

Excision of Melanoma Metastases to Lung:

Problems in Diagnosis and Management

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AS MALIGNANT MELANOMA is considered one of the most lethal and capricious of cancers, it might appear at first that the excision of its lung metastases is an unjustified gamble. To understand the rationale for this surgical aggression, the clinical nature of melanoma is reviewed.

Although undoubtedly formidable, and despite the present ignorance of the mechanisms that influence its course, melanoma is not necessarily as deadly as is generally believed. If a thorough wide removal of the primary lesion is done, and the regional lymphatics remain uninvolved by metastases, the possibility for 5 year survival rises to 70%.^{26,27,36} If the regional lymphatics are involved and are extirpated, either with or subsequent to the excision of the primary tumor, there is at least a 40% chance for 5 year survival.²³

However, melanoma's notoriety is not without foundation. It probably stems, in part, from its exceptionally unpredictable behaviour which often manifests itself in dramatic and antic ways. For instance, in some patients it seems to be autonomous so that very small, superficial lesions can give rise to widespread, voluminous metastases and overwhelm the patient in a short time. In others, there is apparently a balance struck between the tumor and the host that can be maintained for 10 to 15 years or more, at which time the resurgence of the cancer can take place and progress inexorably to cause death.

In still others, immuno-forces presumably may become dominant and spontaneous disappearance of many far-flung metastases occurs, although this is rare.^{24,25,35,43,44}

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Because the mechanisms governing the interplay of host resistance and tumor dissemination are as yet not understood, only tentative opinions can be held about attributing beneficial results to any specific measures, or even as to whether melanoma can ever be considered permanently cured.

Should blood-borne spread occur, it is usually ominous. However, on occasion, instead of multiple metastases, a solitary focus seems to be present and single lesions of this type have been excised from the liver,²⁸ brain³⁰ and intestines.²⁸

If a thorough investigation fails to uncover other metastases, it is conceivable that this one is all that remains of active melanoma within the body; consequently, it may be of value to eradicate it.

Several methods are available to help achieve this purpose; radiation therapy only occasionally can produce local tumor response and is mainly used to relieve pain from osseous deposits; chemotherapy³³ given either systemically or by local perfusion, sporadically retards the growth and diminishes the size and extent of metastases, but this benefit is usually transient; immunotherapy is being investigated but it is too early to judge what contribution it might make to resolving this problem.³⁷

In 1936, Arce⁴ excised a solitary pulmonary melanoma metastasis. The length of his patient's survival is not known. In 1939, Ochsner and DeBakey³⁸ and in 1942, Carlucci and Schleussner¹⁵ reported having performed simple pneumonectomies for this condition. These patients died postoperatively. In the former case, the pri-

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mary melanoma was in the right eye which had been enucleated 23 years beforehand; no tumor source was ever demonstrated for the latter patient. This last is not uncommon, for the primary site of melanoma can be so cryptically placed as to defy discovery even at autopsy.^{21,31,32,39} It may possibly have been a rare condition of primary melanoma of the lung.^{3,41} Another case was reported in 1941 from Massachusetts General Hospital but the length of survival is not known.¹⁶ In 1950, Creech's patient had a simple pneumonectomy for a metastasis that involved the main stem bronchus and there was no recurrence when the report was made 7 months later.²⁰ Since then, there have been occasional references devoted specifically to the removal of melanoma metastases to lung.^{19,29,34} Most reports include a few patients with this tumor as part of a broader study of the subject of excised pulmonary metastases.^{43,44}

Clinical Material

Through 1970 at Memorial Sloan-Kettering Cancer Center, approximately 2500 patients with melanoma were seen. The first melanoma metastasis to the lung was removed in 1949.

From 1949 through 1970, there has been a total of 29 patients who have had varying types of pulmonary resections performed for this condition in an effort to extend survival. It is probable that many more patients with this problem may have been eligible for thoracic surgery which was not done because some staff physicians felt more pessimistic than others about the potential benefit of such procedures. These operations are to be distinguished from those in which many metastases were found and only one was selected for biopsy to establish or confirm histologic diagnosis.

There was complete follow-up on all patients.

Age and Sex

There were 17 males and 12 females. At the time of pulmonary resection, their ages ranged from 24 to 68 years with an average age of 46. Eighteen patients were over 40.

Symptoms

Nine patients had symptoms, some of which were multiple. These included: hemoptysis, cough, "cold," pneumonia, sweats, anorexia, weight loss and pain in chest.

