*Journal of Neuro-Oncology* **35**: 39–45, 1997.


*Clinical Study*

# Prolonged treatment with biologic agents for malignant glioma: A case study with high dose tamoxifen

Timothy F. Cloughesy,[1,3,4] Roger P. Woods,[1,5] Keith L. Black,[2,3,4] William T. Couldwell,[6] Ron E. Law[7] and David R. Hinton[8]

*[1]Department of Neurology; [2]Department of Surgery; [3]Jonsson Comprehensive Cancer Center; [4]Neuro-Oncology Program; [5]Division of Brain Mapping, [6]UCLA School of Medicine and Department of Neurological Surgery, USC and University of North Dakota; [7]Department of Medicine and [8]Department of Pathology, USC School of Medicine, USA*

*Key words:* tamoxifen, malignant glioma, study design, biologic agents

**Summary**

Traditional study design for treatment of malignant gliomas does not allow tumor progression to be greater than 25–50 percent without terminating treatment. This design may prevent recognition of patients who benefit from the treatment either by slowed growth or delayed response. A delayed response or slowed growth may be characteristic of biologic agents being evaluated in the treatment of malignant glioma. Because of the low toxicity of certain biologic drugs, continued treatment through tumor growth can be ethically considered in study design. The effect of biologic agents on a neoplasm may include cellular differentiation, retardation of growth, cytostasis, cytocidal effects, or apoptosis. Such effects may clinically translate into a complete response, partial response, stable disease or retardation of growth with or without an eventual reduction of tumor.

We present a patient with a recurrent malignant glioma who was continued on high dose tamoxifen despite radiologic documented doubling of the tumor size and who eventually showed a delayed response to this agent nine months after initiation of treatment. Strong consideration should be given to the prolonged treatment of non-toxic biologic agents in a controlled clinical trial, where agents have shown some benefit in phase one studies.

## Introduction

Despite multiple treatment modalities, malignant glioma remains an incurable tumor. Significant risks are associated with current therapeutic options, with some potential for benefit. These risks are acceptable given the poor prognosis associated with this tumor. When progression of the tumor is noted, either by imaging study or by clinical examination, the treatment is usually discontinued due to the potential for deleterious side effects and presumed lack of efficacy of therapy. Consequently it is unknown whether a change in outcome could be actualized by the continued use of 'failed' treatments. Chemotherapy and radiation therapy treatments are thought to be straightforward in this regard: if the cell attempts to divide and dies then the treatment is effective; if the cell divides and continues to grow, then the cancer cells have 'outsmarted' the treatment. Biologic treatment may be different in this respect.

There is a steadily increasing understanding of the molecular biology involved in the multiple stages of tumor carcinogenesis which is leading to

new treatments focused on the various stages leading to tumor formation. These treatments may target specific pathways thought to be significant in tumor formation or propagation. These new therapies may induce gradual changes in the cell such as differentiation. Although these therapies may be providing changes slowing growth on the cellular level, cell division may still continue to occur, translating into clinical or traditional imaging progression. These short term traditional endpoints (imaging and clinical) may not provide an accurate assessment of the eventual efficacy of an agent. This consideration may give credence to prolonged treatment with such agents even through the development or progression of the cancer. Treatments which arise from these molecular biologic advances may justify investigators using different endpoints, other than clinical and traditional imaging endpoints, in order to determine the efficacy on the cellular level. In chemoprevention studies, endpoints focus on the tumor cell or the precancerous cell [1–7]. Ideally, biological markers might better determine the effectiveness of the treatment at a cellular level.

Traditional agents are not generally used for prolonged treatment through tumor progression because of the potential toxicity of chemotherapy and radiation treatment. Some biological agents such as tamoxifen have acceptable side effects and can be used in prolonged treatment with relatively low risk to the patient even in the context of malignant glioma progression. We provide a case to illustrate this point in a patient with a malignant glioma treated with high dose tamoxifen through tumor progression.

