Patterns of Metastasis in Lung Cancer: A Review*

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INTRODUCTION

Scientific methodology emphasizes the importance of any discrepancies between an accepted theory and the observed facts. The present study aims to focus attention on the metastatic patterns of lung cancer which are at variance with current concepts.

The accepted theory of lung cancer metastasis was clearly stated by Ackerman and Regato (1): “The lymphatic spread is the most common, and involvement of mediastinal, peritracheal lymph nodes almost always takes place... If tumor grows into the pulmonary veins, systemic dissemination becomes inevitable and brain, bone, suprarenals, and liver become the site of metastases.” This statement reveals the present dual concept of metastasis: first, lymphogenous spread to the lymph nodes; secondly, hematogenous spread to the organs. As Batson (11) pointed out, this dual concept is held by Willis, Walther, and other authorities. The blood stream, according to Fried (46), is looked upon as the essential mode of spread of tumor cells to the distant organs. This view is deducible from Coman’s (28) review of metastatic mechanisms. In my opinion the current hematogenous theory of visceral metastasis dates back to the 19th century (97) and follows the general teachings of the old masters (95).

Fifty years ago, Levin and Sittenfield (82) made a comment of considerable relevance to the problem of metastasis: “This proof of the transporta-
lateral in the main; (e) asymmetrical with respect to the midline; and (f) predominant in certain parts of the involved tissue. Then, it is demonstrated by means of analogy that every one of the unexpected metastatic patterns seen in the organs is compatible with, and probably attributable to, one or more of the delineated lymphogenous patterns. Finally, since tumor cells undoubtedly circulate in numbers in the blood of patients harboring lung cancer, it is urged that attention should be directed toward the elucidation of the reasons why lymph-borne rather than blood-borne tumor cells account for the metastatic patterns in this disease.

UNEXPECTED PATTERNS IN VISCERAL METASTASIS

1. **Limited metastasis.**—Lung cancer cells have only to penetrate the pulmonary veins to reach the left ventricle and aorta and so to be dispersed to metastases in eight organs. In as many as 1,978 organs far and wide. It is, in consequence, "puzzling" to note, as did Ballantyne and his co-workers (7), that there is a lack of widespread distribution of metastases in all patients. In my study of 6,000 cases of lung cancer recorded in 28 Teaching Hospitals (99), note was made of the presence of metastases in eight organs. In as many as 1,978 cases none of these organs was stated to have been invaded. So infrequent indeed was widespread invasion that only 2.6 per cent of the cases exhibited secondary deposits in more than four of the listed organs, the average metastatic frequency being 1.3. Although Rosenblatt (112) and others contend that metastases are widespread in lung cancer, this view was neither corroborated by the necropsy records studied nor substantiated by an analysis of published figures.

Furthermore, even when an organ is actually metastasized, it is not uncommon for one metastatic mass to be detected. In the brain, for instance, the indications are that up to one-third of the deposits may be solitary (44, 52, 60, 76). I believe, with Stern (131), that this distribution is difficult to accept as one of pure chance. Admittedly, some metastases must escape detection. Still, our expectations are jolted; distant deposits are less common than might be expected when the enormous vascularity of the lung is taken into account (129).

2. **Centrifugal metastasis.**—We expect, as did Carnett (23) and Cohnheim (27), that tumor cells dispersed along the systemic arteries would be found growing indiscriminately in organs both far and near. On the contrary, in the experience of Fried (45), the more remote an organ is from the pulmonary primary the more remote are its chances of being metastasized. For example, there is a striking scarcity of ovarian secondaries (38, 74). In my survey of the incidence of secondary deposits in the three bilateral or bilobed upper abdominal organs, the discernible topographical pattern was one in which a centrifugal sequence of spread could not be ruled out (98). In this connection, the bones are of interest, for the thoracic vertebrae are those most frequently invaded (5, 21, 22), the distant bones being less often attacked. Thus, Greene (54) in 1937 was able to collect only ten cases from, and to add one case to, the literature on phalangeal metastases. The centrifugal trend is also noticeable in subcutaneous metastases (24). The combined evidence warrants the conclusion that lung cancer tends to spread centrifugally. This pattern is contrary to our expectation that opportunities for invasion of both far and near organs are equal in this condition.