X-rays

Twenty patients had no thoracic symptoms: in ten of them, the opacities were detected by routine follow-up roentgenography (5 solitary and 5 multiple); in ten others, the x-rays were taken as part of an investigation for suspected extrathoracic recurrences.

Intervals

All pulmonary metastases were metachronous and appeared from 18 months to 16 years after treatment of the primary melanoma. Of the 29 patients, 3 were free of metastases for less than two years; 16 from two to five years; and 10 for more than five years; 5 of these had a free interval of more than ten years. Of these 10, 6 were solitary and 4 were multiple.

Bronchoscopy and Cytology

Thirteen patients with solitary metastases were bronchoscoped. Twelve had negative findings, and biopsy and cytological studies of the remaining patient showed melanoma.

Four patients with multiple metastases were bronchoscoped. Two biopsies showed melanoma and one of these had cytologic evidence of this tumor.

Surgical Procedures

There were 8 wedge resections (2 patients with solitary and 6 with multiple metastases); 8 segmental (5 with solitary and 3 with multiple lesions); 9 lobectomies (one of which was for multiple metastases) and 4 pneumonectomies. Seven of the lobectomies were radical; one was performed for unilateral multiple metastases. The 3 radical pneumonectomies were performed for solitary metastasis because of (a) extensive involvement of the right upper lobe bronchus; (b) involvement of the hilum; (c) a large mass in the right lobe which also invaded the right middle and right lower lobes. One radical pneumonectomy was performed for multiple metastases, one in each lobe with pericardial involvement.

Distribution and Lymph Node Involvement

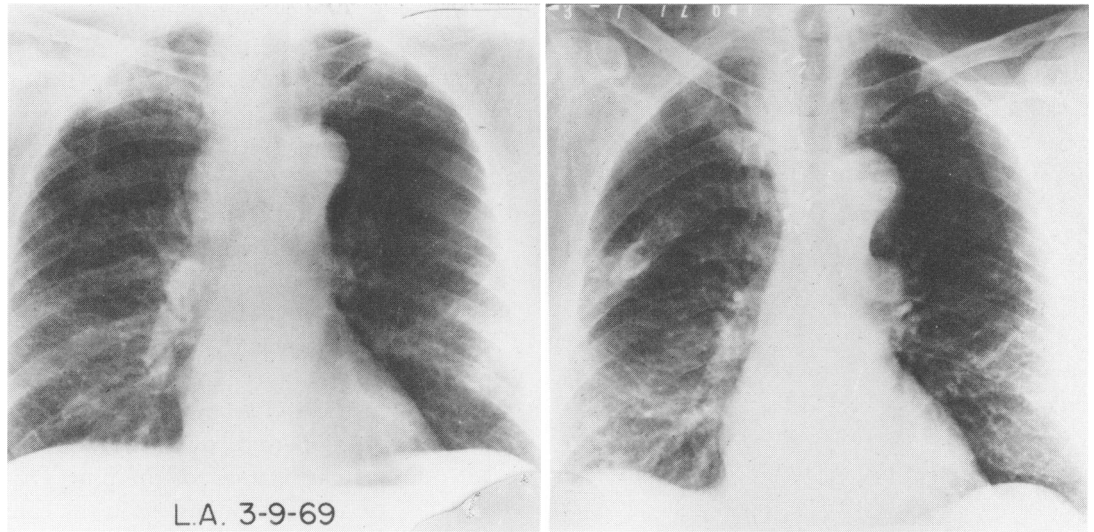
Eighteen patients had unilateral solitary pulmonary metastasis; in 5 others, metastases were unilateral and multiple, and 6 patients had bilateral multiple lesions. Of these 6 patients, three had synchronous metastases and 3 were metachronous with each other.

When possible, the regional lymphatics of the lobe or lung containing a metastasis were examined for daughter, or second generation, metastases. Apparently this additional spread frequently occurs in melanoma. Although a specific analysis of lymph nodes in 9 out of 29 patients in this study showed regional lymphatic involvement by metastases, it is probable that even more were present because, at first, no extra effort was made to remove these nodes for biopsy.

Five of 18 patients with solitary metastasis and 4 of 11 patients with multiple metastases had pulmonary lymphatic involvement. Of the 5 with solitary metastasis, 2 had hilar and mediastinal involvement; 2 hilar; 1 hilar and periesophageal. Of the 4 with multiple

FIG. 1a. (left) (L.A.) PA view showing right mediastinal lymphadenopathy deviating trachea to left.

