

Pseudoprogression of malignant glioma in Chinese patients receiving concomitant chemoradiotherapy

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Key words

Antineoplastic agents, alkylating;
 Biological markers; Brain neoplasms;
 Glioblastoma; O(6)-Methylguanine-DNA
 methyltransferase

Hong Kong Med J 2012;18:221-5

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Objectives To investigate the frequency of pseudoprogression of glioblastoma in Chinese patients receiving concomitant chemoradiotherapy and investigate its association with pseudoprogression and tumour molecular marker O⁶-methylguanine-DNA methyltransferase promoter methylation status.

Design Case series with internal comparisons.

Setting University teaching hospital, Hong Kong.

Patients Patients with glioblastoma treated with concomitant chemoradiotherapy during April 2005 to June 2010 were reviewed. Magnetic resonance imaging brain scans, pre- and post-concomitant chemoradiotherapy and 3-monthly thereafter were reviewed by an independent neuroradiologist according to Macdonald's criteria. Relevant patient information (clinical condition, performance score, development of new neurological deficits, use of steroids, and survival) was retrieved. For each patient, O⁶-methylguanine-DNA methyltransferase methylation status was investigated with genomic DNA from formalin-fixed or paraffin-embedded sections of tumour tissues by methylation-specific polymerase chain reaction.

Results During the study period, 28 primary glioblastoma patients underwent concomitant chemoradiotherapy. The mean age of the patients was 48 (range, 16-71) years. Thirteen patients (13/28, 46%) developed early radiological progression of the tumour after completion of concomitant chemoradiotherapy, of whom five (39%) were subsequently found to have had pseudoprogression. Patients with pseudoprogression showed a trend towards longer survival (22 months in pseudoprogression vs 17 months in all others vs 11 months in those with genuine progression). Among the 27 patients tested for O⁶-methylguanine-DNA methyltransferase promoter status, 12 (44%) were methylated. Two (2/12, 17%) in the methylated group had pseudoprogression, while three (3/15, 20%) in the unmethylated group had pseudoprogression.

Conclusions Nearly half of all patients (46%) developed early radiological progression (within 3 months of completing concomitant chemoradiotherapy). Moreover, about one in three of such patients had pseudoprogression. Pseudoprogression is an important clinical condition to be aware of to prevent premature termination of an effective treatment.

New knowledge added by this study

- In local Chinese patients with glioblastomas, tumour pseudoprogression is a common treatment response (one in six) after concomitant chemoradiotherapy.
- Nearly half of all patients (46%) developed early radiological tumour progression (within 3 months of completion of concomitant chemoradiotherapy), of whom about one in three had pseudoprogression.

Implications for clinical practice or policy

- Tumour pseudoprogression is an important clinical response to be aware of to prevent premature termination of an effective treatment.

同步化放療治療惡性膠質瘤假性進展的華籍患者

目的 找出接受同步化放療的華籍患者其惡性膠質瘤假性進展的數目，並探討膠質瘤假性進展與O⁶-甲基鳥嘌呤-DNA甲基轉移酶基因（MGMT）甲基化關係。

設計 含群組內部比較的病例系列。

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患者 回顧2005年4月至2010年6月期間惡性膠質瘤假性進展的華籍患者接受同步化放療的紀錄。一名獨立腦神經放射科醫生根據Macdonald準則檢示病人接受同步化放療前後，以及每三個月進行的腦磁共振影像，亦記錄患者其臨床狀況、表現評分、神經功能缺損的發展、類固醇的使用及生存期的資料。採用甲基化特異性聚合酶鏈反應，把患者的醛固定或石臘包埋腫瘤組織樣本抽取其基因組DNA，來檢示其MGMT甲基化的情況。

結果 研究期間共28名膠質瘤患者接受同步化放療，他們平均年齡48歲（介乎16至71歲）。28例中，13例（46%）完成同步化放療後出現影像上的早期進展，其中5例（39%）其後發現為假性進展。假性進展患者有較長的生存期（假性進展患者：22個月；其餘患者：17個月；有真正進展患者：11個月）。27名接受MGMT測試的患者中，12例（44%）有甲基化現象，當中2例（17%）為假性進展。無甲基化現象的15例中，3例（20%）為假性進展。

結論 接近一半患者（46%）在完成同步化放療的3個月內出現影像上的早期進展。這些患者中，每3人便有1人有假性進展。假性進展是一個很重要的臨床狀況，醫生要留意以免提早為病人終斷有效的治療。

Introduction

With the introduction of the oral chemotherapeutic agent, temozolomide, it is now standard practice to offer concomitant chemoradiotherapy (CCRT) to patients with histologically confirmed glioblastoma multiforme. More and more evidence in Caucasians

shows that 20 to 30% of patients receiving CCRT develop tumour pseudoprogression. Awareness of this phenomenon has a major bearing on the avoidance of premature termination of an effective chemotherapy. However, the frequency of this phenomenon in the Chinese is unknown.

