BJR
© 2023 The Authors. Published by the British Institute of Radiology

https://doi.org/10.1259/bjr.20230124

Received: 07 February 2023 | Revised: 09 July 2023 | Accepted: 21 August 2023 | Published online: 10 October 2023

Cite this article as:
Pezzulla D, Di Franco R, Zamagni A, Pastore F, Longo S, Dominici L, et al. Radiotherapy of orbital metastases: a systematic review of management and treatment outcomes on behalf of palliative care study group of Italian association of radiotherapy and clinical oncology (AIRO). *Br J Radiol* (2023) 10.1259/bjr.20230124.

SYSTEMATIC REVIEW

Radiotherapy of orbital metastases: a systematic review of management and treatment outcomes on behalf of palliative care study group of Italian association of radiotherapy and clinical oncology (AIRO)

[1]DONATO PEZZULLA, MD, [2]ROSSELLA DI FRANCO, MD, [3]ALICE ZAMAGNI, MD, [4]FRANCESCO PASTORE, MD, [4]SILVIA LONGO, MD, [5]LUCA DOMINICI, MD, [6]SARA LILLO, MD, [7]ANTONELLA CIABATTONI, MD, [8]FABIO ARCIDIACONO, MD, [1,9]FRANCESCO DEODATO, MD, [2]PAOLO MUTO, MD, [3,10]ALESSIO GIUSEPPE MORGANTI, MD, [4]FRANCESCO CELLINI, MD and [11]ERNESTO MARANZANO, MD

[1]Radiation Oncology Unit, Responsible Research Hospital, Largo A. Gemelli 1, Campobasso, Italy
[2]Department of Radiation Oncology, Istituto Nazionale Tumori-IRCCS-Fondazione G. Pascale, Naples, Italy
[3]Radiation Oncology, Department of Experimental Diagnostic and Specialty Medicine (DIMES), Alma Mater Studiorum-Bologna University, Bologna, Italy
[4]Dipartimento di Diagnostica Per Immagini, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, UOC di Radioterapia Oncologica, Radioterapia Oncologica ed Ematologia, Rome, Italy
[5]Department of Radiotherapy, Humanitas Clinical and Research Center–IRCCS, Rozzano, Milan, Italy
[6]Radiation Oncology Unit, Department of Biomedical, Dental Science and Morphological and Functional Images, University of Messina, Messina, Italy
[7]UOC Radioterapia, Ospedale San Filippo Neri, ASL Roma 1, Rome, Italy
[8]Radiotherapy Oncology Centre, "S. Maria" Hospital, Terni, Italy
[9]Università Cattolica del Sacro Cuore, Istituto di Radiologia, Milan, Italy
[10]Radiation Oncology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy
[11]University of Perugia-Faculty of Medicine and Surgery Radiotherapy Oncology Centre-"S. Maria" Hospital, Terni, Italy

Address correspondence to: Dott Donato Pezzulla
E-mail: *donato.pezzulla@responsible.hospital*

The authors Francesco Cellini and Ernesto Maranzano contributed equally to the work.

Objectives: We search the current literature on data regarding the role of RT in OM treatment, focusing on the improvement of symptoms and patient quality of life.
Methods: This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.
Results: From 340 citations, 60 papers were finally selected: 45 case reports and 15 case series. The case reports accounted for 47 patients. In 37/39 cases (95%), EBRT was done. Patients were mainly treated with 3DCRT, IMRT, and with SBRT. The most used RT regimens were 30 Gy in 10 fractions (23%) and 20–25 Gy in 5 fx (13%). No sever toxicity was reported. A median LC of 11 months (range 1–54 months) and a median OS of 12 months (range 1–54 months) were registered. Among the case series, a total of 457 patients were examined, 227 of whom underwent RT. The main used techniques were 3DCRT, CK, GK, SBRT, and BRT. RT doses could vary from 30 Gy/10 fractions to 60 Gy/30 fractions, 50 Gy/5 fractions, or 16.5–21 Gy in single fraction. No toxicity above G2 was reported. ORR could vary between 75 and 100%. Only two study provided information on response duration: a mean LC time of 22.8 months and a mean time to local progression of 5 months (range: 3–7). Regarding OS, the data were heterogeneous, ranging between 1 and 54 months.
Conclusions: RT for OM seems to be a safe and feasible option. More information on the RT ideal techniques and dose are still needed.
Advances in knowledge: This paper tried to sum up the few and fragmented data on the use of radiotherapy for orbital metastases: the possible option ranged from 3D- and 2D-CRT to SBRT, CK, and GK, with different possible fractionations (30Gy in 10 fractions, 60 Gy/30 fractions, 20-50 Gy/5 fractions, or 16.5-21 Gy in single fraction). Regardless of the chosen approach, almost all treated patients experienced a benefit after RT in terms of OM-related symptom intensity reduction and a good acute and late toxicity profile.

INTRODUCTION

Metastatic disease represents 1–13% of all orbital tumours and can significantly lead to debilitating visual impairment.[1–3] Orbital metastases (OM) usually occur at later stages of primary tumours with diffuse location in anterior or lateral orbit, rarely invading intracranial structures.[1,2,4] Orbital fat and rectus muscles are the sites most frequently affected by the disease.[5–8]

Symptoms associated with OM can be diplopia, blurred vision, pain, loss of vision, limited ocular motility, proptosis, the presence of a palpable mass, and ptosis.[7]

Several management strategies have been used to treat OM: surgical resection, orbital exenteration, and complementary therapies. A debulking of these tumours may temporarily alleviate symptoms. Systemic chemotherapeutic regimens offer the best chance for systemic tumour control, but their benefit varies according to the primary tumour type.

Radiotherapy (RT) provides meaningful relief of symptoms and can result in at least temporary improvement in quality of life.[9–11] There are experiences in the literature that have documented complete relief of symptoms after radiotherapy.[6,12]

In this systematic review, we evaluated the management strategies and in particular the role of RT in the treatment of OM, focusing on improvement of symptoms and patient quality of life.

METHODS AND MATERIALS

Study selections

This systematic review was performed following recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[13]

The search on MEDLINE published from January 2000 to August 2022 was performed. Keywords used were Radiotherapy AND orbital AND metastases.

The computer search was supplemented manually using reference lists for all available review articles, primary studies, meeting abstracts, and bibliographies of books to identify studies not encountered in the computer search.

Inclusion and exclusion criteria

Prospective and retrospective studies, case series, or case reports focusing on lesions of the orbital cavity (defined as the bony cavity and its associated muscles, vessels, and nerves) were included in this analysis. Inclusion criteria were: English language, full-text articles, and the presence of detailed toxicity data. Exclusion criteria were: only abstracts, letters, proceedings from scientific meetings, editorials, expert opinions, reviews without original data, studies lacking toxicity and/or safety outcomes, repetitive data, animal studies, and studies focusing on lesions of the ocular globe. Retrieved records underwent title-and-abstract review and then full-text review. Independent reviewers (RDF, FP, AZ) screened the studies in duplicate using the eligibility criteria reported above. Five independent reviewers (DP, SL, LD, SLo, AC, FC, FA,) performed data extraction. Reasons for exclusion at full-text review were recorded. Disagreements among reviewers were infrequent (<20%) and were resolved by discussion.

Data extraction

Data were extracted from one author (DP) and then independently verified by five additional authors (RDF, PM, FD, AGMl, EM).

Data included were: author, year, study design, age, gender, primary tumour, time interval between primary tumour and OM, laterality, orbital localization, tissue infiltration, intracranial extension, symptoms, imaging features, extent-of-surgery, surgery techniques, complementary treatment strategies, radiation protocols (*i.e.,* type, fractionation, total dose), clinical/radiological treatment responses, OM recurrence, local control (LC), overall survival (OS), and survival status.

Statistical analysis

The over mentioned information was gathered and analysed through descriptive analysis methods. When allowed, LC was calculated on a "per lesion" basis from treatment end until death, last follow-up visit, or lost to follow-up, while OS was calculated on a "per patient" basis from treatment end to the date of death, last follow-up visit, or lost to follow-up.