FIG. 1b. (right) (L.A.) PA view 3 years later showing surgical clips, trachea in midline; right paratracheal fibrosis.



metastases, 2 had positive hilar and mediastinal lymph nodes; 1 with subpleural lymph nodes and 1 with hilar lymph node involvement.

Survival after Excision

Of the 29 patients, 19 died within 2 years after pulmonary excision; 9 patients had solitary and 10 had multiple metastases. Six patients survived 2–5 years, one with multiple metastases. Of 12 patients who had their pulmonary excisions 5 or more years ago, 4 are alive and free of disease.

Case Report

(L.A.) One other experience with intrathoracic melanoma is pertinent. A 58-year-old male had an excision elsewhere of a primary melanoma of the skin of the right arm in February, 1968. Eleven months later, at this institution, he had a right radical axillary lymph node dissection for multiple lymph node metastases. At the same time, a chest x-ray revealed ipsilateral mediastinal lymphadenopathy (Fig. 1a, 1b). At exploratory thoracotomy, no parenchymal lesions were found. However, there were lymph nodes 2 to 4 cms. in diameter in the right superior mediastinum around the trachea and between it and the esophagus and superior vena cava. There were also enlarged nodes in the peribronchial and subcarinal areas. A mediastinal lymphatic dissection was performed and subsequent histological studies showed that all lymph nodes except for the subcarinal group, contained metastases. The patient has survived for 34 months and is without evidence of pulmonary recurrence. This unusual case history is another example of the surprisingly beneficial consequences that occasionally ensue following the extirpation of melanoma metastases whenever and wherever possible.

Separate Primary Lung Cancers

During the period covered by this report, 5 patients had separate primary lung cancers. In 3 patients, these were discovered 9, 10 and 12 years after the melanoma had been excised. In this latter group, symptoms alone

prompted taking the chest X-ray and the subsequent investigation which led to the diagnosis. Unfortunately, by that time, all 3 patients were inoperable.

In 2 patients, melanoma was synchronous with the lung cancer. In these patients, the pulmonary lesions were discovered as part of a preoperative work-up. In each instance, the shadow was assumed to be a metastasis. One showed anaplastic epidermoid carcinoma and the other, adenocarcinoma. The epidermoid carcinoma (Fig. 2) was excised 3 weeks after the resection

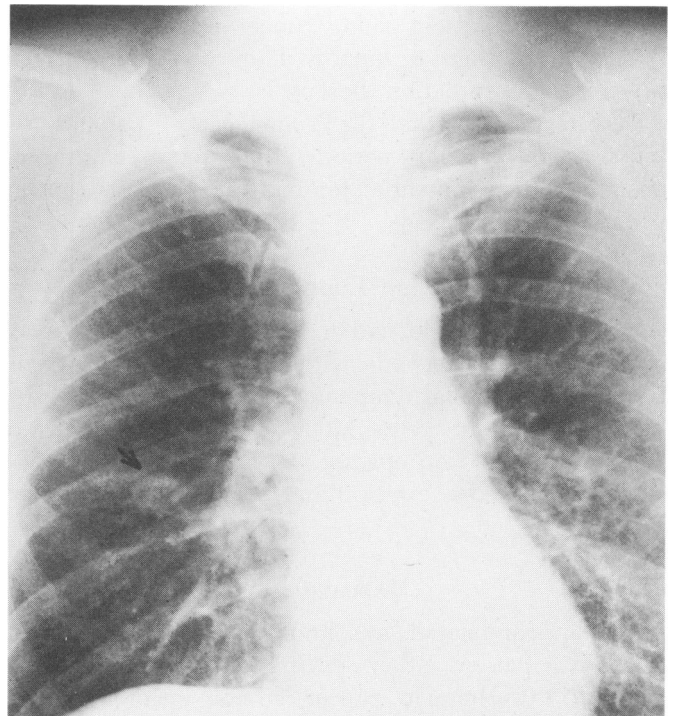


FIG. 2. (P.P.) Shadow in right lung which proved to be epidermoid carcinoma synchronous with skin melanoma.

