



Uveal Melanoma with Thickness between 4 and 6 mm Treated with two Different Radioisotopes (I125 or Ru106): Single Institution Experience

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OBJECTIVE

This study aims to evaluate if a disease thickness cut-off of 5 mm can be considered the best choice to select gamma emitter sources, as ¹²⁵I, for the treatment of uveal melanomas.

METHODS

The records of patients affected by primary uveal melanoma and treated in our institutional IOC (Interventional Oncology Center) from December 2006 to December 2016 were retrospectively reviewed. Only patients with a disease thickness between 4 mm and 6 mm treated with ¹⁰⁶Ru or ¹²⁵I plaque were considered for this analysis.

RESULTS

Between December 2006 and December 2016, 107 patients (107 eyes) with UM received brachytherapy treatment with tumor thickness between 4 and 6 mm. Nine patients developed local recurrence while seven patients had distant metastases. No statistically significant difference ($p=0.36$) was observed between the two groups (¹²⁵I versus ¹⁰⁶Ru) concerning DFS. Five patients treated with ¹²⁵I (19.2%) experienced radiation maculopathy; this finding is noteworthy because this toxicity was experienced by 21 patients treated with ¹⁰⁶Ru (25.9%).

CONCLUSION

In this study, we report that the use of ¹²⁵I seeds for UM with a thickness between 5 mm and 6 mm is not associated with a statistically significant increased risk of radiation maculopathy. It is desirable that further multicentric investigations may help to confirm the results of our study.

Keywords: Brachytherapy; interventional radiotherapy; ocular oncology; uveal melanoma.

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Introduction

Uveal melanoma (UM) has an average annual age-adjusted incidence of 1.3–8.6 cases per million per year in Europe according to data from the European Cancer Registry (EUROCARE). UM arises from the uveal tract, most commonly from the choroid (85–90%), but also from the iris (3–5%) and ciliary body (5–8%).[1] Brachytherapy (interventional radiotherapy) is a conservative and functional preserving therapeutic approach which may be used with a local control rate in the range of 88–98% at five years. [2] In addition, evidence from the literature has demonstrated that there is no survival advantage of enucleation over brachytherapy.[3–5] However, interventional radiotherapy may lead to visual function impairment due to radiation maculopathy;[6,7] the area of the eye that appears to be most sensitive to radiation damage is the posterior pole and radiation maculopathy typically develops when radiation exposure extends beyond tissue tolerance.[8]

A multidisciplinary approach is strongly suggested, since the management selected for UM depends on several factors, including tumor's features and patient's general health and personal desires.[9,10]

International guidelines highlight how several isotopes are used in different countries across the globe: the American Brachytherapy Society-Ophthalmic Oncology Task Force (ABS-OOTF) found that ^{125}I and ^{103}Pd are used mainly in North America, ^{125}I or ^{106}Ru in Europe, both ^{106}Ru or ^{90}Sr in Russia and ^{106}Ru in Japan.[11]

The main difference among these isotopes relies on their physical characteristics: in fact, for example, ^{106}Ru is a beta emitter source, while ^{125}I is a gamma source. The choice of the isotope is of pivotal importance also for clinical reasons: gamma emitters can potentially be associated with a higher risk of side effects and should be therefore used for thicker lesions that present a higher risk of recurrence.[12]

Unfortunately, no uniform consensus has been reached in the literature about the criteria guiding the choice between ^{106}Ru and ^{125}I . Some institutions propose a 6 mm disease's thickness cut-off,[13] whereas other institutions prefer 5 mm:[14] the absence of randomized trials investigating this specific topic does not allow reaching definitive conclusions. The present study aims to evaluate if a disease thickness cut-off of 5 mm can be considered the best choice to select gamma emitter sources, as ^{125}I , for the treatment of uveal melanomas.

