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Radiotherapy of choroidal metastases[1]

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Abstract

Purpose: This retrospective study was undertaken to clarify the role of high energy external beam radiation therapy (EBRT) and to determine its safety and efficacy on local control and visual acuity in patients suffering from choroidal metastases (CM).

Materials and methods: The records of 58 consecutive patients treated with EBRT between 1970 and 1993 were analyzed. The female to male ratio was 2.9 and the median age was 59 years (range 40–81 years). Thirty-six patients (62%) had unilateral CM and 22 patients had bilateral CM. The mean number of lesions per eye was two. Retinal detachment was present in 65% of cases. The primary tumour (PT) was breast carcinoma for 38 patients (75%), lung carcinoma for 10 patients (17%) and gastrointestinal, genitourinary or unknown PT for the remaining 10 patients. The median interval of time between the PT and the CM was 55 months (range 0–228 months). All patients were treated with megavoltage irradiation. The median prescribed dose was 35.5 Gy (range 20–53 Gy) normalized at a 2 Gy per fraction schedule with an α/β value of 10 Gy. Various techniques were used and whenever possible the lens was spared. Ten patients with unilateral disease were treated in both eyes.

Results: The tumour response was slow. When assessed after 3 months or more, the complete response rate was 53% with significantly better results for doses higher than 35.5 Gy (72 versus 33%; $P = 0.009$). Visual acuity was improved or stabilized in 62% of patients, with also significantly better results when doses higher than 35.5 Gy ($P = 0.014$) were administered. Amongst 26 patients with unilateral CM who had no elective contralateral irradiation, three developed metastasis in the opposite eye versus none of the 10 patients who had bilateral irradiation. Five complications occurred (three cataracts, one retinopathy and one glaucoma).

Conclusion: Radiation therapy is an efficient and safe palliative treatment for choroidal metastases and it helps the preservation of vision. Thus, there is a major impact on the quality of life in a group of patients with an almost uniformly fatal prognosis. Both tumour response and visual acuity are significantly improved if doses higher than 35.5 Gy are administered. Whenever possible, a lens sparing technique should be used.

Keywords: Eye metastases; Choroid metastases; Palliative treatment; Radiation therapy; Eye complication

1. Introduction

Choroidal metastases (CM) are the most common intraocular neoplasms. Bloch and Gartner [3] examined the eye and orbit post-mortem in 230 cancer patients and found 28 eyes with metastases, with an overall incidence of 12%. Nelson et al. [11] similarly found a 9% incidence of intraocular metastases in 716 eyes [11]. However, the incidence of clinically symptomatic intraocular secondary tumours is lower. Albert et al. [1] in the 1960s estimated it to be 2.3%. The uveal tract is the most common site of intraocular metastases, probably due to anatomical reasons and blood vessel supply. With the improvement in cancer treatment and prolongation of survival, it is likely that more and more patients will present symptomatic choroidal metastases. As a result, the most common symptom, decreased vision, can have major repercussions on the quality of live of those patients who are generally in a poor physical condition. In this study, we retrospectively analyzed all consecutive patients with uveal metastases treated by external beam radiation therapy in our institution, in order to assess the safety and efficacy of the treatment.

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2. Materials and methods

The records of 58 consecutive patients admitted in the Radiation Oncology Department of the Centre Hospitalier Universitaire Vaudois (CHUV) in Lausanne for treatment of CM between 1970 and 1993 were reviewed. The majority of these patients as well as the majority of follow-up examinations were at the Hôpital Ophtalmique Jules Gonin, University of Lausanne. All information regarding the date and site of the primary, tumour local status of the primary at the time when CM was diagnosed, date of CM diagnosis, symptoms, localization and number of lesions in the eye, radiation treatment and technical parameters was collected. To evaluate the treatment results, all the ophthalmologic clinical observations were gathered, as well as the date and localization of any new metastasis and the date of death.

The main study end-points were clinical response, visual improvement, retinal reattachment and postradiation ocular complications. Survival analysis was also performed to determine the overall prognosis of this particular patient population.

2.1. Patient characteristics

Of the 58 patients, 43 were female and 15 were male giving a sex ratio of 2.9. The ages ranged from 40 to 81 years, with a median of 59 years (Table 1).

