Introduction
The treatment of choice for primary solid tumors without evidence of distant metastatic spread is surgical excision. Surgery for the primary tumor and regional lymphatics, combined in certain cases with postoperative adjuvant radiation therapy and/or chemotherapy, offers the best chance for cure. Patients with tumors that have metastasized to distant sites, however, are not usually offered surgery as part of their comprehensive treatment plan.

Current therapy for distant metastasis is inadequate. In fact, during the past 30 years, there has been no overall improvement in the survival of most patients with solid neoplasms metastatic to distant sites. Conventional cytotoxic chemotherapy is unsatisfactory; responses are rarely complete, five-year survival rates are less than 5%, and chemotherapeutic agents are toxic and expensive. The neovascularity associated with large tumors is characterized by abnormal flow; this diminishes the likelihood that a systemic agent will reach its intended target, reduces the activity of antineoplastic agents, and facilitates development of drug resistance. Thus, even if responses are complete, they are rarely durable.

New approaches to metastatic cancer are needed. Conventional logic suggests that surgical therapy is not indicated in patients with multiple metastases at distant organ sites because the cancer is widely disseminated and beyond the reach of a local therapy. Nevertheless, a number of series show long-term survival following resection of multiple distant metastases for all histologic types of solid neoplasms. This suggests that it is time to reposition surgery in the treatment paradigm for metastatic cancer.

This commentary discusses treatment options for patients with distant metastases, focusing on a form of cytoreductive surgery—complete metastasectomy—for patients with distant metastases at soft tissue and visceral sites such as the lung and liver. It reviews evidence that cytoreductive surgery is really a form of immunotherapy with a long-term clinical benefit that depends on the host’s immune response to a surgical reduction in tumor burden. Finally, this review examines melanoma, the most intensively studied immunogenic tumor in humans, and
discusses why it is the ideal target for a combination of cytoreductive surgery and active specific immunotherapy.

**Treatment Options For Distant Metastases From Solid Neoplasms**

**Chemotherapy for Distant Metastases**

Long-term survival following the diagnosis of distant metastases (American Joint Committee on Cancer [AJCC] stage IV) requires a complete response to treatment. All malignant cells must be eradicated by surgical resection or by a systemic therapy, i.e., cytotoxic chemotherapy, biologic therapy, or immunotherapy. Chemotherapy is the conventional approach, and the most widely embraced model of cytotoxic chemotherapy for tumor regression is the Skipper-Schnabel-Wilcox model. This log-kill model predicts that a given chemotherapy will kill a certain fraction of tumor cells if the cells are homogeneous in their chemosensitivities. If, however, the cells are heterogeneous, a multidrug regimen is necessary to achieve a complete response.

Even then, individual cancer cells may circumvent the cytotoxic mechanism of the chemotherapeutics, developing multidrug resistance. Thus, while the log-kill model may be useful to predict how many cycles of chemotherapy are necessary to kill $10^9$ or $10^{10}$ tumor cells, it does not account for heterogeneous deposits of tumor cells that survive and grow in the presence of previously active chemotherapeutics.

For a patient with a 2-cm visceral metastasis, a chemotherapeutic regimen that kills only 90% of cells is essentially palliative treatment. The remaining 10% of cells will eventually grow, leading to an overwhelming tumor burden. Palliation may be significant, but it is achieved at the cost of considerable toxicity, both during and after drug infusion. In contrast, although tumor masses of 2 cm or more are difficult to eradicate with systemic therapy, they can be easily removed by surgery. This is a compelling argument for combining a local treatment—surgery—with the administration of systemic agents, even in patients with metastatic disease.

**Surgery for Distant Metastases**

Surgery for metastatic disease is based on the concept of site-specific organ metastasis. More than 100 years ago, Paget proposed a “seed and soil” hypothesis to explain the nonrandom distribution of metastases in autopsy specimens. Paget observed a preferential spread of breast cancer to bone, and a preferential spread of ocular melanoma to liver. He theorized that certain cancer cells can only spread to certain organs. Ewing then proposed a “mechanical” theory that linked metastasis to blood flow. According to this theory, circulating tumor cells lodge in the first capillary network from the primary neoplasm. Thus, colon cancers would metastasize to the liver, whereas sarcomas would spread to the lung.

