# Adjuvant external beam radiotherapy following enucleation of eyes with extraocular extension from uveal melanoma

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## PRÉCIS

In 51 patients with extraocular extension of uveal melanoma undergoing enucleation, none developed clinically apparent orbital recurrence and no difference in all-cause mortality between observation versus adjuvant external beam radiotherapy was found.

ABSTRACT

**Purpose:** To report local disease control and all-cause mortality in patients with extraocular extension (EOE) of uveal melanoma (UM) undergoing enucleation followed by observation or external beam radiotherapy (EBRT).

**Methods:** Charts of patients enucleated between January 1st, 1997 and December 31st, 2019, with histopathological evidence of EOE of UM were reviewed.

**Results:** The cohort comprised 51 patients with a mean age of 67 ± 15 years, 22 (43%) of whom underwent adjuvant post-enucleation EBRT. Risk factors for metastasis included presence of epithelioid cells (29/45; 88%), closed loops (20/43; 47%), monosomy 3 (16/25; 64%) and gain of 8q (20/22; 91%). Patients undergoing EBRT had more extensive EOE (median: 5.1 mm vs 2.6 mm, p = 0.008) and surgical excision was less likely to be histologically complete (2/20; 10% vs 14/25; 56%, p = 0.002). Local side effects following EBRT were seen in 64% (14/22). At latest follow up, 59% of patients (30/51) were alive, with a median follow-up of 1.8 years [IQR 2.9, range 0.1 – 6.5]. By Kaplan Meier survival analysis, the 5- and 10- year overall survival rates were 56% and 12% respectively. There was no difference in all-cause mortality between those receiving adjuvant EBRT and those who were observed (log rank, p = 0.273). No cases of orbital recurrence were documented.

**Conclusions:** Orbital EBRT causes significant morbidity. Cases with relatively small EOE undergoing enucleation can be safely observed, without adjuvant EBRT. Multi-center studies are required to better assess the role of EBRT when EOE is more extensive.

## INTRODUCTION

Extraocular extension (EOE) occurs in 2-6 % of all eyes with uveal melanoma (UM)[1-4] and approximately 13% of cases undergoing enucleation.[5-8] The 8th edition of the American Joint Committee on Cancer (AJCC) includes EOE in its models for predicting metastatic death, categorizing any extraocular nodules according to whether they exceed 5 mm in diameter.

The treatment for UM with EOE has been debated for several decades. In 1964, Hogan recommended enucleation with limited exenteration followed by prophylactic radiotherapy.[9] In 1977, Shammas and Blodi advocated for exenteration in all cases of EOE from UM, regardless of the extent of orbital involvment.[10] In 1980, Affeldt et al reported that exenteration did not improve survival[5] and in 1985, Kersten et al found long-term survival to be the same whether or not exenteration was performed, except in patients with surgically transected or non-encapsulated EOE.[11] In an effort to avoid disfiguring surgery, in 1990, Hykin et al. reported their positive experience using external beam radiotherapy (EBRT) as an alternative to exenteration in preventing orbital tumour recurrence.[12] However, EBRT can cause significant morbidity, such as socket contracture precluding prosthesis wear in upwards of 40% of patients.[13]

Although the use of post-operative orbital radiotherapy is often mentioned anecdotally, to the best of our knowledge, only a handful of case-series have been reported, all of which had relatively small numbers of patients.[12-15] Since Hykin et al reported outcomes from our institution in 1990,[12] we have noticed very little local relapse and therefore, the authors practice has evolved over time to giving adjuvant radiotherapy primarily in cases of large or incompletely resected EOE. The purpose of the present study was to improve evidence-based management of patients with EOE from UM undergoing enucleation.

