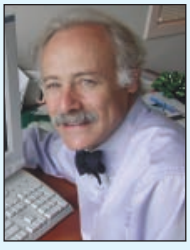
MELANOMA CARE OPTIONS™

DECEMBER 2006

FOSTERING AN INTERDISCIPLINARY APPROACH TO MELANOMA CARE

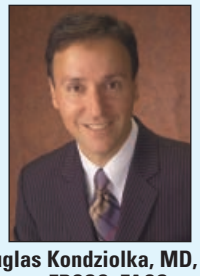
Issue 3: Distant Disease

Contributing Authors



Marc S. Ernstoff, MD (Editor)

Douglas S. Reintgen, MD



Douglas Kondziolka, MD, MSc, FRCSC, FACS

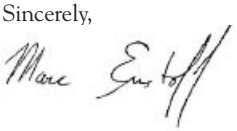
Jon D. Smith, RN

Editor's note . . .

Welcome to the third issue of the 2006 *Melanoma Care Options* publication series. Previous publications this year have focused on primary and regional disease, while this publication focuses on distant disease topics, including the role of surgery, systemic therapy options, and methods for management of brain metastases. Individual working groups of the coalition contributed to these cases, which illustrate salient teaching points for clinical practice. Self-assessment questions have been incorporated into each of the cases presented so that you can compare your management approach with that of our expert panel, while reviewing the evidence to support each of the recommended strategies.

As you can see from the cases, certain areas of melanoma management remain controversial, and various levels of evidence support individual strategies. Our goal is to provide evidence in areas where melanoma management is clear and to offer an exchange of ideas in less well defined areas. Thank you for participating in this interdisciplinary dialogue about the challenging problem of distant melanoma.

Sincerely,



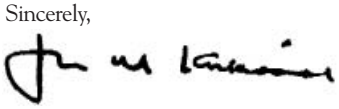
MARC S. ERNSTOFF, MD

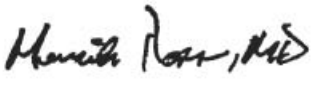
A note from the Chairmen

Welcome to the third issue of the 2006 *Melanoma Care Options* publication series from the **Melanoma Care Coalition**. This coalition was founded in 2004 to foster an interdisciplinary approach to melanoma care. This year, our case discussions have been grouped within disease stage categories—primary, regional, and distant metastatic melanoma. Individual working groups of the coalition contributed these cases, which illustrate salient teaching points for clinical practice. As in previous issues of *Melanoma Care Options*, self-assessment questions are incorporated into each of the cases presented so that you can choose your management approach and compare it against that of our expert panel and review the evidence supporting the recommended strategies

As you will see from this and previous publications in this series, a number of areas of melanoma management remain controversial, and individual strategies are supported by various levels of evidence. We hope that this program illustrates the areas of clear consensus in melanoma management while providing dialogue and insight into the evolving controversies. We welcome your thoughts on this publication series, and we encourage you to participate in the **Melanoma Care Coalition** programs—see www.melanomacare.org for ongoing programs and for future offerings. Thank you for participating in this interdisciplinary dialogue, which promises to improve our ability to care for patients.

Sincerely,





JOHN M. KIRKWOOD, MD — MERRICK I. ROSS, MD, FACS

Co-Chairs, Melanoma Care Coalition Steering Committee

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Instructions for Participation:
- Read the case presentations and comments in the newsletter
- Complete the posttest questions and evaluation form at the end of the newsletter, and fax or mail them to our office

To receive a maximum of 1.5 AMA PRA category 1 credits for this activity:
Within 4 weeks of successful completion, you may access your credit transcript at http://ccehs.upmc.edu/
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- Within 4 weeks of successful completion, a certificate will be mailed to the address provided
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Target Audience
This activity is directed toward dermatologists, dermatologic surgeons, surgical and medical oncologists, general surgeons, oncology nurses, primary care physicians, and other health care professionals who treat or screen for melanoma.

Statement of Need
The prognosis for patients with distant metastatic melanoma, classified as stage IV melanoma by the American Joint Committee on Cancer (AJCC) staging system, is poor with currently available therapies. Therefore, it is important that clinicians be familiar with the most current evidence-based treatment for the management of distant metastatic melanoma to improve long-term survival. This publication describes in detail the management of distant metastatic melanoma and discusses important controversies that arise when caring for this patient population.

Learning Objectives:
After completing this activity, the participants will be able to:
- Describe the role of surgical resection in distant metastatic melanoma
- Compare and contrast systemic therapy options for distant melanoma
- Outline the role of the nurse as part of the team managing distant metastatic melanoma
- Describe options for management of melanoma brain metastases

Accreditation and Credit Designation
The University of Pittsburgh School of Medicine is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The University of Pittsburgh School of Medicine designates this educational activity for a maximum of 1.5 AMA PRA Category 1 Credits™. Each physician should claim only those credits commensurate with the extent of his or her participation in the activity.

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Contributing Authors and Disclosure
We gratefully acknowledge an educational grant from Schering-Plough Corporation in support of this activity.

Marc S. Ernstoff, MD
Professor of Medicine
Dartmouth-Hitchcock Medical Center
Lebanon, New Hampshire
Grants/Research Support: National Institutes of Health, Bristol-Myers Squibb, Berlex Laboratories, Chiron Inc, Schering-Plough Corporation, Pfizer, Inc; Consultant: Chiron Inc; Speakers' Bureaus: Berlex Laboratories, Chiron Inc, Schering-Plough Corporation, Pfizer Inc.

Douglas Kondziolka, MD, MSc, FRCSC, FACS
Peter J. Jannetta Professor
Vice-Chairman of Neurological Surgery
Professor of Radiation Oncology
University of Pittsburgh
Pittsburgh, Pennsylvania
Consultant: Elekta Instruments.

Douglas S. Reintgen, MD
Director, Lakeland Regional Cancer Center
Lakeland, Florida
Speakers' Bureau: Schering Oncology.

Jon D. Smith, RN
Clinical Nurse Coordinator
Seattle Cancer Care Alliance
Seattle, Washington
Speakers' Bureau: Schering-Plough Corporation.

Date of Original Release: December 15, 2006
Expiration Date: December 15, 2007
Date of last review: December 15, 2006

This newsletter is published by PharmAdura, LLC, Orangeburg, NY.

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Steering Committee

Publisher
PharmAdura, LLC
523 Route 303
Orangeburg, NY 10962
publisher@pharmadura.com

Managing Editors
David Sklar
Millie Poliakoff

Art Director
Laurie Lohne, Creative MediaWorks

Scientific Directors
Lisa A. Faltyn, PhD
Rhonda S. Williams, RN

Faculty

Bruce J. Averbook, MD
Associate Professor of Surgery
Metro Health Medical Center
Case Western Reserve University
Cleveland, Ohio
Speakers' Bureau: Schering Oncology Biotech

Matthew T. Ballo, MD
Associate Professor of Radiation Oncology
University of Texas M.D. Anderson Cancer Center
Houston, Texas
Consultant, IMPAC Medical Systems

Ernest C. Borden, MD
Director
Center for Cancer Drug Discovery & Development
Cleveland Clinic Cancer Center and Lerner Research Institute
The Cleveland Clinic Foundation
Cleveland, Ohio
Consultant: Cleveland Biolabs; Speakers' Bureaus: Novartis Pharmaceuticals Corporation, Pfizer Inc

Deborah A. Boyle, RN, MSN, AOCN, FAAN
Project Leader
Gero-Oncology & Survivorship Nursing Studies Program
Banner Good Samaritan Medical Center
Phoenix, Arizona
No financial relationships to disclose

Tania Bridgeman, RN, PhD
Director of Clinical Path Development
University of California, Irvine Medical Center
Orange, California
No financial relationships to disclose

David R. Byrd, MD
Professor of Surgery
Department of Surgery
University of Washington Medical Center
Seattle, Washington
No financial relationships to disclose

Daniel G. Coit, MD, FACS
Co-leader
Melanoma Disease Management Team
Memorial Sloan-Kettering Cancer Center
New York, New York
No financial relationships to disclose

C. Wayne Cruse, MD
Professor of Surgery
University of South Florida
Tampa General Hospital
Tampa, Florida
Speakers' Bureaus: Schering-Plough Corporation, Intron Oncology

Clara Curiel-Lewandrowski, MD
Assistant Professor of Dermatology
University of Arizona
Tucson, Arizona
No financial relationships to disclose

James G. Douglas, MD, MS
Associate Professor of Radiation Oncology, Pediatrics, and Neurologic Surgery
University of Washington Medical Center
Seattle, Washington
Grants/ Research Support: MedImmune Inc

David E. Elder, MB, ChB, FRCPA
Professor of Pathology
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania
No financial relationships to disclose

Marc S. Ernstoff, MD*
Professor of Medicine
Dartmouth- Hitchcock Medical Center
Lebanon, New Hampshire
Grants/ Research Support: National Institutes of Health, Bristol-Myers Squibb, Berlex Laboratories, Chiron Inc, Schering-Plough Corporation, Pfizer, Inc; Consultant: Chiron Inc; Speakers' Bureaus: Berlex Laboratories, Chiron Inc, Schering-Plough Corporation, Pfizer Inc

Rosemary Giuliano, ARNP, MSN
Surgical First Assistant
Morton Plant North Bay Hospital
New Port Richey, Florida
Speakers' Bureau: Schering-Plough Corporation

James S. Goydos, MD, FACS*
Associate Professor of Surgical Oncology
Robert Wood Johnson Medical School
Cancer Institute of New Jersey
New Brunswick, New Jersey
Speakers' Bureau, Schering-Plough Corporation

James M. Grichnik, MD, PhD
Associate Professor
Duke University Medical Center
Durham, North Carolina
Stockholder: DigitalDerm, Inc; Consultant/Grants: Electro-Optical Systems Inc.

