Coming of age : treatment and outcomes in older patients with breast cancer

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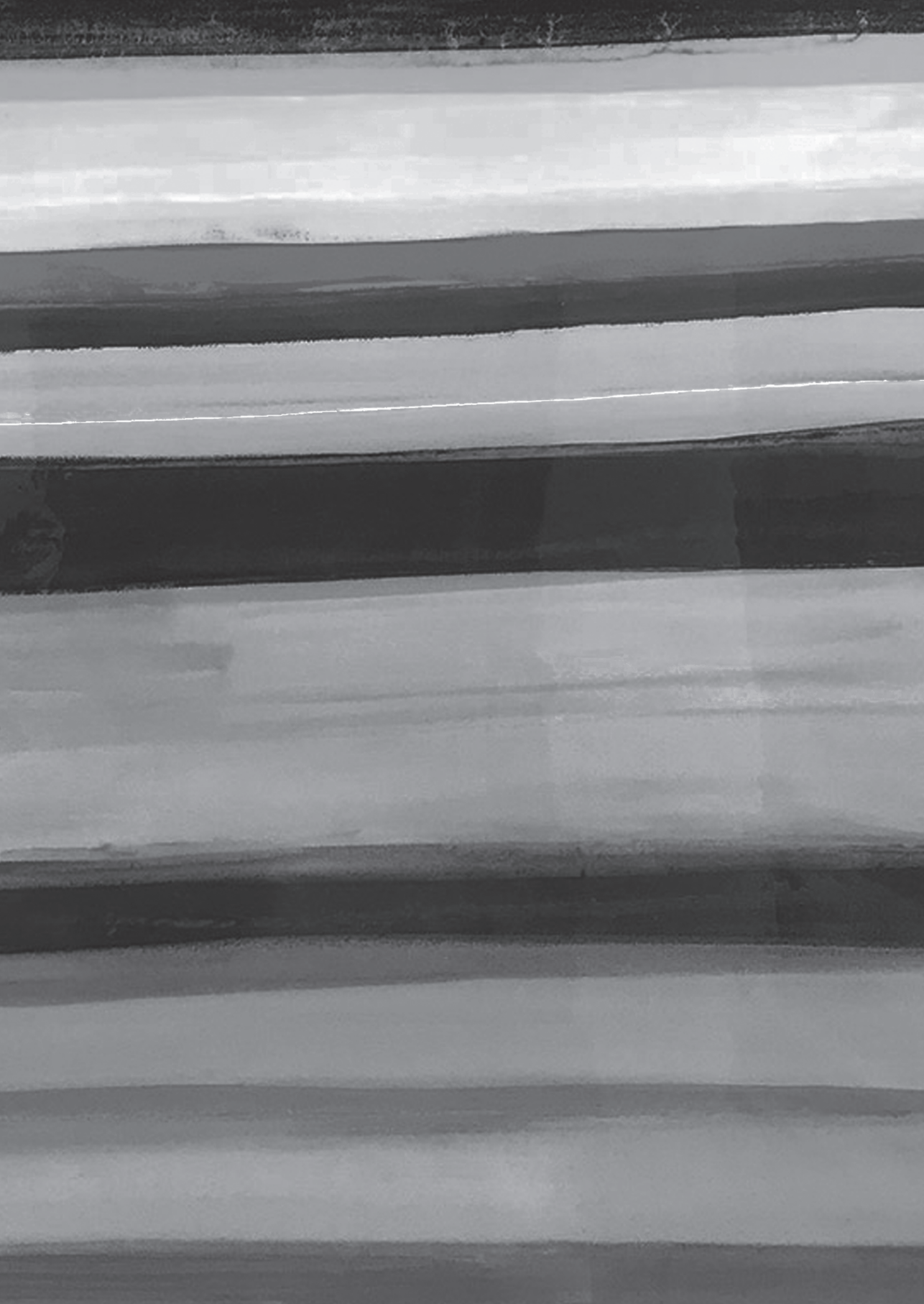

CHAPTER 9

Health is in the eye of the beholder: new endpoints for cancer trials in older patients

