Patterned Distribution of Metastases from Malignant Melanoma in Humans

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ABSTRACT

Malignant melanoma has an unpredictable clinical course in terms of metastatic behavior, and further understanding might lead to improved therapeutic intervention with immune agents or antagonists. To determine whether metastases show patterns or are randomly distributed, we analyzed the distributions of metastases in the 56 patients with metastatic malignant melanoma, subjected to complete autopsy at The Johns Hopkins Hospital, using parametric statistics and cluster analysis. Variables examined included age, race, sex, location of primary tumor, length of survival, mode of therapy, histology of tumor, location of metastases, and extent of tumor infiltration at each metastatic site. The results indicate that the distributions of metastases from malignant melanoma are patterned such that significant positive correlations (\( p < 0.05 \) or better) were observed among various tissues and organs. We identified several aggregations with respect to the distributions of metastases: (a) central nervous system; (b) mesodermal; (c) endocrine; (d) reticuloendothelial; and (e) foregut. Organs and tissues comprising each aggregation were interrelated by their similar developmental origins or functions. A very highly significant negative correlation between central nervous system and hepatic metastases (\( p < 0.001 \)) was also demonstrated by cluster analysis. We concluded that the distributions of metastases from malignant melanoma are not random; the patterns of metastases may be related to the embryological derivation of tissues involved.

INTRODUCTION

Malignant melanomas have protean clinical presentations and often unpredictable metastatic behavior (1). Since patients with malignant melanoma and other malignant neoplasms usually succumb to metastatic disease, further understanding of metastatic processes could lead to improved therapeutic interventions and prolonged survival. Although factors such as size and depth of invasion of the primary melanomas are correlated with the occurrence of metastases from malignant melanoma (7, 9, 22, 23), little is known about variables which affect the distributions of metastases and organophilic behavior of tumors in humans.

Despite the fact that malignant melanomas have been observed to metastasize to virtually every tissue, certain organs such as liver, lung, brain, and heart are clearly favored in terms of frequency of involvement (27). In addition, upon reviewing 12,000 consecutively autopsied patients in The Johns Hopkins Hospital file, we noted that melanomas accounted for a disproportionate percentage of CNS metastases (11). A similar finding was reported by others (3). These observations suggest that the distributions of metastases from malignant melanomas are non-random and nonuniform.

Previous attempts to predict behavior and therapeutic responsiveness of malignant neoplasms have focused largely on the use of macromolecular markers to characterize cells (5, 16, 18, 32). However, in several studies using animal models and/or in vitro assays, various aspects of tumor behavior were analyzed in terms of growth patterns (13, 26) and distributions of metastases (17, 26). In particular, several clones which characteristically differ from one another with regard to their invasive and metastasizing potentials (29) and organ preference of metastases (8, 14, 15, 30, 32, 33) have been derived from the B-16 murine malignant melanoma. These findings suggest that some experimental primary tumors are heterogeneous and are composed of malignant cells with different organophilic behaviors (31).

In this study, we reviewed autopsy cases of metastatic malignant melanoma and analyzed the data using parametric statistics and cluster analysis. The aims were to determine: (a) whether the distributions of metastases were patterned or simply random as would be predicted by the distribution of blood flow; and (b) whether the occurrence of CNS metastases could be predicted from the distribution of extra-CNS tumor. The heterogeneous nature of malignant melanomas was analyzed with respect to the correlations among various metastatic sites.

MATERIALS AND METHODS

The autopsy records of patients with metastatic malignant melanoma were reviewed. Only patients in whom complete autopsies had been performed at The Johns Hopkins Hospital from 1889 to 1981 were included in the study. Patients in whom metastases were not present at autopsy, or in whom only partial autopsies had been performed, were excluded from the data analysis.

Information derived from the clinical histories, gross autopsy protocols, and review of histological slides included: (a) location of the primary tumor; (b) type of therapy administered; (c) survival from the earliest point of tumor detection or symptoms related to the tumor (whichever was earlier); and (d) locations and extent of metastatic lesions. The locations of metastases were recorded with respect to: (a) anatomic region of body, e.g., head, thorax, abdomen, etc.; (b) organ or structure involved; (c) type of tissue involved, e.g., pleura, myocardium, gray matter, etc.; and (d) broad categories of the embryological derivation of affected tissue, e.g., mesoderm, neural crest, endoderm, etc. The extent of tumor involvement of each organ or structure was graded from 0 to 4+ as follows: 1+ for less than 5% organ replacement; 2+ for up to 20% organ replacement; 3+ for up to 50% organ replacement; and 4+ for massive, i.e., greater than 50% tumor infiltration. In addition, tumor metastases were assigned 5 different overall grades from 0 to 4+ with regard to degrees of melanin production, spindling, and anaplasia.

