations by widely available PCR sequencing techniques is suggestive but not definitive in establishing relatedness. Reliance on mutation pattern should be tempered by the general prevalence of these mutations and the moderate frequency of discordance between primary and metastatic sites in obviously disseminated disease. Mutation pattern must be considered together with other data (e.g., clinical, radiologic, and morphologic).

A detailed genetic assessment such as CGH may have greater discriminative power but has been used in only a few small studies. There appears to be some discordance compared with other assessments of tumor relatedness, and correlation with survival is poor. Much more sophisticated techniques such as next-generation sequencing and comparison of exact breakpoints in gene rearrangements is promising; however, the data are limited, the assessment is complex, and at this time it is more applicable as a research than a clinical tool. Finally, the demonstration of reseeding of primary sites from metastatic sites[94] may hamper our ability to compare molecular profiles in multiple cancers.

Results: Patient Outcomes after Treatment

Five-year OS after definitive local therapy is high (~70%) in patients with stage I NSCLC and low (~15%) in those with (oligo)metastatic disease.[95] (We defined definitive local therapy as lobectomy or segmentectomy for stage I NSCLC; the efficacy of wedge resection or stereotactic body radiation therapy is more ambiguous and potentially confounded [e.g., comorbidities, staging, and limited margins]. Thus, good or poor OS after resection of two pulmonary sites of cancer strongly suggests either synchronous stage I cancers or (oligo)metastatic disease. The absence of a rapid appearance of distant metastases could also distinguish these entities, but this outcome is rarely reported.

However, good outcomes may be seen in indolent tumors regardless of treatment (e.g. adenocarcinoma in situ and minimally invasive adenocarcinoma), and poor outcomes may result from factors unrelated to the tumor biology (e.g., comorbidities or not undergoing definitive therapy). Outcomes in patients who are not treated with definitive or effective local therapy are not helpful.

Our systematic review of synchronous lung cancers (Table 1) shows that good 5-year survival was achieved (especially for patients with stage N0 disease). The centers appear to have appropriately identified synchronous primary cancers but are vague about how this was done. The survival rates have generally improved over time—with some variability, possibly due to selection (e.g., favorable oncologic or physiologic characteristics), inclusion criteria (e.g., incidental, bilateral lesions), resection extent (e.g., rate of pneumonectomy or wedge), or other factors.

Cited Criteria to Distinguish Multiple Primary Lung Cancers from Pulmonary Metastases. The Martini and Melamed (MM) criteria (Supplementary Table 2, Supplementary Digital Content 1), proposed in 1975, were empirically derived, applied to only 50 patients (18

Table 1. Survival of Patients with Synchronous Second Primary Lung Cancers

First Author	No. Patients	Definition	% Incidental[a]	% Resected	% Limited Resection[b]	% Op Mort	% 5-Year Survival		% 5-Year Survival by Histotype		
							All	pI	Same	Diff	*p* Value
Yu[66]	97	Girard	–	100	51	0	70	70[c]	65	74	0.3
Zuin[96]	23	MM?	–	100	–	–	40	–	–	–	–
Shah[59,d]	47	–[d]	0	100	83	2	29	–	23	40	0.9
Fabian[60]	67	–	–	100	60	2	53	–	49	42	0.9
Jung[70]	32	MM	3	100	50	9	61	69	100	36	0.003
Kocaturk[62]	26	Unclear	–	92	38	8	50	–	25	78	0.2
Finley[61]	175	Girard	42	100	27	1	52	64[e]	(67)[f]	(50)[f]	>0.05
Voltolini[65]	50	–	0	>90	65	7	31	57	34	33	0.6
Riquet[57]	118	Unclear	–	100	16	5	26	–	33	20	0.4
Rostad[58]	94	Unclear	79	100	16	9	33	–	No diff		0.3
De Leyn[55,d]	36	–[d]	–	100	72	3	38	–	31	45	0.3
Trousse[97]	125	MM?	–	100	14	11	34	51	–	–	–
Chang[98]	92	–	–	100	11	1	35	53	–	–	–
Vansteenkiste[99]	35	Unclear	–	100	23	9	33	–	–	–	–
Van Rens[100]	85	MM?	32	100	13	14	20	23	No diff		–
Okada[50]	28	MM?	39	96	7	0	70	79[g]	–	–	–
Antakli[51]	26	Antakli	19	92	42	–	5	–	–	–	–
Average[h]			**27**		**37**	**5**	**40**	**58**	**45**	**46**	

