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Rectal Adenocarcinoma with Synchronous Brain Metastasis and Prolonged Overall Survival (OS)

By Losada Vila B, Gutiérrez Abad D, De Torres Olombrada MV & Pereira Pérez F

Fuenlabrada University Hospital

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Then, radiation therapy (RT) of brain with radiosurgery and short course 5x5 of the primary tumor with low anterior resection was completed. After 2 months of brain RT, liver progression was discovered and then we decided neoadjuvant chemotherapy mFOLFOX6 and bevacizumab x 5 cycles with stable liver metastases and no other lesions. Following, limited liver resection and adjuvant chemotherapy was performed with the same schedule.

No signs of tumor recurrence and more than 13 and 24 months of disease-free survival (DFS) and overall survival (OS) respectively was achieved in a metastasic cancer (brain metastasis) with usually OS 3 months.

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I. Introduction

Colorectal cancer is the second leading cause of death in Spain and up to 20% is diagnosed in an advanced stage, normally with hepatic or lung metastasis. Brain metastases are an uncommon complication of colorectal cancer (1.8-5% of all BM), even more unusual in the beginning (<1%). Overall survival(OS) after diagnosis of BM is 2.6 to 7.4 months. However, we try to perform metastesectomies whenever possible.

We submit a rare case whith unique frontal brain metastases of rectal adenocarcinoma without affecting other organs. Emphasize on a multidisciplinary approach to achieve a prolonged survival.

II. Case Presentation

A 61 year-old woman, with no personal previous history who debut with dizziness, gait disturbance and memory loss. Performance Status 1. Occasional bleeding tools. No fever.

First of all, brain CT showed a single lesion in left frontal lobe, so she was admitted to complete the study. To better qualify the lesion, brain MRI showed the same nodule, suggesting a metastasic disease (figure 1). As digestive disorders were recent too, colonoscopy was the third test: mass occupying lesión 100% of the circumference and medium rectum location. PA: low-grade colorectal adenocarcinoma. (figure 2)

CT chest-abdom-pelvis: no further disease. Pelvis MRI: 7cm tumor from anal margin.

Clinical statage: cT3N1M1 (single brain metastasis). According to give a treatment with a curative intention, Tumor Committee decided brain surgery followed by short course rectal RT and low anterior resection (LAR).

III. Differential Diagnosis

Approaching to a brain lesion discovered with no previous recent trauma, bleeding or halo images suggesting infection or abscess; first possibilities are malignancies and the most frequent ones are lymphoma, metastasis and astrocytoma / glioblastoma multiforme. Less common are ependymoma, tumors of the pineal gland or choroid plexus.

In primary malignancies with brain metastases such as melanoma, lung, kidney or thyroid, brain lesions bleeding would be usual and MRI should be hyperintense on T2 lesion if bleeding was within 6 hours or hypointense on T2 if bleeding was after 24 hours.

Central view for MRI is hyperintense with abscess, while in the tumor is hypointense.

Definitive diagnosis is based on histology, and when the lesion is technically resectable, surgery resection must be performed with intraoperative confirmation.

IV. Treatment

Digestive Tumor Committee decided neurosurgery because it was an unique and resectable lesion (10.09.2013). Performance Status 1.

Definitive Histological diagnosis was a 3.1 x 2.2 x 2 cm metastasis of colorectal adenocarcinoma (CK20 +, CK7 - and CEA +) with extensive tumor necrosis. Microscopical surgical margin affected.

Author α: Department of Medical Oncology, Fuenlabrada University Hospital, Madrid, Spain. e-mail: beatriz.losada@salud.madrid.org
Author σ: Department of Medical Oncology, Fuenlabrada University Hospital, Madrid, Spain. e-mail: dgutierreza@salud.madrid.org
Author ρ: Department of Radiation Oncology, Fuenlabrada University Hospital, Madrid, Spain.
e-mail: mariavictoria.detorres@salud.madrid.org
Author ω: Department of Digestive Surgery, Fuenlabrada University Hospital, Madrid, Spain. e-mail: fernando.pereira@salud.madrid.org

RT of primary tumor including pelvis and rectum in short course 5 sessions of 5Gy and subsequent LAR was accomplished on 25/11/13.

