plant, following induction therapy with etoposide/ifosfamide/cisplatin.

Renato Lenzi, M.D., of the University of Texas M. D. Anderson Cancer Center in Houston, has two trials using paclitaxel, cisplatin, 5-FU, and folic acid against adenocarcinomas of unknown primary origin.

A longstanding goal in research on unknown primaries has been the development of prognostic factors. Beginning in the late 1970s, several researchers including Greco and Hainsworth's group reported that patients with particular subtypes of unknown primary cancers, identifiable on pathology slides as poorly differentiated carcinoma or poorly differentiated adenocarcinoma (PDC/PDA) were more responsive to chemotherapy than others with unknown primaries. However, it was later discovered that through the use of immunoperoxidase staining — a method for detecting tumor-specific antigens — many of these cancers could be identified as lymphomas, germ cell tumors, and others known to be responsive to chemotherapy.

Cytogenetic tests can identify other types, Greco said. For instance, a chromosomal abnormality called isochromosome 12 is specific for germ cell tumors, and a translocation of chromosomes 11 and 22 is a marker for neuroepithelioma.

In the May 1997 Journal of Clinical Oncology, Lenzi and colleagues reported that in a series of 1,400 patients at M. D. Anderson, they failed to confirm previous reports of better outcomes for PDC/PDA patients. The authors note that unlike these earlier studies, their study population excluded patients whose tumors could be identified via immunoperoxidase staining as treatable types.

"The data presented here emphasize that the most critical aspect of the evaluation of UPC [unknown primary carcinoma] patients is the accurate pathologic assessment of the malignant tissue ... in conjunction with pertinent clinical data," the authors wrote. "Such close collaboration between clinician and pathologist may lead to further pathologic evaluation, including the use of special stains and immunohistochemical studies."

**Predicting Responsiveness**

Several clinical factors have been identified as predicting better drug responsiveness. As reviewed by Hainsworth and Greco in the July 22, 1993, New England Journal of Medicine, these include predominant tumor location in the retroperitoneum or peripheral lymph nodes, metastases limited to one or two sites, younger age, and no history of smoking.

Kenneth R. Hess, Ph.D., a biostatistician and co-author of the article, is working with Lenzi, James Abbruzzese, M.D., and other M. D. Anderson colleagues to create mathematical models based on metastatic patterns, clinical features, and demographics for predicting the location of primary tumors that can't be pinned down by conventional or pathologic exams.

"We're still laying the groundwork by looking at patients with known primaries," he said. "In that group, our models have proven 85% accurate, so we hope that in the future we will be able to apply them to patients presenting with unknown tumors, which could facilitate more timely and effective treatment."

— Tom Reynolds

**Patients With Unknown Primaries Face Unusual Insurance Problems**

In addition to the daunting medical obstacles, patients with unknown primaries often face problems with insurance reimbursement, said F. Anthony Greco, M.D., of the Sarah Cannon-Minnie Pearl Cancer Center in Nashville. Because the diagnosis of unknown primary site is not listed in the entries for various drugs in the United States Pharmacopoeia Dispensing Information, Medicare and many private insurers will not pay drug costs for these patients.

To circumvent this problem, Greco said, "Many of these patients are being called something they're not — they're being labeled lung cancer or ovarian cancer or something else — because if they're called unknown primary they aren't reimbursed." As a result, Greco believes that the true incidence of this disease "is probably a lot higher than reported." Some researchers say 5% to 10% of cancer cases are carcinoma of unknown primary, including all cell types. The National Cancer Institute's PDQ database cites a more conservative estimate of about 3%.

Keith Johnson, director of information development at the U.S. Pharmacopoeia, said USP staff and advisors are reviewing data on the efficacy of various drugs for unknown primaries, and predicted that the diagnosis will be added sometime this year.

— Tom Reynolds