All data were expressed in the form of mnemonic codes and were typed and proofread on a Raytheon VT 1303 video display-based word processor with communications software. Data were transmitted in asynchronous ASCII code by dial-up or direct line to a Digital Equipment Corporation PDP 11/70 minicomputer running an American National Standards Institute MUMPS operating system and language interpreter in the Department of Laboratory Medicine, The Johns Hopkins Medical Institutions (8). All statistical analyses, including cluster analysis (see

1 Supported by NIH Grant LM 03651 from the National Library of Medicine.
2 To whom requests for reprints should be addressed, at Department of Pathology, The Johns Hopkins Hospital, Baltimore, Md. 21205.
3 The abbreviation used is: CNS, central nervous system.

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below), were carried out with short MUMPS programs (less than 60 lines) on the PDP 11/70 minicomputer.

Presence/absence data were analyzed statistically with $\chi^2$ contingency tables, and quantitative data were analyzed with correlation coefficients (Pearson’s $r$) and Student’s $t$ tests. We applied a modification of the “maximum-parsimony” cluster analysis technique (25) to determine whether groups of cases with characteristic patterns of metastases could be identified. A maximum-parsimony clustering technique is one which connects individual cases, one to another, in a tree-like arrangement (or “dendrogram”) such that the number of presence/absence transitions along the connecting links is minimized, i.e., most parsimonious. The usual application of maximum parsimony cluster analysis is evolutionary studies, in which the cases correspond to animal species and the presence/absence transitions correspond to the appearance or disappearance of a morphological feature or biochemical marker. In the present cluster analysis, we constrained the solution procedure such that it was impossible to experience a transition from “tumor present” to “tumor absent” between ancestor case and descendant case (“back replacement”), since we felt that clusters formed in this manner would not reflect the usual progressive behavior of metastatic tumors. Cases were sorted in ascending order using the number of anatomic sites having metastatic involvement from a total of 14 potential sites. The “primary-only” node represented cases with no metastases and were at the top of the sorted list. Successive cases in the sorted list were attached either directly to the primary-only node or to a previously placed node already on the dendrogram. The criterion used to decide where to place each successive case on the tree was that a minimum additional number of tumor-present metastatic sites be added to the tree linking the new case to the preexisting tree. The algorithm was complete when all cases in the sorted list had been attached to the dendrogram.

**RESULTS**

**Location and Treatment of Primary Tumors (Table 1)**

In The Johns Hopkins Hospital autopsy files between 1889 and 1981, there are 73 cases of malignant melanoma; 56 of which were included in this study. Seventeen cases were excluded because either complete autopsies had not been performed (11 cases), or metastases were not present at autopsy (6 cases). Among the 56 cases included in this study, spanning the period 1916 to 1981, 43 (79%) of the primary tumors occurred in skin; 4 (7%), in the eye; 3 (5%), in the intestinal tract; 1 (2%), in a bronchus; 1 (2%), in the cerebral leptomeninges; and 4 (7%), in unknown sites. There were 37 males (66%) and 19 females (34%). The majority of patients were white (52 of 56; 93%), and the few remaining were black (4 of 56; 7%). The mean age of all patients was 47.5 ± 2.1 years (S.E.), and the mean age of males (47.1 ± 2.6 years) was not significantly different from that of females (46.2 ± 4.3 years).

Survival was not affected by age, race, sex, location of primary tumor, type of therapy, or distributions of metastases outside the CNS. Although we observed no correlation between survival and therapy, this may have been due to patients being treated at different stages and/or depths of invasion of the primary tumors. However, prolonged survival was positively correlated with marked histological degree of spindling of tumor cells ($p < 0.05$) and significantly lower frequencies of metastases in dura mater and/or leptomeninges of the CNS ($p < 0.05$). In addition, prolonged survival was correlated with more extensive (although not more frequent) metastases in liver ($p < 0.05$). The most common form of therapy was surgical excision of the primary tumor (33 of 56; 59%). Eighteen (32%) patients were treated by surgery alone, while 15 were treated by a combination of surgery and systemic chemotherapy (7 of 56; 13%) or radiation (8 of 56; 14%). Twelve patients (21%) received no treatment. The remainder were treated by radiation (4 of 56; 7%), systemic chemotherapy (4 of 56; 7%), or both in combination with immu-