Definitive Histological diagnosis: rectum adenocarcinoma ypT4b N2a (4/39) L0V1 R1 (radial margin) Wild KRAS type and mutated NRAS.

Because of surgery infection, no possible "adjuvant" chemo. As brain margin affected and no chance of chemo, radiosurgery treatment in Central Nervous System (total dose of 35 Gy) was completed from 02/05/14 to 02/17/14.

PET-CT reassessment at 2 months (figure 3): liver metastatic spread in both lobes (Sg II 6 mm, 19 mm Sg III, VIII 7 mm Sg, Sg V 20 mm) without other evidence of disease.

Not seen in previous CT, probably present.

Performance Status 1. Chemotherapy treatment mFOLFOX6 + Bevacizumab schedule (25/02/14) was proposed due the new metastatic liver lesions. CEA normalization achieved after 5 cycles and CT showed stable disease and resectable liver metastases. Limited hepatic resection (06.18.14) in those segments with lateral ileostomy closure. Definitive Histologic Diagnoses was liver metastases sg II, III, V and VIII with 0.2 cm of clear margin.

Adjuvant treatment was mFOLFOX6 + Bevacizumab x 3 cycles and final toxicity was diarrhea and neuropathy. CT showed no signs of tumor recurrence at the end of treatment on 24/09/14. Actually Performance Status 0 and no neurologic symptoms.

Outcome and Follow-Up

More than 26 months of DFS and more than 36 months of OS.

V. Discussion

Initial presentation as cerebral involvement is unusual, being 1-4% the incidence of brain metastases associated to colorectal cancer. According to Ko Chu Fang, 3773 patients with colorectal cancer were reviewed, which 37 (1.03%) developed metastases between 1970 and 1996. 55% had a solitary lesion while 45% were multiple. Regarding location, 62% were in temporoparietal lobes, 13% in cerebellum, 13% cerebellum and cerebrum, 8% frontal lobe and 4% in posterior fossa brain. Rectal origin occurs in 56.4%. [1]

This case is unusual in rectal cancer disease because of the synchronous diagnosis and absence of metastatic disease in other organs (liver and lung as usual). In Kye series, 39 patients presented with colorectal brain metastases, 79.5% presented with pulmonary metastases and only 1% as an exclusive involvement in brain. [2] In E Magni serie of 41 patients, 4.9% did not involve other extracranial metastatic locations [3]

Diagnosis of brain metastases appear after a mean of 36 +/- 19 months and diagnosis of colorectal cancer in 77% of reported cases, with just a remaining 23% present in the beginning. In E Magni serie, 17.1% was synchronous too.

According to the treatment, a literature review only describes very few cases treated with radiosurgery, being this indication increasing in those patients with multiple lesions <35 mm, minimum mass effect and affected margins.

Results in NCCTG N0574 (Alliance) demonstrated better OS and quality of life with radiosurgery + RT [4]. Recently, a literature review of 80 patients with brain metastasis reported OS of 6 months in patients who recevied gamma knife radiosurgery (22 patients), 3 months in whole radiotherapy and 13 months in 10 patients on gamma knife + whole radiotherapy. [5]

Among a serie of 41 patients (E Magni) OS after diagnosis of brain metastases was 5 months: 4.2 months in patients treated with radiotherapy (29.3%), 11. 9 months in those with radio and chemotherapy (21.9 %),and 21.4 months in those with surgery +/- radio or chemotherapy (29.3%).

We emphassyze our case with OS 24 months, never published.

Also, prognostic factors in colorectal cancer has been studied to determine the best therapeutic approach. KRAS mutated patients use to present more common pulmonary and CNS involvement (62 and 56.5%), and liver metastasis are less common. [6].