## METHODS

This retrospective study was approved by the Moorfields Eye Hospital clinical audit department (No; 521) and was conducted in accordance with the Declaration of Helsinki. An electronic repository was searched for the key words: “extra-scleral or extraocular extension” and “uveal melanoma” occurring in clinical letters dictated between January 1st, 1997 and December 31st, 2019. Patient files were reviewed for demographic details, histopathological findings, cytogenetic results, details regarding EBRT, evidence of local tumour recurrence, metastasis and death. The term ‘pseudo-encapsulation’ was used to describe cases in which the entire extra-ocular nodule of tumour was covered by at least a thin layer normal tissue, consisting of Tenons for posteriorly located lesions and conjunctiva +/- Tenons for anteriorly located tumours. Those undergoing EBRT received 50 Gy in 20 fractions with 6MV x-rays, typically administered over 4 weeks, as this was the protocol reported by Hykin et al. from our institution in 1990.[15] Patients who did not have a date of death listed in the electronic medical record, and who had not been seen in clinic within six months of the study close were contacted via telephone to determine their vital status and exclude orbital recurrence.

Conventional descriptive statistics were employed and the data presented as mean ± standard deviation (SD) when normally distributed or as median [interquartile range and range], if not. All variables were assessed for normality using the Shapiro-Wilk and Kolmogorov-Smirnov tests. The students t-test was used when continuous variables were normally distributed and the variance between groups was again checked using Levene’s test for quality of variances. When not normally distributed, the Mann-Whitney U test was employed. Differences in categorical variables were assessed using Fisher's exact test with the Freeman-Halton extension. A p-value of $<0.05$ was considered statistically significant. Kaplan-Meier survival estimate curves were used to predict all-cause mortality. All data was analysed using commercially available software (Stata Statistical Software. StataCorp LP and SPSS®; IBM Corporation, Armonk, NY, USA).

## RESULTS

A total of 51 patients with a mean age of 67 ± 15 years who underwent enucleation with histopathological evidence of EOE from UM were included. There were slightly more males (59%) than females. Most patients (39/51; 77%) underwent enucleation as primary treatment. Twelve patients (24%) were enucleated because of failed plaque brachytherapy (N= 10), plaque and proton beam radiotherapy (N= 1); and EBRT (as the lesion was initially diagnosed as choroidal metastasis) (N= 1). The mean LBD and tumour thickness were 18.5 ± 6.0 mm and 9.2 ± 4.2 mm, respectively. Fifty-five percent of the tumours included in this study were therefore AJCC T4 (28/51; 55% [T4c: 4 cases, T4d: 15 cases, T4e: 9 cases]). Similarly, 18% (9/51) were stage IIIA, 20% (10/51) were stage IIIB and 47% (24/51) were stage IIIC.

On histopathology, mixed/epithelioid cell type was the most common cytomorphology (29/45; 88%). In approximately half of the cases, mitotic count per $mm^2$ was >2 (29/51; 57%) and closed loops were identified (20/43; 47%). Cytogenetic testing using fluorescence in situ hybridization (FISH) was routinely performed only after 2010 and omitted after secondary enucleation because of concerns that genetic modification might occur following radiotherapy of the tumour.[16] Therefore, data on chromosomal aberrations were available for 25 cases. Monosomy 3 was found in 64% (16/25) and gains in 8q were demonstrated in almost all cases tested (20/22; 91%). The median size of EOE was 5.0 mm [IQR: 4, Range: 1 - 11]. Excision of EOE was histologically considered complete in 36%

(16/45) and the nodule was reported to be completely enclosed within a pseudo-capsule of overlying normal tissue in 29% (10/35).

Of the 51 patients included in this study, 22 underwent EBRT (22/51; 43%). Four patients undergoing EBRT (4/22; 18%) had failed prior radiotherapy as primary treatment (plaque brachytherapy in 3 patients; plaque and proton beam radiotherapy in one patient). Radiotherapy was administered as per the protocol employed in the London Ocular Oncology Service (i.e., 50 Gy in 20 fractions with 6MV x-rays, typically administered over 4 weeks).[15] There was no difference in mean age (p=0.334), intraocular tumour LBD (p=0.779) or thickness (p=0.374) between patients undergoing EBRT compared to those who were observed. With respect to histopathologic features, eyes undergoing EBRT were more likely to have larger EOE (median = 5.1 mm versus 2.6 mm; p = 0.008) and less likely to have complete surgical excision of EOE (21% versus 56%; p = 0.002). There were no statistically significant differences in incidence of closed loops (p = 0.547), cell type (p = 0244), mitotic count (p = 0.731), pseudo-encapsulation of EOE (p = 0.098), monosomy 3 (p = 0.098) or gain of 8q (p = 0.238) between the intraocular tumours of the two groups. (Table 1)