Medians and life tables were computed using the product-limit estimate by Kaplan and Meier method. Statistical analysis was performed using SPSS statistical software (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp).

RESULTS

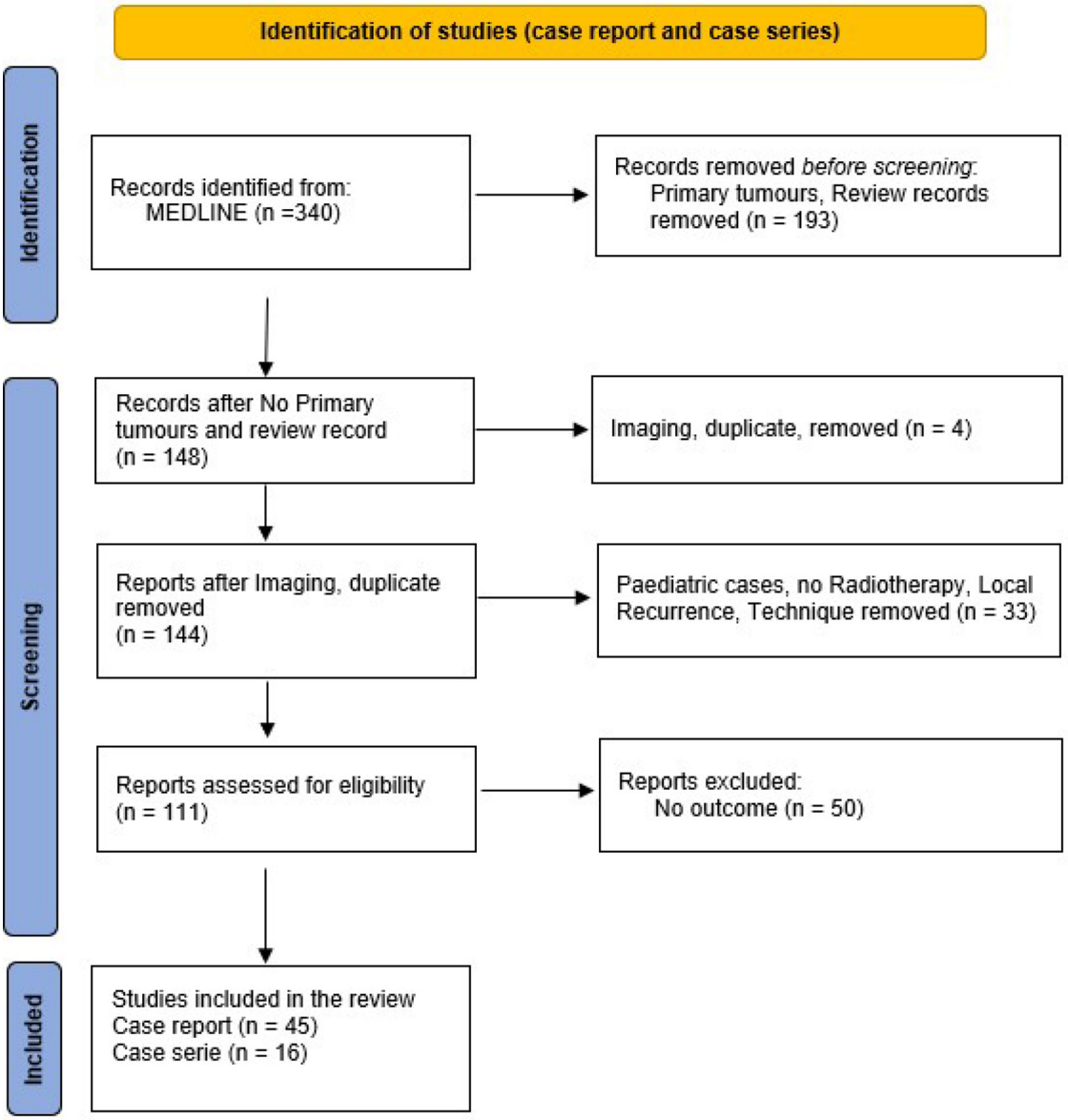
A total of 340 citations were found; among the excluded works, 11 were reviews, 1 a duplication, and 4 paediatric ones. Sixty papers were finally selected: 45 were case reports and 15 were case series; more details are described in 1 (PRISMA)

Case reports

A total of 45 case reports were examined,[14–57] accounting for 47 patients affected by metastatic lesion of the orbital cavity. Median age was 53 years (15–94 years) with a male/female ratio of 1.14 (male: 24, female: 21). The main represented histologies were breast (29.8%) and lung cancer (8.5%), and the median time from primary diagnosis and the orbital lesions was 8 months (range, 0–144 months). Intracranial extension was observed in 15 case s[21,24,26,29,34,40,41,44–46,48–51,56] and surgery was performed only in 2 cases.[14,47] More clinical detail, regarding lesion laterality, tissue infiltration, and clinical symptoms before RT are described in Table 1.

Data on the radiological exams performed before RT were available only for 23 patients, computed tomography (CT) was done in 23 cases, magnetic resonance imaging (MRI) in 24 cases, and Positron emission tomography (PET) in 7 cases. Surgical exenteration was performed in only one (2%) case, and chemotherapy in 29 (62%) cases.

Figure 1. PRISMA Literature Search.



Regarding RT, information on the used technique was available only in 39 cases: in the majority of cases (37/39, 95%), external beam radiotherapy (EBRT) was done. Data on the techniques used were only available in 25 of them: 15 patients were treated with three-dimensional conformal radiotherapy (3DCRT), two with intensity modulated radiotherapy (IMRT), one with cyber knife accelerator (CK), one with cobalt-60, and six with stereotactic body radiotherapy (SBRT) without any indication on the type of machine used. There was no information available in the remaining cases. Only 23 reports described data on total dose and fractionation: the most commonly used RT regimens were 30 Gy in 10 fractions (fx) (23%) or 20–25 Gy in 5 fx (13%). The two authors who did not provide information on doses and fractionations,[34,44] defined the treatment as palliative.

An approach with hypofractionated SBRT was used in five cases; doses ranging from 30 to 45 Gy in 5 fx were used in three patients, 24 Gy in single fraction in one patient, and 39 Gy in 3 fx for another one. In two cases, a non-standard fractionation, defined by the authors as "SBRT", was given, 45 Gy in 18 fx and 40 Gy in 20 fx,[14,52] although the used fractionation could not be defined as such by actual definitions. One patient underwent RT with cobalt-60 receiving 44 Gy in 22 fractions.[37]

The best radiological responses were reported only in 24 (51%) cases: 10 had a complete response, 11 had a partial responses, and 3 had a stable disease. Additionally, for the other 16 (34%) patients, only the maximum symptomatic response was noted and judged as complete and partial response in 10 and 6 cases, respectively.

