Author's response to reviews

Title: Tertiary lymphoid structures are associated with higher tumor grade in primary operable breast cancer patients.

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Author's response to reviews: see over
Dear Editor,

Thank you for reviewing our manuscript entitled: “Tertiary lymphoid structures are associated with higher tumor grade in primary operable breast cancer patients”. We would like to thank the reviewers for critically reading the manuscript. The manuscript has been revised according to their comments as described below.

Comments by Referee 1:

Major compulsory revisions

1. “TLS are described as a special form of organized immune cell aggregates. Given that fact, the positive association between the presence of TLS and organized immune cell aggregates seems to be a rather trivial one. Why then is this association presented as a major finding?”

Response:
As pointed out by the reviewer, the association between the presence of TLS and organized aggregates is a rather trivial fact. What we have presented in the result section and focused on in the study is the association with the immune cell aggregates that are not organized versus the organized ones (TLS). We agree with the reviewer and have rewritten the following sentence:

Page 9, line 22:
“Histopathological analyses revealed immune cell infiltrates with aggregate formation in 50.5 % of the patient samples of which 38.6 % were TLS positive (Table 1).”

Furthermore, in the section “Association between TLS formation and clinicopathological parameters” we have rewritten the sentence on page 10, line 21:
“There was a strong positive association ($r^\phi = 0.796, p < 0.01$) between detection of TLS and immune cell aggregates formed in tumors.”

By making these changes we hope that the association between formation of immune cell aggregates and TLS detection is described properly. Thus our major findings in this study are that TLS are more frequently found in tumors with higher histological grade as well as higher degree of immune cell infiltration.

Minor essential revisions

1. Page 4, line 22:
   “Tumor infiltrating T lymphocyte populations are shown to have favourable clinical outcome, ...’
T lymphocyte populations do not have clinical outcome.”

   Response:
   We changed the sentence to: “Patients with tumor infiltrating T lymphocyte populations are shown to have favourable clinical outcome, especially tumors with higher levels of CD8+ T lymphocytes are associated with better patient survival rates [27-29].”

2. Page 5, line 2:
   “…tumor infiltrating CD20+ B lymphocytes plays a role in anticancer immune responses...
   ... play a role ...”

   Response:
   We changed the sentence to: “Even though tumor infiltrating CD20+ B lymphocytes play a role in anticancer immune responses and are a common occurrence in breast tumors [9, 30], the role in patients’ clinical outcome is still unclear.”

3. Page 9, line 16:
   “CD8+ T lymphocytes were moderate dispersed within the T cell zone ...
   ... moderately”

   Response:
   We changed the sentence to: “CD8+ T lymphocytes were moderately dispersed within the T cell zone (Figure 2D).”

4. Table legends:
   “r#: phi. Better phi coefficient (or mean square contingency coefficient).”

   Response:
   The table legend for Table 3 and Table 4 has been changed from “r#: phi to r#: phi coefficient.”
Comments by the referee 2:
1. The paper is acceptable in its present form; however, I think that adding TIL evaluation would add value.

Response:
We agree that the presence of TILs in human breast tumors are interesting. In our study we have observed and categorized various degrees of infiltration of tumor associated lymphocytes (presented in table 3). The scope of this article was, however, to study the formation of TLS and its association with clinico-pathological parameters.

We thank you again for providing us with the opportunity to revise the manuscript and we hope that our revisions meet the requests from the reviewers.

Sincerely,

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