Uveal Melanoma in Israel in the Last Two Decades: Characterization, Treatment and Prognosis

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ABSTRACT: **Background:** Uveal melanoma is the most common primary intraocular tumor in adults. In the last two decades the Hadassah-Hebrew University Medical Center ocular oncology clinic has become a referral center for uveal melanoma patients.
Objectives: To describe the characteristics of uveal melanoma patients in Israel, their treatment modalities and outcomes during the years 1988–2007.
Methods: Data were collected from the files of uveal melanoma patients in the departments of ophthalmology and oncology in our facility. Statistical analysis was performed using JMP statistical software.
Results: Data were available for 558 patients. The annual incidence of uveal melanoma in the last 5 years was 47.2 ± 7.1 new cases per year (mean ± standard error). There were 309 women (55.4%). The age at diagnosis was 60.8 ± 16.5 years (range 5–95). Overall, 6.6%, 16.8% and 86.9% involved the iris, ciliary-body and choroid, respectively. Tumors were classified as small, medium and large (9.0%, 64.5% and 17.9%, respectively) according to the COMS grouping criteria. The most common primary treatment was brachytherapy (74%), followed by enucleation (17.9%). Local recurrence was noted in 11.1% of patients, while metastases developed in 13.3%. The 5, 10 and 15 year melanoma-related mortality rate was 11.4%, 17.0% and 23.3%, respectively. Of the overall study population 9.3% died of metastatic uveal melanoma.
Conclusions: Uveal melanoma patients in Israel have tumors with characteristics similar to those in other countries. Brachytherapy is the predominant treatment, the local recurrence rate is low, and survival is comparable to that reported in the medical literature.

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KEY WORDS: uveal melanoma, metastases, survival, epidemiology

Uveal melanoma is the most common primary intraocular tumor in adults [1], with a reported annual incidence per million of 6.37 among Caucasians, 0.91 among Hispanics and 0.24 among Blacks [2]. It is a highly malignant neoplasm that threatens the patient with metastatic death, loss of the eye, and irreversible visual deficit. Patients may be diagnosed after developing symptoms of blurred vision, a shadow obscuring part of the visual field during a routine eye examination, or while under follow-up for various eye diseases, or in routine examination. Not all patients experience symptoms that lead to examination and diagnosis. For example, only 55% of the patients in a study in Britain presented with symptoms. Most of the symptomatic patients were men (65%), who also happened to have larger tumors at the time of diagnosis than the tumors diagnosed in women in this study group [3].

In 1978, Zimmerman et al. [4] published their hypothesis that enucleations were responsible for disseminating uveal melanoma leading to metastases. This claim urged ophthalmologists not only to revise the enucleation technique but also to reevaluate other treatment modalities, such as local irradiation (brachytherapy) and external irradiation (proton beam). The Collaborative Ocular Melanoma Study was designed to test whether brachytherapy has comparable results with "safe" enucleations even though the tumor is left inside the body. The result was unequivocal: patients who underwent either enucleation or brachytherapy had the same survival rates and the same risk for metastatic disease [5]. Still, brachytherapy has a better cosmetic result and may even save vision. These results as well as those of other studies that advanced our knowledge of factors influencing the survival of uveal melanoma patients [5-7] changed the treatment protocols for this tumor. The role of enucleation has diminished significantly in favor of brachytherapy and other eye-preserving methods over the last two decades.

Tumors respond to brachytherapy with a reduction in the tumor's height at an initial rate of approximately 3% per month, with stabilization on average of 61% of the initial height after approximately 18–24 months. Larger tumors (height > 8 mm) have a faster initial decrease in height and stabilize at a lower percentage of their initial height (50%) compared with smaller tumors (70%) [8].