2.2. Primary tumour characteristics

The primary tumour characteristics are summarized in Table 1. Most of the patients presented primary breast cancer (38/58) or lung cancer (10/58), while the remainder were primary prostate, kidney, oesophagus, stomach, rectum carcinoma, unknown primary and retroperitoneal soft tissue sarcoma. Histology was mainly adenocarcinoma (50/58), while two patients presented with squamous cell carcinoma, two patients presented with small cell carcinoma, one patient presented with clear cell carcinoma, one patient presented with signet cell carcinoma and one patient presented with leiomyosarcoma. Of note is the fact that the CM was the first clinical manifestation of cancer disease for eight patients. The median time between CM and the discovery of the primary tumour was 55 months (range 0–228 months). The time interval was much shorter for lung cancer (2.5 months) than for breast cancer (68 months).

In half of the patients the primary cancer was locally controlled at the time of CM diagnosis.

Table 1

Age and time to choroidal metastasis since diagnosis of primary tumour according to gender and primary tumour[a]

	No. of patients	Median age (years) (range)	Median time (months) (range)
Male	15	61 (48–70)	12 (0–62)
Female	43	55 (40–81)	68 (0–228)
Breast cancer[b]	38	56 (40–81)	68 (0–228)
Lung cancer	10	61 (48–75)	2.5 (0–40)
Other primary	13	61 (44–81)	11 (0–108)

[a]Three patients had double primary localization.
[b]In addition five women had bilateral breast cancer.

Table 2

Number of lesions per eye and primary site

Primary tumour	No. of eyes	No. of lesions					
		1	2	3	4	5	>5
Breast	52	26	10	4	6	5	1
Lung	13	8	2	1	0	0	2
Others	15	5	3	0	5	0	2
Right eye	40	20	8	2	6	2	2
Left eye	40	19	7	3	5	3	3

2.3. Choroidal metastases characteristics

Altogether, 80 eyes in 58 patients were affected by metastases. For 36 patients (62%) CM were unilateral with an equal distribution between the right and the left side and for 22 patients (38%) CM were bilateral. The posterior pole of the choroid was affected in 53 eyes (66%), the iris in three cases (4%), and in the remaining 24 eyes, the CM were localized in the periphery of the choroid. In nine cases the lesion infiltrated the ciliary body.

In half of the eyes the metastasis was solitary, while in the remainder the number of metastases varied from two to eight. Table 2 shows the number of CM considering eye side and primary. Retinal detachment was present in 50 eyes.

Table 3 describes the frequency of symptoms, blurred vision being the most commonly encountered. The diagnosis of CM was made on the basis of clinical examination in most cases and was confirmed by fluorescein angiography and ultrasonography, except for one case where it was obtained by needle biopsy. Fourteen patients with 21 involved eyes were unsuccessfully treated prior to irradiation with various modalities (chemotherapy, 12 eyes; hormonal therapy, seven eyes; photocoagulation, two eyes).

Table 3

Symptoms and frequency in choroidal metastases presentation

Symptoms	No. of patients (%)
Blurred vision	53 (91)
Visual field defect	13 (22)
Photopsia, xanthopsia	9 (15)
Metamorphopsia	7 (12)
Inflammation (red eye)	2 (3)
Visible tumour, iris lesion	2 (3)
Pain	1 (1)

Table 4
Treatment techniques

Treatment	Lens-sparing technique (no. of patients)	No lens-sparing technique (no. of patients)	Total (patients)	Total (eyes)
Bilateral irradiation	21[a]	9	30	60
Unilateral irradiation	18[b]	10	28	28
Total	39	19	58	88

[a]Includes 10 patients with unilateral choroidal metastases.
[b]Includes two patients with bilateral choroidal metastases irradiated on one side (see text).

2.4. Treatment

Altogether, 88 eyes were irradiated by EBRT with 6 MV photons or electron beams of various energies. Of the 80 eyes actually affected with metastases, 78 were irradiated and two were not, in one case because of prior enucleation and in the other one for an unknown reason. Thus, the remaining 10 treated eyes, which were not affected, could be considered as being irradiated electively.

During the observed period of time, the irradiation techniques varied substantially, i.e. the eyes were treated either by one lateral, oblique or anterior field, or by two lateral or crossed fields. For further analysis, we grouped the different techniques as follows: (1) bilateral irradiation with two lateral fields, (a) with or (b) without a lens-sparing technique; (2) unilateral irradiation (a) with or (b) without a lens-sparing technique (Table 4). The doses varied from 20 to 53 Gy in 10–30 fractions. For the purpose of this analysis, doses were normalized to 2 Gy per fraction equivalent, using the linear-quadratic model with an α/β value of 10 Gy. This large variation of techniques and doses was essentially due to changes in the medical teams and policy of treatment during a 23-year period.

