The Effect of Extent of Resection on Recurrence in Patients with Low Grade Cerebral Hemisphere Gliomas

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Background. **To evaluate the role of radical resection for low grade cerebral hemisphere gliomas, the authors analyzed the preoperative and postoperative radiographic tumor volumes (computed tomography hypodensity, magnetic resonance imaging–T2 signal hyperintensity) in 53 patients.**

Methods. **Using a previously described method of computerized image analysis, the authors evaluated whether the percent of resection and volume of residual disease, postoperatively, influenced the incidence of recurrence, time to tumor progression, and histology of the recurrent tumor. Survival was not analyzed in this study.**

Results. **No recurrence was detected, regardless of percent of resection and volume of residual disease, in patients with preoperative tumor volumes less than 10 cm^3 (mean follow-up, 41.7 months). Patients with tumors measuring 10–30 cm^3 had an incidence of recurrence and time to tumor progression of 13.6% and 58 months, respectively, compared with tumors measuring greater than 30 cm^3, which had an incidence of recurrence and time to tumor progression of 41.2% and 30 months, respectively ($P = 0.016$). All patients (n = 13) who underwent a 100% resection had a recurrence-free follow-up period (mean, 54 months). In the remaining patients (n = 40), as the percent of resection decreased, the incidence of recurrence increased along with a shorter time to tumor progression ($P = 0.03$). Patients with a volume of residual disease of greater than 10 cm^3 had a higher incidence of recurrence (46.2%) and a shorter time to tumor progression (30 months) compared with patients with a tumor volume of residual disease of less than 10 cm^3 (incidence of recurrence, 14.8% and time to tumor progression, 50 months) ($P = 0.002$). Forty-six percent of patients with a tumor volume of residual disease of more than 10 cm^3 had a recurrence of higher histologic grade, and this was significantly more frequent than patients with a volume of residual disease less than 10 cm^3 (3.7%) ($P = 0.0009$). Age, radiotherapy, and histologic subtype had no influence on recurrence patterns.**

Conclusion. **For tumors greater than 10 cm^3, the authors' data suggest that a greater percent of resection and a smaller volume of residual disease conveys a significant advantage, that is, terms of incidence of recurrence and the recurrent tumor phenotype, for patients with low grade cerebral hemisphere gliomas, compared with those who have a less aggressive resection or biopsy. While this may also be the case with tumors less than 10 cm^3, further follow-up is necessary to determine the effect of surgery on recurrence patterns for this subset of patients. *Cancer* 1994; 74:1784–91.**

Key words: extent of resection, low grade glioma, recurrence, time to tumor progression.

The management of low grade cerebral hemisphere gliomas is controversial, especially as it pertains to the extent of tumor resection. Despite the lack of a prospective randomized clinical study that addresses the issue of extent of resection, there are several retrospective studies that analyze results based on the effect of gross total, near total, and subtotal resections and biopsy alone determined at the time of surgery or by qualitatively assessing tumor resection on the postoperative imaging studies.[1–6] Evaluation of the extent of resection is usually based on the neurosurgeon's description in the operative report, which is not quantitative and often not correlated with postoperative imaging studies. In addition, the effect of tumor removal on survival is unclear, and there are difficulties interpreting these results due

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Supported by the Clinical Investigator Development Award K08 NS0153-01, American Cancer Society Career Development Award, and Clinical Professorship of Oncology and National Institutes of Health Clinical Neurosurgery Training Grants NS17111, 21724, and 20482.

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Received February 9, 1994; revision received May 3, 1994; accepted May 3, 1994.

to considerable variability in patient characteristics and therapeutic modalities.

A wide range of glial tumors initially diagnosed as low grade gliomas may recur at a higher histologic grade, however, the true incidence of this occurrence is unknown.[1,3–5,7–9] This so-called "dedifferentiation" or "upgrading" may partly be due to histologic heterogeneity or errors in tissue sampling of these tumors at the time of initial diagnosis.[1,10,11]

In this study, using a computerized image analysis technique that was previously described by our group,[12] we retrospectively evaluated the preoperative and postoperative tumor volumes to determine the percent of resection and the volume of residual disease as it relates to the incidence of recurrence, time to tumor progression, and the recurrent tumor phenotype. Unlike previous studies, this is an attempt to evaluate the influence of resection determined volumetrically on the patterns of recurrence in patients with low grade cerebral hemisphere gliomas. The study population was not followed long enough to evaluate survival, which will be analyzed separately.

