wound infections. In addition, some of the psychological and cosmetic impact of surgery might be avoided. Rare anesthetic problems and complications such as thromboembolic disease would also not occur, and considerable inpatient resource savings would be made." Seroma is a frequent complication after breast cancer surgery (26).

In general, where a clinical trial fails to show that treatment A has a different efficacy than treatment B, the decision-making process then shifts to the safety profile and to the quality of life profile. If safety or quality of life for treatment A is superior, then the investigators may be justified in recommending that treatment A be used.

VIII. DISEASE-FREE SURVIVAL AND OVERALL SURVIVAL ARE USEFUL TOOLS FOR TESTING AND VALIDATING PROGNOSTIC BIOMARKERS – THE BEPLER STUDY

The following demonstrates the utility of the RRM1 gene and PTEN gene as prognostic markers. Bepler et al. (27) acquired two sets of frozen lung tumor samples. The first set was the *exploratory set*, while the second set was the *validation set*. The exploratory tissue samples were acquired from a tissue procurement facility. The validation set was from 77 patients enrolled in the Bepler study. Tissue samples were all frozen within 20 minutes after collection, according to a standard procedure, and stored at minus 80 degrees C. Essentially all of the patients used for the exploratory tissue set were treated with surgery only (no chemotherapy, no radiation). The use of surgery only totally eliminates the possibility that any radiation or drugs would influence gene expression.

Analysis of gene expression in the exploratory tissue set showed an increased expression of the RRM1 gene was significantly associated with increased overall survival ($P = .013$), and that increased expression of the PTEN gene was also significantly associated with increased overall survival ($P = .011$). Survival was longer for patients whose tumors expressed high levels of the respective gene compared with low levels (median survival time of 52 months versus 24 months for RRM1, and 62 months versus 23 months for PTEN).

The results from the prospective study were as follows. As seen from the published Kaplan-Meier plots of the DFS endpoint and the overall survival endpoint, the results were striking and dramatic. In viewing the DFS data, a clear separation between high gene expressing patients and low gene expressing patients could be seen by ten months into the clinical trial. But with the overall survival data, a clear separation could not

[26] Hashemi E, Kaviani A, Najafi M, Ebrahimi M, Hooshmand H, Montazeri A. Seroma formation after surgery for breast cancer. *World J Surg Oncol*. 2004;2:44–49.

[27] Bepler G, Sharma S, Cantor A, et al. *RRM1* and *PTEN* as prognostic parameters for overall and disease-free survival in patients with non-small-cell lung cancer. *J Clin Oncol*. 2004;22:1878–1885.