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In Reply: We thank Dr Nasti and his colleagues for their interest in our study,[1] and welcome their ideas to improve outcome in patients with resectable liver metastases from colorectal cancer. They explain some concerns regarding the use of neoadjuvant chemotherapy in patients who may not benefit from this approach, and favor an alternative treatment schedule including positron emission tomography (PET) to identify responders after a single chemotherapy cycle.

The authors outline in their reply that patients with stable or progressive disease while receiving chemotherapy lack the potential of a surgical intervention. We would like to emphasize that achieving stable disease while receiving chemotherapy is still believed to be an attainment and improves outcome parameters in these patients. However, it is correct that the identification of progressive disease is important, but in contrast to the opinion of the authors, to our knowledge these patients will not benefit from a surgical intervention even if they can stil undergo resection, and should therefore undergo second-line chemotherapy instead.[2,3]

The identification of predictors for response is an important issue and the use of a [18F]fluorodeoxyglucose-PET for an early evaluation is certainly one of the methods currently under investigation. It seems specifically interesting in patients receiving antiangiogenic drug–containing regimens because that a certain percentage of the liver metastases in these patients seem to respond to treatment without fulfilling the Response Evaluation Criteria in Solid Tumors criteria of response. This is demonstrated in a higher percentage of pathologic tumor necrosis,[4] an increase in pathologic complete response rates,[1] a higher PET response compared with computed tomography response,[5] and a decrease in contrast enhancement.[6]

To date, we have not recognized a different response pattern depending on tumor size, demonstrated in our article, where a significant tumor size reduction in a patient with a large metastasis is illustrated.

In summary, we support the necessity to identify responding patients during neoadjuvant treatment with early predictors and thereby increase the optimal sequence of chemotherapy and surgery.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Another STEPP in the Right Direction

To the Editor: We welcomed the editorial by Royston and Sauerbrei,[1] which highlighted the importance of evaluating the magnitude of treatment effect differences as a function of continuously measured covariates in clinical research. Our work in this area includes the development of the subpopulation treatment effect pattern plot (STEPP),[2,3] a statistical method that assesses treatment effects for overlapping subgroups of patients defined by a covariate of interest such as age. STEPP relies on estimates obtained from standard survival curves, such as those produced with the Kaplan-Meier methodology.[3] The approach recommended by Royston and Sauerbrei is based on models of multivariable fractional polynomial interaction (MFPI) and searches over a set of possible functional forms for the relationship between the covariate and the survival end point.[4,5]

Royston and Sauerbrei faulted STEPP because, in contrast to MFPI, STEPP does not provide a single numerical measure of an interaction. We consider this a strength, however, because STEPP avoids distilling potentially complicated patterns of effect modification into a single number. Instead, graphical methods are used to display these patterns, showing the clinically relevant absolute treatment effect as the covariate ranges from low to high values. These graphs are readily interpretable by clinicians, as illustrated in the recent

analysis of Viale et al,[6] which evaluated the predictive value of estrogen and progesterone receptors in breast cancer. This is similar to the use of Kaplan-Meier survival curves for comparing treatments. There is no single summary measure, yet the usefulness of displaying estimated survival curves is well recognized.

Though we agree that STEPP is useful as an exploratory tool, we disagree with the suggestion that its primary role is to check MFPI results. This is analogous to preferring a parametric model (eg, exponential) to estimate survival distributions and using Kaplan-Meier estimates to check the model fit. Clearly, there are advantages in directly estimating effects using nonparametric methods. Of course, we support the continued development of both parametric (or semiparametric) and nonparametric methods and point out that another useful analytic approach has been developed by the National Surgical Adjuvant Breast and Bowel Project statistical group.[7]

Finally, we note that the study of treatment-covariate interactions typically requires large sample sizes to produce reliable results. Even in a large-scale clinical trial, subtle levels of effect modification may be difficult to detect with STEPP or MFPI. We are currently extending STEPP to evaluate the magnitude of treatment effect differences in meta-analyses.

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In Reply: We thank Bonetti et al for their letter in which they highlight the importance of investigating interactions with continuous covariates and refer to a related approach developed by the National Surgical Adjuvant Breast and Bowel Project statistical group.[1] They also mention extending subpopulation treatment effect pattern plot (STEPP) to evaluate treatment effect differences in meta-analysis. Similarly, our parametric method of modeling interactions (MFPI[2]) can be extended by averaging treatment effect functions over studies. The methodologic issues have already been described.[3] We have developed an approach for the meta-analysis of dose-response functions that will be presented soon. In contrast to Bonetti et al, we think that a major advantage of MFPI is its applicability to the context of parametric multivariable (generalized) regression models. MFPI can efficiently screen several covariates for interactions with treatment, either with or without adjustment for other variables. This is particularly important for correlated variables such as estrogen and progesterone receptors in breast cancer. An example is the detection of an interaction between treatment (immunotherapy or hormonal therapy) and WBC count in the Medical Research Council RE01 trial.[4]

In contrast, STEPP seems to be less-well suited to screening for interactions. There are two versions, sliding window and tail oriented, both of which have several parameters critical to their performance. We know of no guidelines to choose the parameters, or even whether the sliding window or tail-oriented version is preferable. In Figure 2 of our editorial,[4] we presented the STEPP display we found easiest to interpret. However, additional STEPP results from the renal cancer study with different parameter settings and other variables lead to large differences in interpretation.[5] These examples seem to illustrate what Bonetti et al call complicated patterns of effect modification, whereas we believe that STEPP simply overfits the data. Our approach generates a single number (a *P* value for a test for interaction) that summarizes the evidence for an interaction, a small *P* value suggesting that an interaction is probably present. The treatment effect function gives a graphical depiction of the interaction on the relative hazard scale. To protect against overfitting, we proposed simple checks.

In most cases, we doubt that effect modifications really follow a complicated pattern. Usually a simple monotonic function (eg, linear or log) should describe effect modifications quite adequately; in exceptional cases, a U-shaped function may describe such effects better. Jeong and Costantino's approach[1] combines STEPP with a smoothing technique. Based on parameters chosen to analyze the National Surgical Adjuvant Breast and Bowel Project studies B-14 and B-20, we have the impression that the approach is suitable only for large studies. The Medical Research Council RE01 trial would probably have been too small for it. Difficulties of using the methodology in a multivariable context are discussed in the last paragraph of the article.

Smoothing results from STEPP analyses is another step toward deriving simple treatment effect functions for continuous variables. With large values of the bandwidth (as chosen by Jeong and Costatino[1]), functions similar to those obtained using MFPI will likely be produced. MFPI is generally applicable if the sample size is reasonable and gives interpretable results that can be checked by simple, standard techniques to protect against overfitting. We