Regarding the toxicity profile, data were described in 35 (74%) patients with three cases accusing RT-induced toxicity, one case of atrophy,[15] one of dry eye,[41] and one of red eye[45] (no

Table 1. Case report

Author, year (reference)	Number of patients	Primary Tumor	Side	Tissue infiltration[a]	Symptoms pre-RT	RT (technique)	RT dose (Gy)/ fractions	Best observed response	Recurrence	LC	LC (months)	FU (months)	Improved symptoms post-RT	OS (months)
Dieig A, 2004[14]	1	Breast	L	yes	D	SBRT	35/7	PR	yes	yes	14	14	yes	14
	2	Breast	L	no	D	SBRT[b]	45/18	PR pall	no	yes	10	10	yes	10
Anupriya A, 2006[15]	1	Cervix	L	no	*p* + PT+BV	IMRT	30/10	CR pall	no	yes	12	12	yes	12
Ludmir,E B, 2014[16]	1	Colon	R	no	IEM	3DCRT	30/10	CR pall	no	yes	6	6	yes	6
Dutton J J, 2018[17]	1	Seminoma	R	yes	BV	EBRT	24/1	CR	no	yes	42	42	yes	42
Kim J H, 2011[18]	1	Breast	*R* + L	yes	P	CK	39/3	CR	no	yes	12	12	yes	19
Lin I H, 2021[19]	1	Breast	*R* + L	no	BV	3DCRT	30/10	CR	no	yes	6	6	yes	6
Halliday L A, 2020[20]	1	Carcinoid	*R* + L	yes	*D* + IEM	3DCRT	30/10	SD	no	yes	12	12	yes	12
Rafi M, 2019	1	Condrosarcoma	L	yes	OP + BV	3DCRT	30/10	ND	ND	ND	ND	ND	ND	ND
Framarino-DeiMalatesta M, 2019[22]	1	Breast	R	yes	*D* + IEM+BV	SBRT	40/5	CR	no	no	20	20	yes	20
Mian I, 2020[23]	1	Mesotelioma	*R* + L	yes	*D* + BV	3DCRT	25/5	ND	no	yes	5	5	yes	5
Rajabi M T, 2015[24]	1	Osetosarcoma	*R* + L	yes	*p* + BV	3DCRT	30/10	ND	ND	ND	ND	ND	ND	ND
Zarogoulidis P, 2011[25]	1	Lung	*R* + L	no	*D* + OP+BV	3DCRT	30/10	PR	no	yes	ND	ND	yes	ND
Lin P-Y, 2005[26]	1	Osteosarcoma	L	yes	*p* + OP+BV	3DCRT	40/20	CR pall	no	yes	24	24	SD	24
Parghane R V[27]	1	Neuroendocrin	*R* + L	yes	*p* + BV	3DCRT	20/ND	SD	no	yes	18	18	yes	18
Tezcan Y, 2013[28]	1	Lung (SCLC)	*R* + L	yes	*p* + OP+BV	3DCRT	30/10	ND	ND	ND	ND	ND	ND	ND
Bakraoui E K, 2020[29]	1	Breast	L	no	*M* + BV	EBRT	60/30	CR pall	no	yes	14	14	ND	14
Sanchez Orgaz M, 2017[30]	1	Breast	R	yes	*p* + IEM+OP + BV+RE	EBRT	60/30	CR pall	yes	no	0 (LC not achieved)	ND	yes	ND
Kouvaris J R, 2008[31]	1	Breast	*R* + L	no	D	EBRT	47,5/19	PR pall	ND	ND	ND	12	yes	12
Murthy R, 2011[32]	1	Breast	*R* + L	no	*D* + IEM	EBRT	54/ND	CR	no	yes	18	18	yes	18
Callejo S A, 2000[33]	1	Soft Tissue	L	yes	*p* + RPD+IEM + M	EBRT	30/ND	ND	no	yes	9	9	ND	9
Berdasco K F, 2019[34]	1	Oesophagus	L	yes	*p* + D+IEM + BV+RE	EBRT	ND/ND	ND	no	yes	1	1	ND	1
Nifosì G, 2018[35]	1	Breast	L	no	*p* + D+IEM + OP	SBRT	30/5	CR pall	no	yes	9	9	yes	9
Wiltshire K L, 2009[36]	1	Bladder	*R* + L	no	[td]	3DCRT	20/5	CR pall	no	yes	54	54	yes	54
Nirmala S, 2008[37]	1	Breast	R	yes	BV	Cobaltum	44/22	CR pall	no	yes	24	24	yes	24
Goto S, 2019[38]	1	Stomach	L	no	*p* + D+IEM + OP+S + RE	EBRT	20/5	CR pall	no	yes	3	3	yes	3
Ergenc H, 2016[39]	1	Lung	*R* + L	no	BV	3DCRT	30/10	ND	no	yes	4	4	ND	4

(Continued)

Table 1. (Continued)

Author, year (reference)	Number of patients	Primary Tumor	Side	Tissue infiltration[a]	Symptoms pre-RT	RT (technique)	RT dose (Gy)/ fractions	Best observed response	Recurrence	LC	LC (months)	FU (months)	Improved symptoms post-RT	OS (months)
Quick A-M, 2009[40]	1	Liver	R	no	*p* + D+IEM + BV+RE	IMRT	58/30	CR	no	yes	20	20	yes	20
Walls G, 2014[41]	1	Breast	*R* + L	no	BV	EBRT	20/5	PR pall	no	yes	6	6	yes	6
Khaw K P, 2001[42]	1	Carcinoid	L	no	P	EBRT	16/4	PR pall	no	yes	1	1	yes	1
	2	Carcinoid	*R* + L	no	*p* + D+IEM	3DCRT	36/18	CR pall	ND	ND	ND	ND	yes	ND
Pirlamara A K, 2018[43]	1	Melanoma	R	yes	*p* + BV	SBRT	35/5	PR pall	ND	ND	ND	ND	yes	ND
Seker M M, 2014[44]	1	Soft Tissue	L	no	VL	EBRT	ND/ND	PR pall	ND	ND	ND	ND	yes	ND
Hird A E, 2008[45]	1	Breast	L	yes	D	3DCRT	20/5	PR	no	yes	ND	ND	yes	ND
Atasoy B M, 2013[46]	1	Breast	R	yes	BV + E	3DCRT	30/10	PR	no	yes	5	5	yes	5
Leiboithvic I, 2006[47]	1	Merckel	R	yes	*p* + S	ND	ND/ND	CR	no	yes	5	5	yes	5
Haddow J, 2007[48]	1	Anus	*R* + L	yes	BV + PH	ND	ND/ND	PR	no	yes	3	3	yes	ND
Tagami K, 2012[49]	1	Non-Hodgkin Lynphoma	L	yes	S	ND	40/20	CR	no	yes	36	ND	ND	ND
McLean K D, 2016[50]	1	Timus	L	yes	BV + S	ND	50.4/28	PR	ND	ND	2	2	ND	ND
Muratori L, 2019[51]	1	Thyroid	L	yes	*D* + BV	ND	44/22	CR	no	yes	22	22	yes	22
Murthy R, 2011[32]	1	Breast	*R* + L	yes	D	EBRT	54/27	PR	ND	yes	22	22	yes	ND
D'Alpino Peixoto R, 2013[52]	1	Liver	R	yes	*p* + RE	SBRT[b]	40/20	PR	no	yes	18	18	yes	18
Sterling M E, 2016[53]	1	Testis	*R* + L	yes	OP + BV	ND	ND/ND	PR	no	yes	15	54	ND	54
Strohbehn A L, 2015[54]	1	Lung	L	no	BV	ND	30/10	PR	no	yes	5	5	yes	5
Rath S, 2009[55]	1	Corpus ciliaris	R	no	N	ND	50/25	CR	no	yes	13	13	ND	13
Anoop T M, 2010[56]	1	Thyroid	R	yes	*p* + S	ND	ND/ND	PR	no	yes	3	3	yes	3
Verity D h, 2000[57]	1	Timus	R	ND	BV	ND	30/17	SD	no	yes	5	5	ND	5

BV, blurred vision; CR, complete response; CR pall, complete response for palliation symptoms; D, diplopia; E, oedema; IEM, impaired Eye motility; L, left; M, mass effect; N, none; ND, no data; OP, orbital pain; P, proptosis; PH, phosphene; PR, partial response; PR pall, partial response for palliation symptoms; PT, proptosis; R, right; RE, red eye; S, swelling; SD, stable disease; VL, vision loss.

[a]Ocular globe excluded.

[b]The authors defined the treatment in this case as SBRT, even though the used fractionation could not be defined as such by actual definitions.

information on the grading and timing of the reported toxicity was shown).

Data on LC and OS were available in 39 of 45 (87%) patients, registering a median LC of 11 months (range 1–54 months) and a median OS of 12 months (range 1–54 months). In terms of status, it was registered only in 35 of 45 (78%) patients: 13 died from the disease while 22 were still alive with disease.