At latest follow up, 59% of patients (30/51) were alive and these patients were followed for a median of 1.8 years [IQR 2.9, range 0.1 – 6.5 years]. By Kaplan Meier survival analysis, the 5- and 10- year overall survival rates were 56% and 12%, respectively. (Figure 1) There was no statically significant difference in survival between those receiving EBRT compared to those who were observed (p=0.273). (Figure 2) One patient had undergone plaque brachytherapy 4 years prior to enucleation for local recurrence. This patient developed systemic metastatic disease within 3 weeks of enucleation; therefore, it is possible that the orbital component of this tumour was a local metastasis, rather than a direct extension of the intraocular lesion. This patient was still alive at the study close, 8 months post-enucleation.

There were no clinically apparent orbital recurrences in any patient included in this study. Fourteen of the 22 patients (64%) receiving EBRT had radiotherapy-related side-effects, including socket contracture (4 patients), persistent inflammation of the eyelids and socket (8 patients), implant exposure (1 patient) and ongoing socket discomfort necessitating removal of the implant (1 patient). Of the four patients undergoing EBRT who had previously been treated with either plaque brachytherapy and/or proton beam radiotherapy, there were no significant complications following EBRT.

## DISCUSSION

### *Main findings*

The main findings of our study were: (1) a high mortality, with no significant difference between patients who received EBRT and those who were observed; (2) no clinically apparent orbital recurrences in either group; and (3) significant orbital morbidity in most patients who had been treated with EBRT.

### *Orbital recurrence*

The reported incidence of orbital recurrence following enucleation with EOE from uveal melanoma ranges from 6 – 23%.[5,10,12,17,18] Risk factors for orbital recurrence include greater intraocular tumour size, optic nerve invasion, as well as surgical transection and non-encapsulation of EOE.[5] Interestingly, size of the epi-bulbar tumour nodule was not found to be a statistically significant predictor of local recurrence; however, these findings should be interpreted with the caveat that only 6 patients in this study developed orbital recurrence.[5] Although we have reported a 0% local recurrence rate, both for patients who were observed and for those undergoing adjuvant radiotherapy, this figure should be interpreted with caution given our relatively short follow up times (median: 1.8 years; mean: 2.7 years; IQR: 3.0 years; range: 0.1 – 10.2 years). However, these findings are likely representative of the real-world situation, given that many patients with EOE may not develop an orbital recurrence, to some extent because of poor life expectancy. From our data, Hanley's 'Rule of Three' formula would estimate the expected population probability of orbital recurrence in patients observed without EBRT following enucleation to be 10.3% (3/29; accepting a standard 0.05 type-1 error).[19] Furthermore, there is limited data in the literature to determine whether or not the development of orbital recurrence impacts survival, as some patients with orbital recurrence live for many years.[20] However orbital recurrence, when it occurs, can be very difficult to manage especially when there is an orbital implant in situ, resulting in significant morbidity.

While previous studies report that most cases of orbital recurrence following enucleation occur within the first three post-operative years (mean: 2 years),[18] there are some exceptional cases of orbital recurrence occurring 20-,[21] 26-,[22] 28-,[23] 35-[20] and 42-years[24] following enucleation. In keeping with this, more recent reports suggest that secondary melanoma within the orbit tends to follow a bimodal distribution, with a group of patients presenting early (<1 year following treatment for the primary tumor) and another cohort developing orbital disease much later (>5 years later).[20] Treatment modalities for orbital recurrence include exenteration, surgical debulking, radiotherapy, chemotherapy or a combination thereof.[20] Recently, neoadjuvant intra-arterial melphalan has been used in an effort to cytoreduce orbital recurrence of uveal melanoma prior to surgery.[25]

*Neo-adjuvant and adjuvant radiotherapy*

In 1990's, the Collaborative Ocular Melanoma Study (COMS) group investigated pre-enucleation radiotherapy for large choroidal melanomas.[26] In their report on long-term outcomes, they concluded that there was no survival advantage attributable to pre-operative radiotherapy and reported an overall survival of 32% at 10-years.[27] Unfortunately, this trial excluded patients with evidence of EOE >2 mm detected either by ultrasonography or clinical examination, and as such, it is unclear whether or not these results can be extrapolated to patients with EOE ≥2 mm undergoing enucleation.