Note: Inclusion criteria: studies from December 1995 to April 2015 of at least 20 patients with synchronous second primary lung cancers reporting survival data.
[a]Percentage found incidentally at time of resection.
[b]Percentage of patients who underwent wedge resection or segmentectomy.
[c]Includes 8% T3N0M0 for largest tumor.
[d]Bilateral tumors only.
[e]Stage Ia only.
[f]Three-year survival excluded from average calculation.
[g]Stages I and II.
[h]Excluding values in parentheses.
Antakli, criteria proposed by Antakli; Diff, different; Girard, MM plus detailed histologic evaluation similar to Girard; MM, Martini and Melamed criteria; MM?, Martini and Melamed criteria cited but do not appear to have been strictly adhered to; No diff, no difference; Op Mort, operative mortality; pI, pathologic stage I.

synchronous), and intended as a clinical management tool rather than a definition of multiple primary cancer.[101] At that time only tumor location and nodal status was available (i.e., no computed tomography, positron emission tomography, magnetic resonance imaging, or molecular profiling). The criteria are based primarily on major histotype, an arbitrary time interval for metachronous tumors (2 years), and a rationale emanating from a view of metastasis as the physical translocation of a malignant cell (considered metastasis if in different segments but with carcinoma in lymphatics common to both—seemingly implying retrograde lymphatic migration to the metastatic site?).

The MM criteria are widely cited as being used (Table 1); however, in many studies they seem to have been used loosely and supplemented by clinical judgment. In some series other criteria were used. In 2003 the ACCP proposed criteria that differed only slightly from MM (Supplementary Table 2, Supplementary Digital Content 1). The seventh edition of the TNM classification states the following: "Multiple tumours of similar histologic appearance should only be considered to be synchronous primary tumours if in the opinion of the pathologist, based on features such as differences in morphology, immunohistochemistry and/or molecular studies, or in the case of squamous cancers, are associated with carcinoma in situ, they represent differing subtypes of the same histopathologic cell type. Such cases should also have no evidence of mediastinal nodal metastases or of nodal metastases within a common nodal drainage."[102–104] Thus, this categorization blends the comprehensive histologic assessment with some features of MM. However, it only defines pathologic assessment and does not consider other clinical features (imaging characteristics).

Little formal testing of these criteria has been performed. Girard et al. compared differentiation of multiple primaries and metastases according to MM against comprehensive histologic assessment and against molecular characterization in 20 patients (42 tumors).[83] There were significant discrepancies in the categorization by each method (20% different by molecular characterization and 12% by comprehensive histologic assessment versus MM). The authors used survival as a gold standard; all underwent curative-intent resection

(but nodal status was not reported). Significantly better survival for patients categorized as having separate primary versus metastasis was found only by using the comprehensive histologic assessment; both MM criteria and molecular characterization demonstrated only a nonsignificant trend. Of note, although MM criteria are cited as having been used, 15% of patients were selected for curative-intent resection despite MM classification of their tumors as metastatic.[83]

Section Summary

Published studies only vaguely define patient characteristics and selection criteria for curative treatment. Nevertheless, the observed OS is similar to what is expected for separate primary cancers. The MM criteria are most frequently cited but appear to have been supplemented by clinical judgment; the retrospective nature and lack of detail hampers assessment of the selection criteria. The MM criteria have not performed well when compared against a comprehensive histologic assessment. Nevertheless, such a comprehensive assessment is only possible after resection. Thus, data from outcomes provide limited specific information to define separate primary lung cancer versus metastases.

