Most patients with cancer present with an obvious primary site of their disease. A certain treatment is recommended after the extent of spread has been determined, and the probable effectiveness is taken into account when considering whether local treatment with or without systemic treatment is appropriate. A significant number of patients, however, present with metastatic cancer without an obvious primary site, and these patients represent a series of clinical challenges. How far should investigation be taken to search for the primary site and define the sites of metastases? What treatment should be used, and when should it be started? These challenges are particularly taxing because most patients with unknown primary cancers (CUP) have survival measured in weeks, while some patients treated appropriately may be cured. It is important that patients do not miss out on effective treatment, but the problems of identifying these individuals are considerable.
Epidemiology

The definition of unknown primary cancer varies. Several experts exclude tumors of epidermoid histology presenting with cervical lymphadenopathy, for in these cases locoregional therapy offers a favorable prognosis. A pragmatic definition of unknown primary cancer is as follows: a biopsy-proven cancer that is inconsistent with a primary tumor at that site, and the primary site is not apparent despite thorough history, physical examination, and appropriate additional laboratory and radiologic investigations.

The incidence of CUP depends on the thoroughness of the investigations and the population studied. Few cancer registries collect relevant information, but in Australia, CUP is the fourth most common cause of cancer deaths in males and the third most common in females. CUP patients represent up to 15% of new referrals to large hospital oncology units. The incidence of CUP increases with age; it is low under the age of 40, and the average age of diagnosis is 60.

Conceptually, CUP can be considered to be a heterogeneous cluster of tumors with a propensity to early dissemination before the primary tumor is evident. Since, at the time of death, substantial numbers of patients with CUP may have no primary tumor detected at autopsy, it is plausible to consider the possibilities of spontaneous regression of the primary tumor. This phenomenon might best be characterized in melanoma or in a primary tumor with a long doubling time that has given rise to metastases proliferating more rapidly.

Pathology

The frequencies of different histological types of CUP vary widely. The majority of CUP have adenocarcinoma or undifferentiated histology. Less frequently, squamous cell carcinomas, melanoma, sarcoma, and neuroendocrine tumors may present as CUP. The proportion of squamous histology varies depending particularly upon whether cases of CUP with high cervical lymphadenopathy at presentation are included. Some data include cases in women with peritoneal carcinomatosis of unknown primary site, but these patients are often considered to have epithelial ovarian cancer.

Optimal histologic evaluation requires review by an experienced pathologist, preferably of adequate material obtained by open biopsy. Histologic misclassification can occur, and rebiopsy may be warranted. The yield from special tissue stains and electron microscopic methods is not well documented, and steroid hormone receptor measurements are not of definitive value. Monoclonality in lymphoproliferative disorders can be