QUALITY OF EVIDENCE ABOUT EFFECTIVENESS OF TREATMENTS FOR METASTATIC UVEAL MELANOMA

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ABSTRACT

Purpose: To evaluate and comment on the published peer-reviewed literature for evidence of effectiveness of treatments for metastatic uveal melanoma.

Methods: Literature search and analysis of satisfactory articles on treatment of metastatic uveal melanoma published between 1980 and 2007.

Results: Of 71 identified articles, 10 (14.1%) were review articles without original case information, 2 (2.8%) were review articles combined with case reports, 17 (24.0%) were case reports, 15 (21.1%) were retrospective descriptive case series reports, 3 (4.2%) were pilot studies of a novel intervention, 2 (2.8%) were reports of a prospective nonrandomized phase I clinical trial, 7 (9.9%) were reports of a prospective nonrandomized phase I/II clinical trial, 14 (19.7%) were reports of a prospective nonrandomized phase II clinical trial, and 1 (1.4%) was a report of a prospective randomized phase II clinical trial. None of the articles was a report of a prospective randomized phase III clinical trial. None of the reports of a prospective study included a comparison group of similar but untreated patients. The largest reported unselected patient groups had a median survival time after detection of metastasis in the range of 3 to 4 months. In contrast, the largest selected patient groups tended to have substantially longer median survival times.

Conclusions: Although median survival time following diagnosis of metastatic uveal melanoma tends to be substantially longer in selected subgroups of patients subjected to aggressive invasive interventions than it is in unselected groups, and although this difference is frequently considered to be evidence of treatment-induced prolongation of patient survival, much if not most of this apparent difference in survival is likely to be attributable to selection bias, surveillance (lead time) bias, and publication bias rather than treatment-induced alteration of the expected outcome. Information about the impact of treatment of any type for patients with metastatic uveal melanoma that has been reported in the peer-reviewed literature is of extremely low quality and does not provide compelling evidence of a beneficial effect of such treatment on survival.

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INTRODUCTION

Patients who develop metastasis from primary uveal melanoma rarely survive more than a few years following initial detection of that metastasis. The median survival time after diagnosis of metastasis in the largest published series of unselected patients with metastatic uveal melanoma was 3.6 months.[1] Cumulative actuarial survival in this series was 20% at 1 year, 13% at 2 years, 5% at 3 years, 2% at 4 years, and <1% at 5 years. In spite of the generally acknowledged poor prognosis of patients with metastatic uveal melanoma, one occasionally encounters an article that purports to show substantially prolonged survival of selected patients who were subjected to certain aggressive interventions, most notably surgical resection of metastatic tumors (metastectomy) and various techniques of regional perfusion chemotherapy.[2-5] In spite of such claims, many oncology groups and individual clinicians remain unconvinced about the beneficial impacts of currently available treatments on survival time.[6-8]

The current study was designed to evaluate the quality of evidence[9] regarding the impact of treatment on overall survival time in patients with metastatic uveal melanoma that has been reported in published peer-reviewed articles during the past quarter century. Four specific aspects of quality (see "Methods" section for details) were addressed in this study: (1) type of report, (2) category of reported subgroup, (3) baseline clinical variables evaluated and reported, and (4) control or comparison group reported.

METHODS

The authors performed a literature search to identify all original articles on metastatic uveal melanoma that were published in peer-reviewed medical journals during the period 1980 through 2007. The first step in this search was to perform a MEDLINE search online evaluating the terms *uveal melanoma, choroidal melanoma, ciliary body melanoma, ciliochoroidal melanoma, iris melanoma, iridociliary melanoma, intraocular melanoma,* and *ocular melanoma*. Articles dealing with laboratory investigations using animal models were excluded. The set of articles identified by this preliminary search was then evaluated for the additional terms metastasis and metastatic disease.

An abstract of each of the articles identified at this step was reviewed by one of the authors to confirm that its subject was truly metastatic uveal melanoma and determine whether it described treatment of any sort for the metastatic disease. A printed copy of each article identified at this step was obtained and reviewed in detail by one of the authors. Each satisfactory article was classified by the senior author according to its hierarchical type as follows: review article; case report (1 to 3 patients); retrospective descriptive case series report, subclassified as small (4 to <30 patients), medium size (≥30 to <100 patients), or large (≥100 patients); prospective pilot study; prospective phase I clinical trial; prospective phase I/II clinical trial; prospective phase II clinical trial; or prospective phase III

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randomized clinical trial.