Caron M. Grin, MD
Clinical Professor of Dermatology
UniversityUniversity of Connecticut Health Center
Farmington, Connecticut
Speakers' Bureau: Schering- Plough Corporation

Frank G. Haluska, MD, PhD
Clinical Director, Cancer Center
Tufts-New England Medical Center
Boston, Massachusetts
Grants/ Research Support: Genzyme Corporation; Consultant: Celgene, Genta Inc, Genzyme Corporation, Teva, CTL/MannKind; Speakers' Bureau: Schering- Plough Corporation; Advisory Boards: Genta Inc, Xoma; Stockholder: Genta Inc

James G. Jakowatz, MD
Director, Melanoma Center
Associate Professor of Surgery
University of California, Irvine Medical Center
Orange, California
No financial relationships to disclose

Mohammed Kashani-Sabet, MD
Associate Professor of Dermatology
Director, Melanoma Center
UCSF Cancer Center
University of California San Francisco School of Medicine
San Francisco, California
Consultant: CancerVax Corporation; Speakers' Bureau: Schering-Plough Corporation

Howard L. Kaufman, MD, FACS*
Associate Professor of Surgery and Pathology
Columbia University
New York, New York
Grants/ Research Support: National Institutes of Health, Dana Foundation; Consultant: Therim Biologics, Neogenix Oncology; Speakers' Bureaus: Chiron Corporation, Schering-Plough Corporation

Douglas Kondziolka, MD, MSc, FRCSC, FACS*
Peter J. Jannetta Professor
Vice-Chairman of Neurological Surgery
Professor of Radiation Oncology
University of Pittsburgh
Pittsburgh, Pennsylvania
Consultant, Elektra Instruments

David H. Lawson, MD
Professor of Hematology/Oncology
Winship Cancer Institute
Atlanta, Georgia
Grants/ Research Support, Consultant, and Speakers' Bureaus: Chiron Therapeutics, Schering-Plough Corporation, Point Therapeutics, Berlex Laboratories

Sancy Leachman, MD, PhD
Associate Professor
University of Utah Department of Dermatology
Salt Lake City, Utah
No financial relationships to disclose

Patricia K. Long, MSN, FNP
Physician Extender/Nurse Practitioner
University of North Carolina
Chapel Hill, North Carolina
No financial relationships to disclose

Charlene D. Love, RN, BSN
Melanoma Nurse Coordinator
Wagner & Associates Plastic and Reconstructive Surgery Consultants of Indiana
Indianapolis, Indiana
No financial relationships to disclose

Jennifer Maitlen, RN, BSN, CCRP*
Clinical Research Specialist
University of Colorado Cancer Center
Clinical Investigators Core
Aurora, Colorado
No financial relationships to disclose

Ashfaq A. Marghoob, MD, FAAD
Associate Clinical Member
Clinical Director, Skin Care Center
Memorial Sloan-Kettering Cancer Center
Hauppauge, New York
No financial relationships to disclose

R. Dirk Noyes, MD, FACS
Co-Director, Surgical Oncology
Multidisciplinary Melanoma Clinic
University of Utah
Huntsman Cancer Institute
Salt Lake City, Utah
Speakers' Bureau, Schering-Plough Corporation

Steven J. O'Day, MD*
Chief of Research
Director of Melanoma Program
The Angeles Clinic and Research Institute
Associate Professor of Medicine
Keck School of Medicine
University of Southern California
Santa Monica, California
Grants/ Research Support: Berlex Laboratories, Chiron Therapeutics; Consultant, Synta Pharmaceuticals

Thomas E. Olencki, DO
Clinical Professor
Division of Hematology/Oncology
James Cancer Hospital and Solove Research Institute
Ohio State University
Columbus, Ohio
Speaker's Bureaus: Schering-Plough Corporation, Celgene Corporation

David W. Ollila, MD*
Associate Professor of Surgery
Director, Multidisciplinary Melanoma Program
University of North Carolina School of Medicine
Chapel Hill, North Carolina
No financial relationships to disclose

Victor G. Prieto, MD, PhD
Professor of Pathology and Dermatopathology
The University of Texas M.D. Anderson Cancer Center
Houston, Texas
No financial relationships to disclose

Douglas S. Reintgen, MD*
Director, Lakeland Regional Cancer Center
Lakeland, Florida
Speakers' Bureau: Schering Oncology

Krista M. Rubin, MS, RN, FNP-C*
Nurse Practitioner, Center for Melanoma
Massachusetts General Hospital
Division of Hematology/Oncology
Boston, Massachusetts
No financial relationships to disclose

Wolfram Samlowski, MD*
Professor, Department of Oncology
Huntsman Cancer Institute
University of Utah
Salt Lake City, Utah
Grants/Research Support: Pfizer Inc; Consultant: MacroMed Inc; Speakers' Bureaus: Pfizer Inc,Chiron Therapeutics, Bayer, AOI, Sci Med

Kenneth K. Tanabe, MD
Chief, Division of Surgical Oncology
Massachusetts General Hospital
Associate Professor of Surgery
Harvard Medical School
Boston, Massachusetts
Speakers' Bureau: Schering-Plough Corporation

Alan Valentine, MD
Associate Professor of Medicine
The University of Texas M.D. Anderson Cancer Center
Houston, Texas
No financial relationships to disclose

Robert W. Weber, MD*
Associate Director
Northern California Melanoma Center
St Francis Memorial Hospital
San Francisco, California
No financial relationships to disclose

Martin A. Weinstock, MD, PhD
Professor of Dermatology and Community Health
Brown University
Barrington, Rhode Island
No financial relationships to disclose

Stacie Wenck, MSN, RN, ANP, CCRP
Nurse Practitioner/Clinical Research Coordinator
Wagner & Associates
Indianapolis, Indiana
No financial relationships to disclose

Richard L. White, Jr, MD, FACS
Chief, Division of Surgical Oncology
Carolinas Medical Center
Blumenthal Cancer Center
Charlotte, North Carolina
Speakers' Bureaus: Schering Oncology, Chiron Therapeutics

*Indicates Melanoma Care Coalition faculty members who contributed to the generation of content for this newsletter.

Introduction

Unlike many other cancers, melanoma generally is found in a younger patient population and is notorious for its tendency to metastasize. Additionally, therapeutic options for the disease are limited. In the United States, the percentage of people who develop melanoma has more than doubled in the past 30 years. Although melanoma represents only 4% of skin cancers, it is responsible for almost 80% of skin cancer deaths.[1]

Distant metastases from malignant melanoma commonly involve nonvisceral sites, including the skin, subcutaneous tissue, and distant lymph nodes, but also occur frequently in the lungs, liver, brain, bone, and small intestine. Up to 60% of patients with metastatic melanoma develop brain metastases, which account for at least 20% of deaths from melanoma.[2] Prognostic factors in patients with distant metastatic melanoma include the site of the distant metastasis, the number of metastatic sites, serum lactate dehydrogenase (LDH) levels, and performance status.[3] Although identification of these prognostic factors is important, median survivals in patients with a poor prognosis and those with a good prognosis only vary by months.

The prognosis of metastatic melanoma is generally poor; however, long-term survival can be realized in some instances with surgical resection of isolated metastasis. Unfortunately, the majority of patients with metastatic melanoma have multiple organs involved and multiple lesions within those organs; surgical resection in these patients is not an option and long-term survival is uncommon. The 5-year survival rate for distant melanoma is 16%.[4] This publication focuses on issues surrounding distant metastatic melanoma (stage IV melanoma).[5] In this monograph, we present 3 cases of distant metastatic melanoma, each including a discussion of the relevant issues introduced in the case.

CASE 1 What Is the Appropriate First-Line Treatment for Metastatic Melanoma?

By Douglas S. Reintgen, MD; Marc S. Ernstoff, MD; and Jon D. Smith, RN

CASE PRESENTATION

A 42-year-old previously healthy man presented with a 2.3-mm melanoma on the back. Past medical history was negative; he had a 20-pack-per-year smoking history. He had been married for 15 years, had 3 children, and was an engineer. He underwent wide local excision and sentinel lymph node (SLN) biopsy. The SLN biopsy was positive and he then underwent a therapeutic lymph node dissection, which revealed two positive lymph nodes (of 12). The patient refused 1 year of high-dose interferon (IFN) alfa-2b at that time. He was followed every 3 months. Fifteen months after diagnosis, a chest x-ray demonstrated a pulmonary nodule.

Before proceeding to the next step, in addition to a history and physical exam, routine labs, and a chest x-ray, which of the following would you obtain, if any?

1. Magnetic resonance imaging (MRI) or computed tomography (CT) of the brain
2. CT scan of the chest/abdomen/pelvis
3. Positron emission tomography (PET) scan
4. 1 and 2
5. 1 and 3
6. All of the above
7. None of the above

The faculty recommends an MRI or brain CT, a CT scan of the chest, abdomen, and pelvis, and a PET scan, if available (option 6 above). CT scans may be used in evaluation of suspected pulmonary, mediastinal, and pleural metastases. CT scans are most useful in cases in which results could affect the treatment plan or to evaluate eligibility for a clinical trial. MRI of the brain is the preferred method for evaluation of CNS metastases. PET is useful in detecting occult metastasis and its use has been steadily gaining acceptance in detecting occult metastases and for evaluating response to therapy.[3] Another advantage of PET scanning is assessment of bones, a less common site for melanoma metastases. The faculty's position is consistent with that of the NCCN guidelines: for patients presenting with stage IV distant metastatic disease, the NCCN recommends performing chest x-ray or CT and LDH testing, plus considering an abdominal/pelvic CT, with or without PET, and/or head MRI. The NCCN also suggests that other imaging studies are appropriate if clinically indicated.[6]

Case #1 Revisited

The patient's physical examination, laboratory studies, and brain MRI were unremarkable. CT and PET demonstrated a single pulmonary nodule, measuring 2.2 cm in diameter, in the right lower lung, consistent with metastatic disease. A fine needle aspiration (FNA) biopsy of the pulmonary nodule revealed metastatic melanoma.

Caveats on Decision Making in Metastatic Melanoma

Making treatment decisions in metastatic melanoma requires an understanding of the natural history of the disease, specifically metastatic disease. Patients and physicians should understand and agree on the goals of therapy. Patients should be made fully aware of their treatment

options, and the risks and potential benefits associated with each treatment should be described. When the patient is appropriately staged, the health care team, including the oncology nurse, should discuss the prognosis and the available therapeutic options. In a melanoma setting, the oncology nurse can play a pivotal role in coordinating the various elements of the treatment plan. He or she may act as patient advocate, educator, and coordinator of input from other members of the care team. This will maintain ongoing communication between the health care team and the patient, resulting in a more positive experience for the patient. The patient then has the opportunity to participate more fully in treatment decisions, with a better understanding of the impact of those decisions.

Effective decision making can be challenging, especially if patients present with comorbidities or are unable to tolerate certain toxicities. Other patient issues include the patient's physical and emotional health and presenting symptoms, the disease-free interval, and the aggressiveness of the disease. Treatment-related issues include the morbidity of the treatment, prior systemic therapy, access to clinical trials, the patient's support system, and patient education. Again, the entire health care team needs to assess these factors with the patient on a continuous basis.

Is there a role for surgical resection of metastatic melanoma?