Materials and Methods

The records of patients affected by primary uveal melanoma and treated in our institutional IOC (Interventional Oncology Center) [15] from December 2006 to December 2016 were retrospectively reviewed. The data were harvested from the intranet hospital multidivisional electronic database. All patients signed the institutionally approved informed consent after a multidisciplinary discussion in which the indication of brachytherapy treatment was confirmed. Uveal Melanoma (UM) presenting a ≤ 5 mm thickness is generally treated with ^{106}Ru plaques, while ^{125}I seeds are used for thicker disease presentations. For these reasons, only patients with a disease thickness between 4 mm and 6 mm treated with ^{106}Ru or ^{125}I plaque were considered for this analysis. We considered a disease thickness cut-off value of 5 mm for the isotope selection, according to the INTERACTS (INTERventional Radiotherapy ACTIVE Teaching School) guidelines.[14]

All patients were treated with ^{106}Ru plaques or ^{125}I seeds, according to disease's thickness, as described above, and prescription dose to tumor's apex was 100Gy and 85Gy, respectively. Since in interventional radiotherapy procedures it is important to follow a precise quality assurance protocol,[16] the patients taken into consideration have been treated according to the INTERACTS protocol.[14]

The statistical analysis was carried out according to the usual methods of descriptive statistics: frequency distribution and percentages. Demographic and clinical data were also described concerning median. The primary endpoint was to determine the disease-free survival (DFS) difference between the two groups of patients. The secondary endpoint included the difference in toxicity registered in the two groups.

Results

Between December 2006 and December 2016, 107 patients (107 eyes) with UM received brachytherapy treatment. The baseline patient demographics, clinical features, and tumor characteristics are summarized in Table 1.

There are major differences in the groups both in patient numbers and in treatment characteristics. In fact, of the overall 107 patients included in this analysis, 26 patients underwent ^{125}I brachytherapy, while ^{106}Ru was used for the remaining 81 patients.

The median tumor thickness was 4.8 mm and the median largest basal tumor diameter was 12.0 mm for

Table 1 Patients' demographics, clinical features and tumor characteristics

	Ru-106	I-125
Laterality: Right/left (%)	48/52	46/54
Mean age (year)	62	67
Diabetes (%)	11	4
Shape: Bilobated/mushroom/plateau (%)	1.1/9.9/89	15/15/70
Location: Choroidal/ciliochoroidal/ciliary/iridociliary (%)	90/3.7/2.6/3.7	73/15/0/12
Quadrant: Superior/temporal/inferior/nasal (%)	27/31/16/26	38/34.6/7.7/27.4

lesion treated with ¹⁰⁶Ru, while lesions treated with ¹²⁵I had a median tumor thickness of 5.8 mm and the median largest basal tumor diameter was 12.1 mm.

The median distance of the posterior margin of the tumour to the fovea was 12.4 mm for lesion treated with ¹⁰⁶Ru, while it was 18.6 mm for UM treated with ¹²⁵I.

The distance to fovea was 12.4 mm for the ¹⁰⁶Ru group, and this value was 18.6mm for the ¹²⁵I group. The patients treated with ¹²⁵I received a dose at tumour apex of 85 Gy; the prescribed apical dose for all the 81 patients treated with ¹⁰⁶Ru was 100.

The median dose of the fovea was 77Gy in the ¹⁰⁶Ru group and was 56 Gy for the ¹²⁵I group.

The median follow-up time was 35 months; all patients included in this study had a regular follow-up. Nine patients developed local recurrence, while seven patients had distant metastases. No statistically significant difference (p=0.36) was observed between the two groups (¹²⁵I versus ¹⁰⁶Ru) concerning DFS, although the patients' prognosis should be worse because of a higher thickness of the lesion, as shown in Figure 1.

Five patients treated with ¹²⁵I (19.2%) experienced radiation maculopathy; this finding is noteworthy because this toxicity was experienced by 21 patients treated with ¹⁰⁶Ru (25.9%). Such data showed that no increase of radiation maculopathy rate was observed in the group treated with ¹²⁵I: rather, a positive trend was registered, even though not statistically significant.

The multivariate analysis did not highlight any statistical difference concerning maculopathy development due to diabetes incidence between the two groups.