Results: Proposed Criteria to Distinguish Synchronous Second Primary Lung Cancer

Taking all the information gleaned from this review together, we developed criteria for clinical and pathologic identification of synchronous separate versus related pulmonary tumors (Tables 2 and 3). We suggest that for clinical definition, all available information be considered, including imaging, biopsy, and clinical features. Most factors can be viewed only as suggestive; an adequate biopsy specimen showing different histotypes is the only feature that by itself defines separate primary cancers (but the converse is only suggestive!).

For pathologic definition, a comprehensive histologic assessment can be viewed as definitive if it demonstrates that tumors are different but is only suggestive if they appear similar. The pattern of biomarker alterations should only be viewed as suggestive, whether similar or different. In all cases, the pathologic information should be supplemented with available clinical information.

Tumors should be categorized as separate primary cancers or metastases according to the preponderance of the evidence. A quantified approach is not possible (e.g., the number of suggestive factors) because the strength of a particular factor must be weighed (e.g., the extent of available prior imaging, biopsy tissue quality, degree of imaging or histologic similarity). Ideally, the decision regarding how to categorize two lesions in a patient should be made with multidisciplinary input upon considering all available information (i.e., a tumor board).[9]

Table 2. Clinical Criteria for Separate versus Related Pulmonary Tumors

Clinical criteria[a]
Tumors may be considered separate primary tumors if
They are clearly of a different histologic type (e.g., squamous carcinoma and adenocarcinoma).
Tumors may be considered to be arising from a single tumor source if
Matching breakpoints are identified by comparative genomic hybridization.
Relative arguments that favor separate tumors:
Different radiographic appearance or metabolic uptake
Different pattern of biomarkers (driver gene mutations)
Different rates of growth (if previous imaging is available)
Absence of nodal or systemic metastases
Relative arguments that favor a single tumor source:
The same radiographic appearance
Similar growth patterns (if previous imaging is available)
Significant nodal or systemic metastases
The same biomarker pattern (and same histotype)

[a]Note that a comprehensive histologic assessment is not included in clinical staging, as it requires that the entire specimen has been resected.

Discussion

This article represents an expert consensus based on a comprehensive literature review of available data to

Table 3. Pathologic Criteria for Separate versus Related Pulmonary Tumors

Pathologic criteria (i.e., after resection)[a]
Tumors may be considered separate primary tumors if
They are clearly of a different histologic type (e.g., squamous carcinoma and adenocarcinoma).
They are clearly different by a comprehensive histologic assessment.
They are squamous carcinomas that have arisen from carcinoma in situ.
Tumors may be considered to be arising from a single tumor source if
Exactly matching breakpoints are identified by comparative genomic hybridization.
Relative arguments that favor separate tumors (to be considered together with clinical factors):
Different pattern of biomarkers
Absence of nodal or systemic metastases
Relative arguments that favor a single tumor source (to be considered together with clinical factors):
Matching appearance on comprehensive histologic assessment
The same biomarker pattern
Significant nodal or systemic metastases

[a]Pathologic information should be supplemented with any clinical information that is available.

guide categorization of two synchronous pulmonary tumors in a patient as being separate primary cancers or related to one another. This is a relatively common clinical issue, and currently there is great variability in how patients are classified.[3,4] This not only creates potential harm from inappropriate management but also thwarts the ability to carry out research based on recorded classification.

A review of what is known about the mechanism of metastasis reveals extensive evidence demonstrating a complex process. Rationale based solely on a physical route of dissemination of cancer cells ignores the myriad of factors that control the complex process of metastasis. Terms such as *lymphatic metastasis* or *hematogenous metastasis* are gross oversimplifications, and classification or management of patients on the basis of simplistic concepts is not justified.

A reliable assessment that tumors are unrelated can be made if they have a different histotype or appear different on a detailed histologic assessment of tumor subtypes and stromal features. However, two lesions having the same histologic appearance does not prove that tumors are related; most separate primary cancers are of the same histotype, and clonality studies also suggest that most often they are not related. Classifying tumors as related should be done carefully, taking into account the aggregate of available information. When there is doubt, it may be better to regard the tumors as separate, given the evidence reviewed in this article.