This study aimed to investigate the frequency of early pseudoprogression in Chinese glioblastoma patients receiving concomitant chemo-irradiation and to investigate any possible association between pseudoprogression and the tumour molecular marker O⁶-methylguanine-DNA methyltransferase (MGMT) promoter methylation status.

Methods

Patients diagnosed with primary glioblastoma who had completed CCRT in the period of April 2005 to June 2010 were recruited. Patients unable to complete the 6-week CCRT or who did not follow the pre-planned scanning schedule were excluded. Regarding their radiotherapy, there was a consistent protocol with either conformal radiotherapy or intensity-modulated radiotherapy that delivered 54 to 59.4 Gy (median, 59.4 Gy) over 30 to 33 fractions (median, 33 fractions) in 6 weeks to the surgical bed as well as the gross residual disease (as seen on pre- and post-operative imaging). The chemotherapy regimen followed that described by Stupp et al¹ using temozolomide at 75 mg/m²/day during radiotherapy, and 150 to 200 mg/m²/day on days 1-5 every 4 weeks for 6 cycles. None of the patients received other treatments, such as gliadel wafer implants or anti-angiogenesis agents. Patients were subjected to a scanning schedule with a magnetic resonance imaging (MRI) scan on day 1 after the operation, 2 weeks after completing CCRT, and every 3 months thereafter (Fig 1). Radiographic progression was determined by an independent neuroradiologist according to the Macdonald's response criteria² to quantify the changes in enhancing lesions on the scans. Patients were seen every 4 weeks during the course of chemotherapy. Each patient's clinical

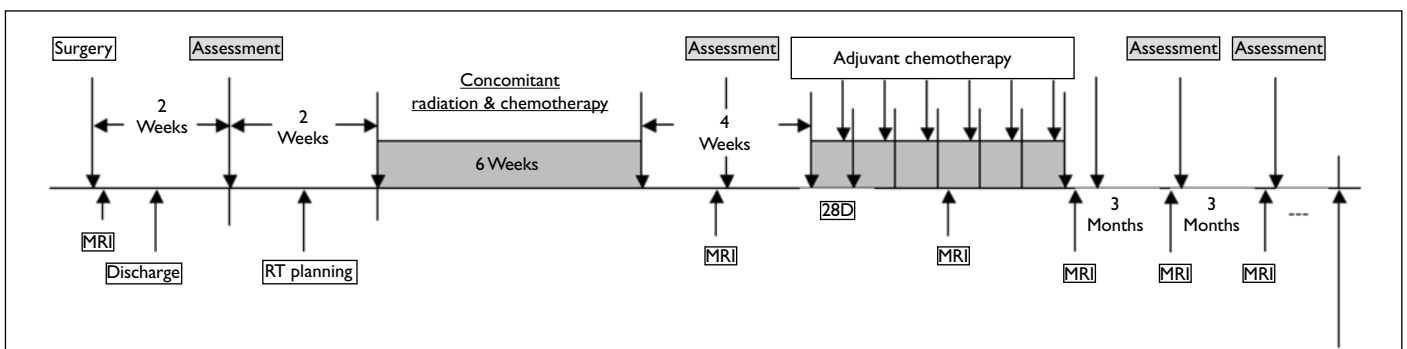


FIG 1. Scanning schedule

MRI denotes magnetic resonance imaging, and RT radiotherapy

condition, performance score, use of steroids, and development of new neurological deficits were noted.