1. Yes
2. No

The faculty agrees that there is a role for surgical resection of metastatic melanoma, especially for this patient, who is relatively young and healthy. Evaluating the site(s) of metastasis and serum LDH levels assists in delineating distant melanoma into three M categories: M1a, M1b, and M1c.[5] M1a melanomas are those in patients with normal LDH levels and distant metastases in the skin, subcutaneous tissue, or distant lymph nodes, while melanomas with metastasis to the lung (in patients with normal LDH) are classified as M1b melanoma. The M1c melanoma classification includes melanomas with metastases to all other visceral sites and melanomas in patients with serum LDH levels consistently elevated above the upper limits of normal, regardless of the site of metastasis. Patients with melanomas with the M1a classification have the most favorable prognosis and patients with M1c melanoma have the worst prognosis, as demonstrated in differences in median and 5-year overall survival, summarized in **Table 1**.[7]

Table 1: Outcomes for Resectable AJCC Stage IV Melanoma[7]

Stage IV	Median Survival (mo)	Hazard Ratio (Relative to M1c)	*P* Value (Relative to M1c)
M1a (n=13)	7 (95% CI, 4 to 10)	0.576	.140
M1b (n=32)	17 (95% CI, 9 to 26)	0.362	.001
M1c (n=167)	6 (95% CI, 4 to 7)	–	–

The Role of Surgery in Distant Melanoma

Results of nonsurgical approaches to treating distant melanoma are generally disappointing, reflecting the typically low response rates with systemic therapy (conventional chemotherapy and biologic therapy).[8] Theoretically, the use of surgical resection is a viable treatment option for patients with distant melanoma and is supported by several technologic advances that may render surgery more effective. Recent advances in imaging techniques such as CT and PET scanning have enabled better differentiation between single and multiple metastatic sites of disease, making it possible to plan surgical resection of all metastatic sites in one procedure. Additionally, some researchers (including the authors of this publication) believe that resection of the initial organ metastasis may delay the metastatic cascade and may improve immune functioning. Another argument supporting favorable outcomes for surgical resection is that because of improvements in anesthesia, surgical techniques, and postoperative monitoring, the morbidity and mortality associated with major surgical procedures has declined dramatically. Finally, resection of all metastatic disease provides the patient with the highest chances of prolonged survival with a quality of life better than expected without the surgical resection.[8] However, the timing of resection is predicated on the estimated pace of the disease and warrants a thoughtful discussion with the patient and the rest of the team (see **Sidebar**).

In a study at the John Wayne Cancer Institute, Barth and colleagues[9] looked at the records of 1521 patients with stage IV disease over a 22-year period, many of whom received surgical resection. The median age of patients was 51 years, they

Sidebar 1

Surgery: To Wait or Not to Wait?

The balance between an active surgical treatment approach and a "watchful waiting" approach is delicate in melanoma patients with distant disease. In the case of patients with a solitary, asymptomatic, visceral melanoma recurrence (such as the lung), observation for a few months may allow enough time to determine whether there are additional occult micrometastases present prior to moving ahead with surgery. Without a waiting period, the patient may undergo the surgical procedure only to find evidence of additional metastases in a few months. However, if one waits too long, the solitary lesion may grow to an inoperable state or provide the seeds for additional disease. The health care team needs to discuss these factors with the patient so that the patient can make an informed decision. The oncology nurse may play a special role in this process by clarifying the clinical information and helping the patient define his or her own goals and choose an appropriate management strategy. The nurse is also in a position to provide ongoing assessment of the patient's status as it relates to these decisions and to continue providing support to the patient while maintaining communication with the rest of the health care team.

had a variety of primary sites, and 61% were male. The majority of patients (86%) had only one site of metastasis, but 6% had 3 or more metastases. The median survival time of the 1521 patients was 7.5 months, and the estimated 5-year survival rate was 6%. Patients with cutaneous, nodal, or gastrointestinal metastases had the most favorable outcomes (a median survival of 12.5 months and an estimated 5-year survival rate of 14%), compared with a median survival of 8.3 months and estimated 5-year survival rate of 4% in patients with pulmonary metastases. Patients with metastases to the liver, brain, or bone had the worst outcomes (a median survival of 4.4 months and an estimated 5-year survival rate of 3%). Overall, favorable prognostic variables included initial site of metastasis (cutaneous, nodal, or gastrointestinal vs other sites, $P<.0001$), long disease-free interval before metastasis (≥72 mo vs <72 mo, $P = .0001$), and earlier stage of disease preceding distant metastasis (AJCC stage I/II vs stage III, $P = .0001$).[9]

Surgery for Lung Metastases

In the general population of patients with cancer, surgical resection is now considered standard of care for properly selected patients with pulmonary metastases.[10] However, the role of lung metastasectomy is less clear in melanoma and needs to be better defined by future prospective studies. Surgery for melanoma is most effective when the sites of metastasis are limited to a single tissue or organ. Initially, nearly 90% of patients present with only one metastatic organ site.[8]

The International Registry of Lung Metastases (IRLM) was established in 1991 to assess the long-term results of pulmonary metastasectomy.[10] As of 1995, a total of 5290 cases of lung metastasectomy were enrolled, covering the period of 1945 through 1995. Among 5206 patients with sufficient available data for analysis, the primary tumor was melanoma in 328. Of these, 282 underwent complete resection. Multiple metastases were resected in 39% of melanomas. The 5-year survival was 21% and 10-year survival was 14% in patients who underwent complete melanoma resection—the median survival of these patients was 19 months. The probability of melanoma relapse was 64%; 73% of relapses involved extrathoracic organs.[10] In situations involving incomplete resection, there were no long-term survivors (46 patients, $P<.01$).[11]

Table 2: Outcomes for Resectable Gastrointestinal Metastases

Author	Curative Resection (n)	Median Survival (mo)	5-Year Overall Survival (%)
Ricaniadis, 1995[14]	22	27.6	28.3%
Ollila, 1996[15]	46	48.9	41%
Agrawal, 1999[12]	19	14.9	38%

In subsets of patients with limited sites of disease, 5-year survival rates around 29% are noted,[11] which are superior to 5-year survival rates reported in patients who receive chemotherapy or biotherapy for their disease. The authors recommend that resection of pulmonary metastases be used in patients who have only one site of metastasis and a good performance status. Metastasectomy should be considered in patients who are eligible for certain clinical trials, in order to expand the knowledge base. In addition, the authors support consideration of visually assisted thoracoscopic surgery as a minimally invasive alternative that may be used in the initial diagnosis or as a therapeutic option for patients with lung metastasis.

Would your opinion change if this were a solitary resectable abnormality of the adrenal gland, small bowel, or soft tissue?

1. Yes
2. No

The faculty's opinion of surgical resectability would not change if this were a solitary resectable abnormality of the adrenal gland, small bowel, or soft tissue. Melanoma is one of the most common causes of metastatic diseases involving the gastrointestinal tract; metastasis to the small intestine is one of the more common presentations, with metastases to the colon occurring a bit less frequently. Other less common sites of gastrointestinal metastasis from melanoma include the stomach, the esophagus, and the anus. Distant melanoma in the gastrointestinal tract may be manifested as asymptomatic iron deficiency secondary to chronic indolent bleeding (with or without anorexia and weight loss), acute bleeding with hematemesis or melena, a small-bowel obstruction with abdominal pain and nausea/vomiting, or intussusception. Many patients with metastases to the gastrointestinal tract from metastatic melanoma can achieve palliation of symptoms by surgical intervention with minimal morbidity and mortality. A percentage of those patients can be rendered free of disease and may achieve prolonged survival.[12]

Outcomes for gastrointestinal metastases can be relatively favorable. As discussed previously, one analysis, in which a large proportion of patients received surgical resection, reported a median survival of 12.5 months in patients with metastases to the gastrointestinal tract.[9] Wood and colleagues[13] at the John Wayne Cancer Institute evaluated the role of surgical resection from a prospectively acquired database of 60 patients with melanoma metastatic to the intra-abdominal solid organs who underwent adrenalectomy, hepatectomy, splenectomy, or pancreatectomy. Median overall survival was significantly better in the 44 patients who had complete resections (27.6 mo) than in those who had incomplete resections (8.4 mo); 5-year survival was 24% for patients undergoing complete resection vs 0 for those who had incomplete resections ($P = .0001$). The median overall survival of patients with single organ-site versus multiple organ-site metastases was similar. The median disease-free survival in the complete resection group was 15 months. The 2-year disease-free survival was 53% in those with synchronous multi-site metastases compared with 26% in those with single-site metastasis.[13]

In other studies, median overall survival in patients with visceral metastases who underwent curative resection ranges from 15 to 49 months, with 5-year survivals of 28% to 41%, as summarized in **Table 2**.[12, 14, 15]

Management of Gastrointestinal Metastases

Surgical management of gastrointestinal metastases should include active

communication between medical and surgical oncologists and availability of fusion PET/CT. In the opinion of the authors, patients appropriate for surgical resection of gastrointestinal metastases include those with a prolonged disease-free interval (>8 to 12 months), patients with 1 or 2 visceral sites of disease, and those in whom a complete metastasectomy is feasible. Resection is the treatment of choice for the management of gastrointestinal metastases of melanoma in patients who are good surgical candidates. Patients with obstructive symptoms or bleeding from gastrointestinal metastases may benefit from surgical intervention from a palliative perspective, and complete surgical resection is possible in patients with limited gastrointestinal metastases. In patients with unresectable metastases, systemic therapy is a viable treatment option.[3]

A retrospective review of 124 patients with metastatic melanoma to the gastrointestinal tract showed clear differences between outcomes in patients with palliative vs complete surgical resections.[15] Forty-six of the 124 patients had a complete surgical resection, and 23 patients had palliative procedures; 97% of patients experienced relief of their presenting gastrointestinal symptoms postoperatively. The median survival in patients who underwent complete resection was 48.9 months, compared with 5.4 months in patients who had palliative procedures and 5.7 months in those who received nonsurgical intervention.[15]

A univariate analysis demonstrated that resection with curative intent, prior diagnosis of stage III disease, the gastrointestinal tract as the initial site of stage IV disease, and the disease-free interval significantly affected survival in patients who had a surgical procedure for gastrointestinal metastasis.[15]

A review of the melanoma database at the Memorial Sloan-Kettering Cancer Center identified 68 patients who had undergone a surgical procedure for metastases to the gastrointestinal tract.[12] Of these patients, 91% had involvement of the small intestine, and 79% of patients had a small-bowel resection. Ninety percent of patients experienced symptomatic relief of their presenting gastrointestinal symptoms postoperatively. Postoperative morbidity was 8.8%, and 2 patients (2.9%) died postoperatively.[12]

Case Revisited

The patient had normal pulmonary functioning tests and he underwent a wedge resection of the lesion. Metastatic melanoma was identified and the pathologist's examination revealed negative surgical margins. The patient's postoperative course was uneventful and he returned for follow-up 3 weeks later to discuss further care and therapy.

Which of the following would you recommend?

