Revisione sistematica

Clin Ter 2020; 171 (1):e89-98. doi: 10.7417/CT.2020.2195

Meta-analysis on the utility of radiotherapy for the treatment of Ocular Melanoma

D. Messineo[1], G. Barile[2], S. Morrone[2] , G. La Torre[2], P. Turchetti[3], L. Accetta[4], E. Trovato Battagliola[4], E. Agostinelli[5], F. Pacella[4]

[1]*Department of Radiology, Oncology, and Anatomopathological, University Sapienza, Rome;* [2]*Department of Public Health and Infectious Diseases, Sapienza University of Rome, Rome;* [3]*National Institute for Health, Migration and Poverty (INMP/NIHMP), Rome;* [4]*Department of Sense Organs, University of Rome "Sapienza", Rome;* [5] *International Polyamines Foundation-ONLUS, Rome, Italy*

Abstract

Introduction. Uveal melanoma is the most common intraocular tumor in the adult population. It can affect any part of the uveal tract: the iris, ciliary body, and choroid. Historically, enucleation has been the mainstay of treatment for primary melanoma. In the last decade, however, radiotherapy has acquired an increasingly important role and has now become our first-line modality. However, it is still widely debated what is the most effective radiotherapy technique for this tumor. Purpose to perform a literature review on the utility of radiotherapy for primary ocular melanoma and determine the most effective radiotherapy technique.

Materials and Methods. We included all systematic and narrative reviews on the topic, published between September 2007 and November 2017 on PubMed and SCOPUS. Two independent reviewers assessed the eligibility criteria for each article using the PRISMA checklist. The methodological quality of narrative and systematic reviews was evaluated with the INSA and AMSTAR checklists, respectively.

Results. Our study analyzed a total of 23 studies, including 18 narrative reviews and 5 systematic reviews. Radiotherapy with Brachytherapy, Proton Therapy, SRS/SRT with gamma knife and cyber knife, are the most common choices for the treatment of primary ocular melanoma. These techniques allow for excellent lesion spread control, eye, and vision conservation, and improve overall patients' quality of life. Among the narrative reviews, the highest INSA score was 5/7, the lowest 2/7, the mean was 3.83/7 and median was 4/7. Among the systematic reviews, the highest AMSTAR score was 9/12, the lowest 4/12, the mean 5.6/7 and median 4/7.

Conclusion. The number of studies available on this topic is scarce. Among those published, the methodological quality is modest, as assessed with the INSA and AMSTAR checklists. As a result, we are not able to determine what the most effective radiotherapy technique is.
Clin Ter 2020; 171(1):e89-98. doi:10.7417/CT.2020.2195

Key words: *ocular melanoma, brachytherapy, proton therapy, radiosurgery, systematic review, narrative review.*

Introduction

Uveal melanoma is the most common primary intraocular neoplasia in the adult population (1, 2). Mean age of diagnosis is 60 years and is more common in males (3). This tumor originates from melanocytic cells of the choroid (90% of the times), ciliary body (7%) or iris (2%) (4). The aetiology of uveal melanoma is multifactorial and includes both genetic and environmental factors. In people with a fair skin complexion, a lower melanin concentration is associated with a greater susceptibility to ultraviolet rays and a greater risk for the development of this neoplasm (5,6,7). This risk is even higher with the presence of atypical nevi in the choroid, iris, or skin (8,9). High estrogen levels might represent another risk factor. In fact, the incidence of uveal melanoma and its growth rate are higher during pregnancy (10). A genetic mutation of the onco-suppressor gene BAP1 predisposes to a hereditary cancer syndrome with a greater incidence of several tumors, including uveal melanoma. The same gene is also implicated in the metastatic potential of this intraocular tumor (11).

Uveal melanoma can present anteriorly on the iris, or posteriorly in the ciliary body or choroid. When anterior, it presents as a discoloration in the iris (heterocromia) or as pupillary distortion (corectopia). When posterior, it causes visual changes, such as vision (38% of times), photopsia (9%), floaters (7%), and visual field loss (6%). However, some patients can remain totally asymptomatic (2, 12). The presence of a mass is generally confirmed with indirect ophthalmoscopy and echography (13).

Treatment for uveal melanoma can be radical or conservative. The radical approach involves the surgical removal of the mass which is not always easy to surgical procedure (14). When a conservative approach is preferred, radiotherapy is first-line treatment. Chemotherapy is not generally used, due to its scarce efficacy against this type of tumor (15). Anterior melanoma generally has a much better prognosis than posterior melanoma. Reasons might include younger age at presentation, earlier diagnosis, and possibly a lower biological activity (16,17,18). Posterior melanoma shows a worse prognosis and a greater predisposition for metastatic spread. The most common target organs are liver (89%), lungs (29%), bones (17%), and skin (12%) (19). Factors associated with a worse prognosis include advanced age at diagnosis, secondary glaucoma, higher tumor thickness, tumor margins extending to the iris root or to the angle of the

Correspondence: Fernanda Pacella, Department of Sense Organs, Sapienza University of Rome, P. le A. Moro 5, 00185, Rome, Italy. E-mail: fernanda.pacella@uniroma1.it. Tel. +39 3333534396

ISSN 1972-6007

anterior chamber, or extra-ocular extension (20, 21, 22).

Histopathology changes that are associated with a worse prognosis include: the presence of epithelioid cells, high mitotic activity, increased diameter in the largest 10 nucleoli, increased vascular density, presence of micro-vascular nets, increased expression of insulin-like growth factor 1 receptors and HLA antigens (22,23).

Study objective and Design

We performed a systematic review of all available articles on the utility of radiotherapy for the treatment of ocular melanoma.

The quality of each study was evaluated using the INSA and AMSTAR checklists (29,30).

Materials and Methods

We defined the search strategy, eligibility criteria, and quality assessment criteria prior to start.

This review has been conducted following PRISMA guidelines (25, 26) (Table 1).

