# Choroidal Metastases from Breast Carcinoma: Case series

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## Introduction

Choroidal metastases were first reported in 1872 by Perls[1], who noted an intraocular metastatic lung carcinoma. Since then, choroidal metastases have become well established as the most common intraocular malignancy[2]. Choroidal metastases have not been documented to be a frequent finding in disseminated breast cancer. Ocular symptomatology in a breast cancer patient should alert the physician to undertake a thorough examination of the eye.

## Background

Breast cancer is one of the most common malignant diseases with a lifetime risk of approximately 10% in females and is also one of the major causes of cancer related mortality among women worldwide. Attempts to improve survival have targeted early diagnosis and development of adjuvant and neoadjuvant chemotherapy regimens. Breast cancer screening programs for early diagnosis have been incorporated in many international guidelines in the hopes of improving survival rates[3].

Frequent or well described sites of metastases include bone, liver, lung, pleura, skin, brain and eye, but tumor manifestations have been reported in nearly all anatomic regions. Breast cancer possesses the highest incidence of ocular metastatic involvement and the choroids because of their high vascularity are the most common site for ocular metastases. This is followed by the anterior segment and the optic nerve among solid tumors (female patients with breast cancer and male patients with lung cancer). The metastatic involvement of ocular structures in breast cancer seems to be a rare clinical entity; nevertheless, histopathological inquiries propose that 10-37% of patients with breast cancer have detectable ocular or orbital metastases[2].

In 12-31% of affected individuals, eye metastases were reported to be the first sign of malignant disease or metastatic spread2. Choroidal metastases in advanced asymptomatic breast cancer patients were determined to be 5% of ophthalmological screening. Risk factors included spread of disease to more than one organ and the coexistence of lung and brain metastases increased the risk to 11%[4]. The median period from diagnosis of breast cancer to the development of choroidal metastases is reported to be 4 years with a median survival of 5 to 17 months[5]. A large survey of 520 eyes with uveal tract metastases revealed that 88% were located in the choroid, 9% in the iris, and 2% in the ciliary body. Due to recent advances in breast cancer treatment which has impacted on improved survival rates, clinicians should begin incorporating a complete ophthalmological examination for tumoral spread as part of a routine screening program, particularly in high risk patients or in the setting of disseminated disease. This thorough incorporation of an ophthalmologic exam and the improved life expectancy of patients with metastatic disease will make the diagnosis even more prevalent.

## Case reports

Six cases of Choroidal metastases from breast cancer were detected at Tawam Hospital, Al-Ain, U.A.E., over a period of five years (2004-2008).

**These case reports are discussed in brief below.**

*Case 1…* A 50 y/o female with no known co-morbid conditions initially diagnosed with left breast carcinoma by FNA (fine needle aspiration). Later on she had a lumpectomy with axillary clearance followed by adjuvant radiotherapy (T1N0M0) in 1992. Histopathology revealed an infiltrating ductal carcinoma; grade II, ER/PR positive, Cerb2 negative. All lymph nodes were negative. She had no further hormonal therapy or chemotherapy. In February 2004, she had mediastinal lymphadenopathy and lung secondaries. Biopsy confirmed metastatic IDC, ER positive, PR negative and Cerb2+3. She received 2 cycles of chemotherapy with Docetaxel and Capecitabine. Due to poor tolerance, this was switched to Docetaxel and Gemcitabine. She completed six cycles with good response on CT scans. After 8 months she presented with progressive lymphadenopathy. She was again started on systemic chemotherapy with FEC (FEC = 5-FU, Epirubicin, Cyclophosphamide). After 4 days in the 2nd cycle, she began complaining of left eye pain and blurring of vision. Funduscopic evaluation by an ophthalmologist revealed whitish sub retinal exudates. Fundus fluorescein angiography (FFA) and B-scan were consistent with choroidal metastases. MRI brain and orbits showed normal orbits with small variable sized lesion in the left frontal, left post parietal, and right high parietal regions, suggestive of cerebral deposits.
She commenced on whole brain radiotherapy including orbits after appropriate

simulation using 6MV photon beams on LA on 11/07/05. A dose of 30 Gy in 10 fractions was delivered using opposing lateral techniques, which was completed on 24/07/05. After radiotherapy completion; patient lost follow up.