<table>
<thead>
<tr>
<th>No. of cases</th>
<th>Age (yrs)</th>
<th>Male/female</th>
<th>White/black</th>
<th>Primary site</th>
<th>Survival (mos.)</th>
<th>Extra-CNS metastases</th>
<th>No. of cases with CNS metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>56</td>
<td>47.6 ± 2.1*</td>
<td>37/19</td>
<td>52/4</td>
<td>40.5 ± 8.9</td>
<td>9.4 ± 0.7</td>
<td>41 (73)*</td>
</tr>
<tr>
<td>With CNS metastases</td>
<td>41</td>
<td>48.7 ± 2.4</td>
<td>26/16</td>
<td>40/3</td>
<td>30.8 ± 6.2</td>
<td>9.8 ± 0.9</td>
<td>41 (100)</td>
</tr>
<tr>
<td>Without CNS metastases</td>
<td>15</td>
<td>44.2 ± 4.1</td>
<td>11/3</td>
<td>13/1</td>
<td>71.8 ± 31.3</td>
<td>8.4 ± 1.1</td>
<td>0 (0)</td>
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<tr>
<td>Skin primary</td>
<td>43</td>
<td>47.0 ± 2.3</td>
<td>31/13</td>
<td>41/4</td>
<td>37.8 ± 6.5</td>
<td>9.7 ± 0.8</td>
<td>32 (74)</td>
</tr>
<tr>
<td>Non-skin primary</td>
<td>13</td>
<td>49.8 ± 5.3</td>
<td>6/6</td>
<td>12/0</td>
<td>47.3 ± 34.4</td>
<td>8.4 ± 1.5</td>
<td>9 (69)</td>
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</table>

* Mean ± SE.
* Numbers in parentheses, percentage.
notherapy (3 of 56; 5%). Patients who received no treatment were significantly more likely to have had their primary tumors located in sites other than skin ($p < 0.05$).

**Distribution of Extra-CNS Metastases (Table 2)**

In Table 2, the frequency of metastases in various organs is given for patients with and without CNS involvement. When considered in terms of general regions of the body, the overall frequencies of metastases were as follows: abdomen, 53 of 56 cases (95%); thorax, 50 of 56 cases (89%); CNS, 41 of 56 cases (73%); extremities, 20 of 56 cases (36%); pelvis, 20 of 56 cases (36%); neck, 18 of 56 cases (32%); and head, 15 of 56 cases (27%). Within the abdomen, metastases were observed most frequently in liver (38 of 53 cases; 72%), lymph nodes (33 of 53; 62%), gastrointestinal tract (30 of 53; 57%), adrenal glands (29 of 53; 55%), with 28 of 29 in adrenal medulla and 20 of 29 in adrenal cortex), pancreas and spleen (22 of 53; 42% each), kidneys (20 of 53; 38%), and mesothelial or serosal surfaces (18 of 53; 34%).

In the thorax, metastases occurred most frequently in lung (42 of 50; 84%), heart (26 of 50; 52%, and especially in myocardium, 20 of 26; 77%), mediastinal lymph nodes (16 of 50; 32%), bone marrow (12 of 50; 24%), diaphragm (12 of 50; 24%), and mesothelial or serosal surfaces (8 of 50; 16%). Metastases in the extremities were restricted primarily to soft tissues (12 of 20; 60%), skin (6 of 20; 30%), lymph nodes (5 of 20; 25%), and bone marrow (4 of 20; 20%) of proximal regions of arms and legs. Metastases in the pelvic area occurred mainly in reproductive organs (16 of 20; 80%) including ovary, testis, and prostate. Other sites of pelvic metastases were bladder (6 of 20; 30%) and pelvic lymph nodes (3 of 20; 15%). In the neck, metastases occurred most often in thyroid (14 of 20; 70%); diaphragm (12 of 20; 60%), and the heart (p < 0.001), particularly in the stomach (p < 0.05), the thyroid gland (p < 0.05), and the heart (p < 0.001). The last observation probably accounts for the expression, "charcoal heart," which has been used in reference to a patient with metastatic malignant melanoma in the heart (35). Greater degrees of anaplasia were correlated with more extensive liver metastases ($p < 0.05$). The presence of spindling was not correlated with metastases in any particular location. There was no correlation between degree of anaplasia and number of metastases or survival, but patients who were treated by radiation and/or chemotherapy had more anaplastic tumors than did untreated patients ($p < 0.001$). Degrees of spindling and melanin production were not correlated with therapy.

