Background/Discussion/Critique

The New England Journal publications in 1997 from Denmark and Canada demonstrated a survival benefit for postmastectomy radiation therapy (RT) in premenopausal women with high risk breast cancer. The benefits of tamoxifen in postmenopausal patients have been established in numerous prospective trials. On the heels of those influential papers, Dr. Marie Overgaard et al. has published another Danish trial regarding the benefits of RT on survival in high risk postmenopausal breast cancer women. This trial was a three-arm trial with randomization postmastectomy to tamoxifen alone, tamoxifen + RT or tamoxifen + CMF chemotherapy (Cyclophosphamide, Methotrexate and 5FU). The patients had a total mastectomy (pectoral muscles remained intact) along with an axillary lymph node dissection of levels I and II (not full dissection). They were considered high risk if they were LN positive, had a tumor greater than 5 cm, involved pectoral fascia or skin. There were significant improvements in long term outcome with the addition of RT to tamoxifen over tamoxifen alone.

The lack of data on the third arm (tamoxifen + CMF) is rather disconcerting. The validity of the authors' conclusions cannot be verified without the data on one of the study arms. In the discussion section of this article, the authors claim that the results, preliminarily, of the tamoxifen + CMF arm were similar to tamoxifen alone in the locoregional control (LRC) and overall survival (OS). They also claim that the disease free survival (DFS) in this unpublished data set was the same as the RT + tamoxifen arm, because there were fewer distant metastases. Another statement declared that the OS was no different from the two arms that were published. These statements are contradictory, since there was an OS advantage of adding RT to tamoxifen. In addition, if the OS survival is the same with CMF or RT, why should patients get radiation? The question becomes what is the toxicity between CMF or RT if the OS and DFS are the same (obviously no comparative data on that was presented). Finally on this point of contention, when we do get the results of all three arms, perhaps a trial of trimodality (RT + chemotherapy and a therapeutic endocrine agent) versus bimodality will be needed to determine if any further benefit can be derived.

Other issues to be addressed were the suboptimal surgery performed duration of tamoxifen treatment and lack of toxicity and second malignancy data.

The surgery performed was a total mastectomy and lymph node sampling (60% of patients had less than 8 axillary lymph nodes taken). The usually standard of care is a modified radical mastectomy, which includes removal of the entire breast, pectoral fascia, and pectoralis minor along with the nerve (not all the time). Could the radiation be making up for non-standard surgery in improving local control and, thus, survival? In the case of only performing a lymph node sampling, the prognostic and stratification information is lost. Table 5 indicates that those who had less than 8 axillary lymph nodes sampled did better with DFS at 2 years and OS at 4 years with the RT + tamoxifen. However, no difference was found in patients with greater than or equal to 8 axillary lymph nodes taken in DFS and actually an increase in early deaths (within 4 years) with the addition of RT to tamoxifen. RT's early benefit may be due to the inadequacy of the mastectomy and/or the lymph node dissection.

The standard duration of tamoxifen treatment during the inception of the trial was 1 year. It has now been established that 5 years of tamoxifen is the current standard of care for invasive breast cancer. This may be a minor point, since tamoxifen is utilized on all arms and its benefit should not bias the data of one arm over the other. Future investigators should be aware of this and incorporate that duration in upcoming trials.

Toxicity and second malignancy data were not presented and may have been useful when comparing the two treatment arms.
published. A brief mention of no cardiac morbidity was made along with a mention that the data on toxicity was incomplete.

In conclusion, enthusiasm should be tempered about this trial, since the authors have only given us a small peek at the entire data. Validation of RT's efficacy will perhaps come when it is finally compared with the CMF + tamoxifen.