Each article that reported original patient data on a group of patients in a retrospective descriptive study or prospective clinical trial (ie, each article other than a review article or case report) was also classified in terms of the category of the reported patient subgroup: *unselected subgroup* (ie, a seemingly representative subgroup of all patients with metastasis from primary uveal melanoma who had been treated for their primary intraocular tumor at single center [in a single center study] or in a collaborating center [in a multicenter study] and subsequently developed metastatic disease during available follow-up, or a subgroup of patients who were encountered initially following detection of metastatic disease in a particular center that was not known as a referral center for a specific form of treatment) vs *selected subgroup* (ie, a subgroup of all potential patients with metastatic uveal melanoma who were selected using explicit inclusion and exclusion criteria or who were referred to a center known for a particular treatment specifically to undergo or be considered for that treatment), the clinical variables that were evaluated at the time of detection of the metastasis and reported by the authors, and the absence vs presence and nature of any control or comparison group that was reported.

RESULTS

Preliminary MEDLINE search identified 3263 published articles on uveal melanoma during the specified interval. Of these, 553 dealt with some aspect of metastatic disease evaluation or treatment in human subjects. Review of the abstracts of these 553 articles identified 65 that dealt specifically with treatment of metastatic uveal melanoma. Examination of the list of references associated with each of these articles identified 6 additional relevant articles not identified by the computer-generated search.

CATEGORY OF ARTICLE

Of the 71 satisfactory articles, 10 (14.1%) were categorized as review articles without any original case information,[7,10-18] 2 (2.8%) were categorized as review articles combined with case reports,[19,20] 17 (24.0%) were classified as case reports,[21-37] 4 (5.6%) were classified as small retrospective descriptive case series reports,[4,38-40] 6 (8.5%) were categorized as medium size retrospective descriptive case series reports,[41-46] 5 (7.0%) were classified as large retrospective descriptive case series reports,[1,2,47-49] 3 (4.2%) were classified as pilot studies of a novel intervention,[5,50,51] 2 (2.8%) were classified as reports of a prospective nonrandomized phase I clinical trial,[52,53] 7 (9.9%) were classified as reports of a prospective nonrandomized phase I/II clinical trial,[54-60] 14 (19.7%) were categorized as reports of a prospective nonrandomized phase II clinical trial,[3,61-73] and 1 (1.4%) was classified as a report of a prospective randomized phase II clinical trial (of 2 alternative intravenous chemotherapy regimens).[74] No article was classified as a report of a prospective randomized phase III clinical trial.