**Factors Affecting Distribution of Extra-CNS Metastases**

Variations in the distribution of extra-CNS metastases occurred as a function of age, sex, survival, total number of metastatic sites observed at autopsy, mode of treatment of the primary tumor, and histological grade of the tumor.

**Age and Sex.** Advanced age was associated with significantly more extensive ($p < 0.05$), but not more frequent, pulmonary metastases. Females were found to have proportionately greater frequencies and more extensive metastases in reproductive organs (10 of 20; 50%; $p < 0.05$), especially ovary, and in the large intestine (9 of 20; 45%; $p < 0.005$). Females also had more extensive ($p < 0.05$), but not more frequent, metastases in skin compared to those of males.

**Survival.** Prolonged survival was associated with more extensive metastases in liver ($p < 0.05$), although the frequency of liver metastases did not vary significantly as a function of survival. Prolonged survival was also correlated with more extensive histological spindling of tumor cells ($p < 0.05$). There was no correlation between length of survival and degree of anaplasia or extent of melanin production. These findings are consistent with the observations of others (10, 22, 23, 36) but discordant with the findings of Amer et al. (2), who observed accelerated death in patients with extensive visceral metastases. However, in their study only short-term survival was assessed in critically ill patients with advanced metastatic disease, and systematic quantitation of tumor burden was not performed at autopsy. In this study, we assessed survival from the onset of disease or earliest point at which disease was detected.

**Number of Metastases.** There was no correlation between number of metastatic lesions and patient age, sex, race, length of survival, mode of therapy, or degree of tumor cell anaplasia or spindling. However, tumors with large numbers of metastases exhibited significantly increased melanin production compared to those of cases with fewer metastases ($p < 0.05$).

**Histological Grade of Tumors.** In the metastatic lesions, melanin production was correlated with spindling such that heavily pigmented tumors tended to have more extensive spindle cell components than did tumors with less overall pigment production ($p < 0.005$). Intense melanin production was correlated with increased frequencies of metastasis in the gastrointestinal tract ($p < 0.05$), particularly in the stomach ($p < 0.05$), the thyroid gland ($p < 0.05$), and the heart ($p < 0.001$). The last observation probably accounts for the expression, "charcoal heart," which has been used in reference to a patient with metastatic malignant melanoma in the heart (35). Greater degrees of anaplasia were correlated with more extensive liver metastases ($p < 0.05$). The presence of spindling was not correlated with metastases in any particular location. There was no correlation between degree of anaplasia and number of metastases or survival, but patients who were treated by radiation and/or chemotherapy had more anaplastic tumors than did untreated patients ($p < 0.001$). Degrees of spindling and melanin production were not correlated with therapy.

**Therapy.** Patients who received no therapy had significantly higher frequencies of metastases in reproductive organs (6 of 10; 60%; $p < 0.05$). Radiation therapy resulted in significantly lower frequencies of metastases in lymph nodes (6 of 15; 40%; $p < 0.05$). Treatment with systemic chemotherapy resulted in significantly higher frequencies of metastases in mesothelial or serosal surfaces in the thorax and abdomen (9 of 13 cases; 69% $p < 0.005$).