Materials and Methods

Two hundred thirty-one patients with low grade glial tumors evaluated at the University of Washington Medical Center in Seattle between January 1977 and June 1990 were retrospectively analyzed. Kernohan's Grade I and II astrocytomas, mixed gliomas (i.e., oligoastrocytomas), and oligodendrogliomas located in the cerebral hemispheres were included in the current study. Gangliogliomas, pilocytic astrocytomas, pleomorphic xanthoastrocytomas, subependymal giant cell astrocytomas, gemistocytic astrocytomas and Grade III and IV astrocytomas as well as those tumors arising from noncerebral hemisphere sites were excluded.

Availability of preoperative and postoperative computed tomography (CT) or magnetic resonance imaging (MRI) scans and a minimum follow-up of 2 years was necessary for inclusion in the study. The cause of death for patients who died during the follow-up period was determined from the death certificate or autopsy report. Two patients who died within the first 4 postoperative weeks were excluded from analysis in the study.

Patient and Tumor Characteristics

Fifty-three patients who fulfilled the entry criteria were identified, and their hospital records and neuroradiologic studies were analyzed. Patients ranged in age from 6 to 74 years (mean age, 37.5 years) and included 27 females (51%) and 26 males (49%). The main symptom at presentation was seizure activity in 47 patients (89%). The majority of seizures (43%) were generalized tonic clonic (grand mal), whereas the remaining patients had either simple partial (23%) or complex partial seizures (34%). Three of the patients with seizures also had a mild motor deficit, and two additional patients had mild language dysfunction.

The predominant tumor location was the frontal lobe in 20 patients (38%), followed by the temporal lobe (n = 19 [36%]), parietal lobe (n = 11 [21%]), and occipital lobe (n = 3 [5%]). The majority of tumors were located in the left hemisphere (n = 32 [60%]). The histologic profile of the tumors is as follows: 19 astrocytomas (36%), 18 oligodendrogliomas (34%), and 16 mixed gliomas (30%).

All patients in the current study underwent surgery. Depending on the relationship of the tumor to physiologically eloquent cortical regions, brain-mapping techniques were used during surgery to maximize the extent of resection and obtain optimal control of seizures, as previously described.[13–17] After surgical resection, 40 patients (75%) received focal radiation therapy within a dose range of 4500–6000 cGy. The mean follow-up for the entire study group was 48.7 months (range, 24–172 months).

Determination of the Extent of Resection

All patients included in the current study had preoperative CT with or without MRI scans, with the latter study preferred after 1984. The preoperative and the first postoperative CT or MRI scans were digitized and used for the measurement of preoperative and postresection tumor volumes, using a previously described image analysis software program.[12] From these data, the percent of resection and volume of residual disease were calculated for each operation. Tumor volume measurements were determined using MRI scans for 39 patients (74%) and CT scans for 9 patients (17%). A preoperative CT scan and a postoperative MRI scan was used for the remaining 5 patients who were operated on during the CT to MRI transition period at our institution. Most patients did not have contrast-enhancing tumors, although sparse contrast was identified in a heterogenous fashion in four oligodendrogliomas. The tumor volume was considered as the hypodense and the hyperintense (T2-weighted) area on each axial CT and MRI scan, respectively. Preoperative scans were obtained 0–42 days (mean, 11 days) before the operation, followed by postoperative scans 2 days to 19 weeks after surgery (mean, 10 weeks). This latter variability reflected different past opinions of the attending surgeons regarding the proper timing of imaging studies taken

after the tumor resection. Currently, all patients receive MRI imaging within 1–2 weeks after surgery.

In each patient in whom progressive disease or recurrence of a completely resected tumor developed, histologic findings were verified. However, in one patient, presumptive evidence of a change in the histologic findings was based on a diffuse homogeneous contrast enhancement pattern throughout the residual tumor that originally did not enhance with contrast. Time-to-tumor progression was based on a comparison between the first postoperative scan and evidence of recurrence on subsequent radiographic studies for totally resected tumors or progression for tumors not completely resected initially. "Total resection" was defined as no evidence of hypodense or T2-weighted hyperintense tumor demonstrated on postoperative CT or MRI scans, respectively.