*Case 2…* A 49 y/o female with no known co morbid conditions was diagnosed with right breast infiltrating ductal carcinoma with FNA. This was followed by a right breast lumpectomy with axillary clearance. Histopathology revealed an infiltrating ductal carcinoma; grade III, Triple negative on 02/06/08. She received 1st cycle of chemotherapy; FEC regimen. Post chemotherapy, she was admitted for febrile neutropenia. During the hospitalization, she began complaining of left eye diplopia. A CT scan of the orbits and brain was performed which revealed a normal brain with left sided retinal detachment, choroidal metastases and optic nerve involvement.
The patient was evaluated by ophthalmology. On examination, right eye was normal, left eye disc margins were not clear, yellowish white mass over and around the disc and inferior part of retina. B-scan revealed retinal detachment with choroidal infiltration. She received radiotherapy to the left orbit at a dose of 30 Gy in 10 fractions from 31/05/06 to 06/06/06; after radiotherapy completion; patient lost follow up.

*Case 3…* An 80 y/o female patient with hypertension, acute renal failure, and hypercalcaemia was diagnosed with right breast carcinoma via core biopsy in April 2008. Histopathology was consistent with an infiltrating ductal carcinoma, ER positive, PR negative, and Cerb2 negative. A bone scan revealed extensive bone metastases. She was started on the aromatase inhibitor Letrozole. A few months later, she developed diplopia. A CT scan of the brain and orbits revealed a normal brain with a right orbital mass about 17.0x15.0x7.0 mm along the medial wall and causing compression of the optic nerve. The patient was evaluated by ophthalmology and later referred to radiotherapy. She received 20 Gy in 5 fractions with conformal technique. Shortly thereafter, she was lost to follow-up.

*Case 4…* A 49 y/o female with primary infertility was diagnosed with a triple negative infiltrating ductal carcinoma of the right breast on 27/05/2008. Metastatic workup revealed diffuse bone metastases, including the lumbar spine. She received 20 Gy in 5 fractions to the lumbar spine. She was then started on systemic chemotherapy, FEC regimen on 13/06/08. One week later, she presented with blurred vision in the left eye. An MRI of orbits confirmed choroidal metastases. Upon these findings, she received 30 Gy in 10 fractions to both orbits including optic nerves from 30/06/08 – 16/07/08. During radiotherapy, she developed a massive pulmonary embolism which was treated with anticoagulant. Upon stabilization, she was started on Epirubicin and Taxotere from 23/07/08 and completed a total of 6 cycles with a good PR. Three months later, she presented with new liver lesions and was started on Capecitabine and Bevacizumab. Up to last follow-up, she had received 4 cycles with improvement in her liver lesions.

*Case 5…* A 62 y/o female was diagnosed with infiltrating ductal carcinoma of left breast in June 2005. The tumor was pT3 N2 M0, ER+, PR+, and HER-2 +. She received adjuvant chemotherapy with 4 FEC and 4 Taxotere with Trastuzumab. The patient also received radiotherapy to the chest wall and axilla and maintenance Trastuzumab. Hormonal therapy with an aromatase inhibitor was started after completion of the radiotherapy. In July 2006, she was admitted for loss of vision in the left eye and blurred vision in the right eye. An MRI revealed bilateral choroidal metastases. She received 40 Gy in 20 fractions to both eyes between July and August 2006. Hormonal therapy was changed to Tamoxifen. After radiotherapy, she was started on Capecitabine and Trastuzumab was recommenced. Unfortunately, she developed a right pathological hip fracture and expired after the first cycle due to deterioration of her condition.