**CNS Metastases (Table 3)**

In the CNS, metastases from malignant melanoma occurred

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Table 2

<table>
<thead>
<tr>
<th>Malignant melanoma: distribution of metastases in 56 cases</th>
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<tbody>
<tr>
<td>No. of cases</td>
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<td>with CNS</td>
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<tr>
<td>metastases</td>
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<tr>
<td>CNS</td>
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<td>Cortex</td>
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<td>Meninges</td>
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<td>Extra-CNS</td>
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<td>Lung</td>
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<td>Liver</td>
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<td>Lymph node</td>
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<td>Gut</td>
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<td>Serosa</td>
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<td>Skin</td>
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<tr>
<td>Gonads</td>
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<td>Anterior pituitary</td>
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* Numbers in parentheses, percentage.
most often in: (a) gray matter of cerebral cortex (36 of 41; 88%); (b) leptomeninges (26 of 41; 63%); (c) dura mater (10 of 41; 24%); (d) ventromedial structures of the diencephalon (10 of 41; 24%), including hypothalamus and hypothalamic stalk (6 of 10; 60%), posterior lobe of the pituitary gland (2 of 10; 20%), and leptomeninges and/or dura mater (7 of 10; 70%); (e) cerebellum (10 of 41; 24%), including mainly cortex (6 of 10; 60%) and/or leptomeninges (9 of 10; 90%); and (f) leptomeninges of brainstem (7 of 41; 17%) and spinal cord (7 of 41; 17%). Within the entire CNS, the frequency of metastases followed a rostral-to-caudal distribution such that metastases occurred most often in the telencephalon (39 of 41; 95%), less often in the diencephalon (10 of 41; 24%) and cerebellum (10 of 41; 24%), and least often in brainstem (8 of 41; 20%) and spinal cord (8 of 41; 20%).

Correlations among Various Regions of the CNS

Metastases in the leptomeninges and periventricular zones of the telencephalon and/or diencephalon were correlated with metastases in the leptomeninges and subarachnoid spaces of the cerebellum (ρ < 0.005), brainstem (ρ < 0.01), and spinal cord (ρ < 0.005). Similarly, metastases in the cerebellum were correlated with significantly increased metastases in leptomeninges of the brainstem (ρ < 0.005) and in the leptomeninges and subarachnoid spaces of the spinal cord (ρ < 0.005). In addition, the presence of tumor in perivascular (Virchow-Robin) spaces within the cerebral hemispheres was correlated with metastases in brainstem (ρ < 0.05) and spinal cord (ρ < 0.001). This pattern of tumor distribution suggests that at least some of the metastases located in more caudal regions of the CNS occurred secondary to "downstream" seeding of tumor cells from the telencephalon and/or diencephalon.

Metastases in cortical gray matter were correlated with metastases in leptomeninges (ρ < 0.005) and in adjacent subcortical white matter (ρ < 0.05), but not in gray matter nuclei, central white matter tracts, or dura mater. Metastases in nuclei occurred independently of metastases located elsewhere in the CNS. Metastases in dura mater were correlated with metastases in leptomeninges (ρ < 0.005). The correlations between leptomingeal and cortical metastases, and between leptomingeal and dura mater metastases, were interpreted to have resulted from direct extension of tumor between adjacent tissues. This was particularly evident in cases where tumor was primarily located in cortical gray, but also extended focally in subcortical white matter or into overlying leptomeninges.

Factors Affecting the Distributions of CNS Metastases

General. The presence and distribution of CNS metastases were correlated with several variables including age, therapy, number of extra-CNS metastases, and survival. There was a negative correlation between age and leptomingeal metastases, such that younger patients developed leptomingeal metastases with higher frequency than did older patients (ρ < 0.05). While treatment with systemic chemotherapy, with or without surgical excision of the primary tumor, was correlated with less extensive overall CNS metastases (ρ < 0.05), it did not prolong survival, and the frequency of CNS metastases was the same as for all other patients, both treated and untreated. As the number of extra-CNS metastases increased, the frequency of metastases in leptomeninges increased significantly (ρ < 0.05). However, the frequency and extent of metastases in cortical gray matter, gray matter nuclei, white matter, and dura mater were not affected by the number of extra-CNS metastases. Metastases in leptomeninges and/or dura mater, but not in cortex or other parenchymal structures, were correlated with significantly decreased survival (ρ < 0.05) compared to that of patients without CNS metastases. Frequency and extent of CNS metastases were not correlated with different degrees of tumor cell anaplasia, spindling, or melanin production, or race or sex of the patients.

Structural Correlations. Metastases in leptomeninges were correlated with significantly higher frequencies of metastases in thyroid gland (ρ < 0.01), pancreas (ρ < 0.01), kidney (ρ < 0.005), heart (ρ < 0.05), and reproductive organs (ρ < 0.001), especially ovary (ρ < 0.01). Metastases in dura mater were correlated with higher frequencies of metastases in thyroid gland (ρ < 0.01), pancreas, kidney, bone, and gonads (ρ < 0.05). In other words, metastases in endocrine and mesoderm-derived structures (including gonads) were correlated with metastases in leptomeninges and dura mater, but not with metastases in neuroectoderm-derived structures of the CNS, i.e., cortical gray matter, white matter, or gray nuclei. At this point, it is of interest to note that metastases in endocrine and extra-CNS mesoderm-derived structures were also intercorrelated (see below).