## Case report

Figure 1 provides a graphic representation of the patient's history as well as tumor volume and dexamethasone dose. A 24 year old, right-handed male presented at UCLA with complaints of running into objects in his left visual field starting in November of 1992. Neurological evaluation found the patient to have optic ataxia in his left visual field. An MRI scan revealed a multi-lobular, cortically based, enhancing lesion in the right posterior parietal lobe. The patients had a negative work-up for metastatic disease as well as for any infectious process. A surgical gross total resection was performed showing glial based tumor. In March of 1993 the patient complained of increasing clumsiness, and an MRI scan at that time showed new tumor enhancement near the resection cavity, as well as an increase in peritumoral edema. A SPECT thallium was obtained showing an increased uptake with a ratio of 3.5, consistent with recurrent malignant brain tumor. A craniotomy was performed in April of 1993. Again, a gross total imaging resection was performed. Pathology was consistent with an anaplastic astrocytoma.

The patient was then treated with pre-irradiation chemotherapy using high dose ifosfamide, receiving 14 gm/m$^2$ over five days in monthly cycles. He tolerated two monthly cycles. The patient developed one febrile event as well as reactivation of chronic hepatitis-B due to a rapid steroid taper which was incorporated into the ifosfamide treatment. An MRI scan obtained after his second cycle of treatment in July of 1993 (Figure 1) showed progression of the tumor with new enhancement in the right occipital lobe. Radiation therapy was started in August of 1993. The patient was treated regionally with 25 fractions at 180 cGy per fraction to 45 cGy. In addition, a tumor boost of 1,440 cGy was given for a total of 5,940 cGy. Radiation treatment was completed on 9/21/94. An MRI scan on 9/28/94 (Figure 1) showed further tumor progression with an increase in the existing enhancing lesion as well as spread of the contrast enhancing area in the right occipital lobe across the splenium of the corpus callosum and into the left occipital lobe.

In October of 1993 the patient developed a sudden onset of headaches, nausea and vomiting. He was placed on dexamethasone with minimal relief of these symptoms. A CT on 10/17/93 showed continued growth while on 6 mg of dexamethasone. On 10/19/93 the patient had debulking surgery with pathology which was consistent with recurrent anaplastic astrocytoma. The postoperative MRI (10/21/93) is shown in Figure 2 [22] and tumor volume in Figure 1.

In mid-November of 1993, more than six weeks after completion of radiation therapy, the patient was started on tamoxifen with a dose escalation to