1. Routine surveillance without treatment
2. Radiation therapy to the lung and hilum
3. Adjuvant high-dose IFN for 1 year
4. A clinical trial if available
5. Another systemic agent(s)

The faculty agrees that surveillance is a reasonable approach at this time pending preliminary results of ongoing adjuvant trials. Following complete surgical metastasectomy, there is no proven systemic adjuvant therapy. The standard of care, therefore, is observation or enrollment in a clinical trial. The faculty suggests that patients should be encouraged to enroll in clinical trials to provide the best chance for improved outcomes.

Significant progress in adjuvant therapy for melanoma has not been made since the Eastern Cooperative Oncology Group (ECOG) trials showed durable benefits of IFN on relapse-free survival and somewhat less consistent events on overall survival in stage IIB and III melanoma.[16-19] Studies are evaluating the benefit of adjuvant therapy in patients with resectable, stage IIIB, stage IIIC, and limited stage IV melanoma. Investigators have specifically looked at the role of granulocyte-macrophage colony–stimulating factor (GM-CSF) in combination regimens. The major impact of GM-CSF is on overall survival with a lesser effect on disease recurrence.[20] GM-CSF may impact survival by changing the biologic behavior of the disease, such that recurrences can be surgically resected. The appearance of a solitary recurrence in the face of GM-CSF therapy may not necessarily indicate treatment failure. The investigators hypothesized that macrophages activated by GM-CSF might eradicate small metastatic tumor nodules, preventing the appearance of systemic metastases, but may not be able to overcome larger nodules that would subsequently appear as a localized metastasis.[20]

The first of these trials, E4697,[21] is based on a preliminary phase II adjuvant study of GM-CSF.[20] E4697 is a 4-arm, randomized, placebo-controlled, phase III trial of yeast-derived GM-CSF versus peptide vaccination versus GM-CSF plus peptide vaccination versus placebo in patients with no evidence of disease following complete surgical resection of locally advanced (stage IIIB or IIIC) or stage IV Melanoma.[21] Accrual to this study is full (811 patients), and preliminary results are expected in 2008. S0008, led by the Southwest Oncology Group and based on preliminary studies at M.D. Anderson Cancer Center,[22] looks at biochemotherapy vs immunotherapy alone. The study is comparing 1 year of IFN alfa-2b alone with 9 weeks of a combination regimen of cisplatin, vinblastine, and dacarbazine (DTIC), interleukin (IL)-2, and IFN alfa for 2 to 3 months with high-dose IL-2 for 1 year.[23]

Summary

For staging patients presenting with stage IV distant metastatic disease, the NCCN guidelines recommend appropriate biopsy techniques, radiography and chest CT, and consideration of additional studies, such as MRI or PET scans, as clinically indicated. Because patients with metastatic melanoma have a rather high incidence of brain metastases, a brain MRI or CT scan with contrast should be performed in patients with even minimal symptoms or physical findings consistent with central nervous system involvement, or if the results of either scan would influence treatment decisions.

For patients with isolated stage IV metastases, a complete surgical metastasectomy can offer significant long-term benefit and should be considered. Surgical resection for solitary, especially symptomatic, gastrointestinal involvement is reasonable and an appropriate palliative procedure. Surgery should be considered when the patient has only a few localized gastrointestinal metastases; patients with symptomatic visceral recurrences, (eg, bowel obstruction from gastrointestinal metastasis) should undergo an appropriate palliative procedure. Following a complete surgical metastasectomy for distant disease, no systemic adjuvant agent has been shown to be of benefit in rigorous clinical trials.

CASE 2

Systemic Therapy for Stage IV Disease

By Douglas Kondziolka, MD, MSc, FRCSC, FACS, and Marc S. Ernstoff, MD

CASE PRESENTATION

A 42-year-old, white man presented with a 1.5-mm ulcerated melanoma of the right ear. The SLN biopsy was positive, and the patient underwent partial ear resection and right modified radical neck dissection; none of the additional 35 lymph nodes were positive. The patient refused adjuvant high-dose IFN. Two years later, he was found to have recurrent melanoma adjacent to the site of the original resection, which was surgically excised. Two years following excision of the recurrent disease, a pre-employment chest x-ray revealed new bilateral hilar and fewer than 5 parenchymal nodules, measuring 1 cm to 2 cm. An MRI of the brain and CT scans of the abdomen were normal. The patient's past medical history includes sarcoidosis, which had been asymptomatic for more than 20 years. The patient had no other medical problems and his performance status was 0.

Would you recommend that a biopsy be performed?

1. Yes
2. No

The faculty recommends that a biopsy be performed, because information obtained from a biopsy will make the diagnosis definitive and may assist in treatment planning. Additionally, the NCCN guidelines agree that it is appropriate to confirm the suspicion of metastatic disease with either FNA (preferred) or with open biopsy of the lesion.[6]

A mediastinoscopy confirms metastatic melanoma. What further management would you recommend?

1. Observation
2. Single-agent chemotherapy with DTIC or temozolomide (TMZ)
3. DTIC-based polychemotherapy
4. Biochemotherapy with IL-2 and IFN
5. High-dose IL-2
6. Clinical trial
7. None of the above

The faculty recommends a clinical trial as the preferred option. Clinical trials may involve chemotherapy, biologic therapies, or targeted therapies in the treatment of metastatic melanoma. While some trials evaluate new combinations of agents, other trials evaluate new single agents compared with placebo or the current standard therapy, such as DTIC or other currently available therapies. It is important to consider the anticipated value of all available options when making initial treatment decisions, because the choice of first-line treatment may render patients ineligible for further clinical trials or otherwise limit available treatment options if the patient experiences disease progression. Information about cancer treatment and clinical trials in progress throughout the country can be found at the National Cancer Institute Web site, http://www.cancer.gov. Patients should thoroughly understand their treatment options before making treatment decisions.

The faculty emphasizes the importance of maintaining access to trials, especially for patients who are not being treated at major research institutions participating in the relevant trials. Physicians and patients in centers or geographic areas without a clinical trial program can take advantage of the Clinical Trials Support Unit, a service of the National Institutes of Health. The Clinical Trials Support Unit is a pilot project to make phase III cancer treatment trials sponsored by the National Cancer Institute available to physicians nationwide. As such, it gives physicians access to more studies and educational materials for their patients. More information on this program can be obtained at http://www.ctsu.org.

Systemic Therapy for Distant Melanoma

Unfortunately, advanced melanoma is refractory to most standard systemic therapies; hence the recommendation that newly diagnosed patients with advanced melanoma should be considered for a clinical trial. DTIC has been the standard of comparison for the treatment of metastatic melanoma since the 1970s, with response rates as high as 20% in early studies, but more generally in the 8% to 10% range, particularly in later studies. The median duration of response with DTIC ranges from 4 to 6 months. Other cytotoxic agents with single-agent activity include the vinca alkaloids (vincristine and vinblastine), the taxanes (paclitaxel and docetaxel), cisplatin, and TMZ. Additionally, biologic agents, such as IFN and IL-2 have been evaluated as single agents in the treatment of patients

Table 3: Summary of Single-Agent Therapy for Treatment of Advanced Melanoma.

Agent	Evaluable Patients	Response Rate (CR+PR, %)	95% CI (%)
Chemotherapy			
Dacarbazine	1936	20	18-22
Carmustine	122	18	11-25
Cisplatin	188	23	17-29
Vincristine	52	12	3-20
Vinblastine	62	13	5-21
Paclitaxel	65	18	9-28
Biologic Agents			
IFN alfa	380	16	N/A
IL-2	270	16	

Adapted from Balch et al, Chapter 46 of DeVita, 1993.[24]

with advanced melanoma. **Table 3** summarizes results of clinical trials evaluating single agents in the treatment of advanced melanoma.

Some of the single-agent therapies have other characteristics related to the pharmacologic profile that are of interest in melanoma management. For example, TMZ, an oral agent, is able to cross the blood-brain barrier, and 1 complete response and 8 partial responses (objective response rate = 6%) for melanoma brain metasases has been reported in a phase II study of this agent conducted in 151 patients.[25] A randomized, phase III trial[26] compared single-agent TMZ with DTIC in patients with advanced melanoma. This trial demonstrated a significant difference in median progression-free survival (1.9 mo in patients receiving TMZ vs 1.5 mo with DTIC, *P*=.012); however, this did not translate into a significant survival advantage. The Kaplan-Meier curve of overall survival is shown in **Figure 1**.[26]

Combinations of 2 or 3 cytotoxic agents have also been used in clinical trials for the treatment of advanced melanoma. While some of these combinations have resulted in a modest survival improvement when compared with DTIC, these studies have not consistently demonstrated a survival advantage over single-agent DTIC.

IL-2 has been evaluated extensively in clinical trials and appears to be the most active biologic therapy in this patient population. Response rates for IL-2 range from 8% to 22%. A variety of administration schedules have been evaluated, and high-dose bolus IL-2 appears to provide the best opportunity for complete response and long-term survival. Alternatively, long-term administration on a daily or a 3-times-per-week schedule appears to have some effectiveness and is generally well tolerated.[27-30]

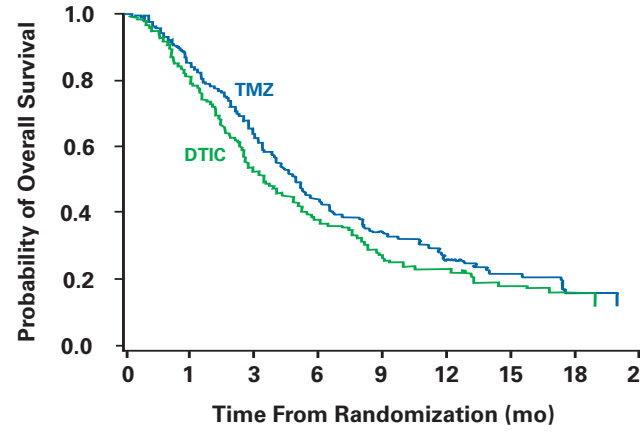
Candidates for IL-2 therapy for melanoma include patients with a performance status of 0 or 1 who are free of brain metastasis. The use of IL-2 should be restricted to patients with normal cardiac and pulmonary functions as defined by a normal thallium stress test and a normal pulmonary function test. Extreme caution should be used when administering IL-2 to patients with a history of cardiac or pulmonary disease.