Case series

A total of 16 studies were selected,[58–73] they were all retrospective in nature. The majority of these experiences had a very varied sample size, ranging from the four patients for Ulrich et al[71] to the 202 patients evaluated by Xu at al.[64] All the studies showed data on age and gender, except for Xu et al[64] : the median age of the patients varied from 42 to 84 years, with a male/female ratio of 82/163.

The most represented primary histologies were breast and lung cancers with mainly unilateral lesion. Only six studies had data on extracranial extension, while none of the patients this kind of extension.[58–63] In 129 patients reported in 11 studies,[59–63,66,67,69–72] chemotherapy was administrated together or sequentially to RT. Surgery was performed only in 31 patients described in seven studies.[59,61,63,69–73] More lesion characteristics are shown in Table 2.

In this series, 457 patients with OM were examined, 227 of whom underwent RT. Data on the radiological exams performed before RT were available only for 10 papers, in which CT and/or MRI were used in 9 cases alone or in combination,[58,64,67,69] MRI alone in one case,[67] and in another case PET-CT was also performed.[69]

Data on technique, doses, and fractionations were not always described in the papers. Regarding techniques, 10 lesions were treated with two-dimensional RT, 13 with 3DCRT, 3 with IMRT, 1 with SBRT, 31 with not better specified EBRT, 5 with electrons, 51 with CK, 11 with GK, and 7 with brachytherapy (BRT) (Table 2).

As shown in Table 2, radiotherapy doses and fractionations were different according to the treatment intent (*i.e.,* palliative versus radical) varying from a lower dose of 30 Gy in 10 fractions to higher doses of 60 Gy in 30 fractions, 50 Gy in five fractions, or a single fraction of 16.5–21 Gy (Table 2).

Almost every experience reported no sever acute or late toxicity which was effectively limited to one cataract,[62] one G1 corneal and cutaneous erythema,[65] two conjunctivitis, two transient orbital pain, one G2 xerophthalmia, and one Grade 2 dermatitis.[73] The most frequent symptoms before RT were vision loss, diplopia, and motility dysfunction. In the eight papers reporting data on the symptom response after RT, a partial or complete response was recorded in the majority of cases (Table 2).

Only five papers analysed LC which was generally reached as a complete response, partial response, or stability. In some cases, also overall response rate was registered and varied between 75 and 100%.[58,73] Only two study provided information on the duration of response. Riva et al[62] described a mean LC time of 22.8 months, while Desideri et al[73] reported a mean time to local progression of 5 months (range: 3–7). Regarding OS, the data were heterogeneous, with some experience providing the mean or median OS, whereas others only the OS range, which varied between 1 and 54 months (Table 2).

DISCUSSION

Metastases to the ocular and peri-ocular structures are uncommon, accounting for approximately 1–13% of all neoplasms found in the orbit,[62] and the possible therapeutic approach generally ranges from surgery to radiotherapy, or a combination of these options.

Surgery is associated with a high morbidity rate due to the complex anatomy and critical neurovascular structures of the orbital apex.[74] Keeping the optic structures intact is usually unsuccessful, and most patients suffer from partial or complete vision loss after surgery.[75–77] Other possible complications include ptosis, enophthalmos, diplopia, cerebrospinal fluid leakage, intracranial injury, meningitis, and frontalis palsy.[78–80] Therefore, RT has become more and more attractive in the last decades, especially with the introduction of more focused and precise techniques that could reduce toxicity risk.

In this systematic review, we decided to focus on treated lesions located in the orbital cavity only, excluding the ocular structure: in our opinion, the ocular globe represents a completely different clinical setting with other types of issues and possible treatment strategies, which is best to analyse in a separate experience.

According to our findings, case reports and retrospective case series are the most commonly reported experiences in the current literature (Tables 1 and 2). However, data on histology, outcomes, and proposed treatment are very disparate and, in some cases, not described.

In the experiences where the therapeutic approach was detailed, the 3D/2D-CRT treatment with a palliative dose, generally around 30 Gy in 10 fractions, was the main option,[17,20–22,24–29,39,58,66] followed by more "aggressive" approaches in terms of doses and with the use of more sophisticated techniques such as IMRT,[16,40,66] or SBRT administered with GK,[64] CK[18,62,64,73] or non-dedicated linear accelerators using hypofractionation or standard fractionation of dose.[14,22,35,43,52,66] These differences in strategy are most likely due to some drawbacks that radiation oncology may find in this kind of clinical setting. The first one is the possible lesion localization, with the consequent need of sparing relevant near organ at risk in order to preserve a minimum of functionality and quality of life. This problem could be partially solved with the use of more focused techniques like IMRT and SBRT with the possibility to administer higher radiation doses in few fractions.[14,16,18,22,35,40,43,52,62,64,66,73] Another element that could have played a role in the therapeutic choice, in terms of doses and techniques, could be both the patients performance status and the different experiences that every centre had in this clinical setting.

Table 2. Case series

Author, year (ref)	N patients evaluable/ N total	Primary Tumor (%)	Side (%)	Tissue infiltration[a]	Symptoms pre-RT (%)	RT technique	RT dose (Gy) and fractions	Follow-up median	Best observed response	LC %	LC months	Symptoms post-RT	OS months
Chik,J Y K, 2020[58]	15/15	lung (26.7); breast (26.7) lymphoma (40.0); sarcoma (6.7)	U 73.3% B 26.7%	no	DV 73.2%; S 33.3% P 13.3%; PT 6.7% D 6.7% R 28.5% (choroidal mts)	2DCRT: three pt 3DCRT: 12 pt	6 Gy/1 fx (2pt) 30 Gy/15 fx (2pt) 30 Gy/10 fx (5pt) 20 Gy/5 fx (4pt) 24 Gy/12 fx (1pt) 4 Gy/1 fx (1pt)	8 months (3.2–26)	DV: PR 11 (84.6%), SD 2 (15.4%) S (n = 5) --> PR 4 (80%), CR 1 (20%) P (n = 2) 2 PR(100%) PT (n = 1) one partial recovery (100%)	CR 33.3% PR 50% SD 6.6% ORR of 100%	All the other patients remained disease free except one.	CR or PR after one months in all patients (symptoms control rate 84–100%.)	median OS 9.1 months (3.2 to 23.6 months).
Grajales-Alvarez R, 2020[59]	28/28	breast (100)	U75% B25%	yes	DV 64.2%; P 57.1% A 28.5% ; M 28.5% E 21.4%	ND	ND	ND	33% patients received local treatment with poor results.	ND	ND	ND	OS 26.4 months (1–98 months) mean PFS of 13.7 months (1–48 months)
Kamieniarz L, 2020[60]	27/27	neuroendocrine (100)	U 56% (Left 44%) B 7.4%	yes	PT 45%; D 36% DV 36%; P 9%	EBRT six pt	ND	median follow-up period from o-NENM diagnosis of 8 years	0	ND	No radiological progression was noted in o-NENM during follow-up period (median follow-up period from o-NENM diagnosis of 8 years).	CR 5/11.	5 year OS 84.1%; 10 year OS 71.0% median OS from diagnosis of 11.3 years (95% CI: 9.42–13.24)
Montejano-Milner R,, 2022[61]	10/10	breast (36); bladder (27) lung (18); ovary and cavum (9)	NA	yes	D 60%; M 40% P 30%	NA	ND	1–52 months.	ND	ND	ND	ND	treated patients mean OS 29.2 months (range 1–54 months)
Riva G, 2019[62]	21/21	breast (63); lung (17) kidney (8); thyroid (4) lymphoma (4); leiomyosarcoma (4)	UR 63% UL 37%	yes	P 63%; DV 50% D 17%; S 8% PT 8%; EP 4% RE 4%	CK	Median dose 18 Gy (range, 15–24 Gy) /2–3 fx	22.8 months (range, 6–30.0)	CR/PR (in particular concerning pain relief and increase in visual acuity and/or visual field). One patient developed ipsilateral cataract 9 months after **RT**	ND	22.8 months	pain CR in all patients CR or PR in all symptomatic patients	Mean OS 22,8 months