Patients are at risk to develop metastases up to 20 years after the initial diagnosis [5,9]. The most common site for metastatic uveal melanoma is the liver [10]. The COMS identified 5 and 10 year cumulative metastasis rates of 25% and 34% respectively, with 80% of the metastatic patients dying within one year and 92% within 2 years after the diagnosis of metastases [10]. The fact that even an enucleated patient may develop metastases years after the treatment led to the speculation that micro-metastases had already been seeded at the time of diagnosis [11,12], Later, factors that are yet unknown factors

COMS = Collaborative Ocular Melanoma Study

release them from "hibernation" and cause metastatic disease and death. Thus, all patients should be followed throughout life; new methods are being developed in an attempt to detect the metastases as early as possible and to offer treatment aimed at prolonging the survival of patients with metastases [13,14].

The average annual incidence of uveal melanoma in Israel was calculated to be 5.7 per million for the period until 1989 [15]. Shargal and Pe'er [16] reported on the clinical characteristics of uveal melanoma patients treated prior to 1989 and compared the survival of different treatment groups [16]. The aim of the present study is to assess how the above-mentioned changes in treatment modalities affected the course of uveal melanoma patients in Israel. We describe the characteristics of uveal melanoma patients in one referral center in Israel, their tumors, treatment modalities and outcomes.

PATIENTS AND METHODS

All patients with a diagnosis of uveal melanoma who were followed at the ocular oncology clinic of the Hadassah-Hebrew University Medical Center from 1 January 1988 to 1 January 2008 were included in this study. Patients were excluded only if there were no data available.

Patients were diagnosed, treated and followed every 6 months. The systemic evaluation included abdominal ultrasonography and liver function tests (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transpeptidase, and lactate dehydrogenase). An upward trend in the liver function tests, even without exceeding the normal values [8], or suspicious lesions in the abdominal ultrasound were verified by computed tomography of the abdomen. When the combination of FDG-PET (fluorine-18 fluordeoxyglucose positron emission tomography) with CT became available in 2004 we added PET-CT to the evaluation of suspicious liver lesions. A chest radiograph was performed only at the time of diagnosis of uveal melanoma.

We collected the following information from the patients' medical records: demographic details, age at diagnosis, laterality of ocular involvement, intraocular location of the tumor, status of the extra-ocular disease, treatments for the ocular disease, time to metastasis, length of follow-up, and cause of death if applicable.

Tumors were classified according to the size of the largest basal diameter (LBD) and the maximal tumor's height (H), based on the COMS criteria for grouping tumors into medium and large tumors (medium: 2.5 < H ≤ 10 mm and LBD < 16 mm; large: H > 10 mm or LBD > 16 mm) [17,18]. Thus, tumors with LBD ≤ 10 mm were considered small, 10 < LBD ≤ 16 mm were considered of medium size, and > 16 mm were considered large. Tumors with H ≤ 2.5 mm were considered small, 2.5 < H ≤ 10 mm were considered of medium size, and > 10 mm were considered large.

Statistical analysis (Kaplan-Meier survival curves and analysis of variance) was performed using JMP Statistical Discovery Software 5.0 (SAS Institute, Cary, NC, USA). Patients who failed to attend follow-up in the last 12 months, and were not known to have died, were excluded from the survival analyses.