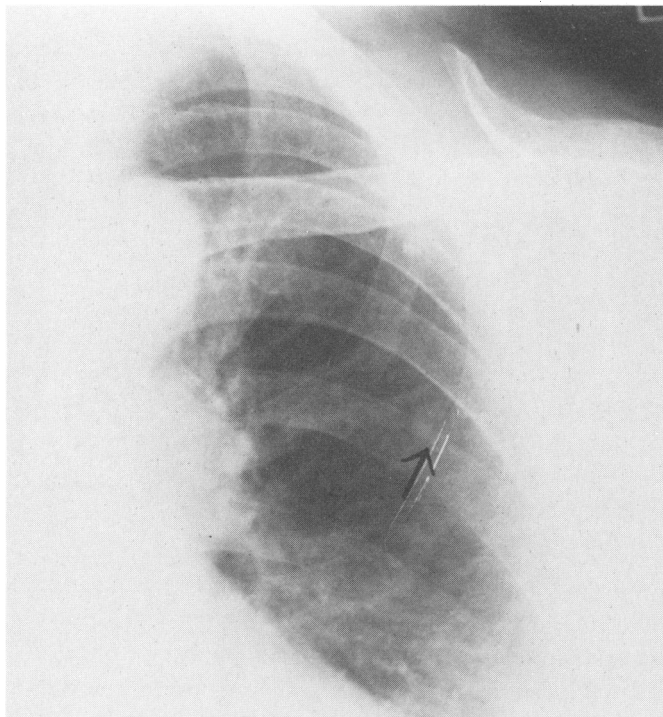


FIG. 3. (H.B.) Shadow in left lung of melanoma patient which proved to be a hamartoma.

of a cutaneous melanoma en bloc with its axillary lymph nodes. This patient died of melanomatosis shortly after discovery of these lesions. The diagnosis of the second patient's lung cancer was by exfoliative cytology. He died 9 months later of melanomatosis after receiving radiation therapy.

Despite the fact that the 5 lung cancer patients did not survive for long periods, they serve as graphic examples of the potential for multiple primary cancers in one individual.

Benign Lung Tumor

A 63-year-old male had a melanoma of the skin of the abdomen removed with a simultaneous right axillary and inguinal lymphatic dissection (negative for metastases). Four years later, a routine chest X-ray (Fig. 3) revealed an opacity in the left lung. This was removed by wedge excision and proved to be a hamartoma.

Discussion

The appearance of a solitary opacity in the chest X-ray of a patient either synchronous or metachronous with an extrathoracic cancer is not uncommon and there are many reports describing various aspects of its management.^{1,6,8-11}

Years ago, when an opacity of this type was discovered,

it was assumed to be a metastasis and as such, the visible representative of other cryptically-placed metastases elsewhere. It was also believed to be the first evidence of many more deposits that would inevitably appear. With the maturation of thoracic surgery, more attempts were made to extirpate these lesions.² As a result, it became evident that the shadow did not always prove to be a metastasis, as originally supposed, but instead was a new primary lung cancer (particularly in patients over 40) or a benign lung condition.

This was the experience at this institution where over 125 solitary lung metastases have been excised that originated from virtually all areas of the body. In this same period, over 451 adult patients have had a new primary cancer of the lung (Fig. 4), either synchronous or metachronous with a cancer at another site. In addition, we have collected 12 cases with extrathoracic cancer in which the solitary lung shadow proved to be benign:¹⁴ 9 were hamartomas; one each was a dermoid cyst, a granuloma and a fat pad.

This surgical aggression for a solitary pulmonary metastasis has resulted in an unexpectedly high 5 year survival rate of 36%. For those who had a second new primary cancer of the lung removed, this rate was 26%.

Undoubtedly, the surgical approach to these enigmatic lesions has gained increasing acceptance; nevertheless, there are still those who are hesitant to advise operation as an initial step in their management. To some extent, this attitude is attributable to a reluctance to put a patient through the pain, risk and expense of a

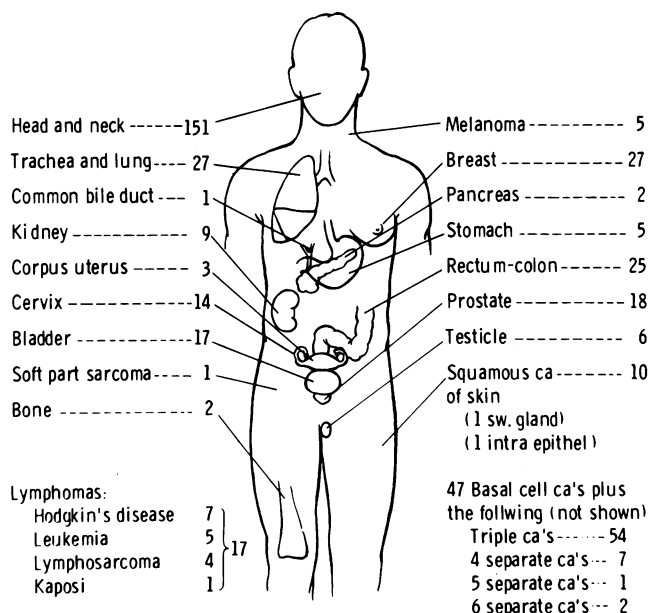


FIG. 4. 451 Multiple primary cancers, one of which was lung. (Anatomic Sites).

surgical procedure believing it to offer so little prospect of reward.