The literature on post-enucleation radiotherapy for patients with EOE is sparse. Adjuvant radiotherapy is often mentioned anecdotally as a means of treating presumed residual microscopic disease; however, only a handful of studies have reported outcomes of post-enucleation radiotherapy. From the authors institution, Hykin et al reported a series of 17 patients undergoing EBRT following enucleation.[12] Only one of these patients developed orbital recurrence, which was diagnosed 10 weeks following enucleation and 3 weeks after completing a course of radiotherapy (consisting of 60 Gy megavoltage photons in 30 fractions). Based on this experience, in our high-volume Ocular Oncology Service, we offer EBRT to patients with a surgically visible nodule (usually > 5 mm) of EOE especially when the tumour capsule is breached. EBRT is given at 3 months post-surgery to allow for surgical wound healing. Finger et al reported high-dose-rate interstitial brachytherapy of the orbit in nine patients after enucleation for UM with EOE, one of whom had a massive orbital tumour at the time of the radiotherapy.[14] None of their patients developed orbital recurrence after a median of 18 months (range, 1-62). These results are in keeping with our own study, in which we did not identify any cases of orbital recurrence after either observation or EBRT.

High-dose irradiation following enucleation for UM with EOE can lead to severe socket contraction[28] in approximately 40% of patients.[13] Nasser et al reported the outcomes of 12 patients requiring socket reconstruction following EBRT. While reconstruction using oral mucous membrane grafting was successful, a significant proportion of their patients (42%; 5/12) died from metastatic disease shortly after their diagnosis of UM (range, 7 – 27 months).[13]

*Survival*

In our study, the actuarial 10-year overall survival rate was only 12%. Several studies have found both the presence, and size >5 mm of EOE to be associated with poorer prognosis.[7,8,29] Coupland et al found that EOE correlated with several histopathologic and cytogenetic features in the intraocular tumour that are known to be associated with an increased risk of metastasis, including epithelioid cellularity, closed loops, high mitotic count and monosomy 3.[6] Therefore, the presence of EOE, regardless of the extent, may merely serve as an indicator of increased underlying tumour malignancy.[6] In support of this, many older studies have found the size of EOE to be prognostically irrelevant.[5,10,12,30] Our extremely poor 10-year survival outcome of 12% is in keeping with AJCC survival estimates based on the large size of intraocular tumors included in this study (mean LBD and thickness: 18.5 ± 6.0 mm and 9.2 ± 4.2 mm, respectively) and the presence of EOE.

*Treatment of uveal melanoma with EOE*

While exenteration may occasionally be necessary for cases of massive (>1,000 $mm^3$) orbital involvement from UM,[31-33] the past four decades have seen a general shift towards more conservative management. Some cases of EOE can be successfully managed with globe-sparing modalities, including proton beam radiotherapy[34,35] or plaque brachytherapy;[36,37] however, enucleation is still widely performed due to significant radiation complications that may arise following plaque brachytherapy or proton beam therapy of large, anteriorly located tumours.

