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DIAGNOSTIC PITFALLS OF BRAIN METASTASES AFTER BRAIN IRRADIATION.

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ABSTRACT

Although brain metastases are one of the most frequently diagnosed sequelae of systemic malignancy, their optimal management still is not well defined. In that respect the different diagnostic and therapeutic approaches of BMs patients is an issue for serious discussions. Among the most commonly used diagnostic tools are computed tomography (CT) scans, magnetic resonance imaging (MRI) scans, single photon emission computed tomography (SPECT) and positron emission tomography (PET) scans etc. Nowadays the aforementioned diagnostic modalities are usually combined in order to obtain complete diagnostic information important for establishing the optimal treatment.

With the present report we try to elaborate on the value of the modern diagnostic tools in differentiating between tumor progression versus radiation necrosis in irradiated patients with resected brain metastases.

Although the present advancement of the modern imaging modalities differentiating between tumor progression versus radiation necrosis is often difficult. Application of the metabolic imaging modalities like SPECT, PET and proton magnetic resonance spectroscopy (1H-MRS) contributes for the diagnose but still pathological specimens remain a gold standard for distinguishing tumor from necrosis, because none of the imaging modalities is possible to reliably differentiate necrosis from progression in 100% of the cases.

Key words: brain metastases, gamma knife, surgical resection, stereotactic radiosurgery, metabolic imaging modalities

INTRODUCTION

According the published data, the number of the patients with malignant diseases, also the patients in the final IV stage of the TNM Classification of Malignant Tumours (**TNM**), respectively the patients with BMs constantly and steadily increase, despite the tremendous and continuous advancement of the modern medicine.[25,26] All this inevitably results in increase of the number of the patients with metastases, and in particular patients with brain metastases (BMs).[11]

According to the literature about 20-40% of the patients with neoplastic diseases develop BMs and presently comprise about 0,15% of the population of the earth.(2, 9, 11)

It is known that presence of brain metastases indicate that patients are in the final IV stage (TNM) with the respective prognosis for the life expectancy for less than a year. Irrespective of the bad prognosis, a correctly chosen therapeutic approach adds to the survival and improvement of the quality of life mainly through the reduction of the intracranial hypertension, neurologic deficiency, pain, etc.

Although brain metastases are one of the most frequently diagnosed sequelae of systemic malignancy, their optimal management still is not well defined.(4, 10, 16) In that respect the different diagnostic and therapeutic approaches of BMs patients is an issue for serious discussions.

Among the most commonly used diagnostic tools are are computed tomography (CT) scans, magnetic resonance imaging (MRI) scans, single photon emission computed tomography (SPECT) and positron emission tomography (PET) scans, etc. Nowadays the aforementioned diagnostic modalities are usually combined in order to obtain complete diagnostic information important for establishing the optimal treatment. Along with the conventional diagnostic tools like CT and MRI - scans, application of the metabolic imaging modalities like SPECT, PET and proton magnetic resonance spectroscopy (1H-MRS) contributes for the complete diagnose.

Usually the surgical resection and gamma knife radiosurgery are considered as an alternative and competitive options for the treatment of the patients with brain metastases.(1, 6, 14, 18) Recently many studies show that microsurgery, radiosurgery and radiation therapy are not mutually exclusive options, but quite the contrary. Nowadays, more than one option is used for the same patient and combining these treatment modalities gives better results than when separately use them. Usually after the surgical resection of BMs , the patients are irradiated - whole brain radiation therapy (*WBRT*) or Gamma Knife surgery (GKS). (6, 7, 12, 13, 20, 23, 24)

With the present report we try to elaborate on the value of the modern diagnostic tools in differentiating between tumor progression versus radiation necrosis in irradiated patients with brain metastases.

Although the present advancement of the modern

imaging modalities differentiating between tumor progression versus radiation necrosis is often difficult.

PATIENTS AND METHODS

Patients who underwent a subsequent resection for a metastatic brain lesion that had been previously treated with GKR form the basis of the current report.

