Title
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Journal
British Journal of Ophthalmology, 97(7)

ISSN
0007-1161

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Publication Date
2013-07-01

DOI
10.1136/bjophthalmol-2012-302490

Peer reviewed

Local treatment failure after globe-conserving therapy for choroidal melanoma

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Received 18 November 2012
Revised 28 February 2013
Accepted 4 March 2013
Published Online First
3 May 2013

To cite: Chang MY, McCannel TA. *Br J Ophthalmol* 2013;**97**: 804–811.

ABSTRACT

Local treatment failure after globe-conserving therapy for choroidal melanoma is a surgical complication with significant morbidity to the vision and eye. Few reports in the literature have addressed this complication exclusively. A review of the published literature with reference to local treatment failure in the management of choroidal melanoma was performed to make known the potential differences in failure rates between treatment modalities and methods. A search of the literature regarding local treatment failure was performed to identify relevant studies using combinations of the following keywords on PubMed: uveal melanoma, choroidal melanoma, local recurrence, local failure, endoresection, gamma knife, radiotherapy, helium, iodine, proton, palladium, ruthenium, trans-scleral resection, transpupillary thermotherapy. Further studies were found by searching the text and references of previously identified studies for articles reporting local treatment failure rates in choroidal melanoma. Among the 49 studies identified, the local treatment failure rate ranged from 0% to 55.6%, with follow-up ranging from 10 to 150 months. The two most widely used forms of radiation therapy, iodine-125 and ruthenium-106 brachytherapy, were both associated with a local recurrence rate of 9.6%. The weighted-average of treatment failure in all radiation therapies was 6.15% compared with 18.6% in surgical and 20.8% in laser therapies. Rates of local treatment failure for globe-conserving therapy of choroidal melanoma varied widely between modalities and between centres using similar modalities. Radiation therapy overall resulted in lower local treatment failures compared with surgical or transpupillary thermotherapy.

INTRODUCTION

Treatment of primary choroidal melanoma without evidence of metastasis is either globe-conserving therapy or enucleation. In a randomised clinical trial of patients with primary choroidal melanoma treated with globe-conserving iodine-125 brachytherapy vs enucleation, the Collaborative Ocular Melanoma Study demonstrated no significant difference in mortality, during the period up to 12 years of post-treatment follow-up.[1] Thus, increasing emphasis has been placed on globe-conserving therapy for choroidal melanoma.

Despite the fact that local treatment failure or local recurrence is a recognised surgical complication of choroidal melanoma treatment, few reports in the literature have addressed this complication exclusively. However, local tumour control is a critical goal in the management of patients with choroidal melanoma, because patients with local treatment failure may have an increased risk of metastasis and decreased survival.[2 3] Moreover, patients with local failure must undergo treatment for their tumour recurrence, which generally involves either further radiation or enucleation, both of which are associated with increased morbidity. Therefore, it is incumbent on those who treat choroidal melanoma to minimise the risk of local treatment failure or recurrence.

This review of the English language literature regarding local treatment failure after globe-conserving therapy presents the reported rates of local failure following the various forms of radiation, surgical ablation and transpupillary thermotherapy for choroidal melanoma. We also report the median tumour size treated with each modality, as larger tumour size has been shown to be associated with a higher rate of local recurrence.[4] Furthermore, we attempt to identify the risk factors of local failure associated with the available treatment modalities, and offer considerations to assist clinicians and patients in treatment planning.

METHODS

A search of the literature regarding local treatment failure was performed using the following keywords on PubMed: uveal melanoma, choroidal melanoma, local recurrence, local failure, endoresection, gamma knife, radiotherapy, helium, iodine, proton, palladium, ruthenium, trans-scleral resection, transpupillary thermotherapy. Additional studies were found by searching the text and references of previously identified studies of articles reporting local treatment failure rates in choroidal melanoma.

Inclusion criteria were: (1) English language article, (2) the intervention had to be primary and consist of one of the following: photon-based external beam radiation, charged particle (proton, helium ion) beam radiation, brachytherapy plaque treatment (any isotope), surgical resection (any method), or transpupillary thermotherapy, (3) minimum reported mean follow-up of 0.5 years, (4) minimum of 10 patients, (5) clear description of follow-up methods.

