Organ Vascularity and Metastatic Frequency

L. Weiss, MD, K. Haydock, BA, J. W. Pickren, MD,
and W. W. Lane, PhD

The "hemodynamic" or "mechanical" theory proposes that the frequency of metastases in different organs is primarily determined by the numbers of cancer cells delivered to them in their arterial blood. This theory has not yet been adequately tested in man because reproducible, noninvasive measurements of organ blood flow have only recently become available. Correlation between these data and the metastatic frequency in 10 organs, in groups of patients with primary cancers in 15 anatomic sites, has therefore been sought. No correlation was obtained between metastatic frequency and organ weights, blood volumes, blood volumes per gram, "transit times," or blood flow. However, correlations significant at the 4-8% level were obtained between organ blood flow per gram and metastatic frequency in 4 of 5 groups of primary cancers with initial venous drainage into the portal system, compared with 1 of 10 draining into the caval system. At present, no definitive explanation can be offered for the apparent compliance of one set of primary cancers with the "hemodynamic" theory of metastasis, but not the others. (Am J Pathol 1980, 101:101-114)

THE ORGAN PATTERNS of metastases from different types of human cancer may vary considerably, and these vagaries in distribution have led to two major macroscopic theories. On the one hand, the "hemodynamic" theory considers that the occurrence of metastases is largely dictated by anatomic considerations of the vasculature supplying different presumptive sites, while, on the other hand, the "seed and soil" theory proposes essentially that the different frequency of overt metastases in different organs is best explained on the basis of differential cancer/host organ interactions, which may be more or less favorable for metastatic development.

In this study we examined human autopsy data on the frequency of metastases in a number of anatomic sites, from primary cancers in 15 locations, in order to assess the contribution of defined vascular factors to metastatic patterns.

Materials and Methods

Autopsy Data Base

The data were selected from a computerized bank of more than 9000 autopsy reports collected over the period 1958 to 1979; a detailed description of the autopsy protocols is

From the Departments of Experimental Pathology and Pathology and the Computer Center, Roswell Park Memorial Institute, New York State Department of Health, Buffalo, New York.

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Address reprint requests to Leonard Weiss, MD, Director of Experimental Pathology, Roswell Park Memorial Institute, New York State Department of Health, Buffalo, NY 14263.

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given by Pickren.[1] We used data from only those patients (2082 of 4516 cases) with primary cancers showing autopsy evidence of distant metastases in the liver or lungs, from primary cancers with initial *main* venous drainage to the portal or caval systems, respectively. After applying these selection criteria, we then restricted our analyses to groups of primary cancers containing more than 30 cases. The data ultimately used were based on a total of 2082 selected autopsies, as shown in Tables 1 and 2.

Primary Cancers

According to the selection criteria described, data were available on 15 primary sites, with initial main venous drainage into either the portal vein (Table 1) (esophagus, stomach, pancreas, colon, and rectum) or into the caval system (Table 2) (kidney, testis, breast, bone, urinary bladder, uterus, cervix uteri, ovary, thyroid, and prostate).

Metastatic Sites

Our choice of metastatic sites was dictated by the availability of reliable recent data on rates of blood flow and blood volumes for these organs. Accordingly, we have included lungs, liver, adrenals, kidneys, bone marrow, spleen, brain, skeletal muscle, thyroid, and skin in this study. The various metastatic site parameters used, which include organ weight, are shown in Table 3.

Statistical Methods

For each type of primary cancer, we tested for linear correlation between each of the metastatic site parameters shown in Table 3 and the frequency of metastases in these sites as shown in Tables 1 and 2. The resulting correlation coefficients (r) are given in Tables 4 and 5; their levels of significance were obtained by using the t test for linear correlation ($t = r\sqrt{n-2}/\sqrt{1-r^2}$) and calculating the probability of a random number falling outside the limits $\pm t$. The significance level indicates both the goodness of fit of individual points to the line, as shown in Text-figure 1, and that the slope of the line is non-zero.

Table1—Primary Cancers With Initial Drainage to the Portal Vein and the Frequencies of Metastases Expressed as Percentages of Selected Cases in the Various Organ Sites.*

Metastatic sites	Primary cancer site				
	Esophagus (38/183)†	Stomach (131/279)	Pancreas (137/178)	Colon (233/412)	Rectum (141/310)
Lungs	60.5	55.0	50.4	61.4	64.5
Liver	100.0	100.0	100.0	100.0	100.0
Adrenals	42.1	30.5	35.0	22.3	24.1
Kidneys	36.8	13.0	13.1	11.6	12.8
Bone marrow	28.9	16.8	10.2	7.3	10.6
Spleen	7.9	9.9	12.4	7.7	2.8
Brain	13.2	6.9	6.6	6.9	2.8
Skeletal muscle	7.9	5.3	3.6	6.4	8.5
Thyroid	13.2	2.3	5.1	4.7	7.1
Skin	0.0	3.8	5.8	4.3	3.5

* Of the total cases coming to autopsy, only those with liver metastases were selected for inclusion.