An analysis of 270 patients treated in 8 clinical trials with high-dose IL-2 administered intravenously for metastatic melanoma demonstrated an overall response rate of 16%, with 6% of patients experiencing complete response and 10% experiencing partial response.[31] The median duration of response was 8.9 months for all responders and 5.9 months in patients who achieved a partial response (**Figure 2**). Median duration of response for patients who achieved a complete response had not been reached at the time these data were reported.[31]

Although high-dose IL-2 resulted in durable responses, some patients treated with this regimen experienced significant morbidity. The toxicities were generally reversible and long-term sequelae were rare. Severe (grade 3/4) toxicities included hypotension, supraventricular tachycardia, adult respiratory distress syndrome and respiratory failure, and mental status changes. There were 6 deaths from treatment-related toxicity (2.2%); bacterial sepsis was the primary cause of death in these patients.[31]

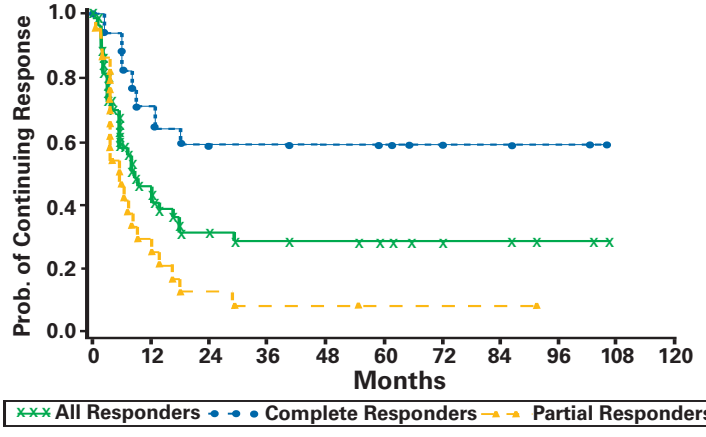
High-dose bolus IL-2 therapy produces durable responses in approximately 5% of patients with metastatic melanoma, including patients who had failed previous chemotherapy. Responding patients had not experienced relapses in 30 months, suggesting that the disease may not recur. Fifty-eight percent of responding patients remained progression-free at 1 year. Local salvage therapy may add to durable disease-free survival; 5 responding patients who developed

Figure 1: Kaplan-Meier curve of overall survival in a randomized, phase III trial comparing single-agent TMZ with DTIC.



From Middleton et al, 2000.[26] Reprinted with permission from the American Society of Clinical Oncology. DTIC indicates dacarbazine; TMZ, temozolomide.

Figure 2: Duration of response in patients responding to IL-2 therapy.



From Atkins et al, 1999.[31] Reprinted with permission from the American Society of Clinical Oncology.

Table 4: Summary of SC IL-2 in Patients With Metastatic Melanoma

Study	Regimen	Patients With Melanoma (n)	Patients Responding (n)	Response Rate (%)
Tagliaferri[28]	1 MU q8h x 5d/2 wk	6	0	0
Leahy[27]	38 MU/d	5	0	0
Eton[29]	6 MU/m^2–15 MU/m^2 5x/wk	19	2	11
Agarwala[30]	9 MU/m^2 bid x2d, 2 MU/m^2 bid x5d (alternating weeks)	153	5	3

isolated relapses underwent surgical resection and remained disease-free for up to 8.5 years at the time their data were reported. The efficacy results and toxicity profile of IL-2 in melanoma patients were comparable to those reported in patients with renal cell carcinoma treated with this regimen.[31]

Subcutaneous (SC) administration of IL-2 in patients with metastatic melanoma resulted in response rates of 0% to 11%. Subcutaneous administration of IL-2 resulted in a significantly lower overall response rate when compared with IV administration for the treatment of metastatic melanoma. **Table 4** summarizes various schedules and doses of IL-2 SC administration.[27-30]

Combination therapy with chemotherapy and biologic agents has been compared with chemotherapy alone in clinical trials; one regimen studied was cisplatin, vinblastine, and DTIC in combination with intermediate-dose IL-2 and IFN alfa.[32] Four phase III studies compared DTIC plus IFN with DTIC alone, with mixed results.[33-36] Results of phase II trials of the combination of cisplatin, carmustine, DTIC, and tamoxifen, known as the Dartmouth regimen, were promising, with response rates as high as 54% in the initial trial.[37] However, when this regimen was compared with single-agent DTIC in a randomized phase III trial,[38] there was no significant difference in survival.

The encouraging response and survival rates shown in smaller phase II studies of biochemotherapy provided the rationale for a phase III study comparing biochemotherapy with combination chemotherapy alone. The use of biochemotherapy (IFN and IL-2 + chemotherapy) has been studied in metastatic melanoma in 3 large, randomized trials but did not demonstrate an improvement in survival or time to disease progression compared with chemotherapy alone[39,40] or chemotherapy plus IFN alfa-2b without IL-2.[41] Additionally, a meta-analysis of 20 randomized trials involving 3273 patients compared single-agent DTIC with combination chemotherapy with or without immunotherapy. This meta-analysis found that the combination of DTIC and IFN alfa produces a higher overall response rate but no difference in overall survival.[42] While ongoing phase II and III trials are comparing complex biochemotherapy regimens with chemotherapy alone, there is currently no evidence that biochemotherapy is superior to chemotherapy.

A phase II study[43] evaluated low-dose, outpatient biochemotherapy with TMZ, GM-CSF, IFN alfa, and IL-2 for the treatment of metastatic melanoma. Patients received TMZ 200 mg/m^2 daily for 5 days followed by immunotherapy (GM-CSF 125 μg/m^2, IL-2 4 MU/m^2, IFN alfa 5 MU) SC daily for 12 days. The overall objective response rate was 26%; all but 1 of the responding patients had M1c disease. The median progression-free survival was 4.9 months and the median overall survival was 13.1 months. The overall survival rate was 52% at 12 months and 25% at 24 months. Grade 4 toxicity occurred in 3% of the cycles (thrombocytopenia in 2% and psychosis in 1%).

This low-dose outpatient biochemotherapy regimen produced clinical responses in patients with metastatic melanoma, even in those with M1c disease, but needs to be confirmed in multicenter phase III studies.

Another phase II study[44] evaluated TMZ plus concomitant subcutaneous pegylated IFN alfa in patients with histologically confirmed stage IV melanoma (N = 35). Eleven patients (31%) experienced a response to therapy; 3 patients (9%) experienced a complete response. Median survival was 12 months. No grade 4 toxicity was reported.[44]

Case Revisited

The patient received high-dose IL-2 and achieved a partial response. Despite additional IL-2 at 3-month intervals, he experienced disease progression and had 2 new 3-cm liver metastases 1 year from diagnosis. At this time, he was working full-time and had no complaints.

What would you now recommend for treating this patient?

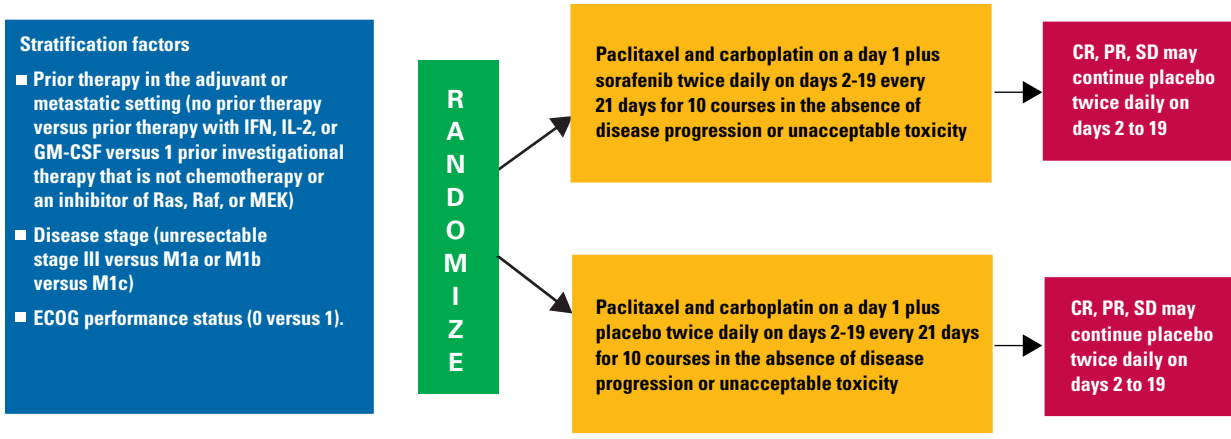
1. DTIC
2. TMZ
3. Polychemotherapy with cisplatin, vinblastine, and DTIC
4. Clinical trial (including phase I)
5. Observation until symptoms occur
6. Referral to hospice

The faculty agrees that a clinical trial is the best option for eligible patients, because there are no randomized clinical trials that support the use of second-line therapy in patients with advanced melanoma.

New Agents for Treatment of Metastatic Melanoma

Patients with advanced melanoma should be considered for clinical trials evaluating new forms of chemotherapy and/or biologic therapy (specific monoclonal antibodies, IL-2, IFN), or vaccines. Agents that have been evaluated in the treatment of advanced melanoma but have failed to demonstrate a survival advantage include lenalidomide (CC 5013; Celgene), Bcl-2 antisense oligonucleotide, and histamine dihydrochloride. Agents currently being evaluated in phase III clinical trials include the anti-CTLA4 antibody alone or in combination with vaccine and sorafenib in combination with chemotherapy. Phase II trials are currently evaluating angiogenesis inhibitors in various combinations and modified paclitaxel.[45] A review of the clinical trials Web site, ClinicalTrials.gov, found 200 active or pending trials for melanoma.[45] Ongoing studies include over 50 trials of vaccines, over 50 studies evaluating T-cell or dendritic cell manipulation, several studies evaluating anti-CTLA4, more than 20

Figure 3: Study Schema for E2603



studies evaluating IL-2, and more than 10 studies involving TMZ. Other agents being evaluated in patients with distant melanoma include lenalidomide, sorafenib, paclitaxel, bevacizumab, denileukin, and azacitidine.