ILLUSTRATIVE CASES

Case # 1(Fig.1)

A 57-year-old man presented with left-sided hemiparesis due to symptomatic mass lesion in the right frontal lobe (Fig.1A) shown by follow up MRI after established lung adenocarcinoma. The lesion had been excised (Fig.1B) (gross total resection before the 1st GKS). Histopathological examination showed brain metastasis from lung adenocarcinoma. After the resection the patient had been referred for SRS targeting the resection cavity (Fig.1C). On follow ups 14 months after the brain tumour initial resection, local tumor relapse had been found on Gd-MRI (Fig.1D). The lesion had been considered as a recurrent metastatic brain tumour and the patient had been referred again to GKS center for treatment of the recurrent lesion (Fig.1E). 20 months after second GKS the patient developed left hemiparesis with poor response to steroid. The patient had been operated again and the symptomatic lesion had been excised (Fig.1F). Local recurrence of metastasis was confirmed by histology (Fig.1G, Fig.1H). After surgery, perifocal oedema on MRI and the hemiparesis were improved.

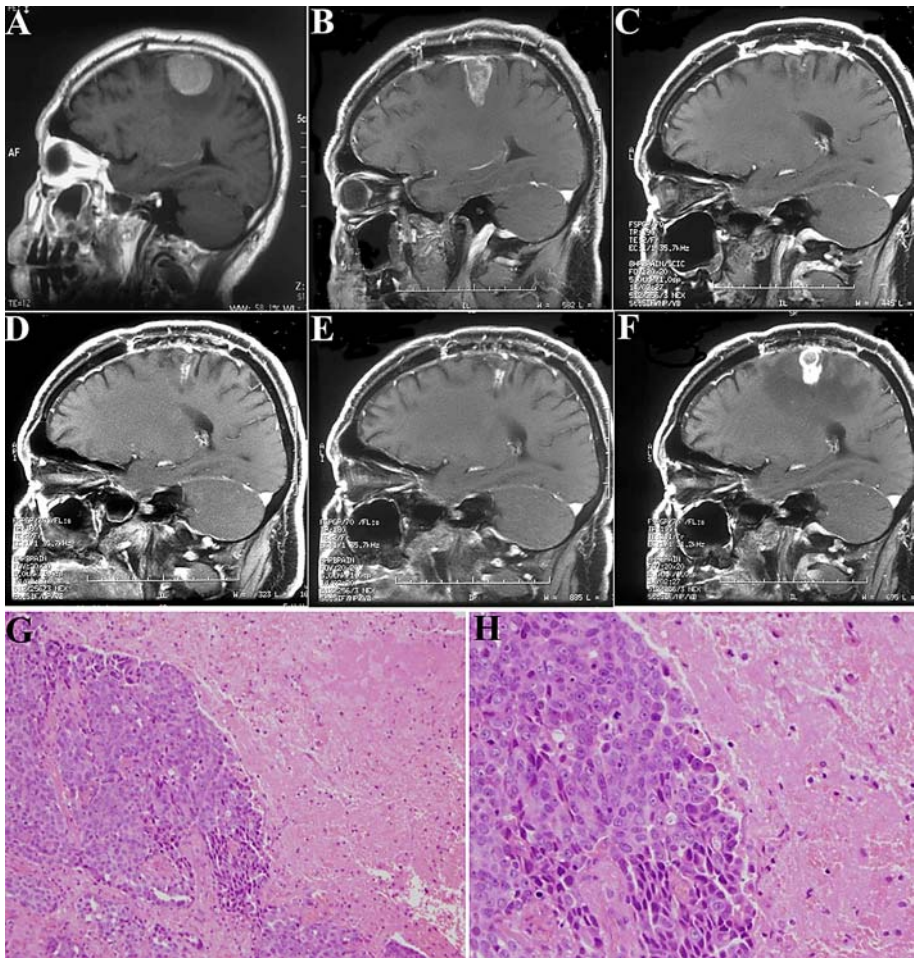

Figure 1. (Fig.1A) Follow up MRI of symptomatic mass lesion in the right frontal lobe after established lung adenocarcinoma of 57-year-old man presented with left-sided hemiparesis; (Fig.1B) Follow up MRI after the lesion had been excised. Histopathological examination showed brain metastasis from lung adenocarcinoma; (Fig.1C)After the resection the patient had been referred for SRS targeting the resection cavity; (Fig.1D) Follow up 14 months after the brain tumour resection, demonstrating a local tumor relapse on Gd-MRI; (Fig.1E) The lesion had been considered as a recurrent metastatic brain tumour and the patient had been referred again to GKS center for treatment of the recurrent lesion. 20 months after the second GKS the patient developed left hemiparesis with poor response to steroid and anticoagulant treatment; (Fig.1F) The symptomatic lesion had been operated and excised; (Fig.1G, Fig.1H) Local recurrence of metastasis was confirmed by histology.