Instead, any conservative alternative is embraced, so that when this condition is detected, the patient may just be observed and treated symptomatically or given radiation and/or chemotherapy. Then if these fail, excision may be tried.

However, the data of this and other studies demonstrate that the basic principle which holds true for other cancers, also applies to melanoma. In this report, 6 melanoma patients had a pulmonary shadow that was called a "metastasis" by the radiologist, but proved to be a *new* primary cancer of the lung in 5 instances and in the sixth, it was a hamartoma. Furthermore, even if the shadow did prove to be a metastasis, there is no reason for defeatism sufficient to negate surgical aggression since 4 out of 12 melanoma patients survived whose pulmonary excisions were done five or more years ago.

Management

In this series, 9 patients developed metastases 6 to 16 years after their primary melanoma had been excised. This demonstrates that the usual guideline for cancer control, the so-called five year cure, does not necessarily apply.

To insure proper surveillance, a systematic follow-up program must be maintained. The optimum interval between examinations is, at best, arbitrary, but to some extent is determined by actuarial statistics. These show that the probability of metastasis is highest within two years after detection of the primary cancer. Consequently, we believe that for the first year, monthly examinations should be made; for the second year, these should be bi-monthly; and after that, they should be done at least three to four times a year until the fifth anniversary has been reached. From then on, semi-annual examinations are maintained indefinitely with particular attention directed to evidence suggesting lung, lymph node or hepatic metastases.

As an integral part of follow-up, postero-anterior and lateral chest x-rays should be taken 3 times a year for 2 years and semi-annually thereafter; sooner if symptoms warrant. Fluoroscopy should not be used for screening lungs as it is inadequate for detecting small opacities and is an impermanent record.⁴² Chest roentgenograms are essential to the care of the cancer patient as the lungs are common sites for metastases. Two out of 3 patients in this group were asymptomatic and their metastases were detected by routine chest X-rays. Once a pulmonary shadow is detected it is essential to obtain an orderly progression of roentgenographic studies: (1) Previous chest X-rays for comparison; (2) Stereoscopic views in the postero-anterior and occa-

sionally in the lateral projections; (3) Tomograms—these can delineate equivocal shadows and have uncovered otherwise invisible opacities; (4) Chest fluoroscopy with barium opacification of the esophagus to show mediastinal abnormalities such as enlarged lymph nodes. Other studies such as skeletal surveys are done as indicated.

Laboratory studies are done to detect disseminated disease. However, although certain abnormal blood chemistries, liver and bone scans may raise the suspicion of visceral or skeletal metastases, they are not, of themselves, totally reliable indices of the presence or absence of metastasis, having often been misleading in both directions.⁴⁵ As a consequence, it is unwise to decide upon a course of action based solely upon any one laboratory finding; instead, all studies should be evaluated in the clinical context.

The only trustworthy arbiter of these equivocal settings is microscopic analysis. Consequently, every effort should be made to obtain histologic confirmation of a suspected metastasis. Exfoliated cells in sputum and/or bronchial washings can help distinguish the nature of the opacities, even if they are metastases.^{5,7} If the cells are of lung origin, they can establish the presence of a new primary cancer of that organ.

Bronchoscopy with biopsy, when feasible, is recommended for those whose symptoms suggest bronchial involvement¹⁷ such as productive cough. It is also used for centrally-placed lesions and for peripheral shadows that are 2 cms. or larger.

Scalene lymph node biopsy is done only if the lymph nodes in that area are palpable. Mediastinoscopy and aspiration biopsies are done only in selected situations. These preliminary studies take only a few days to complete. If the diagnosis remains in doubt, or if, in the aggregate, the studies fail to reveal any incontrovertible evidence of extrathoracic spread, an exploratory thoracotomy should be done.

Surgical Management

In these settings, and subject to the patient's general condition, the extent of pulmonary resection depends upon whether the lesion appears to be peripheral or central, solitary or multiple, unilateral or bilateral.