Response to treatment was defined as (1) tumour shrinkage: (a) complete response (CR), complete tumour shrinkage replaced by a scar; (b) partial response (PR), less than complete shrinkage of tumour with scar formation; (c) no change (NC), no change in tumour volume; (d) progressive disease (PD), increase in tumour volume; (2) improvement of vision: (a) visual acuity improved or stable; (b) visual acuity worse than before treatment; (3) retinal reattachment: (a) CR, complete reattachment; (b) PR, any detectable reattachment; (c) NC, no change in detachment; (d) PD, increase in detachment of retina.

2.5. Statistical methods

Survival was estimated by the Kaplan–Meier method [9] and standard errors of survival were estimated by the Greenwood formula [5]. All patients were included in the analysis and potential losses of follow-up were considered as censored observations at the date of last known survival. Survival differences were tested by the log-rank test [13]. Differences in distributions of clinical response and vision were tested by the χ^2-test [2]. The cumulative incidence of competing events (death, complication and others metastases) for the event-free survival was estimated by appropriate methodology [8].

3. Results

3.1. Response to treatment

The majority of eyes achieved a complete disappearance or at least a detectable shrinkage of the tumour mass. Only three of 67 eyes (14 eyes were never evaluated after treatment) presented no change or progression of the tumour mass and thus CR and PR were achieved in 53 and 29% of cases, respectively. When we compare treatment results for two dose levels (more than 35.5 Gy versus less than 35.5 Gy), CR was achieved in 72 and 33%, and PR was achieved in 18 and 41% of cases, respectively. This difference in CR according to dose was highly significant ($P = 0.009$). Visual improvement or stabilization was achieved in 62% of eyes. Again, visual improvement was significantly better when higher doses (>35.5 Gy) were applied, i.e. 72 versus 51% ($P = 0.014$). The rate of complete retinal reattachment was 32% and the rate of partial reattachment was 22%. For this particular end-point, no dose response could be demonstrated ($P = 0.457$) (Table 5).

It is quite interesting to note that the response to the treatment was delayed with time. For almost all the patients who were examined within 6 weeks after treatment and then re-examined at or after 3 months, we observed an improvement in response and for only one patient did we observe deterioration of response with time.

Table 5
Treatment results on local control in the eye

Results	No follow-up data	CR (*n*) (%)	PR (*n*) (%)	NC or PD (*n*) (%)	*P*-value
Clinical response					
Overall	11	41 (53)	23 (29)	3 (4)	
<35.5 Gy	8	13 (33)	16 (41)	2 (5)	
>35.5 Gy	3	28 (72)	7 (18)	1 (2)	0.009
Retinal reattachment					
Overall	18	16 (32)	11 (22)	5 (10)	
<35.5 Gy	11	6 (22)	7 (26)	3 (11)	
>35.5 Gy	7	10 (44)	4 (17)	2 (9)	0.457
Vision		Stable or improved	Worse		
Overall	19	48 (62)	11 (14)		
<35.5 Gy	15	20 (51)	4 (10)		
>35.5 Gy	4	28 (72)	7 (18)		0.014

See text for definition of responses.
[a]For some patients data were available, for example, for vision, whereas retinal reattachment or tumour shrinkage were not assessed.

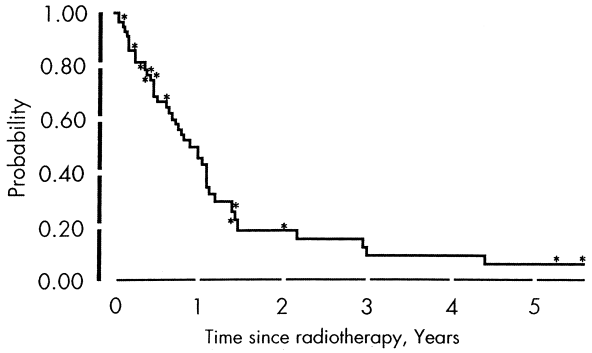

Fig. 1. Overall survival since radiotherapy for the entire group.

3.2. Complication

Five radiation-induced complications were noted during the follow-up period at doses of 36.5, 51.4, 52.0, 44.0 and 32.5 Gy (normalized at a 2 Gy per fraction schedule with an α/β value of 10 Gy) after 0.5, 0.5, 1.5, 3.5 and 3.5 years, respectively, following treatment (Fig. 3).