3. **Selective metastasis.**—Since the days of Hodgkin (69), the fact that a tumor seems, on occasion, to select a particular organ for attack has been a puzzling feature of metastasis. As early as 1910, Bramwell (13) wondered whether the selection of the adrenals in lung cancer was a mere coincidence. This phenomenon has since been a subject for curiosity and comment (83, 128, 152). An apt commentary comes from Robbins (107): "For obscure reasons, bronchogenic carcinoma sometimes singles out the adrenals as sites of spread."

This problem would have been easy of solution on the theory of soil susceptibility if adrenal selectivity had been all that demanded explanation. However, as a number of contributors recognize (9, 15, 70, 120), other organs including the brain, heart, liver, pancreas, and kidney may also be selectively involved.

Since lung cancers show considerable polymorphism under the microscope (6, 48, 136, 144), it is improbable that the mischief is made by particular cell types singling out particular organs. Indeed, there are conflicting views on the role of the cell type in metastasis to individual organs. Thus, in the case of the brain, squamous-cell (41), adenocarcinoma (117), small-cell (120), and undifferentiated-cell types (160) have all been indicted for their proclivity to spread to this organ, although Halpert (59) is emphatic in denying that the cell type bears any relation to the frequency of intracranial metastasis. It would seem, therefore, that unless we can with propriety invoke soil suitability in each lone organ seemingly singled out for metastasis we are confronted by a distribution pattern least expected from a tumor whose opportunities for widespread dispersal are myriad.

4. **Contralateral metastasis.**—Over a century
ago, the old authors drew attention to the way in which lung cancer tended to spare the contralateral lung (17, 65). Since then many authorities, and Osler (101) was among them, have made this point. In fact, so characteristic is this that Barnard (9) and Weller (151) both counseled that, when metastases are present in the contralateral lung, an extrathoracic primary must needs be excluded.

In 1882 Fenwick (43) reviewed published cases of lung cancer and discovered that only 13 per cent had metastasized to the other lung. This same figure was obtained in a recent paper (25), the range being from 10 to 30 per cent (41, 85, 131, 137, 158).

According to Eerland (36) and Hébert (67), contralateral pulmonary metastasis is hematogenous. Why, then, do blood-borne emboli fail so often to flourish in the opposite lung? There are, be it noted, multifarious blood-vascular routes which should insure successful transference across the midline: (a) bronchial branches of the aorta (109), (b) the thoracic venous system (10), (c) the thoracic duct either in its role as a conduit (142) or when it is itself infiltrated (159), (d) the superior vena cava and its tributaries (49), (e) the venous radicles of invaded lymph nodes (80), and (f) the venous return which carries not only emboli terrestrially liberated by established secondary deposits in the venous return which carries not only emboli but also those which successfully negotiated the capillaries of distant tissues (163).

Owing to the facilities afforded by these channels, not only the egress of tumor cells from the lung of origin but also their ingress into the contralateral lung should be easy. Why, then, do primary tumors of the lung show, as Budinger (18) pointed out, so conspicuous a tendency to invade the other lung? Unless it is contested that bronchial and alveolar soils differ markedly, it is noteworthy that in the contralateral lung the malignant seeds are being sown on a soil from which the parent tumor sprouted. In this respect, the fact that “alveolar cell” carcinoma of the lung also show a low metastatic frequency (139) fortifies our suspicion that in this situation the infrequency of contralateral metastasis reveals a clash between the hematogenous theory and the observed facts.

5. Asymmetrical metastasis.—Bilaterality of invasion of paired organs has long been accepted as a point in favor of the theories of hematogenous metastasis (103, 148) and suitability of soil (53, 73). However, since millions of tumor cells in all probability circulate in the blood stream daily (88), it is reasonable to expect that paired organs would be exposed more or less equally and simultaneously to the ensuing cancerous bombardment daily.