Eligibility criteria included narrative-type systematic reviews, published in English between September 2017 and November 2017, available as full-text articles, discussing radiotherapy techniques for primitive ocular melanoma.

We decided to include the articles of the last decade only for the following reasons:

The advancements in radiotherapy techniques and clinical management of ocular melanoma in the last decade have rendered obsolete all preceding standards of treatment.

PRISMA guidelines have significantly improved the quality of systematic reviews. They were introduced in 2009.

We excluded all articles without original data (posters, editorial articles, clinical reviews), or reviews not published in English, or articles not available as full texts.

Bibliographic search was conducted on PubMed and Scopus databases. The following keywords were used: Choroidal Melanoma, or Uveal Melanoma; Radiotherapy, or Brachytherapy, or Proton therapy, or Stereotactic radiosurgery (27, 28).

Study selection was performed by two independent investigators and any discrepancy was solved.

Results of the two search engines were compared using the software JabRef. V.4.

Scientific quality of narrative and systematic revisions was assessed using the International

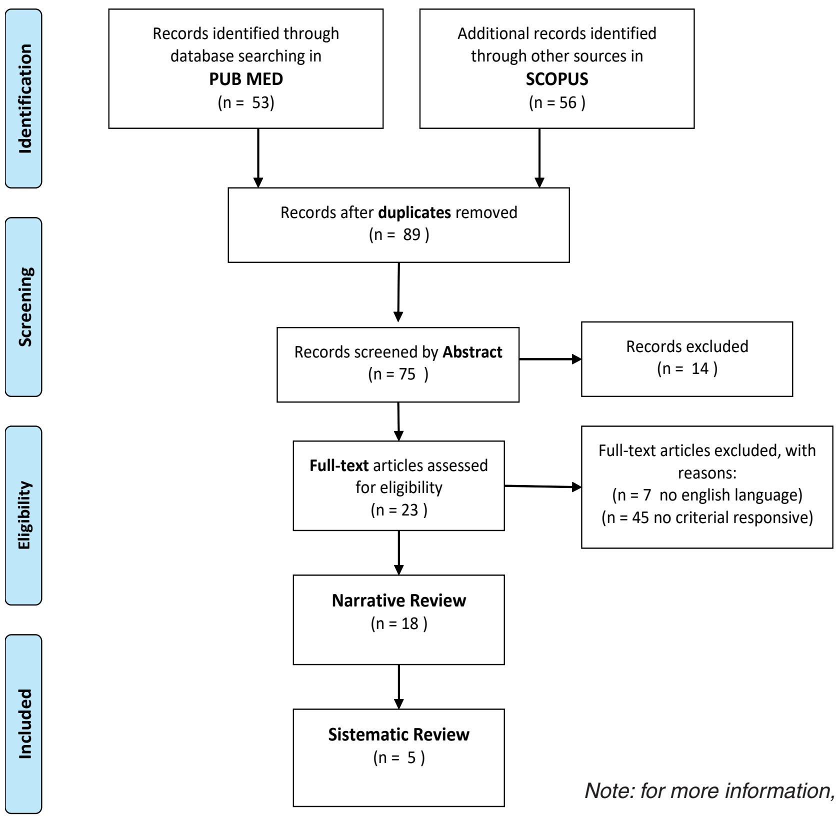
Narrative Systematic assessment (INSA) and A Measurement Tool to Assess Systematic Reviews (AMSTAR) checklists respectively (29, 30).

The initial search included 109 results (53 from PUBMED and 56 from SCOPUS). After excluding duplicates, each of the remaining 89 articles was assessed independently by two investigators.

Results

Using the schematic depicted above, we selected a total of 23 revisions, there of 5 systematic and 18 narrative (Table 2,3,4).

Table 1. The PRISMA flow diagram of selection process, 2009.



Note: for more information, visit www.prisma-statement.org.

Table 2. Research results.

Systematic revisions	Narrative revisions	Total
5	18	23

Table 3. Data Study description: Narrative Reviews.

Author	Year	Country	Included Study	Technique	Comparison	Results	Quality (INSA)
Groenewald C. et Al.[29]	2013	UK , Liverpool	57	SRS, Plaque Brachytherapy, PBRT	None	Treatment of primary melanoma and radio-induced effects can improve overall survival.	5
Mishra K. et Al.[29]	2016	USA, California	38	PBRT (helium proton, carbon)	Plaque Brachytherapy, SRS, Conventional RT	Proton therapy has been considered, since the last decade, the gold standard for the primary treatment of ocular melanomas. Better local control and management costs.	4
Shildkrot Y. Wilson MW et Al.[31]	2009	USA, Memphis	87	SRS, Gamma Knife, PBRT, Plaque Brachytherapy,	Enucleation, Endoresection, TTT.	Evaluation of melanoma types improves metastasis-free survival.	4
Tarlan B. et Al.[32]	2016	Turkey, Ankara	175	SRS (Gamma Knife, Cyber Knife), Brachytherapy, PBRT.	TTT, Surgery, Enucleation,	The effectiveness of systemic treatment could be improved with adjuvant therapies that target micrometastasis (due to malignant cells already circulating in the early stage of the tumor) instead of macrometastasis.	3
Kapoor A. et Al.[33]	2016	Egypt	50	PTBR (protons, helium), Brachytherapy, SRS	TTT, Surgery, Enucleation,	Personalized treatment as the best strategy for the choice of therapy in the different presentations of uveal melanoma.	5
Damato B. et Al.[34]	2010	UK , Liverpool	23	Brachytherapy,	Surgery, Enucleation,	It is not possible to determine which between enucleation and brachytherapy has the best prognosis because of the lack of results made available by the literature.	3
Krantz B.A. et Al.[35]	2017	USA, New York	120	PBRT, Brachytherapy	Surgery, TTT, Laser Therapy	The new therapeutic approaches are based on the selective treatment of cancer with the use of recombinant molecules.	5
Afshar A.R.[36]	2015	USA, California	72	PTBR	None	Proton Therapy as primary, adjuvant and neo-adjuvant treatment of uveal melanoma.	3
Tarlan B. et Al.[37]	2012	Turkey, Ankara	87	PBRT, Brachytherapy, Gamma Knife,	TTT, Surgery, Enucleation, PDT	The effectiveness of the systemic treatment could be improved with adjuvant therapies that target the micro-metastases present in the tissues.	4