† Selected cases/total cases.

Table 2—Primary Cancers With Initial Drainage Into the Caval System and the Frequencies of Metastases Expressed as Percentages of Selected Cases in the Various Organ Sites†

Metastases sites	Primary cancer site									
	Kidney (76/131)	Testis (38/60)	Breast (676/1022)	Bone (81/113)	Urinary bladder (86/332)	Uterus (32/88)	Cervix (151/502)	Ovary (125/363)	Thyroid (51/137)	Prostate (86/406)
Lungs	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Liver	55.3	63.2	72.6	29.6	61.6	75.0	59.6	68.0	35.3	74.2
Adrenals	59.2	13.2	31.2	16.0	34.9	31.3	31.1	21.6	41.2	31.4
Kidneys	42.1	21.1	17.0	21.0	18.6	15.6	25.8	10.4	19.6	11.6
Bone marrow	35.5	15.8	61.8	33.3	25.6	34.4	20.5	11.2	29.4	73.3
Spleen	9.2	7.9	18.9	13.6	17.4	18.8	10.6	18.4	5.9	11.6
Brain	22.4	28.9	22.8	11.1	7.0	12.5	8.6	5.6	9.8	9.3
Skeletal muscle	6.6	0.0	15.5	19.8	8.1	6.3	9.9	8.0	9.8	5.8
Thyroid	5.3	2.6	24.0	6.2	11.6	15.6	10.6	5.6	2.0	2.3
Skin	11.8	5.3	19.5	16.0	4.7	3.1	2.6	4.8	9.8	3.5

* Of the total cases coming to autopsy, only those with pulmonary metastases were selected for inclusion.
† Selected cases/total cases.

Table 3—The Various Parameters of Arterial Blood Supply Used for the Listed "Target" Organs

Organ	Weight (g)	Blood volume (ml)	Blood volume per unit weight (ml/g)	Blood flow (ml/min)	"Transit time" (volume/flow) (min)	Blood flow per unit weight (ml/min/g)	Source of blood flow data
Lungs	440	530	1.205	6000	0.09	13.60	Snyder[2]
Liver	1800	250	0.139	1475	0.17	0.82	Snyder[2]
Adrenals	14	3	0.214	91	0.04	6.50	Altman and Dittmer[3]
Kidneys	310	70	0.225	1000	0.07	3.23	Snyder[2]
Bone marrow (red)	1500	80	0.053	600	0.13	0.40	Cowles et al[4]
Spleen	180	90	0.500	170	0.53	0.94	Huchzermeyer et al[5]
Brain	1400	110	0.079	602	0.18	0.43	Snyder[2]
Skeletal muscle	28000	700	0.025	594	1.18	0.02	Cowles et al[4]
Thyroid	20	4	0.200	100	0.04	5.00	Söderberg[6]
Skin	2600	65	0.230	375	0.17	0.14	Snyder[2]

Table 4—Correlation Coefficients Obtained for Individual Groups of Primary Cancers With Initial Drainage to the Portal Vein When the Metastatic Frequencies in the Various Target Organs (Excluding Lungs and Liver) Were Tested Against the Indicated Parameter*

	Primary cancer site				
	Esophagus	Stomach	Pancreas	Colon	Rectum
Organ weight (g)	−.33	−.28	−.36	−.22	−.07
Organ blood volume (ml)	−.34	−.30	−.39	−.24	−.13
Organ blood volume/ weight (ml/g)	−.12	.04	.25	.11	−.15
Organ blood flow (ml/min)	.21	−.13	−.32	−.16	−.08
"Transit time" (volume/ flow) (min)	−.47	−.32	−.36	−.28	−.26
Organ blood flow/ weight (ml/min/g)	.64	.54	.69	.69	.73
P	.083	.167	.058	.058	.040

* In the case of organ blood flow per gram, the probability values (*P*) from *t* tests are also given.

Results

The results that are summarized in Tables 4 and 5 reveal no significant correlations between the frequency of metastases in the eight organs or organ pairs listed, which exclude the lungs and liver, and organ weight, blood volume, blood volume per gram, blood flow or "transit times."