Statistical Analysis

Age, histopathology, postoperative radiotherapy, preoperative and residual tumor volumes, and percent of resection were the variables analyzed using Kaplan–Meier survival curves with the Mantel–Cox test.[18] The analysis was carried out using the BMDP Program 1L (BMDP Statistical Software, Inc., Los Angeles, CA).

Results

There was no operative mortality in the study group. In no patient did the postoperative Karnofsky score decrease permanently when compared with its preoperative value. The lack of operative morbidity is due largely to the senior author's experience with intraoperative physiologic mapping (see Materials and Methods) techniques, which were used when operating near functional regions.

Tumor recurrence developed in 10 patients (19%). Although three patients continued to have the same low grade histologic findings at the time of recurrence, the remaining seven patients developed recurrence at a higher histologic grade, that is, anaplastic astrocytoma (two patients) or glioblastoma (five patients). The mean time to tumor progression was 37.8 months (range, 12–91 months).

Preoperative Tumor Volume

Preoperative tumor volumes ranged from 1.04 cm^3 to 115.86 cm^3, with a mean value of 26.57 cm^3. When the patients were grouped according to the size of their tumor, no recurrence was detected in the group of patients with a preoperative tumor volume less than 10 cm^3 (Table 1). In the groups of patients with larger tumors, that is, 10–30 cm^3 and greater than 30 cm^3, a higher incidence of recurrence was demonstrated, 13.6% and 41.2%, respectively. A shorter time to tumor progression, that is, 30 and 58 months, was noticed for tumors larger than 30 cm^3 compared with those between 10 and 30 cm^3 of volume, respectively (P = 0.016). None of the tumors in the latter group recurred at a higher histologic grade, whereas all recurrences in patients with tumors larger than 30 cm^3 were malignant gliomas, and this difference was statistically highly significant (P = 0.0007).

Postoperative Tumor Volume

The volume of residual disease ranged from 0 to 83.13 cm^3, with a mean of 8.75 cm^3. None of the patients who had undergone a radiographically total resection had a recurrence during a mean follow-up of 54 months (Table 2). Patients with a volume of residual disease greater than 10 cm^3 had a higher incidence of recurrence (46.2%) and a shorter time to tumor progression (30 months) compared with patients with a volume of residual disease less than 10cm^3 (14.8% and 50 months, respectively) (P = 0.0023). In the group of patients with a volume of residual disease of more than 10 cm^3, 46% (n = 6) of the patients developed a higher grade recurrence, and this was significantly more frequent than the incidence of high grade recurrence in patients with a volume of residual disease less than 10 cm^3, that is, 3.7% (n = 1, P = 0.0009).

Percent of Resection

Percent of resection calculated from preoperative and postresection tumor volumes ranged from 10.7% to 100%, with a mean of 76.5%. All patients who underwent 100% resection had a recurrence-free follow-up period (mean, 54 months). As the percent of resection decreased, the incidence of recurrence increased along with a shorter time to tumor progression, as shown in Table 3 (P = 0.03). Although an association between higher grade recurrences and a smaller percent of resection was noticed, it did not reach statistical significance.

Recurrences according to the percent of resection and preoperative tumor volumes are summarized in Table 4. There were no recurrences in patients with tumors less than 10 cm^3 of volume regardless of percent of resection. All recurrences in patients whose tumors were larger than 30 cm^3 were high grade, that is, malignant, gliomas. The likelihood of recurrence in this latter group decreased directly with the percent of resection, and no

Table 1. The Effect of Preoperative Tumor Volumes on Recurrence, Recurrence at a Higher Grade Histology, and Time to Tumor Progression*

Preoperative tumor volume	< 10 cm^3	10–30 cm^3	> 30 cm^3
Patients (no.)	14	22	17
Age (yr)	35.9 (7–64)	39.6 (19–70)	36.3 (6–74)
Follow-up (mo) (range)	41.7 (24–121)	51.4 (26–150)	50.4 (24–172)
Postoperative tumor volume (cm^3) (range)	0.46 (0–3.84)	5.38 (0–24.89)	19.93 (0–83.18)
Pathology (%)			
Astrocytoma	71	23	24
Oligodendroglioma	21	45	29
Mixed glioma	8	32	47
Radiotherapy (% received)	43	86	88
Recurrence (%), patients (no.)	0	13.6, n = 3	41.2, n = 7
Recurrence at higher grade histology (%), patients (no.)	0	0	41.2, n = 7
Time to tumor progression (mo) (range)	NA	58 (12–91)	30 (13–45)

NA: not applicable.