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BACKGROUND

Historically, effectiveness of treatment has been measured from a biomedical perspective, which is deeply rooted in biology, biochemistry and physiology. It is from this reasoning that trial endpoints in cancer research focus on tumor oriented endpoints such as disease free survival or progression free survival.[1] Determining the effect of treatment on the length of life is necessary and this should be considered as the starting point of most new medical treatments. However, only measuring the effect of treatment on survival might not be sufficient. Especially when approaching the end of life, maintaining a good quality of life becomes all the more important.[2] Over the last two decades, it has increasingly been acknowledged that experience of the patients themselves should be taken into account in the estimation of benefit of treatment. An abundance of questionnaires were developed to assess quality of life as a representation of patient experience in clinical trials. These questionnaires cover various domains of functioning such as physical, cognitive, sexual or social functioning, independence in daily living, and disease-related symptoms. These domains are chosen and weighted by physicians and researchers and result in a sum score that aims to reflect quality of life.

It is debatable if the assumptions underlying the quality of life questionnaires correspond to the needs and wishes of the individual patients. The choices on which domains should be included and how to weigh them are defined by researchers, they do not necessarily include aspects of life that are considered important for quality of life by an individual patient. The patient's perception of his or her quality of life is highly dependent on the patients' thoughts, feelings, and preferences. Moreover, from the field of sociology it has been firmly established that wellbeing reaches its nadir during middle age and subsequently increases despite the concomitant loss in functional determinants with ageing. From this 'disability paradox' it is self-evident that wellbeing is not directly related to functional determinants that are currently measured in quality of life questionnaires. Therefore, current quality of life questionnaires reflect a state of functioning rather than quality of life as actually perceived by the patient perspective.

If we aim to measure quality of life from a patient perspective, wellbeing would be an appropriate candidate to focus on. Wellbeing as an outcome has been used extensively in the field of social sciences and economics. The concept of wellbeing encompasses four quadrants (Figure 1) depending on whether it relates to passing or enduring experiences of happiness and whether it relates to the entire lifespan or parts thereof.[3] Here will focus on two quadrants as they are regarded the driving forces of wellbeing: happiness as a measurement of how good someone feels within a short time span and life satisfaction as a measure of the overall feeling content with his or her life as a whole. Both happiness and life satisfaction are

measured from the perspective of the individual: the patient rates their current or overall happiness without any predefined assumptions on which domains should be included or how they should be weighed.

Here we introduce new endpoints that can be applied in clinical trials to reflect wellbeing as experienced by patient rather than measuring its functional outcomes. We propose to measure happiness, life satisfaction and overall survival. Additionally, we combine the measure of happiness with the length of life to develop a balanced estimate of harms and benefits in the treatment of older patients with cancer. We provide a statistical approach using simulated data from a hypothetical clinical trial.

METHODS

Introducing new endpoints

Happiness

To measure wellbeing for this endpoint, we will focus on the left upper part of the quadrant: happiness as a measurement of how good someone feels within a short time span. Happiness is measured on a single item scale asking patients how happy they feel at that moment. By asking patients how they feel at that moment, focus is directed to the affective component of their happiness. The answer is rated using a visual faces scale ranging from 0 (extremely unhappy) to 10 (extremely happy). Patients are asked to report this on a daily interval using the Experience Sampling Method; patients are prompted to rate their happiness using an application on their smartphone or other electric device at a random moment of the day.[4] With this method a real-time, day-to-day experience of happiness is recorded during the time that patients are alive.

If happiness is measured for two treatment arms in a randomized clinical trial, for each treatment arm it will represent a curve of perceived happiness over time. At the start of the study, happiness will be equal between both arms due to randomization. Over time, happiness might change between the two arms. The variation between the two arms over time can be estimated by comparing all measurements by treatment arm and can be tested if there is a statistical difference between the two arms. If a difference is observed further analysis regarding the behavior of happiness over time between the two treatment arms is required. We propose a way of estimating this further below.

Life satisfaction

Life satisfaction (Figure 1, right lower quadrant) is the degree to which an individual rates the overall feeling of contentment with his or her life as a whole. This assessment combines

both past and future perspectives and is therefore an evaluation over a longer period of time. Life satisfaction is measured using the validated Cantril Self-Anchoring scale.[5] This is a single measurement on a visual scale represented as a ladder ranging from 0 to 10 where 0 represents the worst possible life imaginable and 10 represents the best possible life imaginable. Patients are asked where on the ladder they feel to stand at time of randomization and at specified time points during the follow-up.