PET = positron emission tomography
LBD = largest basal diameter

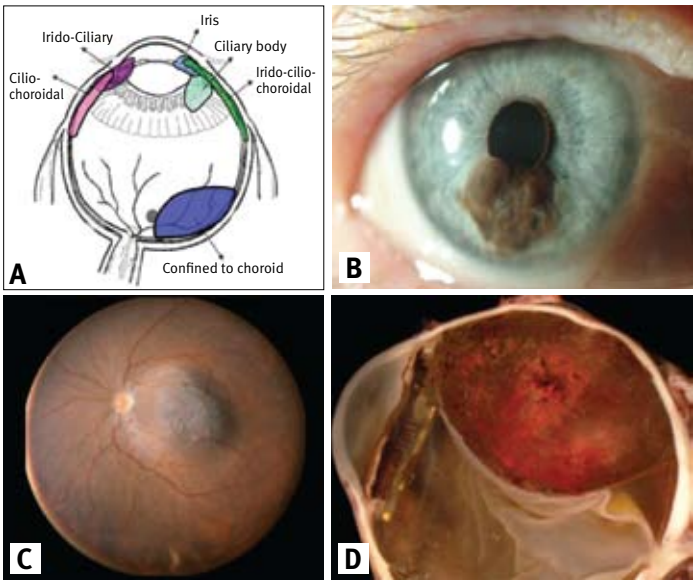
RESULTS

For the period 1 January 1988 to 1 January 2008, data were available for 558 uveal melanoma patients. There were 309 women (55.4%) and 249 men (44.6%). The mean age at diagnosis (± standard deviation) was 60.8 ± 16.5 years (range 5–95 years). Based on the population size in Israel, as published by the Central Bureau of Statistics, the mean yearly incidence in the past 5 years was 47.2 ± 7.1 new cases per year (mean ± standard error) (6.7/1,000,000/ year).

INTRAOCULAR LOCATION OF THE TUMORS

The intraocular location of the tumor, based on biomicroscopy, fundoscopy and ultrasonography, was noted in the following distinct areas of the eye: iris, ciliary body and choroid. The choroid location was further classified as anterior to equator, equator, posterior to equator, posterior pole, and juxtapapillary [Figure 1]. The probability of a tumor being

Figure 1. [A] Illustration of the discrete anatomic locations at which tumors can be found. **[B-C]** Clinical pictures of uveal melanoma: **[B]** slit-lamp picture of an iris melanoma, **[C]** Panoret (Medibel, Yokneam, Israel) fundus photo of a choroidal melanoma, **[D]** gross picture of a pupil-optic nerve section of a cilio-choroidal melanoma in an enucleated eye.



in a discrete anatomic location and the probability of the actual combinations of these locations are given in Table 1. Overall, 6.6% of the tumors involved the iris, 16.8% involved the ciliary body and 86.9% the choroid.

INITIAL TUMOR SIZE

When grouped by height, 10.9% of the tumors were small, 74.9% were medium and 14.2% were large. When grouped according to LBD, 39.2% were small, 49.9% were medium and 10.9% were large [Table 2]. Using the COMS criteria for grouping tumors by size, which combine LBD and height, 9.0% of the tumors in our study were small, 64.5% were medium and 17.9% were large. No size measurements were available for 8.6% of our patients. There was no significant difference in the initial tumor size between men and women (Pearson $\chi^2 = 1.938$, $P = 0.3795$).

INITIAL TREATMENT

Brachytherapy was the most prevalent initial treatment (74.0%), followed by enucleation (17.9%), local resection (2.5%) and proton beam irradiation (1.1%). Twenty-five patients (4.5%) were followed for small tumors (initial tumor height 2.7 ± 1.9 mm, mean ± SD) and did not receive treatment during the time of the study (median follow-up time 70.4 months, range 1.3–204.9 months). Ruthenium (Ru-106) was used for the brachytherapy in 98.5% of the patients. Four patients were treated elsewhere with iodine (I-125), one with palladium (Pd-103), and one with strontium (Sr-90). One of the patients undergoing brachytherapy was treated with a radioactive plaque immediately after a wall resection of the tumor. When treating the tumor with brachytherapy, we aim for 10,000 cGy to the tumor's apex. We limit the dose to the base of the tumor to 100,000 cGy to prevent scleral melting. For extra-large tumors (LBD > 20 mm or height > 10 mm) we recommended enucleation. In 58 of the brachytherapy-treated patients (14.0%) the tumor responded to the treatment, as measured by a reduction in tumor size, but later recurred. Thirty-three of these patients were retreated with brachytherapy. In all of them the tumor responded to the additional treatment, but seven patients had a second relapse with an increase in tumor size and the eye was then enucleated. In 24 patients additional irradiation could not be added because the tumor recurred in a diffuse pattern, was too large for a radioactive plaque, or was at risk for scleral melting (initial irradiation dose to the base 100,000 cGy). In these patients the eye was enucleated. In one patient the tumor re-grew around the optic nerve, and the patient was referred for proton beam irradiation. Among the 14 patients who underwent local resection, 3 underwent enucleation at a later date: 2 because of tumor growth and 1 because of a choroidal detachment that led to phthisis 4 months after a trans-scleral cyclochoroidectomy. The eye of one of the six patients who were initially treated with proton beam irradiation became blind and painful and was enucleated.