Let us, therefore, compare the deposits found in the adrenal gland on either side. Gillespie (51) discovered on making this comparison that the one growth is usually larger than the other. So conspicuous may the resulting disparity in size become that Beattie and Dickson (12) called attention to this fact thus: “Note the minute secondary growth in the opposite organ.” In a case which I reported from this hospital the difference in the weights of the adrenals was 460 gm. (91); in Case 5998 of the Postgraduate Medical School of London the difference was as much as 2,388 gm.

Hitherto, these cases have masqueraded merely as bilateral metastases, but I would draw attention to the phenomenon of size disparity which lies behind the façade of bilaterality. Although each member of such an organ pair had from the first been open to attack by blood-borne cancer cells, yet one of them succumbs long before the other. We may consider the issue from another angle. Of 400 cases of adrenal metastases collected from the literature (8, 19, 21, 42, 61, 77, 85, 110, 116), as many as 132, i.e., one-third, were unilateral. Why, we ask, does one adrenal nurture the invading cells to the point at which deposits are noticeable, although the other gland is as yet innocent of tumor tissue? The unilateral growth, it should be noted, need not be small. In one of my cases the tumor mass weighed 190 gm., although the other adrenal was unscathed (94). Senoo’s case attained 80 gm. in similar circumstances (124). Hence, despite the similarities of paired organs both in their soil and in their opportunities for blood-borne invasion, there are nevertheless dissimilarities—and these may be astounding—in their metastatic involvement.

6. Uncorrelated metastasis.—Although the kidneys receive about one-quarter of the total resting cardiac output (157), yet lung cancer metastasizes less often to the kidneys than to the tiny adrenals. Apparently, the total quantity of cancer-containing blood received by an organ is not correlated with its metastatic frequency. Since blood flow to the adrenals per unit weight of tissue is high (81), their relatively high rate of metastasis may conceivably be due to this fact. However, this argument would leave unexplained the higher incidence in the liver, an organ which is, weight for weight, very poor in arterial blood supply (125).

Perhaps it is best to compare the metastatic frequency in two portions of the same organ. In the brain, for instance, the cerebellum is only about one-eighth of the size of the cerebrum (105). However, 38 per cent of brain metastases secondary to lung cancer were found in the cerebellum (47), a figure suggesting that the cerebellum exhibits metastases half as often as the cerebrum. This
proportion is borne out by my collected data (94) and those of Willis (153) and Meyer and Reah (87), data being those related to tumors in general. Although some think that the cerebellum shows no distinctive metastatic features (34), the available data indicate, as Dorothy Russell states (114), that the cerebellum must be considered as a site of predilection. Until it is shown either that the cerebellum offers to blood-borne tumors a soil markedly different from that in the cerebrum or that the true proportional incidence of cerebellar and cerebral metastases is not that usually recorded, it is fair to conclude that the distribution of metastases in the brain is at odds with the current emphasis on arterial dissemination.

The liver may also be considered. This organ is symmetrical in primitive animals (71). In man the left lobe is only about one-quarter of the size of the right lobe (145). Nevertheless, in my study of 200 cases of pulmonary and other extra-portal tumors with hepatic deposits (92), there was no commensurate concentration of the metastatic masses in the right lobe. In effect, this lack of correlation with blood supply belies the current hematogenous theory of metastasis.

7. Spatial metastasis.—Spatial relationships are manifest in visceral metastasis. Perhaps the most widely recognized example is that seen in the adrenal gland, whose medulla is more often the seat of secondary deposits than the cortex (20, 31, 111). Medullary localization is of particular pertinence to the theory of hematogenous metastasis, because the medulla is thought to obtain its blood supply largely through capillary vessels which have already passed through the cortex (63). Therefore, it comes as a surprise that the medulla rather than the cortex seems to trap tumor emboli more commonly (127). Unless the comparative frequency of medullary metastases is an erroneous observation, this distribution pattern conflicts with the accepted theory of blood flow through the adrenal.

TOPOGRAPHICAL PATTERNS IN LYMPHOGENOUS METASTASIS

In keeping with methodological principles (156), I have presented above a number of "falsifying instances" of the theory that lung cancer spreads to the organs via the blood stream; we turn now to the problem of deciding whether these are "confirming instances" of another theory. We begin by delineating topographical patterns which characterize lymph-borne metastasis.