With regard to other tissues of the CNS, there was a negative correlation between the frequency and extent of metastases in liver and metastases in gray and white matter of the cerebral and cerebellar cortex (ρ < 0.01). There was also a negative correlation between metastases in mesothelial or serosal sur-
faces and metastases in cortical gray matter \( (p < 0.05) \), which was more striking when metastases in serosal surfaces were extensive \( (p < 0.005) \). Restated, patients with hepatic and serosal surface metastases had significantly lower frequencies and less extensive metastases in gray and white matter of the CNS. However, the frequency and extent of leptomeningeal and dura mater metastases were unaffected by the presence of metastases in liver or on serosal surfaces. From these observations, it may be concluded that metastases in particular extra-CNS sites were correlated with nonrandom distributions of metastases in characteristic locations within the CNS.

**Correlations among all Metastatic Sites**

In an attempt to discern the relationships among metastases in various organs, the significant positive correlations among selected tissue sites are depicted in Chart 1. This chart purposefully illustrates the complex interrelationships among metastatic sites and, in part, reflects the tendency for multiple sites to be involved by metastases in individual patients. Not shown on the diagram is a significant \( (p < 0.01) \) negative correlation between metastases in cortex and liver; however, cerebral cortex and liver form opposite poles of the diagram. The aggregations of the metastatic sites are shown by the circumscribed zones and are referred to as: (a) CNS; (b) mesodermal; (c) endocrine; (d) reticuloendothelial; and (e) foregut derivatives. These particular groupings of intercorrelated metastatic sites have developmental relationships.

The CNS aggregation is composed of cerebral and cerebellar cortex, leptomeninges, and dura mater. This group is connected to the other aggregations by way of leptomeningeal and dura mater metastases. Metastases in cortex occurred independently of metastases in extra-CNS locations, but were correlated with metastases in other neural ectoderm-derived structures of the CNS, namely, white matter and leptomeninges. Leptomeninges are largely derived from the neural crest component of neural ectoderm \((20)\), although secondary infiltration by mesodermal elements occurs \((21)\). Metastases in cortex, white matter, and gray matter nuclei were not correlated with metastases in dura mater which is of purely mesodermal origin.

The mesodermal aggregation is composed of heart, kidney, and genitalia, and also includes the coverings of the CNS. The endocrine aggregation consists of adrenal, pituitary, thyroid, and parathyroid. There are intercorrelations between the mesodermal and endocrine groups.

The reticuloendothelial group, comprised of bone, spleen, and liver, shows few correlations with other sites. The foregut-derived organs of liver, lung, pancreas, and gut are also related to the mesodermal and endocrine groups; and the liver is considered to be a member of both foregut and reticuloendothelial aggregations.

**Cluster Analysis**

While the above statistical analysis demonstrated correlations among metastatic sites, particularly a separation of CNS and liver metastases, and a nonrandom distribution of tumor metastases, the large number of variables which entered into this analysis made it difficult to appreciate a sense of the metastatic distribution among individual patients. Cluster analysis was used to approach the question from the perspective of individual patients.

By use of cluster analysis, 3 major clusters of tumor metastases emerged: a CNS-predominant cluster; a liver-predominant cluster; and a gut-predominant cluster (Chart 2). These 3 clusters

![Chart 1. Positive correlations among various anatomic sites involved by metastatic malignant melanoma. Four progressive increases in thickness of connecting lines, significant correlations by the \( \chi^2 \) test of \( p < 0.05, p < 0.01, p < 0.005 \), and \( p < 0.001 \), respectively. Encircled areas, CNS, mesodermal, endocrine, reticuloendothelial, and foregut derivative aggregations of intercorrelated metastatic sites. ADR, adrenal; GEN, genitals; LEPTO, leptomeninges; PANC, pancreas; PARA, parathyroid; PIT, anterior pituitary; THYROID, thyroid.](chart1.png)

