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| **Table 9.1 Stereotypic Patterns of Metastasis to Distant Organs by Cancer Type** |
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| ***Cancer Type*** | ***Site of Metastasis*** |
| Breast carcinomas | Primarily bone, lung, pleura, and liver; less frequently, brain and adrenal. ER-positive tumors preferentially spread to bone; ER-negative tumors metastasize more aggressively to visceral organs. |
| Lung cancers | The two most common types of lung cancer have different etiologies. Small cell lung cancer disseminates rapidly to many organs including the liver, brain, adrenals, pancreas, contralateral lung, and bone. Nonâ€“small cell lung carcinomas often spread to the contralateral lung and the brain, and also to adrenal glands, liver and bones. |
| Prostate carcinoma | Almost exclusively to bone; forms osteoblastic lesions filling the marrow cavity with mineralized osseous matrix, unlike the osteolytic metastasis caused by breast cancer. |
| Pancreatic cancer | Aggressive spread to the liver, lungs, and surrounding viscera. |
| Colon cancer | The portal circulation pattern favors dissemination to the liver and peritoneal cavity, but metastasis also occurs in the lungs. |
| Ovarian carcinoma | Local spread in the peritoneal cavity. |
| Sarcomas | Various types of sarcoma; mesenchymal origin; mainly metastasize to the lungs. |
| Myeloma | Hematologic malignancy of the bone marrow that causes osteolytic bone lesions, sometimes spreading to other organs. |
| Glioma | These brain tumors display little propensity for distance organ metastasis, despite aggressively invading the central nervous system. |
| Neuroblastoma | Pediatric tumors arising from nervous tissue of the adrenal gland. Forms bone, liver, and lung metastases, which in some cases spontaneously regress. |
| ER, estrogen receptor. |

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Despite apparent similarities in clinical and/or histologic features, different cancer types do not exhibit the same proclivity to metastasize to the same organs, and the same cancer type can preferentially metastasize to different organs (Table 9.1). Breast cancer most commonly metastasizes to the bone, lung, and brain. Colorectal tumors tend to relapse in the liver. Prostate cancer primarily colonizes bone. Sarcomas and squamous cell carcinomas have a high propensity for the lung. Melanomas can metastasize to a variety of visceral and nonvisceral organs. This tissue tropism has long been recognized and has intrigued clinicians and pathologists to seek an explanation. In 1889, Stephen Paget proposed his â€œseed and soilâ€ hypothesis (reviewed in ref. 9). This stated that the propensity of different cancers to form metastases in specific organs was because of the dependence of the seed (the cancer) on the soil (the distant organ). In contrast, James Ewing and others argued that tissue tropism could

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be accounted for based on mechanical factors and circulatory patterns of the primary tumor. For example, colorectal cancer can enter the hepatic-portal system, explaining its propensity for liver metastasis, and prostate cancer can traverse a presacral plexus that connects the periprostatic and vertebral veins, explaining its propensity for metastases to the lower spine and pelvis. Supporting the arguments for both views, current understanding would suggest that both seed and soil factors and anatomic considerations contribute to metastatic tropism. A modern interpretation of the seed and soil hypothesis is an active area of investigation, with molecular definitions accumulating for both the cancer and the microenvironment.

Basic Steps in the Metastatic Cascade

Invasion and motility

Tumor cells display diminished cellular adhesion, allowing them to become motile, a fundamental property of metastatic cells.

* Tumor cells use their migratory and invasive properties in order to burrow through surrounding extracellular stroma and to gain entry into blood vessels and lymphatics.

Intravasation and survival in the circulation. Once tumor cells enter the circulation, or intravasate, they must be able to withstand the physical shear forces and the hostility of sentinel immune cells.

Arrest and extravasation. Once arrested in the capillary system of distant organs, tumor cells must extravasate, or exit the circulation, into foreign parenchyma

Growth in distant organs. Successful adaptation to the new microenvironment results in sustained growth.

Clinically, many patients treated by local excision of a primary cancer but with micrometastatic disease at the time of diagnosis will show a long latency period before distant disease develops.