Early disease progression was defined as an increase of 25% or more of contrast enhancement in the largest cross-sectional area on the post-CCRT contrast brain scan, with or without neurological deterioration. Real disease progression was defined and documented when the patients with early disease progression developed additional disease progression within the following 6 months. Pseudoprogression was defined if patients with early disease progression showed a more than 50% decrease in enhancing cross-sectional area in the subsequent scan or remained clinically and radiologically stable for at least 6 months without any further treatment (other than adjuvant cycles of the Stupp's regimen).¹

Clinical features of patients with real progression and pseudoprogression were compared. Their MGMT methylation status was investigated with genomic DNA from formalin-fixed or paraffin-embedded sections of tumour tissues by methylation-specific polymerase chain reaction, which was a method described by our group.³ Association between MGMT methylation status and occurrence of pseudoprogression was assessed. Overall survival was defined as the period from the date of the first operation to death. Kaplan-Meier survival curves were used to analyse survival of the two groups.

Results

From April 2005 to June 2010, there were 95 potential primary glioblastoma patients, of whom 67 were excluded: 45 had not received chemotherapy and 22 did not conform to the scanning schedule. In all, 28 patients underwent CCRT (Stupp's regimen). The mean age of the latter patients was 48 (range, 16-71) years. In all, 13/28 (46%) developed early radiological tumour progression evident in the MRI 2 weeks post-CCRT. Two patients underwent re-operation

for debulking and pathology confirmed tumour recurrence. The remainder continued to follow the treatment policy and follow-up schedule. All patients had events (progression) assessed, mostly till they died. Their median overall survival was 16 months.

Regarding the 13 early progression patients, five (39%) had pseudoprogression (Table), whilst the other eight had genuine progression. Based on the log-rank test, patients with pseudoprogression showed a trend towards longer median survival (22 months in pseudoprogression vs 17 months in all others vs 11 months in those with genuine progression; Fig 2). So the overall pseudoprogression frequency among our local Chinese glioblastoma patients receiving the CCRT was 18% (5/28).

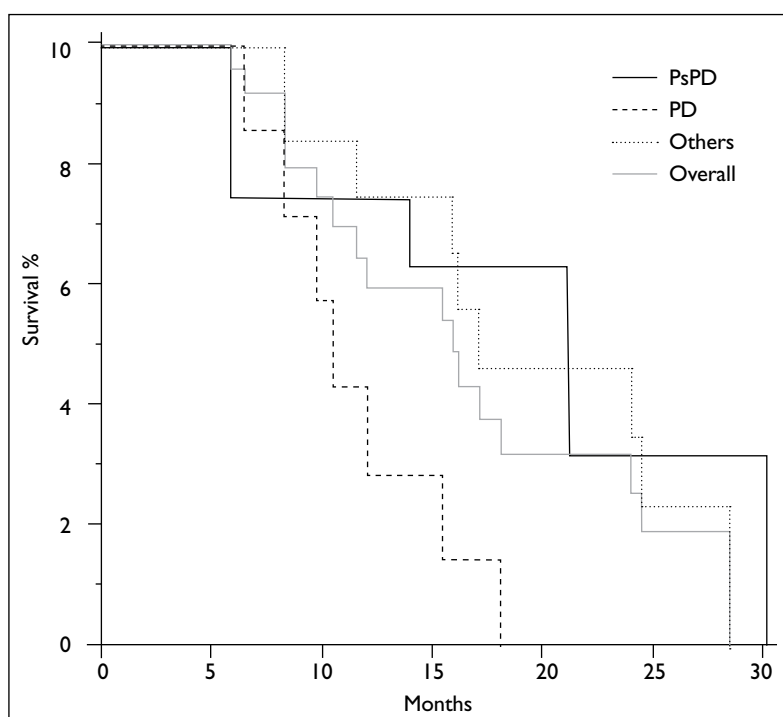


FIG 2. Survival curves
Overall = all cases (16 months); PsPD = pseudoprogression (22 months); PD = progressive disease (11 months); Others = cases without PD or PsPD (17 months)

TABLE. Data on the five patients with pseudoprogression*

Patient No.	EOR at post-op MRI (day 1-3)	Steroid use (dexamethasone mg/day) [†]			PFS (months)
		Post-CCRT	Post 3 months	Post 6 months	
1	>95%	PD: 4 mg/day x 4 weeks	PR: no steroid	SD: no steroid	17
2	>95%	PD: no steroid	PR: no steroid	SD: no steroid	23
3	60-70%	PD: 8 mg/day x 4 weeks, then 4 mg/day x 2 weeks, then stopped	PR: no steroid	SD: no steroid	15
4	80-90%	PD: 4 mg/day x 2 weeks, then 2 mg/day x 2 weeks, then 2 mg/day x 2 weeks, then stopped	SD: no steroid	SD: no steroid	10
5	>95%	PD: 2 mg/daily x 2 weeks	SD: no steroid	SD: no steroid	10