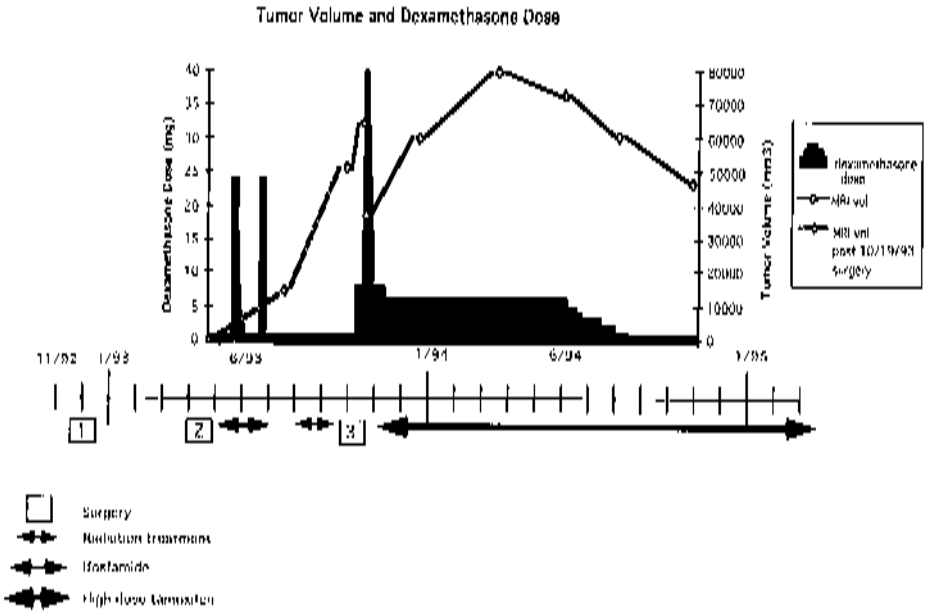


*Figure 1.* Chart of date vs. dexamethasone dose and imaging tumor volume and treatment course. All volumes were performed using NIH image 1.58b30. Image 10/17/95 is a CT scan with contrast using 5 mm thick slices that are contiguous. All other images are MRI with 5 mm thick slices with a 1.5 mm skip. All volumes were obtained by the summed products of area and slice thickness. MRI slices were calculated with 6.5 mm slice thickness and CT with 5 mm slice thickness. Graphic timeline schematic of patient's history is also provided.

100 mg PO b.i.d. over ten days as a salvage therapy. Tamoxifen was used on the basis of its effect on glioma cells [8, 12, 13, 15, 16], evidence regarding efficacy of high doses in malignant glioma patients, and the minimal side effects of treatment [3, 4, 18, 21, 22]. The patient tolerated the escalation of tamoxifen without difficulty. Follow-up MRIs were done on 12/21/93 and on 3/22/94 (Figures 1, 2). The patient was on 6 mg of dexamethasone daily. Both scans showed progression of the tumor despite being on the tamoxifen treatment for one and four months respectively. The patient was considered to have failed tamoxifen, but was not interested in further treatment trials. Due to the lack of side effects of the tamoxifen on the patient, he agreed to continue tamoxifen with the hopes of slowing further tumor growth. An MRI on 6/7/94 (Figures 1, 2) showed stable disease with a slight decrease in tumor volume, and the patient was then able to be tapered off dexamethasone by 8/9/94. At that time, his MRI scan showed continued evidence of decreasing tumor size (Figures 1, 2). An MRI obtained on 11/1/94 showed significant decrease in the MRI contrast enhancement and the peritumoral mass edema (Figures 1, 2).

In February 1995 the patient developed increasing left leg clumsiness and weakness. He woke on 2/21/95 with pain behind the right eye and nausea and vomiting. An MRI showed progression tumor in the right temporal and occipital lobe. SPECT Thallium of the brain showed increased uptake in the right posterior temporal lobe with a ratio of 2.4, consistent with recurrent high grade glioma. Dexamethasone was restarted at 2 mg po BID with recovery of headache and emetic symptoms. He declined other surgical or chemotherapeutic options but agreed to continue on high dose tamoxifen. He stopped treatment with tamoxifen on 5-1-95 after gradual worsening of his neurological status and entered a home hospice program. He died on 7-10-95.

## Discussion

This patient with a recurrent malignant brain tumor was treated with a biologic agent (tamoxifen) and