* How and if an extravasated tumor population grows in a distant organ lies at the core of the seed and soil hypothesis.

Heterogeneity in Cancer Metastasis and Rarity of Metastatic Cells

that less than 0.01% of tumor cells gave rise to metastases.

metastasis is an inefficient process

primary tumors are heterogeneous in their metastatic ability. Because of the numerous barriers to metastasis that must be overcome, the proportion of tumor cells that can successfully metastasize is exceedingly low.

Many clinicopathologic traits such as lymphovascular invasion and regional lymph node involvement represent successful completion of some of the steps in the metastatic cascade but not necessarily all. The clinical observation that metastatic risk increases with tumor size is explained by mathematical considerations predicting that genetic changes accumulate faster with increased population size. Larger tumors are more likely to contain rare cells that are metastatically competent, making metastasis a late event in tumorigenesis.

One of the primary objectives in the clinical management of cancer is to prevent or decrease the risk of metastasis

Invasion starts with alterations in cell adhesion. In many cases this entails the loss of E-cadherin, which is the prototype member of the cadherin family of cell-cell adhesion molecules

The migration of tumor cells toward new blood/lymphatic vessels and penetration through them (intravasation) facilitates the spread of cancer. It is unlikely that intravasation is a stochastic process resulting from wandering cancer cells.

Metastatic Progression and Metastatic Virulence

Survival in the Circulation

From experimental model systems, it has been estimated that approximately one million cancer cells per gram of tumor tissue can be introduced daily into the circulation.64 Direct inoculation of tumor cells into mice demonstrate that metastasis can be an inefficient process because, despite large numbers of circulating tumor cells, relatively few metastasis form.10 In humans, the inefficiency of circulating cancer cells to give rise to detectable metastases was inadvertently demonstrated in ovarian cancer patients who received peritoneal-venous shunts for palliation of malignant ascites.65

the mere entry of tumor cells into the circulation often is not a rate-limiting step in metastasis. Other obstacles must be overcome

Extravasation and Colonization

After arresting in capillaries, tumor cells that are able to survive can grow intravascularly. This can lead to a physical disruption of the vessels.70 However, more selective and certainly more elegant methods of extravasation exist. Cancer cells can mimic leukocytes and bind to endothelial E- and P-selectins.71

Invasion and Metastasis

The Evolution and Pathogenesis of Metastasis

Clinical, Pathologic, and Anatomic Correlations

Metastasis is often associated with several clinical and pathologic characteristics. Among these, tumor size and regional lymph node involvement are consistently associated with distant relapse. For tumor size, no clear threshold exists, but trends are clear. For example, metastatic risk for breast cancer rises sharply after 2 cm,6 and in sarcoma, distant metastasis is more common for tumor sizes larger than 5 cm.7 The involvement of regional lymph nodes is often, but not always, a harbinger for increased risk of distant metastasis. For head and neck cancer, the association between lymph node involvement and metastasis is predictable. Metastasis rarely occurs without prior involvement of cervical neck lymph nodes,

8 For breast cancer, the presence of positive lymph nodes is the strongest clinicopathologic prognostic marker for distant relapse

Tumor grade. Tumors that are poorly differentiated, or retain few features of their normal tissue counterparts, are generally considered to be high grade. High-grade tumors often exhibit infiltrative rather than pushing borders and show signs of rapid cell division. Breast cancer and sarcomas are well recognized for displaying a markedly elevated risk of metastasis with higher tumor grade. (2) Depth of invasion beyond normal tissue compartmental boundaries. Some cancers, like melanoma and gastrointestinal malignancies, are staged by how deeply they extend beyond the basement membrane. Violation of deeper layers of the dermis, or invasion through the lamina propria, muscularis mucosa, and serosa, represent progressively more extensive invasion and higher risk of metastasis. (3) Lymphovascular invasion. Tumor emboli seen in the blood or lymphatic vessels generally carry a poorer prognosis than cancer without these features. Breast cancer and squamous cell cancers of the head and neck or female cervix are examples.