* EOR denotes extent of resection, MRI magnetic resonance imaging, CCRT concomitant chemoradiotherapy, and PFS progression-free survival

[†] PD denotes progressive disease (increase of ≥25% of contrast enhancement in largest cross-sectional area), PR partial response (showed a >50% decrease in enhancing cross-sectional area), and SD stable disease (between PD and PR)

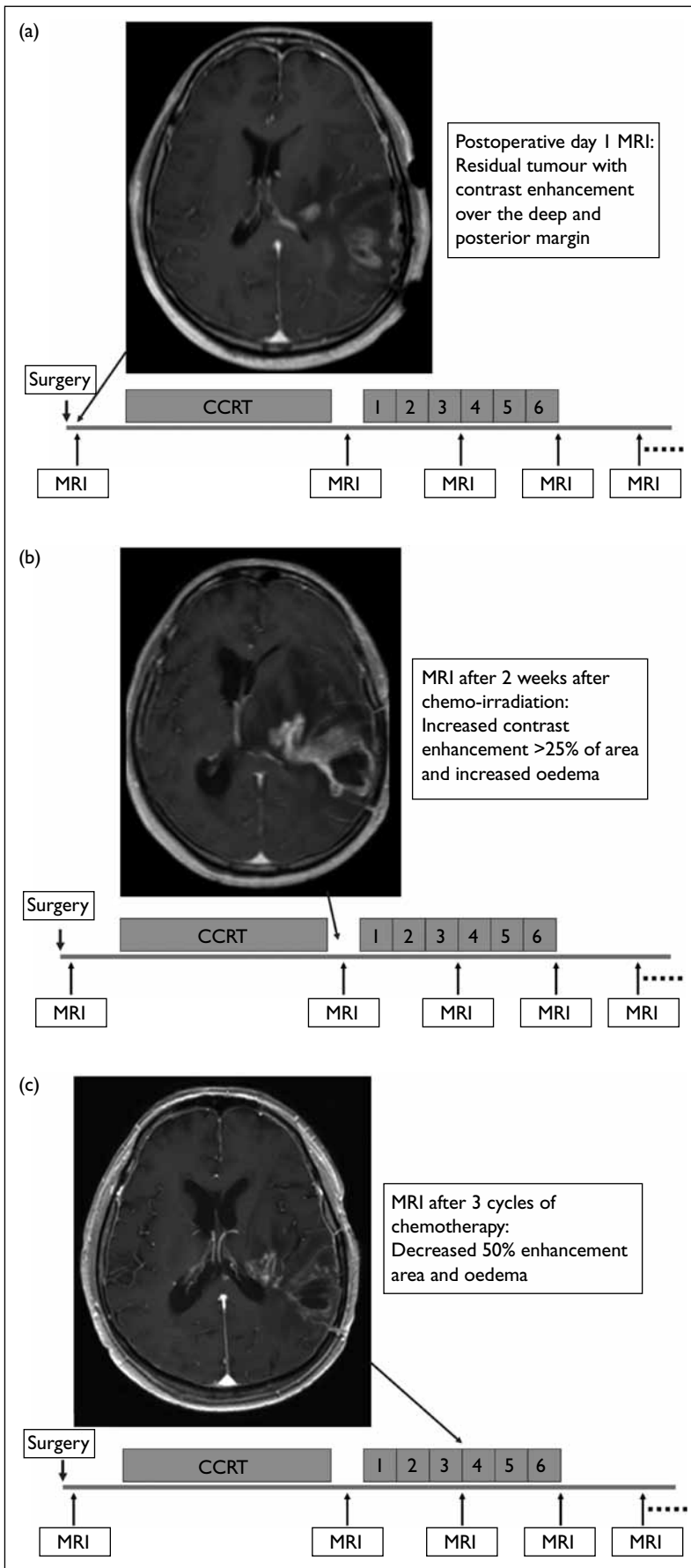


FIG 3. Magnetic resonance imaging (MRI) scans (a) on postoperative day 1, (b) at 2 weeks after chemo-irradiation, and (c) after three cycles of chemotherapy. CCRT denotes concomitant chemoradiotherapy

Among the 27 patients tested for MGMT promoter status, 12 (44%) were methylated. Two (2/12; 17%) with pseudoprogression were in the methylated group while three (3/15; 20%) were in the unmethylated group.