Both theories are probably partially correct but neither considers the complexity of the metastatic process. First, the cancer cell must enter the bloodstream, either by invading adjacent capillaries/venules or via its own neovascular system. Once in the bloodstream, the cancer cell must adhere to the vascular endothelium of the target organ by an interaction between site-specific adhesion molecules and organ-specific endothelial receptors. The cancer cell must then produce enzymes to degrade the basement membrane of the vascular endothelium, so that it can invade the parenchymal tissues of the secondary organ site. Even then, unless the cancer cell can attract specific growth factors and angiogenesis factors from the invaded organ, or produce autocrine growth factors and angiogenesis factors, it will remain dormant. Thus, the establishment of a visceral metastasis is a complex process, and only a small fraction of tumor cells circulating in the blood are successful in establishing a metastasis that is capable of growth at a distant visceral site.

Metastasectomy, which is the surgi-
cal resection of visceral metastases with tumor-free surgical margins, has not been popular for AJCC stage IV patients with multiple metastases because surgery is considered a local therapy and therefore of little value for management of disseminated disease. However, a complete surgical metastasectomy can render a patient disease-free with only short-term postoperative morbidity. Most patients fully recover from the surgical procedure within three to six weeks, returning to most or all activities. Long-term survival has been reported in many series of patients with a variety of tumor histologies following resection of multiple distant metastases, indicating that metastasectomy does have a role in the management of patients with stage IV disease.

Only 14% of melanoma patients have synchronous metastases at multiple distant organ sites; 86% initially present with metastases confined to a single organ site, such as the lung, and many months later develop asynchronous metastases at other organ sites. This suggests that the initial metastases—not the primary tumor—may be the source of subsequent metastases (Fig. 1). We have found that most patients with melanoma have only one to three initial synchronous metastases at a single organ site, and 80% to 90% of these metastases can be completely removed by surgery.

**Pulmonary Metastases**

Several single-institution reports have demonstrated prolonged median and five-year survival in properly selected patients undergoing a pulmonary metastasectomy. Critics of these series object to the small patient populations and limited follow-up. In 1990, the International Registry of Lung Metastases was started in an effort to establish a large international database that could be used to answer clinical questions. The first report from this registry presented the long-term results of pulmonary metastasectomy in 5,206 patients from 18 thoracic surgery departments worldwide. These patients were considered to have undergone a complete pulmonary metastasectomy if there was no residual microscopic or macroscopic disease. The overall procedure-related mortality was 1.3%. Patients had epithe-
lial tumors (43%), sarcomas (42%), germ cell tumors (7%), melanomas (6%), or other tumor types (2%). For patients undergoing a complete metastasectomy, the median survival was 35 months, and the five-year, 10-year, and 15-year survival rates were 36%, 26%, and 22%, respectively. Median survival for those in whom all metastases could not be completely resected was 15 months, with five-year, 10-year, and 15-year survival rates of 13%, 7%, and 7%, respectively.

By multivariate analysis, the significant variables were primary tumor type, number of metastases, and disease-free interval before diagnosis of stage IV disease. Patients with germ cell tumors had the highest five-year survival rate (68%), whereas melanoma patients had the lowest (21%). Even, the 21% rate of five-year survival, however, substantiates recent single-institution reports19,20 and is far superior to reported five-year survival rates for melanoma patients managed with chemotherapy.23,24 Although survival rates were 10% to 15% higher for patients with single versus multiple metastases, even patients with 10 to 20 pulmonary metastases had five-year and 10-year survival rates of 20% to 25%.

Any disease-free interval between resection of the primary tumor and pulmonary metastasectomy was associated with improved overall survival, but the relative risk of death appeared lowest for patients who remained disease-free for at least 36 months after the initial surgical resection. This is not surprising because disease-free interval reflects tumor doubling time: The longer the disease-free interval, the slower the growth of the tumor and the longer it takes to double in size. In melanoma patients with pulmonary metastases, we have shown that patients with tumor doubling times of 60 days or more have significantly better prognoses than patients with shorter doubling times.25

