May 3, 1994

Dear Editor:

The article by Paty et al., "Treatment of Rectal Cancer by Low Anterior Resection with Coloanal Anastomosis," was an important contribution to surgical oncology.[1] It has been well documented that local recurrence after limited surgery is not a survival hazard for patients with breast cancer.[2–6] Local recurrence may be an indicator of a poor prognosis without being its cause. This unexpected observation has not been documented for patients with cancer of the rectum.

Paty et al. reported that 5 of 130 patients (4%) developed isolated local recurrence. From their data, it appears that two of these patients were alive and well, two were living with disease, and one was dead of disease. The death occurred in a patient with a T3 tumor and mesenteric implants. These results are remarkably good and suggest that promptly treated local recurrence may not be a survival hazard for patients with this disease. I previously have suggested an explanation for these results.[7] As with breast cancer, it may be prudent to treat local recurrence with simple excision. I commend the authors on their excellent results and their presentation of data in a manner that permits this analysis.

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June 20, 1994

Dear Editor:

In his letter, and in a previously published manuscript,[1] Dr. Evans discusses the relationship between survival and local recurrence after limited surgery for solid tumors. Survival, he argues, is determined by distant metastases, which develop because of deficiencies in host defense. Local recurrence, on the other hand, may sometimes occur despite competent host defenses and may, therefore, be salvageable. Reports of successful surgical salvage of local failures after lumpectomy for breast cancer are cited.

In our study of low anterior resection for rectal cancer, 13 patients (10%) developed pelvic recurrence, 5 of whom had no evidence of distant metastases. Three recurrences were amenable to complete resection by salvage abdominoperineal resection. Two patients are alive and well at 12 and 2.5 years after salvage surgery. The remaining 11 patients who developed pelvic recurrence have died of disease.

In our experience, most pelvic recurrences are associated with diffuse pelvic or distant metastatic disease and cannot be surgically salvaged. These tumors might, therefore, be expected to be biologically aggressive, and this conclusion is supported by our analysis of histopathologic markers in the primary tumors.

Pelvic recurrence after low anterior resection is not analogous to local recurrence after lumpectomy for breast cancer, where an at-risk organ is intentionally left behind and then subsequently removed at a salvage operation. We suggest local excision for rectal cancer may be a treatment more analogous to lumpectomy for breast cancer and a more appropriate group for studying the impact of local recurrence after limited surgery on patient survival.

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April 17, 1994

Dear Editor:

We would like to commend Singer et al. on the publication of their article.[1] Their thorough examination of a large series of patients with soft-tissue sarcomas has served to confirm the importance of well-known prognostic factors, such as primary tumor size and grade.

The place of mitotic activity in the prognosis of soft-tissue sarcomas is not new. Reports during the last decade have addressed this relationship, with some groups showing no correlation between mitotic rates and survival,[2–4] whereas others have demonstrated the opposite.[5,6] In the light of the latters' findings, we were surprised at the authors' insistence in their abstract and twice in their discussion that mitotic rate has not been shown previously to be of prognostic value. Even though Singer et al. have stressed the importance of multivariate analysis as part of their assessment, the relationship between mitosis and survival has been analyzed by this method before,[5,6] and results similar to the authors' article have been reported. It would be interesting to know what was meant by a high power field by the authors; this may be one explanation for the divergent findings between reporting groups. For inter-group comparisons to be made, a standardized method is required. In this regard, Ellis and Whitehead[7] recorded a 600% variation in the

area of a "high power field," depending on which microscope was used.

On the point of patient review, we believe that the strength of the findings of Singer et al. may come under some criticism for the short follow-up that some patients may have had. We note that the study was conducted between 1970 and 1992. As the paper was accepted for publication in July of 1993, some patients may have had less than 1 year of follow-up, if the last day of the study was the end of December 1992. Because most studies report that the majority of metastases occur within 2 years, a minimum 2-year follow-up period is required. On a minor point, we note that there are 276 months between the start of 1970 and the end of 1992, thus, we are intrigued at how Dr. Singer et al. managed to have a range of follow-up extending to 321 months.