TYPE OF SUBGROUP

Forty-two of the 71 identified articles (59.2%) reported a series of patients numbering 4 or greater.[1-5,38-74] Eight of these 42 articles (19.0%) described an unselected patient group.[1,38,41,42,44,47-49] The other 34 articles (81.0%) described a distinctly selected patient group.[2-5,39,40,43,45,46,50-74] The principal selection criteria for the subgroups reported in these articles included number of anatomic sites involved, specific anatomic site or sites involved, metastatic tumor burden, and clinical decision regarding resectability of the metastatic tumors. However, in the cited reports of selected subgroups of patients evaluated in prospective clinical studies, multiple specific inclusion and exclusion factors (which differed greatly from article to article) were applied by the various groups of investigators. These factors included patient age (most patients <18 years old and some patients >70 or >75 years old were disqualified from investigational treatments), predicted life expectancy if no treatment were provided (patients with an expected survival time of <2 months, <3 months or <4 months were frequently disqualified from enrollment and treatment in a clinical trial [even though none of the reports indicated how this determination was made]), systemic performance score (patients with a Karnofsky score of <70 or <60 or an ECOG-WHO score of >1 or >2 were commonly disqualified from many clinical trials), anatomic sites of involvement (patients with symptomatic brain metastasis and those with >1 or >2 organs or tissues involved by metastasis were frequently disqualified from certain treatments), largest linear dimension of largest measurable tumor (patients with no discrete measurable metastatic tumors [usually due to diffuse military involvement of the affected organ] were almost always disqualified from clinical trials of surgical metastectomy and those with a measurable cutaneous metastatic tumor >10 mm in diameter or a measurable visceral metastatic tumor >20 mm in diameter were sometime disqualified from certain clinical trials), percentage of liver replaced by metastatic tumors (patients with >60% or >70% hepatic replacement [by preoperative imaging studies of the abdomen] were frequently disqualified from certain therapies), hepatic function status (patients with a serum level of any liver enzyme or total bilirubin that was >2× or >2.5× the upper limit of normal for the laboratory where the testing was done were frequently disqualified from specific treatments), hematologic status (patients with anemia [usually regarded as a hemoglobin level <10 g/dL], neutropenia [usually regarded as a total white blood cell count of <3500/mm^3], or thrombocytopenia [usually regarded as a platelet count <100,000/mm^3] were commonly disqualified from chemotherapy trials), cardiac status (patients with angina, severe coronary artery disease, or congestive heart failure were commonly disqualified from both chemotherapy trials and surgical treatment trials), renal status (patients with chronic or acute renal failure were routinely disqualified from most chemotherapy trials), oncologic status (patients with prior or concurrent cancer other than uveal melanoma or nonmelanoma skin cancer were regularly disqualified from most protocols), mental status (patients with severe depression, psychosis, dementia, or other serious, severe or major psychiatric or neurologic disease were frequently excluded from clinical trials), intercurrent systemic disease status (patients with any severe, serious, major, or uncontrolled systemic disease [including diabetes mellitus, hypertension, infection, or autoimmune disease] were commonly disqualified from most trials), and anatomic configuration of hepatic vasculature (patients with anomalous hepatic

vasculature unsatisfactory for placement of an infusion catheter for hepatic artery infusion chemotherapy commonly were disqualified from hepatic artery infusion chemotherapy or chemoembolization treatment). None of the evaluated articles employed all of these selection factors.

CLINICAL VARIABLES EVALUATED AND REPORTED

The clinical variables evaluated at the time of detection of the metastasis and reported by the authors varied widely from article to article. Articles published in the ophthalmic literature were more likely to contain information about the original intraocular tumor prior to development and detection of metastatic disease and less likely to contain detailed information about metastatic tumor burden, systemic symptoms, systemic performance status, and biochemical abnormalities revealed by blood testing than were articles published in general medical-surgical or oncologic journals. For example, the article reporting the largest series of unselected patients (n = 739 from the Collaborative Ocular Melanoma Study[1]) contains no information about systemic performance scores of affected patients, no mention of number or size of metastatic tumors detected on imaging studies performed at the time of cancer staging evaluation, no report of percentage hepatic replacement by tumor, and no data on levels of liver enzymes or total bilirubin. In contrast, an article reporting a relatively small series of selected patients (n = 26 patients from Helsinki University)[59] contains virtually no information about the primary uveal tumors but presents detailed summary data on systemic performance (Karnofsky) scores, largest linear dimension of the largest detected metastatic tumor, and serum level of alkaline phosphatase in the study patients.

TREATMENTS PROVIDED FOR METASTATIC UVEAL MELANOMA

First-line treatment provided for metastatic uveal melanoma varied considerably depending on the category of article and type of subgroup. The most commonly reported initial treatments in the unselected patient groups were supportive care without any specific antitumor therapy, intravenous chemotherapy (all regimens characteristically lumped together), and palliative radiation therapy to symptomatic metastatic foci. In contrast, the most commonly reported initial treatments for metastasis in the case reports and selected patients groups were surgical metastectomy, various specific regimens of intravenous chemotherapy without or with supplemental immunotherapy or biotherapy, and various techniques and regimens of hepatic artery infusion chemotherapy without or with embolization.

SURVIVAL FOLLOWING DETECTION OF METASTATIC UVEAL MELANOMA

Patients in the reported groups differed substantially in median survival time following diagnosis of metastatic disease (Tables 1 and 2). The median survival times reported for the two largest unselected groups of patients in the evaluated articles were 3.6 and 3.7 months.[1,47] All of the smaller unselected groups had a median survival time longer than these values (Table 1). In fact, one of these groups had a median survival time >12 months.[49] Review of these articles shows that most of the unselected groups that had unexpectedly long median survival times had a substantially larger proportion of the patients whose metastatic disease was identified at an asymptomatic stage by surveillance testing than that reported in the largest unselected groups. In contrast, the median survival times for patients in the selected patient subgroups (Table 2) were all longer than the 3.6 to 3.7 months reported in the largest of the unselected case series. Twelve of these articles reported median survival times >12 months, and 4 of them reported median survival times >18 months.