Colorectal Hepatic Metastases
In multiple series of 100 or more patients collected over the past 15 years,11,12,26-31 the rate of five-year survival following hepatic resection has been consistently between 25% and 40%, with an overall average of 31% and a mortality of only 4%. These results are better than those for primary surgical treatment of esophageal, pancreatic, and even lung cancer. Recently, the Association Francaise de Chirurgie (AFC) reported one of the largest series of patients undergoing hepatic resection for metastatic colorectal carcinoma.32 This multicenter review examined data for 1,895 patients treated at numerous institutions throughout France. Data included primary tumor characteristics, extent of hepatic metastases, operative records, and disease-free and overall survival. The overall procedure-related mortality was 1.4%. There were no five-year survivors among the 77 patients who underwent incomplete hepatic metastasectomy. By contrast, five-year survival rate was 26% for the 1,818 patients who underwent complete surgical resection. Multivariate analysis showed that the only statistically significant hepatic factor related to survival was complete hepatic metastasectomy. By contrast, five-year survival rate was 26% for the 1,818 patients who underwent complete surgical resection. Multivariate analysis showed that the only statistically significant hepatic factor related to survival was complete hepatic metastasectomy with at least a 1-cm margin. Location of the tumor, size and number of metastases, and postoperative adjuvant chemotherapy were not significant.

Although the AFC study can be criticized for the selection bias inherent in any retrospective review, its size lends validity to its findings. Moreover, the results confirm many smaller studies of hepatic metastasectomy in populations numbering only in the hundreds. By comparison, patients undergoing systemic chemotherapy for advanced colorectal cancer have a complete response rate of less than 3% and rarely survive five years.33 Thus, the best chance for five-year survival in patients with hepatic metastases is hepatic resection of all disease with at least a 1-cm margin.

Cytoreductive Surgery
As part of a planned multidisciplinary approach to metastatic disease, cytoreduc-
tive surgery induces a clinically complete remission by resecting all known metastatic sites in patients who have a high likelihood of residual subclinical metastatic sites. When a complete metastasectomy is undertaken as a form of cytoreductive surgery, it becomes part of a multidisciplinary attempt to destroy all tumor cells and effect a durable cure. Surgery is a locoregional therapy; removal of a visceral metastasis by en bloc resection with tumor-free surgical margins may provide excellent local control but does not directly address the potential existence of occult tumor cells at other sites or in the circulation. Therefore, even if all clinically evident tumor is surgically excised, the patient is likely to have subclinical metastases that require effective postoperative systemic adjuvant therapy, whether with immunotherapy and/or chemotherapy.

**CYTOREDUCTIVE SURGERY AS A FORM OF IMMUNOTHERAPY**

Cancer cells generate factors that facilitate tumor growth by causing both general and specific suppression of the immune system. The degree of general immunosuppression correlates with the total burden of cancer cells in the body. Cancer cells also shed specific tumor antigens into the bloodstream. These antigens either combine with antibodies to form antigen-antibody complexes or circulate as free antigens. In either form, they can induce factors that block the ability of lymphocytes to kill cancer cells. They can also activate T cells to suppress the anti-tumor response (Fig. 2). In essence, the cancer cell is a factory producing specific and non-specific immunosuppressive factors that facilitate its growth by turning off the host’s anti-tumor immune response. Cytoreductive surgery, therefore, removes most of the cancer cell factory, allowing the host’s anti-tumor immune response to recover. If the residual tumor burden after surgery is too large, the regrowth of cancer cells will again cause host immunosuppression and overpower the patient’s immune anti-tumor response. In contrast, if the number of tumor cells remaining after surgery is small, the patient’s immune response can deal effectively with these residual micrometastases.

The clinical efficacy of surgical therapy does not require mechanical removal of every cancer cell from the body. Thus, the rate of five-year survival following resection of multiple metastases is 15% to 20%, even though most of these patients must have residual occult metastases. Also, tumor cells have been identified postoperatively in the blood and/or wound drainage fluid of patients who never develop clinical evidence of distant metastasis. Conversely, recurrent tumor may become clinically apparent after a disease-free interval of 10 to 20 years following surgical treatment of the primary neoplasm. These findings suggest that tumor cells can be present without disease progression, remaining dormant for prolonged periods until some event interferes with the host’s previously effective immune response.

By its mechanical reduction of the immunosuppressive tumor burden, cytoreductive surgery for many stage III and IV solid neoplasms can allow recovery of the host’s immune response to control the progression of residual occult metastases. Thus, cytoreductive surgery might be considered a form of immunotherapy.