![Chart 2. Cluster analysis of patients with metastatic malignant melanoma. Ovals, individual patient; central oval (Primary Only), state of having a primary lesion but no metastases. Three clusters (CORTEX, LIVER, GUT) are identified by the analysis. Site names beside connecting lines, additional metastatic sites involved in the next patient or node (8) on the tree. Areas covered by silhouettes of brain or liver, patients who have, respectively, CNS metastases with no liver metastases and liver metastases with no CNS involvement. ADR, adrenal; GEN, genitals; LEPTO, leptomeninges; PANC, pancreas; PARA, parathyroid; PIT, anterior pituitary; THYROID, thyroid; MESO, mesothelial or serosal surfaces.](chart2.png)
showed significant inhomogeneities in the distribution of liver and CNS metastases \( (p < 0.001) \). However, the CNS-predominant and gut-predominant clusters overlap extensively and, in terms of frequency of metastases in liver and CNS, the 2 groups did not differ significantly from one another. In the CNS-predominant cluster, all cases had metastases in cortical gray matter, and the frequency of liver metastases was significantly lower than that in the liver-predominant cluster \( (p < 0.001) \). In the liver-predominant cluster, all cases had liver metastases, and the frequency of cortical gray metastases was significantly lower than in the CNS-predominant cluster \( (p < 0.001) \). In fact, only in cases at the periphery of the liver-predominant cluster were there metastases in the CNS at all and, in those instances, metastases were largely confined to leptomeninges and dura mater. Note also that, while metastases in lung were commonly associated with liver metastases \( (p < 0.05) \), and both sites participate at the core of the liver-predominant cluster, metastases in lung were only variably present in the CNS-predominant cluster. Furthermore, there was no correlation between metastases in lung and metastases anywhere in the CNS. The validity of these clusters is reinforced by the negative correlation between metastases in liver and metastases in cortical gray matter \( (p < 0.01) \). In a previous study of neuroblastic tumors, we observed a similar discordance between CNS and liver metastases \( (12) \).

**DISCUSSION**

The results of this study indicate that, among patients with metastatic malignant melanoma, the most significant variables associated with prolonged survival were the absence of metastases in the cerebral leptomeninges and the presence of spindling in tumor cells. Variables such as number and extent of overall metastases, mode of therapy, and degree of tumor cell anaplasia were apparently unimportant in terms of mean survival of patients who developed metastatic disease. The implication here is that certain malignant melanomas have the potential to metastasize, and the subsequent clinical course in terms of distribution of metastases and survival is unaltered by any form of therapy. Recent studies indicate that malignant melanomas with metastasizing potential can be recognized by the size and configuration of the primary tumors \( (7, 10) \).

In this study, 73% of the 56 patients had CNS metastases, and the great majority of cases had metastases in cerebral and cerebellar cortex. With the exception of the negative correlation between metastases in liver or serosal surfaces and gray and white matter structures, the development of metastases in CNS parenchyma was not predictable from the pattern of extra-CNS metastases, nor did it correlate with age, race, sex, number of extra-CNS metastases, location of primary tumor, histology of tumor, or mode of therapy. In contrast, metastases in dura mater and leptomeninges were correlated with metastases in certain extra-CNS locations. Our interpretation of these observations is that the apparent preferential involvement of cortical gray matter, as compared to white matter, and the independent nature of the development of metastases in gray matter structures is directly related to the inherent neurotrophic potential of metastasizing malignant melanomas, and that these neurotrophic properties are separate and distinct from all other patterns of metastases both within and outside of the CNS.

The distributions of extra-CNS metastases were also patterned as determined from the results of the several statistical methods used. The hierarchy in terms of frequency of metastases throughout the body does not correspond to the expected distribution based upon differential blood flow in various organs. Independent experiments have demonstrated a descending order of differential organ blood flow \( (19, 24, 34) \), percentage of cardiac output received \( (19) \), and metabolic rate of oxygen consumption \( (34) \). These data, along with the distribution of metastases from malignant melanoma in the cases studied here, are presented in Table 4. Based upon the comparisons among these studies, the observed patterns of metastases from malignant melanoma cannot be accounted for solely on the basis of organ blood flow, percentage of cardiac output, or organ metabolic rate, since none of these orderings correspond to the rank order of the metastatic spread of tumor. In addition, factors such as blood flow cannot account for the various intercorrelations among organ metastases, e.g., those involving predominantly endocrine organs or reticuloendothelial structures. Furthermore, the correlations between metastases occurring in particular extra-CNS locations and in leptomeninges or dura mater but not in CNS parenchyma reinforce the concept that the distribution of metastases from malignant melanoma is patterned.

In an attempt to explain the grouping of metastases in particular organs, we examined different features of the tissues and organs involved and determined that the grouping of metastatic sites could be, to a large extent, related to the embryological derivations of the various tissues and organs involved, and also to some of the functional interrelationships among various organs and tissues.

