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Tumour Review

Management of choroidal metastases

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ABSTRACT

Background: Choroidal metastases (CM) are the most common malignant intraocular lesion observed in up to 4–12% of necropsy series of patients with solid cancer. The spectrum of presentations varies from prevalent CM in disseminated cancer to isolated CM. CM are responsible for visual deterioration. Depending on the primary cancer, estimated life expectancy, overall cancer presentation and ocular symptoms, the management of CM varies widely. We address the multidisciplinary management of CM and technical aspects of radiotherapy.
Material and methods: A systematic review of literature was performed from 1974 to 2014.
Results: Choroidal metastases occur preferentially in breast and lung carcinomas but are reported in all cancer types. The standard treatment remains external beam radiotherapy, applying 30 Gy in 10 fractions or 40 Gy in 20 fractions. The reported complete response and improved visual acuity rates are 80% and 57% to 89%, respectively. Some chemotherapy or new targeted therapy regimens yield promising CM response rates.
Discussion: Radiation therapy consistently shows rapid symptom alleviation, yield excellent local control and functional outcomes. However, there are only few reports on late toxicities after 6 months given the unfavorable prognostic of CM patients. Selected patients may live more than two years, underlying the need to better assess mean and long term outcomes. Some authors have favored exclusive systemic strategies with omission of irradiation. The current literature suffers from the scarcity of prospective trials. Duration of tumor response following systemic therapy is rarely reported but appears less favorable as compared to radiotherapy. Systemic treatments may be proposed for pauci-symptomatic CM in a polymetastatic context while radiation therapy remains necessary in symptomatic CM either upfront or as an alternating treatment. Focalized radiation like brachytherapy and proton therapy may be proposed for isolated CM with long disease-free interval between primary and CM, as these techniques have the potential to yield better tumor and functional outcomes in patients with long life expectancy.

Introduction

Metastatic carcinoma is the most common malignant lesion in the eye and metastasis at the choroid the most frequent localization. The prognostic is usually considered very poor. CM occur in 4–12% of patients with solid tumors (mainly breast and lung cancers but also any other tumor type) in autopsy series and 0–11% in screening programs for patients with disseminated breast or lung cancers [1–4].

The choroid is a 0.1–0.2 mm thick vascular coat of the eye, lying between the retina and the sclera. Its role is to provide oxygen and nutrients to the outer layers of the retina and its photoreceptor cells. Choroid, ciliary body and iris form the uveal tract. The blood supply of the uvea, the macula and the anterior part of the optic

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nerve, comes from the posterior ciliary arteries, collateral branches of the ophthalmic artery that are piercing the sclera with no anastomoses between them. That rich terminal vascularization may explain the metastatic predilection for the uveal tract. The blood-ocular barriers are formed by the blood-aqueous and the blood-retina barriers [5,6]. Intercellular tight junctions (zonula occludens) are major components of these barriers and, as their brain counterpart, prevent many drugs to diffuse into ocular components. The VEGF-TRAP (R1R2) tight junction regulator can suppress choroidal neovascularization and VEGF-induced breakdown of the blood-retinal barrier [7,8]. So do TNF alpha and other molecules [9,10]. Molecular yet unraveled interactions might explain preferential metastatic routes to the choroid, consistent with the visionary "seed and soil" hypothesis coined by Stéphane Paget in 1889 (where the non-random pattern of metastasis is explained by the interactions between the cancer cells-"seed" and the specific microenvironment of the tissue-"soil") [11].

Radiotherapy is the most common treatment applied and thus, the better studied. Although, the management of CM is not standardized and varies between centers and physician's local habits and medical resources. Quick alleviation or prevention of symptoms would preserve the quality of life, especially concerning the risk of blindness. In a context where patients have limited life expectancy, sophisticated treatments (more complex technically or stronger, with higher doses of radiation or by combination of chemo- and radiotherapy for instance) are controversial. But the question still remains open if this approach can lead to better complete response rates and/or yields better functional results. Identifying patients that could benefit from it becomes one of the decisional values.

This review addresses the current controversy with respect to multidisciplinary management and focus on radiation therapy. The goal is to help physicians to make therapeutic choices by having a bright view on the former studies. They are indeed highly susceptible to be confronted at least once to this disease in oncologic centers during their all careers.