Results of a phase III trial of a polyvalent melanoma cell vaccine (Canvaxin™, CancerVax Corp) were reported in early 2006. Overall survival for the 496 patients with resected stage IV melanoma was higher than that reported in previous clinical trials; however, the overall survival for patients who received the vaccine was 31.5 months, compared with 38.7 months in patients who received placebo. CancerVax has discontinued additional phase III trials in patients with stage IV melanoma.[46]

Sorafenib in Melanoma

Sorafenib is a small molecule that decreases tumor-cell proliferation and angiogenesis, targeting both the tumor cell and the tumor vasculature.[47] A phase II, placebo-controlled, randomized discontinuation trial with sorafenib[48] was conducted in patients with advanced melanoma. A total of 33 patients completed the 12-week sorafenib run-in phase. Four additional patients with melanoma discontinued therapy because of adverse events before the week 12 assessment. Of 34 patients evaluable for response, 1 patient (3%) had a partial response and continued on open-label sorafenib; 6 patients (16%) experienced stable disease and were randomly assigned to receive placebo or sorafenib. All 3 patients receiving sorafenib experienced disease progression by week 24. Two of these were discontinued from the study, but the third continued for symptomatic relief. All three of the patients receiving placebo experienced disease progression by week 24 and crossed over to receive sorafenib. One patient who crossed over to receive sorafenib was considered to receive clinical benefit.[48]

Sorafenib was also evaluated in a phase II trial[49] in combination with DTIC in patients with metastatic melanoma. The primary study objectives were to determine the efficacy and tolerability of sorafenib in combination with DTIC. Patients received sorafenib 400 mg twice daily plus DTIC 1000 mg/m^2 on day 1 of each 21-day cycle. Five patients (16.7%) experienced a partial response to therapy, and 13 patients (43.3%) experienced stable disease. The median progression-free survival for all patients was 3.6 months (range, 0.9 to 6.1 months). Grade 3/4 drug-related adverse events included neutropenia (23%), thrombocytopenia (17%), and fatigue (7%).[49]

The combination of sorafenib, paclitaxel, and carboplatin is being compared with paclitaxel and carboplatin alone in a randomized, phase III trial in patients with unresectable stage III or stage IV melanoma.[50] The primary study objective is to compare the overall survival of patients with unresectable stage III or stage IV melanoma treated with carboplatin and paclitaxel with sorafenib versus without sorafenib. Secondary objectives are to compare progression-free survival and response rates and the safety of the two combination regimens. Eligible patients must have histologic or cytologic confirmation of either unresectable stage III melanoma or stage IV melanoma. The melanoma must be cutaneous, mucosal, or from an unknown primary site. Disease must be measurable, and there must be no history or clinical evidence of brain metastasis by brain MRI, an ECOG performance status of 0 or 1, no uncontrolled hypertension, and no clinically significant cardiovascular disease. Prior IFN, IL-2, GM-CSF, or vaccine is allowed in the adjuvant or metastatic setting. The anticipated accrual is 800 patients. The schema for E2603 is shown in **Figure 3**.

Summary

Currently, only DTIC and high-dose IL-2 are approved by the US Food and Drug Administration for the treatment of metastatic melanoma. Durable, complete responses with IL-2 have been reported. Noninvestigational second-line chemotherapy with DTIC or TMZ is an option, but a clinical trial is the optimal choice. Clinical trials have demonstrated that combination chemotherapy regimens increase toxicity without evidence of survival benefit. Sequential administration of therapy has been evaluated; however, further research is needed to explore the effects of sequential therapy on clinical outcome and toxicity.

CASE 3 MANAGEMENT OF CNS METASTASES

By Douglas Kondziolka, MD, MSc, FRCSC, FACS, and Marc S. Ernstoff, MD

CASE PRESENTATION

A 50-year-old man had a pigmented lesion removed from the right side of his neck. Pathology on the biopsy specimen revealed melanoma: 4.2-mm Breslow thickness, ulcerated, Clark level IV. He was treated with wide local excision of the primary site; there was no residual disease and the surgical margins were negative. SLN biopsy was negative. The patient declined adjuvant therapy. Two years later, he developed severe headaches; an MRI of the head demonstrated a single frontal lesion, 2.5 cm, with surrounding edema that was suspicious for metastases. Additional staging PET/CT scan failed to demonstrate any evidence of metastasis outside of the central nervous system (CNS). With the exception of the headaches, the patient had no other symptoms or medical problems.

Which of the following would you recommend as initial therapy for this patient?

1. Whole brain radiation therapy (WBRT) alone
2. Stereotactic radiosurgery (SRS)
3. Craniotomy and surgical resection
4. Surgery + whole brain radiation
5. Systemic chemotherapy
6. Supportive care alone

While WBRT alone, craniotomy and surgical resection, and systemic chemotherapy are all reasonable choices, the faculty agrees that local therapy (SRS or surgery) and WBRT would be the first option to consider, and that SRS alone would be the second choice of therapy.

Clinical manifestations of brain metastases occur in up to 60% of patients with metastatic melanoma; cerebral metastases may account for 20% to 54% of melanoma deaths.[3] A retrospective database analysis[51] suggested that melanoma is associated with the second highest incidence of brain metastases, after lung cancer. Among patients with distant metastases, melanoma was associated with the highest incidence of brain metastasis. Brain metastases are the most common brain tumors and are more common than primary brain tumors.[51, 52] They present special challenges in management:

1. Tumors occur commonly (periodic staging scans should be obtained in asymptomatic patients)
2. Tumors are traditionally considered "radioresistant"—this does not apply to radiosurgery, which has higher biologic effects
3. Tumors may hemorrhage (50% of symptomatic melanoma brain tumors have some element of hemorrhage)[53]
4. Immunotherapy approaches require no steroids
5. Chemotherapy options may be limited

Historically, surgical resection of brain metastases was considered palliative, but more recently it has been found to improve survival in selected patients (reviewed in Vogelbaum and Suh, 2006).[52] Promising results from SRS of brain metastases have also been reported. An analysis[54] was conducted to determine whether improved survival in patients treated with resection was related to therapy alone or was partially due to patient selection. This analysis found the best survival rates in patients younger than 65 years with a Karnofsky performance status of at least 70 and a controlled primary tumor in which the brain was the only site of metastasis, suggesting that patient selection does impact outcome.[54]

Management of Solitary Metastasis

Three randomized trials of surgery plus WBRT compared with WBRT alone in patients with solitary brain metastasis have yielded inconsistent results (2 positive studies, 1 negative),[55-59] but the combination of surgery and WBRT appears to be a reasonable choice in selecting patients who may benefit from aggressive therapy. The choice between surgery and radiosurgery is less clear. Factors favoring the use of SRS include the presence of multiple lesions, tumors smaller than 35 mm, tumors with a minimal mass effect, tumors in or near the eloquent cortex, deep lesions, histologically radioresistant tumors, and patients with poor anesthesia risk. Factors favoring surgery over SRS include uncertain diagnosis, tumors with mass effect, tumors in the posterior fossa with edema, patients who require seizure control, and tumors greater than 3.5 cm.[52] According to the faculty, surgery is also preferable in patients with larger tumors and/or with symptoms not responsive to steroids.

Management of Multiple Lesions

What if the patient presented with three 2-cm lesions that involved both cerebral hemispheres? Would that change your opinion regarding the initial management?

1. Yes
2. No

Which of the following would you recommend as initial therapy for this patient?

1. WBRT alone
2. Stereotactic radiosurgery (SRS)
3. Craniotomy and surgical resection
4. Surgery + WBRT
5. Systemic chemotherapy
6. Supportive care alone

The first choice of the faculty for this patient with multiple lesions would be SRS. WBRT alone would be the second choice of treatment in this patient. Retrospective analyses evaluated treatment results of gamma-knife radiosurgery with or without WBRT compared with various other modalities in patients with solitary cerebral metastases. These analyses suggested that survival may be prolonged with the use of gamma-knife SRS or surgical excision plus WBRT when compared with radiation alone[60] and that radiosurgery alone can result in local tumor control rates equal to those for

surgery plus WBRT in selected patients.[61] In addition, postoperative WBRT is not necessary in patients receiving gamma-knife radiosurgery.[61, 62] It appears that survival depends not only on treatment but also on patient selection. The results of a retrospective analysis suggested that significant factors associated with improved survival included surgical treatment ($P<.0001$), the absence of concurrent extracerebral metastases ($P<.0001$), younger age ($P = .0007$), and longer disease-free interval ($P = .036$).[63] Additional retrospective analysis supports the extent of extracranial disease as a factor predictive of outcome.[64]

Are Results Poorer for More Tumors?

Results of RTOG 9508, which compared WBRT with or without SRS boost for patients with 1 to 3 brain metastases, suggested that WBRT and stereotactic boost improved Karnofsky performance status for all patients and improved survival in patients with a solitary brain metastasis.[65] Bhatnagar and colleagues[66] evaluated the use of SRS in patients with 4 or more intracranial metastases with a variety of primary tumors, including melanoma. They concluded that radiosurgery seemed to provide a survival benefit in this patient population but that total treatment volume was a more significant predictor of survival than the actual number of metastases.[66] However, the survival impact may be related to patient characteristics. In their study of radiosurgery followed by observation in patients with 1 to 3 brain metastases, Lutterbach and colleagues studied the predictive value of recursive partitioning analysis (RPA) on overall survival and also evaluated the impact of radiosurgery on local control.[67] In this RPA system proposed by the Radiation Therapy Oncology Group,[68] patients are classified into three groups: Class 1 (Karnofsky Performance Scale [KPS] score of at least 70, age less than 65, controlled primary site, no extracranial metastases); Class 3 (KPS less than 70); and Class 2 (all others).[68] Median survival was 13.4 months in class 1, 9.3 months in Class 2, and 1.5 months in Class 3 patients.[67] Lutterbach and colleagues concluded that RPA predicts survival in this population and suggested that it should be used in making treatment decisions. They also found that radiosurgery alone yielded high local control rates.

Case Revisited

Returning to the initial presentation of this case, with the solitary lesion, the patient was taken to surgery for exploration and resection. Pathology showed metastatic melanoma, which was completely resected. The patient recovered uneventfully and returned to work. He returned 2 weeks after surgery for additional recommendations and follow-up. Repeat staging did not demonstrate any evidence of additional metastatic disease.

What treatment should be offered to the patient at this time?

1. Observation
2. WBRT
3. Systemic chemotherapy
4. Adjuvant IFN alfa-2b

After considering available treatment options, the patient decided to receive WBRT. Five months later, the patient remained free of additional CNS metastasis; however, a follow-up chest x-ray demonstrated pulmonary nodules. Staging scans revealed 4 bilateral 1-cm to 2-cm pulmonary masses, and 2 small (<1.5-cm) liver metastases. The patient was asymptomatic and working full-time.

Would you consider this patient a candidate for systemic therapy at this time?

1. Yes
2. No

Patients with high-risk, stage IIIB or IV melanoma should be screened for brain metastases. Brain metastases should be treated (consider SRS for ≤5–7 lesions) and monitored for CNS progression. Retreatment with WBRT or SRS is a viable treatment option. Systemic therapy may be considered once the CNS metastases are controlled. Unfortunately, many clinical trials exclude patients with brain metastases, but more recently eligibility criteria have changed to allow patients with controlled CNS metastasis to participate in clinical trials. The systemic therapy options discussed previously are viable options for consideration. In one study, the combination of temozolomide plus whole brain irradiation did not result in substantial antitumor activity in patients with melanoma metastases to the brain.[69] The combination of temozolomide/thalidomide and whole brain radiation produced similar results to other therapeutic modalities.[42] These data suggest that more investigation is required to optimize the management of this challenging condition.

