Endocrine Organ Metastases From Breast Carcinoma

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Breast carcinoma frequently metastasizes to endocrine organs, a behavior which may have prognostic or therapeutic relevance. Whether endocrine organ involvement represents a trophic influence on some carcinomas or is simply a "mass effect" of tumor dissemination is uncertain. To investigate this question, the authors reviewed the clinical and pathologic features of 187 subjects with metastatic breast carcinoma, all of whom had been subjected to complete autopsy at The Johns Hopkins Hospital. Metastases to primary endocrine organs, ie, the anterior pituitary, thyroid, parathyroid, or adrenal cortex, occurred in 57%, and metastases to secondary endocrine organs, ie, the pineal, posterior pituitary, thymus, adrenal medulla, or pancreas, occurred in 62% of patients. In general, patients with endocrine organ metastases were significantly younger and had significantly greater numbers of metastases and greater overall tumor burden than those without endocrine organ metastases (all $P < 0.001$). There was no correlation between endocrine organ metastases and survival, therapy, histologic type of tumor, or grade of anaplasia or desmoplasia. Metastases to primary endocrine organs were correlated with one another and with metastases in secondary endocrine organs. Metastases in secondary endocrine organs were intercorrelated and also correlated with several nonendocrine organs, chiefly the heart, liver, and gut (all $P < 0.005$). These findings indicate that metastases of breast carcinoma to endocrine organs occur in a setting of widely disseminated tumor. However, the observed correlations among metastatic sites suggest that the distributions are nonrandom; these distributions may reflect fundamental properties of some breast carcinomas with respect to hormone receptors, biologic behavior, or environmental growth requirements. (Am J Pathol 1984, 114:131–136)

THE RESPONSIVENESS of breast carcinomas to endocrine therapy has been recognized for years, and epidemiologic data implicate hormones, particularly estrogen, in the etiology of breast cancer.[1] These observations led to the frequent use of endocrine therapy, including organ ablation, antiestrogen treatment, and corticosteroids in the management of patients with breast carcinoma. The therapeutic effectiveness of endocrine therapy, and the finding that factors such as age are correlated with significant differences in the distributions of metastases and responsiveness to therapy,[2] suggest that the body's internal metabolic or hormonal milieu may alter the biologic behavior of breast carcinoma. Additional advances in the treatment of patients with breast carcinoma may require further understanding of this phenomenon. Because breast cancer frequently metastasizes to endocrine organs, we studied a large group of autopsy subjects with metastatic breast carcinoma to determine whether involvement of endocrine organs represents a trophic influence or simply a mass effect of tumor dissemination. In this study, particular attention was paid to the relations between endocrine organ metastases and therapy, survival, tumor burden, and the overall distribution of metastases.

Materials and Methods

The clinical histories, gross autopsy protocols, and histologic slides of deceased patients with metastatic breast carcinoma subjected to complete autopsy at The Johns Hopkins Hospital between 1965 and 1983 were reviewed. Those in whom metastases were not present at autopsy or on whom only partial autopsies had been performed were excluded from the data analysis.

Endocrine organs were designated as "primary" or "secondary." Primary endocrine organs were defined

Supported by NIH Grant LM-03651 from the National Library of Medicine.

Accepted for publication July 28, 1983.

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as those structures that are traditionally regarded as having a purely endocrine function, ie, the anterior pituitary, thyroid, parathyroid, and adrenal cortex. Secondary endocrine organs were defined as those structures with major endocrine functions that could not be regarded strictly as endocrine organs, ie, the posterior pituitary, pineal gland, thymus, adrenal medulla, pancreas, ovaries, and testes.

Information obtained from the clinical histories, autopsy protocols, and review of histologic slides included 1) location of the primary tumor, 2) type of therapy administered, 3) survival from the earliest detection of tumor or onset of relevant symptoms (whichever was earlier), and 4) location and extent of metastatic lesions. The locations of metastases were recorded with respect to 1) anatomic region of the body, eg, head, thorax, etc.; 2) organ or structure involved; 3) type of tissue involved, eg, pleura, myocardium, etc.; and 4) broad categories of the embryologic derivation of the affected tissue, eg, mesoderm, neural crest, etc. The extent of tumor involvement of each organ or structure was graded from 0 to 4+ as follows: 1+, a single metastatic focus or less than 5% organ replacement by tumor; 2+, two to five separate gross metastatic lesions, or up to 20% organ replacement; 3+, more than five separate gross metastases, or up to 50% organ replacement; and 4+, extensive tumor infiltration, or greater than 50% replacement. In addition, tumor burden in the body was given an overall grade (0–4+) on the basis of the degree of metastatic involvement in several major organs. Tumor metastases were assigned two different overall histologic grades from 0 to 3+ for anaplasia and desmoplasia.