**HOST IMMUNE RESPONSE FOLLOWING CYTOREDUCTIVE SURGERY**

Investigators at the John Wayne Cancer Institute have been studying the prognostic value of a 90-kd glycoprotein tumor antigen (TA90) that is expressed by most melanoma cells. Using an enzyme-linked immunosorbent assay to measure optical density, they have demonstrated a circulating immune complex (IC) of TA90 and anti-TA90 IgG antibody in the sera of melanoma patients. A positive TA90-IC assay, i.e., TA90-IC values higher than 0.41 optical density, has been linked to decreased disease-free and overall survival of patients with surgically resected stage II,
III, and IV metastatic melanoma.45-48

A recent study examined TA90-IC values in cryopreserved serial serum samples from 23 patients who developed recurrence of melanoma after a disease-free interval of at least 10 years following initial diagnosis (Hsueh EC, Gupta RK, Morton DL, unpublished data). These patients were matched by age, sex, Breslow thickness, and site of primary tumor with 23 patients who remained free of disease for at least 10 years after surgery. TA90-IC values were positive in 23 of 23 patients who recurred but in only three of 23 patients who remained disease-free. Interestingly, TA90-IC values gradually became negative and remained negative in the three patients who remained disease-free, which suggests destruction of occult micrometastases by host defenses during the postoperative period.

Figure 3 shows TA90-IC values in the blood of a 30-year-old woman with AJCC stage II melanoma (T3N0M0), who had a positive TA90-IC assay following wide excision and axillary node dissection for a primary melanoma on the back. Over the next three years, TA90-IC values gradually became negative and the patient has remained free of disease for 20 years. Figure 4 shows TA90-IC values for a patient with AJCC stage I melanoma (T3N0M0), who underwent wide excision and neck dissection for a primary melanoma. Although the regional lymph nodes did not contain tumor cells, TA90-IC values remained positive throughout the next six years of serum collection, and the patient developed pulmonary and adrenal metastases 14 years after surgery.

Collectively, these findings suggest that prolonged disease-free survival depends on the ability of the host’s cellular and/or humoral immune system to control the growth of any residual occult tumor cells that the surgical procedure fails to remove. The optimal host immune response, cellular and/or humoral, responsible for these prolonged disease-free intervals requires further investigation.

**Adjuvant Immunotherapy**

The immunogenicity of melanoma makes it the prototypical tumor in which to study novel immunotherapeutics. The following sections briefly review current active immunotherapy strategies for regional and distant metastatic melanoma, the various melanoma vaccines in phase III trials for AJCC stage III melanoma, and the immunotherapeutic possibilities in patients receiving adjuvant therapy for AJCC stage IV melanoma.

Unlike chemotherapy, active immunotherapy does not directly affect the growth of tumor cells. Instead, it must act indirectly by activating host immune responses in a specific or non-specific fashion. Specific immunotherapeutic agents upregulate the antibody response or the cytotoxic T-cell response to certain tumor-associated or melanoma-associated antigens. Non-specific immunotherapeutic agents, such as intact microorganisms, microbial cell wall products, haptens, glucans, and protein products, stimulate the immune system to respond to antigens on the autologous tumor cells but are not directed at specific tumor antigens.

In the laboratory, successful identification and characterization of melanoma antigens has shifted attention from non-specific immunostimulants to antigen-specific immunotherapy. Melanoma vaccines formulated from whole cells or cell lysates produce a complex cellular and humoral response to defined and undefined antigenic components of the cell, whereas vaccines made of purified antigens produce an antibody response specific to the purified antigen(s). Complex vaccines are polyvalent and therefore can stimulate immune responses to many tumor antigens, which increases the strength and diversity of the overall immune response. In addition, the anti-tumor activity of a polyvalent vaccine is less susceptible to antigen modulation by cancer cells. Antigenic competition due to immune responses to irrelevant antigens is a theoretical but as yet unproven problem. Vaccines made...
This 30-year-old female with AJCC stage II melanoma remained free of disease after wide excision of a primary melanoma on the back (Clark level III, Breslow thickness 2.75 mm) and an axillary lymph node dissection that removed 21 tumor-negative lymph nodes.
This 38-year-old male initially diagnosed with AJCC stage I melanoma underwent wide excision of a primary melanoma on the neck (Clark level III, Breslow thickness 0.82 mm) and a cervical lymph node dissection that removed 52 tumor-negative lymph nodes. Fourteen years later, he developed distant metastases (AJCC stage IV melanoma).