Case # 2 (Fig. 2)

A 69-year-old man presented with left sided hemiparesis due to symptomatic mass lesion in the right parietal lobe shown by follow up MRI 9 months after resected lung adenocarcinoma. (Fig.2A) The patient had been twice referred for SRS targeting the lesion (Fig.2B). 17 months after the second GKS (Fig.2C) the patient developed left hemiparesis with poor response to steroid treatment. The patient had been operated and the symptomatic lesion (FIG.2D) had been excised. Local recurrence of metastasis was confirmed by histology (Fig.2E, Fig.2F). After surgery, perifocal oedema on MRI and the hemiparesis were improved.

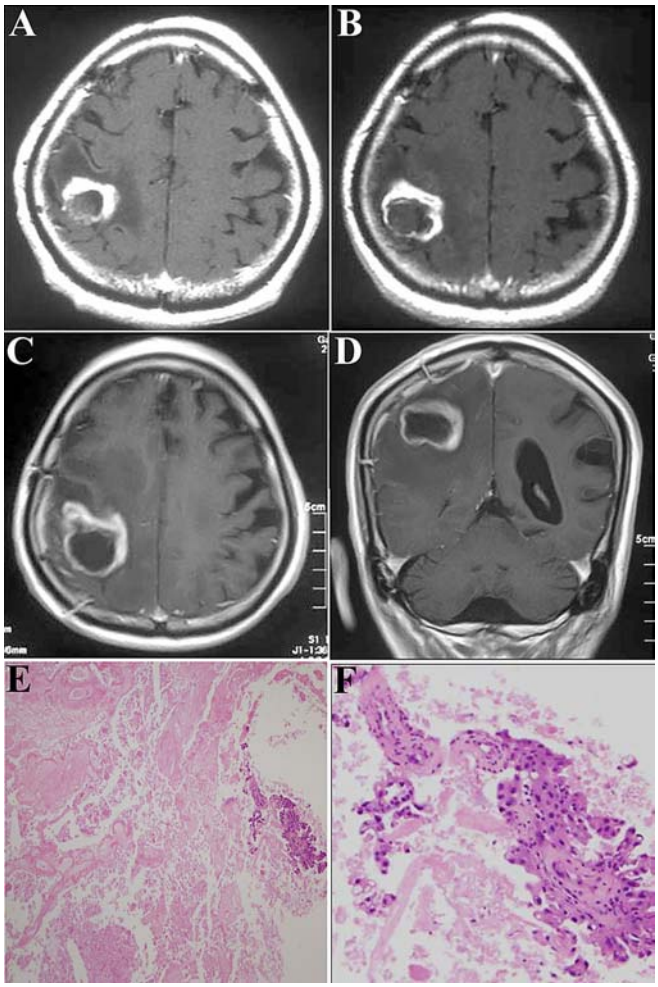

Figure 2. (Fig. 2A) Follow up MRI of 69-year-old man presented with left sided hemiparesis due to symptomatic mass lesion in the right parietal lobe 9 months after resected lung adenocarcinoma; (Fig. 2B).The patient had been twice referred for SRS targeting the lesion; (Fig. 2C) 17 months after the second GKS the patient developed left hemiparesis with poor response to steroid treatment; (Fig. 2D) The symptomatic lesion had been excised; (Fig. 2E, Fig. 2F) Local recurrence of metastasis was confirmed by histology.

Case # 3 (Fig. 3)

A 61-year-old female presented with left sided hemiparesis due to symptomatic mass lesion(FIG.3A) in the right parietal lobe shown by follow up MRI 29 months after resected colon adenocarcinoma. The lesion (FIG.3A) had been excised. Histopathological examination showed brain metastasis from lung adenocarcinoma. After the resection the patient had been referred for SRS targeting the resection cavity. 6 months after the last GKS the patient presented again with left sided hemiparesis (Fig.3B) found to be progressing on the follow-ups (Fig.3C). The findings from PET-scan with Choline (Fig.3E), FDG (Fig.3F) and Methionine (Fig.3G) suggested radionecrosis. Due to prgessive deterioration (Fig.3D) the patient had been operated again. Local recurrence of metastasis was confirmed by histopathology.

The tree ILLUSTRATIVE CASES present a different aspects of the problem for the reliability of the imaging modalities available for the differentiation between BM – recurrence and radionecrosis.