All data were expressed in the form of mnemonic codes and typed and proofread on a Raytheon VT1303 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 with MUMPS operating system and programming language in the Department of Laboratory Medicine of The Johns Hopkins Medical Institutions. Presence/absence data were analyzed statistically with Fisher's exact test, and quantitative data were analyzed with correlation coefficients (Pearson's r) and the Student t test.

Results

General Population Profile

A total of 187 patients were included in this study. There were 184 (98%) women and 3 (2%) men and 115 (62%) whites and 72 (38%) blacks, and the mean age of the population was 56.6 ± 0.9 years at death. There were 168 (90%) duct carcinomas, 12 (6%) lobular carcinomas, 6 (3%) medullary carcinomas, and 1 (1%) case of malignant cystosarcoma phylloides. There were no significant differences in the frequencies of endocrine organ metastases among the different histologic types of breast carcinoma.

Fifty-seven percent of the patients had primary endocrine organ metastases, 61% had secondary endocrine organ metastases, and 30% had no endocrine organ metastases. Patients with either primary or secondary endocrine organ metastases were significantly younger than those without endocrine organ metastases ($P < 0.001$), and premenopausal patients, ie, those less than 46 years old, had significantly higher frequencies of either primary or secondary endocrine organ metastases than postmenopausal patients ($P < 0.005$). Patients with primary or secondary endocrine organ metastases had significantly greater overall tumor burden ($P < 0.001$) and greater numbers of metastatic sites ($P < 0.001$), even with endocrine organs excluded from the list of sites ($P < 0.001$). However, there was no correlation between endocrine organ metastases and race, therapy, or survival.

Frequencies of Endocrine Organ Metastases (Tables 1–3)

Among primary endocrine organs, metastases occurred most frequently in the adrenal cortex (43%), followed by the thyroid (20%), anterior pituitary (15%), and parathyroid glands (6%). Among secondary endocrine organs, metastases occurred most frequently in the adrenal medulla (38%), followed by the ovary (29%), pancreas (19%), thymus (16%), posterior pituitary (15%), and pineal gland (2%). Among patients with primary endocrine organ metastases, 52% had metastases to a single primary endocrine organ, 21% had metastases to two different sites, 22%

Table 1 – Frequencies of Metastases to Endocrine Organs

Primary endocrine organs		
Anterior pituitary	(28/183)*	15%
Thyroid	(37/187)	20%
Parathyroid	(12/187)	6%
Adrenal cortex	(77/181)*	43%
Secondary endocrine organs		
Posterior pituitary	(28/183)*	15%
Pineal	(3/187)	2%
Thymus	(29/187)	16%
Adrenal medulla	(68/181)*	38%
Pancreas	(35/187)	19%
Ovary	(42/146)*	29%

* The autopsy subjects with surgically absent endocrine organs were excluded from the data analysis.

Table 2—Profile of Patients With Metastases to Primary Endocrine Organs

	Number of primary endocrine organs affected					
	0	1–4	1	2	3	4
Number of patients	81 (43%)	106 (57%)	55 (29%)	22 (12%)	23 (12%)	6 (3%)
Mean age*	60.3† ± 1.4	53.7 ± 1.1	54.8 ± 1.5	52.1 ± 2.1	52.3 ± 2.6	55.8 ± 4.2
Survival* (months)	50.2 ± 5.1	45.3 ± 4.2	46.6 ± 6.6	42.9 ± 8.1	42.2 ± 7.2	59.6 ± 20.9
Metastatic sites*	8.1† ± 0.5	14.8 ± 0.6	11.8 ± 0.6	14.9 ± 1.2	20.7 ± 1.4	19.8 ± 2.1

* Mean ± standard error.
† $P < 0.001$.

had metastases to three different primary endocrine organs, and 5% had metastases in all four primary endocrine organs at autopsy. Among patients with secondary endocrine organ metastases, 53% had metastases in one secondary endocrine organ, 29% had metastases in two organs, 9% had three different organs involved, 7% had four different organs involved, and 3% had metastases in five different secondary endocrine organs. In each group, the overall number of metastases increased dramatically as the number of endocrine organ metastases increased, but this phenomenon was not correlated with significant differences in survival.