	Passing	Enduring
Part	**Happiness**	Domain satisfaction
Whole	Top experience	**Life satisfaction**

Figure 1: Theoretical framework of wellbeing

For both treatment arms, at each prespecified time point, the difference between life satisfaction can be measured among the two treatment arms for those patients that are alive at that time point (Figure 2). At baseline, life satisfaction should be comparable between the two arms as a result of randomization, but it might change between the two treatment arms as a result of the different treatments.

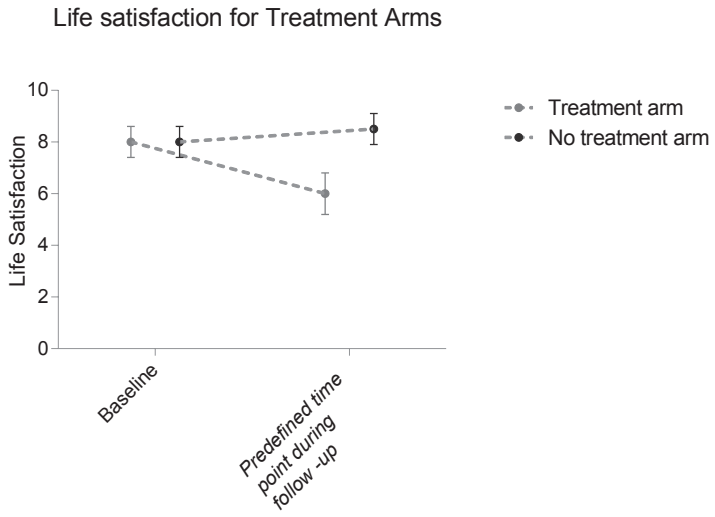

Figure 2 Measurement of life satisfaction

The combined estimate of happiness and length of life: Happy life years

To quantify the experienced happiness over the duration of being alive we propose to combine the measurement of happiness with the length of life by calculating the product of overall survival and happiness as an Area Under the Curve (AUC). This AUC is named HAPPy life Years (HAPPY's). The HAPPY is calculated per individual (Figure 3A) and can be used to perform a statistical analysis and compare the two randomized arms (Figure 3B). In clinical practice, both the shape of the curve and the area of the curve will be valuable for decision making. From a mathematical perspective this resembles the calculation of Quality Adjusted Life Years (QALY). However, it differs substantially in its conceptual design. The HAPPY combines an objective one dimensional endpoint (overall survival) with a subjective self-anchored single question that reflects the experience and happiness of patients regardless the domains that they themselves consider are important. It therefore is a more accurate reflection of wellbeing than a QALY.