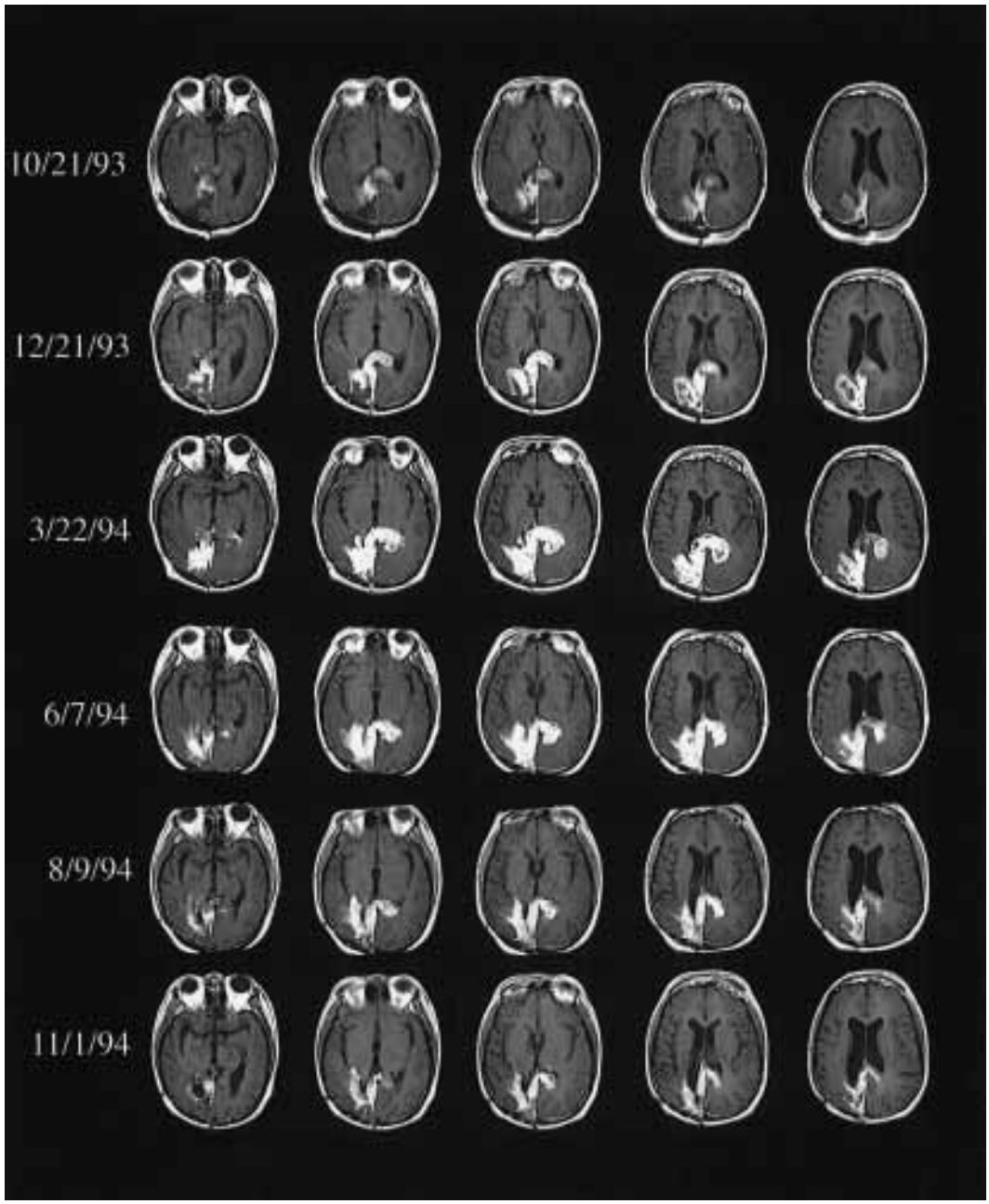


*Figure 2.* Registration of MRIs obtained at different dates showing progression of contrast enhancing portion of tumor followed by eventual regression. MRI registration was performed using a rapid automated algorithm for aligning and reslicing tomographic images [22].

had progression of disease, more than doubling the size of the contrast enhancing tumor through the initial 4–5 months of treatment while on a stable dose of dexamethasone (Figures 1, 2). This was followed by a dramatic decrease in tumor size at 9–11 months after initiation of treatment (Figures 1, 2). Using the traditional response criteria for malignant glioma, progressive disease is defined by increasing tumor size (typically 25%), new areas of tumor or unequivocal neurologic deterioration [11].