Discussion

Even though surgical enucleation historically represents the elective treatment for UM, the COMS confirmed in 2001 that a conservative approach using brachytherapy was both effective and safe,[17] demon-

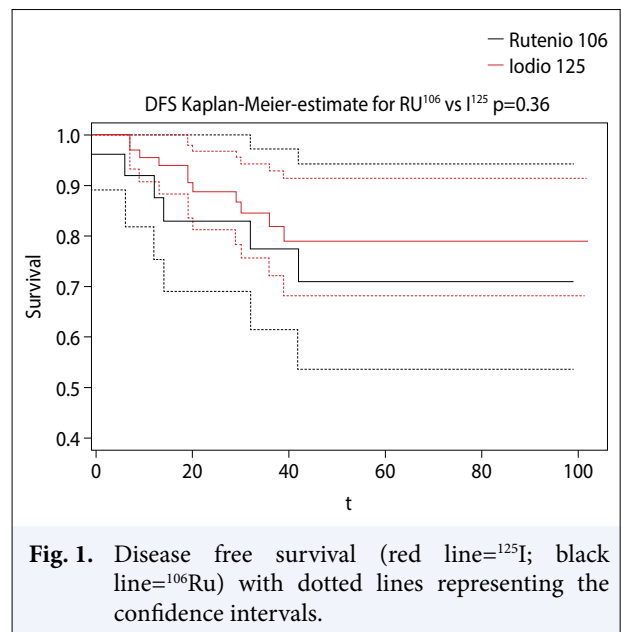


Fig. 1. Disease free survival (red line=¹²⁵I; black line=¹⁰⁶Ru) with dotted lines representing the confidence intervals.

strating no differences in survival between the two therapeutic approaches.

Thanks to the evidence generated by the COMS study and to the growing role of the multidisciplinary management of UM, brachytherapy has to date reached a vast diffusion and has become the most common form of radiotherapy for patients affected by this disease.[18-20]

No uniform consensus has been reached in the literature about the precise value of disease thickness to be used as a cut-off for the choice between beta and gamma emitters. Some authors propose a 6mm thickness value [21] while others use a 5mm cut-off, this grey zone lacks supporting evidence since no randomized trials have investigated this specific problem. In daily clinical practice, the use of gamma emitter sources is currently in thicker UM and could be associated with a higher risk of toxicity-related events, whereas beta emitters are commonly used for smaller lesions and are generally associated with a lesser risk of side effects. In

a recent review of 15 studies, both prospective and retrospective, ^{125}I plaque brachytherapy with a radiation dose of 85.0 Gy to tumor apex was proposed as the gold standard for the conservative treatment of UM with a thickness superior to 5 mm.[22]

Radiation maculopathy as a predictor of possible visus reduction represents one of the main focuses of our analysis since strong evidence about the correlation between maculopathy and visus reduction was described. Visual loss represents indeed the main concern in this disease presentation and the brachytherapy approach clinically balances toxicity issues with functional and aesthetic outcomes. Among different studies using ^{125}I , maculopathy incidence varies between 10% and 63%, while for patients treated using ^{106}Ru plaque,[23] the incidence reported varies between 19.6% and 50%. In our work, radiation maculopathy developed in 25.9% of patients treated using ^{106}Ru and in 19.2% of the patients treated with ^{125}I . The use of clinical nomograms that consider patients and tumor's characteristics has been recently made available and may become a useful tool for toxicity prediction in the near future,[24] helping clinicians in tailoring the therapeutic approach for each patient.[25]

In this context, the use of interdisciplinary standardized data collection systems,[26] which has already been introduced in several institutions for patients affected by head and neck malignancies treated with interventional radiotherapy,[27] represents a very promising approach allowing the enrolment of more numerous samples.

In our study, there are major differences in the two groups, both in patient number and in treatment characteristics, as highlighted in the results section.

In particular, the distribution of the toxicities between the two groups needs to be considered both the distance to the fovea and the median dose of the fovea, which considerably differ as reported before.

Even though we included many patients particularly significant as the population for a single centre, it was not sufficient to detect statistically significant differences between the two treatment groups. However, the trends observed both concerning DFS and maculopathy are in favour of the use of ^{125}I in UM with a thickness between 5 and 6 mm. We calculated that to obtain a significant difference concerning DFS with a confidence of 95% and a statistical power of 80%, with the trend obtained in our group, we would have needed to reach 1032 patients. In consideration of the rarity of UM, and keeping in mind that we evaluated only a small subset of patients for our analysis (the range between 4 and 6 mm), and also considering that not all the centres can use both isotopes we

believe that even though not statistically significant our results are noteworthy.