1. Limited metastasis.—Virchow (147) stressed the pathological importance of the interruptions which the nodes offer to the flow of lymph. In particular, in neoplastic diseases the nodes act as interrupters and filters (123, 139). On this account, malignant cells are prone to lodge in, but tend to be localized by, the nodes (50, 108). Consequently, even with cancers which show considerable propensity for metastasis, only relatively few nodes are actually involved in most cases (149).

Only one of the 37 cases of lung cancer reported by Hashem (64) exhibited generalized enlargement of the lymph nodes. The only case in my series of 25 detailed dissections in which there was generalized lymph node metastasis is shown in Figure 1. We conclude, therefore, that lymphogenous metastasis is characterized by, but is not wedded to, limited distribution.

2. Centrifugal metastasis.—Paget (102) was aware that cancer is prone to spread to the proximal rather than to the distal lymph nodes. This centrifugal sequence is apparent in lung cancer (58, 79). Thus, it is the lower rather than the upper cervical nodes and, conversely, the upper rather than the lower abdominal nodes that are more often metastasized (16, 68). As Willis (154) depicted, lung cancers "often exhibit discrete deposits in the abdominal and cervical glands, these diminishing in centrifugal order." Figures 1, 2, and 4 illustrate this fact. We deduce, in consequence, that centrifugal metastasis is one of the characteristics of lymphogenous invasion.

3. Selective metastasis.—In addition to recognizing the centrifugal nature of lymphatic metastasis, Paget (102) knew also that at times metastases appear in distant rather than in proximate lymph nodes. Herbut (67) and Kolodny (78), among others, refer picturesquely to this phenomenon as "skip" metastasis. Lymph node skipping, a general neoplastic manifestation (39, 104, 149), is reported in lung cancer (2, 14, 135). It is discernible in Figures 1 and 2. The significance of this phenomenon should be clear: it shows that tumor cells spreading lymphogenously may be conducted past some nodes en route before attacking a more remote node. We may generalize: in lymphogenous metastasis certain tissues along the line of spread may be skipped over and a more distant tissue selectively invaded on account of the existence of direct lymphatic connections.

4. Contralateral metastasis.—Although anastomotic lymph vessels link up both hemithoraces (146), experience shows that for some time at least only the nodes on one side of the chest are attacked in lung cancer (15, 32). Figures 2 and 3 exemplify this trend. Despite the proximity of the nodes of either side, whereas the ipsilateral groups suffer, the contralateral nodes are often spared. We
infer, consequently, that low frequency of contralateral metastasis is a lymphogenous phenomenon.

3. Asymmetrical metastasis. — Since metastasis commences on one side, the final metastatic pattern tends to be asymmetrical. As Fagge (40) argued, “For obvious reasons the disease is then confined to one side, or at least far more marked on one side than on the other.” This size disparity is noticed not only in the proximal nodes (121) but also in those more distant (130). Figures 1 and 4 are illustrative. Hence, we deduce that asymmetry in metastatic development is a hallmark of lymphatic spread.

6. Spatial metastasis.—Spatial relationships are manifest in lymph node metastases. As the textual figures of Cappell (32) and Willis (154) demonstrate, in the node the earliest tumor deposits are found in the subcapsular (peripheral) sinus, except in cases of retrograde metastasis in which the earliest deposits may be found in the hilum (medulla) of the node (32, 152). These localization peculiarities were confirmed by the experiments of Zeidman (161, 162), who demonstrated that the locus in which a deposit develops in a node is determined by the manner of arrival of the current of lymph. Therefore, we conclude that in lymphogenous metastasis the site of earliest deposit formation is governed by, and varies according to, the dynamics of lymph flow to the part.

ANALOGY BETWEEN VISCERAL AND NODEAL PATTERNS

Having scrutinized the metastatic patterns not only in the viscera but also in the nodes, let us seek for analogies between them. All lymph nodes offer fertile soils to tumor emboli (159, 154), just as all nodes receive nutrient arterial blood supply. Now, the blood of lung cancer patients must carry emboli to the lymph nodes. Therefore, it is reasonable to believe that the fertile soils of distant lymph nodes seldom exhibit metastases in lung cancer. Are blood-borne cancer cells ineffective agents of invasion of lymph nodes? If they are ineffective, ought we not to question their effectiveness as invaders of the organs? It would seem that we should draw analogy between the fact that near nodes are most often metastasized and the fact that near organs suffer most often.