Exclusion criteria were: (1) the criteria used for diagnosing local treatment failure or recurrence was not reported, (2) rates of local control were reported by enucleation rate rather than an increase in tumour growth, (3) patients who had previously failed treatment for choroidal melanoma were included, (4) publications including patient cohorts that were subsequently included in reports of local treatment failure with larger cohorts or longer follow-up time, (5) the authors did not report median or mean tumour largest basal diameter (LBD) and/or height.

We extracted the following information from each article that met inclusion criteria: number of patients included, local treatment failure rate, median or mean tumour LBD and height, and length of follow-up (mean, median, or Kaplan–Meier estimate). If the patient population was restricted (eg, only patients with juxtapapillary tumours were included), this was noted.

When more than one local treatment failure rate was reported in a given study, based on different lengths of follow-up, we presented the rate of local failure for the follow-up time closest to 60 months, to facilitate comparison among studies. The 60-month follow-up time was chosen because it was the length most often used for Kaplan–Meier estimates, and also because it was the length of time reported by the Collaborative Ocular Melanoma Study.[4]

To facilitate comparison of different treatment modalities, studies were grouped by treatment modality. Groups included studies that used radiation, surgery and laser. Studies reporting on radiation treatment were then further subgrouped based on whether brachytherapy, photon-based external beam therapy, or charged particle therapy was used. For each group and subgroup, a weighted average of failure rate was calculated based on the number of patients included in the respective studies.

RESULTS

Articles numbering 136 were identified with the search criteria. After applying inclusion and exclusion criteria, 49 articles remained for analysis. Rates of local treatment failure ranged from 0% to 55.6%, and length of follow-up ranged from 10 months to 150 months. Study sizes ranged from 11 to 2435 patients, and the total number of patients included in the 49 articles was 12 524. The characteristics of the studies, including first author, treatment centre, local treatment failure or recurrence rate, tumour LBD, tumour height, follow-up time, and number of patients are summarised in table 1. Studies were grouped by treatment modality, and the average local treatment failure or recurrence rate for each treatment modality, weighted by number of patients, was reported.

In table 2, radiation, surgical and laser modalities are compared using the weighted mean rate of local treatment failure or recurrence in the reports for each respective modality. Among the treatment modalities using radiation, the mean local failure rate ranged from 4.0% to 9.6%. Among surgical modalities, the weighted mean local treatment failure or recurrence rate ranged from 4.6% to 21.3%. Transpupillary thermotherapy was the only laser modality used, and the weighted mean local treatment failure rate for this modality was 20.80%. The weighted average of local treatment failure or recurrence rates for radiation and surgical modalities were 6.15% and 18.6%, respectively. The tumours treated by surgical modalities were largest, with a weighted mean tumour LBD and height of 12.96 mm and 7.98 mm, respectively. Tumours treated by radiation were smaller, with a weighted mean tumour LBD and height of 12.90 mm and 5.21 mm, respectively. The smallest tumours were treated by transpupillary thermotherapy, with a weighted mean tumour LBD of 7.0 mm and height of 2.50 mm.

In table 3, the weighted mean local treatment failure rates of various radiation modalities are compared. Among brachytherapy modalities, the weighted mean rate of local treatment failure ranged from 4.0% to 9.6%. Among modalities using photon-based external beam radiation therapy, the weighted mean local failure rate ranged from 6.2% to 9.5%. Charged particle radiation treatment modalities had a mean local failure rate ranging from 4.2% to 4.6%. The weighted average of local treatment failure rates for brachytherapy, photon-based external beam radiation therapy, and charged particle radiation therapy were 9.5%, 7.9% and 4.2%, respectively. The two most commonly used forms of brachytherapy, iodine-125 and ruthenium-106, were both associated with a weighted mean local failure rate of 9.6%. The size of tumours treated among the various radiation modalities were comparable. The weighted mean tumour LBDs for brachytherapy, photon-based external beam radiation therapy, and charged particle radiation therapy modalities were 11.00 mm, 11.40 mm and 13.93 mm, respectively. The weighted mean tumour heights among these modalities were 4.48 mm, 6.15 mm and 5.54 mm, respectively.