At exploratory thoracotomy, a solitary peripheral lesion that can be encompassed by a wedge or segmental resection is initially excised for tissue diagnosis. If it proves to be a melanoma metastasis, or a primary lung cancer, a radical lobectomy is completed.^{12,40} This procedure is recommended because at least 9 (31%) parenchymal melanoma deposits in this series showed daughter metastases to the regional lymphatics. For the same reason, should a metastasis (or a primary

lung cancer) involve the main stem bronchus or extensively invade more than one of the major lobes, a radical pneumonectomy is recommended.¹³

This concept is given further emphasis in that two of the four 5-year survivors herewith reported had metastases in the hilar and mediastinal lymph nodes in the radical lobectomy specimens. Wedge and segmental resections are now reserved for poor risk patients. All of the 5-year survivors had an excision of a solitary metastasis. It should be noted that all had positive regional lymph node involvement in the primary. Beyond this, the analysis of their case histories fails to reveal any clinical features in common which would have foreshadowed or explained the beneficial results. The interval between the primary cancer and the appearance of its metastasis is often considered by some to betoken a decreased or increased probability of survival; i.e., the shorter this interval, the less likely the chance for control; the longer, the better. However, in this study, this correlation did not occur. Of the 5-year survivors, 4 had metastases removed 3, 4, 4½ and 12 years after removal of the primary source. In 4 other patients, the fact that a shadow appeared as long as 11, 12, 15 and 16 years after the primary lesion, did not seem to enhance survival and these patients lived only for 3, 19, 25 and 28 months respectively following pulmonary surgery. In them, the reappearance of the melanoma seemed to signal a breakdown of resistance to the disease and melanomatosis occurred thereafter.

It would appear that most patients who are going to succumb to melanoma after the excision of its pulmonary metastases, either solitary or multiple, will do so within two years.²⁰ Therefore, the prospect of survival is encouraging for two additional patients whose solitary deposits were excised 33 and 35 months ago and who show no evidence of recurrence at present.

Multiple Metastases

The value of excising more than one metastasis is still being investigated. These deposits have to be few enough so that, by their removal, the lung seems clear of cancer yet remains a well-functioning organ.

In this series of melanomas, when ipsilateral *multiple* lesions were found (arbitrarily no more than 4 to 5), one was excised for frozen section and if it proved to be a metastasis, all others that could be encompassed by wedge resections were similarly removed, unless confined to one lobe, when a radical lobectomy or a radical pneumonectomy was done.

One of 6 melanoma patients who had excisions for multiple unilateral metastases lived for more than 2 years. Six patients had bilateral pulmonary metastases; 3 synchronous and 3 metachronous with each other.^{18,22} Four had unilateral excisions and 2 bilateral excisions

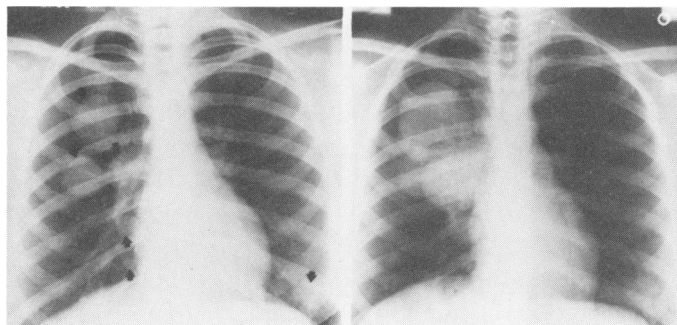


FIG. 5. (P.M.) Enlargement of unresected bilateral melanoma metastases. Eventual encroachment on the right hilum.

(5 weeks and 5 months apart and died 11 and 25 months postoperatively respectively). Although these figures appear discouraging for prolonged survival, 6 patients had no subsequent pulmonary recurrence and therefore might be said to have had palliation achieved by delaying or preventing the eventual encroachment of the metastases upon the intrathoracic structures (Fig. 5).

With such an extraordinarily unpredictable disease as melanoma, and with so few cases to analyze, it is only possible to theorize at present as to whether a contribution was made to survival, not only by excision of the pulmonary metastases but also by the additional lymphatic dissection. However, it is not unreasonable to suppose that the removal of as much tumor as possible wherever and whenever it is feasible, is to be preferred to leaving it in place.

Undoubtedly, further experience is needed to determine whether this extra effort is justifiable.