Correlations Among Endocrine Organs

As a group, primary endocrine organ metastases were correlated with metastases in several secondary endocrine organs, including the posterior pituitary, adrenal medulla, pancreas, and ovary (all $P < 0.001$). In addition, primary endocrine organ metastases were positively correlated with metastases in several nonendocrine organs, including cortical gray matter ($P < 0.001$) and leptomeninges ($P < 0.005$) of the cerebellum, heart ($P < 0.001$), pleura ($P < 0.005$), contralateral breast tissue ($P < 0.005$), liver ($P < 0.001$), spleen ($P < 0.001$), uterus ($P < 0.005$), and bone ($P < 0.005$). In contrast, primary endocrine organs were not correlated with metastases in several major organs, including the lung, kidney, gastrointestinal tract, skin, and lymph nodes.

Metastases in secondary endocrine organs were correlated with metastases in all primary endocrine organs (all $P < 0.005$ or better). In addition, they were correlated with metastases in the liver ($P < 0.001$), heart ($P < 0.005$), portions of the gastrointestinal tract ($P < 0.001$), including the esophagus ($P < 0.005$) stomach ($P < 0.001$), and small bowel ($P < 0.001$), uterus ($P < 0.001$), fallopian tubes ($P < 0.005$), and serosal surfaces ($P < 0.001$). In contrast, metastases in secondary endocrine organs were not correlated with metastases in the cerebral cortex, dura mater, lungs, lymph nodes, spleen, kidneys, or bone.

Correlations Among Specific Primary Endocrine Organs (Table 4)

Anterior Pituitary

Metastases to the anterior pituitary were only correlated with metastases to the other primary endocrine organs ($P < 0.005$ or better) and the posterior pituitary ($P < 0.001$).

Table 3—Profile of Patients With Metastases to Secondary Endocrine Organs

	Number of secondary endocrine organs affected						
	0	1–5	1	2	3	4	5
Number of patients	72 (39%)	115 (61%)	61 (33%)	33 (18%)	10 (5%)	8 (4%)	3 (2%)
Mean age*	60.7† ± 1.5	54.0 ± 1.0	54.3 ± 1.2	55.5 ± 1.7	53.1 ± 3.6	49.5 ± 6.1	47.3 ± 10.3
Survival* (months)	48.3 ± 5.9	46.9 ± 4.4	45.4 ± 7.1	44.1 ± 6.2	61.6 ± 12.5	54.9 ± 16.2	35.3 ± 12.4
Metastatic sites*	7.6† ± 0.5	14.6 ± 0.6	11.4 ± 0.5	15.3 ± 0.8	21.3 ± 2.4	23.8 ± 2.4	25.3 ± 2.9

* Mean ± standard error.
† $P < 0.001$.

Table 4—Correlations of Metastases to Primary Endocrine Organs

	Endocrine organ		Nonendocrine organ	
Anterior pituitary				
	Posterior pituitary	($P < 0.001$)		
	Thyroid/parathyroid	($P < 0.005$)		
	Adrenal cortex	($P < 0.001$)		
Thyroid/parathyroid				
	Anterior pituitary	($P < 0.005$)	Heart	($P < 0.001$)
	Posterior pituitary	($P < 0.001$)	Lung	($P < 0.005$)
	Adrenal cortex	($P < 0.001$)		
	Ovary	($P < 0.001$)		
Adrenal cortex				
	Anterior pituitary	($P < 0.001$)	Liver	($P < 0.001$)
	Posterior pituitary	($P < 0.001$)	Serosa	($P < 0.001$)
	Thyroid/parathyroid	($P < 0.001$)	Bone	($P < 0.001$)
	Adrenal medulla	($P < 0.001$)	Spleen	($P < 0.005$)
	Pancreas	($P < 0.001$)	Kidneys	($P < 0.005$)
	Ovary	($P < 0.001$)		

Thyroid/Parathyroid

Metastases in these structures were correlated with metastases in the anterior ($P < 0.005$) and posterior ($P < 0.001$) pituitary, adrenal cortex ($P < 0.001$), ovary ($P < 0.001$), heart ($P < 0.001$), and lungs ($P < 0.005$).

