

METASTASIS

Metastases are tumor implants discontinuous with the primary tumor. *Metastasis unequivocally marks a tumor as malignant because benign neoplasms do not metastasize.* The invasiveness of cancers permits them to penetrate into blood vessels, lymphatics, and body cavities, providing the opportunity for spread. *With few exceptions, all malignant tumors can metastasize.* The major exceptions are most malignant neoplasms of the glial cells in the central nervous system, called *gliomas*, and basal cell carcinomas of the skin. Both are locally invasive forms of cancer, but they rarely metastasize. It is evident then that the properties of invasion and metastasis are separable.

In general, the more aggressive, the more rapidly growing, and the larger the primary neoplasm, the greater the likelihood that it will metastasize or already has metastasized. There are innumerable exceptions, however. Small, well-differentiated, slowly growing lesions sometimes metastasize widely; conversely, some rapidly growing, large lesions remain localized for years. Many factors relating to both invader and host are involved.

Approximately 30% of newly diagnosed individuals with solid tumors (excluding skin cancers other than melanomas) present with metastases. Metastatic spread strongly reduces the possibility of cure; hence, short of prevention of cancer, no achievement would be of greater benefit to patients than methods to block metastases.

Pathways of Spread

Dissemination of cancers may occur through one of three pathways: (1) direct seeding of body cavities or surfaces, (2) lymphatic spread, and (3) hematogenous spread. Although direct transplantation of tumor cells, as for example on surgical instruments, may theoretically occur, it is rare and we do not discuss this artificial mode of dissemination further. Each of the three major pathways is described separately.

Seeding of Body Cavities and Surfaces.

Seeding of body cavities and surfaces may occur whenever a malignant neoplasm penetrates into a natural “open field.” Most often involved is the peritoneal cavity, but any other cavity—pleural, pericardial, subarachnoid, and joint space—may be affected. Such seeding is particularly characteristic of carcinomas arising in the ovaries, when, not infrequently, all peritoneal surfaces become coated with a heavy layer of cancerous glaze. Remarkably, the tumor cells may remain confined to the surface of the coated abdominal viscera without penetrating into the substance. Sometimes mucus-secreting appendiceal carcinomas fill the peritoneal cavity with a gelatinous neoplastic mass referred to as *pseudomyxoma peritonei*.

Lymphatic Spread.

Transport through lymphatics is the most common pathway for the initial dissemination of carcinomas, and sarcomas may also use this route. Tumors do not contain functional lymphatics, but lymphatic vessels located at the tumor margins are apparently sufficient for the lymphatic spread of tumor cells. The emphasis on lymphatic spread for carcinomas and hematogenous spread for sarcomas is misleading, because ultimately there are numerous interconnections between the vascular and the lymphatic systems. *The pattern of lymph node involvement follows the natural routes of lymphatic drainage.* Because carcinomas of the breast usually arise in the upper outer quadrants, they generally disseminate first to the axillary lymph nodes. Cancers of the inner quadrants drain to the nodes along the internal mammary arteries. Thereafter the infraclavicular and supraclavicular nodes may become involved. Carcinomas of the lung arising in the major respiratory passages metastasize first to the perihilar tracheobronchial and mediastinal nodes. Local lymph nodes, however, may be bypassed—so-called “skip metastasis”—because of venous-lymphatic anastomoses or because inflammation or radiation has obliterated lymphatic channels.

In breast cancer, determining the involvement of axillary lymph nodes is very important for assessing the future course of the disease and for selecting suitable therapeutic strategies. To avoid the considerable surgical morbidity associated with a full axillary lymph node dissection, *biopsy of sentinel nodes* is often used to assess the presence or absence of metastatic lesions in the lymph nodes. A sentinel lymph node is defined as “the first node in a regional lymphatic basin that receives lymph flow from the primary tumor.” Sentinel node mapping can be done by injection of radiolabeled tracers and blue dyes, and the use of frozen section upon the sentinel lymph node at the time of surgery can guide the surgeon to the appropriate therapy. Sentinel node biopsy has also been used for detecting the spread of melanomas, colon cancers, and other tumors.

In many cases the regional nodes serve as effective barriers to further dissemination of the tumor, at least for a while. Conceivably the cells, after arrest within the node, may be destroyed by a tumor-specific immune response. Drainage of tumor cell debris or tumor antigens, or both, also induces reactive changes within nodes. Thus, enlargement of nodes may be caused by (1) the spread and growth of cancer cells or (2) reactive hyperplasia. Therefore, *nodal enlargement in proximity to a cancer, while it must arouse suspicion, does not necessarily mean dissemination of the primary lesion.*

Hematogenous Spread.

Hematogenous spread is typical of sarcomas but is also seen with carcinomas. Arteries, with their thicker walls, are less readily penetrated than are veins. Arterial spread may occur, however, when tumor cells pass through the pulmonary capillary beds or pulmonary arteriovenous shunts or when pulmonary metastases themselves give rise to additional tumor emboli. In such vascular spread, several factors influence the patterns of distribution of the metastases. With venous invasion the blood-borne cells follow the venous flow draining the site of the neoplasm, and the tumor cells often come to rest in the first capillary bed they encounter. Understandably the liver and lungs are most frequently involved in such hematogenous dissemination, because all portal area drainage flows to the liver and all caval blood flows to the lungs. Cancers arising in close proximity to the vertebral column often embolize through the paravertebral plexus, and this pathway is involved in the frequent vertebral metastases of carcinomas of the thyroid and prostate.

Certain cancers have a propensity for invasion of veins. Renal cell carcinoma often invades the branches of the renal vein and then the renal vein itself to grow in a snakelike fashion up the inferior vena cava, sometimes reaching the right side of the heart. Hepatocellular carcinomas often penetrate portal and hepatic radicles to grow within them into the main venous channels. Remarkably, such intravenous growth may not be accompanied by widespread dissemination. Histologic evidence of penetration of small vessels at the site of the primary neoplasm is obviously an ominous feature. Such changes, however, must be viewed guardedly because, for reasons discussed later, they do not indicate the inevitable development of metastases.

Many observations suggest that mere anatomic localization of the neoplasm and natural pathways of venous drainage do not wholly explain the systemic distributions of metastases. For example, breast carcinoma preferentially spreads to bone, bronchogenic carcinomas tend to involve the adrenals and the brain, and neuroblastomas spread to the liver and bones. Conversely, skeletal muscles and the spleen, despite the large percentage of blood flow they receive and the enormous vascular beds present, are rarely the site of secondary deposits.

Comparisons between Benign and Malignant Tumors

Characteristics	Benign	Malignant
<i>Differentiation/anaplasia</i>	Well differentiated; structure sometimes typical of tissue of origin	Some lack of differentiation with anaplasia; structure often atypical
<i>Rate of growth</i>	Usually progressive and slow; may come to a standstill or regress; mitotic figures rare and normal	Erratic and may be slow to rapid; mitotic figures may be numerous and abnormal
<i>Local invasion</i>	Usually cohesive expansile well-demarcated masses that do not invade or infiltrate surrounding normal tissues	Locally invasive, infiltrating surrounding tissue; sometimes may be seemingly cohesive and expansile
<i>Metastasis</i>	Absent	Frequently present; the larger and more undifferentiated the primary, the more likely are metastases