(segue)

Zehetmayer M. et Al.[38]	2012	Austria, Vienna	40	Gamma Knife, Cyber Knife	None	SRT and SRS with Gamma Knife and Cyberknife represent interesting future options in the treatment of ocular melanoma.	2
Pe'er J.[39]	2012	Israel , Jerusalem	64	106 Ru Brachy-therapy	None	The brachytherapy with Ruthenium plates alone or in combination with other techniques is indicated in the treatment of melano-mas up to 7mm thick, with excellent results of local control.	4
Yonekawa Y. et Al.[40]	2012	USA, Boston	100	PBRT, Brachythe-rapy	None	Cytogenetics improves long-term metastasis-free survival.	4
Dogrusöz M. et Al.[41]	2017	USA, Cali-fornia	115	PBRT, SRS, Bra-chytherapy,	Laser Therapy, Surgery	The key role of cytogene-tics in improving treatment and prognosis.	4
Kaliki S., Shield C.L.[43]	2016	India	101	PBRT (Helium ion), Cyber knife, Gamma knife, Linear Accelerator	Laser Therapy, Surgery, PDT, TTT	Cytogenetic identification of ocular melanomas for the choice of treatment.	5
Levy R. et Al.[44]	2012	USA	12	PBRT (helium, carbon, proton)	Brachytherapy	Charged particle radiosur-gery shows significant ad-vantages for the treatment of large melanomas.	4
Khalil D. et Al.[45]	2014	USA, New York	35	PBRT, Brachy-therapy, SRS, Surgery, TTT	None	Radiotherapy (brachythe-rapy and proton therapy) is the most common and effective treatment choice for ocular melanoma.	2
Seregard S. et Al.[46]	2013	Sweden, Stockholm	41	PBRT, Brachythe-rapy, SRS.	Surgery, Enucle-ation	Despite the excellent results achieved in the conservative treatment of primary melanoma, the treatment of systemic ef-fects remains controversial and is the leading cause of death.	3
Pereira P.R. et Al[47]	2013	Canada	60	PBRT, Brachy-therapy. SRS .	Surgery, Enuclea-zion, TTT, PDT, Local Resection, Chemiotherapy	Overall survival is influ-enced by genetic mutations underlying melanoma	5

Abbreviations: Proton beam radiation therapy PBRT; Transpupillary thermotherapy TTT, photodynamic therapy PDT, stereotactic radiosurgery SRS, Radiotherapy RT, Brachytherapy with I-125 and Ru-106 is the most common treatment for primary melanoma. It guarantees a good local spread control but can only use for small- or medium-size lesions (from 2.5 mm to 10 mm diameter, with a margin of 2.5 mm from the optic nerve). Side-effects include radio-induced retinopathy or neovascular glaucoma that can lead to secondary enucleation.

Proton therapy is the most effective treatment in terms of local spread control of lesions up to 16 mm in diameter, with a minimum distance of 2 mm from the optic nerve. It is associated with lower levels of secondary enucleation and better visual acuity improvement. Side-effects of this methodology include cataract formation and neovascular glaucoma. Furthermore, its high cost limits its availability.

The stereotactic radiosurgery (SRS) and stereotactic radiation therapy (SRT) with gamma knife or cyberknife represents an alternate methodology. With small- and medium-size lesions, it has shown similar efficacy and side-effects to Proton therapy.

Other therapies such as Transpupillary thermotherapy (TTT) or photodynamic therapy (PDT) have been dismissed due to poor results, but they might still be used in combination with radiotherapy.

Groenewald C. ***et Al.*** explain the radiation effects on tumor cells and the surrounding tissues (retina, iris, choroid, optic nerve, lens and sclera). Radiotherapy is useful in regressing tumor size, but inevitably damages other structures. This can lead to retinopathy, neo-vascular glaucoma, optic neuropathy, and cataract (29).

Shildkrot Y. and Wilson ***et Al.*** recommend a genetic analysis of tumor cells to select the best radiotherapy technique. Their research demonstrates the presence of silent liver micro-metastases even in the early stages of uveal melanoma. The pathophysiology has not been completely elucidated yet (31).

Damato ***et Al.*** claim that there is not still enough evidence on what the best clinical or surgical management of uveal melanoma is. **Tarland B.** ***et Al.*** emphasize the importance of conducting a cytogenetic analysis of tumor cells. They classify uveal melanomas in either Class 1 or 2, with respectively a low and high risk for metastatic spread. This classification helps in determining the best treatment strategy and prognosis for each patient (34,37).

Zehetmayer M. presents some promising results on stereotactic radiotherapy (Gamma knife, Cyberknife and Linac). Even though this technique gives good local spread control in up to 90% of cases, it remains inferior to the gold-standard, which is Proton Therapy. The same author claims that SRS and SRT have great potential for future applications, because they are minimally invasive and are cheaper to operate than Proton Therapy (38).

Pe'er J. concludes that Brachytherapy with Ru-106 is indicated for melanomas of up to 7-mm in thickness, offering excellent local spread control, low enucleation rates and tumor recurrence. When compared to other isotopes, Ru-106 causes less damage to the surrounding tissues and better preserves visual acuity, if it is placed far from the macula and optic nerve. It can also be used in combination with other techniques, such as Iodium-125, TTT and resection (39).

Yonekawa ***et Al.*** conclude that Proton Therapy is more effective than Brachytherapy for larger tumors. In fact, it shows better local spread control, less complications, but metastatic spread remains the cause of death in these patients. Authors also emphasize that cytogenetics play an important role in early diagnosis of metastatic spread (40).