As was long suspected (26), the abdominal nodes are usually invaded lymphogenously from the chest (154). It is easy to picture lung cancer cells as they travel retrogradely in the thoracoabdominal lymphatics, but it is difficult to imagine them discriminating between one lymph vessel and another by entering those vessels which lead toward the nodes but adroitly avoiding similar vessels which lead equally retrogradely to the organs. Until it is shown that the mechanism of retrograde lymph flow toward an organ is different from that toward a node, we cannot but accept that retrograde lymphatic metastasis occurs not only to the nodes but also to the viscera. Hence, if the lymph nodes intercept tumor cells traveling toward more distant nodes, they must in this way be intercepting cells making for the viscera. The filtering action of lymph nodes not only limits the number of lymph nodes attacked but also the number of organs invaded.

Why are brain metastases commonly solitary? What underlies the curious position which the cerebellum occupies in the hierarchy of intracranial metastases? According to Symonds and Cairns (141), the lower half of the brain is the more common seat of secondaries. This is what we would expect from centrifugal metastasis along lymphatic pathways; but many believe that the brain is without lymphatics and so cannot be invaded by way of this system (38, 84, 106, 132, 134). Elsewhere (100), I have argued against this opinion; here, I should like to reiterate, as did Gull (57) in the Harveian Oration for 1870, that the negative results of scientific experiments stultify progress when they impose limits that may not really exist. As Wisdom (155) emphasized, the results of scientific experiments are inherently provisional in nature. Therefore, to attach finality to the results hitherto obtained from experiments on brain lymphatics is erroneous. Rouviere (113) advised us not to dismiss the possibility of the existence of lymph vessels in the central nervous system. We now have the comprehensive review of Rusznyak, Foldi, and Szabo (115), who concluded that “Connections... exist between the central nervous and the lymph vascular system, connections that are highly significant anatomically, physiologically and pathologically.” In my view such lymphatic connections must be postulated before the distribution patterns of intracranial metastases become meaningful (94).

Why is one organ selectively involved, even though all are showered with malignant cells? Let us hypothesize that the selected organ received its potent invaders not through the blood stream—a channel open to all—but through the lymph stream—a channel that has special connections. This hypothesis does no violence to, but takes a leaf from, orthodox teaching. Thus, today it is assumed (118) that, when one organ is selected, as it were, for metastasis, all the other organs had failed to nourish their own blood-borne emboli. It is, therefore, but a simple extension of this idea if we also assume that the organ selectively metastas-
sized failed, too, to nourish its blood-borne emboli but was attacked by retrograde metastasis via its lymphatics. It is noteworthy that the lymphatic system does provide the means of effecting selective metastasis. Thus, the clinical sign, Virchow's node, is essentially the selective invasion of a supraclavicular node in the absence of general lymph node metastases in the neck. Here, the thoracic dust is the metastatic pathway (161). Bearing in mind the role of this well-defined channel, we should look for less obvious channels in other sites. For instance, there are direct lymphatic connections between the adrenals and intrathoracic nodes (20, 56, 73, 113). Accordingly, lung cancers can selectively attack the adrenals. Other organs may have similar direct lymphatic connections (86); these organs in like manner could be attacked selectively.

The one-sided tendency in lymphogenous metastasis is seen when lung cancer causes pulmonary lymphangitis carcinomatosa (45, 130). Now, this undeniably lymphogenous process is acknowledgeably extensive and yet often remains unilateral, as do lymph node metastases. We expect, then, that the less florid manifestation, namely, discrete lymphogenous metastasis, would also tend to be unilateral. In other words, the striking low frequency of contralateral pulmonary metastases in lung cancer is what we should expect if this tumor attacks organs and nodes lymphogenously more often than not.

