Evaluation of tumor-infiltrating lymphocytes in breast cancer; proposal of a simpler method

The publication by Salgado et al. [1] on evaluating tumor-infiltrating lymphocytes (TILs) in breast cancer (BC) is very important, and we admire their effort in seeking a consensus on standardized methodology in this field. However, we found some concerns in following their recommendations.

First, the method is too detailed to use routinely. We evaluated TILs on full-face slides from 20 randomly selected ER-negative BC samples resected at Matsuyama Red Cross Hospital (ethics committee approval, #446). On average, two board-certified pathologists needed 9.3 min (AIH) and 3.0 min (YO) to follow their procedure, which differed because of the extent of their assessments.

Second, low- and high-magnification assessments conflicted. As the paper instructed, AIH evaluated TILs on both low- (×40, in three groups of minimal, intermediate and high scores) and high-power fields (×200, by continuous percentage). Of these 20 cases, 3 had discordant results (supplementary Table S1, available at Annals of Oncology online), the correct values of which were unclear.

Third, we have a fast, practical and simpler method. From the Sagara Hospital database, we retrieved 164 consecutive specimens of triple-negative BC (TNBC) treated with curative surgery and standard adjuvant chemotherapy (ethics committee approval, #14-06). We screened representative full-face slides for hot spots on a low-power field, and then evaluated TILs on a medium-power field (×100). Percentages of area infiltrated by lymphocytes within the tumor itself plus adjacent stroma were defined as low (<10%), intermediate (10%–50%) or high (>50%) TILs. The invasive edge was included, but the tertiary lymphoid structures in the surrounding area of the tumor and lymphoid aggregates around intraductal components were excluded as instructed by Salgado et al. At the median follow-up period of 36 months, overall survival analysis (log-rank) shows TILs to be prognostically significant (Figure 1).

This simple method took us (AIH and YO) much less time (mean: 5.7 min/10 cases). Assuming a pathologist’s salary in Japan is US$10 000/month, their time costs ~US$63/h [2]. Therefore, at 6.2 min/case (on average) or US$65/10 cases, the cost of the recommended method is >10 times that of our simpler method (US$6/10 cases).

Simplicity is needed for a pathological methodology to be accepted widely. The easier method we propose has enough prognostic power for TNBC. Use of area percentage does not depend on tumor shape, although stromal TILs are difficult to estimate in diffuse tumors. Hot-spot evaluation is simple as it focuses on one representative area. However, average assessment will need more direction in defining the ‘average’; research and clinical practice may require different techniques. More efficient stratification of BC treatment also warrants further evidence.

In conclusion, progress on this methodology requires integrated discussion.

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