Levy R. ***et Al.*** compare Brachytherapy, Proton Therapy (Protons, Helium ions, Carbon ions), and Stereotactic Proton Therapy. They conclude that stereotactic radiosurgery with charged particles is especially effective against larger tumors or tumors with irregular margins. It also causes less damage to surrounding tissues and less adverse effects (44).

Seregard S. ***et Al.*** **and Khalil D. N.** ***et Al.*** explain how conservative radiotherapy treatment is preferred over enucleation, unless tumor size is large, or tumor is especially difficult to treat. Brachytherapy is the most accessible technique. Rutenium 106 is more frequently used in Europe, whereas Iodium-125 is more common in the US. Despite its good efficacy against the primary tumor, metastatic disease is the primary cause of death in these patients. Khalil D. N. et Al. add that Proton Therapy is indicated for larger tumors or closer to the macula or optic nerve, since this treatment causes less surrounding tissue damage. Other available techniques are Transpupillary Termotherapy, which causes tumor necrosis using electromagnetic waves, and Photocoagulation, which uses a laser to convey thermal energy and lyse tumor cells (46,48).

Afshar A.R. ***et Al.*** explain how Proton Therapy can be used either as the primary treatment, as salvage therapy for recurrent tumors, as neo-adjuvant therapy before surgical resection, and as adjuvant therapy following surgical resection. It can be used for tumors up to 28 mm in diameter or 14 mm in thickness (36).

Pereira P.R. ***et Al.*** and **Tarlan B.** ***et Al.*** conclude that, despite modern therapies, most of patients with uveal melanoma will develop metastases. Prognosis is generally poor at this point, but life expectancy can be slightly improved if therapy targets specific cytogenetic alterations and micrometastases (47, 32).

Mishra K. ***et Al.*** also compare the efficacy of Proton Therapy to standard radiotherapy, brachytherapy or enucleation. Proton Therapy is again classified as the current gold-standard for the treatment of intraocular tumors. In fact, radiation dosage can be better localized to target area, with less dispersion to surrounding tissues. Local spread control reaches 95% at 5-year follow-up. Overall life expectancy is about 80%, but variable upon TNM classification. Secondary enucleation rate is around 10%, which in half of cases is indicated due to neo-vascular glaucoma. Treatment with Helium ions has shown better local spread control, better vision preservation and better survival rates at 12-year follow-up (30).

Kapoor A. ***et Al.*** conclude that TTT can be effective with melanomas up to 3-mm in size; Brachytherapy and Proton Therapy are preferred with medium-size melanomas; whereas, enucleation is indicated for large tumors. Treatment should be personalized to tumor physical and cytogenetic characteristics (33).

Krantz B.A. ***et Al.*** believe that, despite good local spread control, the overall course of uveal melanoma has not changed much. They suggest "target-therapy", an alternate approach that targets membrane receptors of tumor cells with recombinant protein complexes (35).

Dogrusöz M. ***et Al.*** explains that the most appropriate treatment for uveal melanoma depends on tumor size and its proximity to the fovea or the optic nerve. In their opinion, the actual utility of radiotherapy is still controversial, because of the numerous side-effects and poor improvement in long-term survival (41). Both Dogrusöz M. *et Al.*, Saliki S. and Shields C.L. attribute a key role to cytogenetic analysis in planning the appropriate treatment.

Yousef A. Y.***et Al.*** reviewed the incidence of ocular melanoma in the first two years of life. They included 13 cases. Treatment was surgical: 11 eyes were enucleated, 2 were exenterated. Adjuvant therapy was administered in 2 cases. Two patients presented with metastatic disease at 25 months follow-up. Authors commented that infantile ocular melanoma is often associated with Atypical Cutaneous Lesion Syndrome and generally carries a better prognosis than adult-onset ocular melanoma (49).

Chang M. Y. ***et Al.*** evaluated failure of local spread control following conservative therapy. TTT had the highest failure rate (20.8%), followed by endo-resection or trans-scleral resection (18.6%), and radiotherapy (6.15%). Brachytherapy with Ru-106 or I-125 has shown higher failure rates than other radiotherapy techniques. However, success rate can be improved by positioning the radioactive plaque with ultrasound guidance. On the other hand, even though Proton Therapy and Gamma Knife guarantee a better local control of tumor, they are associated with more side-effects. In general, radiotherapy gives better results than other techniques, such as surgery, which can be largely operator dependent. Chang M. Y. *et Al.* conclude that surgical treatment alone is associated with higher risk of metastatic spread, worse vision, and higher ocular morbidity. For best results, they suggest combining surgery with radiotherapy (50).

Wang Z. ***et Al.*** present the superiority of radiotherapy with charged particles (CPT) over brachytherapy with Iodium-125 for the treatment of uveal melanoma. Even though the overall survival or secondary enucleation rates are comparable between the two techniques, CPT presents the following advantages: better tumor local control, less tumor recurrence rate, and less radio-induced side-effects (cataract or retinopathy), as compared to standard brachytherapy. Secondary enucleation was mostly performed due to neo-vascular melanoma (52).