The tumor height and largest basal diameter for patients who underwent brachytherapy was 5.2 ± 2.3 mm (mean ± SD), 4.7 mm (median) and 1.0–11.8 mm (range) for height, and 10.9 ± 3.3 (mean ± SD), 13.1 (median) and 1.6–20.2 mm (range) for largest basal diameter. The same parameters for tumors that were initially treated by enucleation were 10.2 ± 4.4 mm, 11.5 mm, and 2.3–19.4 mm for height, and 13.8 ± 6.2, 15.0, and 3.1–29.2 mm for largest basal diameter. The smallest enucleated tumor occurred in a 5.5 year old child with an expanding diffuse iris melanoma that involved the angle. Tumors that were treated by enucleation were significantly higher and wider than those treated with brachytherapy (*t*-test: $P < 0.0001$, $r^2 = 0.31$, and $P < 0.0001$, $r^2 = 0.06$, respectively).

RECURRENCE RATE

Sixty-two patients (11.1%) had recurrence, indicated by an increase in tumor size after an initial response to the treatment by a measurable size reduction of the tumor, or appearance of tumor tissue after a previous resection (58

Table 1. Probability of a tumor to be in a discrete anatomic location

Intraocular location	Prevalence
Iris	**6.6%**
Confined to iris	2.0%
Irido-ciliary	2.5%
Irido-cilio-choroidal	2.2%
Ciliary body	**16.8%**
Confined to ciliary body	1.4%
Irido-ciliary	2.5%
Irido-cilio-choroidal	2.2%
Cilio-choroidal	10.8%
Choroid	**86.9%**
Irido-cilio-choroidal	2.2%
Cilio-choroidal	10.8%
Confined to choroid	74.0%
Unknown (presumed choroid)	**7.2%**

Table 2. Tumors divided according to their size at the time of diagnosis, as measured by ultrasound

	Small	Medium	Large
Largest basal diameter	LBD ≤ 10 39.2%	10 < LBD ≤ 16 49.9%	16 < LBD 10.9%
Height	H ≤ 2.5 10.9%	2.5 < H ≤ 10 74.9%	10 < H 14.2%

LBD = largest basal diameter, H = height

after brachytherapy, 2 after enucleation and 2 after a local resection). Recurrence occurred after a median time of 26.2 months (95% confidence interval 20.8–33.0 months). The cumulative recurrence rate was 2.2% at 1 year, 8.8% at 5 years, and 11.1% at 10 years after the treatment. At the initial diagnosis, the tumor height and largest basal diameter for the recurring tumors were: 5.9 ± 2.6 mm (mean ± SD), 5.5 mm (median), and 1.4–11.0 mm (range) for height, and 11.8 ± 4.3, 15.1, and 5.3–19.1 mm for largest basal diameter. These measurements were no different from tumors that did not recur ($P = 0.7528$ for height and $P = 0.2175$ for LBD). Only 5% of the recurring tumors were in the group with the greatest height, but 20% were in the group with the widest LBD. Of all the large tumors 4.1% of the high tumors recurred and 19.6% of the wide tumors (large LBD) recurred.