Conclusion

We report that the use of ^{125}I seeds for UM with a thickness between 5mm and 6mm is not associated with a statistically significant increased risk of radiation maculopathy. It is desirable that further multicentric investigations may help to confirm the results of our study, identifying a thickness cut-off value able to guide the choice of the isotope.

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References

1. Virgili G, Gatta G, Ciccolallo L, Capocaccia R, Biggeri A, Crocetti E, et al. Incidence of uveal melanoma in Europe. *Ophthalmology* 2007;114(12):2309–15.
2. Jensen AW, Petersen IA, Kline RW, Stafford SL, Schomberg PJ, Robertson DM. Radiation complications and tumor control after ^{125}I plaque brachytherapy for ocular melanoma. *Int J Radiat Oncol Biol Phys* 2005;63(1):101–8.
3. Collaborative Ocular Melanoma Study Group. The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma: V. Twelve-year mortality rates and prognostic factors: COMS report No. 28. *Arch Ophthalmol* 2006;124(12):1684–93.
4. Diener-West M, Earle JD, Fine SL, Hawkins BS, Moy CS, Reynolds SM, et al. The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma, III: initial mortality findings. COMS Report No. 18. *Arch Ophthalmol* 2001;119(7):969–82.
5. Sieving PA. Fifteen years of work: the COMS outcomes for medium-sized choroidal melanoma. *Arch Ophthalmol* 2001;119(7):1067–8.
6. Pagliara MM, Tagliaferri L, Azario L, Lenkowicz J, Lanza A, Autorino R, et al. Ruthenium brachytherapy for uveal melanomas: Factors affecting the development of radiation complications. *Brachytherapy* 2018;17(2):432–8.