Overall survival (OS) in terms of humoral (IgM antibody) and cellular (delayed-type hypersensitivity [DTH] skin test) responses to postoperative adjuvant therapy with CancerVax. Adapted from Hsueh et al, with permission.
from purified antigens are easier to manufacture, and the patient’s response to a single antigen is easier to study. Nevertheless, single-antigen vaccines can be rendered ineffective by the emergence of resistant antigen-negative tumor clones.51

The immune response to active specific immunotherapy is both humorally and cellularly mediated. Humoral immunity involves antibody production from mature B lymphocytes and usually requires the presence of antigen-specific helper T cells. Cell-mediated immunity involves stimulation of CD4+ T cells by an antigen presented on the surface of an antigen-presenting cell, a mechanism restricted to major histocompatibility (MHC) class II cells. Alternatively, antigen can directly stimulate CD8+ T cells through an MHC class I-restricted process.

The relative importance of a humoral versus cell-mediated immune response is debated, but if the vaccine’s clinical benefit is achieved by activation of immune defenses, there should be a correlation between the strength of the immune response and survival. Patients who exhibit both humoral and cell-mediated responses fare better than those who demonstrate only one type of response or no response (Fig. 5).46,52 This suggests that the efficacy of a cancer vaccine can be measured by the strength of the immune response and its effect on survival.

REGIONAL METASTATIC MELANOMA

When melanoma spreads from the primary site to the regional nodes (AJCC Stage III), the chance of long-term survival drops precipitously. Prognosis depends in part on the primary tumor’s anatomic site, Breslow thickness, and the patient’s gender, but the most significant factors are the clinical status and number of tumor-involved regional lymph nodes.

Over the past two decades, numerous investigators have proposed various vaccines as less toxic alternatives to chemotherapy or biologic therapy. Many phase I and II trials have been published but thus far, no prospective, randomized multicenter study has demonstrated a survival advantage for patients receiving immunotherapy as a postsurgical adjuvant treatment. In general, phase III studies of postoperative adjuvant therapy53 for AJCC stage III melanoma have met with little success, and until recently no agent has shown promise for changing the five-year survival rate of 30% to 35%.

Interferon alfa-2b

Treatment for patients with surgically resected high-risk melanoma was significantly changed in January 1996 with the publication of results from the Eastern Cooperative Oncology Group (ECOG) Trial #1684 by Kirkwood et al (J Clin Oncol 1996;14:7-17). This trial showed that high-dose interferon alfa-2b (IFNα-2b) administered at maximum tolerated doses of 20 million units/m2/day, intravenously, for four weeks followed by 10 million units/m2, three times a week, subcutaneously, for 48 weeks, significantly prolonged both relapse-free and overall survival. Based on the results of this trial, the FDA approved IFNα-2b as adjuvant therapy following surgery in patients with AJCC stage IIB (Breslow thickness greater than 4.0 mm) and stage III malignant melanoma. Unfortunately, the results of an intergroup confirmatory trial (#1690) failed to demonstrate an overall survival benefit for patients receiving high-dose IFNα-2b versus no postoperative adjuvant therapy.54 The overall survival of the observation group was longer in the #1690 trial than in its predecessor, perhaps as a result of more accurate staging using our recently introduced technique of sentinel lymphadenectomy.55 Both trials confirmed that high-dose interferon is costly and toxic. In the ECOG #1684 trial, dose modifications due to toxicity were required in 65% of patients, 43% during the induction phase and 46% during maintenance therapy. Approximately 78% of patients on IFNα-2b treatment experienced Grade 3 or greater toxicity and 23% could not complete the one-year treatment regimen.56 Neverthe-

CA Cancer J Clin 1999;49:101-116
less, IFN-α-2b is the only FDA-approved adjuvant treatment for high-risk stage IIB and III melanoma.

Allogeneic Living Whole Cell Vaccine

Investigators at the John Wayne Cancer Institute have developed a polyvalent melanoma cell vaccine (CancerVax™) comprising three allogeneic melanoma cell lines.57 These cell lines, chosen for their high content of tumor-associated antigens and melanoma-associated antigens, express at least 20 different antigens that are immunogenic in humans (Table).49,58 Thirteen of the 20 antigens are shared by other types of tumors, whereas seven are unique to melanoma.