Before attributing this response to tamoxifen, it is important to consider whether any of the other treatments could be credited for the observed decrease in tumor size. Steroid treatment can cause a shrinking of the enhancing tumor volume in patients with malignant gliomas [1, 19]. Figure 1 shows the dexamethasone dosage along with the tumor volumes. After an initial bolus of dexamethasone, given around the time of the postoperative 10/21/93 scan, the dexamethasone dosage was stable until there was clear evidence of a decrease of tumor volume. Dexamethasone was tapered off at a time of tumor volume reduction. The initial 10/19/93 postoperative dexamethasone taper could account for some of the increase in volume measured in the 12/21/93 scan, but not the continued tumor extension into the left occipital lobe. Delayed radiation effect must also be considered. The patient had tumor progression through radiation treatment with 250% growth comparing 7/18/93 scan to 9/28/93 scan. Further growth (25%) was noted from 9/28/93 to 10/17/93. This is too early for the 'early-delayed encephalopathy' effects of radiation [6]. Additionally, one month after radiation was completed, tissue removed with debulking surgery showed pathology consistent with viable tumor. Six weeks after radiation, tamoxifen was started and there was continued progression of the tumor shown on imaging studies up to six months post radiation therapy. All of this points to the ineffectiveness of radiation treatment for this patient. A delayed radiation effect more than 6 months after radiation therapy with continued progression while on a stable dose of dexamethasone is not likely. Importantly, progression during or within 8 weeks of radiation portends a short survival when compared to responsive or stable malignant gliomas [7, 18, 21].

Radiation necrosis with initial mass-like symptoms and imaging changes followed by eventual resolution must also be considered. This patient had progression of disease during radiation therapy followed by a debulking procedure which showed pathology consistent with tumor, not radiation necrosis. The tumor progression continued over the ensuing 4 months, which would be unusually early for typical radiation necrosis given the doses of radiation delivered. It is unlikely that radiation induced changes are accountable for the significant imaging changes noted.

The effects of ifosfamide are difficult to account for but there was clear progression through the ifosfamide treatment and further significant progression through and after the radiation treatment. Some have advocated that the effects of standard chemotherapy may allow for a single cell division without further growth of these daughter cells. With the substantial growth noted after the failure of the ifosfamide treatment it seems extremely unlikely that it had any effect on the patient after the failure of the radiation treatment.

No additional medications were given during tamoxifen therapy that could account for the described changes or that could alter the rate of metabolism of tamoxifen and its metabolites. It is possible that the steady state level of tamoxifen was not reached at the time of scans showing initial growth. Tamoxifen and its metabolites in serum rise to reach a steady state level at 4 to 6 weeks [10, 14]. By the time the patient had the 12/21/93 scan, tamoxifen and its active metabolites should have reached steady state, yet there was continued imaging growth of the tumor at four months from the initiation of treatment. One patient studied by Couldwell et al. showed tumor progression while on 40 mg/day but responsed to 200 mg/day [4] implying that a higher dose of tamoxifen can lead to eventual response. However, our patient remained on a stable dose of tamoxifen throughout the clinical and radiographic progression and delayed response.

How can the delayed response to tamoxifen treatment in this patient be rationalized based upon our *in vitro* knowledge of the growth inhibition of this agent on glioma cells? The phase specific mechanism of growth inhibition of this agent, known to arrest glioma cell growth in the G1 phase (prior to entrance into DNA synthesis or S-phase), presents the possibility that tumor cells may complete a phase of cell division prior to becoming vulnerable to inhibition of cellular proliferation with this agent [5]. This phase-specific inhibition of cellular growth precedes the induction of apoptosis produced by continuous treatment with tamoxifen [2]. Moreover as demonstrated in Figure 1, the previously exponential increase in the volume of tumor noted