There were three cataracts, one radiation-induced retinopathy and one glaucoma. The one case of glaucoma was due to subretinal haemorrhage and the patient needed enucleation 8 months after treatment. Radiation-induced retinopathy was observed in a patient who underwent fine needle biopsy for diagnosis. None of the patients who presented a cataract underwent phakectomy. We did not observe any case of dry eye syndrome.

As previously mentioned, 10 eyes without CM were electively irradiated and none developed any new CM during the follow-up period. Conversely, among the 26 healthy contralateral eyes which were not electively irradiated, three had new metastases. We did not observe any complication in any of the healthy eyes after irradiation.

3.3. Survival

The overall 1-, 2- and 3-year survival rates after CM diagnosis for the entire group of patients were 47, 19 and 10%, respectively. For the breast cancer group, they were 59, 30 and 19% and for the lung cancer group they were 20, 7 and 0%, respectively. The difference according to the primary tumour localization was significant ($P = 0.018$) (Figs. 1 and 2).

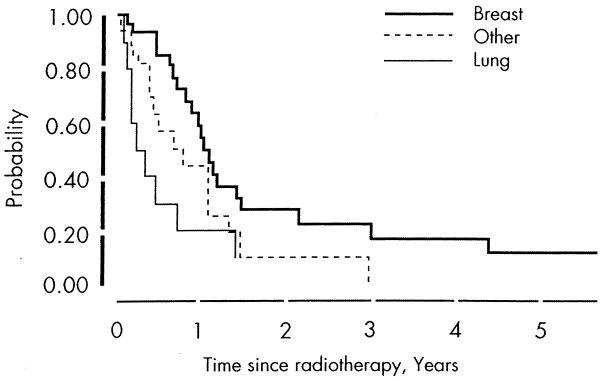

Fig. 2. Overall survival since radiotherapy according to PT.

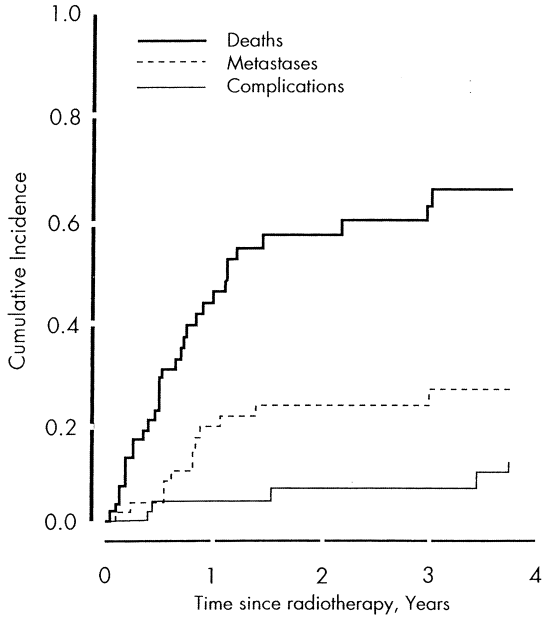

Fig. 3. Cumulative incidence for death, new extra-ocular metastasis and complication in the eye after treatment.

The cumulative incidence of competing events such as death, extra-ocular metastases and complication is shown in Fig. 3. At 1 year the cumulative incidence of complication remains low (<10%).

4. Discussion

As described in previous series, our data confirm that CM are mostly seen in a female population with primary breast cancer, the second most frequent primary tumour being lung cancer [1,3,6,15,21].

According to some hypotheses, the higher incidence of CM in patients with breast cancer could be due to a greater affinity of this tumour type to the eye tissue. However, the median time from PT to the diagnosis of CM was much shorter for lung cancer patients (2.5 months) than for breast cancer patients (68 months). Thus, the higher incidence may simply reflect the longer natural history of breast cancer. As a matter of curiosity, there were 34 women and four men with CM from breast cancer with a female to male ratio of 8.5. In general the sex ratio in breast cancer is around 100:1 (M/F).

Some authors suggest that multiple CM is specific for patients with breast cancer [19], but in our series multiple lesions were present regardless of the primary tumour site.

As reported by others, the predominant histologic type of the PT in our study was adenocarcinoma [1].

The typical presentation of a CM is a homogeneous creamy yellow choroidal lesion, which is often complicated by secondary retinal detachment. The differential diagnosis with ocular melanoma or other ocular lesions can be made

by clinical evaluation, including a previous cancer history, ophthalmoloscopic examination, ultrasonography, computer tomography and fluorescein angiography. Some investigators advocate needle aspiration biopsy to improve the diagnosis [14,17]. We feel, however, that it should only be done in very exceptional and difficult diagnostic situations because of a significant risk of a seeding along the biopsy track, which may preclude efficient radiotherapy or cause other complications.

