About the article "Hepatic steatosis is associated with higher incidence of liver metastasis in patients with metastatic breast cancer; an observational clinical study" by Duran et al.

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Dear Editor,

We have read with great interest the report written by Duran and colleagues [1]. They have stated in their manuscript that hepatic metastases of breast cancer at diagnosis and during follow-up were more frequent in patients with hepatic steatosis (HS), especially in premenopausal patients. Also they concluded that HS, diagnosed by computed tomography, is an effective prognostic indicator for the risk of hepatic metastasis in patients with breast cancer. However, the statistical methods and discussion of the manuscript need some consideration.

The authors stated in their manuscript that "Obesity is considered a risk factor for the development and poor prognosis breast cancer and also an independent prognostic factor for the risk of disease recurrence and shorter overall survival when compared with patients with normal weight [2,3]". Also it is widely known that obese patients are more prone to have hepatic steatosis [4]. As the authors did not evaluate their hypothesis by univariate and multivariate analyses, it is ambiguous and difficult to conclude whether having more frequent hepatic metastasis is caused by being obese or having HS.

In this study, the authors also have quoted the Murono et al. Study [5] and they stated that "the mechanism proposed by Murono et al. supports the accuracy of our findings". But the mechanisms proposed by Murono et al. show protective effect of HS on liver metastasis formation. Hence, we also do not agree with this conclusion.

To sum up, in this article there are some missing statistical methods which may have an effect on the outcome.

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Reply to Dr. Kocoglu et al. comments

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Dear Editor,

We concluded that hepatic steatosis (HS), diagnosed by computed tomography (CT), is an effective prognostic indicator for the risk of hepatic metastasis (HM) and this may be the underlying mechanism of poor prognosis in patients with breast cancer (BC) in the July-August issue 2015 of JBUON [1]. We read with interest the comment to the editor by Dr. Kocoglu et al. about our article. We thank them and reply to these interesting comments.

The authors criticized us on the lack of statistical analysis methods to conclude whether having more frequent HM is caused by being obese or having HS. For this separation, multivariate analysis could be used, but in our study we pointed in the result section that, when patients

were evaluated according to obesity, both pre- and post-menopausal groups showed similar rates of HM at diagnosis and during follow-up regardless of obesity status (p>0.05; Table 3). Despite the widely known information about the relationship between obesity and the development and poor prognosis of BC [2], we did not find a significant relationship between obesity and HM. Therefore we did not include obesity and body mass index parameters in the multivariate analysis.

Secondly, Murono et al. [3] hypothesised that steatosis may possibly create an unfavorable microenvironment for metastatic formation in the liver. They also suggested that fibrotic changes in the liver are associated with loss of the protective effect of HS on liver metastasis formation. We did not claim that the result of this study supports the accuracy of our findings, but we claimed that these mechanisms (the effects of HS on the liver tissue microenvironment, such as adipose-derived inflammation, lipotoxicity,

fibrosis and insulin resistance) support the accuracy of our findings, especially fibrosis.

And finally, we do not believe that there are some missing statistical methods which might have an effect on the outcome of the study.

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About the article: "Cutaneous melanoma in Turkey: analysis of 1157 patients in the Melanoma Turkish Study" by Abali et al.

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Dear Editor,

We read with great interest the article published in a recent issue of the JBUON by Abali et al. (Melanoma Study Group of Turkish Oncology Group) entitled "Cutaneous melanoma in Turkey: analysis of 1157 patients in the Melanoma Turkish Study" [1]. We thank the authors for their valuable investigation evaluating retrospectively the demographic and clinicopathological characteristics of patients with melanoma in Turkish population. The authors concluded that patients presented with more advanced stages had worse prognosis compared to SEER database [2]. However, we think that some important issues should be discussed.

The authors stated in their manuscript that 5-year overall survival (66.0%), which is much lower than the SEER database (91.3%), is probably related to stage distribution in their registry. But according to SEER database (2003-2011) when we calculated 5-year overall survival and relative survival we determined them as 81.9% and 91.3%, respectively [2,3]. It is known that older age is associated with higher incidence of melanoma death [3]. The median age of Turkish patients with melanoma was 56 years whereas it was 62 years in US population. Despite these facts, detecting better survival in US population could be caused from invalid comparison (method-

ological error).

According to SEER database, 5-year relative survival by stage was 84% for stage I & II, 9% for stage III, and only 4% for stage IV. But in this study there was no knowledge about survival by stage. Also, according to SEER database, 4.1% of the patients had stage IV melanoma in US population whereas 19.6% of the Turkish patients had stage IV melanoma. As mentioned in their study, Turkish patients presented with more advanced stages. Thus, we think that the characterization of survival in Turkish population is worse than US population, and comparison of both data without correcting for age and stage (regional or metastatic stage) should be re-evaluated.

As the authors did not share the age distribution of their data it is ambiguous and difficult to conclude whether or not lower survival was caused only from stage distribution.

In conclusion, it is quite obvious that the study by Abali et al. offers valuable data to the medical literature. Also, clarifying these concerns would provide a clearer picture to the readers.

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Reply to Dr. Kocoglu et al. comment

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Dear Editor,

We would like to thank dr.Kocoglu et al. for their interest and their valuable contribution to our study. Kocoglu et al. criticize our conclusions about the survival findings in our study, although we have clearly and honestly stated that our findings about survival should be interpreted with caution (Discussion, paragraph 6).

In their comment, it seems that they expected better survival in our study than in SEER database just because of the younger age of our patients (56 vs 62 years). As stage is the most important prognostic factor, we think that explaining the difference solely by age difference is difficult. Their 3rd reference is on the localized melanoma and it is not a population based study [1]. There may be many other confounding factors, like stage at diagnosis, biology, practice patterns (for example: quality of surgery), comorbidities, and survival expectation of the whole population. It is not easy to tease out so many factors. We do not think that only a 6-year difference of age difference play a major role in the prognostic difference between SEER and our study.

The data on survival by stage can be easily inferred from Kaplan-Meier curve in Figure 3, although we did not present the figures in the results section.

We could not explain our survival rate of 19.6% in stage IV patients. It may be due to a statistical error and we could not speculate more. We have to repeat that survival data in our study must be interpreted with caution.

References

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