Our previous study in this journal49 presented phase II data for CancerVax in AJCC stage III patients. Ten-year overall survival rates were 49% and 33% (p<0.0002) in 283 vaccine and 1,474 nonvaccine historical control patients, respectively, with five-year overall survival rates of 53% and 39%, and median survival times of more than 90 months and 35.1 months, updating an earlier report.57 Those data are particularly compelling because the single most important prognostic factor, namely the number of involved lymph nodes, was similar between the two groups of patients. Interestingly, the median survival (>90 months) and the five-year survival rate (53%) of CancerVax patients were the highest yet observed for a large series of AJCC Stage III patients. A phase III prospective trial is underway to examine CancerVax plus bacille Calmette-Guérin (BCG) as postoperative adjuvant therapy for patients with completely resected AJCC stage III melanoma (Fig. 6).

Lysate Vaccines

Human studies with cell lysates induced by a wide variety of viruses, including vaccinia, suggested a possible therapeutic role for viral lysates. Wallack and colleagues59 developed a vaccinia lysate vaccine, melanoma oncolysate (VMO), by infecting four established allogeneic melanoma cell lines with live vaccinia virus and then extracting a nucleus-free cell lysate by centrifugation. A phase II trial of postoperative VMO adjuvant immunotherapy plus a vaccinia booster vaccination demonstrated a statistically significant prolongation in disease-free interval;60 however, this was not confirmed in a phase III prospective, randomized multi-institutional trial of VMO vaccine versus vaccinia virus alone.61 Hersey62 developed a vaccinia melanoma cell lysate (VMCL) vaccine using only one allogeneic melanoma cell line. A phase II trial of VMCL plus cyclophosphamide (an adjuvant) for AJCC stage III melanoma patients demonstrated five-year survival rates of 50% for vaccine recipients versus 34% for historical controls.63 A prospective, randomized phase III study of VMCL versus no immunotherapy for stage IIB and III melanoma patients has completed patient accrual and will yield results in two to three years.
Mitchell et al.64 mechanically disrupted two melanoma cell lines to create a lysate vaccine without associated viral antigens. This lysate vaccine (Melacine®) is administered with the adjuvants DETOX (monophosphoryl lipid A and a purified mycobacterial cell-wall skeleton) and intravenous cyclophosphamide (300 mg/m²). Interim results from a multicenter phase II nonrandomized trial of Melacine in 114 AJCC stage IV melanoma patients demonstrated a median survival of 14 months.65 A recent phase III trial of Melacine versus combination chemotherapy in 106 patients with nonresectable AJCC stage IV melanoma revealed no difference in median survival (9.4 months for Melacine versus 12.3 months for dacarbazine, cisplatin, carmustine, and tamoxifen; \( p = 0.16 \)).66 Eighteen patients who failed Melacine were given IFNα-2b at a dosage of 5 x 10⁶ U/m² subcutaneously, three times per week: Eight experienced a partial response. A phase III trial comparing Melacine plus IFNα-2b with IFNα-2b alone is underway.

**Shed-Antigen Vaccine**

Bystryn67 developed a partially purified, polyvalent melanoma antigen vaccine made from surface material shed into a culture medium by a pool of selected melanoma cells. This shed-antigen vaccine theoretically provides a broad array of ganglioside and other tumor antigens without the irrelevant and perhaps immunosuppressive factors that may be present in preparations of whole cells or even cell lysates. Melanoma cell lines selected for their differential expression of surface tumor-associated antigens are grown in serum-free media, and the shed material is harvested, characterized, and purified. Humoral and/or cellular immune responses elicited by this vaccine have been correlated with improved survival. Alum seems to be the most effective adjuvant.

**Carbohydrate Antigen Vaccines**

The early work of Livingston and associates68,69 with vaccines containing purified ganglioside antigens, namely GM₂, was initially very exciting because of the IgM antibodies produced. These antibodies lysed melanoma cells expressing the GM₂ antigen via a complement-mediated pathway. Unfortunately, no cytotoxic T cells were induced and no IgG antibodies were produced.