Adrenal Cortex

Metastases in the adrenal cortex were significantly correlated with metastases in the anterior and posterior pituitary, thyroid and/or parathyroid glands, adrenal medulla, pancreas, and ovary (all $P < 0.001$). Adrenal cortex metastases were also correlated with metastases in several nonendocrine structures, including the liver ($P < 0.001$), spleen ($P < 0.005$), kidneys ($P < 0.005$), bone ($P < 0.001$), and serosal surfaces ($P < 0.005$).

Correlations Among Specific Secondary Endocrine Organs (Table 5)

Posterior Pituitary

Metastases in the posterior pituitary were correlated with metastases in the anterior pituitary, thyroid and/or parathyroid glands, adrenal cortex, and pancreas (all $P < 0.001$). Metastases in the posterior pituitary were also correlated with metastases in several nonendocrine structures, including the heart ($P < 0.005$), liver ($P < 0.001$), hypothalamic stalk, and dura mater and leptomeninges surrounding the ventral diencephalon ($P < 0.001$).

Pineal Gland

Metastases in the pineal gland were not correlated with other metastatic sites, perhaps because there were only three examples of pineal metastasis among the patients studied.

Thymus

Metastases in the thymus were only correlated with metastases in the gastrointestinal tract ($P < 0.001$).

Adrenal Medulla

Metastases to the adrenal medulla were positively correlated with metastases in the adrenal cortex ($P < 0.001$) and pancreas ($P < 0.001$); among nonendocrine organs, the esophagus ($P < 0.005$) and small bowel ($P < 0.001$); and serosal surfaces ($P < 0.001$). In addition, metastases to the adrenal medulla were correlated with more extensive, but not more frequent, metastases to the lungs ($P < 0.005$).

Pancreas

Metastases in the pancreas were correlated with metastases in the posterior pituitary ($P < 0.005$), adrenal cortex ($P < 0.005$), adrenal medulla ($P < 0.001$), and ovary ($P < 0.001$). In addition, pancreatic metastases were correlated with more frequent metastases in the gastrointestinal tract ($P < 0.001$), particularly the stomach ($P < 0.005$) and small bowel ($P < 0.001$), heart ($P < 0.001$), and liver ($P < 0.005$), and more extensive but not more frequent pulmonary metastases ($P < 0.005$).

Ovary

Metastases in the ovary were correlated with metastases in the thyroid and/or parathyroid glands ($P < 0.001$), adrenal cortex ($P < 0.001$), and pancreas ($P < 0.001$). Among nonendocrine organs, metastases in the ovary were correlated with metastases throughout most of the gastrointestinal tract ($P < 0.001$), including stomach ($P < 0.005$), small bowel ($P < 0.001$), and large bowel ($P < 0.005$), liver ($P < 0.005$), and heart ($P < 0.001$). Ovarian metastases were also correlated

Table 5—Correlations of Metastases to Secondary Endocrine Organs

	Endocrine organ		Nonendocrine organ	
Posterior pituitary				
	Anterior pituitary	($P < 0.001$)	Liver	($P < 0.001$)
	Thyroid/parathyroid	($P < 0.001$)	Heart	($P < 0.005$)
	Adrenal cortex	($P < 0.001$)	Dura	($P < 0.001$)
	Pancreas	($P < 0.001$)	Meninges	($P < 0.005$)
			Hypothalamic stalk	($P < 0.001$)
Thymus			Gut	($P < 0.001$)
Adrenal medulla				
	Adrenal cortex	($P < 0.001$)	Gut	($P < 0.001$)
	Pancreas	($P < 0.001$)	Serosa	($P < 0.001$)
Pancreas				
	Posterior pituitary	($P < 0.001$)	Gut	($P < 0.001$)
	Adrenal cortex	($P < 0.001$)	Heart	($P < 0.001$)
	Adrenal medulla	($P < 0.001$)	Liver	($P < 0.005$)
	Ovary	($P < 0.001$)		
Ovary				
	Thyroid/parathyroid	($P < 0.001$)	Gut	($P < 0.001$)
	Adrenal cortex	($P < 0.001$)	Heart	($P < 0.001$)
	Pancreas	($P < 0.001$)	Liver	($P < 0.005$)

with significantly less extensive metastases to the central nervous system ($P < 0.001$). Metastases were not observed in the testes.