* Age, follow-up, postoperative tumor volume, and time to tumor progression are expressed as a mean value, and ranges are shown in parentheses.

recurrence was documented in two patients with complete resections who originally had lesions greater than 30 cm^3.

Other Variables

Age did not significantly affect the incidence of recurrence, likelihood of recurrence at a higher histologic grade, or time to tumor progression. There was no statistically significant difference among histologic entities or with postoperative radiotherapy when evaluating the incidence of recurrence, a higher histologic grade recurrence, or the time to tumor progression. Although a shorter time to tumor progression was noticed with astrocytomas (mean, 22 months) versus oligodendrogliomas (mean, 46 months) and mixed gliomas (mean, 51 months), these data failed to reach statistical significance. When the effect of postoperative radiotherapy was further analyzed in terms of preoperative tumor volume, percent of resection, and volume of residual disease, there continued to be no favorable trend in terms of time to tumor progression and incidence of recurrence with the use of radiotherapy (Table 5).

Table 2. The Effect of Postoperative Tumor Volumes on Recurrence, Recurrence at a Higher Grade Histology, and Time to Tumor Progression*

Postoperative tumor volume	0 cm^3	< 10 cm^3	> 10 cm^3
Patients (no.)	13	27	13
Age (yr), (range)	29.8 (6–59)	39.6 (7–74)	41.2 (31–55)
Follow-up (mo), (range)	54.4 (24–172)	47.9 (24–150)	44 (24–60)
Preoperative tumor volume (cm^3) (range)	14.16 (1.9–48.95)	21.72 (1.04–53.06)	49.07 (18.95–115.86)
Percent of resection (range)	100	83.1 (24.5–98.3)	38.8 (10.7–67.2)
Pathology (%)			
Astrocytoma	77	18	31
Oligodendroglioma	0	56	23
Mixed glioma	23	26	46
Radiotherapy (% received)	46	85	85
Recurrence (%), patients (no.)	0	14.8, n = 4	46.2, n = 6
Recurrence at higher grade histology (%), patients (no.)	0	3.7, n = 1	46.2, n = 6
Time to tumor progression (mo), (range)	NA	50 (12–91)	30 (13–45)

NA: not applicable.

* Age, follow-up, preoperative tumor volume, percent of resection, and time-to-tumor progression are expressed as a mean value, and ranges are shown in parentheses.

Table 3. The Effect of Extent of Resection on Recurrence, Recurrence at a Higher Grade Histology, and Time to Tumor Progression*

Percent of resection:	< 50%	50–89%	90–99%	100% or more
Patients (no.)	8	18	14	13
Age (yr), (range)	36.4 (12–55)	42.2 (25–70)	39.6 (7–74)	29.8 (6–59)
Follow-up (mo), (range)	42.1 (24–60)	43 (24–124)	53.8 (24–150)	54.4 (24–152)
Preoperative tumor volume (cm^3), (range)	41.56(104–115.86)	28.49 (5.47–58.59)	27.07 (8.03–53.06)	14.16 (1.9–48.95)
Postoperative tumor volume (cm^3), (range)	32.54 (0.79–83.18)	14.58 (0.84–28.04)	1.24 (0.12–4.88)	0
Pathology (%)				
Astrocytoma	50	16	14	77
Oligodenodroglioma	12	56	50	0
Mixed glioma	38	28	36	23
Radiotherapy (% received)	63	94	86	46
Recurrence (%), patients (no.)	37.5, n = 3	27.8, n = 5	14.3, n = 2	0
Recurrence at higher grade histology (%), patients (no.)	37.5, n = 3	16.7, n = 3	7.1, n = 1	0
Time to tumor progression (mo), (range)	24 (13–31)	36 (12–64)	63 (34–91)	NA

NA: not applicable.

* Age, follow-up, preoperative and postoperative tumor volumes, and time to tumor progression are expressed as a mean value, and ranges are shown in parentheses.