DISCUSSION

The most striking finding of our review was that there was a wide range of local treatment failures across centres. Overall, radiation therapy was superior to surgical and laser therapies for achieving local tumour control, with weighted mean local treatment failure rates averaging 6.15% for radiation modalities, 18.6% for surgical modalities, and 20.8% for laser modalities. Weighted mean tumour size was largest among surgical modalities, followed by radiation modalities. The smallest tumours were treated by laser with transpupillary thermotherapy. The rate of local failure was lowest in eyes undergoing iodine-125 brachytherapy with intraoperative ultrasound localisation. The rate of local failure was the highest in eyes undergoing transscleral resection.

We recognise that the studies are heterogeneous because of differences in follow-up time, patient population, surgical technique and threshold for defining local treatment failure or local recurrence. Nonetheless, we consider the weighted mean local failure rates determined to be an approximation of the true rate for each treatment modality.

Radiation modalities

Radiation treatment modalities had the lowest rate of treatment failures identified. Among radiation modalities, brachytherapy and photon-based external beam radiation therapy had similar rates of local treatment failure at 9.5% and 7.9%, respectively. Charged particle radiation therapy, however, had a lower weighted average rate of local failure at 4.2%. Local control in radiation-treated choroidal melanomas is related to radiation dose, dose rate, tumour location and length of follow-up. Additionally, early failures are likely due to a 'geographic miss' of the tumour—that is, the entire tumour may not have been in the radiation-targeted zone.[5] Differences in any of these variables may account for the variability in local control rates observed among different types of radiation therapy and also among different centres using the same radiation modality (eg, iodine-125 brachytherapy).

Brachytherapy

Brachytherapy failure rates were comparable among the various isotopes used. However, local failure rates seemed to be affected by whether or not ultrasound confirmation of brachytherapy plaque placement was performed. Among the various isotopes used for brachytherapy, iodine-125 and ruthenium-106 were the most common.

Iodine-125 is a powerful, short-range gamma emitting radiation source with excellent tissue penetration.[6] Iodine-125 brachytherapy has local treatment failure rates ranging from 0% to 18%, with a weighted average of 9.6%. Notably, the widely quoted multicenter Collaborative Ocular Melanoma Study reported a 5-year local treatment failure rate of 10.3%,[4] while several smaller studies reported lower failure rates. Among the reports, two studies with

Table 1 Local treatment failure rates, tumour dimensions, months of follow-up, and number of patients reported in the studies that met inclusion criteria, by treatment modality