In summary, patients who developed primary or secondary endocrine organ metastases were significantly younger, including most premenopausal patients (72% primary, 77% secondary), and had more widely disseminated tumor than those without endocrine organ metastases. Although endocrine organ metastases were strongly correlated with numbers of metastatic sites and overall tumor burden ($P < 0.001$), stepwise multivariate linear regression analysis showed that age was an independent predictor of endocrine organ metastases ($P < 0.05$). Metastases to primary endocrine organs were primarily correlated with metastases in other endocrine organs, both primary and secondary. In addition, metastases in the adrenal cortex were correlated mainly with metastases in nonendocrine structures within the abdomen, and metastases in the thyroid and/or parathyroid were correlated with metastases to the heart and lungs. Metastases in secondary endocrine organs were consistently correlated with metastases in the heart, liver, and/or gastrointestinal tract. The frequency of endocrine organ metastases and overall distributions of tumor were not correlated with therapy or survival.

Discussion

This study demonstrates that breast carcinoma frequently metastasizes to endocrine organs; and although patients with endocrine organ metastases had more widely disseminated tumor, most of the additional metastatic sites were endocrine organs. Breast carcinoma is not unique in its tendency to metastasize to endocrine organs. Thirty percent to 50% of persons with lung carcinoma,[3,4] malignant melanoma,[5,6] or neuroblastomas[7] also have metastases in endocrine organs at autopsy. For these particular tumors, the frequencies of metastases to the adrenal gland are uniformly high, and comparable to the figure reported here for breast carcinoma. However, with the exception of the adrenal gland, the frequencies of metastases to other individual endocrine organs vary considerably for tumors of different histogenetic origin. Organophilic behavior of metastasizing cells has been observed experimentally with the use of various colonies derived from the B16 malignant melanoma cell line.[8]

In this study, the extensive intercorrelations observed among endocrine organs suggest that endocrine organ metastases do not occur at random, and instead are patterned. This concept is reinforced by the finding that metastases to primary and secondary endocrine organs were correlated with metastases to particular nonendocrine structures. Perhaps the most intriguing observation was that patients who developed endocrine organ metastases were an average of 5 to 10 years younger than those who did not. Furthermore, 72% of premenopausal patients had primary and 77% had secondary endocrine organ metastases at autopsy. No significant differences in mean age were observed with respect to metastases in other major locations such as the lungs, kidneys,

heart, or liver. Since endocrine organ metastases were not correlated with survival or therapy, another hypothesis must be sought to explain the occurrence of this apparently age-related phenomenon.

Previous studies have demonstrated that metabolic activity and endocrine function decline with increasing age. In particular, the hypothalamic-pituitary axis, thyroid gland, pancreas, gonads, and to some extent the adrenal glands become atrophic and/or less responsive to stimuli in elderly individuals.[9] The responsiveness of some breast carcinomas to endocrine therapy, including organ ablations, such as oophorectomy,[10] hypophysectomy,[10,11] adrenalectomy,[10] and antiestrogen treatment,[12] has been recognized for years. The presence of receptors for thyroid hormone,[13] prolactin,[11] and vitamin D[14,15] in breast carcinoma cells suggest that the growth of breast tumors may be stimulated by these agents. Furthermore, *in vitro* studies have shown that the growth of breast carcinoma primary cultures or cell lines may be supported or potentiated by various peptides[16] and hormones such as insulin[17-19] placental lactogen,[18] and steroids.[15,18-20] From these studies it may be inferred that at least some breast carcinomas have hormone-dependent growth requirements. However, since endocrine treatment only prolongs remission, or "controls" the rate of tumor growth, rather than rendering the patients cured, it is probable that at least some of the malignant cells comprising various breast carcinomas do not require hormones for growth. In other words, breast carcinomas are probably heterogeneous with respect to environmental growth requirements.

The finding that youth was an independent predictor of endocrine organ metastases is of particular interest in light of our understanding of the age-related changes in endocrine functions. When considered with the observations on hormone-dependent growth of breast carcinoma cells, it seems likely that the significantly increased frequencies of endocrine organ metastases observed in young patients might have been due to their more active endocrinologic and metabolic internal milieu. Perhaps the more active endocrine organ function in younger patients is important for supporting growth of some components of breast carcinomas. In contrast, many hormone-dependent breast carcinoma cells may be less likely to survive in elderly patients who have significantly less endocrine organ activity. We propose that endocrine organ metastases occur in younger patients because the endocrine organs themselves provide a trophic influence for metastasizing breast carcinoma cells, which require particular hormones for growth.

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