problems including chronic arm morbidity, pain, seroma formation, and 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. DFS AND OVERALL SURVIVAL ARE USEFUL TOOLS FOR TESTING AND VALIDATING PROGNOSTIC BIOMARKERS—THE BEPLER STUDY

This 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 min after collection, according to a standard procedure, and stored at −80°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 increased expression of the *RRM1* gene was significantly associated with increased overall survival ($P = 0.013$), and that increased expression of the *PTEN* gene was also significantly associated with increased overall survival ($P = 0.011$). Survival was longer for patients whose tumors expressed high levels of the respective gene compared with low levels (median survival time of 52 months vs 24 months for *RRM1*, and 62 months vs 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 10 months into the clinical trial. But with the overall survival data, a clear separation could not be seen until about 20 months. Data on DFS and overall survival were collected until about 100 months.

The hazard ratios were disclosed for the endpoint of overall survival. In dividing the patients into high-*RRM1*-expressing tumors, and into low-*RRM1*-expressing tumors, and drawing two curves corresponding to overall survival for the high-*RRP1*-expressers and the low-*RRP1*-expressers, the resulting hazard ratio was HR = 0.452.

Hazard ratio data also showed an association between expression (high vs low) with survival, for the *PTEN* marker. The hazard ratios were disclosed for the endpoint of overall survival. In dividing the patients into high-*PTEN*-expressing tumors, and into

[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;2:44−9.

[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;22:1878−85.