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Prognostic value of detecting recurrent glioblastoma multiforme in surgical specimens from patients after radiotherapy: should pathology evaluation alter treatment decisions?

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Summary The prognostic significance of the histologic type and grade of gliomas at initial surgery is well established, but the value of histologic findings in resections after radiotherapy is unclear. Despite this uncertainty, pathologic interpretation of specimens after radiotherapy influences immediate treatment decisions. It is important to determine if, and to what extent, treatment decisions should be based on this information. We aimed to determine the prognostic value of pathologic evaluation in postradiation specimens from 54 patients with similar clinical features who underwent a second surgery for the treatment of radiologic worsening after external beam radiotherapy. We categorized the specimens from the second surgery as either *recurrent tumor* (category 1) or *radionecrosis* (category 2). Patients in category 1 had actively proliferating neoplasms with classical features of glioblastoma, whereas patients in category 2 had no evidence of tumor in their surgical specimens. Cases in which a clear-cut definition could not be made were labeled *indeterminate* (category 3). Despite the morphological evidence of tumor, there were no significant differences between categories 1 and 2 in any of the survival parameters tested. The only difference between groups was higher frequency of iodine 125 (^{125}I) placement at second surgery in category 1 patients ($P < .028$). Patients in category 1 with or without ^{125}I treatment had similar survival characteristics. We conclude that histopathologic evaluation of postradiotherapy specimens was not helpful in predicting outcome or dictating further management. A comprehensive prospective study with advanced radiologic, pathologic, and molecular analyses may be more useful to determine prognostically valuable parameters.

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1. Introduction

Glioblastoma multiforme (GBM) is the most common malignant glioma and is typically treated with surgery and subsequent radiation treatment. Because of its infiltrative nature, GBM is often incurable by surgery alone. Although radiation treatment prolongs survival of patients with GBM, it is not curative either [1,2]. Almost all patients with GBM have a progression of their disease after initial surgery and radiation treatment, and this is often reflected by the worsening of the radiologic appearance [3]. This worsening after radiation treatment can be due to tumor regrowth that is pathologically recognized as recurrent tumor, but it can also be due to radiation-induced injury, in other words, radionecrosis [4-7]. The symptoms of radionecrosis are similar to those of the recurrent tumor [8]. Radionecrosis is also difficult to distinguish from recurrence by conventional radioimaging techniques [4,9]. Recent studies reported that positron emission tomography [10-13] and magnetic resonance spectroscopy [14,15] may be useful in differentiating recurrent tumor from radionecrosis, but these modalities still fail to provide a clear-cut answer. Therefore, a second surgery to remove the radiologically abnormal tissue is often indicated to differentiate recurrent tumor from radionecrosis. In such cases, the surgical pathologist is asked to determine the cause of radiologic worsening as either recurrent tumor or radionecrosis. Subsequent treatment decisions are often influenced by this evaluation. Patients with recurrent tumor are often treated with further therapy, whereas adjuvant therapy can be withheld (at least initially) for patients with radionecrosis.

Despite the practical role of the pathologic diagnosis in influencing subsequent treatment, such a practice has not been validated. The data on the predictive value of pathologic evaluation in the second surgeries are quite limited. Previous studies analyzed the value of stereotactic biopsies in the evaluation of recurrent tumor versus radionecrosis [5-7]. Because no study directly addressed this

Table 1 Patient characteristics in categories and the group as a whole

		Recurrent tumor (category 1)	No recurrent tumor (category 2)	Undetermined (category 3)	Overall	*P*
Age	n (valid cases)	31	15	8	54	NS
	Mean (median)	48.29 (50)	51.8 (52)	52.38 (50)	49.87 (51.5)	
	SD	12.0	11.9	14.2	12.2	
Sex	Female	10	5	2	17	
	Male	21	10	6	37	
Initial KPS	n (valid cases)	24	13	6	43	NS
	Median	90	90	85	90	
	Range	60-90	70-100	80-90	60-100	
Location	n (valid cases)	31	15	8	54	
	R/L/bilateral	18:13:00	10:05:00	5:02:01	33:20:01	
Extent of first surgery	n (valid cases)	31	15	8	54	NS
	Gross total	4 (13%)	4 (27%)	1 (13%)	9	
	Subtotal	20 (65%)	6 (40%)	5 (63%)	31	
	Biopsy	3 (10%)	3 (20%)	2 (25%)	8	
	Unknown	4 (13%)	2 (13%)	0	6	
Dose of initial EBRT	n (valid cases)	20	11	5	36	NS
	Median	5940	5940	6000	5940	
Extent of second surgery	n (valid cases)	31	15	8	54	NS
	Gross total	6 (19%)	3 (20%)	0	9 (17%)	
	Subtotal	21 (68%)	12 (80%)	7 (88%)	40 (74%)	
	Unknown	4 (13%)	0	1 (12%)	5 (9%)	
Initial boost radiotherapy	n (valid cases)	27	14	7	48	NS
	Yes	7 (26%)	7 (50%)	2 (29%)	17 (35%)	
	^{125}I implant	4 (15%)	5 (36%)	0	9 (19%)	
	Gamma knife	3 (11%)	2 (14%)	2 (29%)	7 (16%)	
Time between first and second surgery	n (valid cases)	31	15	8	54	NS
	Median	7.4	7.4	3.7	7.3	
	Range	3-22	4-19	3-10	3-22	
KPS at second surgery	Median	90	80	75	85	NS
	Range	70-100	70-90	40-90	40-100	

NOTE. NS implies *P* values greater than .1 for comparisons between categories 1 and 2.
Abbreviations: R, right; L, left; EBRT, external beam radiotherapy.