First author	Treatment modality	Treatment centre	Local failure rate (%)	Tumour LBD (mm)	Tumour height (mm)	Months of follow up	No. pts.	Notes
Radiation								
Brachytherapy								
Jampol (COMS group)[4]	Iodine-125	Multicentre	10.3	11.5	4.2	60	650	
Correa[27]	Iodine-125	Catalan Institute of Oncology, Barcelona	11.8	12.2	5.9	60	120	
Tabandeh[8]	Iodine-125	Bascom Palmer	1.7	9.6	4.2	37	117	Used intraoperative ultrasound
Sia[28]	Iodine-125	Royal Perth Hospital, Australia	14.2	9.5	5.5	39.5	49	
Quivey[29]	Iodine-125	UC San Francisco	18	10.9	5.5	60	239	
Jensen[30]	Iodine-125	Mayo Clinic	8	11.2	4	74	156	
Karlovits[31]	Iodine-125	Allegheny GH, Pittsburgh	0	13.5	7.8	60	35	
Sobrin[32]	Iodine-125	Bascom Palmer	2.2	9.2	2.9	62.4	45	
Leonard[33]	Iodine-125	Tufts University	27	12.3	6.3	100	37	
Wilson[14]	Iodine-125	St Bartholemew's Hospital, Moorfields Eye Hospital, London	4.2	10.2	5.9	47.3	190	
Puusaari[16]	Iodine-125	Helsinki University	7	16.1	10.7	60	54	
Sagoo[34]	Iodine-125	Wills Eye	14	10	3.5	60	242	Juxtapapillary choroidal melanomas, 95% treated with iodine-125, other 5% treated with ruthenium-106, cobalt-60
McCannel[7]	Iodine-125	UCLA	0	10.8	4.8	32.4	170	Used intraoperative ultrasound
Weighted average (n=13)	Iodine-125		9.6%	11.1	4.8	Total no. pts=2014		
Rouberol[35]	Ruthenium-106	Hospital de la Croix Rousse, Lyon, France	21.7	9	5	60	213	
Novak-Andrejcic[36]	Ruthenium-106	University Eye Clinic, Ljubljana, Slovenia	15.4	10.63	4.79	90.8	65	
Verschueren[12]	Ruthenium-106	Leiden University	4	10.9	4.2	60	425	86.1% of patients also received adjuvant TTT
Damato[11]	Ruthenium-106	Royal Liverpool University Hospital	2.1	10.6	3.2	60	458	9.0% of patients received adjuvant TTT
Wilson[14]	Ruthenium-106	St Bartholemew's Hospital, Moorfields Eye Hospital, London	10.7	9.7	4.2	45.3	140	
Papageorgiou[37]	Ruthenium-106	St Bartholemew's Hospital, London	14	9.5	3.7	60	189	
Frenkel[38]	Ruthenium-106	Hadassah-Hebrew University	14	13.1	4.7	66.6	413	
Weighted average (n=7)	Ruthenium-106		9.6%	10.9	4.1	Total no. pts=1653		
Finger[39]	Palladium-103	New York Eye Cancer Centre	4.0	10.3	3.9	55	100	
Weighted average (n=1)	Palladium-103		4.0%	10.3	3.9	Total no. pts=100		
Leonard[33]	Cesium-131	Tufts University	9	12.6	5.4	20	11	
Weighted average (n=1)	Cesium-131		9%	12.6	5.4	Total no. pts=11		
Photon-based external beam radiation therapy								
Modorati[40]	Gamma knife radiosurgery	San Raffaele Scientific Institute, Milan	9	N/A	6.1	31.3	75	
Zehetmayer[41]	Gamma knife radiosurgery	University of Vienna	2	14.2	7.8	28.3	62	
Sarici[42]	Gamma knife radiosurgery	Istanbul University Cerrahpasa Medical School	10	10.3	8.7	40	50	
Simonova[43]	Gamma knife radiosurgery	Na Homolce Hospital, Prague	16	N/A	8.5	32	75	
Weighted average (n=4)	Gamma knife radiosurgery		9.5%	N/A	7.7	Total no. pts=262		