Among the early progression group (13 patients), two out of the five with pseudoprogression were MGMT-methylated, while only two out of eight with real progression were MGMT-methylated. There was no association between MGMT methylation status and the development of pseudoprogression (P=0.2929 by Fisher's exact test).

Discussion

Since the introduction of CCRT as the standard of care for patients with glioblastoma, there has been increasing awareness of the phenomenon of pseudoprogression.^{4,7} This is believed to be a treatment effect instead of tumour progression.^{4,6} It occurred in 20 to 40% of patients immediately after the end of CCRT.^{5,8} Patients often remain clinically asymptomatic or only mildly disturbed clinically, despite radiologically evident progression. In subsequent scans, the lesions decrease or stabilise in size without additional treatment (Fig 3). This phenomenon is believed to result from CCRT (temozolomide—an alkylating agent and radiotherapy) giving rise to a higher degree of tumour cell killing and endothelial cell injury, leading to secondary oedema and abnormal vessel permeability, mimicking tumour progression.^{4,5,8} Our series showed that pseudoprogression occurred in 18% of our local Chinese glioblastoma patients. Concerns about progression occurred in almost half (46%) of our patients receiving CCRT, of whom one in three actually had pseudoprogression. Termination of adjuvant chemotherapy at this point of time would have deprived the patients of an effective treatment, and any subsequent salvage therapy might have been falsely assessed as effective.^{4,6} We encountered a low frequency of pseudoprogression (18%) whilst it was reported to be up to 50% in the literature,^{7,8} possibly because our criteria were more stringent than those used by others. Notably, most reports defined pseudoprogression within 3 months of CCRT,^{5,8} whereas we defined it as radiological and clinical improvement or stability for 6 months. In a series of 86 patients, 36 developed early progression 4 weeks after CCRT,⁷ of whom 50% (18/36) had pseudoprogression, whereas 36% (13/36) were only biopsy-proven (based on a large residual tumour bulk for CCRT). A large proportion (19/36) of their patients were scanned by computed tomography after CCRT and then followed up by MRI. In our series, only 3/28 (11%) of the patients had a biopsy. We followed up our patients with an earlier MRI scan, which was 2 weeks after the CCRT.

All these differences may have contributed to the low frequency we noted.

So as to reliably assess radiological progression, a scanning schedule should be used with CCRT and adjuvant chemotherapy (Stupp's regimen); our schedule is shown in Figure 1 and started on the day after surgery. Assessment of the extent of resection by contrast enhancement (MRI-T1) is confounded by postoperative changes 72 hours after surgery. Thus, early postoperative scans serve two purposes, namely: (1) accurate assessment of the extent of glioma resection, and (2) provision of a baseline for comparison with subsequent scans. It is at such second scans that early radiological progression is detected. In recognition of pseudoprogression, it is recommended that adjuvant chemotherapy (temozolomide) be continued unless real progression is suspected and clinical deterioration is significant. In which case, surgical biopsy (or excision if feasible) should be performed. If the biopsy mainly shows necrosis, chemotherapy should be continued. Subsequent 3-monthly scans may confirm pseudoprogression or real progression.

The molecular marker MGMT promoter of methylation status was reported to be an important prognostic factor in glioblastoma.⁹ The 2-year

survival rate of glioblastoma in methylated MGMT promoter-treated patients with CCRT was 3 times that of those treated with unmethylated MGMT.⁹ The development of pseudoprogression was significantly correlated with the MGMT promoter methylation status.⁸ In the methylated MGMT group, 91% of the patients developed pseudoprogression while only 41% of unmethylated MGMT patients did so.⁸ It was suggested that MGMT methylation status could be an early clue to pseudoprogression. Our group reported 43% MGMT methylation in southern Chinese glioblastoma patients.¹⁰ We showed a trend towards better treatment response in the MGMT-methylated group. Our current results, however, did not suggest any association between development of pseudoprogression and MGMT methylation status.

Conclusions

Pseudoprogression is an important clinical condition to be aware of because one in six glioblastoma patients receiving CCRT exhibits this entity. Nearly half of all patients (46%) developed early radiological progression, of whom about one in three had pseudoprogression. Pseudoprogression is an important clinical condition to be aware of to avoid premature termination of an effective treatment.

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