from 6/93 through to the surgical debulking performed in 10/93 (despite radiation therapy, and prior to the initiation of high dose tamoxifen), was clearly impacted upon shortly after the initiation of tamoxifen treatment. Close examination of the slope of the plot in Figure 1, while demonstrating initial increasing tumor volume after the administration of tamoxifen, clearly shows a steady decrease in the slope of the curve shortly following the initiation of treatment, which continued until 11/94, suggesting that the rate of tumor growth was being inhibited much earlier. The slow response to this agent in clinical use has been observed previously, with extended periods of stabilization occurring before an insidious classic tumor response (> 50% reduction in volume of gadolinium enhancement on serial MRI studies) occurring over weeks to months (WTC; personal observations [3]). Based on the kinetics of the response to this agent, the initial tumor progression seen in the patient in the present resport may represent a more protracted kinetic response than usual. Therefore, we attribute the decrease in tumor size to a delayed response from tamoxifen. This suggests that a true understanding of the eventual efficacy of tamoxifen may not be realized in clinical studies if the drug is discontinued due to evidence of 'progressive disease'. Although this is only a case study, it suggests that biologic therapies with relatively non-toxic biologic agents such as tamoxifen which show at least a minor benefit of therapy could be considered, in a carefully designed study, for continued treatment in patients with progressive disease. In the setting of protocol study, if prolonged treatment is considered, survival could be used as an endpoint, rather than tumor progression; historical controls could be used for comparison.

With the appropriate study design, the effect of tamoxifen, or other biologics, on malignant gliomas could show many responses including the traditional measures (complete response, partial response, stable disease) as well as retardation of tumor growth and eventual stabilization or regression of tumor even after growth. Due to the minimal side effects associated with tamoxifen, prolonged treatment, in a controlled clinical trial setting, can be provided ethically with careful vigilance for adverse events. If, as we suspect, there is an advantage to continued treatment, then the ideal time for the use of a biologic agent such as tamoxifen would be in the 'up-front' setting. In this way, a maximum effect can take place at a time when the tumor creates minimal neurological deficit. Also, if there is some progression during the early stages of treatment there may still be opportunity to effect changes upon the tumor before its' increase in size creates serious disability. This also could be of possible benefit to the patient by delaying the time to tumor progression and prolonging survival.

The effects of biologic agents may occur over a period of time, as long as several cell cycles. A variety of surrogate endpoints are being developed for chemoprevention trials using biologic agents in prostate, breast and head and neck cancers in an attempt to accurately determine the efficacy of an agent [9]. These tumor types can lend themselves to frequent samplings and opportunities to evaluate appropriate biologic endpoints such as DNA ploidy, S-phase analysis, expression of proliferative markers, and uptake of radionucleotides [9, 20]. Brain cancer does not lend itself to multiple tissue sampling and, therefore, it is currently difficult to ethically utilize biological surrogate endpoints. Presently magnetic resonance imaging, FDG-PET, SPECT Thallium and magnetic resonance spectroscopy are either unproven or insensitive as endpoints for biologic agents. Since an ideal endpoint does not exist to detect molecular and biochemical changes induced in brain tumors by biologic agents, the potential effectiveness of these agents may only be appreciated by continuing them in spite of traditional short term imaging and clinical progression and using survival or long term imaging and clinical status as an endpoint.

## Conclusion

Treatment with tamoxifen in patients with malignant glioma has shown efficacy, and a variety of responses may be seen including a delayed response even after initial progression of the tumor in malignant gliomas. Biologic agents affect cancer cells differently than chemotherapy and radiation therapy

and may need surrogate endpoints in order to properly assess their efficacy so as to not prematurely stop a potentially effective treatment in the face of tumor growth. In the absence of surrogate endpoints that can be evaluated in the short term, the full potential of biologic agents may only be recognized by continuing treatment in spite of apparent progression and looking for longterm evidence of efficacy by using traditional endpoints such as tumor size, clinical status and survival. As new biologic agents become available for the treatment of malignant glioma and show at least some evidence of benefit, appropriate study design will be needed in order to properly understand the potential for efficacy of these agents. Basic *in vitro* studies are likely to be useful in identifying agents that warrant a prolonged treatment approach.