Continued

Table 1 Continued

First author	Treatment modality	Treatment centre	Local failure rate (%)	Tumour LBD (mm)	Tumour height (mm)	Months of follow up	No. pts.	Notes
Dunavoelgyi[44]	Fractionated radiotherapy (stereotactic)	Medical University of Vienna	4.1	11.2	4.8	60	212	
Al-Wassia[45]	Fractionated radiotherapy (stereotactic)	McGill University Health Centre	15	12	4	60	50	
Weighted average (n=2)	Fractionated radiotherapy		6.2%	11.4	4.6	Total no. pts=262		
Charged particle radiation therapy								
Gragoudas[46]	Proton beam	Massachusetts Eye and Ear Infirmary	3.2	13	5.3	60	1922	
Dendale[47]	Proton beam	Curie Institute	4	13	4.8	60	1406	
Mosci[48]	Proton beam	Universita di Genova, Centre A. Lacassagne Cyclotron Biomedical—Nice	8.4	14.2	6.2	46.8	368	
Damato[49]	Proton beam	Royal Liverpool University, Clatterbridge Centre for Oncology	3.5	10.1	3	60	349	
Egger[50]	Proton beam	Paul Scherrer Institute, Switzerland	4.2	16.14	6.15	60	2435	
Wilson[14]	Proton beam	St Bartholemew's Hospital, Moorfields Eye Hospital, London	5.2	11.7	6.6	43	267	
Fuss[51]	Proton beam	Loma Linda University	9.5	10	6	60	78	
Weighted average (n=7)	Proton beam		4.2%	14.0	5.5	Total no. pts=6825		
Char[52]	Helium ion	UC San Francisco	4.6	11.9	6.7	150	218	
Weighted average (n=1)	Helium ion		4.6%	11.9	6.7	Total no. pts=218		
Surgery								
Garcia-Arumi[53]	Endoresection	Hospital Vall d'Hebron, Barcelona	5.8	9.9	10.1	70.6	34	
Kertes[54]	Endoresection	Louisiana State University	3.1	8	5.3	40.1	32	
Karkhaneh[55]	Endoresection	Farabi Eye Hospital, Tehran	5	11.67	8.51	89.6	20	
Weighted average (n=3)	Endoresection		4.6%	9.6	7.9	Total no. pts=86		
Bechrakis[56]	Trans-scleral resection	Innsbruck Medical University, Austria	24	14.5	9.4	60	141	
Damato[57]	Trans-scleral resection	Royal Liverpool University	20	13.2	7.4	36	310	
Weighted average (n=2)	Trans-scleral resection		21.3%	13.6	8.0	Total no. pts=451		
Laser								
Aaberg[58]	Transpupillary thermotherapy	Emory University, Michigan State University	23	8.5	2.3	60	135	
Shields[19]	Transpupillary thermotherapy	Wills Eye	22	6.5	2.7	36	256	
Stoffelns[59]	Transpupillary thermotherapy	Johannes Gutenberg University, Germany	0	8.2	3	10	20	
Godfrey[60]	Transpupillary thermotherapy	Emory University	6.7	6.78	1.79	16	14	
Harbour[61]	Transpupillary thermotherapy	Washington University in St Louis	24	7.3	2.6	21	32	
Parrozzani[62]	Transpupillary thermotherapy	University of Padova, Italy	11.6	6	2	48.7	77	
Spire[63]	Transpupillary thermotherapy	Hospital de la Croix Rousse, Lyon, France	55.6	7.24	3.5	24.7	18	
Weighted average (n=7)	Transpupillary thermotherapy		20.8%	7.0	2.5	Total no. pts=552		

COMS, Collaborative Ocular Melanoma Study; LBD, largest basal diameter; N/A, not available; no., number; pts, patients; TTT, transpupillary thermotherapy; UC, University of California; UCLA, University of California, Los Angeles; WA, weighted average.

Table 2 Comparison of radiation, surgical and laser treatment modalities

Modality	No. of studies included	Weighted mean rate of local failure (%)	Weighted mean tumour LBD (mm)	Weighted mean tumour height (mm)	No. of pts. included
Radiation (n=11435)					
Iodine-125 brachytherapy	13	9.60	11.10	4.80	2104
Ruthenium-106 brachytherapy	7	9.60	10.90	4.10	1653
Palladium-103 brachytherapy	1	4.00	10.30	3.90	100
Cesium-131 brachytherapy	1	9.00	12.60	5.40	11
Gamma knife radiosurgery	4	9.50	N/A	7.70	262
Fractionated radiotherapy	2	6.20	11.40	4.60	262
Proton beam radiation therapy	7	4.20	14.00	5.50	6825
Helium ion radiation therapy	1	4.60	11.90	6.70	218
Weighted average		6.15	12.90	5.21	
Surgical (n=537)					
Endoresection	3	4.60	9.60	7.90	86
Trans-scleral resection	2	21.3	13.60	8.00	451
Weighted average		18.6	12.96	7.98	
Laser (n=552)					
Transpupillary thermotherapy	7	20.80	7.00	2.50	552
Weighted average		20.80	7.00	2.50	

LBD, largest basal diameter; No., number; Pts., patients.

among the lowest treatment failure rates of 0% and 1.7% used routine intraoperative ultrasound for plaque localisation during brachytherapy.[7 8] These data suggest that intraoperative ultrasound plaque localisation during brachytherapy may reduce the risk of local treatment failure. One can speculate that the optimised plaque placement reduces geographic misses, thereby improving local treatment success rates.