Summary

A large percentage of patients with metastatic melanoma have clinical manifestations of brain metastases, and cerebral metastases may account for a substantial portion of melanoma deaths.[3] Historically, surgical resection of brain metastases was considered palliative but recent data have demonstrated an improvement in survival in selected patients who undergo surgical resection for brain metastases.[52] Radiosurgery alone is an appropriate treatment alternative in patients with solitary brain metastasis from melanoma.[70] Retrospective analyses evaluating treatment results of surgery plus WBRT or gamma knife radiosurgery in patients with solitary cerebral metastases suggest that survival may be prolonged with the use of gamma knife SRS or surgical excision plus WBRT when compared with radiation alone.[60] Patients with brain metastases should be monitored for CNS progression. Retreatment with WBRT or stereotactic surgery is a viable treatment option and systemic therapy may be considered once the CNS metastases are controlled. Historically, many clinical trials have excluded patients with brain metastases; however, recent clinical trials have allowed patients with controlled CNS metastases to participate in clinical trials.

References

1. Liu Z-J, Herlyn M. Molecular biology of cutaneous melanoma. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer: Principles & Practice of Oncology.* 7th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2005. 1745-1753.
2. Essner R. Surgical treatment of malignant melanoma. *Surg Clin North Am.* 2003;83:109-156.
3. Balch CM, Atkins MB, Sober AJ. Cutaneous melanoma. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer: Principles & Practice of Oncology.* 7th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2005. 1754-1809.
4. American Cancer Society. *Cancer Facts & Figures 2006.* Atlanta, Ga: American Cancer Society; 2006.
5. Balch CM, Buzaid AC, Soong S-J, et al. Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. *J Clin Oncol.* 2001;19:3635-3648.
6. National Comprehensive Cancer Network. *Clinical Practice Guidelines in Oncology–v.2.2006: Melanoma.* Jenkintown, Pa: National Comprehensive Cancer Network; 2006.
7. Khan MA, Andrews S, Ismail-Khan R, et al. Overall and progression-free survival in metastatic melanoma: analysis of a single-institution database. *Cancer Control.* 2006;13:211-217.
8. Young SE, Martinez SR, Essner R. The role of surgery in treatment of stage IV melanoma. *J Surg Oncol.* 2006;94:344-351.
9. Barth A, Wanek LA, Morton DL. Prognostic factors in 1,521 melanoma patients with distant metastases. *J Am Coll Surg.* 1995;181:193-201.
10. Pastorino U, Buyse M, Friedel G, et al, for the International Registry of Lung Metastases. Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. *J Thorac Cardiovasc Surg.* 1997;113:37-49.
11. Leo F, Cagini L, Rocmans P, et al. Lung metastases from melanoma: when is surgical treatment warranted? *Br J Cancer.* 2000;83:569-572.
12. Agrawal S, Yao TJ, Coit DG. Surgery for melanoma metastatic to the gastrointestinal tract. *Ann Surg Oncol.* 1999;6:336-344.
13. Wood TF, DiFronzo LA, Rose DM, et al. Does complete resection of melanoma metastatic to solid intra-abdominal organs improve survival? *Ann Surg Oncol.* 2001;8:658-662.
14. Ricaniadis N, Konstadoulakis MM, Walsh D, Karakousis CP. Gastrointestinal metastases from malignant melanoma. *Surg Oncol.* 1995;4:105-110.
15. Ollila DW, Essner R, Wanek LA, Morton DL. Surgical resection for melanoma metastatic to the gastrointestinal tract. *Arch Surg.* 1996;131:975-979.
16. Kirkwood JM, Strawderman MH, Ernstoff MS, Smith TJ, Borden EC, Blum RH. Interferon alfa-2b adjuvant therapy of high-risk resected cutaneous melanoma: the Eastern Cooperative Oncology Group trial EST 1684. *J Clin Oncol.* 1996;14:7-17.
17. Kirkwood JM, Ibrahim JG, Sondak VK, et al. High- and low-dose interferon alfa-2b in high-risk melanoma: first analysis of Intergroup trial E1690/S9111/C9190. *J Clin Oncol.* 2000;18:2444-2458.
18. Kirkwood JM, Ibrahim JG, Sosman JA, et al. High-dose interferon alfa-2b significantly prolongs relapse-free and overall survival compared with the GM2-KLH/QS-21 vaccine in patients with resected stage IIB-III melanoma: results of Intergroup trial E1694/S9512/C509801. *J Clin Oncol.* 2001;19:2370-2380.
19. Kirkwood JM, Manola J, Ibrahim J, Sondak V, Ernstoff MS, Rao U. A pooled analysis of Eastern Cooperative Oncology Group and Intergroup trials of adjuvant high-dose interferon for melanoma. *Clin Cancer Res.* 2004;10:1670-1677.
20. Spitler LE, Grossbard ML, Ernstoff MS, et al. Adjuvant therapy of stage III and IV malignant melanoma using granulocyte-macrophage colony-stimulating factor. *J Clin Oncol.* 2000;18:1614-1621.
21. Vaccine therapy and/or sargramostim in treating patients with locally advanced or metastatic melanoma. NCT00005034. ClinicalTrials.gov Web site. Available at: http://www.clinicaltrials.gov. Accessed November 3, 2006.
22. Legha SS, Ring S, Eton O, et al. Development of a biochemotherapy regimen with concurrent administration of cisplatin, vinblastine, dacarbazine, interferon alfa, and interleukin-2 for patients with metastatic melanoma. *J Clin Oncol.* 1998;16:1752-1759.
23. Chemotherapy plus biological therapy in treating patients with melanoma. NCT00006237. ClinicalTrials.gov Web site. Available at: http://www.clinicaltrials.gov. Accessed November 1, 2006.
24. Balch C, Houghton AN, Peters LJ. Cutaneous melanoma. In: DeVita VT, ed. *Cancer: Principles and Practice of Oncology.* 4th ed. Philadelphia, Pa: J.B. Lippincott; 1993:1612-1661.
25. Agarwala SS, Kirkwood JM, Gore M, et al. Temozolomide for the treatment of brain metastases associated with metastatic melanoma: a phase II study. *J Clin Oncol.* 2004;22:2101-2107.
26. Middleton MR, Grob JJ, Aaronson N, et al. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. *J Clin Oncol.* 2000;18:158-166.
27. Leahy MG, Pitfield D, Popert S, Gallagher CJ, Oliver RT. Phase I study comparing continuous infusion of recombinant interleukin-2 by subcutaneous or intravenous administration. *Eur J Cancer.* 1992;28A:1049-1051.
28. Tagliaferri P, Barile C, Caraglia M, et al. Daily low-dose subcutaneous recombinant interleukin-2 by alternate weekly administration: antitumor activity and immunomodulatory effects. *Am J Clin Oncol.* 1998;21:48-53.
29. Eton O, Rosenblum MG, Legha SS, et al. Phase I trial of subcutaneous recombinant human interleukin-2 in patients with metastatic melanoma. *Cancer.* 2002;95:127-134.
30. Agarwala SS, Glaspy J, O'Day SJ, et al. Results from a randomized phase III study comparing combined treatment with histamine dihydrochloride plus interleukin-2 versus interleukin-2 alone in patients with metastatic melanoma. *J Clin Oncol.* 2002;20:125-133.
31. Atkins MB, Lotze MT, Dutcher JP, et al. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. *J Clin Oncol.* 1999;17:2105-2116.
32. Bajetta E, Del Vecchio M, Nova P, et al. Multicenter phase III randomized trial of polychemotherapy (CVD regimen) versus the same chemotherapy (CT) plus subcutaneous interleukin-2 and interferon-α2b in metastatic melanoma. *Ann Oncol.* 2006;17:571-577.
33. Young AM, Marsden J, Goodman A, Burton A, Dunn JA. Prospective randomized comparison of dacarbazine (DTIC) versus DTIC plus interferon-α (IFN-α) in metastatic melanoma. *Clin Oncol (R Coll Radiol).* 2001;13:458-465.
34. Thomson DB, Adena M, McLeod GR, et al. Interferon-alpha 2a does not improve response or survival when combined with dacarbazine in metastatic malignant melanoma: results of a multi-institutional Australian randomized trial. *Melanoma Res.* 1993;3:133-138.
35. Falkson CI, Falkson G, Falkson HC. Improved results with the addition of interferon alfa-2b to dacarbazine in the treatment of patients with metastatic malignant melanoma. *J Clin Oncol.* 1991;9:1403-1408.
36. Bajetta E, Di Leo A, Zampino MG, et al. Multicenter randomized trial of dacarbazine alone or in combination with two different doses and schedules of interferon alfa-2a in the treatment of advanced melanoma. *J Clin Oncol.* 1994;12:806-811.
37. Lattanzi SC, Tosteson T, Chertoff J, et al. Dacarbazine, cisplatin and carmustine, with or without tamoxifen, for metastatic melanoma: 5-year follow-up. *Melanoma Res.* 1995;5:365-369.
38. Chapman PB, Einhorn LH, Meyers ML, et al. Phase III multicenter randomized trial of the Dartmouth regimen versus dacarbazine in patients with metastatic melanoma. *J Clin Oncol.* 1999;17:2745-2751.
39. Atkins MB, Lee S, Flaherty LE, Sosman JA, Sondak VK, Kirkwood JM, for the US Melanoma Intergroup. A prospective randomized phase III trial of concurrent biochemotherapy (BCT) with cisplatin, vinblastine, dacarbazine (CVD), IL-2 and interferon alpha-2b (IFN) versus CVD alone in patients with metastatic melanoma (E3695): an ECOG-coordinated intergroup trial [abstract 2847]. *Proc Am Soc Clin Oncol.* 2003;22:708.
40. Del Vecchio M, Bajetta E, Vitali M, et al. Multicenter phase III randomized trial of cisplatin, vindesine and dacarbazine (CVD) versus CVD plus subcutaneous (sc) interleukin-2 (IL-2) and interferon-alpha-2b (IFN) in metastatic melanoma patients (pts) [abstract]. *Proc Am Soc Clin Oncol.* 2003;22:abstract 2849.
41. Keilholz U, Punt CJ, Gore M, et al, for the EORTC Melanoma Group. Dacarbazine, cisplatin and IFN-α2b with or without IL-2 in advanced melanoma: final analysis of EORTC randomized phase III trial 18951 [abstract]. *Proc Am Soc Clin Oncol.* 2003;22:abstract 2848.
42. Huncharek M, Caubet JF, McGarry R. Single-agent DTIC versus combination chemotherapy with or without immunotherapy in metastatic melanoma: a meta-analysis of 3273 patients from 20 randomized trials. *Melanoma Res.* 2001;11:75-81.
43. Weber RW, O'Day S, Rose M, et al. Low-dose outpatient chemobiotherapy with temozolomide, granulocyte-macrophage colony stimulating factor, interferon-α-2b, and recombinant interleukin-2 for the treatment of metastatic melanoma. *J Clin Oncol.* 2005;23:8992-9000.
44. Hwu W-J, Panageas KS, Menell JH, et al. Phase II study of temozolomide plus pegylated interferon-α-2b for metastatic melanoma. *Cancer.* 2006;106:2445-2451.
45. Clinical Trials. Available at http://www.clinicaltrials.gov. Accessed November 2, 2006.
46. CancerVax Corporation. CancerVax announces results of phase 3 clinical trials of Canvaxin™ in patients with stage III and stage IV melanoma [press release]. Market Wire [Web site]. Available at: http://www.marketwire.com/mw/release_html_b1?release_id=114480. Accessed September 19, 2006.
47. Wilhelm SM, Carter C, Tang L, et al. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. *Cancer Res.* 2004;64:7099-7109.
48. Eisen T, Ahmad T, Flaherty KT, et al. Sorafenib in advanced melanoma: a Phase II randomised discontinuation trial analysis. *Br J Cancer.* 2006;95:581-586.
49. Lorigan P, Corrie P, Chao D, et al. Phase II trial of sorafenib combined with dacarbazine in metastatic melanoma patients [abstract]. *J Clin Oncol.* 2006;24(18S):abstract 8012.
50. Carboplatin and paclitaxel with or without sorafenib in treating patients with unresectable stage III or stage IV melanoma. NCT00110019. ClinicalTrials.gov Web site. Available at: http://www.clinicaltrials.gov. Accessed November 3, 2006.
51. Barnholtz-Sloan JS, Sloan AE, Davis FG, Vigneau FD, Lai P, Sawaya RE. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. *J Clin Oncol.* 2004;22:2865-2872.
52. Vogelbaum MA, Suh JH. Resectable brain metastases. *J Clin Oncol.* 2006;24:1289-1294.
53. Kondziolka D, Bernstein M, Resch L, et al. Significance of hemorrhage into brain tumors: clinicopathological study. *J Neurosurg.* 1987;67:852-857.
54. Gaspar L, Scott C, Rotman M, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. *Int J Radiat Oncol Biol Phys.* 1997;37:745-751.
55. Noordijk EM, Vecht CJ, Haaxma-Reiche H, et al. The choice of treatment of single brain metastasis should be based on extracranial tumor activity and age. *Int J Radiat Oncol Biol Phys.* 1994;29:711-717.
56. Mintz AP, Cairncross JG. Treatment of a single brain metastasis: the role of radiation following surgical resection. *JAMA.* 1998;280:1527-1529.
57. Patchell RA, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med.* 1990;322:494-500.
58. Mintz AH, Kestle J, Rathbone MP, et al. A randomized trial to assess the efficacy of surgery in addition to radiotherapy in patients with a single cerebral metastasis. *Cancer.* 1996;78:1470-1476.
59. Vecht CJ, Haaxma-Reiche H, Noordijk EM, et al. Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery? *Ann Neurol.* 1993;33:583-590.
60. Stone A, Cooper J, Koenig KL, Golfinos JG, Oratz R. A comparison of survival rates for treatment of melanoma metastatic to the brain. *Cancer Invest.* 2004;22:492-497.
61. Muacevic A, Kreth FW, Horstmann GA, et al. Surgery and radiotherapy compared with gamma knife radiosurgery in the treatment of solitary cerebral metastases of small diameter. *J Neurosurg.* 1999;91:35-43.
62. Sneed PK, Lamborn KR, Forstner JM, et al. Radiosurgery for brain metastases: is whole brain radiotherapy necessary? *Int J Radiat Oncol Biol Phys.* 1999;43:549-558.
63. Fife KM, Colman MH, Stevens GN, et al. Determinants of outcome in melanoma patients with cerebral metastases. *J Clin Oncol.* 2004;22:1293-1300.
64. Kondziolka D, Martin JJ, Flickinger JC, et al. Long-term survivors after gamma knife radiosurgery for brain metastases. *Cancer.* 2005;104:2784-2791.
65. Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet.* 2004;363:1665-1672.
66. Bhatnagar AK, Flickinger JC, Kondziolka D, Lunsford LD. Stereotactic radiosurgery for four or more intracranial metastases. *Int J Radiat Oncol Biol Phys.* 2006;64:898-903.
67. Lutterbach J, Cyron D, Henne K, Ostertag CB. Radiosurgery followed by planned observation in patients with one to three brain metastases. *Neurosurgery.* 2003;52:1066-1074.
68. Gaspar L, Scott C, Rotman M, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. *Int J Radiat Oncol Biol Phys.* 1997:37:745-751.
69. Margolin K, Atkins B, Thompson A, et al. Temozolomide and whole brain irradiation in melanoma metastatic to the brain: a phase II trial of the Cytokine Working Group. *J Cancer Res Clin Oncol.* 2002;128:214-218.
70. Mori Y, Kondziolka D, Flickinger JC, Kirkwood JM, Agarwala S, Lunsford LD. Stereotactic radiosurgery for cerebral metastatic melanoma: factors affecting local disease control and survival. *Int J Radiat Oncol Biol Phys.* 1998;42:581-589.