Appleton J.P. and Bridge P. also compared Proton Therapy to standard Brachytherapy, in terms of ocular morbidity and tumor growth control. Efficacy varies according to tumor size, its position and the isotope used in Brachytherapy. In fact, Proton Therapy is preferred with larger tumors or located near critical structures of the eye, such as the fovea or optic nerve. In terms of vision conversation, there is not significant difference between the two techniques. In terms of lesion control, Proton Therapy has been shown to

Table 4. Systematic Reviews: Systematic Reviews

Author	Year	Country	Included studies	Technique	Compares	Results	Quality (AMSTAR)
Yousef A.Y. et Al.[49]	2015	Jordan, Amman	13	External radiation therapy	Chemio-therapy, Enucleation	Eye melanoma in the first 24 months of life is very rare and has a better prognosis than that of adulthood.	4
Chang M.Y. et Al.[50]	2013	USA, California	49	PBRT, Brachy-therapy, Gamma Knife,	TTT, Surgery, Enucleation,	It is important to prioritize the achievement of local tumor control from the outset by combining the most optimal surgical technique with a better radiant treatment.	4
Bekkering G.E. et Al.[51]	2009	Belgium	37	PBRT	None	Proton Therapy seems to report good local control and a reduction of adverse effects in the treatment of ocular melanoma; however, the lack of more evidence does not allow an effective evaluation.	8
Wang Z. et Al.[52]	2013	USA, Minnesota	27	PBRT (helium, carbon, proton)	I-125 plaque	Treatment with CTP ensures better control of the location and lower rates of retinal disease and cataract formation.	12
Appleton J.P. et Al.[53]	2010	UK , Denbigh-shire	48	PBRT	Brachytherapy Plaque (I-125, Ru-106)	There is no clear difference between Brachytherapy and Proton Therapy, the latter showing significant advantages in the treatment of large melanomas, but the high operating costs limit their spread and use.	3

Abbreviations: Charged particle therapy (CPT).

be superior to Brachytherapy at both 5-year and 10-year follow-ups. However, authors conclude that Brachytherapy should be preferred in most cases, because it is generally more accessible and much less expensive. Proton Therapy should be then used in those few cases in which it has demonstrated clear superiority (53).

Analysis of Methodological Quality

Narrative reviews have been evaluated using the INSA checklist. The highest calculated score was 5/7, which was obtained by four studies: Groenewald C. et Al., Krantz B.A. et Al., S Kaliki and CL Shields , Pereira R. et Al. The worst score was 2/7, which was obtained by two studies: Zehetmayer et Al., Khalil D. et Al. Mean score was 3.83. Median score was 4.

Systematic reviews have been evaluated using the AMSTAR checklist. Wang Z. Et Al obtained the highest score of 9/12. The worst score of 4/12 was attributed to two studies: Yacoub A. Yousef et Al., e Melinda Y Chang. Mean score if 5.6. Median score is 4.

Discussion

In recent years, radiotherapy has been the preferred treatment for uveal melanoma. In fact, it gives survival rates similar to enucleation, but also preserves vision and improves overall patient's quality of life. We performed this systematic review to demonstrate the utility of radiotherapy against uveal melanoma in terms of survival rates, control of tumor growth and metastatic spread. We also assessed the quality of each included study using standardized checklists.

Among the 23 reviews included (18 of narrative-type and 5 of systematic-type), it is evident that brachytherapy is the most common technique. It is widely accessible and less expensive than other forms of radiotherapy. Iodium-125 and Rutenium-106 are most effective against small and medium-size melanomas. Treatment efficacy can be improved if radioactive plaques are positioned via ultrasonographic guidance, or when brachytherapy is combined with TTT (sandwich therapy) or conservative surgery.

In terms of survival rates, brachytherapy and proton therapy have similar efficacy overall. However, Proton Therapy offers better control of tumor growth and gives less complications.

Proton Therapy has demonstrated clear superiority with larger melanomas or melanomas located near critical elements of the eye, such as the fovea or the optic nerve. Side effects are decreased even further with stereotactic proton therapy. Mishra K. Et Al believe that Proton Therapy can be considered the current gold-standard for uveal melanoma, but its high cost limits its spread and application.

In the last decade, stereotactic radiosurgery with Gamma Knife and Cyberknife has offered encouraging results in terms of overall survival rates, control of tumor growth, and side-effects. However, due to the absence of long-term follow-ups, it is hard to compare it with Proton Therapy.

Table 5. INSA scores obtained by the narrative reviews.