TABLE 1. MEDIAN SURVIVAL TIMES IN REPORTED UNSELECTED CASE SERIES OF METASTATIC UVEAL MELANOMA, LISTED IN ASCENDING ORDER

SOURCE (SIZE OF REPORTED STUDY GROUP)	MEDIAN SURVIVAL (MONTHS)
Diener-West,[1] COMS, 2005 (n = 739)	3.6
Gragoudas,[47] Harvard, 1991 (n = 145)	3.7
Bedikian,[41] M.D. Anderson Hospital, 1981 (n = 73)	7.0
Rajpal,[42] Roswell Park Memorial Institute, 1983 (n = 35)	8.3
Eskelin,[44] Helsinki University, 2003 (n = 91)	8.4
Kath,[38] Universität Essen, 1993 (n = 24)	9.0
Hsueh,[48] John Wayne Cancer Center, 2004 (n = 112)	11.0
Rietschel,[49] Memorial Sloan-Kettering, 2005 (n = 119)	12.5

COMS, Collaborative Ocular Melanoma Study.

PROGNOSTIC FACTORS FOR SURVIVAL TIME AFTER DETECTION OF METASTASIS

Different investigators evaluating different groups of patients with metastatic uveal melanoma have identified a substantial number of potential prognostic factors for survival time after detection of that metastasis. The factors that have been identified as prognostic for survival time by more than one group include patient age (older age unfavorable), patient gender (male sex unfavorable), symptoms attributable to tumor (asymptomatic favorable, symptomatic unfavorable), systemic performance score (worse score unfavorable),

detection category of metastasis (detection by surveillance testing favorable, detection by symptom prompted testing unfavorable), metastasis-free interval (shorter interval unfavorable), anatomic sites involved by metastasis (isolated extrahepatic involvement favorable, hepatic involvement unfavorable), number of anatomic sites involved by metastasis (larger number of metastatic sites unfavorable), percentage of liver replaced by metastatic tumor (larger percentage unfavorable), largest linear dimension of largest detected metastatic tumor on baseline imaging studies (larger size unfavorable), level of liver enzymes in blood (best expressed as a fraction of the upper level of normal for the specific enzymes in the laboratory where testing was performed; higher levels unfavorable), and level of total bilirubin in the serum blood (also best expressed as a fraction of the upper level of normal in the laboratory where testing was performed; higher level unfavorable). In addition, in patients subjected to intensive chemotherapy without or with immunotherapy or to hepatic artery infusion chemotherapy, local tumor response to treatment (classified as complete regression, partial regression, no change, or progression; progression unfavorable) has been associated with longer survival time by many groups. Finally, in patients subjected to metastectomy, completeness of resection (incomplete resection unfavorable) has also been associated with longer posttreatment survival. As surprising as it may seem, none of the articles reviewed in this study reported any evaluation of pathologic features of the metastatic tumors or cytogenetic/molecular biologic features of the metastatic tumors as potential prognostic factors for survival time.

TABLE 2. MEDIAN SURVIVAL TIMES IN REPORTED SELECTED CASE SERIES OF METASTATIC UVEAL MELANOMA, LISTED IN ASCENDING ORDER AND SEPARATELY FOR RETROSPECTIVE AND PROSPECTIVE CASE SERIES*