The weighted mean tumour LBD and height among studies using iodine-125 brachytherapy were 11.1 mm and 4.8 mm, respectively. In the Collaborative Ocular Melanoma Study, tumours eligible for iodine-125 brachytherapy were less than 16.0 mm in LBD and 10.0 mm in height.[9] The maximum tumour height was 8.0 mm when the tumour was near the disc. Many studies use these parameters to determine eligibility for globe-sparing therapy. At the Jules Stein Eye Institute, we use the following maximal dimensions for iodine-125 brachytherapy: apical height of 10 mm, and LBD of 16–17 mm, with absolute necessity for ultrasound confirmation of borders.

Ruthenium-106 emits β-particles that only travel a limited distance (4–5 mm)[10]; therefore, ruthenium-106 is most appropriate for brachytherapy of tumours less than 5.4 mm in height.[5 11] The weighted mean local failure rate among studies using ruthenium-106 brachytherapy was 9.6%, identical to the rate calculated for iodine-125. Local recurrence may be reduced when adjuvant transpupillary thermotherapy is used in combination with ruthenium-106 brachytherapy. The two studies that used ruthenium-106 plaques and reported the lowest local failure rates both used adjuvant transpupillary thermotherapy.[11 12]

Photon-based external beam radiation therapy

The rate of local treatment failure with photon-based external beam radiation therapy (gamma knife radiosurgery or

Table 3 Comparison of radiation modalities

Modality	No. of studies included	Weighted mean rate of local failure (%)	Weighted mean tumour LBD (mm)	Weighted mean tumour height (mm)	No. of pts. included
Brachytherapy (n=3868)					
Iodine-125 brachytherapy	13	9.60	11.10	4.80	2104
Ruthenium-106 brachytherapy	7	9.60	10.90	4.10	1653
Palladium-103 brachytherapy	1	4.00	10.30	3.90	100
Cesium-131 brachytherapy	1	9	12.60	5.40	11
Weighted average		9.45	11.00	4.48	
Photon-based external beam radiation therapy (n=524)					
Gamma knife radiosurgery	4	9.50	N/A	7.70	262
Fractionated radiotherapy	2	6.20	11.40	4.60	262
Weighted average		7.85	11.40	6.15	
Charged particle radiation therapy (n=7043)					
Proton beam radiation therapy	7	4.20	14.00	5.50	6825
Helium ion radiation therapy	1	4.60	11.90	6.70	218
Weighted average		4.21	13.93	5.54	

N/A, not available; No., number; pts., patients.

fractionated radiotherapy) is similar to that of brachytherapy (7.9% vs 9.5%). However, the risk of radiation-related ocular side effects in the anterior segment is higher with external beam radiotherapy, since the radiation beam travels through the anterior segment in order to reach the tumour.[5] This may result in complications such as neovascular glaucoma, which ultimately may require enucleation.

Charged particle radiation therapy

Proton beam and helium ion charged particle radiation treatments are generated in a cyclotron, accelerated and delivered as a particle beam. Their low scatter and focusability to a maximum penetration ('Bragg peak') make them ideal for treating limited-sized lesions.[13] However, all the tissue through which the beam passes up to the Bragg peak, is exposed to the nearly full radiation dose. This review found that the average local treatment failure rate of charged particle radiation therapy (proton beam or helium ion) was 4.2%. This rate is approximately one-half that of all forms of brachytherapy (9.5% vs 4.2%). One disadvantage of charged particle therapy is that, similar to photon-based external beam radiation therapy, there is collateral radiation damage in the tissues through which the beam travels, usually the anterior segment structures. Radiation-related side effects and complications of the anterior ocular structures include chronic, severe dry eye, loss of lashes and other eyelid abnormalities. There may also be a higher rate of neovascular glaucoma.[5] These complications are known to occur at higher rates following charged particle treatment than brachytherapy, and visual outcomes may be less favourable in patients undergoing charged particle treatment.[14 15] Moreover, the use of charged particles is limited in availability, with the majority of centres reporting outcomes located in Europe. There is an increased interest in building new centres in North America, however, and charged particle therapy may become more widely available in the future.