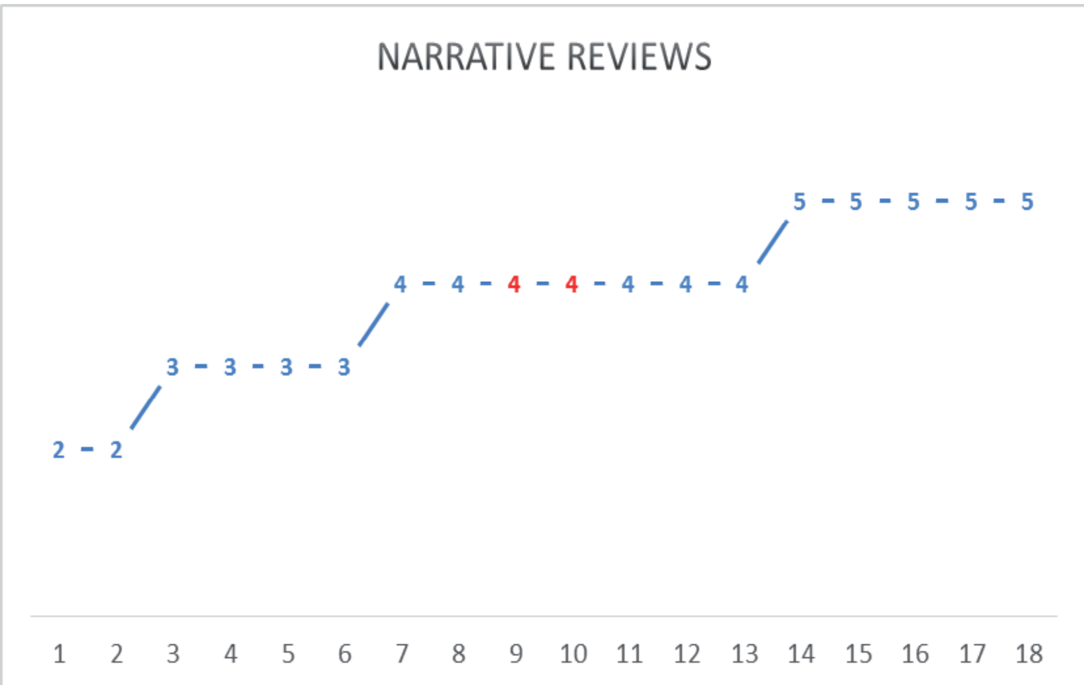
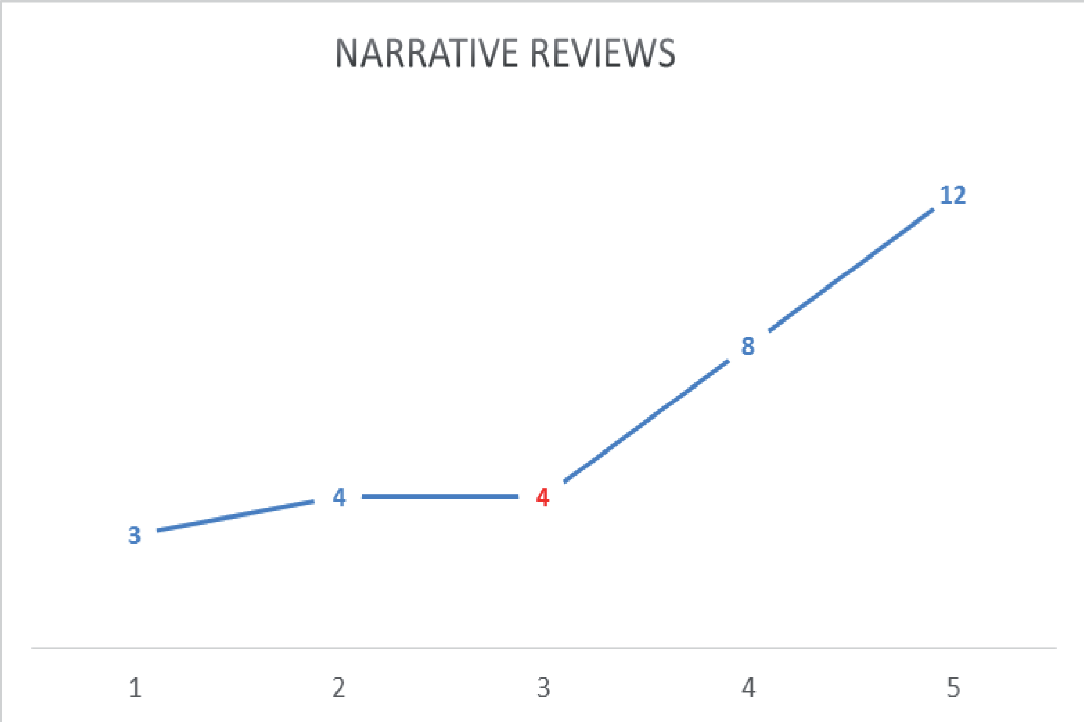


Table 6. AMSTAR scores obtained by the systematic reviews.



Even though current treatment modalities have shown excellent results in limiting local tumor growth, metastatic spread remains the main cause of death in patients with uveal melanoma. According to some studies, MRI or CT scan can detect liver micro-metastases early during the course of the illness. Most authors agree on the importance of performing a cytogenetic analysis to identify the most aggressive forms of melanomas. Future developments will allow us to personalize treatment for each patient based on their cytogenetic mutations (54-57).

Conclusions

In summary, radiotherapy is the preferred treatment for uveal melanoma. Brachytherapy is the most widely used, because it is more readily accessible and less expensive. Proton Therapy is a very promising technique but is much less accessible because of its high operating costs. Due to scarce scientific evidence, we are not able to conclude what radiotherapy technique is the most effective for uveal melanoma.

Acknowledgments

Financial support. This study had no funding.
Potential conflicts of interest. All authors report no conflicts of interest relevant to this article.

References

1. Beroukhim K, Pourang A, Eisen DB. Risk of second primary cutaneous and non-cutaneous melanoma following cutaneous melanoma diagnosis: A population-based study. J Am Acad Dermatol. 2019 Oct 15. pii: S0190-9622(19)32908-1. doi: 10.1016/j.jaad.2019.10.024
2. Kaliki S, Shields CL. Uveal melanoma: relatively rare but deadly cancer. Eye (Lond). 2017 Feb; 31(2): 241–257. doi: 10.1038/eye.2016.275
3. Delgado-Ramos GM, Thomas F, VanderWalde A, et al. Risk factors, clinical outcomes, and natural history of uveal melanoma: a single-institution analysis. Med Oncol. 2019 Jan 21;36(2):17. doi: 10.1007/s12032-018-1230-4
4. Berçin Tarlan, Hayyam Kıratlı. Uveal Melanoma: Current Trends in Diagnosis and Management. Turk J Ophthalmol. 2016 Jun; 46(3):123–137
5. Moon H, Donahue LR, Choi E, et al. Melanocyte Stem Cell Activation and Translocation Initiate Cutaneous Melanoma in Response to UV Exposure. Cell Stem Cell. 2017 Nov 2;21(5):665-678.e6. doi: 10.1016/j.stem.2017.09.001. Epub 2017 Oct 12.
6. Grancara S, Dalla Via L, García-Argáez AN, et al. Spermine cycling in mitochondria is mediated by adenine nucleotide translocase activity: mechanism and pathophysiological implications. Amino Acids. 2016 Oct;48(10):2327-37. doi: 10.1007/s00726-016-2264-6. Epub 2016 Jun 2
7. Fehér J, Kovács I, Pacella E, et al. Correlation of the microbiota and intestinal mucosa in the pathophysiology and treatment of irritable bowel, irritable eye, and irritable mind syndrome. Orv Hetil. 2014 Sep 14;155(37):1454-60. doi:

10.1556/OH.2014.29987. Review. Hungarian
8. Dalvin LA, Shields CL, Ancona-Lezama DA, et al. Combination of multimodal imaging features predictive of choroidal nevus transformation into melanoma. Br J Ophthalmol. 2019 Oct;103(10):1441-1447. doi: 10.1136/bjophthalmol-2018-312967. Epub 2018 Dec 6
9. Caruntu C, Mirica A, Roșca AE, et al. The Role of Estrogens And Estrogen Receptors in Melanoma Development and Progression. Acta Endocrinol (Buchar). 2016 Apr-Jun;12(2):234-241. doi: 10.4183/aeb.2016.234
10. Nichols EE, Richmond A, Daniels AB. Tumor Characteristics, Genetics, Management, and the Risk of Metastasis in Uveal Melanoma. Semin Ophthalmol. 2016;31(4):304-9. doi: 10.3109/08820538.2016.1154175
11. Damato B, Heimann H. Personalized treatment of uveal melanoma. Eye (Lond). 2013 Feb;27(2):172-9. doi: 10.1038/eye.2012.242
12. Pettit TH, Barton A, Foos RY, Christensen RE. Fluorescein angiography of choroidal melanomas. Arch Ophthalmol 1970; 83 (1):27–38
13. Souto EB, Zielinska A, Luis M, et al. Uveal melanoma: physiopathology and new in situ-specific therapies. Cancer Chemother Pharmacol. 2019 Jul;84(1):15-32. doi: 10.1007/s00280-019-03860-z. Epub 2019 May 11
14. Pacella E, Mipatrini D, Pacella F, et al. Suspensory Materials for Surgery of Blepharoptosis: A Systematic Review of Observational Studies. PLoS One. 2016 Sep 15;11(9):e0160827. doi: 10.1371/journal.pone.0160827. eCollection 2016. Review
15. Kaliki S, Shields CL, Mashayekhi A, et al. Influence of age on prognosis of young patients with uveal melanoma: a matched retrospective cohort study. Eur J Ophthalmol 2013; 23 (2): 208–216. DOI: 10.5301/ejo.5000200
16. Diener-West M, Reynolds SM, Agugliaro DJ, et al. Development of metastatic disease after enrollment in the COMS trials for treatment of choroidal melanoma: Collaborative Ocular Melanoma Study Group Report No. 26. Arch Ophthalmol 2005; 123: 1639–1643. DOI: 10.1001/archopht.123.12.1639
17. Violanti SS, Bononi I, Gallenga CE, et al. New Insights into Molecular Oncogenesis and Therapy of Uveal Melanoma. Cancers (Basel). 2019;11(5):694. Published 2019 May 19. doi:10.3390/cancers11050694
18. Pacella E, Pacella F, De Paolis G, et al. Glycosaminoglycans in the human cornea: age-related changes. Ophthalmol Eye Dis. 2015 Jan 27;7:1-5. doi: 10.4137/OED.S17204. eCollection 2015
19. Shields CL, Furuta M, Thangappan A, et al. Metastasis of uveal melanoma millimeter-by-millimeter in 8033 consecutive eyes. Arch Ophthalmol 2009; 127 (8): 989–998
20. Shields CL, Kaliki S, Shah S, et al. Iris melanoma features and prognosis in children and adults in 317 patients. The 2011 Leonard Apt Lecture. J AAPOS 2012; 16:10–16
21. Shields CL, Kaliki S, Cohen MN, et al. Prognosis of uveal melanoma based on race in 8100 patients: The 2015 Doyne Lecture Eye (Lond) 2015 Aug; 29(8): 1027–1035. Published online 2015 Aug 7. doi: 10.1038/eye.2015.51.
22. La Torre G, Pacella E, Saulle R, et al. The synergistic effect of exposure to alcohol, tobacco smoke and other risk factors for age-related macular degeneration. Eur J Epidemiol. 2013 May;28(5):445-6. doi: 10.1007/s10654-013-9798-7. Epub 2013 Mar 31. No abstract available
23. Souri Z, Wierenga APA, Mulder A, et al. HLA Expression in Uveal Melanoma: An Indicator of Malignancy and a Modifiable Immunological Target. Cancers (Basel). 2019 Aug 7;11(8). pii: E1132. doi: 10.3390/cancers11081132
24. Martinis P, Grancara S, Kanamori Y, et al. Involvement of the biogenic active amine agmatine in mitochondrial membrane permeabilization and release of pro-apoptotic factors. Amino Acids. 2019 Oct 25. doi: 10.1007/s00726-019-02791-6
25. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. PLoS Med. 2009 Jul; 6(7): e1000100. Published online 2009 Jul 21. doi: 10.1371/journal.pmed.1000100
26. Matthew J. Page, David Moher. Evaluations of the uptake and impact of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) Statement and extensions: a scoping review. Syst Rev. 2017; 6: 263. Published online 2017 Dec 19. doi: 10.1186/s13643-017-0663-8
27. US National Library of Medicine. 2017 key MEDLINE indicators. https://www.nlm.nih.gov/bsd/bsd_key.html. Updated 2017. Accessed 12/29, 2017
28. Scopus® https://www.scopus.com/home.uri. Updated 2017. Accessed 12/29, 2017
29. La Torre G, Backhaus I, Mannocci A. Rating for narrative reviews: concept and development of the International Narrative Systematic Assessment tool. Senses Sci 2015; 2 (2):31-35doi: 10.14616/sands-2015-2-3135
30. Shea BJ, Hamel C, Wells GA, et al. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. J Clin Epidemiol. 2009 Oct;62(10):1013-20. doi: 10.1016/j.jclinepi.2008.10.009. Epub 2009 Feb 20
31. Groenewald C, Konstantinidis L, Damato B. Effects of radiotherapy on uveal melanomas and adjacent tissues. Eye (Lond). 2013 Feb;27(2):163-71. doi: 10.1038/eye.2012.249. Epub 2012 Nov 30. Review
32. Mishra KK, Chiu-Tsao ST, Orton CG. Point/Counterpoint. Particle therapy is ideal for the treatment of ocular melanomas. Med Phys 2016;43:631-4, DOI: 10.1118/1.4939223
33. Shildkrot Y, Wilson MW. Update on posterior uveal melanoma: treatment of the eye and emerging strategies in the prognosis and treatment of metastatic disease. Current Opinion in Ophthalmology, 01 Nov 2009, 20(6):504-510, DOI: 10.1097/icu.0b013e328330b549
34. Tarlan B, Kıratlı H. Uveal melanoma: Current trends in diagnosis and management. Turk Oftalmoloiji Derg. 2016;46:123–137. doi: 10.4274/tjo.37431
35. Kapoor A, Beniwal V, Beniwal S, et al. Management of uveal tract melanoma: A comprehensive review. J Egypt Natl Canc Inst. 2016 Jun;28(2):65-72. doi: 10.1016/j.jnci.2016.02.003
36. Damato B. Does ocular treatment of uveal melanoma influence survival? Br J Cancer. 2010 Jul 27;103(3):285-90. doi: 10.1038/sj.bjc.6605765
37. Krantz BA, Dave N, Komatsubara KM, et al. Uveal melanoma: epidemiology, etiology, and treatment of primary disease. Clin Ophthalmol. 2017 Jan 31;11:279-289. doi: 10.2147/OPTH.S89591
38. Afshar AR, Stewart JM, Kao AA, et al. Proton beam radiotherapy for uveal melanoma. Expert Review of Ophthalmology. 2015:10(6):577-585, doi.org/10.1586/17469899.2015.1120671.
39. Tarlan B, Kıratlı H. Uveal melanoma: Current trends in diagnosis and management. Turk Oftalmoloiji Derg. 2016;46:123–137. doi: 10.4274/tjo.37431