Chu et al. [4], in their analysis of CM of breast cancer, divided the choroidal lesions into three grades according to the severity of the retinal detachment and extent of the lesion. This type of analysis was not possible in our work because of the wide variation in the size of metastases with or without retinal detachment. In addition, the methods of measurements changed during the period of this analysis; in the 1970s the size was reported according to the surface of the lesions, whereas current measurements also take thickness into account. For this reason we could not make any dose–volume response assessments.

In previously published analyses, the effect of radiation therapy on CM was assessed only on the basis of subjective or objective visual improvement [7,10,15,16,19,20]. Hoogenhout et al. [6] reported their results both in terms of visual improvement and tumour regression or retinal reattachment.

Our data allows us to separately analyze tumour shrinkage, retinal reattachment and preservation of vision. Even if the mechanism of retinal reattachment is quite complex, we feel that irradiation plays a major role. It should be emphasized that after irradiation of CM, the lesions become progressively flatter, with a typical pigment epithelial proliferation over the surface of the lesions [10]. This partially atrophic surface is considered as a 'scar', which can even be larger than the metastasis prior to treatment. This particular phenomenon allows a better retrospective estimate of the real initial surface of CM. If all patients who underwent an ophthalmological re-evaluation are taken into account, our data show that with EBRT, the overall response rate is 96% and the complete response rate is 61%. Regarding retinal reattachment, the overall reattachment rate is 84% and the complete reattachment rate is 50%. However, this corresponds to the patients' ophthalmological status at the last visit. It is possible that the proportion of patients who had incomplete or no retinal reattachment and who could not come for their next visit actually improved their eyes' status. It is then possible that our data underestimate the overall reattachment rate. Vision was improved or was stabilized in 81% of the eyes. Results were significantly better when total doses were higher than 35.5 Gy. The number of patients was too small to analyze the treatment response according to primary site. In two patients of this series, no response to EBRT was achieved; they were then treated successfully with proton beam radiotherapy [21]. One should also add that in the case of solitary metastasis, plaque radiotherapy can be successfully used if EBRT fails [18]. Shields et al. [18] advocate this technique because of its short treatment time (3–4 days), unlike the 3–4 weeks needed for EBRT treatment. However, plaque radiotherapy can be applied only to inpatients whereas EBRT is used for outpatients.

The total dose recommended in the literature is not uniform and varies from 21 Gy in seven fractions to 40 Gy in 14 fractions [4,6,15,19]. Both total dose and dose per fraction should be considered in assessing the risk of treatment complications. Four of five radiation-induced complications have been seen in our series with doses above 35.5 Gy.

In our experience, cataract was infrequent and was found in only three of 78 treated eyes. Nineteen eyes were treated without any lens-sparing technique. This low figure is likely to be explained by a high number of early deaths, given the rather long delay between therapy and radiation-induced cataract. In any case attempts should be made whenever possible to spare the lens. We did not observe any case of dry eye syndrome. Admittedly, it was not possible to retrospectively estimate the proportion of lacrimal glands which were completely or partially irradiated. Additionally, the rather low doses and the relatively poor survival rates are possible explanations for the absence of dry eye syndrome in our study [12].

In our series, 38% of patients suffered from bilateral synchronous CM. If the contralateral eye was not primarily irradiated, metachronous metastases occurred in three out of 26 patients, whereas none were observed when bilateral irradiation was given (0/10). On the basis of these results and contrary to the results of Ratanatharathorn et al. [14], it seems reasonable to recommend bilateral irradiation whenever CM are to be treated, given the lack of contralateral complication and technical ease of this RT technique.

The difference in survival varies according to the site of the primary lesion and only reflects the natural history of each tumour site. In our experience the differences were significant in favour of breast cancer patients.

5. Conclusions

Radiation therapy is an efficient and safe palliative treatment for choroidal metastases and helps the preservation of vision and thus the quality of life in a group of patients with an almost uniformly fatal prognosis. Moderate doses (>35.5 Gy) of radiation with a conventional fractionation (2–2.5 Gy/fraction) should be used. We feel it appropriate to recommend bilateral irradiation even in unilateral uveal involvement. Whenever possible, a lens-sparing technique should be used.

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