How Big Is Big Enough? Thinking About Contralateral Prophylactic Mastectomy

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When evaluating the benefit of a therapy, we must consider the effects of uncertainty and the magnitude of the gain or loss, having decided on a metric for outcome differences. With two alternatives (A and B) under consideration, there are three possible conclusions: Option A is substantially better; option B is substantially better; and the options are more or less equal—that is, the decision is a close call or toss up (1). When considered to sufficient precision, it would be unusual for two strategies to be exactly equivalent. Thus, the boundary between a close call and a clear benefit or harm is dependent on the purpose of the comparison, the perspective of the analysis (who the decision maker is), and the preferences of the decision maker.

In recent decades, such comparisons have been sharpened by developing models of the choice and the prognoses using decision analysis that explicitly reveals the underlying assumptions and perspectives. Prognosis and its uncertainty can be summarized by probabilities or probability distributions. The relative value of possible outcomes can be summarized by utilities or utility distributions. Sometimes utilities reflect not only hard data, such as survival, but also quality of life, which clearly varies based on whose preferences are being considered. Such decision models also require the explicit specification of the time horizon being considered (2). When the problem being represented involves evolution over time, it is commonplace to use a Markov or state transition model (3), which “follows” the prognosis of a cohort of similar patients over time as they move from one health state to another health state, with transitions governed by the probabilities derived from available data. Eventually the cohort gets absorbed in the so-called “Dead” state. The sum of the incremental utilities over the time frame of the model is used as a measure of the value of each strategy under consideration.

Whether or not to undergo a contralateral prophylactic mastectomy (CPM) after being treated for breast cancer is a difficult choice for many women. The goal of such aggressive therapy is to lower the likelihood of a second primary carcinoma developing. The downsides are operative risk, impairment of the woman’s self-image, and short-term and long-term morbidities. In this issue of the Journal, Portschy and colleagues from the University of Minnesota offer a Markov model of this choice (4). They consider average women with breast cancer and not those with a genetic predisposition such as BRCA 1 or 2. These investigators consider a 20-year time horizon and life expectancy (or average survival), but not quality of life or cost. The analysis covers variation in age, estrogen receptor status and stage of cancer to address the spectrum of clinical scenarios that might arise. Their analysis shows that there is a benefit from CPM that persists under most changes in the analytic assumptions, but that the benefit in 20-year survival is small (less than 1%) and seen largely in younger women, implying that “the juice may not be worth the squeeze.”

This is a well-done analysis from an experienced group of investigators and based on the currently available data. Given the JNCI audience, we shall refrain from nigging points about modeling. Rather, we will stick to the big picture and clinical implications. Although the survival benefit from CPM is small as demonstrated in this model, it is greater than zero, which suggests that for some patients even that small gain may be enough to make CPM a not unreasonable choice. Of course, from a societal perspective, which was not addressed by Portschy et al, the associated costs of CPM, including the cost of the procedure, its complications, reconstruction and perhaps psychotherapy, may outweigh the modest benefit CPM provides (4). The small denominator of the cost-effectiveness ratio, were one to be calculated, would imply that the ratio would be very high, making CPM a sub-optimal use of healthcare dollars. Further, we suspect that adding quality of life to the analysis would diminish the benefit and well might turn it into a net harm, in particular for patients with high concern for negative impact of CPM on cosmesis, self image, and morbidity. However, in a fraction of patients who are very troubled by a 0.7% risk of a second, contralateral cancer, CPM might still provide an acceptable benefit. The balance between harms and benefit depends on the patient’s preferences and highlights the importance of capturing the patient’s values and expectations before considering CPM.

The modest difference in the expected (or average) values between the two strategies in this analysis is not atypical for decision analyses (5). Even for “obviously” beneficial therapies, decision models often demonstrate surprisingly small differences. That said, in this case the difference is very modest. In terms of average survival, the benefit of CPM (even without deducting for impact on quality of life) is only one to seven months of survival, depending on age or estrogen receptor status.

Of course, these conclusions are based on analysis of women who are at average risk for a contralateral second primary. In women at substantially higher risk (based either on family history.
or genetics), the benefit of CPM might be far greater, and CPM might be a good choice for the patient or for society.

References


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