SOURCE (SIZE OF REPORTED GROUP)	TREATMENT	MEDIAN SURVIVAL (MONTHS)
Retrospective case series		
Flaherty[43] (n = 64)	IV chemotherapy	5.2
Bedikian[2] (n = 201)	Subgroup dependent options	7.0
Pawlik[39] (n = 16)	Hepatic metastectomy	8.8
Kodjikian[45] (n = 63)†	Subgroup dependent options	15.0
Rivoire[46] (n = 63)†	Subgroup dependent options	15.0
Siegel[40] (n = 18)	HAI chemotherapy	22.0
Aoyama[4] (n = 12)	Metastectomy	27.0
Prospective case series		
Patel[69] (n = 24)	HA chemoembolization	5.2
O'Neill[72] (n = 15)	IV chemotherapy	7.5
Schmittel[70] (n = 19)	IV chemotherapy	7.7
Schmittel[71] (n = 33)	IV chemotherapy	7.7
Salmon[56] (n = 75)	Metastectomy + HAI chemo	9.0
Noter[60] (n = 8)	HAI chemotherapy	9.9
Kivelä[59] (n = 24)	IV chemotherapy + interferon	10.6
Mavligit[54] (n = 30)	HA chemoembolization	11.0
Alexander[57] (n = 22)	HAI chemotherapy ± immunotherapy	11.0
Pyrhönen[66] (n = 48)	IV chemotherapy + interferon	12.0
Alexander[57] (n = 29)	HAI chemotherapy + hyperthermia	12.1
Becker[64] (n = 48)	Subgroup dependent options	13.3
Leyvraz[55] (n = 31)	HAI chemotherapy	14.0
Peters[73] (n = 101)	HAI chemotherapy	15.0
Cantore[62] (n = 8)	HAI chemotherapy	15.0
Pföhler[67] (n = 13)	IV chemotherapy	15.3
Vogl[51] (n = 12)	HA chemoembolization	21.0
Egerer[5] (n = 10)	HAI chemotherapy	24.0

HA, hepatic artery; HAI, hepatic artery infusion; IV, intravenous.
*Only articles that reported median overall survival after detection of metastasis are listed.
†The groups described in these concurrent publications from the same center appear to be identical.

COMPARISON OF CONTROL SUBGROUPS

Virtually all of the groups of authors mentioned the expected survival of an unselected historical group of patients with metastatic uveal melanoma either in their "Introduction" or "Discussion." However, none of the groups attempted to perform any formal retrospective comparison of survival in their treatment group or subgroups with that of any historical group. One group reported on comparative survival in randomly assigned but highly selected subgroups treated by different intravenous chemotherapy regimens in a small phase II randomized clinical trial.[74] No group compared survival of their study patients with that of similar patients who were left completely untreated. Many of the authors of the articles reviewed in this study reported that selected subgroups of their patients were subjected to different treatments in their centers. One group of investigators employed statistical adjustment in an attempt to adjust for recognized differences in selected baseline variables between treatment subgroups[48]; however, these authors adjusted for only a few of the recognized prognostic factors listed above. Consequently, the effectiveness of this statistical manipulation of the data cannot be determined.

DISCUSSION

To estimate the unbiased impact of any method of treatment on survival in metastatic uveal melanoma, investigators must either compare the survival experience of subgroups of patients identified by randomization in a prospective phase III clinical trial or, for retrospective comparisons, know all of the important prognostic variables for survival time in the patients who were allocated to particular treatments selectively, have evaluated all of these prognostic factors by equivalent methods prior to treatment in all of the patients, exclude patients from each treatment group who would not have been eligible for both treatments, and perform multivariate statistical adjustment to minimize the impacts of residual intergroup differences in those prognostic factors uncovered during survival data analysis.[75] On the basis of this analysis of the published literature on treatment of metastatic uveal melanoma, there is no evidence than any group of investigators has done so to date. Consequently, one must conclude that current evidence is insufficient to justify claims that certain aggressive interventions for metastatic uveal melanoma provide any clinically important or statistically significant prolongation of overall survival compared with no treatment at all.

Many of the selection factors employed by investigators in prospective clinical trials of treatments for metastatic uveal melanoma are strongly associated with death from causes other than metastatic uveal melanoma (eg, patient age, cardiac status, intercurrent systemic disease status), unlikelihood of return for regular posttreatment follow-up, or expected inability to tolerate or understand the proposed investigational treatment. Others (eg, hepatic arterial vasculature) pertain to patient suitability for very specific aspects of certain treatments. However, many of these factors are also prognostic for survival time following detection of that metastasis. Although median survival time following diagnosis of metastatic uveal melanoma tends to be substantially longer in selected subgroups of patients subjected to aggressive invasive interventions than it is in unselected groups, and although this difference is frequently considered to be evidence of treatment-induced prolongation of patient survival, much if not most of this apparent difference in survival is likely to be attributable to selection bias rather than treatment-induced alteration of the expected outcome.[76]