*Case 6….* A 38 years old female was diagnosed with left breast cancer in August 2002. She underwent a lumpectomy with axillary clearance. Pathology revealed invasive lobular carcinoma, grade 2, ER +, PR +, HER-2 positive. Adjuvant chemotherapy was given with 4 cycles of Vinorelbine and Epirubicin (part of a clinical trial) followed by 4 cycles of Paclitaxel. Adjuvant radiotherapy was given to the left breast and supra clavicular region for a total of 50 Gy in 25 fractions; this was followed by an additional boost to the tumor bed giving 9 Gy in 3 fractions making the total dose of radiation therapy given 59 Gy in 28 fractions. Post radiotherapy, she was commenced on Tamoxifen. In September 2004; biopsy proven lung metastases was present. She was restarted on Docetaxel and Trastuzumab. After 4 cycles and a good PR, a CT scan of the chest revealed progressive disease, so she was switched to Letrozole with Goserelin and Trastuzumab was continued. In February 2006, a CT scan revealed progression of the lung lesions, Trastuzumab was stopped and patient was started on Capecitabine and Bevacizumab. From February 2006 until May 2010 patient had several lines of chemotherapy. In May 2010 patient presented with blurred vision in the left eye. MRI of the orbits revealed choroidal metastasis to the left eye. Radiotherapy was given for 25 Gy in 5 fractions to the left eye. In August 2010 patient was restarted on Trastuzumab, Lapatinib, and Caelyx. After 4 cycles of chemotherapy a CT scan to the chest and abdomen revealed a new metastatic lesion in the liver. In August 2010 patient was switched to Ixabepilone, Capecitabine, Lapatinib, and Trastuzumab. Another CT scan in December 2010 revealed stable disease.

## Pathophysiology

Intraocular metastases arise when the neoplasm at the primary site spreads through the blood to the eye. Due to the high vascularity of the uveal and, specifically, the choroid - there is a greater likelihood that metastases will enter and remain there. Most choroidal metastases are carcinomas; they are seldom melanomas or sarcomas[6].

## Workup

Workups for choroidal metastases include an MRI of the head to rule out brain metastases and to determine the extent of the tumor. Incidence of central nervous system (CNS) metastases increases from 6% to 28% after development of ocular metastases[7]. Patients with an unknown primary site of origin should obtain a thorough physical examination and have a chest radiograph and mammogram. If the primary site is known, serum chemical analysis, plasma carcinoembryonic antigen (CEA), liver function tests, chest radiography, isotope bone scan, and CT scan of abdomen should be obtained[8].

## Treatment

There are a wide variety of treatment options for patients with Choroidal metastases, the choice of which depends on many factors, including the patient's systemic state, the presence of visual symptoms, tumor activity, tumor size, location, primary site, and whether the patient is concurrently receiving chemotherapy. The report by Shields et al. presented a breakdown of common

treatment options and the percentage of patients who were receiving these corresponding therapies. They included: chemotherapy (8%), external beam radiation (39%), plaque radiation (7%), hormone therapy (1 %), resection (6%), observation (14%), and combination therapy (24%)[9].

In cases of regressed lesions or visually asymptomatic patients with advanced systemic disease, the judicious option is to observe6. For visually asymptomatic patients, many lesions will respond to systemic chemotherapy, hormone therapy, or immunotherapy. Brinkley[10] used a five drug chemotherapy protocol for treatment of metastatic breast cancer and found that choroidal metastases responded to chemotherapy with the same sensitivity as metastases elsewhere in body[11]. If the lesion is unresponsive to chemotherapy, the patient is visually symptomatic, or the patient is not able to tolerate chemotherapy, palliative radiation therapy may be implemented. There are two types of radiation: external beam radiation therapy (teletherapy) and episcleral plaque therapy (Brachytherapy). Both aim for tumor flattening and pigment proliferation. The decision on which option to choose depends on the size of the lesion and the patient's life expectancy.

Because choroidal metastases are radiosensitive, external beam radiation therapy (EBRT) is the most commonly used treatment for these lesions. This treatment is administered with the goal of saving the vision and the globe and provides quick tumor regression. The response rate is 80% but if untreated leads to blindness[15]. In some studies chemotherapy was also as effective as radiotherapy[16]. The procedure is performed in an outpatient setting. Radiation from a remote source is directed at the lesion, and is often performed with a block to limit the radiation to anterior ocular structures and to the contra lateral eye. Total doses of 30 to 40 Gy are administered in daily doses of 2 Gy for 4 weeks.