7. Wen JC, McCannel TA. Treatment of radiation retinopathy following plaque brachytherapy for choroidal melanoma. *Curr Opin Ophthalmol* 2009;20(3):200–4.
8. Tagliaferri L, Pagliara MM, Masciocchi C, Scupola A, Azario L, Grimaldi G, et al. Nomogram for predicting radiation maculopathy in patients treated with Ruthenium-106 plaque brachytherapy for uveal melanoma. *J Contemp Brachytherapy* 2017;9(6):540–7.
9. El Saghir NS, Keating NL, Carlson RW, Khoury KE, Fallowfield L. Tumor boards: optimizing the structure and improving efficiency of multidisciplinary management of patients with cancer worldwide. *Am Soc Clin Oncol Educ Book* 2014;e461–e6.
10. Pillay B, Wootten AC, Crowe H, Corcoran N, Tran B, Bowden P, et al. The impact of multidisciplinary team meetings on patient assessment, management and outcomes in oncology settings: A systematic review of the literature. *Cancer Treat Rev* 2016;42:56–72.
11. American Brachytherapy Society - Ophthalmic Oncology Task Force. The American Brachytherapy Society consensus guidelines for plaque brachytherapy of uveal melanoma and retinoblastoma. *Brachytherapy* 2014;13(1):1–14.
12. Blasi MA, Pagliara MM, Tagliaferri L, Caputo CG, Villano A, Balestrazzi E. Brachytherapy with Iodine 125 or Ruthenium 106 for treatment of choroidal melanomas measuring 5-7 mm in thickness. *Investigative Ophthalmology & Visual Science* March 2012;53:3404.
13. Tarmann L, Wackernagel W, Ivastinovic D, Schneider M, Winkler P, Langmann G. Tumor parameters predict the risk of side effects after ruthenium-106 plaque brachytherapy of uveal melanomas. *PLoS One* 2017;12(8):e0183833.
14. Tagliaferri L, Pagliara MM, Boldrini L, Caputo CG, Azario L, Campitelli M, et al. INTERACTS (INTERventional Radiotherapy ACTIVE Teaching School) guidelines for quality assurance in choroidal melanoma interventional radiotherapy (brachytherapy) procedures. *J Contemp Brachytherapy* 2017;9:287–95.
15. Kovács G, Tagliaferri L, Valentini V. Is an Interventional Oncology Center an advantage in the service of cancer patients or in the education? The Gemelli Hospital and INTERACTS experience. *J Contemp Brachytherapy* 2017;9(6):497–8.
16. Piermattei A, Grimaldi L, D'Onofrio G, Cilla S, Viola P, Craus M, et al. In-vivo portal dosimetry by an ionization chamber. *Phys Med* 2005;21(4):143–52.
17. Melia BM, Abramson DH, Albert DM, Boldt HC, Earle JD, Hanson WF, et al. Collaborative ocular melanoma study (COMS) randomized trial of I-125 brachytherapy for medium choroidal melanoma. I. Visual acuity after 3 years COMS report no. 16. *Ophthalmology* 2001;108(2):348–66.
18. Brewington BY, Shao YF, Davidorf FH, Cebulla CM. Brachytherapy for patients with uveal melanoma: historical perspectives and future treatment directions. *Clin Ophthalmol* 2018;12:925–34.
19. Autorino R, Vicenzi L, Tagliaferri L, Soatti C, Kovacs PG, Aristei C. A national survey of AIRO (Italian Association of Radiation Oncology) brachytherapy (Interventional Radiotherapy) study group. *J Contemp Brachytherapy* 2018;10(3):254–9.
20. Tagliaferri L, Pagliara MM, Fionda B, Scupola A, Azario L, Sammarco MG, et al. Personalized re-treatment strategy for uveal melanoma local recurrences after interventional radiotherapy (brachytherapy): single institution experience and systematic literature review. *J Contemp Brachytherapy* 2019;11(1):54–60.
21. Rospond-Kubiak I, Wróblewska-Zierhoffer M, Twardosz-Pawlik H, Kocięcki J. Ruthenium brachytherapy for uveal melanoma - single institution experience. *J Contemp Brachytherapy* 2017;9(6):548–52.
22. EcheGARAY JJ, Bechrakis NE, Singh N, Bellerive C, Singh AD. Iodine-125 Brachytherapy for Uveal Melanoma: A Systematic Review of Radiation Dose. *Ocul Oncol Pathol* 2017;3(3):193–8.
23. Takiar V, Voong KR, Gombos DS, Mourtada F, Rechner LA, Lawyer AA, et al. A choice of radionuclide: Comparative outcomes and toxicity of ruthenium-106 and iodine-125 in the definitive treatment of uveal melanoma. *Pract Radiat Oncol* 2015;5(3):e169–76.
24. Damiani A, Masciocchi C, Boldrini L, Gatta R, Dinapoli N, Lenkowicz J, et al. Preliminary Data Analysis in Healthcare Multicentric Data Mining: a Privacy-preserving Distributed Approach. *Journal of e-Learning and Knowledge Society* 2018; 14(1)71–81.
25. Tagliaferri L, Kovács G, Autorino R, Budrukkar A, Guinot JL, Hildebrand G, et al. ENT COBRA (Consortium for Brachytherapy Data Analysis): interdisciplinary standardized data collection system for head and neck patients treated with interventional radiotherapy (brachytherapy). *J Contemp Brachytherapy* 2016;8(4):336–43.
26. Valentini V, Maurizi F, Tagliaferri L, Balducci M, Cellini F, Gambacorta MA, et al. SPIDER: Managing Clinical Data of Cancer Patients Treated through a Multidisciplinary Approach by a Palm Based System. *Italian J Public Health* 2008;5(2):66–76.
27. Tagliaferri L, Budrukkar A, Lenkowicz J, Cambeiro M, Bussu F, Guinot JL, et al. ENT COBRA ONTOLOGY: the covariates classification system proposed by the Head & Neck and Skin GEC-ESTRO Working Group for interdisciplinary standardized data collection in head and neck patient cohorts treated with interventional radiotherapy (brachytherapy). *J Contemp Brachytherapy* 2018;10(3):260–6.