Multiple groups have demonstrated that periodic systemic surveillance testing for metastatic disease in patients who have undergone definitive local treatment for their primary uveal melanoma tends to detect metastasis when it is much more limited in extent (eg, fewer anatomic sites involved, fewer discrete measurable metastatic tumors, less extensive hepatic replacement, more normal levels of serum liver enzymes and bilirubin) than does symptom-prompted patient evaluation. Even though surveillance testing does not bias a group in the same way that use of selection criteria does, it clearly identifies a subgroup of patients that is expected to have longer median survival time after detection of the metastatic disease than a subgroup identified by symptom-induced evaluation. This type of bias (usually referred to as either surveillance bias or lead time bias)[76] is likely to explain at least some of the differences in median survival times reported for the unselected patient subgroups in the evaluated articles (Table 1).

A single patient or small group of patients with a certain condition that experiences a surprisingly good response to a particular treatment is much more likely to be reported in the peer-reviewed literature than a similar patient or small group that fared poorly after the same treatment.[77] For example, a patient with a symptomatic isolated brain metastasis from primary uveal melanoma who undergoes craniotomy with successful complete excision of that tumor, has an uneventful postoperative recovery, experiences full recovery from the symptoms that led to detection of the brain metastasis, and lives for a relatively long time following that treatment[33] is much more likely to be reported than a similar patient whose attempted surgical resection was incomplete or complicated such that survival time was shortened substantially rather than prolonged. This type of publication bias is most evident in case reports but is also a problem with descriptive case series reports, especially ones that are small, retrospective, or both.[77]

Many if not most patients who have tolerated their treatment well and experienced relatively long survival after treatment and many medical and surgical oncologists who have managed such patients are likely to object to the implications of our current study. These individuals are likely to point out the several positive impacts the various treatments can have, including reduction of tumor burden (which is provided by successful instances of metastectomy and surgical debulking of metastatic tumors, and some instances of hepatic artery infusion chemotherapy [especially when coupled with embolization] or intravenous chemotherapy without or with supplemental immunotherapy) and elimination of certain symptoms attributable to metastatic disease (eg, seizure disorder attributable to brain tumor). While we concede these positive impacts of treatment, we also recognize some negative impacts related to such aggressive therapeutic interventions, including an increased cost of care and at least occasional instances of treatment-induced symptoms, morbidities, and death.[56,57] We also recognize that the majority of patients who appear to benefit the most in terms of

length of survival after treatment are also persons who reported few if any symptoms attributable to their metastasis when treatment for that condition was provided.

CONCLUSION

The quality of evidence about effectiveness of treatments for metastatic uveal melanoma appears to be very limited. No randomized phase III clinical trials of any alternative treatments or of a treatment vs no treatment have yet been reported. Similarly, no nonrandomized prospective clinical trials that provide statistical adjustment for all recognized prognostic factors for survival time between treatment subgroups have been reported. Currently available evidence from published peer-reviewed articles does not provide scientifically compelling evidence that aggressive treatments for metastatic uveal melanoma prolong overall survival.

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PEER DISCUSSION

DR. DEVRON H. CHAR**:** I have always admired the terse eloquence of Dr. Augsburger's presentations. I whole-heartedly agree with him that in this setting "the emperor has no new clothes". As he has nicely demonstrated, while less than 5% of metastatic uveal melanoma patients with either an isolated focal hepatic metastasis or those with relatively focal subcutaneous metastasis do better,

there is little evidence, from an excellent meta-analysis, that treatment for the vast majority of metastatic uveal melanoma patients either prolongs life or improves their quality of survival.[1]

Where do we go from this data? Several issues are worth discussing. We are now able to precisely delineate the sub-population of primary uveal melanoma patients who are at high-risk for developing metastatic disease at the time of initial eye tumor diagnosis. In the 1980s my group and I demonstrated that fine needle biopsy could be used to accurately predict prognosis in eyes prior to radiation. Cell type was an independent risk factor for tumor-related mortality. In the early 1990s we showed that CGH (comparative genomic hybridization) could be used to delineate loss of chromosome 3.[2,3] We showed this technique could be used on fine needle biopsies but it did not give significant insight into novel therapeutic approaches, since loss of a chromosome does not detail the up or down regulation of individual melanoma genes.