Surgical modalities

Overall, surgical modalities had a higher rate of local treatment failure compared with radiation modalities (18.6% vs 6.15%). The weighted average local treatment failure rate using endoresection was 4.6%. However, the weighted average local failure rate for trans-scleral resection was 21%. The higher rate of local treatment failure in patients treated with globe-conserving trans-scleral resection may be related to the difficulty in achieving clear surgical margins.[16 17] The use of adjuvant ruthenium-106 plaques has been advocated for improving local failure rates in patients treated with these surgical modalities, but this has not significantly improved the local control rate.[17] However, it should be noted that the tumours selected for endoresection or trans-scleral resection were larger than those treated by radiation, with a weighted mean tumour height of 8.0 mm compared with 5.21 mm. These tumours may have an inherently faster growth rate with an associated increased risk for local treatment failure.[3]

Laser modality: transpupillary thermotherapy

Of the treatment modalities reviewed, transpupillary thermotherapy had the largest reported variation of local treatment failure from 0% to 55.6%, with a weighted average of 20.8%. Some of the variability may be due to differences in tumour characteristics, and the possibility of this treatment leaving some tumour cells untreated.[18] Shields *et al* showed that tumours overhanging the optic disk and those that required more than three transpupillary thermotherapy treatments had a greater risk of local failure, and when such patients were excluded from the study, the local failure rate decreased from 22% to 10%.[19] Transpupillary thermotherapy is generally considered as a treatment option for small choroidal melanomas, and the tumours treated by this modality were the smallest in this series (weighted mean tumour LBD and height were 7.0 mm and 2.5 mm, respectively). Due to the high local failure rate associated with transpupillary thermotherapy, it may be of more benefit as an adjunctive rather than a primary therapy. As previously noted, ruthenium-106 brachytherapy may be associated with lower local recurrence rates when combined with transpupillary thermotherapy.

Furthermore, continued support for the use of transpupillary thermotherapy in 'small choroidal melanomas' may be based on a perceived better efficacy for these lesions. However, based on the knowledge and theories of transpupillary thermotherapy's efficacy in treating melanomas, any perceived superiority of this treatment for 'small melanomas' may result from the considerable likelihood that these small lesions were actually benign nevi. Observation continues to be an appropriate approach for managing most benign choroidal lesions.

Morbidity associated with local treatment failure

The two main concerns regarding local treatment failure are (1) increased morbidity to the eye and vision and (2) potential risk of continued systemic tumour dissemination. There is no established management for cases of local treatment failure. The ultimate goal of controlling recurrent local growth may be accomplished most conservatively by enucleation. If sparing the globe is desired, repeat brachytherapy or transpupillary thermotherapy treatments may also be considered at the cost of possible increased ocular morbidity. Additional radiation increases the risk of vision-threatening ocular side effects, such as optic neuropathy, radiation vasculopathy and neovascular glaucoma, which may lead to eventual enucleation. The need for retreatment also comes with a psychological toll for the patient. In the Collaborative Ocular Melanoma Study Quality of Life study report, patients who required enucleation after brachytherapy had lower scores on all physical and mental health measures than patients treated with either brachytherapy or enucleation alone.[20]

Patients with local treatment failure also have a higher risk of developing metastatic disease.[3 21] However, it is not known whether metastasis is influenced by the surgical complication of local treatment failure or by the inherently aggressive nature of the primary cancer. Given our current molecular understanding of choroidal melanoma, metastatic risk may be more influenced by the molecular make-up of the tumour, rather than by proliferating cancer cells left in the eye after treatment. Certain cytogenetic abnormalities, most notably monosomy 3, have been consistently associated with metastatic spread and death in choroidal melanoma. Monosomy 3 is the most robust predictor of metastatic death that has been identified to date.[22 23] Although it has not been proven, adequate local tumour control may decrease metastatic risk by preventing tumour growth that would ultimately lead to unfavourable cytogenetic abnormalities more conducive to metastasis.[24]