The GM₂ antigen used in the vaccine preparation was initially obtained from the brain tissue of cats with Tay-Sachs disease, through a series of separations and purifications. GM₂ is currently obtained from bovine brain tissue by cleaving a terminal galactose on the GM₁ ganglioside. The vaccine was created by placing purified GM₂ in suspension with Tice strain BCG. It was administered via intradermal injections (6 to 10/vaccination) into an extremity biweekly for three sessions; then maintenance immunizations were given at two and five months. One week prior to the first and fourth vaccinations, cyclophosphamide was ad-
ministered intravenously as an adjuvant.

A prospective, randomized trial compared \( {\text{GM}}_2/\text{BCG} \) vaccine and cyclophosphamide (adjuvant) with \( \text{BCG} \) alone after complete surgical resection of AJCC stage III melanoma. \(^{70} \) \( {\text{GM}}_2/\text{BCG} \) immunotherapy induced an IgM antibody response in a majority of patients but did not improve disease-free or overall survival. Subset analysis, however, revealed that patients who produced the anti-\( {\text{GM}}_2 \) IgM antibody had a longer disease-free and overall survival.

To improve the humoral response, \( {\text{GM}}_2 \) has been conjugated to keyhole limpet hemocyanin (KLH), which acts as the carrier protein, and administered with the adjuvant QS-21. This \( {\text{GM}}_2 \)-KLH/QS-21 vaccine is superior to the \( {\text{GM}}_2/\text{BCG} \) vaccine with respect to generation of cytotoxic antibodies. \(^{71} \) A phase III trial of \( {\text{GM}}_2 \)-KLH/QS-21 versus IFN\( \alpha \)-2b for patients who have undergone surgical resection of AJCC stage III melanoma is underway.

**DISTANT METASTATIC MELANOMA**

The overall survival of patients with distant metastatic melanoma (AJCC stage IV) has not improved over the past 20 years. Median survival remains 7.5 months and the rate of five-year survival is less than 5% (Fig. 7). \(^{17} \) Despite advances in surgical techniques, anesthesia, and monitoring, surgery is infrequently the initial intervention in patients with one or more distant metastases. The surgeon’s role in the management of distant metastatic melanoma is usually limited to an occasional complete resection of a solitary visceral metastasis, or to a palliative resection for symptomatic metastases, such as a bowel obstruction or tumors causing neurologic symptoms. Most of these patients become the sole responsibility of the medical oncologist and are treated primarily with systemic chemotherapy or biotherapy.

Nonsurgical approaches to distant melanoma metastases, however, remain inadequate. Conventional chemotherapy is unsatisfactory; responses are rarely complete and five-year survival rates are less than 5%. \(^{23,24} \) Moreover, chemotherapy is toxic and expensive. The results of biologic therapy with interleukin-2 (IL-2) also are unsatisfactory: Complete response rate is only 7%, and five-year survival rate is less than 5%. \(^{72} \) Moreover, the toxicity associated with high-dose bolus IL-2 is considerable, and treatment-related deaths have been reported. Combination chemotherapy plus biologic therapy has demonstrated the best complete response rate (20% to 30%), \(^{73-77} \) but the durability of these responses remains in question.

**Cytoreductive Surgery Plus Adjuvant Immunotherapy in AJCC Stage IV Metastatic Melanoma**

During the past decade, investigators at the John Wayne Cancer Institute have embarked on a protocol of cytoreductive surgery plus postoperative adjuvant CancerVax immunotherapy for patients with AJCC stage IV melanoma. Surgery is not considered unless all tumor visualized by preoperative imaging studies (computed tomography, magnetic resonance imaging, or positron emission tomography) is resectable. If all macroscopic tumor is excised, then the patient is a candidate for postoperative adjuvant immunotherapy with CancerVax.

Our previous report in this journal \(^{49} \) compared the survival of stage IV melanoma patients receiving CancerVax after complete metastasectomy with the survival of stage IV historical control melanoma patients who did not receive postoperative CancerVax therapy. For patients with resected visceral metastases (M1b disease), the five-year overall survival was 33% with vaccine therapy versus 10% with nonvaccine therapy; corresponding median survival was 32.3 months versus 12.6 months (\( p = 0.01 \)).