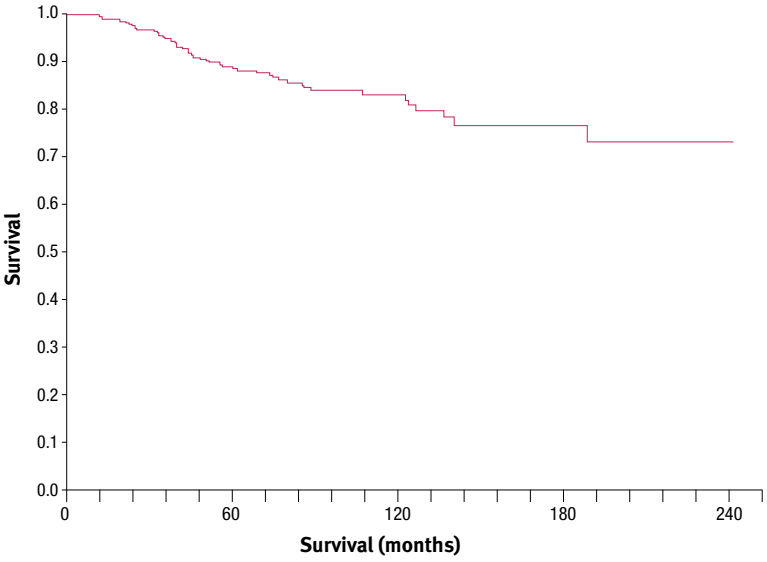
METASTASES

Seventy-four patients (13.3%) developed metastatic disease after a median time of 35.0 months (95% CI 26.0–44.9 months). Metastases developed in 37 men and 37 women. Men developed metastases closer to the initial diagnosis than women, but the time difference was statistically insignificant (median time to metastases 29.2 months, 95% CI 17.6–35.0 for men vs. 43.8 months, 28.4–63.3 for women; Wilcoxon $\chi^2 = 2.5065$, $P = 0.1134$). Tumors confined to the iris did not metastasize. Tumors involving the ciliary body metastasized more than tumors in other locations (21.3% vs. 12.4%, respectively, Pearson $\chi^2 = 5.111$, $P = 0.0238$). Tumors with larger initial size tended to metastasize more than medium and small tumors (35.3% vs. 16.2% vs. 3.4%, respectively, Pearson $\chi^2 = 39.430$, $P < 0.0001$ for the LBD groups, and 23.3% vs. 13.3% vs. 2%, respectively, Pearson $\chi^2 = 12.623$, $P = 0.0018$ for the height groups). They also tended to present with metastatic disease sooner after the initial diagnosis (median time to metastases 46.2, 35 and 26 months for the small, medium and large LBD groups, respectively, Wilcoxon $\chi^2 = 5.3614$, $P = 0.0685$). Of the different primary treatments, tumors that were enucleated metastasized more than others (Pearson $\chi^2 = 10.045$, $P = 0.0015$).

SURVIVAL

The mean follow-up time was 66.6 ± 2.6 months (mean ± SE). Ninety-seven patients died of all causes in the study period. Fifty-two of them (53.6% of those who died, 9.3% of the overall study population, and 70.3% of the metastatic patients) died with metastatic disease. The 5, 10 and 15 year melanoma-related mortality rates were 11.4%, 17.0% and 23.3%, respectively [Figure 2]. At the end of the study period, there was no difference in the all-cause mortality rate between men and women (63.1% of the women had survived vs. 59.1% of the men, Wilcoxon $\chi^2 = 0.0168$, $P = 0.8037$). However, women had a smaller melanoma-related mortality rate than men (20.4% for the women vs. 34.1% for the men, Wilcoxon $\chi^2 = 5.5718$, $P = 0.0183$), and had a lower risk of dying of the metastases (risk ratio 0.76, CI 0.57–1.00). Women also tended to live longer from the time of diagnosis of metastatic disease (median metastatic survival 12.1 months, 95% CI 6.8–14.6 for men vs. 20.2 months, 95% CI 10.3–41.3 for women; Wilcoxon $\chi^2 = 2.6630$, $P = 0.1027$). Patients whose primary treatment was enucleation had a lower melanoma-related survival rate than patients who underwent brachytherapy (44.8% vs. 75.9%, Wilcoxon $\chi^2 = 21.6048$, $P < 0.0001$). Involvement of the ciliary body resulted in a statistically significant worse prognosis (57.7% vs. 75.2%, Wilcoxon $\chi^2 = 15.0760$, $P = 0.0001$). The median survival from the time of diagnosis of metastatic disease (metastatic survival) was 13.3 months (95% CI 11.5–23.7). Patients with a smaller tumor at diagnosis had higher 5 and 10 year melanoma-related survival rates: 5 years: 100.0%, 83.9% and 53.8% for the small, medium and large LBD groups, respectively (Wilcoxon $\chi^2 = 46.7771$, $P < 0.001$); 10 years: 97.1%, 71.6% and 53.8% for the small, medium and large LBD groups, respectively (Wilcoxon $\chi^2 = 45.1269$, $P < 0.0001$). However, when testing the metastatic survival, the initial tumor size did not affect survival significantly (Wilcoxon $\chi^2 = 1.6531$, $P = 0.1985$).