Posttest Questions

Erratum: The previous version of this publication had an error in the answers for question #3. The choices have now been corrected. If you already took the test, this question has been censored from the CME test. We apologize for this error.

Please answer each question in the space provided on page 16.

1. The use of surgical resection is a viable treatment option for patients with distant melanoma and is supported by:
   A. Recent advances in imaging techniques such as CT and PET scanning
   B. The possibility that resection of the initial organ metastasis may delay the metastatic cascade and may improve immune functioning.
   C. Improvements in anesthesia, surgical techniques, and post-operative monitoring
   D. Recent findings that resection of all metastatic disease provides the patient with the highest chances of prolonged survival with a quality of life better than would be expected without the surgical resection
   E. All of the above

2. Surgery for melanoma is most effective when the sites of metastasis are limited to a single tissue or organ; initially, nearly ___ of patients present with only 1 metastatic organ site.
   A. 26%
   B. 68%
   C. 86%
   D. 95%

3. In subsets of patients with limited sites of disease, 5-year survival rates of up to ___ have been reported in patients who undergo pulmonary metastasectomy.
   A. 10%
   B. 29%
   C. 45%
   D. 36%

4. Melanoma is one of the most common causes of metastatic diseases involving the
   A. Gastrointestinal tract
   B. Brain
   C. Pulmonary system
   D. Bone

5. Following complete surgical metastasectomy,
   A. There is no proven systemic adjuvant therapy; therefore, the standard of care is observation or a clinical trial
   B. Adjuvant therapy is the currently recognized standard of care
   C. S0008 and E4697 clinical trials demonstrated that adjuvant therapy does not provide a survival benefit
   D. Clinical trials are ongoing to evaluate adjuvant therapy in melanoma patients
   E. A and C
   F. A and D

6. DTIC has been the standard of comparison for the treatment of metastatic melanoma since the 1970s, with early response rate as high as 20%, but more generally in the ___ to ___ range.
   A. 6%; 12%
   B. 8%; 10%
   C. 13%;15%
   D. 5%; 8%

7. Candidates for IL-2 therapy for melanoma should have
   A. A performance status of 0 or 1
   B. No brain metastasis
   C. Normal cardiac and pulmonary functions as defined by a normal thallium stress test and a normal pulmonary function test
   D. All of the above

8. A patient with distant melanoma received high-dose IL-2 and achieved a partial response. Despite additional IL-2 at 3-month intervals, he experienced disease progression and had 2 new 3-cm liver metastases 1 year from diagnosis. The best treatment option for this patient is
   A. DTIC
   B. TMZ
   C. CVD polychemotherapy
   D. Clinical trial (including phase I)
   E. Observation until symptoms occur
   F. Referral to hospice

9. A patient's pathology on biopsy revealed melanoma with a 4.2-mm Breslow thickness, ulcerated, Clark level IV. The patient was treated with wide local excision of the primary site. There was no residual disease and the surgical margins were negative. SLN biopsy was negative. The patient declined adjuvant therapy. Two years later, he developed severe headaches; MRI of the head demonstrated a single frontal lesion, 2.5 cm, with surrounding edema that was suspicious for metastases. Additional staging PET/CT scan failed to demonstrate any evidence of non-CNS metastasis. With the exception of the headaches, the patient had no other symptoms or medical problems. Which of the following would you recommend as the initial treatment for this patient?
   A. WBRT alone
   B. SRS
   C. Craniotomy and surgical resection
   D. Surgery + WBRT
   E. Systemic chemotherapy
   F. Supportive care alone

10. It is estimated that up to ___ of patients with metastatic melanoma have clinical manifestations of brain metastases; cerebral metastases may account for 20% to 54% of melanoma deaths.
   A. 86%
   B. 73%
   C. 60%
   D. 45%

Evaluation Form

Please use the scale below in answering these questions. Fill in the circle completely. You may use pen or pencil to fill in the circles.

Very Low Low Moderate High Very High

1. To what extent were the following educational objectives achieved?

A. Describe the role of surgical resection in distant metastatic melanoma

❍ ❍ ❍ ❍ ❍

B. Compare and contrast systemic therapy options for distant melanoma

❍ ❍ ❍ ❍ ❍

C. Outline the role of the nurse as part of the team managing distant metastatic melanoma

❍ ❍ ❍ ❍ ❍

D. Describe options for management of melanoma brain metastases

❍ ❍ ❍ ❍ ❍

2. To what extent were you satisfied with the overall quality of the educational activity?

❍ ❍ ❍ ❍ ❍

Very Low Low Moderate High Very High

3. To what extent was the content of the program relevant to your practice or professional responsibilities?

❍ ❍ ❍ ❍ ❍

4. To what extent did the program enhance your knowledge of the subject area?

❍ ❍ ❍ ❍ ❍

5. To what extent did the program change the way you think about clinical care and/or professional responsibilities?

❍ ❍ ❍ ❍ ❍

6. To what extent will you make a change in your practice and/or professional responsibilities as a result of your participation in this educational activity?

❍ ❍ ❍ ❍ ❍

7. To what extent did the activity present scientifically rigorous, unbiased, and balanced information?

❍ ❍ ❍ ❍ ❍

8. To what extent was the presentation free of commercial bias?

❍ ❍ ❍ ❍ ❍

Answer Posttest Questions Here

1. ☐ 2. ☐ 3. ☐ 4. ☐ 5. ☐ 6. ☐ 7. ☐ 8. ☐ 9. ☐ 10. ☐

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