(Continued)

Table 2. (Continued)

Author, year (ref)	N patients evaluable/ N total	Primary Tumor (%)	Side (%)	Tissue infiltration[a]	Symptoms pre-RT (%)	RT technique	RT dose (Gy) and fractions	Follow-up median	Best observed response	LC %	LC months	Symptoms post-RT	OS months
Schick U, 2006 [63]	11/11	breast (27); lung (46) HN (9); uterus (9) unknown (9)	NA	yes	PT 28%; VD 18% M 7%; EN 9% P 18%	NA	35–45 Gy	15 months	At last follow-up three further patients had developed widespread metastases	ND	ND	CR/PR 4 SD 6 PD 1	mean OS 15 months
Xu D.,2010[64]	11/202	lung (100)	ND	ND	ND	GK	16–20	ND	ND	PR 8/11 SD 3/11	ND	ND	ND
Zwicker F, 2008[65]	7/7 (nine lesions)	breast (100)	NA B 28%	ND	PT: 4/7; D: 4/7 M: 6/7; P: 2/7 PTO: 1/7; DV: 4/7 EN: 1/7 (in both eyes) V 1/7; OH: 1/7	electons/ photons 2D-EBRT (only one pt CT-based 3D planned RT)	20–50 Gy in 2 Gy/fx	ND	3/4 PR	ND	ND	D 1/7 M: 1/7 PTO: 1/7 DV: 2/7 EN: 1/7 (in both eyes)	Mean 7.3 months[3–13]
Blohmer M, 2020[66]	20/28 (25 RT treatments)	breast (100)	UR 40% UL 25% B 35%	ND	ND	3DCRT: 16 pt IMRT: three pt elettroni: five pt SBRT: one pt	10–60 in 2–30 fx (median 12)	ND	ND	ND	ND	ND	median OS: 13.5 mo ; mean OS 21.3 mo
Klingenstein A, 2012[67]	14/14 (16 lesions)	breast (37); melanoma (21) prostate (21); Kidney (7) pancreas (7); pharynx (7)	ND	ND	D: 28%; P: 7% VD: 14%	CK	16.5-21/1 fx	mean six mo	9/16 SD 4/16 PR 1/16 CR clinical outcome: CR pall 3/8; PR pall 1/8	CR: 14/16	ND	D: 2/14 P: 1/14 VD: 1/14	ND
Pierson T M, 2016[68]	13/20	breast (100)	NA	yes	PT: 10%; D: 25% P: 10%; DV: 55%	ND	NA	NA	90% PR pall	NA	NA	NA	median OS 24 mo (whole cohort)
[71]Holland H D, 2003[69]	20/20	breast (40); prostate (10) lung (10); liver (15) others (25)	U 85% B 15%	ND	D: 50%; PT: 5% S: 55%; RE: 45% DV: 15%; EN: 5%	ND	40/10 fx	14.7	ND	ND	ND	ND	Mean OS 14.7
[72]Savar A, 2010[70]	3/13	soft tissue (100)	ND	ND	ND	ND	51.1 (37.5–60)	26 (2–84)	ND	CR: 12	ND	ND	ND
[73]Ullrich K, 2019[71]	4/4	breast (50); mieloma (25) lung (25)	B 100%	yes	ND	ND	ND	ND	ND	ND	ND	ND	ND
[74]Vaarwerk B, 2019[72]	7/18	rabdomiosarcoma (100)	ND	ND	ND	BRT	50/5 fx	ND	CR: 6	CR: 6	ND	ND	2.7–21.7

(Continued)

Table 2. (Continued)

Author, year (ref)	N patients evaluable/ N total	Primary Tumor (%)	Side (%)	Tissue infiltration[a]	Symptoms pre-RT (%)	RT technique	RT dose (Gy) and fractions	Follow-up median	Best observed response	LC %	LC months	Symptoms post-RT	OS months
Desideri I., 2018[73]	16/19 (20 RT treatments)	Breast (25); Sarcoma (38): Lung cancer (12); Basalioma (12): Plasmocitoma (12); Lymphoma (6): Colon cancer (6); Apocrine carcinoma (6); HCC (6); Adenoid cystic carcinoma (6): Lacrimal gland adenocarcinoma (6):	UR 21% UL 68% B 11%	yes	NSS 73% DV 26% M 16%	CK	24–35 Gy in 1–5 fx	14.2 (0–58) [mean]	DV: 2/19 PR P: 1/19 PR Ex: 1/19 PR	ORR 75% CR 4 PR 2 LC rate: 79%	Mean time to best measured response 15.16 months (range: 2–58) Mean time to local progression: 5 months (range: 3–7)	Acute toxicity: two conjunctivitis, two transitory orbital pain, one Grade two xerophthalmia one Grade two dermatitis No late toxicity	13 patients were alive

A, amaurosis; B, bilateral; CK, cyber knife; D, Diplopia; 3DCRT, conformal radiotherapy; DV, decreased vision; E, Oedema; EBRT, external beam radiotherapy; EN, Enophthalmos; EP, epiphora; Ex, exophthalmos; GK, gamma knife; IMRT, intensity modulated radiotherapy; LU, left unilateral; M, Eye motility; N, not; ND, no data; NSS, not specified symptoms; OH, ocular hypertension; ORR, overall response rate; P, pain; PT, proptosis; PTO, ptosis; R, retinal detachment; RE, red eye; RT, radiotherapy; RU, right unilateral; S, swelling; U, unilateral; V, vertigo; Y, yes.
[a]Ocular globe excluded.

Regardless of the chosen approach, almost all treated patients experienced a benefit after RT in terms of OM-related symptom intensity reduction and a good acute and late toxicity profile. Reported adverse events were only of grade G1-G2 and were registered in few cases: one cataract after 9 months from the EBRT,[62] one corneal and cutaneous erythema,[65] two conjunctivitis, two transient orbital pain, one xerophthalmia, and one dermatitis.[73]

Analysis of LC data was quite difficult due to the lack of well-characterized information reported only in few experiences,[14–58,64,67,70,72,73] and to the heterogeneity of the chosen outcomes used to describe it. As proof of this, while the median LC and computing life tables with Kaplan-Meier method could be achieved by retrieving the required data from the case reports, it was not possible for the case series for these same problems. However, among the case reports, the LC at one and two years were 97.3 and 86.5%, respectively, while every series detailing these data[14,58,67,70,72,73] showed variable form of response after the treatment (Tables 1 and 2).

Similar conditions apply to the survival data, to which we must add the impact of different histologies and the lack of information on the patient disease burden at the moment of RT. Another aspect from which it was not possible to obtain much information was the possible association with other therapeutic strategies, in particular the timing between systemic therapies or surgical approaches and RT. Considering the heterogeneity and limited sample size of these experiences on OM treatment, the data seem to suggest that the RT approach in this clinical setting is a feasible and safe strategy. However, more information on the RT ideal techniques and dose are still needed, as well as more data on eventual concomitant treatments, especially considering the introduction of new therapeutic strategy, such as immunotherapy or PARP-inhibitors, that could have a synergistic effect with RT.

Due to the relative rarity of OM and the consequent paucity and low quality of the publications in this topic, the Study Group of Palliative Radiotherapy of the Italian Association of Radiotherapy and Clinical Oncology (AIRO) are proposing a collection on a database of OM patients treated in Italy to uniformly analyse RT effectiveness and feasibility.

KEY MESSAGE

What is already known on this topic

Radiotherapy is one of the few strategies for orbital metastases, but only few experiences are actually described in this setting, generally retrospective ones.

What this study adds

Only retrospective experiences were described in literature: Radiotherapy option ranged from 3D- and 2D-CRT to SBRT, CK, and GK, with different possible fractionations: 30 Gy in 10 fractions, 60 Gy/30 fractions, 20–50 Gy/5 fractions, or 16.5–21 Gy in single fraction. Regardless of the chosen

approach, almost all treated patients experienced a benefit after RT in terms of OM-related symptom intensity reduction and a good acute and late toxicity profile.