Figure 2. Kaplan-Meier survival analysis plot of the melanoma-related death rate from metastatic uveal melanoma



DISCUSSION

In the past two decades the ocular oncology clinic at the Hadassah-Hebrew University Medical Center has become a referral center for patients with a suspected diagnosis of uveal melanoma. Patients have been diagnosed, treated

and then followed bi-annually for life. Our study comprised uveal melanoma patients at this clinic for the past 20 years. Iscovich and colleagues [15] calculated its annual incidence in Israel until 1989 based on the National Cancer Registry. The annual incidence that was noted in the last 5 years in our clinic is slightly higher than that calculated until 1989 (6.7 vs. 5.7/1,000,000/year). This increase in incidence may be due to a true increase in the incidence of uveal melanoma in Israel but is most likely due to the fact that we now have a national referral center and more inclusive data.

The intraocular distribution of the tumors is more diverse than reported by Shields et al. [19], with more tumors involving the ciliary body and the iris in our study group. In the COMS histopathological report the number of tumors involving the iris was similar to that in our patient population, but twice the number of tumors involving the ciliary body (34.5%) [20].

In accordance with the worldwide trend towards eye-sparing treatments, the irradiation-to-enucleation ratio in Israel changed in the last 20 years from 43%:34% [16] to 74%:18%. Some peri-papillary tumors may be treated with a notched plaque, while others are referred for external beam irradiation (proton beam treatment). When enough irradiation can be delivered to the tumor's apex by the radioactive plaque, brachytherapy is the treatment of choice. However, when the tumor is too high, or when a large tumor is located in the ciliary body, where melting of the sclera is more common, enucleation is recommended. Another indication for enucleation is extraocular extension of the tumor. Obviously, the patient's wishes should be taken into account. Thus, a few patients requested to have their eye enucleated even when the tumor was treatable by brachytherapy, while others requested brachytherapy for high tumors even after receiving a thorough explanation that the tumor will not receive the full irradiation dose to the apex.