Regarding primary tumor treatment, Shin et al published the results of RT short course schedule (5 days x 5 Gy) and it seems to be effective in local control and "down-staging" with 85% R0 resections. [7,8]

However, when hepatic progression is demonstrated, chemo is the preferred treatment. Adam showed a survival benefit after surgery in liver tumors in response, however this benefit was lower in progression disease. In the case, we decided initially neoadjuvant CT (ESMO Guidelines) with Bevacizumab (KRAS mutated) (Cairo-2, ARTIST): 45-55% RR, PFS 9-12 months. [9,10,11]. As a partial response was achieved after chemo and liver resection was feasible too, liver surgery was performed because of the impact on survival. [12]

And our last point: chemo maintenance? OPTIMOX trial showed no difference in survival compared to maintenance treatment until progression, so both options are a good idea and depends on the tolerabilty and performance status of each patient[13]

Learning Points/Take Home Messages

- ✓ Debut of rectal cancer with synchronous single and unique frontal brain metastasis is unusual.
- ✓ Overall survival in brain metastases from colorectal cancer is less than 6 months; achieving with

radiosurgery + radiotherapy up to 11 months in literature and in our case >24 months.

- ✓ Differential diagnosis of single brain lesion by image is inconclusive. Definitive diagnosis can be achieved with surgery.
- ✓ Radical surgery treatment of metastatic brain lesion improves prognosis and quality of life. Thinking in isolated brain metastasis as oligometastasic disease.
- ✓ In this case we demostrate liver progression with PET-CT. This technique is useful for surgical decisions.
- ✓ Overall survival > 2 years from the debut despite poor prognostic factors (KRAS mutated, brain and liver metastases).
- ✓ Benefit of multidisciplinary approach.

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Figure Captions

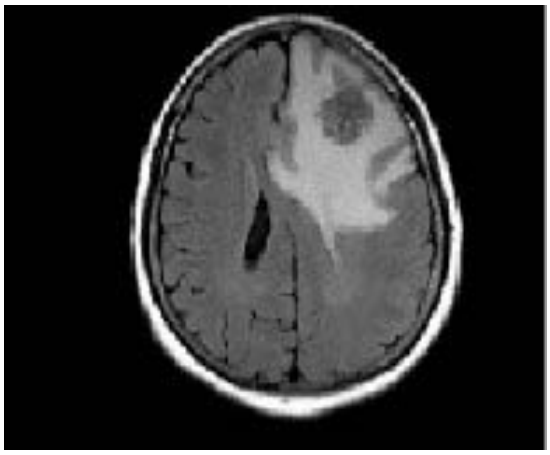

Figure 1: Unique frontal brain metastases

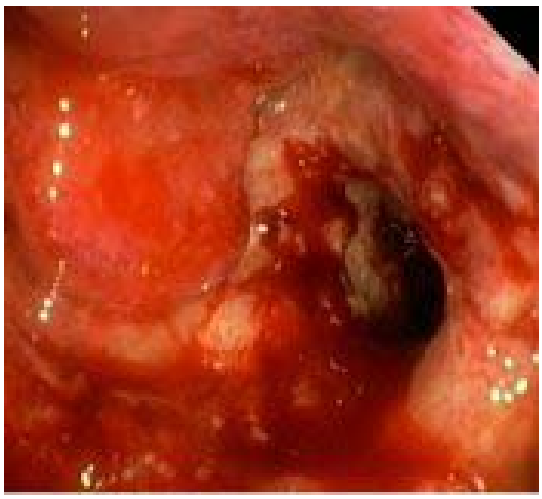

Figure 2: Low-grade colorectal adenocarcinoma

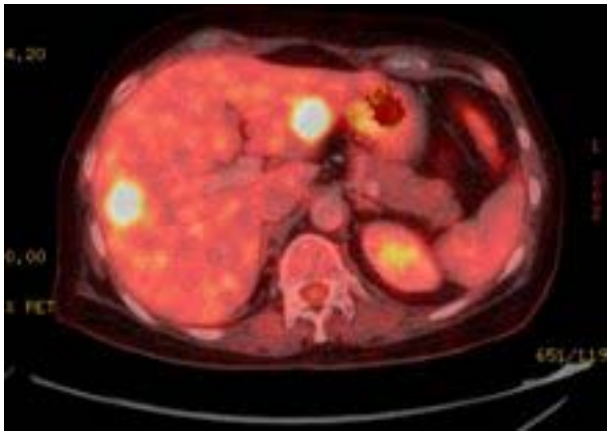

Figure 3: Liver metastatic spread in both lobes (Sg II 6 mm, 19 mm Sg III, VIII 7 mm Sg, Sg V 20 mm)