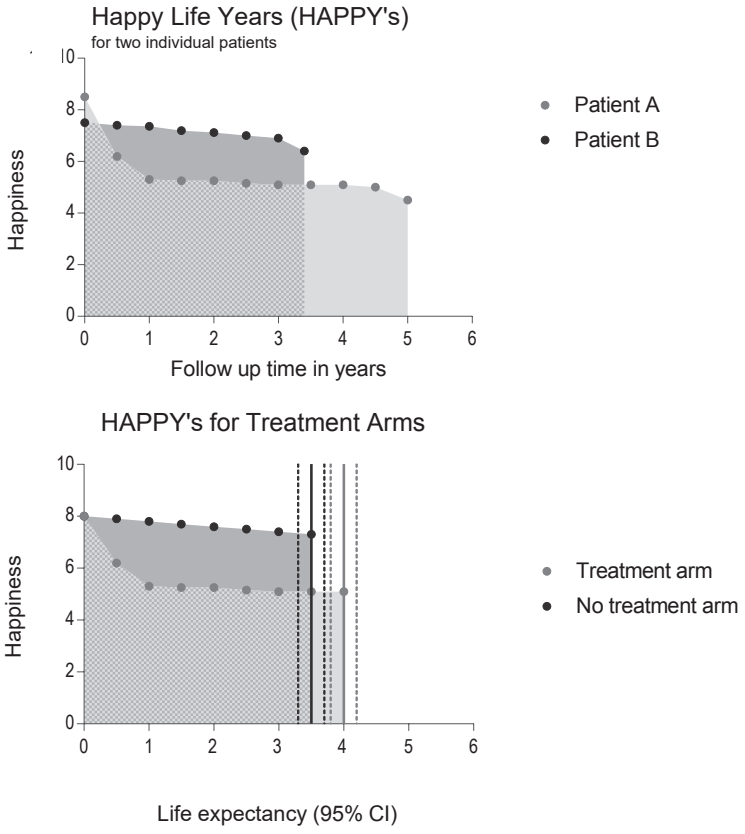

Figure 3 Happy Life Years for (A) two individuals and (B) two treatment arms

RESULTS

A statistical example of the new endpoints using simulation data

DISCUSSION

Ultimately, patients and clinicians aim to maximize both length and quality of life. We believe that the newly introduced endpoints reflect this goal better than the traditional endpoints used in clinical trials for older patients with cancer.

In this paper we have discussed the importance of including the patient perspective on quality of life in the evaluation of treatment benefit. With these new endpoints, quality of life is measured as a function of happiness or life satisfaction, without any underlying assumptions from researchers or clinicians on which aspects define quality of life. Therefore, the measurement of quality of life reflects the experience of patients more adequately than traditional questionnaires. Measuring the patient perspective on quality of life instead of the research perspective is part of a long-lasting debate in the field of anthropology and healthy ageing.[6,7] Especially among older patients, it is important to acknowledge the difference between the patient's perspective and the perspective of the researchers when evaluating quality of life.[8,9]

The usefulness of experience sampling method (ESM) for psychiatric and somatic evaluation in clinical trials has been described previously, but to our knowledge it has not been applied in clinical research.[10] The ESM method is an appealing method for the evaluation of happiness as it measurements are made in the natural flow of real life. The collection of repeated measures over time improves the validity, reliability and transparency of individual patterns and this increases the sensitivity to detect changes over time. In the of field happiness research, this method is now frequently used to understand the real time dynamics of happiness in everyday life. Previously, such research methods were cumbersome and expensive. Over the last years several web applications for smartphones have been developed that enables researchers to create large databases to study the influence of daily activities and experiences on emotional wellbeing.[11] We believe that such a research method could be applied to evaluate the wellbeing of patients in clinical research and during treatment in routine practice.

Some other methods have been proposed previously to evaluate length of life and quality of life in a single endpoint. These methods are the Extended Q-TWiST method and the

Quality Adjusted Life Years (QALY).[12,13] For both methods, outcomes are calculated using an average sum score of a quality of life questionnaire or a predefined weight at one time or a few times during follow up. As outlined above, the traditional quality of life questionnaires reflect a state of functioning on various domains and therefore these methods are a measurement of functioning over a time period and not necessarily a reflection of the experienced quality of life.

Evaluation of life satisfaction using the Cantril's ladder is an established method with high validity and reliability. We could only identify two studies that applied the Cantril's ladder as a tool for life satisfaction among patients with cancer.[14,15] However, the tool has been extensively used in population based cohort studies in older people to evaluate the relation between age and life satisfaction and patterns of life satisfaction over time.[16]

Already described by Ira Wilson and Paul Cleary in 1995, there is a need to link clinical outcomes with quality of life in the evaluation of treatment.[17] In their conceptual model,[17] they describe a framework that connects this biomedical model through several levels such as physiological factors, symptoms and functioning to overall quality of life. Although overall quality of life is considered as the ultimate outcome in their model, traditional questionnaires have focused on the intermediate levels; the domains they assess are comparable to the levels in the model of Wilson and Cleary. Our proposed endpoint is the first that directly connects the biomedical model in terms of life expectancy with the overall quality of life. From our simulation studies, we have shown that these new endpoints are valid under various scenarios in clinical trials in older patients with cancer. Moreover, with the introduction of the HAPPY endpoint, we provide more insight in the costs and benefits of treatment as the shape of the area under the curve reflects the balance of treatment in terms of increasing length of life at the cost of possible decrease in quality of life.

With the introduction of this new endpoint, we do not argue that the domains currently assessed in traditional quality of life questionnaires should are not relevant. As outlined in the model by Wilson and Cleary, we propose to include these measures of functioning and symptoms as explanatory factors for variation in overall quality of life rather than the main endpoints. Subsequently, factors that influence overall quality of life can be used as targets for interventions.

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