Burris et al reported a series of case from our institution where anterior EOE was detected preoperatively on slit lamp examination in 100% cases, and therefore the surgical approach was easily converted to include modified enucleation. This paper also reported that ultrasonography can miss posterior EOE especially when located at the insertion of the inferior oblique muscle.[15] The incidence of surgical transection of EOE is relatively high in the reported literature.[10,12] However in our series, histopathological examination of the globes rarely found the nodule of EOE to be incompletely excised with breach of the tumour capsule. This is most likely related to our meticulous surgical approach. We exercise caution if there is any suspicion of EOE, and for completion of the resection use enucleation scissors or the Foster Snare if it can be placed posteriorly enough without disturbing the EOE. If the nodule of EOE is transected, we take meticulous care at the time of surgery to ensure that all visible tumour is removed from the orbit. Similarly, if at enucleation, orbital spread is found, then meticulous orbital exploration to excise any melanoma seeds can be performed at the same operation to achieve local tumour control. We believe this to be a critical step in management of these cases, as residual viable tumour cells left behind will increase the risk of orbital recurrence.

*Study strengths and weaknesses*

The main strength of our study is the large size of our cohort, which to our knowledge is greater than any previously reported. The primary weakness is the short follow-up, which occurred mostly because so many of our patients had died. As a result, it is possible that some of these patients died before a local orbital relapse was detectable. Another weakness is the lack of randomization between observation and adjuvant EBRT with patients receiving prophylactic radiotherapy being more likely to have larger and/or incompletely excised EOE. Additionally, although there was no statistically significant difference in the administration of prior radiotherapy (ie. plaque brachytherapy/proton beam radiotherapy) between the two groups, it is possible that some of the histopathological features were impacted by the primary treatment. As one patient present with systemic metastasis within a month of enucleation, it is possible that this orbital tumour may have been a local metastasis rather than extraocular extension directly from the tumour, as metastasis of treated choroidal melanoma to the contralateral orbit have been previously reported.[38-40] Unfortunately, due to the limitations pertaining to the standardized documentation of metastatic status we were unable compare the risk of distant metastasis between the groups. Likewise, as the cause of death was not known in many patients, we could only report all-cause mortality and overall survival.

*Scope for further studies*

There is scope for further studies. Much of the literature surrounding the incidence of orbital recurrence in eyes undergoing enucleation for uveal melanoma with EOE is more than 30 years old,[5,10,12,17,18] and based on a relatively small number of cases. Therefore, further research is required to determine the contemporary risk of orbital recurrence in the setting of modern-day pre-operative imaging such as MRI and modified surgical techniques. There is also scope for studies aimed at reducing radiation-induced morbidity by employing alternative delivery modalities, such as brachytherapy.[14]

*Conclusions*

The literature reporting outcomes of adjuvant radiotherapy for EOE following enucleation for uveal melanoma is sparse[12-15] and little has been published in the past three decades with respect to the incidence of orbital recurrence following enucleation. Our findings suggest that cases with relatively small EOE of less than 5mm in thickness, with complete excision from the orbital contents can be safely observed without the need for adjuvant radiotherapy. Further multi-centred research is required to definitively determine the role of EBRT in cases with more extensive EOE and in instances when the pseudo-capsule is breached.

TABLE and FIGURE LEGENDS:

Table 1. Demographics, intraocular tumour features and laboratory findings of patients undergoing external beam radiotherapy compared to those who were observed.

Figure 1. Kaplan Meier curve demonstrating all-cause mortality for the entire cohort

Figure 2. Kaplan Meier curve demonstrating all-cause mortality stratified by whether or not external beam radiotherapy was administered.

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Table 1. Demographics, intraocular tumour features and laboratory findings of patients undergoing external beam radiotherapy compared to those who were observed.

