

HOSPITAL PHYSICIAN®

ONCOLOGY BOARD REVIEW MANUAL

STATEMENT OF EDITORIAL PURPOSE

The *Hospital Physician Oncology Board Review Manual* is a study guide for fellows and practicing physicians preparing for board examinations in oncology. Each manual reviews a topic essential to the current practice of oncology.

PUBLISHING STAFF

PRESIDENT, GROUP PUBLISHER

Bruce M. White

EDITORIAL DIRECTOR

Debra Dreger

SENIOR EDITOR

Bobbie Lewis

ASSOCIATE EDITOR

Rita E. Gould

EDITORIAL ASSISTANT

Farrowh Charles

EXECUTIVE VICE PRESIDENT

Barbara T. White

EXECUTIVE DIRECTOR

OF OPERATIONS

Jean M. Gaul

PRODUCTION DIRECTOR

Suzanne S. Banish

PRODUCTION ASSISTANT

Kathryn K. Johnson

ADVERTISING/PROJECT MANAGER

Patricia Payne Castle

SALES & MARKETING MANAGER

Deborah D. Chavis

NOTE FROM THE PUBLISHER:

This publication has been developed without involvement of or review by the American Board of Internal Medicine.



Endorsed by the
Association for Hospital
Medical Education

Cancer of Unknown Primary

Series Editor:

Arthur T. Skarin, MD, FACP, FCCP

Medical Director, Thoracic Oncology Program, Department of Adult Oncology, Dana-Farber Cancer Institute and Brigham and Women's Hospital; Associate Professor of Medicine, Harvard Medical School, Boston, MA

Contributor:

Erica Linden, MD

Clinical Research Fellow, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Table of Contents

Introduction	2
Pathogenesis	2
Approach to Clinical Evaluation	3
Treatment	7
Prognostic Factors	10
References	11

Cover Illustration by Kathryn K. Johnson

Copyright 2006, Turner White Communications, Inc., Strafford Avenue, Suite 220, Wayne, PA 19087-3391, www.turner-white.com. All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, mechanical, electronic, photocopying, recording, or otherwise, without the prior written permission of Turner White Communications. The preparation and distribution of this publication are supported by sponsorship subject to written agreements that stipulate and ensure the editorial independence of Turner White Communications. Turner White Communications retains full control over the design and production of all published materials, including selection of appropriate topics and preparation of editorial content. The authors are solely responsible for substantive content. Statements expressed reflect the views of the authors and not necessarily the opinions or policies of Turner White Communications. Turner White Communications accepts no responsibility for statements made by authors and will not be liable for any errors of omission or inaccuracies. Information contained within this publication should not be used as a substitute for clinical judgment.

Cancer of Unknown Primary

Erica Linden, MD

INTRODUCTION

Cancer of unknown primary (CUP) is defined as metastatic disease without an identifiable primary site despite comprehensive clinical evaluation. The incidence of CUP has been reported to be 3% to 5% of all malignancies,¹ representing 30,000 cases each year. This incidence is similar to that of pancreatic cancer,² making CUP the eighth most common cancer diagnosed annually in the United States.^{1,3} International registries have reported a similar incidence (2.3%–7.8% of malignancies).^{4,5}

CUP is an unsettling diagnosis for both patients and oncologists. Patients desire certainty and are uncomfortable with the “unknown” nature of their disease. From an administrative standpoint, CUP is challenging because compensation from insurance companies for diagnostic studies and therapy is based on diagnostic codes. Furthermore, oncologists are better able to recommend therapy and prognostic information once a specific diagnosis is attained. Management of CUP, therefore, poses an emotional as well as scientific challenge.

The primary goal in evaluating patients with CUP is to define subgroups that are potentially curable or treatable malignancies. Diagnostic work-up should also attempt to evaluate for a primary tumor comprehensively without exposing patients to unnecessary invasive testing. This review outlines the clinical and pathologic features of CUP, proposes a systematic diagnostic evaluation, and reviews the treatments for CUP.

PATHOGENESIS

The central scientific question in CUP is why are metastatic foci of disease present when the primary tumor is not clinically evident? Several theories attempt to explain this atypical presentation in neoplasia. One theory involves regression of the primary lesion.² Empiric evidence for this theory includes stage III metastatic melanoma in which nodal disease is present although no primary lesion can be identified. In

some instances, there may be a remote history of a “spontaneously” regressing pigmented skin lesion.⁶ Additionally, anecdotal evidence of testicular scarring has been noted in patients with metastatic germ cell tumors without an obvious primary mass.^{7,8}

Another possible explanation for metastasis without a known primary may be that the primary site is present microscopically, evading clinical detection by standard imaging or biopsy (occult primary).³ For example, patients with advanced head and neck cancer may present with cervical lymphadenopathy and no evidence of a primary tumor. In this case, there is a disconnect between the bulk of the primary tumor and metastatic foci.

A third theory challenges the traditional belief that metastasis is a late development in tumor evolution.^{9,10} Supportive evidence for this theory exists through the use of gene expression profiling data. Microarray study of breast cancer cell lines identified 4 highly overexpressed genes that are associated with the ability to metastasize to bone as well as with a poor-prognosis signature.⁹ These genes are present in primary tumors, which suggests that metastatic potential may be present at the inception of oncogenesis and that the forces controlling the survival of the primary tumor and metastases operate independently.

Another proposed explanation for differential survival of the primary tumor and metastases is “angiogenic incompetence.”^{2,11} According to this theory, primary tumors are unable to induce neoangiogenesis adequately to survive and grow. Tumor cells undergo apoptosis and gene instability at a high rate because of angiogenic incompetence. Some cells may evade apoptosis, spreading to visceral organs or lymph nodes, and lie dormant. These metastatic cells either utilize local vasculature and nutrient supply to survive and grow or develop the ability to induce angiogenesis via clonal evolution.

Finally, a number of genetic mutations are commonly found in CUP, in particular, the 1p chromosomal deletion.¹² One hypothesis is that a tumor suppressor gene for metastasis may be located on chromosome 1p, thus resulting in a high propensity for tumors to metastasize. Such a gene has not yet been identified, however.