Dr. Harbour, his group and I demonstrated on fine-needle biopsy specimens of the primary uveal melanomas that gene expression profiles can differentiate class I patients, who are at low risk for metastases, from class II patients who are at very high risk for metastatic disease. This gene profile technique is far more accurate prognostically than analysis for monosomy of chromosome 3.4,5

How does this type of data help in managing uveal melanoma patients with metastatic disease? There are at least three parameters that are important to emphasize. One, up- and down-regulation of genes and their products in high risk as compared to low risk uveal melanoma is interesting. These data demonstrate both potentially useful as well as poor therapeutic targets. Unfortunately, some historic assumptions in the choices of metastatic melanoma therapies, while based on reasonable assumptions, are negated on the basis of gene studies. As an example, melanocytic as compared to epithelial parameters are down regulated in class II poor prognosis tumors, and yet, some of the biotherapies have been based partially on the expression of those gene products.

We can delineate patients who are high-risk and have minimal evidence of metastatic disease. The FNAB data from intraocular high metastatic risk melanomas can be used to optimize treatment strategies, based on up regulated or altered gene products over-expressed in high-risk uveal melanomas.

We are currently initiating a phase II study in high-risk uveal melanomas with adjective therapy. The question asked is whether this approach will decrease tumor related mortality in these patients.

I would like to thank Dr. Augsburger and his colleagues for an eloquent paper that delineates a major problem that we have not come to adequate resolution, namely how do we manage patients with metastatic melanoma? My belief is that trying to approach the high-risk group with earlier intervention on the basis of data we are now learning from gene studies may allow us to improve on this dismal prognosis.

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DR. EVANGELOS J. GRAGOUDAS: I have no financial conflict of interest. This is an important paper. I would like to emphasize that to the AOS membership because, aside from the fact that all the treatments for metastatic melanoma are ineffective, we spend a tremendous amount of time and expense in surveillance of these patients. Recently we looked at our data and divided patients into two groups, those with early detection and those with late detection of metastasis. The early detection group included patients who were found to have metastasis after evaluating liver enzymes, and the late detection group included those in whom symptoms were present. If you look at the difference in survival between the two groups, although there was a slight increase in survival in patients after early detection of metastasis, the survival time from the diagnosis of the tumor to death was not different in the two groups. This is an obvious lead time bias, where the apparent benefit of detecting the metastasis early is due to the fact that these patients are diagnosed earlier. They often go through toxic chemotherapy without having any increase in survival, whatsoever. Also, to emphasize that our data corroborates Dr. Augsburger's findings, we found that patients who had treatment in the 1980s for metastatic melanoma, and those who underwent treatment in the 1990s were no different in terms of survival. It seems that surveillance provides no additional benefit to the patient, but I think it should be done sporadically to keep up with the developments that Dr. Char mentioned. In all probability we are going to have better drugs in the near future. Presently, the majority of experimental protocols that treat metastatic melanoma are for skin metastatic melanoma, and exclude ocular melanoma, because the prognosis is very poor. Thank you.

DR. HANS E. GROSSNIKLAUS: I have no commercial conflicts of interest; I am funded by the NIH to study control of eye melanoma metastasis.

I wish to thank Dr. Augsburger for his excellent presentation, and I echo the comments of Dr. Char and Gragoudas. I think that in order to tackle this important problem, we need to understand the biology of the disease and the biology of how uveal melanoma metastasizes to the liver. We are starting to understand that. We know there is a preponderance of evidence that shows that the melanoma forms dormant micro metastasis, and that these micro metastases may emerge from dormancy based on changes in the host immune response and in intrinsic properties of the tumor itself. I believe these treatment protocols, many of which have been based on the treatment of cutaneous melanomas, are established without understanding or specific attention to the biology of uveal melanoma. Bill Harbour has contributed to understanding the biology of the tumor and I am very hopeful that in the future, as we understand which genes are expressed and can have targeted treatments, we will be able to improve the survival of this group of patients. My question to Dr. Augsburger relates to how many of these protocols that you reviewed were based on cutaneous melanomas. Were any specifically designed to treat uveal melanoma? Thank you.