#1 demonstrates a patient that has been initially operated for a brain metastasis and then reoperated for a symptomatic brain lesion at the site of the initial brain surgery after 2 courses of GKR targeting the initial brain surgery resection cavity. ”

#2 demonstrates a patient that has been initially

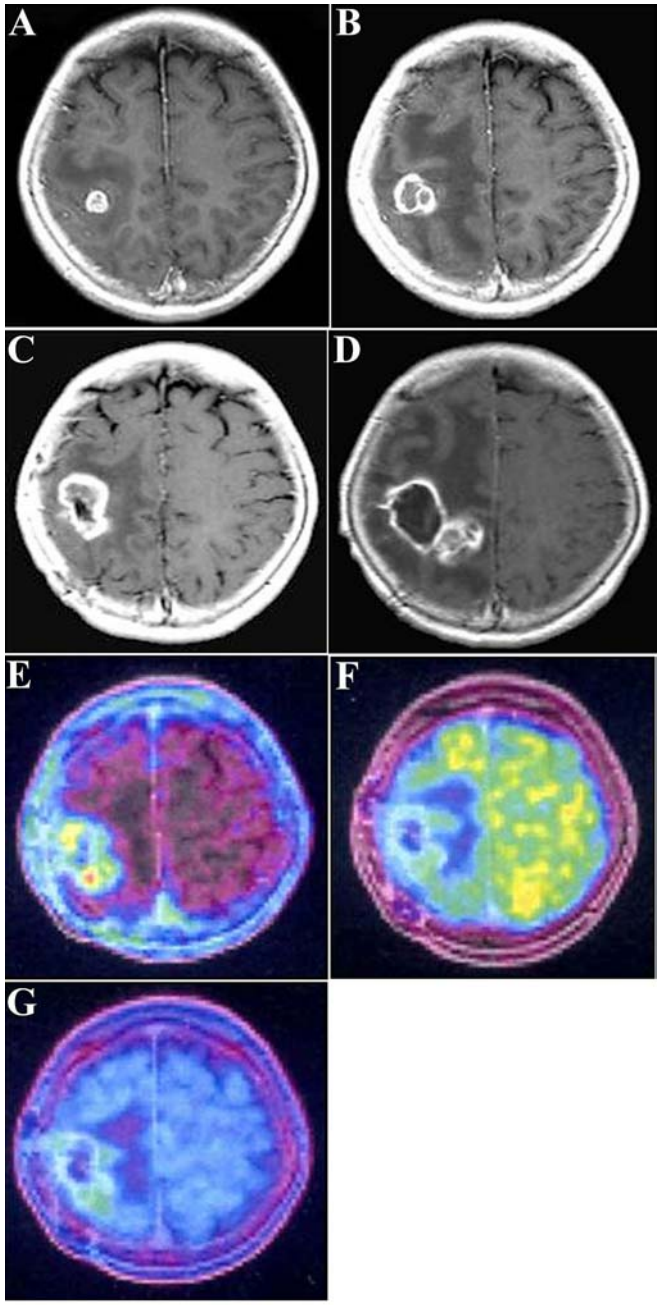

Figure 3. (Fig. 3A) Follow up MRI of 61-year-old female presented with left sided hemiparesis due to symptomatic mass lesion in the right parietal lobe 29 months after resected colon adenocarcinoma. The lesion had been excised. Histopathological examination showed brain metastasis from lung adenocarcinoma. After the resection the patient had been referred for SRS targeting the resection cavity; (Fig. 3B), (Fig. 3C) 6 months after the last GKS the patient presented again with left sided hemiparesis found to be progressing on the follow-ups; The findings from PET-scan with Choline (Fig. 3E), FDG (Fig. 3F) and Methionine (Fig. 3G) suggested radionecrosis; (Fig. 3D) Due to prgessive deterioration the patient had been operated again. Local recurrence of metastasis was confirmed by histopathology.

referred for SRS targeting a symptomatic brain metastasis after resected lung adenocarcinoma. 17 months after the second GKR the patient developed left hemiparesis with poor response to steroid treatment. The patient had been operated and the symptomatic lesion had been excised

#3 demonstrates a patient that has been operated after a PET scan showing necrosis but local recurrence of metastasis was confirmed by histopathology.