Discussion

Extent of Resection and Outcome

Although extent of resection as an influence on outcome for low grade gliomas has not been analyzed in a prospective randomized trial, recent studies suggest that improved survival may be reached when extensive surgical resection is performed.[1,3,5,19,20] In all studies that address this issue, extent of resection is determined either according to the surgeon's intraoperative estimation or based on a qualitative postoperative CT scan assessment. To eliminate interobserver variability and the surgeon's bias on the evaluation of the extent of resection, we quantified tumor volumes on preoperative and postoperative scans using volumetric image analysis. This retrospective investigation was prompted by our impression that recurrence patterns are influenced by the amount of tumor initially removed. Because most of our patients were still alive and the follow-up period was too short for survival analysis, the current study was designed only to assess the effect of extent (i.e., percent) of resection as well as preoperative and residual tumor volumes on recurrence patterns, which included the time to tumor progression and the recurrent tumor histology.

It has been previously reported that 13–85% of glial tumors initially diagnosed as low grade recur at a higher histologic grade.[1,3–5,7–11] However, the factors resulting in the change to a malignant phenotype remain unclear. In the current series, no high grade recurrence was documented in patients who underwent total resection without evidence of residual tumor radiographically. Our data also suggest that the risk of recurrence, either as low grade or at a higher histologic grade, is minimized when less residual tumor volume is present after surgery. In addition, residual tumor volume appears to

Table 4. The Effect of Preoperative Tumor Volume and Extent of Resection on Recurrence, Recurrence at a Higher Grade Histology, and Time to Tumor Progression*

Preoperative tumor volume (% of resection)	< 10 cm^3	10–30 cm^3	> 30 cm^3
< 50	No recurrence (1)	No recurrence (3)	75% recurrence (3), all at a higher grade histology; mean TTP: 24 mo (4)
50–89	No recurrence (2)	18.2% recurrence (2), no recurrence at a higher grade; mean TTP, 38 mo (11)	60% recurrence (3), all at a higher grade histology; Mean TTP, 35 mo (5)
90–99	No recurrence (2)	16.7% recurrence (1), no recurrence at a higher grade; mean TTP, 91 mo (6)	16.7% recurrence (1), all at a higher grade histology; mean TTP, 34 mo (6)
100 or more	No recurrence (9)	No recurrence (2)	No recurrence (2)

* Number of patients in each subgroup is shown in parentheses. TTP: time to tumor progression.

Table 5. The Effect of Preoperative Tumor Volume, Extent of Resection, Postoperative Tumor Volume, and Postoperative Radiotherapy on Recurrence, Recurrence at a Higher Grade Histology, and Time to Tumor Progression*

	Radiation therapy	No radiation therapy
Preoperative Tumor Volume		
< 10 cm^3 (14)	No recurrence (6)	No recurrence (8)
10–30 cm^3 (22)	15.8% (3/19) recurrence, no higher grade recurrent histology; mean TTP, 56 mo	No recurrence
> 30 cm^3 (17)	40% (6/15) recurrence, all at a higher grade histology; mean TTP, 30 mo	50% (1/2) recurrence, all at a higher grade histology; mean TTP, 29 mo
Percent of Resection		
< 50% (8)	40% (2/5) recurrence, all at a higher grade histology; Mean TTP, 22 mo	33.3% (1/3) recurrence, all at a higher grade histology; mean TTP, 29 mo
50–89% (18)	29.4% (5/17) recurrence, 17.6% (3/17) at a higher grade histology; mean TTP, 36 mo	No recurrence (1)
90–99% (14)	16.7% (2/12) recurrence, 8.3% (1/12) at a higher grade histology; mean TTP, 63 mo	No recurrence (2)
100% or more (13)	No recurrence (6)	No recurrence (7)
Postoperative Tumor Volume		
0 cm^3 (13)	No recurrence (6)	No recurrence (7)
< 10 cm^3 (27)	17.4% (4/23) recurrence, 4.3% (1/23) at a higher grade histology; mean TTP, 50 mo	No recurrence (4)
> 10 cm^3 (13)	45.5% (5/11) recurrence, all at a higher grade histology; mean TTP, 30 mo	50% (1/2) recurrence, all at a higher grade histology; mean TTP, 28 mo

* Number of patients in each subgroup is shown in parentheses. TTP: time to tumor progression.

suggest that it may be more important than the percent of resection in predicting either histologic type of recurrence. Similarly, time to tumor progression is longer with more extensive resections associated with a smaller residual tumor volume.