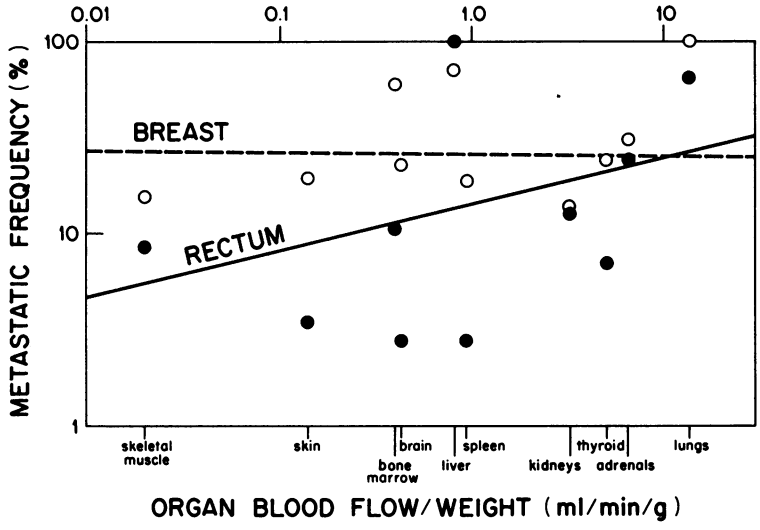
As shown in Table 4, 4 of 5 groups of primary cancer having *main* initial venous drainage into the portal system exhibit correlations significant at better than the 9% level between the frequency of metastases in 8 anatomic sites and the blood flow per gram in these target organs. The exception was the stomach. In the case of those primary cancers having main venous drainage into the caval system, 9 of 10 groups exhibited no correlations significant at better than the 10% level between metastatic frequency and target organ blood flow per gram (Table 5). The exception was metastatic cancer of the cervix uteri, where the correlation was significant at the 8% level. Illustrative graphic examples of both groups of primary cancers (rectum and breast) are shown in Figure 1, where metastatic frequency is plotted against organ blood flow per gram.

It should also be noted that the nature of the correlation between organ blood flow/weight and metastatic frequency does not differ appreciably between the different types of primary cancer draining through the portal system. Upon comparing the regression lines that best fit the points for each primary site, we find that the lines are nearly coincidental, with slopes of 2.4 ± 0.7 and y intercepts of 6.7 ± 2.0. Thus for each ml/g/min increase in blood flow/weight there seems to be approximately a 2.5-fold increase in metastatic frequency.

Table 5—Correlation Coefficients Obtained for Individual Groups of Primary Cancers With Initial Venous Drainage Into the Caval System When the Metastatic Frequencies in the Various Target Organs (Excluding Lungs and Liver) Were Tested Against the Indicated Parameter*

	Primary cancer site									
	Kidney	Testis	Breast	Bone	Urinary bladder	Uterus	Cervix	Ovary	Thyroid	Prostate
Organ weight (g)	−.38	−.48	−.27	.16	−.35	−.44	−.26	−.23	−.20	−.21
Organ blood volume (ml)	−.39	−.40	−.28	.18	−.37	−.43	−.27	−.21	−.23	−.20
Organ blood volume/ weight (ml/g)	−.11	−.16	−.34	−.37	.13	.01	−.03	.50	−.21	−.29
Organ blood flow (ml/min)	.18	.50	−.01	.52	−.19	−.18	.14	−.37	.04	.10
"Transit time" (volume/ flow) (min)	−.51	−.49	−.35	.09	−.36	−.42	−.36	−.05	−.34	−.25
Organ blood flow/ weight (ml/min/g)	.52	−.02	−.02	−.35	.60	.43	.65	.44	.42	−.03
P	.187	.963	.963	.395	.116	.288	.081	.275	.300	.944

* In the case of organ blood flow per gram, the probability values (*P*) from *t* tests are also given.



TEXT-FIGURE 1—For two exemplary types of cancer, the blood flow/weight of each metastatic site is plotted (on a log scale) versus the metastatic frequency in the various organs as illustrated. Solid circles indicate metastatic frequencies from primary cancers of the rectum. These points fit the line which is shown with a correlation coefficient of .73 (which is significant at the 4% level), indicating a definite positive correlation between organ blood flow/weight and metastatic frequency. Open circles indicate metastatic frequencies from primary cancers of the breast, where no linear correlation was found. Since these plots are drawn on a log-log scale, the points show nonlinear distortion, and the goodness of fit cannot readily be assessed by visual inspection.