Reducing local treatment failure

Overall, it is clear that radiation-based treatments are superior at achieving local tumour control than non-radiation techniques. The purpose of this review is not necessarily to convince the reader of a specific treatment modality that is superior, but to make known that significant and perhaps unacceptable variability exists between treatments. Although local treatment failure may be determined by multiple tumour-related factors, it is also very likely that local recurrence rates are affected by treatment and quality-related factors, such as the surgeon's ability and experience.

There are also treatment-related factors that have been described, or can be surmised. Gunduz *et al* found that the two factors predictive of local treatment failure or recurrence in macular choroidal melanomas treated by plaque radiotherapy were distance to optic disk and presence of retinal invasion.[21] The more posterior, or close to the optic disk, a tumour is located, the more challenging it can be to place the brachytherapy plaque accurately to cover the tumours. Under such circumstances, ultrasound-guided placement techniques used intraoperatively may improve the accuracy of plaque placement and reduce the rate of local treatment failure.[8 25] In support of this notion is that the two reports of iodine-125 brachytherapy with intraoperative ultrasound placement confirmation were among the studies with the lowest published local treatment failure rates of 0% and 1.7%.[7 8]

Strengths and limitations

Strengths of this study include the comprehensive nature of the review and the inclusion of all available and applied treatment modalities for globe-conserving management of choroidal melanoma. The major limitation of this review is likely publication bias favouring better outcomes, as poor outcomes are less likely to be reported.[26] Additionally, there is likely under-reporting of surgical complications, such as local treatment failure, due to the retrospective nature of the studies, and their inherent limitation of variable follow-up. Therefore, the true rate of local treatment failure is likely to be higher, perhaps much higher, than the numbers reported herein. Moreover, this review is only able to capture the local failure rates of centres that publish their outcomes data. Tracking of outcomes data for quality improvement purposes has not been widely adopted in *Ophthalmology*, and these results, even when available, are not necessarily published. Furthermore, the lack of cytopathologic diagnosis in nearly all studies, makes it possible that some small lesions treated were not choroidal melanomas, but instead misdiagnosed lesions, such as benign choroidal nevi, metastatic lesions, circumscribed choroidal haemangiomas, or even localized choroidal haemorrhages. This would, again, contribute to an underestimation of the true local failure rate in the treatment of choroidal melanoma. Finally, the generalisability of our review is limited by the lack of uniformity across studies in many factors that contribute to local treatment failure, including tumour location, surgical technique, dosimetry considerations for radiation modalities, threshold for defining local failure and follow-up time. The average local failure rate calculated from these studies may not apply to another group of patients that differs significantly in any of these factors.

Summary

Local treatment failure in choroidal melanoma is a devastating complication for the patient. Overall, radiation-based therapies for primary choroidal melanoma had a lower rate of local failure at 6.15% compared with surgical and laser modalities, at 18.6% and 20.8%%, respectively. Among the various radiation-based treatment modalities, the lowest rates of local treatment failure were 0% and 1.7% reported by centres that used intraoperative ultrasound-guided iodine-125 brachytherapy plaque location confirmation. Charged particle radiation therapy (proton beam and helium ion) was also associated with a low rate of local failure of 4.2%. Because the surgical complication of local treatment failure is associated with an increased risk of metastatic disease, poor patient vision, ocular morbidity and diminished psychological status, it is important to prioritise the achievement of local tumour control from the outset by combining the most optimal surgical technique with a treatment modality demonstrated to have a high local tumour control rate.

Contributors Both authors contributed substantially to the conception and design, acquisition of data, and analysis and interpretation of data. Both authors drafted and revised the manuscript critically for intellectual content and approved of the final published version.

Funding This work was supported by an unrestricted grant from Research to Prevent Blindness and the George E and Ruth Moss Trust.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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