A study by Rudoler et al of 233 eyes with Choroidal metastases treated with EBRT found that EBRT led to tumor control in 90% of eyes, and globe preservation in 98% of eyes. Weigel et found that the standardized treatment of 40 Gy (with daily doses of 2 Gy given 5 days a week) led to complete remission of the tumor in 38% of the patients, partial remission is 27%, minor remission in 18%, and no remission in 17%.Patients with breast cancer had a significantly increased rate of complete tumor remission, and all patients with combined chemotherapy and EBRT had complete remission.

Higher dosages produce better tumor regression; however, the risk of radiation retinopathy or radiation- induced ocular complications is greater. Radiation can cause dry eye, cataract, hair loss, cutaneous erythema, and conjunctival irritation[6]. Late side effects include cataract, glaucoma, and radiation retinopathy[12]. Weigel found that using more than 40 Gy increased the risk of radiation retinopathy. In a retrospective study by Rosset et a112 of 58 patients treated with EBRT, patients treated with higher amounts of radiation had better resolution and acuities, but more complications. Of patients treated with more than 35.5 Gy, 72% had complete resolution (CR) and 18% had partial resolution (PR). Of patients treated with less than 35.5 Gy, 33% had CR and 41% had PR12. Four of the five patients with complications were found in the group receiving more than 35.5 Gy.

Episcleral plaque therapy is focal radiotherapy to the eye performed in an inpatient setting. The benefit is that treatment time is reduced to 3 days. This therapy is recommended for patients with solitary lesions, patients for whom other modes of treatment have been unsuccessful, or for patients whose life expectancy is short and who want to maximize their quality of life[6]. Radioactive seeds such as Iodine-125 sit inside a gold shield, which is sutured to the globe so that there is a short distance to the target tissue. The plaque is surgically attached to the globe at the site of the lesion. A typical amount of 40 Gy of radiation is delivered to the apex of the tumor. Shields15 reported that most patients achieve tumor regression to half the original thickness and resorption of the sub retinal fluid within the first 3 months after treatment. Complications with plaque therapy parallel those of external beam radiation[6].

Other techniques that are used include local resection, laser photocoagulation, transpupillary thermotherapy, and enucleation. Transpupillary thermotherapy is still in the early stages of its use in the realm of treating choroidal metastases; however, case reports in the literature have shown promising results[13]. When the patient is in a great deal of pain or the choroidal metastases have grown out of the scope of treatment options, enucleation is the recommended treatment. Of note, a recent case report of a carcinoid tumor metastatic to the choroid treated with photodynamic therapy (PDT) showed tumor regression and an improvement in visual acuity[14].

## Survival time

Prognosis is poor for patients diagnosed with choroidal metastases. Average survival time is 8 to 9 months after diagnosis6. The major determinant of prognosis for patients with uveal metastases is based on the primary tumor type. Cutaneous tumors have the worst prognosis (1 to 2 months survival time), and breast tumors have the best prognosis (7 to 31 months). Freedman and Folk[7] found that patients with breast cancer had a median survival time of 314 days. They analyzed the patient population with regard to the stage of breast cancer. Patients with Stage 1 or 2 breast cancer with choroidal metastases had a median survival time of 873 days (29.1 months), and patients with Stage 3 or 4 breast cancer with Choroidal metastases had a median survival time of 139 days (4.6 months)[7]. The overall median survival is better in stages I/II than stages III/IV[17].

## Conclusions

Due to the earlier recognition of cancer and the progress of chemotherapeutic medications, the number of patients who manifest Choroidal metastases will continue to increase. It is essential for the practitioner to be able to recognize this disease process to institute proper treatment for metastatic disease and prevent visual loss. A thorough fundus examination, coupled with the use of A-scan and B-scan ultrasonography, will aid in the diagnosis of suspicious choroidal lesions. The goal of therapy is often palliative if the patient is already being treated systemically for cancer.

