by Hegi et al,[2] patients whose samples are not assessable for MGMT methylation do not seem to characterize a specific subset with a different survival; data collected from these patients therefore do not result in any bias. We do not agree with the authors' claim that there is a potential logical correlation between *MGMT* gene promoter methylation and MGMT protein expression: given that MGMT, an inducible enzyme, may be upregulated after chemotherapy or radiotherapy, the concept of low/high MGMT expression should be avoided in this context.

Drs Chamberlain and Glantz appropriately raised the question concerning the concept of adjuvant treatment in GBM, developed in the 1970s with a goal of increasing the cure rate after the complete excision of tumors such as breast cancer, the underlying rationale being to treat microscopic disease when the tumor bulk was at a minimum. However, GBM patients rarely received "true" adjuvant treatment and, in the European Organisation for Research and Treatment of Cancer (EORTC) National Cancer Institute of Canada trial, only 49% of patients underwent complete resection.[3] In our protocol, like those for metastatic disease in other solid tumors, treatment was scheduled up to disease presence, or given in 12 cycles when no disease was found during magnetic resonance (MR) imaging or a complete response was achieved. Furthermore, the proposed administration of 12 cycles was included in the Canadian recommendations for the treatment of GBM, at least for patients who showed continuous improvement on therapy,[4] and this schedule has been suggested as a standard arm in the new experimental protocols of the major international cooperative groups, such as EORTC and Radiation Therapy Oncology Group (ie, EORTC 26052-22053/Radiation Therapy Oncology Group 0525 trial, comparing standard treatment with dose-intensive TMZ in patients with newly diagnosed GBM).

Moreover, Drs Chamberlain and Glantz stated that the standard 5 days every 28 days postradiotherapy TMZ schedule does not have a long-term effect on MGMT tumor content. However, as shown by the references made, the few data available concerning this finding are reported in a study evaluating MGMT inactivation in peripheral-blood mononuclear cells treated with TMZ,[5] but whether this also applies to tumor cells remains to be demonstrated.[6] To date, no data are available on the advantages of a prolonged/alternative schedule versus the standard schedule of 5 days very 28 days.

The authors suggest that histology is the valid method for identifying pseudoprogression; yet, as they state, only a small percentage of patients with suspected pseudoprogression undergo surgery because the tumor mass, which can be controlled by corticosteroids, tends to diminish quite rapidly. Moreover, it is difficult to define the role of necrosis given that, in the histologic setting, it is often present concomitantly with neoplastic cells. Lastly, the role of new imaging tools such as spectroscopic MR imaging, MR scan, MR perfusion and diffusion, or [^{18}F]fluorodeoxyglucose positron emission tomography in discriminating disease progression and pseudoprogression have recently been reviewed.[7] A few of our patients underwent repeat surgery, and others underwent brain functional imaging; however, due to the sporadic nature of this treatment option and the bias in patient selection, no conclusion can be drawn regarding the role of these diagnostic modalities, which should be tested in prospective trials.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Genomics and Challenges Toward Personalized Breast Cancer Local Control

To the Editor: The article by Nguyen et al[1] in *Journal of Clinical Oncology* demonstrates an overall low local recurrence rate after breast-conserving surgery, but varying magnitude of this risk among gene expression profiling–based subtypes. The 5-year local recurrence rates of 793 patients were higher for HER-2 (8.4%) and basal (7.1%) subtypes than for luminal A (0.8%) or luminal B (1.5%) subtypes. Approximating this molecular classification using human epidermal growth factor receptor 2 (HER-2), estrogen receptor (ER), and progesterone receptor (PR) status currently used in routine clinical practice,[2] the authors provide clinically useful information on a potential link among these subtypes and local control.

Why is local control important for long-term survival given the systemic nature of breast cancer? Local failures include local recurrence or a new ipsilateral breast cancer and contralateral breast cancer. With an increasing number of long-term survivors and long-term follow-up data available, objective evidence documents that ipsilateral breast cancer and/or contralateral breast cancer as first isolated events may be associated with increased mortality.[3-5]

Potential pretreatment risk stratification into high, moderate, and low risk for local failure may affect treatment decision. High-risk patients may benefit from a more aggressive surgery, such as unilateral mastectomy and contralateral prophylactic mastectomy rather than the standard breast-conserving surgery for localized disease. Recent data show a dramatic increase of more aggressive surgery in the United States to prevent this local failure.[6] Instead, this generalized surgical overtreatment, a personalized aggressive surgery only to high-risk patients, may prevent local failure and improve survival in these

women while sparing unnecessary complications of an aggressive surgery in low-risk patients.[5]

Of the data reported by Nguyen et al, most clinical interest is focused on the basal-like subtype because the updated treatment has not changed. In contrast, there are limitations for the other subtypes. The current standard targeted agents, trastuzumab for HER-2–positive disease[7,8] and aromatase inhibitors for postmenopausal women with ER/PR-positive disease[9] were not used. These newer therapies reduce local failure[7-9] and thus, data from the Nguyen report on these subtypes are of limited clinical utility.

Basal-like subtype is characterized by lack of expression of HER-2/ER/PR (triple negative), aggressive behavior, limited or no efficacy of available targeted agents, and poor prognosis. These tumors are remarkably similar to tumors arising in *BRCA1* mutation carriers.[10] Given that the patient subgroup with *BRCA1* inherited mutations is thought to be associated with the highest risk of local failure and may benefit from aggressive surgery,[5,11-13] it could be supposed that women with early-stage sporadic triple-negative tumors might also benefit from such an aggressive surgery for local control. However, at present, evidence is still insufficient to support this hypothesis, and long-term results from prospective, large-scale studies should be awaited to drawn rigorous conclusions.

Although all types of recurrence (local, contralateral, or distant) are important, identification of high-risk patients for local failure still remains a dream. Pretreatment genetic testing allows identification of *BRCA1/2* mutations carriers, who account for only a small fraction of high-risk patients.[14] The identification of the remaining high-risk patients among familial *BRCA*-negative patients and those patients with sporadic cancer (no breast cancer family history) is currently impossible. Novel genetic variants have already been identified by genomewide association studies, but they confer only a modest risk to breast cancer initiation.[15-17] Although several other new susceptibility gene variants will be detected by new larger genomewide association studies, the major challenge will remain the assessment of sophisticated interactions between these gene variants and environmental exposure. Future prospective, large-scale, population-based studies (familial *BRCA* and non-*BRCA* patients and sporadic patients with and without local failure) may lead to identification of combined genetic and environmental risk factors as predictive tools for accurate risk stratification and truly personalized local control.

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In Reply: We are grateful to Drs Roukos, Lykoudis, and Liakakos for their thoughtful commentary and discussion about what our data adds to the overall goal of identifying women with breast cancer who are at highest risk for local recurrence.[1] Earlier this year in *Journal of Clinical Oncology*, Kyndi et al[2] also noted our observation of increased local recurrence for the human epidermal growth receptor 2 (HER-2) subtype (estrogen receptor [ER] –negative/progesterone receptor [PR] –negative/HER-2–positive) and basal subtype (ER-negative/PR-negative/HER-2-negative) after breast-conserving therapy (BCT) in patients undergoing mastectomy. In the subgroup of 1,000 women who underwent mastectomy with or without radiation therapy as part of the Danish 82b/c randomized trials and had tissue available for ER/PR/HER-2 evaluation, Kyndi et al similarly reported that both the HER-2 and basal subtypes were significantly associated, on multivariable analysis, with an increased risk of locoregional recurrence compared with luminal subtypes. Given that none of the HER-2–positive patients in either our series or the Danish study received trastuzumab, these findings are most