## References


1. Cairncross JG, Macdonald DR, Pexman JH, et al.: Steroid-induced CT changes in patients with recurrent malignant glioma. Neurology 38: 724–726, 1988
2. Couldwell WT, Hinton DR, He S, et al.: Protein kinase C inhibitors induce apoptosis in human malignant glioma cell lines. Febs Lett 345: 43–46, 1994
3. Couldwell WT, Hinton DR, Surnock AA, et al.: Treatment of recurrent malignant gliomas with chronic oral high-dose tamoxifen. Advances in brief. Clin Cancer Res 2: 619–622, 1996
4. Couldwell WT, Weiss MH, DeGiorgio CM, et al.: Clinical and radiographic response in a minority of patients with recurrent malignant gliomas treated with high-dose tamoxifen. Neurosurgery 32: 485–489, 1993
5. Couldwell WT, Weiss MH, Law RE, et al.: Paradoxical escalation of Ki-67 labeling with protein kinase inhibition of malignant gliomas. J Neurosurg 82: 461–468, 1995
6. Delattre J, Posner J: Neurological complications of chemotherapy and radiation therapy. In: Aminoff M. (ed) Neurology and General Medicine. Churchill Livingstone, New York 365–387, 1989
7. Gaspar LE, Fisher BJ, MacDonald DR, et al.: Malignant glioma – timing of response to radiation therapy. Int J Radiat Oncol Biol Phys 25: 877–879, 1993
8. Grenman S, Worsham M, Van Dyke D: Establishment and characterization of UM-EC-2, a tamoxifen-sensitive, estrogen receptor-negative human endometrial carcinoma cell line. Gynecol Oncol 37: 188–199, 1990
9. Kelloff G, Boone C, Crowell J, et al.: Surrogate endpoint biomarkers for phase II cancer chemoprevention trials. J Cell Biochem 19 (Suppl): 1–9, 1994
10. Legha S: Tamoxifen in the treatment of breast cancer. Ann Int Med 109: 219–228, 1988
11. Macdonald DR, Cascino TL, Schold SJ, et al.: Response criteria for phase II studies of supratentorial malignant glioma. J Clin Oncol 8: 1277–1280, 1990
12. O'Brian C, Housey G, Weinstein I: Specific and direct binding of protein kinase C to an immobilized tamoxifen analogue. Cancer Res 48: 3626–3629, 1988
13. O'Brian C, Liskamp R, Solomon D, et al.: Inhibition of protein kinase C by tamoxifen. Cancer Res 45: 2462–2465, 1985
14. Osborne R, Malik S, Slevin M: Tamoxifen in refactory ovarian cancer: The use of a loading dose schedule. Br J Cancer 57: 115–116, 1988
15. Pollack IF, Randall MS, Kristofik MP, et al.: Effect of tamoxifen on DNA synthesis and proliferation of human malignant glioma lines *in vitro*. Cancer Res 50: 7134–7138, 1990
16. Powis G, Alberts D: Inhibiting intracellular signalling as a strategy for cancer chemoprevention. Eur J Cancer 30A: 1138–1144, 1994
17. Szarka CE, Grana G, Engstrom PF: Chemoprevention of cancer. Curr Probl Cancer 18: 6–79, 1994
18. Urtasun R, Feldstein M, Partington J, et al.: Radiation and nitroimidazoles in supratentorial high-grade gliomas: A second clinical trial. Br J Cancer 46: 101–108, 1982
19. Watling CJ, Lee DH, Macdonald DR, et al.: Corticosteriod-induced magnetic resonance imaging changes in patients with recurrent malignant glioma. J Clin Oncol 12: 1886–1889, 1994
20. Weinstein I: Cancer prevention: Recent progress and future opportunities. Cancer Res (Suppl) 51: 5080–5085, 1991
21. Wood J, Green S, Shapairo W: The prognostic importance of tumor size in malignant gliomas: A computed tomographic scan study by the Brain Tumor Cooperative Group. J Clin Oncol 6: 338–343, 1988
22. Woods RP, Cherry SR, Mazziotta JC: Rapid automated algorithm for aligning and reslicing PET images. J Comput Assist Tomogr 16: 620–623, 1992


*Address for offprints:* T.F. Cloughesy, Department of Neurology, Neuro-Oncology Program, Reed Neurologic Research Center, 710 Westwood Plaza, Rm 1-129, Los Angeles, CA 90024, USA