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**Figures**

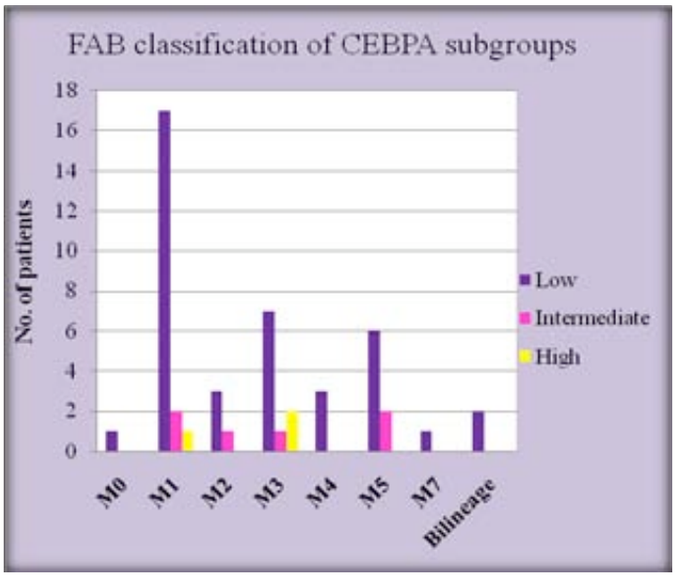


**Fig. 1: C/EBPα subgroups and FAB subtypes in our study group.**

**a** **b**

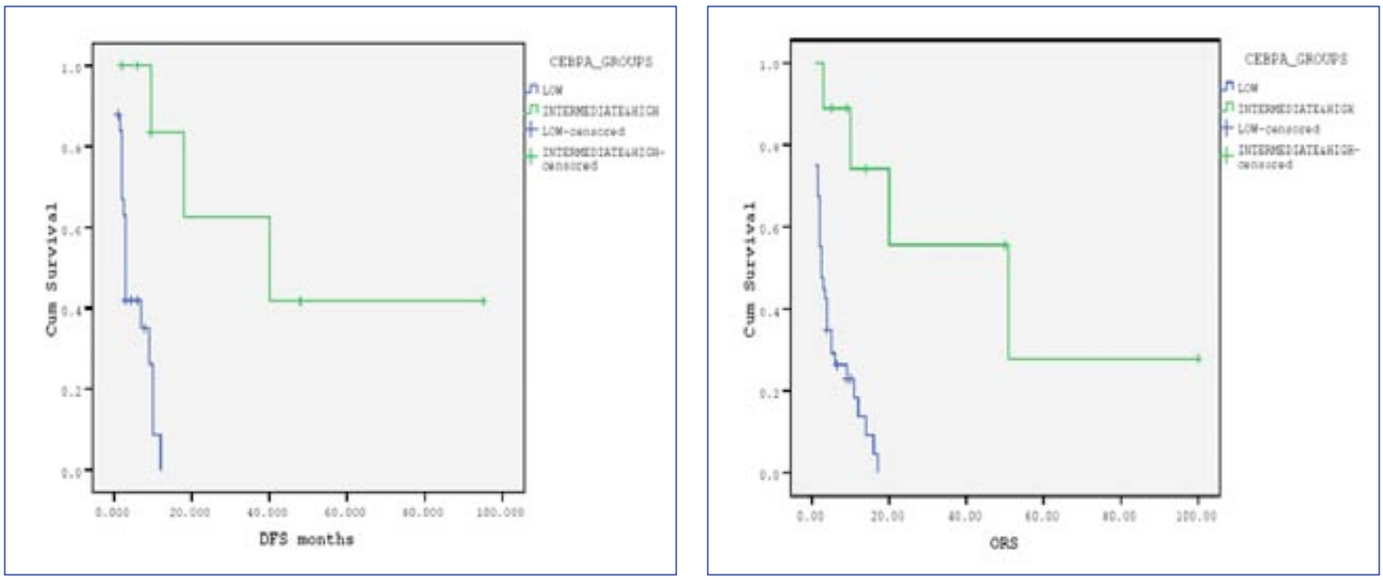


**Fig. 2: Disease free survival (a) and overall survival (b) of AML patients based on C/EBPα expression levels.**