Discussion

Although it is well known that the initial mode of entry of cancer cells into the metastatic process may be via the lymphatics and other routes, appreciation of the connections between the blood and lymphatic circulatory systems, not only via the subclavian veins but also at more microscopic levels,[7,8] serve not only to emphasize the general dominance of hematogenous spread in metastasis, but also to deemphasize the concept that metastasis at all but very early stages can be confined to one system or the other.

In this investigation we have examined human autopsy data in order to determine the degree of correlation between the organ patterns of metastases from primary cancers in 15 sites in relation to the blood supply of 10 metastatic sites. The primary sites were selected to provide examples of cancers draining initially into the portal (Tables 1 and 4) and caval (Tables 2 and 5) venous systems.

If an organ's blood supply largely determines the dose of cancer cells delivered to it, then hemodynamic "mechanical" [9] factors must play a

part in determining metastatic frequency. However, attempts to demonstrate a rate-regulating or dominant role for these factors have so far been confined to a small number of animal systems [10,11] that are not entirely appropriate to the human situation.[12]

It is presently well accepted that in addition to the inherent properties of the involved cancer cells, metastasis formation also depends on an extremely complex series of interactions occurring in target organs after the delivery of cancer cells.[13,14,15] On the one hand, if these events are similar in all organs, then a direct correlation is to be expected between some parameter of their blood supply and the incidence of metastases in them. On the other hand, if the events subsequent to delivery of cancer cells vary substantially between different organs ("seed and soil" [16]), then little or no correlation is expected between vascular parameters and metastatic pattern. Organ selectivity has indeed been demonstrated in animal systems by Sugarbaker,[17] Dunn,[18] Pilgrim,[19] and Parks [20]; and Brunson et al [21,22] have described the selection of subpopulations of the B16 melanoma that exhibit selectivity for organ colonization following intravenous injections into mice. In apparent contrast to these results, deLong and Coman [23] could demonstrate no organ selectivity for growth of tumor transplants in mice, rats, and rabbits.

There is really no reason why the "seed and soil" and "hemodynamic" theories should be mutually exclusive,[24] and Proctor's [25] experiments with the MCI sarcoma illustrate both the dependence of organ transplants in the rat liver and lung on whether cells are injected into the portal vein or vena cava ("hemodynamic") and the differential growth rate of cancer cells delivered to different organs via the arterial system ("seed and soil").

In experiments in which suitably radiolabeled tumor cells were injected into the tail veins of mice [26,27] or the portal veins of rats,[28] the majority of the cells were initially arrested in the lungs and liver, respectively, although most of them were subsequently released over a period of 24 hours; in addition, transpulmonary passage is traumatic for some types of cancer cells.[29,30–32] Thus, either by retention or damage, first organ encounters diminish the number of cancer cells available to form metastases in other organs when metastasis occurs by direct seeding from the primary cancer. In considering human autopsy data in which widespread dissemination of cancer has occurred, it must be remembered that metastases metastasize, thereby complicating patterns. However, by their analyses of human data, Viadana et al [33] have identified some key disseminating sites from which tertiary or quarternary metastases are generated. In the case of primary cancer with initial venous drainage into the caval system, the first key disseminating sites are the lungs; in the case of those

initially draining into the portal vein, the first key disseminating site is the liver, from which cancer cells preferentially metastasize to a second key disseminating site in the lungs. From these considerations of vascular routes, as distinct from the vascular parameters considered here, it was expected that the frequencies of metastases in the liver and lungs would be disproportionately higher than in other organs. The results shown in Tables 1 and 2 confirmed these expectations and indicate that in order to test the hypothesis that metastatic frequency is related to vascularity, one should exclude the lungs and liver from the analyses, and attention should be focused on the other organs to which cancer cells are delivered in arterial blood in an operationally similar yet independent manner.

Even after exclusion of the lungs and liver, the correlation coefficients between metastatic frequency and organ weight, blood volume, or blood volume per gram of organ are not statistically significant. Organ blood flow, which is expected to be a more realistic parameter of rates of delivery of cancer cells in the arterial blood, also does not correlate significantly with metastatic frequency.

The apparently unimpeded passage of cancer cells through the capillary beds of the lungs and liver may take only seconds.[34,35] Alternatively, when cells are arrested and then released, transit through the vasculature of these organs may take hours.[32] In general, it might be expected that the faster the blood flow through an organ, the more cancer cells are delivered to it. However, under conditions of fast flow, the retention of delivered cells is likely to be reduced. A crude estimate of blood transit time through organs may be obtained by dividing their blood volume by blood flow. As shown in Tables 4 and 5, no significant correlations were obtained between these *average* transit times for individual organs and the corresponding metastatic frequency. In view of the hemodynamic complexity of the situation, this finding is hardly surprising!