Summary

From 1949 through 1970 at this institution, 29 patients had excision of pulmonary melanoma metastases in an effort to extend survival. Eighteen of the metastases were solitary and 11 were multiple. Twenty of 29 patients were asymptomatic and their opacities were discovered by routine chest X-rays. A variety of procedures was performed depending upon the location and number of metastases. Secondary involvement of the regional lymphatics of the lung was noted in over 31%. Of 12 patients who had their pulmonary metastases excised five or more years ago, 4 are alive and without evidence of recurrence. All had solitary lesions. Two of them had involved pulmonary regional lymph nodes which were removed as part of a radical lobectomy. The interval between the primary cancer and its pulmonary metastasis did not appear to be a factor influencing survival. A solitary lung shadow in a melanoma patient is a diagnostic dilemma that can be resolved only by microscopic analysis. This basic principle was demonstrated by 18 cases where it proved to be a metastasis.

In 5 others it was a primary cancer of the lung and in one other patient, it was a benign tumor. Any attitude that delays extirpation of solitary lesions is unwarranted, since histologic confirmation is needed to institute appropriate therapy.

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References

- Adkins, P. C., Wesselhoeft, C. W., Jr., Newman, W. and Blades, B.: Thoracotomy on the Patient with Previous Malignancy: Metastasis or New Primary. *J. Thor. and Cardiovascular Surg.*, **56**:351, 1968.
- Alexander, J., and Haight, C.: Pulmonary Resection for Solitary Metastatic Sarcomas and Carcinomas. *Surg. Gynecol. Obstet.*, **85**:129, 1947.
- Allen, M. S., Jr., and Drash, E. C.: Primary Melanoma of the Lung. *Cancer*, **21**:154, 1968.
- Arce, M. J.: Pneumonectomie Totale (Le Tampon-drainage en Chirurgie Endothoracique. *Mem. Acad. de Chir.*, **62**:1412, 1936.
- Betts, R. H.: Carcinoma of the Lung: Bronchoscopic Aspects. *New Eng. J. Med.*, **225**:510, 1941.
- Borrie, J.: Secondary Lung Cancer Treated Surgically: A Nine-year Study. *N. Z. Med. J.*, **69**:71, 1969.
- Burke, M. D., and Melamed, M. R.: Exfoliative Cytology of Metastatic Cancer in Lung. *ACTA Cytologica*, **12**:61, 1968.
- Cahan, W. G., Butler, F., Watson, W. L., and Pool, J. L.: Multiple Cancers: Primary in the Lung and Other Sites. *J. Thor. Surg.*, **20**(3):335, 1950.
- Cahan, W. G.: Lung Cancer Associated with Cancer Primary in Other Sites. *Amer. J. Surg.*, **89**:494, 1955.
- Cahan, W. G.: Multiple Primary Cancers, One of Which is Lung. *Surg. Clinics of North America*, **49**(2):323, 1969.
- Cahan, W. G.: The Management of a Lung Opacity with a Primary Cancer at Another Site. *Cancer Management: A Special Graduate Course on Cancer*, Phila., Lippincott, 475, 1968.
- Cahan, W. G.: Radical Lobectomy. *J. Thor. and Cardiovascular Surg.*, **39**(5):555, 1960.
- Cahan, W. G., Watson, W. L., and Pool, J. L.: Radical Pneumonectomy. *J. Thor. Surg.*, **22**(5):449, 1951.
- Cahan, W. G., and Shah, J.: Benign Lesions of Lung in Patients with Cancer. (In Preparation)
- Carlucci, C. A., and Schleussner, R. C.: Primary (?) Melanoma of the Lung. A Case Report. *J. Thoracic Surg.*, **11**:643, 1942.
- Case Records of the Massachusetts General Hospital, *New Eng. J. Med.*, **239**:408, 1948.
- Clerf, L. H.: Melanoma of Bronchus: Metastasis Simulating Bronchogenic Neoplasm. *Ann. Otol., Rhin. & Laryng.*, **43**:85, 1934.
- Clifton, E., Das Gupta, T. and Pool, J. L.: Bilateral Pulmonary Resection for Primary or Metastatic Lung Cancer. *Cancer*, **17**:86, 1964.