We must also be careful about relying on biomarkers. Although they can suggest that tumors are separate or related, the incidence of discordance in clearly related lesions and concordance in clearly unrelated lesions is relatively high. Test sensitivity, tissue quality, and other factors may account for much of the discrepancy. More sophisticated methods may become broadly available in the future. However, at present, mutational profiling should not be considered definitive.

The MM schema has been a useful starting point but does not have a solid foundation; it is mainly empirically derived, is based on outdated concepts, and has not performed well when compared with newer approaches. It appears to be best to replace this with the criteria suggested here. Unfortunately, few criteria can be proposed that are definitive by themselves, and generally a decision must be made using the aggregate of all information available.

We acknowledge that no data are available that quantify many of the relative criteria to consider in making a clinical judgment that two lesions are separate primary or metastatic lesions (e.g., radiographic metabolic characteristics, growth patterns, or nodal status). Nevertheless, the published experience demonstrates that clinical judgment used to identify patients as having synchronous primary tumors has resulted in reasonably good outcomes.

We have focused on patients with two synchronous lesions; a metachronous presentation involves considerations that are beyond the scope of this article. Various intervals between tumors have been suggested (Supplementary Table 2), but these are arbitrary. We suggest that the data and criteria proposed here for synchronous tumors can also guide classification of metachronous tumors, supplemented by additional clinical judgment arising from consideration of the time interval and stage of the first tumor.

If the proposed criteria and clinical judgment suggest that two lesions are unrelated, they should be classified as separate primary cancers and each one staged and managed individually.[6] If they are categorized as related, the patient should most often be classified as having an additional tumor nodule, as is described in detail elsewhere.[5,6] The exception to this are patients who have multiple nodules with ground glass features (or adenocarcinoma in situ, minimally invasive adenocarcinoma, or lepidic-predominant adenocarcinoma on histologic examination). These patients should be classified as having multifocal lung cancer.[6,7]

From a clinical standpoint, the expertise for comprehensive histologic assessment, as well as the availability of mutation profiling and genomic techniques, is not yet widely available. The need for a significant amount of tissue both to analyze the morphology and to extract sufficient tumor DNA for molecular techniques makes the relevance of those approaches uncertain. Distinguishing primary tumors from metastases is more important before therapeutic intervention than after resection. Unfortunately, limited data are available regarding the imaging or metabolic features of multiple lung tumors. Nevertheless, clinical judgment appears to have worked well in identifying appropriate patients for curative-intent treatment as demonstrated by reported outcomes.

The *process* of clinical evaluation of patients is outside the scope of this article; the ACCP Clinical Guideline recommends careful imaging and invasive evaluation for occult distant and mediastinal metastases for patients with synchronous separate primary lung cancers as well as for patients with additional tumor nodules.[9,105] Treatment recommendations are also not part of this review; however, the data presented here suggest that in properly selected patients curative-intent treatment is associated with good outcomes.

Further research is needed to test and refine the proposed criteria, but the lack of a gold standard that easily and reliably identifies separate versus related tumors in the lung makes this difficult. Prospective studies are needed to assess how well the proposed

criteria identify patients with good outcomes. We hope that this article is helpful not only in categorizing patients but also in stimulating further research.

Conclusion

It is easier to establish that two pulmonary foci of cancer are separate primary tumors than that they are metastatic from one another (for example, most second primary lung cancers are of the same histotype). Few features are sufficiently reliable by themselves, such as different histologic type and differences by a comprehensive histologic assessment of resected specimens or by matching breakpoints by DNA sequencing. Most criteria can be suggestive, but are associated with potential misclassification. These include biomarker patterns, imaging characteristics, and the presence or absence of nodal involvement. The fact that generally only biopsy specimens are available at the time of clinical decision making further adds to the uncertainty and difficulty of the assessment. A constellation of factors is better than any single factor; it is best to make a determination of separate primary versus metastatic lesions through collective judgment of a multidisciplinary tumor board after taking into account all of the available information.

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Appendix

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at http://dx.doi.org/10.1016/j.jtho.2016.01.025.

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