Material and methods

Study selection

PubMed search for English or French articles were conducted or the period 1974–2014 using various key-words: choroid/choroidal, metastasis, uveal, treatment, radiotherapy. Additional related articles provided by the first search were included. Articles related to primary ocular tumors were excluded. Case reports were collected by the combination of "choroidal metastasis" and "breast cancer", "lung cancer", "prostate cancer", "thyroid cancer", "gastric cancer", "colorectal", "melanoma" to identify particular aspects of management (see Fig. 1).

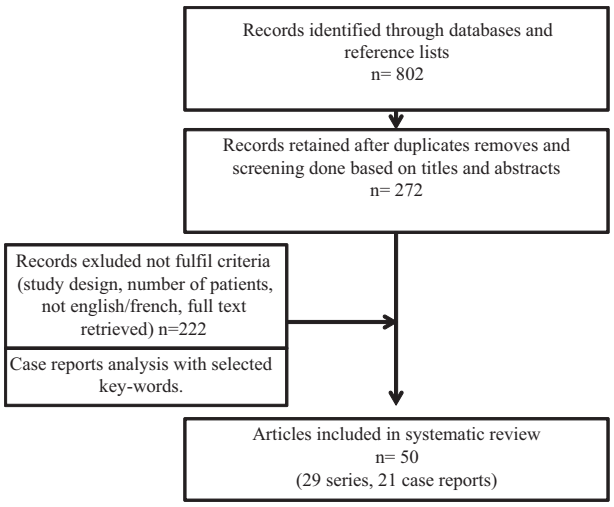

Fig. 1. Prisma flow chart.

Results

Diagnosis: clinical aspects

Symptoms

Most CM is diagnosed on ocular symptoms: deterioration of visual acuity (blurred vision and scotoma), metamorphopsia, photopsia, floaters and pain. However, some studies consisted of systematic ophthalmological screening in selected populations, and underlined the fact that CM could be detected in asymptomatic patients [3,12].

Prevalence and clinical context

Mewis et al. reported in a series of breast cancer patients in two cohorts with or without ocular symptoms 58 CM/152 and 9 CM/98 respectively [13]. Wiegel et al. reported a prevalence of 23% asymptomatic CM in a series of 65 eyes of patients with solid cancers [14]. In a cancer screening program including 120 breast cancer patients (1995–1997), the prevalence was 5% with an increase to 11% when synchronous metastases were present in more than one anatomic site [3]. Other factors associated with a higher prevalence were the presence of lung and brain metastases. In the frame of a lung cancer screening program in 84 consecutive patients, Kreusel et al. found CM in 7.1% of the cases [12]. All of them had disseminated cancer and choroid was the sixth most common metastatic site.

Patient's characteristics

Mean age was 55 years (20–93), with 48 and 61-years old for breast and lung cancer, respectively. Median time between diagnosis of primary cancer and CM (8 studies available) was 49 months (0–16 years).

Primary tumors among 918 patients with CM are reported in Table 1.

Case reports consistently show a majority of breast and lung cancers but also a non-negligible prevalence in thyroid carcinomas, skin melanomas, gastro-intestinal and pelvic cancers (Fig. 2).

Extra-ocular metastases were present in 37–86% (mean 67%) of patients with CM in Table 2. Two studies reported the same high rate (32%) of synchronous brain metastasis [12,26]. In Kreusel's series, 86% of the patients (19/22) had extra-ocular metastases with a median number of three [12]. However, CM were isolated (no other metastases reported at time of diagnosis) in a mean rate of 32% [14–63] of cases (calculation based on 9 studies in Table 2).

Bilaterality

In Demirci's series of 264 breast cancer patients with CM, bilateral metastases were present in 38% of patients at diagnosis. Among patients with asymptomatic CM, 56% had CM in the contralateral eye, detected by systematic examination during a 10-month follow-up [24]. Rudoler, Mewis, Maor and Röttinger reported 40%, 40%, 36% and 50% of breast cancer patients having bilateral CM, respectively [13,16,29,30]. Röttinger et al. observed that bilateral disease was associated with shorter survival than unilateral CM, but not with significant difference (7 versus 11 months after radiation therapy of the involved eye).