Local recurrence was identified in 11.1% of our patients. Half of the recurrences occurred within the first 2 years. There were no identifiable parameters in the initial diagnosis that could predict which tumor would recur. This proportion of treatment failure is within the range reported in the COMS report [21], where 10.3% of plaqued eyes (95% CI, 8.0–13.2%) were enucleated in the first 5 years due to treatment failure. Rouberol and co-authors [22] summarized their experience with Ru-106 plaques and found local recurrence in 16% of their patients after a median of 22 months. They attributed their higher than expected recurrence rate to poor patient selection. Damato et al. [23] reported that only 3% of their patients had local recurrence at 3 years, but they included only small- to medium-sized tumors in their study. The basal diameter of large tumors was found to be a poor prognostic factor for local recurrence [22], but it did not affect the local recurrence rate in our patients in a statistically significant manner. Shields and collaborators [24] analyzed the treatment results of brachytherapy for high tumors (> 8 mm) and found a higher recurrence rate (9%, 13% and 21%, at 5, 10 and 15 years, respectively). Our high-tumor group was defined as tumors thicker than 10 mm. Even if we include in this group patients whose tumor's height was 8–10 mm, only 14% of them had a recurrence at 10 years. This is in contrast with Shields' findings [24] that using a ruthenium plaque resulted in more recurrences than use of iodine, but only 18 of their patients were treated with ruthenium, which constituted only 5% of their patient population, whereas most of the patients were treated with iodine plaques. Although it seems from the comparison between Shields' study and ours that ruthenium plaques may yield a better outcome than iodine for patients with large tumors, only a comparative randomized study can resolve this question. Some of our patients with large tumors (height > 10 mm and a large base) requested to try brachytherapy before enucleation despite an explanation that brachytherapy could not treat their entire tumor mass. There was no increase in the metastatic rate or the melanoma-related death rate (data not shown), while almost half of the patients retained driving-vision (better than 6/12). These results may indicate that effective treatment of the base of the tumor can be as effective as irradiating the entire tumor in terms of the development of metastatic disease.

The metastatic rate found in this study group (13.3%) was lower than the 23% in 10 years found in the COMS [5]. We found a higher metastatic rate in patients whose primary treatment was enucleation. Several explanations can be proposed after ruling out seeding of the tumor at the time of enucleation, a hypothesis that was refuted by the COMS comparison of brachytherapy to enucleation [5]. First, enucleation was chosen as a primary treatment for larger tumors. Assuming a similar growth rate for tumors of different sizes, the larger tumors had more time to metastasize. If we assume different growth rates, then we must assume that the larger tumors are more aggressive, which may explain their higher tendency to metastasize. Second, larger tumors have access to more vessels in the uvea, which may facilitate their hematogenous spread. This hypothesis is supported by the COMS findings of larger basal diameter being a poor prognostic risk factor, and by our findings that a larger basal diameter was associated with an earlier metastatic disease and with a greater tendency to metastasize. Men and women had tumors of comparable sizes and intraocular distribution (data not shown). We did not find a correlation with other data to explain the trend of earlier appearance of metastases in men and their tendency to die sooner than women from metastatic disease. Not only were these trends statistically significant, but the risk ratio to die

of metastatic disease of the women (0.76) compared to the men resulted from a significant Cox proportional hazards calculation.

We found a low melanoma-related mortality rate and a long survival time. This study was not designed to identify prognostic factors; however, we did note a longer survival for smaller tumors. Despite the fact that tumors confined to the iris did not metastasize, there was only a trend for a better survival for these patients in the Kaplan-Meier analyses. We assume that the lack of statistical significance resulted from the small number (2.1%) of patients with isolated iris melanoma. Involvement of the ciliary body, which was identified as a poor prognostic factor [5], resulted in a statistically significant worse prognosis in our patients.

Further studies are being conducted on early detection of metastases and their treatment in an effort to extend patient survival. For this purpose we analyzed sera that were collected from patients at the time of diagnosis and at every follow-up visit, and we found that tumor markers (OPN, S-100β, MIA and TPS) have a 91% sensitivity to detect metastases [13,14] and can even detect metastatic disease before it can be detected by abdominal imaging or liver function tests [25]. We are currently testing patients' sera at every follow-up visit for a combination of tumor markers. The ideal tumor marker and the precise screening methodology are still under investigation.

In summary, patients with uveal melanoma treated in the last two decades at the Hadassah-Hebrew University Medical Center ocular oncology clinic have been treated mostly by ruthenium plaque brachytherapy. This treatment resulted in a low local recurrence rate, a low metastatic rate, and a long survival rate.

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"Learning without thought is labor lost; thought without learning is perilous"

Confucius (c. 551-478 BCE), Chinese philosopher and teacher