How this study might affect research, practice or policy

The data seem to suggest that the RT approach in this clinical setting is a feasible and safe strategy; more information on the RT ideal techniques and dose are still needed, as well as more data on eventual concomitant treatments.

ACKNOWLEDGEMENTS

The Authors thank the Scientific Committee and Board of the AIRO for the critical revision and final approval of the manuscript (Nr. 34/2022).

CONTRIBUTORS

Francesco Cellini and Ernesto Maranzano: share the last autorship.

COMPETING INTERESTS

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

PATIENT CONSENT

All authors gave their consent for publication of the paper.

REFERENCES

1. Allen RC. Orbital metastases: when to suspect? when to biopsy *Middle East Afr J Ophthalmol* 2018; **25**: 60–64. https://doi.org/10.4103/meajo.MEAJO_93_18
2. Magliozzi P, Strianese D, Bonavolontà P, Ferrara M, Ruggiero P, Carandente R, et al. Orbital metastases in Italy. *Int J Ophthalmol* 2015; **8**: 1018–23. https://doi.org/10.3980/j.issn.2222-3959.2015.05.30
3. Strianese D, Grassi P, Bonavolontà G. An analysis of 2,480 space-occupying lesions of the orbit from 1976 to 2011 *Ophthalmic Plast Reconstr Surg* 2013; **29**: 412–13. https://doi.org/10.1097/IOP.0b013e31829f3921
4. Shields JA, Shields CL, Brotman HK, Carvalho C, Perez N, Eagle RC Jr. Cancer metastatic to the orbit: the 2000 Robert M. *Ophthalmic Plast Reconstr Surg* 2001; **17**: 346–54. https://doi.org/10.1097/00002341-200109000-00009
5. Valenzuela AA, Archibald CW, Fleming B, Ong L, O'Donnell B, Crompton J J, et al. Orbital metastasis: clinical features, management, and outcome. *Orbit* 2009; **28**: 153–59. https://doi.org/10.1080/01676830902897470
6. Kamieniarz L, Armeni E, O'Mahony LF, Leigh C, Miah L, Narayan A, et al. Orbital metastases from Neuroendocrine Neoplasms: clinical implications and outcomes. *Endocrine* 2020; **67**: 485–93. https://doi.org/10.1007/s12020-019-02130-5
7. Ahmad SM, Esmaeli B. Metastatic tumors of the orbit and ocular Adnexa. *Curr Opin Ophthalmol* 2007; **18**: 405–13. https://doi.org/10.1097/ICU.0b013e3282c5077c
8. Shome D, Honavar SG, Gupta P, Vemuganti GK, Reddy PVA. Reddy PVA metastasis to the eye and orbit from renal cell carcinoma – a report of three cases and review of the literature. *Surv Ophthalmol* 2007; **52**: 213–23. https://doi.org/10.1016/j.survophthal.2006.12.004
9. Pontoriero A, Iatì G, Conti A, Minutoli F, Bottari A, Pergolizzi S, et al. Treatment of Periocular basal cell carcinoma using an advanced stereotactic device. *Anticancer Res* 2014; **34**: 873–75.
10. Ferini G, Molino L, Bottalico L, De Lucia P, Garofalo F. A small case series about safety and effectiveness of a Hypofractionated electron beam radiotherapy schedule in five fractions for facial non Melanoma skin cancer among frail and elderly patients. *Rep Pract Oncol Radiother* 2021; **26**: 66–72. https://doi.org/10.5603/RPOR.a2021.0013
11. Palmisciano P, Haider AS, Sabahi M, Nwagwu CD, Bin Alamer O, Scalia G, et al. Primary skull base Chondrosarcomas: A systematic review. *Cancers (Basel)* 2021; **13**(23): 5960. https://doi.org/10.3390/cancers13235960
12. Wladis EJ, Lee KW, Nazeer T. Metastases of systemic malignancies to the orbit: A major review. *Orbit* 2021; **40**: 93–97. https://doi.org/10.1080/01676830.2020.1759110
13. Systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2021. Available from: https://www.jclinepi.com/article/ S0895-4356(09)00179-6/fulltext
14. Dieing A, Schulz C-O, Schmid P, Roever AC, Lehenbauer-Dehm S, Jehn C, et al. Orbital metastases in breast cancer: report of two cases and review of the literature. *J Cancer Res Clin Oncol* 2004; **130**: 745–48. https://doi.org/10.1007/s00432-004-0606-3
15. Anupriya A, Saban H, Dhipak AB, Jayanthi P, ThomasSR, John VP. Orbital metastasis of Cervical carcinoma. *Case Report and Review of Literature - J Clin Diagn Res* 2016; **10**(1). https://doi.org/10.7860/JCDR/2016/14400.7085
16. Ludmir EB, McCall SJ, Czito BG, Palta M. Radiosensitive orbital metastasis as presentation of occult Colonic adenocarcinoma. *BMJ Case Rep* 2014; **2014**: bcr2014206407. https://doi.org/10.1136/bcr-2014-206407
17. Dutton JJ, Proia AD. Seminoma metastatic to the orbit - ophthalmic Plast Reconstr Surg. 2018; **34**: 309–12. https://doi.org/10.1097/IOP.0000000000001031
18. Kim JH, Choi SY, Cho CK, Yang KM, Noh WC, Kim M-S. Bilateral orbital metastases from breast cancer: a case report of successful palliation using stereotactic radiotherapy. *Breast J* 2011; **17**: 669–71. https://doi.org/10.1111/j.1524-4741.2011.01165.x
19. Lin IH, Kuo BI, Liu FY. Adjuvant intravitreal Bevacizumab injection for Choroidal and orbital metastases of refractory invasive Ductal carcinoma of the breast. *Medicina* 2021; **57**: 404. https://doi.org/10.3390/medicina57050404
20. Halliday LA, Curragh D, Sia PI, Selva D. Pseudocystic appearance of an orbital Carcinoid metastasis. *Orbit* 2020; **39**: 41–44. https://doi.org/10.1080/01676830.2019.1576739
21. Rafi M, Abbas S, Intakhab B, Shehzad A, Sultan G, Ahmed S, et al. Chondrosarcoma of right big toe with metastases to left orbital and left infra temporal region. *J Pak Med Assoc* 2019; **69**: 896–98.
22. Framarino-Dei-Malatesta M, Chiarito A, Bianciardi F, Fiorelli M, Ligato A, Naso G, et al. Metastases to extraocular muscles from breast cancer: case report and up-to-date review of the literature - BMC cancer. *BMC*