DR. BRADLEY R. STRAATSMA: I have no conflict of interest. I would simply like to make a tangential comment. We need to think of the patient. We have been studying our patient group with some very precise psychological techniques, combining health psychology with ocular oncology. The important thing to keep in mind is that our studies showed that 90% of the patients with melanoma in the eye want to know their prognosis, even if it is good or bad. We need to think in all of this, not only about the tumor, but about the patient.

DR. THOMAS J. LIESEGANG: No financial conflicts. Since Dr. Augsburger introduced the concept, I would like to comment about publication bias. Bias in publication has many different forms, but if you just divide it into two types. The first type of bias that most people believe is that editorial boards do not accept negative reports or inconsequential reports, and the second type relates to what authors chose to submit to journals. If you look at what has been approved by IRBs and what actually gets submitted for publication, by far the greatest publication bias is in failure of authors to submit their research for peer review. It is not editorial boards that cause the most bias; it is mainly that authors' failure to submit. The danger in this submission bias is that it makes the work that is published in the peer reviewed literature what Rennie Drummond calls "happy talk". The literature by and large has positive studies and is happy talk. If one performs a meta-analysis of this happy talk, you have even more happy talk. The complaint or question that Dr. Augsburger raised is very valid, i.e. a lot of the research that has been funded and IRB approved is not even being submitted for peer review. There are multiple reasons for that, but failure to submit is a prime factor to explain why research does not reach the literature. The impression that editorial boards are not interested in negative studies or inconsequential studies is much less important.

DR. JAMES J. AUGSBURGER: I thank all of the discussants for their pertinent remarks. I particularly thank Dr. Char for his supportive comments about our paper and his relevant discussion of the probable future role of cytogenetic studies and gene expression profiling of uveal melanoma cells obtained by fine needle aspiration biopsy (FNAB) at the time of initial detection or treatment of the intraocular tumor. If clinical differentiation between patients who will and will not develop metastasis can be made reliably by FNAB, then the subgroup destined to develop metastasis will be an appropriate target group for future well designed clinical trials of adjuvant therapies to prevent or delay emergence of that metastasis.

Dr. Gragoudas emphasized the related topic of surveillance testing for metastasis following treatment of primary uveal melanomas that is intended to be curative. Although this was not the topic of our paper, my coauthors and I agree completely with Dr. Gragoudas' assertion that surveillance testing also has no scientifically confirmed beneficial impact on survival. Clinicians who recommend regular periodic surveillance evaluations for metastasis appear to be subjecting their patients to substantial cost without any documented corresponding survival benefit.

Dr. Straatsma indicated that many patients desire to know their survival prognosis. Unfortunately, conventional prognostic factors for metastasis and death in patients with primary uveal melanoma, including size of the primary intraocular tumor, intraocular location of the primary tumor, patient age, and histopathologically assigned melanoma cell type, have not proven to be reliable indicators of survival prognosis. However, as Dr. Char indicated, we are optimistic that newer methods such as gene expression profiling of tumor cells will improve our predictive capability substantially. Prospective studies currently underway will hopefully confirm the prognostic reliability of predictions of metastasis and allow us to inform our future patients with uveal melanoma accordingly.

Dr. Grossniklaus commented on the complex sequence of biologic events that must occur to result in metastasis from primary uveal melanoma. Our understanding of this sequence has improved greatly in recent years as a result of the innovative work that Dr. Harbour and many other investigators have performed and reported. Dr. Grossniklaus asked whether any of the articles we reviewed for our paper reported therapeutic protocols designed specifically to treat uveal melanomas. The answer to this question is "No".

Dr. Liesegang echoed our assertion that publication bias is an important consideration when published articles on treatment for metastatic uveal melanoma are evaluated. For the reasons he mentioned, the precise magnitude of this type of bias is impossible to determine.

In conclusion, our study indicated that the evidence of a beneficial impact of currently available treatments for metastatic uveal melanoma on survival is of extremely low quality. In the absence of compelling scientific evidence of substantial clinical benefit of aggressive medical and surgical interventions in such patients, ophthalmologists should insist that our medical and surgical oncology colleagues who advise and perform such interventions design and conduct appropriately controlled clinical studies that will either prove the purported survival benefit or show that one does not exist. Thank you.