| | Observation n = 29 | EBRT n = 22 | p-value |
|---|---|---|---|
| **Age* (mean ± SD) years** | 69 ± 14 | 65 ± 16 | 0.334 |
| **LBD* (mm)** | 18.7 ± 5.7 | 18.2 ± 6.5 | 0.779 |
| **Thickness* (mm)** | 9.7 ± 4.6 | 8.5 ± 3.6 | 0.374 |
| | *n*=12 | | |
| **Prior radiotherapy†** | 8 (67) | 4 (33) | 0.518 |
| | *n=18* | *n=18* | |
| **Size EOE‡ (mean, median, range) (mm)** | 2.9, 2.6, 0.5 – 6.0 | 5.6, 5.1, 1.5 – 12.0 | **0.008** |
| | *n=24* | *n=19* | |
| **Closed Loops† (%)** | 10 (42) | 10 (53) | 0.547 |
| | *n=24* | *n=21* | |
| **Cell Type**** | | | 0.244 |
| **Spindle (%)** | 7 (29) | 9 (43) | |
| **Mixed (%)** | 10 (42) | 10 (48) | |
| **Epithelioid (%)** | 7 (29) | 2 (10) | |
| | *n=22* | *n=20* | |
| **Mitotic count* (mean ± SD)** | 2.5 ± 2.2 | 2.7 ± 2.0 | 0.731 |
| | *n=25* | *n=20* | |
| **Complete surgical excision of EOE†** | 14 (56) | 2 (10) | **0.002** |
| | *n=21* | *n=14* | |
| **EOE pseudo-encapsulated†** | 7 (33) | 3 (21) | 0.704 |
| | *n=14* | *n=11* | |
| **Monosomy 3†** | 11 (79) | 5 (45) | 0.098 |
| | *n=11* | *n=11* | |
| **8q gain†** | 11 (100) | 9 (82) | 0.238 |

LBD: Largest basal diameter
EOE: Extraocular extension
* Students t-test (continuous variables that are normally distributed)
‡ Mann-Whitney U (continuous variables that are not normally distributed)
† Fishers Exact test (categorical variables)
** Chi-square test
Mitotic count is per high power field

Figure 1. Kaplan Meier curve demonstrating all-cause mortality for the entire cohort

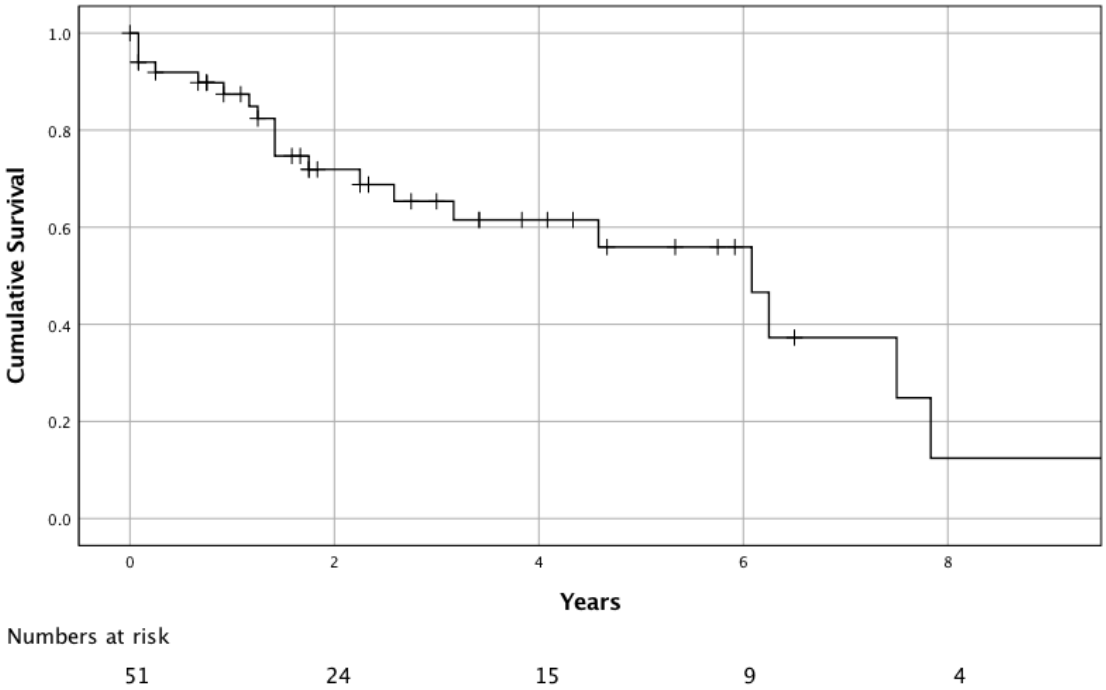

Figure 2. Kaplan Meier curve demonstrating all-cause mortality stratified by whether or not external beam radiotherapy was administered.