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July 5, 1994

Dear Editor:

We would like to thank Drs. Choong, Rydholm, and Gustafson for their comments regarding our article, "Prognostic Factors Predictive of Survival and Local Recurrence for Extremity Soft-Tissue Sarcoma." As we state in our paper, the use of mean mitotic activity for the grading of soft-tissue sarcoma is not new and was based on the NIH studies of Russell and Suit back in 1975. Since this study, pathologists have used mean mitotic activity as one of several parameters for the grading of soft-tissue sarcoma. Despite a careful review of the references cited by Dr. Choong, we stand by our statement that for the first time, we have shown that mean mitotic activity can be used as an independent prognostic factor, even if one accounts for grade and size of the tumor using a multivariate analysis.

The studies that Dr. Choong cites have several shortcomings with regard to concluding the prognostic significance of mitotic activity, independent of grade and size. The study of Hosimoto et al. (*Cancer* 1992) divided mean mitotic activity into only three groups: 0–4 mitoses/10 hpf, 5–9 mitoses/10 hpf, and >10 mitoses/10 hpf. Based on a univariate analysis, these three groups had statistically significant survival difference, ($p < 0.001$). However, a multivariate analysis showed that mean mitotic activity grouped as aforementioned was not an independent factor from grade in their study. For their entire group, tumor necrosis ($p = 0.0001$) and histologic grading ($p = 0.0001$) were shown to be significant prognostic factors by multivariate analysis.

The study by Gustafson in *Cancer* (1992) evaluated 48 patients with soft-tissue leiomyosarcoma of the extremities and trunk. In this study, mean mitotic activity was used to determine grade as well as an estimation of tissue differentiation, cellularity, cellular atypia, and necrosis. In their univariate analysis of mean mitotic activity, they grossly classified mean mitoses per 10 hpf into three categories: 1–5 mitoses/10 hpf, 6–10 mitoses/10 hpf, and >11 mitoses/10 hpf, and found these groups to have statistically different survivals on univariate analysis, as cited. However, in the multivariate analysis the only important prognostic factors that correlated independently with survival were patient age and vascular invasion. Mean mitotic activity was not found to be an independent risk factor when patients were divided into these three main groups.

The third paper cited by Hosimoto et al. in *Cancer* (1986) evaluates only 25 cases of leiomyosarcoma of the soft tissues. Again, although they used mitotic activity in their assessment of grade, they found that only the depth of tumor invasion was best correlated with the prognosis and that size of tumor and mean mitotic activity was not significantly related to prognosis, which they state in their results section. There was no multivariate analysis given in this study. The study cited by Jensen et al. reviewed 278 soft tissue sarcomas, which again were graded using mitotic activity, cellularity, necrosis, and histiogenic subtype, and prognostic factors were studied in relation to metastasis-free survival by univariate and multivariate analysis. Grade was shown to be the prognostic factor associated with the strongest predictive value. Other significant prognostic indicators were age, local recurrence at presentation, and location (superficial *vs.* deep). They did not look at mean mitotic activity as a continuous variable. In fact, they split the high-grade tumors into two groups, those with mitosis between 5 and 20 mitoses/10 hpf and those with >20 mitoses/10 hpf. Patients more than 65 years old, patients with deep-seeded tumors and local recurrence at referral, and patients who had primary operations outside the center had worse prognoses. The histopathologic grade, however, had the strongest predictive value, and these were graded as grades 1, 2, and 3. A careful review of this article again shows that mean mitotic activity was not an independent prognostic factor separate from grade and size. In addition, they did not look at mean mitotic activity as a continuous variable.

Finally, in the study by El-Jabbaour et al. (*Br J Cancer* 1990) mean mitotic activity was a significant factor in the univariate analysis ($p = 0.009$) when grouped as 0–4 mitoses/10 hpf, 5–9 mitoses/10 hpf, and >9 mitoses/10 hpf. They did perform a multivariate analysis in this study; however, there are serious