Cancer 2019; **19**(1): 36. https://doi.org/10.1186/s12885-018-5253-1
23. Mian I, Padiernos E, Hassan R, Ghafoor A. Orbital metastases from malignant Mesothelioma. *Lancet Oncol* 2020; **21**: e117S1470-2045(19)30822-8. https://doi.org/10.1016/S1470-2045(19)30822-8
24. Rajabi MT, Saeedi-Anari G, Ramezani F, Tabatabaie S-Z, Rajabi MB, Asadi Amoli F. Orbital metastatic Osteosarcoma - arch Iran MED. *Arch Iran Med* 2015; **18**: 123–26.
25. Zarogoulidis P, Terzi E, Kouliatsis G, Androudi S, Kontakiotis T, Zaramboucas T, et al. Orbital metastases as the first manifestation of lung adenocarcinoma. *Case Rep Ophthalmol* 2011; **2**: 34–38. https://doi.org/10.1159/000323945
26. Lin P-Y, Chen W-M, Hsieh Y-L, Chen WY-K, Chen T-H. Orbital metastatic Osteosarcoma. *J Chin Med Assoc* 2005; **68**: 286–89. https://doi.org/10.1016/S1726-4901(09)70153-4
27. Parghane RV, Basu S. Bilateral orbital soft-tissue metastases from renal Neuroendocrine tumor: successful Theranostic application of 68Ga/177Lu-DOTATATE with improvement of vision . *J Nucl Med Technol* 2019; **47**: 171–72. https://doi.org/10.2967/jnmt.118.217455
28. Tezcan Y. Bilateral orbital metastases from small cell lung cancer: a case report. *Acta Clinica Belgica* 2013; **68**: 59–61. https://doi.org/10.2143/ACB.68.1.2062722
29. El Bakraoui K, El Morabit B. Orbital metastasis from triple-negative breast cancer: case report and literature review. *Case Rep Oncol* 2020; **13**: 1042–46. https://doi.org/10.1159/000509348
30. Sánchez Orgaz M, Gonzalez Pessolani T, Pozo Kreilinger JJ, Zamora P, Martí Álvarez C, Boto-de-Los-Bueis A. Orbital and Conjunctival metastasis from lobular breast carcinoma. *Orbit* 2017; **36**: 197–200. https://doi.org/10.1080/01676830.2017.1310255
31. Kouvaris JR, Gkongkou PV, Papadimitriou CA, Papacharalampous XN, Antypas CE, Balafouta MJ, et al. Bilateral metastases to extraocular muscles from lobular breast carcinoma - Onkologie. *Onkologie* 2008; **31**: 387–89. https://doi.org/10.1159/000129689
32. Murthy R, Gupta A, Hegde S, Honavar SG. Bilateral multiple extraocular muscle metastasis from breast carcinoma. *Indian J Ophthalmol* 2011; **59**: 381–82. https://doi.org/10.4103/0301-4738.83616
33. Callejo SA, Kronish JW, Decker SJ, Cohen GR, Rosa RH Jr. Malignant granular cell tumor metastatic to the orbit. *Ophthalmology* 2000; **107**: 550–54. https://doi.org/10.1016/S0161-6420(99)00135-9
34. Berdasco KF, Diaz LF, Jiménez FP, Blanco JC, Montanés CB. Unilateral Exophthalmos secondary to Esophageal adenocarcinoma metastasis to the medial rectus muscle - arch Soc ESP Oftalmol. *Engl Ed* 2019; **94**: 510–13. https://doi.org/10.1016/j.oftal.2019.07.003
35. Nifosí G, Zuccarello M. Unilateral localized extraocular muscle metastasis by lobular breast carcinoma - BMJ case Rep. *BMJ Case Reports* 2018; bcr–2018. https://doi.org/10.1136/bcr-2018-224726
36. Wiltshire KL, Laperriere N, Bristow RG. Prolonged survival in a patient with Choroidal metastases from urothelial bladder cancer. *Can Urol Assoc J* 2009; **3**: E36–E38. https://doi.org/10.5489/cuaj.1138
37. Nirmala S, Krishnaswamy M, Janaki M, Kaushik K. Unilateral solitary Choroid metastasis from breast cancer: rewarding results of external radiotherapy. *J Can Res Ther* 2008; **4**: 206. https://doi.org/10.4103/0973-1482.44295
38. Goto S, Takeda H, Sasahara Y, Takanashi I, Yamashita H. Metastasis of advanced gastric cancer to the extraocular muscle: a case report. *J Med Case Reports* 2019; **13**(1). https://doi.org/10.1186/s13256-019-2031-x
39. Ergenc H, Onmez A, Oymak E, Tanriseven R, Celik E, Onmez FE, et al. Bilateral Choroidal metastases from lung adenocarcinoma: A case report - case Rep Oncol. *Case Rep Oncol* 2016; **9**: 530–36. https://doi.org/10.1159/000449154
40. Quick A-M, Bloomston M, Kim E-Y, Hall N-C, Mayr N-A. Nina-A Mayr N-A - complete response to radiation therapy of orbital metastasis from hepatocellular carcinoma. *World J Gastroenterol* 2009; **15**: 6000–6003. https://doi.org/10.3748/wjg.15.6000
41. Walls G, Napier S, Stewart D. Visual impairment due to bilateral multifocal Choroidal metastasis of Parotid adenocarcinoma: a case report. *Front Oncol* 2014; **4**: 136. https://doi.org/10.3389/fonc.2014.00136
42. Khaw P, Ball D, Duchesne G. Carcinoid tumour of the orbital muscles: A rare occurrence. *Australas Radiol* 2001; **45**: 179–81. https://doi.org/10.1046/j.1440-1673.2001.00899.x
43. Pirlamara AK, Tang J, Amin B, Kabarriti R. Vulvar Melanoma with isolated metastasis to the extraocular muscles. *Case Report and Brief Literature Review - Anticancer Res* 2018; **38**: 3763–66. https://doi.org/10.21873/anticanres.12658
44. Seker MM, Uslu AU, Ozer H, Seker A, Kacan T, Babacan N, et al. Orbital metastasis of Endocervical Stromal sarcoma: a rare tumor and an uncommon metastasis - Prz Menopauzalny. *Prz Menopauzalny* 2014; **13**: 356–58. https://doi.org/10.5114/pm.2014.47991
45. Hird AE, Wilson J, Symons S, Sinclair E, Davis M, Chow E. Radiation recall dermatitis: case report and review of the literature - Curr Oncol. *Current Oncology* 2008; **15**: 53–62. https://doi.org/10.3747/co.2008.201
46. Atasoy BM, Çetin İA, Bozkurt SU, Turhal NS. Metastasis to Paranasal sinuses and Orbita of breast cancer with a rare Metachronous tumor of the uterine Cervix. *Journal of Craniofacial Surgery* 2013; **24**: e64–65. https://doi.org/10.1097/SCS.0b013e3182700748
47. Leibovitch I, Davis G, Huilgol SC, Crompton J, James CL, Selva D. An unusual presentation of Periocular Merkel cell carcinoma. *J Cutan Pathol* 2006; **33 Suppl 2**: 39–41. https://doi.org/10.1111/j.1600-0560.2006.00525.x
48. Haddow J, Muthapati D, Arshad I, Gupta M, Agarwal P. Multiple bilateral Choroidal metastasis from Anal Melanoma. *Int J Clin Oncol* 2007; **12**: 303–4. https://doi.org/10.1007/s10147-006-0651-9
49. Tagami K, Tanda S, Kato H, Tashiro A, Saji K, Komaru T, et al. Detection of asymptomatic cardiac metastasis and successful salvage chemotherapy comprising a prednisone, etoposide, Procarbazine, and cyclophosphamide regimen in an elderly Japanese patient suffering from a delayed recurrence of diffuse large B-cell lymphoma - case Rep Oncol. *Case Rep Oncol* 2012; **5**: 62–68. https://doi.org/10.1159/000336447
50. MacLean KD, Cole SC, Ford JR, Owen L, Mamalis N, Patel BCK. Thymic origin Neuroendocrine carcinoma Metastasizing to the orbit in an otherwise asymptomatic patient - ophthalmic Plast Reconstr Surg. *Ophthalmic Plast Reconstr Surg* 2016; **32**: e21–3. https://doi.org/10.1097/IOP.0000000000000375
51. Muratori L, Sperone P, Scagliotti GV. Long-term disease control and high clinical benefit in a patient with advanced thyroid cancer treated with Lenvatinib. *Future Oncol* 2019; **15**: 3–6. https://doi.org/10.2217/fon-2019-0092
52. D'Alpino Peixoto R, Lim HJ, Cheung WY. Neuroendocrine tumor metastatic to the orbit treated with radiotherapy. *World J Gastrointest Oncol* 2013; **5**: 177–80. https://doi.org/10.4251/wjgo.v5.i8.177
53. Sterling ME, Kovell RC, Jaffe WI. Primary seminal Vesicle adenocarcinoma presenting with bilateral orbital metastasis: A case report - Urol case Rep. *Urol Case Rep* 2016; **6**: 33–35. https://doi.org/10.1016/j.eucr.2016.02.011
54. Strohbehn AL, Sohn EH. Evolution of Septated Cavitary Subretinal fluid after