Although these data indicate a significant therapeutic effect of CancerVax in AJCC Stage IV melanoma, the evidence...
Figure 7
Survival Rates of Patients with AJCC Stage IV Melanoma (1971-1993)

Survival rates of 1,521 patients with AJCC stage IV melanoma, according to time interval of treatment. Adapted from Barth et al\textsuperscript{17} with permission.

Figure 8
Postoperative Adjuvant CancerVax Therapy

Matched-pair analysis showing survival benefit of postoperative adjuvant CancerVax therapy in patients undergoing cytoreductive surgery for AJCC stage IV melanoma.
is not definitive because it is difficult to eliminate selection biases in comparisons with historical databases. To minimize the effect of selection bias, a matched-pair analysis of vaccine therapy versus nonvaccine therapy following complete surgical resection was conducted. Fifty-eight pairs of stage IV patients were matched for anatomic site of metastasis, number of tumor-involved organs, and gender. Vaccine and nonvaccine groups had five-year overall survival rates of 35.6% and 17.1%, respectively, median overall survival times of 37.2 and 14.3 months, respectively (p=0.0005), and median disease-free survival times of 9.1 and 4.2 months, respectively (p=0.005). There was no significant intergroup difference in primary melanoma sites, disease-free interval before stage IV disease, or other prognostic factors. By multivariate analysis, vaccine immunotherapy was the most significant prognostic factor for overall survival (p=0.003) and disease-free survival (p=0.0007). Thus, when patients were matched by known prognostic factors, adjuvant CancerVax more than doubled the median survival time and the rate of five-year survival following complete resection of distant metastases (Fig. 8).

When survival was analyzed in terms of immune response to CancerVax, patients who had both an IgM antibody response and a skin test response had a median overall survival of 76 months and a five-year survival of 75% (Fig. 5), compared with 32 months and 36% for either an IgM or skin test response, or 19 months and 8% for no response (similar to the survival data for patients who received non-CancerVax adjuvant therapy). In fact, the immune response to CancerVax was the most important prognostic factor in resected stage IV melanoma and was highly significant both by univariate and multivariate analysis when compared with standard prognostic variables (gender, characteristics of the primary lesion, initial AJCC stage, age at diagnosis, first metastatic site, and number of metastases). We believe that surgery and adjuvant immunotherapy should be the initial treatment for most patients with melanoma metastatic to distant sites because almost 90% of such patients will have only one to three individual metastatic sites, using modern scanning technologies. Adjuvant immunotherapy can be used after the induction of a complete clinical remission by cytoreductive surgery. To exclude selection bias, clinical trials are urgently needed to test this hypothesis. One multicenter phase III trial is underway at the John Wayne Cancer Institute and 30 participating cancer centers. In this trial, melanoma patients are stratified by site and number of distant metastases. Following complete surgical resection, patients are randomized to receive CancerVax plus BCG or placebo plus BCG; the endpoint is disease-free and overall survival (Fig. 9). This pivotal, multicenter phase III trial will determine whether adjuvant immunotherapy is effective in significantly prolonging the survival of patients with resected stage IV melanoma.

The lack of progress during the past

| Stratification Factors |
|------------------------|
| Site of metastases: M1a: soft-tissue & nodal metastases |
| M1b: visceral metastases |
| Number of individual lesions: 1, 2-3, 4-5 |

Figure 9
Phase III Trial: CancerVax vs Placebo

Stratification Factors

- Site of metastases: M1a: soft-tissue & nodal metastases
  M1b: visceral metastases
- Number of individual lesions: 1, 2-3, 4-5

Surgical Resection of all Metastatic Lesions

Randomize

CancerVax + BCG
Placebo + BCG

Phase III prospective, randomized multicenter trial of CancerVax plus BCG versus placebo plus BCG after complete resection of AJCC stage IV melanoma.
30 years in the treatment of metastatic solid cancers with chemotherapy is unlikely to be overcome without the assistance of the surgeon, because abnormal tumor vasculature in large tumor masses creates a diffusion gradient that impairs the efficacy of systemically administered chemotherapeutic drugs. Resection of visible tumor masses is necessary so that adjuvant therapies can become more effective. It is time for surgeons to resume an important role in the treatment of metastatic solid neoplasms and join their colleagues in medical oncology and immunotherapy in a combined modality approach to the treatment of metastatic cancers.

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