- Cornet, E., Kerneis, J. P., Dupon, H., and Gordeef, A.: Metastases Melaniques Intra-pulmonaires: (2 cas Traités Chirurgicalement). *J. Franc. de Med. et Chir. Thor.*, **16**:111, 1962.
- Creech, O.: Metastatic Melanoma of the Lung Treated by Pulmonary Resection: (Report of a Case). *Med. Records and Annals*, **45**:426, 1951.
- Das Gupta, T., Bowden, L., and Berg, J.: Malignant Melanoma of Unknown Primary Origin. *Surg., Gynecol., Obstet.*, **117**:341, 1963.
- Das Gupta, T., and Brasfield, R.: Metastatic Melanoma, a Clinicopathological Study. *Cancer*, **17**:1325, 1964.
- Das Gupta, T., and McNeer, G.: The Incidence of Metastasis to Accessible Lymph Nodes from Melanoma of the Trunk and Extremities—Its Therapeutic Significance. *Cancer*, **17**:897, 1964.
- Everson, T. C., and Cole W. H.: Spontaneous Regression of Cancer: Preliminary Report. *Ann. Surg.*, **144**:366, 1956.
- Everson, T. C., and Cole, W. H.: Spontaneous Regression of Malignant Disease. *J. Amer. Med. Assoc.*, **143**:1758, 1959.
- Fortner, J. G.: Factors in the Treatment of Melanoma. *Med. Clinics of North America*, **45**:643, 1961.
- Fortner, J. G., Maclean, B., and Mulcare, R. J.: Treatment of Recurrent Malignant Melanoma. In *Melanoma and Skin Cancer. Proc. International Cancer Conf. and VIII International Pigment Cell Conference*, Sydney, Australia, (Book in press) 1972.
- Fortner, J. G.: Personal communication, 1972.
- Gliedman, M. L., Horowitz, S., and Lewis, F. J.: Lung Resection for Metastatic Cancer. *Surgery*, **42**:521, 1957.
- Gottlieb, J. A., Frei, E., III, and Luce, J. K.: An Evaluation of the Management of Patients with Cerebral Metastases from Malignant Melanoma. *Cancer*, **29**:701, 1972.
- Hadida, E., Benejam, Y., and Sayag, J.: Melanome Malin Revele par une Metaste Pulmonaire. *Algerie Med. et Chir.*, **66**:648, 1942.
- Hsu Ch'ang-Wen, et al: Melanoma of Lung. *Chinese Med. Journal*, **81**:263, 1962. (From Peking) Shanghai Chest Hospital, Shanghai, Republic of China.
- Johnson, F. D., and Jacobs, E. M.: Chemotherapy of Metastatic Malignant Melanoma: Experience with 73 Patients. *Cancer*, **27**:1306, 1971.
- Johnson, R. M., and Lindskog, G. E.: 100 Cases of Tumor Metastatic to Lung and Mediastinum. *Treatment and Results. J.A.M.A.*, **202**:94, 1967.
- Levison, V. B.: Spontaneous Regression of a Malignant Melanoma. *Brit. Med. J.*, **4911**:458, 1955.
- McNeer, G., and Das Gupta, T.: Prognosis in Malignant Melanoma. *Surgery*, **56**:512, 1964.
- Morton, D. L., Holmes, E. C., Eilber, F. R., and Wood, W. C.: Immunological Aspects of Neoplasia: A Rational Basis for Immunotherapy. *Ann. Int. Med.*, **74**:587, 1971.
- Ochsner, A., and DeBaKey, M.: Primary Pulmonary Malignancy. *Surg. Gynecol., Obstet.*, **68**:435, 1939.
- Pack, G. T., and Miller, T. R.: Metastatic Melanoma with Indeterminate Primary Site. Report of Two Instances of Long-term Survival. *J.A.M.A.*, **176**:55, 1961.
- Ramsey, H. E., Cahan, W. G., Beattie, E. J., and Humphrey, C.: The Importance of Radical Lobectomy in Lung Cancer. *J. Thor and Cardiovascular Surg.*, **58**:225, 1969.
- Rosenberg, L. M., Polanco, G. B., and Blank, S.: Multiple Tracheobronchial Melanomas with Ten-year Survival. *J.A.M.A.*, **192**(8):717, 1965.
- Sherman, R. S., and Cahan, W. G.: Isolated Fluoroscopy. An Evaluation. *New Eng. J. Med.*, **259**:622, 1958.
- Sumner, W. C.: Spontaneous Regression of Melanoma. Report of a Case. *Cancer*, **6**:1040, 1953.
- Sumner, W. C., and Foraker, A. V.: Spontaneous Regression of Human Melanoma. *Clinical and Experimental Studies. Cancer*, **13**:79, 1960.
- Volpe, J. A., Lull, R. J., and Nusynowitz, M. L.: The Liver Scan in Patients with Cancer: Histologic Correlation. *J. Surg. Oncology*, **3**(6):649, 1971.