Similarly, the asymmetrical nature of lymphogenous spread is such that disparity in the size of bilateral deposits is to be expected. The preponderance of deposits in one of a pair of organs is, therefore, in accord with lymphatic metastasis.

The common location of metastases in the medulla of the adrenal is analogous to the medullary localization of retrogradely transported lymph node deposits. Although diverse views are on record, the weight of opinion leans to the conclusion that adrenal lymph emerges from the medulla (29, 55, 62). If this assessment is the correct one, deposits are likely to develop first in the medulla after retrograde lymph carriage. Thus, as with the other metastatic patterns discussed, it is the lymphogenous theory that resolves the known difficulties.

**FUTURE PROSPECTS**

This review spotlights the viewpoint that the metastatic patterns of lung cancer are concordant with lymph-borne spread but discordant with blood-borne invasion. There is need, then, to explore the possibility that blood-borne cancer cells are not the effective agents of invasion that they have hitherto been assumed.

It is not disputed that hematogenous metastasis can occur. However, as the work of Engell (37) and others suggest, the fate of the circulating cancer cell is still unknown. Moore and his associates (89) hazarded a guess and put the percentage of these cells which are "promptly destroyed" as high as 95 to 99. It seems to me that, perhaps, the destruction of these cells in the blood stream may be accomplished to an extent not even dreamt of. In this connection, the long- enunciated (140) but disputed (30) view, that blood and lymph affect cancer cells differently, calls for concerted reappraisal.

Long ago, Armstrong and Oertel (4) surmised that not only the quantity but also the quality of metastasizing cells may be of account. Factors which are thought to be of importance have recently been reviewed by Hawk and Hazard (66). To my mind, the problems which may repay further investigation include (a) the effect of the size of the malignant emboli (90, 150); (b) the role of coagulation and thrombosis in preventing metastasis (72, 138); (c) the relationship between survival of blood-borne cancer cells and duration of the parent tumor (53, 129); and (d) the topographical relationship between the seat of the primary tumor and the location of the secondaries (91-94, 96, 126).

I agree with Drinker (35) that the functional significance of the lymphatic system is probably underrated. If it is ultimately shown that the lymph stream is more important than the blood stream in the dissemination of tumors to both the lymph nodes and the organs, it would be of paramount importance to orientate chemotherapeutic researches toward discovering drugs which are concentrated in the lymph stream. What is envisaged is exemplified by the observation of Schachter (119) that penicillin level is more prolonged in lymph than in blood, an observation adjudged to be of therapeutic interest because of the premier role of the lymph stream in infective diseases. It may be conjectured, in like manner, that if the lymph stream also occupies a premier position in neoplastic diseases then the drugs of choice in cancer therapy may well be those which attain a higher concentration in the lymph than in the blood stream.

**ACKNOWLEDGMENTS**

I am indebted to my chief, Professor D. F. Cappell, for the facilities which he has generously placed at my disposal; to Dr. A. T. Sandison for invaluable discussions; and to Professor C. V. Harrison for access to the records of Hammersmith Hospital, London.
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FIG. 1.—Dissected specimen of lung cancer removed *en bloc* at autopsy. The primary tumor is left-sided; the larynx, thyroid, parts of the lungs, esophagus, and adrenals are left *in situ*. Note the widespread lymph node deposits which diminish in size distally. Also noteworthy are the lower para-esophageal nodes which remain small, having apparently been “skipped.” On the whole, the metastatic deposits are larger on the left than on the right side from the angle of the jaw right down to the aortic bifurcation.

FIG. 2.—A left-sided lung cancer from which extends a Y-shaped chain of metastasized nodes, most of the members diminishing in size centrifugally. The exceptions are the nodes at the top of each arm of the Y. These nodes have probably been “selectively” attacked. Note that the right mediastinal nodes are spared.

FIG. 3.—A large right-sided lung cancer which has infiltrated the neighboring nodes, sparing the contiguous contralateral nodes.

FIG. 4.—A right-sided lung cancer which has invaded all the nodes from the carina right up to the lower poles of the thyroid. Note that the deposits diminish in size centrifugally and that they are larger on the right than on the left side.
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