The failure in the investigations so far discussed to correlate organ blood flow with metastatic frequency does not necessarily lead to rejection of the "hemodynamic" theory, even though the blood flow to these organs must determine the numbers of cancer cells delivered to them. Many *in vitro* studies, particularly those of cell-mediated immune reactions, raise the possibility that some metastasis-determining interactions occurring after cell delivery may well depend upon critical ratios of cancer to target organ cells. Thus, for a more critical evaluation of the "hemodynamic" theory, not only is examination of parameters of numbers of delivered cancer cells required, but also some parameter of the ratios of these numbers and those of the cells with which they interact. An attempt has been made to generate "dosage" data of this type in terms of blood

flow per gram of organ and correlation with metastatic frequency. As shown in Table 4, considering the complexity of the metastatic process, there is good correlation between "dosage" and frequency of organ involvement in 4 of 5 groups of primary cancers with main initial venous drainage via the portal vein that are significant at the 8.3% (esophagus), 5.8% (pancreas), 5.8% (colon), and 4.0% (rectum) levels. The correlation with primary cancers of the stomach were not significant ($P = 16.7\%$). Of the 4 groups showing correlation, the probability value for the esophageal cancers was least significant. Even though the cases in this group were selected on the basis of having hepatic metastases, the probability value may reflect that initial venous drainage from the esophagus is not exclusively into the portal system. From the cervical, thoracic, and cardiac regions of the esophagus, drainage is into the inferior thyroid, hemiazygos, and gastric veins, respectively, thereby also constituting a portacaval shunt. Therefore, in some of the selected cases, the lungs may have been the first organ encountered. In the remaining 10 groups of primary cancers with main initial venous drainage into the caval system, as shown in Table 5, only carcinoma of the cervix uteri showed correlation between "dose" and metastatic frequency that was significant (8.1%) at better than the 10% level.

It is not enough to comment on the observation that 4 of 5 groups of cancers in one set metastasized in a pattern correlating with the dose delivered to their target organs; comment is also required on the observation that 9 of 10 groups of the other set of primary cancers do not. All of the primary cancers shown in Table 1 are carcinomas, as are those in 9 of 10 groups in Table 2. Thus, if the differences are explicable in terms of structural differences between the cancer cells themselves, they are probably too subtle to be detected by conventional histologic techniques.

Patterns of blood-borne dissemination may be perturbed by lymphatic spread, and in some cases spread may occur primarily via lymphatic routes.[36] However, predominant lymphatic spread of this type is usually confined to early cases of the disease and appears to be mainly related to the establishment of initial metastases in the liver and lungs, which serve as generalizing sites for later spread. The present autopsy series were mostly "late" cases and did not include pulmonary and hepatic metastases. We therefore consider it unlikely that the failure to correlate metastatic frequency with delivery via the blood reflects a major lymphogenous mechanism in one set of primary cancers but not in the other.

Another often overlooked problem in the interpretation of autopsy data on metastatic patterns is the effect of therapeutic intervention, since surgical removal of a primary lesion ensures that subsequent dissemination

occurs from existing metastases. If in fact the failure to obtain correlations in the set of tumors initially metastasizing to the lungs is due to a perturbation of pattern produced by primary or adjuvant therapy, then it would have to be argued that this process was not reflected in the group metastasizing initially to the liver. The results of treatment of patients with hepatic metastases are generally poor.[37] The average survival of patients with minimal hepatic involvement at operation varies from 6 to 8 months in patients with primary cancers of the colon to 2 to 3 months in those with pancreatic primary cancers.[38] Depending on the primary site, the 5-year survival for patients with solitary hepatic metastases is 12–20%.[39] These observations compare with an approximate 25% 5-year survival rate following resection of initial (solitary) pulmonary metastases[40,41]; other survival data vary considerably, depending on primary site. In light of these variations between the two sets of primary lesions, we cannot usefully say whether one explanation of their different metastatic frequencies is related to differences in survival.

Many cancer cells initially draining into the portal veins drain into the caval system either directly or by portacaval shunts. Thus, cells from both sets of primary cancers ultimately undergo transpulmonary passage, whether they are released from true primary lesions or from generating sites in the liver or lungs. Therefore the correlative differences between the two sets cannot be primarily due to nonspecific interactions with the lungs. The behavior of cancer cells may be modified by passage through organs,[32] and it is therefore possible that the properties of cancer cells making first organ encounters with the liver are in some way modified to account for the observed correlations. However, we must emphasize that the best that can be expected from the data examined here are suggestions for experiments to elucidate the mechanisms involved, as distinct from determination of the mechanisms themselves.

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