treatment of Choroidal metastasis - ophthalmic Surg lasers imaging retina. *Ophthalmic Surg Lasers Imaging Retina* 2015; **46**: 482–84. https://doi.org/10.3928/23258160-20150422-14
55. Rath S, Honavar SG, Reddy VA, Naik MN, Vemuganti GK, Murthy R. Sebaceous carcinoma of the eyelid Metastasizing to the Lacrimal SAC after 5 years. *Orbit* 2009; **28**: 309–12. https://doi.org/10.3109/01676830903071182
56. Anoop TM, Mini PN, Divya KP, Nikhil S, Jabbar PK. Clinical images. thyroid follicular carcinoma presenting as Intraorbital, intracranial, and subcutaneous metastasis. *Am J Surg* 2010; **199**: e72–4. https://doi.org/10.1016/j.amjsurg.2009.07.048
57. Verity DH, Graham EM, Carr R, van der Walt JD, Stanford MR. Hypopyon uveitis and Iris nodules in non-Hodgkin's lymphoma: ocular relapse during systemic remission. *Clinical Oncology* 2000; **12**: 292–94. https://doi.org/10.1053/clon.2000.9176
58. Chik JYK, Leung CWL, Wong KH. Palliative radiation therapy for patients with orbital and ocular Metastases- Ann Palliat MED. *Ann Palliat Med* 2020; **9**: 4458–66. https://doi.org/10.21037/apm.2019.12.02
59. Grajales-Alvarez R, Gutierrez-Mata A. Orbital metastases from breast cancer: A retrospective analysis of 28 cases. *Cancer Treat Res Commun* 2020; **24**: S2468-2942(20)30021-6: 100184: . https://doi.org/10.1016/j.ctarc.2020.100184
60. Kamieniarz L, Armeni E, O'Mahony LF, Leigh C, Miah L, Narayan A, et al. Orbital metastases from Neuroendocrine Neoplasms: clinical implications and outcomes - endocrine. *Endocrine* 2020; **67**: 485–93. https://doi.org/10.1007/s12020-019-02130-5
61. Montejano-Milner R, López-Gaona A, Fernández-Pérez P, Sánchez-Orgaz M, Romero-Martín R, Arbizu-Duralde A. Orbital metastasis: clinical presentation and survival in a series of 11 cases - arch Soc ESP Oftalmol. *Arch Soc Esp Oftalmol (Engl Ed)* 2022; **97**: S2173-5794(20)30225-5: 81–88: . https://doi.org/10.1016/j.oftale.2020.07.014
62. Riva G, Augugliaro M, Piperno G, Ferrari A, Rondi E, Vigorito S, et al. Cyberknife radiotherapy for orbital metastases: A single-center experience on 24 lesions. *European Journal of Ophthalmology* 2019; **29**: 61–68. https://doi.org/10.1177/1120672118761728
63. Schick U, Lermen O, Hassler W. Management of orbital metastases. *Zentralbl Neurochir* 2006; **67**: 1–7. https://doi.org/10.1055/s-2005-836922
64. Xu D, Liu D, Zhang Z, Zhang Y, Li Y, Liu X, et al. Gamma knife surgery in the management of orbital tumors. *J Neurosurg* 2010; **113 Suppl**: 34–38. https://doi.org/10.3171/2010.7.GKS10857
65. Zwicker F, Herfarth K, Welzel T, Aulmann S, Dithmar S, Hof H, et al. Palliative radiotherapy of retrobulbar orbit metastases due to breast cancer - Onkologie. *Onkologie* 2008; **31**: 529–33. https://doi.org/10.1159/000151625
66. Blohmer M, Zhu L, Atkinson JM, Beriwal S, Rodríguez-López JL, Rosenzweig M, et al. Patient treatment and outcome after breast cancer orbital and periorbital metastases: a comprehensive case series including analysis of lobular versus Ductal tumor histology - breast cancer Res. *Breast Cancer Res* 2020; **22**(1): 70. https://doi.org/10.1186/s13058-020-01309-3
67. Klingenstein A, Kufeld M, Wowra B, Muacevic A, Fürweger C, Schaller UC. Cyberknife Radiosurgery for the treatment of orbital metastases - Technol cancer Res treat. *Technol Cancer Res Treat* 2012; **11**: 433–39. https://doi.org/10.7785/tcrt.2012.500257
68. Pierson TM, Tebit EV, El Sayed A, Smolkin ME, Dillon PM. Orbital metastases from breast cancer: retrospective analysis at an academic cancer center. *Breast J* 2016; **22**: 447–50. https://doi.org/10.1111/tbj.12604
69. Holland D, Maune S, Kovács G, Behrendt S. Metastatic tumors of the orbit: a retrospective study. *Orbit* 2003; **22**: 15–24. https://doi.org/10.1076/orbi.22.1.15.14007
70. Savar A, Trent J, Al-Zubidi N, Huh W, Anderson P, Shinder R, et al. Efficacy of adjuvant and Neoadjuvant therapies for adult orbital Sarcomas - ophthalmic Plast Reconstr Surg. *Ophthalmic Plast Reconstr Surg* 2010; **26**: 185–89. https://doi.org/10.1097/IOP.0b013e3181ba75e6
71. Ullrich K, Bisase B, Kumar S, Malhotra R. Maintaining quality of life: Electrochemotherapy for palliative periorbital malignancy - ophthalmic Plast Reconstr Surg. *Ophthalmic Plastic & Reconstructive Surgery* 2019; **35**: e138–42. https://doi.org/10.1097/IOP.0000000000001468
72. Vaarwerk B, Hol MLF, Schoot RA, Breunis WB, de Win MML, Westerveld H, et al. AMORE treatment as salvage treatment in children and young adults with Relapsed head-neck Rhabdomyosarcoma - Radiother Oncol. *Radiother Oncol* 2019; **131**: 21–26: . https://doi.org/10.1016/j.radonc.2018.10.036
73. Desideri I, Francolini G, Carta GA, Di Cataldo V, Masi L, Meattini I, et al. Efficacy and tolerability of Cyberknife stereotactic Robotic radiotherapy for primary or secondary orbital lesions: A single-center retrospective experience. *Technol Cancer Res Treat* 2019; **18**: 1533033818818561. https://doi.org/10.1177/1533033818818561
74. Berger M, Char DH. Interactive image guidance for surgical localization of orbital apical tumors. *Orbit* 2002; **21**: 199–203. https://doi.org/10.1076/orbi.21.3.199.7180
75. Miller NR. The evolving management of optic nerve sheath Meningiomas. *Br J Ophthalmol* 2002; **86**(11): 1198. https://doi.org/10.1136/bjo.86.11.1198
76. Cristante L. Surgical treatment of Meningiomas of the orbit and optic canal: a retrospective study with particular attention to the visual outcome. *Acta Neurochir (Wien)* 1994; **126**: 27–32. https://doi.org/10.1007/BF01476490
77. Saeed P, Rootman J, Nugent RA, White VA, Mackenzie IR, Koornneef L. Optic nerve sheath Meningiomas. *Ophthalmology* 2003; **110**: 2019–30. https://doi.org/10.1016/S0161-6420(03)00787-5
78. Goldberg RA, Shorr N, Arnold AC, Garcia GH. Deep Transorbital approach to the apex and cavernous sinus. *Ophthalmic Plast Reconstr Surg* 1998; **14**: 336–41. https://doi.org/10.1097/00002341-199809000-00006
79. Kloek CE, Bilyk JR, Pribitkin EA, Rubin PAD. Orbital decompression as an alternative management strategy for patients with benign tumors located at the orbital apex. *Ophthalmology* 2006; **113**: 1214–19. https://doi.org/10.1016/j.ophtha.2006.01.064
80. Hassler W, Eggert HR. Extradural and intradural Microsurgical approaches to lesions of the optic Canal and the superior orbital fissure. *Acta Neurochir (Wien)* 1985; **74**: 87–93. https://doi.org/10.1007/BF01418794