40. Zehetmayer M, Kitz K, Menapace R, et al. Local tumor control and morbidity after one to three fractions of stereotactic external beam irradiation for uveal melanoma. Radiother Oncol. 2000;55:135–144, DOI: 10.1016/s0167-8
41. Pe'er J. Ruthenium-106 brachytherapy. Dev Ophthalmol. 2012;49:27-40. doi: 10.1159/000328254
42. Stålhammar G, See TR, Filì M, et al. No Gender Differences in Long-Term Survival after Brachytherapy of 1,541 Patients with Uveal Melanoma. Ocul Oncol Pathol. 2019 Oct;5(6):432-439. doi: 10.1159/000497186
43. Yonekawa Y, Kim IK, Gragoudas ES, et al. Aggressive skull base metastasis from uveal melanoma: a clinicopathologic study. Eur J Ophthalmol. 2014 Sep-Oct;24(5):811-3. doi: 10.5301/ejo.5000468
44. Dogrusöz M, Bagger M, van Duinen SG, et al. The prognostic value of AJCC staging in uveal melanoma is enhanced by adding chromosome 3 and 8q status. Invest Ophthalmol Vis Sci 2017:58: 833–842
45. Gezgin G, Luk JS, Cao J, et al. PRAME as a Potential Target for Immunotherapy in Metastatic Uveal Melanoma. JAMA Ophthalmol. 2017 Jun 1; 135(6): 541–549. doi: 10.1001/jamaophthalmol.2017.0729
46. Kaliki S, Shields CL. Uveal melanoma: relatively rare but deadly cancer. Eye (Lond). 2017 Feb; 31(2): 241–257. doi: 10.1038/eye.2016.275
47. Levy RP, Schulte RWM. Stereotactic radiosurgery with charged-particle beams: technique and clinical experience. Transl Cancer Res 2012;1(3):159-172, DOI: 10.3978/j.issn.2218-676X.2012.10.04
48. Khalil DN, Carvajal RD. Treatments for noncutaneous melanoma. Hematol Oncol Clin North Am. 2014 Jun;28(3):507-21. doi: 10.1016/j.hoc.2014.02.006
49. Seregard S, Pelayes DE, Singh AD. Radiation therapy: uveal tumors. Dev Ophthalmol. 2013;52:36-57. doi: 10.1159/000351055.140(00)00164-x
50. Pereira PR, Odashiro AN, Lim LA, et al. Current and emerging treatment options for uveal melanoma. Clin Ophthalmol. 2013;7:1669-82. doi: 10.2147/OPTH.S28863
51. Pacella E, Pacella F, Mazzeo F, et al. Effectiveness of vision rehabilitation treatment through MP-1 microperimeter in patients with visual loss due to macular disease. Clin Ter. 2012 Nov;163(6):e423-8
52. Yousef YA, Alkilany M. Characterization, treatment, and outcome of uveal melanoma in the first two years of life. Hematol Oncol Stem Cell Ther. 2015 Mar;8(1):1-5. doi: 10.1016/j.hemonc.2014.09.004
53. Chang MY, McCannel TA. Local treatment failure after globe-conserving therapy for choroidal melanoma. British Journal of Ophthalmology 2013;97:804-811, doi:10.1136/bjophthalmol-2012-302490
54. Bekkering GE, Rutjes AWS, Vlassov VV, et al. The effectiveness and safety of proton radiation therapy for indications of the eye: a systematic review. Strahlenther Onkol. 2009;185(4):211–21. 10.1007/s00066-009-1900-4. 10.1007/s00066-009-1900
55. Wang Z, Nabhan M, Schild SE, et al. Charged particle radiation therapy for uveal melanoma: a systematic review and meta-analysis. Int J Radiat Oncol Biol Phys. 2013 May 1;86(1):18-26. doi: 10.1016/j.ijrobp.2012.08.026. Epub 2012 Oct 3.
56. Dell'Edera D, Pacella E, Epifania AA, et al. Importance of molecular biology in the characterization of beta-thalassemia carriers. Eur Rev Med Pharmacol Sci. 2011 Jan;15(1):79-86
57. Appleton JP, Bridge P. Comparing plaque brachytherapy and proton therapy for choroidal melanoma: a review of the literature Journal: Journal of Radiotherapy in Practice Journal of Radiotherapy in Practice. 2010:9(1), 53-61, doi:10.1017/S1460396909990197