The reticuloendothelial group included spleen, bone marrow, and liver, and metastases in these locations were all intercorrelated. These structures are derived from mesoderm and, in the fully developed human, they form the core of the reticuloendothelial system and participate in the production of blood, inflammatory cells, and immune cells. Therefore, developmental and/or functional arguments can be used to explain the existence of the reticuloendothelial group.

The foregut-derived and mesodermal groups are also explainable on a developmental basis. The correlation between metastases in liver and lung is explainable on developmental grounds.

**Table 4**

Distribution of metastases in malignant melanoma versus organ blood flow and organ metabolic rate

<table>
<thead>
<tr>
<th>Metastases</th>
<th>Blood flow distribution at rest (21, 23)</th>
<th>Blood flow distribution maximal (21)</th>
<th>Proportionate cardiac output (23)</th>
<th>Metabolic rate for oxygen (22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>CNS</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Liver</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Lymph node</td>
<td>4</td>
<td>5</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Gut</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Adrenal</td>
<td>6</td>
<td>7</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Heart</td>
<td>7</td>
<td>7</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Pancreas</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Spleen</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Renal</td>
<td>10</td>
<td>10</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Mesodermal</td>
<td>11</td>
<td>11</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Skin</td>
<td>12</td>
<td>12</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Genital</td>
<td>13</td>
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<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Thyroid</td>
<td>14</td>
<td>14</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Muscle</td>
<td>—</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*— measurement was not reported separately, and blood flow distribution, proportionate cardiac output, and metabolic rate for those organs or tissues were lower than those of the ranked organs.*

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because both organs are largely derived from endodermal epithelium of the foregut. Ovary and testes, except for the germ cell component, are of mesodermal origin, and metastases in gonads were correlated with metastases in other mesoderm-derived organs and tissues including kidney, heart, and dura mater.

Metastases in foregut-derived structures were more closely correlated with each other than with other structures derived from midgut, e.g., small bowel, or hindgut, e.g., large bowel. For example, metastases in the stomach were more significantly correlated with metastases in the pancreas and less significantly with metastases in small or large bowel. Both stomach and pancreas are derived from foregut. Similarly, metastases in thyroid, parathyroid, thymus, and anterior pituitary were all intercorrelated. These structures have in common their derivation from branchial arches, but ultimately they are derived from foregut.

In these organs were variably correlated with metastases in other foregut organs such as stomach or pancreas.

That the patterns of metastases might also be related to functional aspects of involved tissues and organs was suggested by the correlations or simultaneous occurrence of metastases in the following locations: (a) gonads and anterior pituitary; (b) several organs of the reticuloendothelial system; (c) various endocrine organs including adrenals, pituitary, parathyroids, thyroid, and pancreas; and (d) organs and tissues involved in calcium regulation including bone, kidney, thyroid, and parathyroids.

From this analysis, we suggest that the observed patterns of metastases may be related in part to common embryological derivations and/or synchronized or common functional activities of the relevant organs and tissues. Although all of the correlations cannot be explained in these terms, this type of analysis does provide a potential explanation for the hypothesis that distributions of metastases from malignant melanoma are nonrandom.

Malignant melanomas probably represent heterogeneous neoplasms comprised of cells with different metastatic and trophic potentials. Although the tendency of the primary tumor to metastasize is predictable from the growth patterns and degree of invasiveness, the vertical growth, the patterns of metastases are not predictable by these criteria. The trophic patterns observed here by examining metastatic distributions show a descending order of frequency of organ and tissue involvement as follows: neurotrophic, 75%; reticuloendothelial, 45%; endocrine, 35%; and mesodermal, 25%. Examination of metastatic distribution for individual patients showed a separation into predominantly CNS and predominantly liver patterns.

The examination of metastatic behavior of malignant tumors is difficult because of the great variability of distribution observed among different patients. In this study, statistical methods were applied to data obtained from autopsied patients with metastatic malignant melanoma and were used to develop hypotheses on the behavior of malignant tumors. The results obtained using correlations among various metastatic sites and by cluster analysis both show a discordance between involvement of the CNS and the liver. The analysis also suggests that nonrandom patterns of metastases exist and are possibly related to embryological derivations or functional properties of the affected tissues.

REFERENCES


Patterned Distribution of Metastases from Malignant Melanoma in Humans

S. M. de la Monte, G. William Moore and Grover M. Hutchins