The decision for resection after Gamma Knife radiosurgery (GKS) was based on both *clinical and radiological criteria*. Patients developing neurological symptoms and/or steroid dependence attributable to progressive, surgically accessible lesions, in the setting of stable systemic disease and Karnofski Performance Status (KPS) > 60 underwent resection. Asymptomatic patients who demonstrated signs of radiological progression such as lesion growth, persistent surrounding edema, and/or mass effect, were similarly considered for resection. When symptomatic due to brain edema after GKR, we observed the patients for 3 months or longer using steroid.

Histopathological examination revealed massive necrosis with small nests of viable tumor tissue in all of the cases.

All of the patients showed marked clinical improvement within 3 days after surgery.

DISCUSSION

Although brain metastases are one of the most frequently diagnosed sequelae of systemic malignancy, their optimal management still is not well defined.(4, 10, 16) In that respect the different diagnostic and therapeutic approaches of BMs patients is an issue for serious discussions. The treatment options include surgical excision, WBRT, radiosurgery, chemotherapy, immunotherapy, etc. Nowadays the aforementioned treatment modalities are usually combined in different treatment schemes. (ex. Surgical resection+WBRT; GKS+WBRT, Surgical resection+ GKS+ WBRT, etc.) (6, 17)

Many studies confirm that the different treatment modalities like radiosurgery, microsurgery, and radiation therapy are not mutually exclusive options, but quite the contrary. Nowadays, more than one modality is commonly used for the same patient and combining these treatment modalities usually yields better results than when separately use them. Following subtotal or gross-total resection, it is now a standard practice for patients to receive adjuvant postoperative radiation therapy in order to lower the recurrence rate - patients who receive radiation therapy are significantly less likely to suffer a treatment failure in the brain, both at the original resection cavity as well as at distant sites, compared with those who do not receive radiation.(6, 7, 12, 13, 20, 23)

Stereotactic radiosurgery delivered to the tumor resection cavity after gross-total resection is another approach for preventing local tumor recurrence. The benefits from using GKS instead of WBRT is to lower the incidence of the complications that often follow RT. (6)

One of the commonest pattern of failure after WBRT and GKS is radiation necrosis or local/distant recurrence development. (27)

So the two major challenges of management of brain metastases after stereotactic radio surgery and WBRT are 1) differentiating tumor progression from radiation necrosis and 2) deciding when surgical intervention is necessary. (7, 20)

Computerized tomography, MR imaging, SPECT and PET scanning are essential in the evaluation of metastatic brain tumors. Nevertheless, a differential diagnosis between tumor recurrence and radiation necrosis is difficult after radiotherapeutic treatment of brain tumors by using these modalities.(21) Authors of some published reports have shown that PET scanning with the aid of FDG or MET is effective in differentiating recurrent BMs from radiation-induced changes and can provide early detection of a recurrence. (5, 15) It was also reported that the ыndings of ^{201}TlCl-SPECT enable differentiation between radio-induced necrosis and recurrence of a tumor. (5, 19, 22)

Using MRI images to study 1H-MRS, authors report that based on some metabolites and metabolite ratios evaluation, it is possible to differentiate between BM recurrence and radionecrosis. (3, 8)

However pathological specimens still remain the gold standard for distinguishing tumor from necrosis, because non of the imaging modalities is possible to reliably differentiate necrosis from progression in 100% of the cases. (20)

Since currently one can not reliably make differentiation between tumor progression and radiation effect noninvasively, delayed neurosurgical resection does need to be considered *for patients with symptomatic progression of intracerebral lesion after GKS*.

Delayed resection should be considered in symptomatic patients whose tumors show progression after initial SRS. Additional surgical removal for recurrent brain metastases has been already used successfully after an initial surgical removal and following SRS. (7)

Our report supports the value of surgical resection in selected patients with *progressive* and especially *symptomatic* brain lesions following GKR/WBRT treatment irrespective the imaging data suggesting radionecrosis. Therefore, as patients with brain metastases continue to beneыt from systemic therapy it is important to consider the delayed consequences of treatment or disease progression after GKR.

CONCLUSION

Since currently one cannot reliably make differentiation between tumor progression and radiation effect non-invasively, neurosurgical resection should be considered for patients with symptomatic progression, also based on progression demonstrated on contrast enhanced CT and MRT scans.

Differentiating between tumor progression versus radiation necrosis based on T1 and T2 weighted images alone is often difficult. Application of the metabolic imaging modalities like SPECT, PET and 1H-MRS contributes for the diagnose but still pathological specimens remain a gold standard for distinguishing tumor from necrosis, because none of the imaging modalities is possible to reliably differentiate necrosis from progression in 100% of the cases.

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