Timing of Surgery

Although immediate surgical intervention after documentation of the tumor on diagnostic imaging studies is recommended in several recent reviews,[11,21,22] there are other studies advocating a less urgent approach or even questioning the necessity of surgical treatment for low grade glial tumors.[23,24] Preoperative tumor volume has not been evaluated as an independent variable except for a few studies in which preoperative tumor diameter, involvement of multiple lobes, or diameter of the surgical specimen was analyzed in terms of affecting survival.[1,3,25] In one study, a maximal tumor area of less than 25 cm^2 resulted in a statistically significant difference in survival, although the method of measurement used was not described.[26] Contrary to some opinions that patients with low grade gliomas may be conservatively followed with serial CT or MRI scans,[23,24] our results show that delayed surgical intervention may increase the risk of recurrence and malignant transformation in a shorter time period compared with patients operated on while their tumor is smaller. This increased risk caused by deferring surgical therapy is also supported by the finding that tumors less than 10 cm^3 of volume did not recur. In a recent study, 58% of patients who did not initially undergo biopsy and treatment of a suspected low grade glioma after diagnostic imaging studies eventually underwent surgery at a median interval of 29 months, and half of the tumors demonstrated anaplastic features.[24] This is opposed to the patients who underwent surgery at the time of radiographic diagnosis in which none of the tumors was malignant. The authors of this study stated that no difference was observed in terms of survival, despite a higher incidence of malignant transformation at the time of operation and shorter time to tumor progression compared with patients who initially were operated on after radiographic diagnosis. However, factors analyzed in our study, including preoperative and postoperative tumor volumes and percent of resection, were not included in the aforementioned study analysis.

Postoperative Radiotherapy

In our series, which does not analyze survival, postoperative radiotherapy did not influence the outcome regarding recurrence and time to tumor progression. In the literature, the effect of this treatment modality is not

well established, partly because of the various dose regimens administered, improvements in technique and in dosimetry planning over the years, and a common tendency to not radiate patients with gross total resections. In addition to reports that favor the use of postoperative radiotherapy for low grade glial tumors,[20,25,27] several studies failed to show any significant effect on survival.[1,4,5,10,28] The use of postoperative radiotherapy only for incompletely resected low grade gliomas is advocated in some reviews.[11,22,29,30] Our patients were not randomized to assess the effectiveness of postoperative radiotherapy, therefore, our results show a lack of evidence to support the use of postoperative radiotherapy, especially in patients with a preoperative tumor volume of less than 10 cm^3 or in those patients who had a 100% resection with no residual tumor on postoperative imaging studies. However, the follow-up period was not long enough to make a final assessment regarding the effectiveness of radiotherapy, especially as it influences survival.

Summary

Our results suggest that patients with low grade gliomas and a tumor volume greater than 10 cm^3 benefit from radical surgery at the time of radiographic diagnosis in terms of influencing the incidence of recurrence, time to tumor progression, and malignant transformation. It may be that the biology of large (i.e., > 30 cm^3) low grade gliomas is quite different from smaller tumors. Despite the finding that percent of resection appears to directly influence the time to tumor progression, all recurrences of those large tumors demonstrated malignant transformation. This was not the case with tumors in the 10–30 cm^3 range. We have not seen recurrences in patients with tumors less than 10 cm^3. However, for patients with these small tumors, the percent of resection appears not to affect the pattern of recurrence. These data must be interpreted cautiously, because only 3 of 14 patients had less than a 90% resection, thus preventing any conclusions regarding a less aggressive surgical approach on smaller (i.e., < 10 cm^3) tumors, which, in our experience, are more amenable to a radical resection. In patients with larger and more diffusely infiltrative tumors (> 10 cm^3), we were less likely to achieve an extensive resection compared with the smaller tumors. Notwithstanding, we advocate a radical resection of all low grade gliomas, regardless of size, until further natural history data are acquired regarding the outcome of those tumors that have received a nonoperative approach after radiographic diagnosis.

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