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Title: Recruitment of podoplanin positive cancer-associated fibroblasts in metastatic lymph nodes predicts poor prognosis in pathological N2 stage III lung adenocarcinoma

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Body: Background: Cancer-associated fibroblasts (CAFs) directly communicate with cancer cells and play important roles in cancer progression. Recent studies have reported that primary cancer tissue with podoplanin-expressing CAFs predicted a poorer outcome among stage I lung adenocarcinoma patients. However, whether podoplanin(+)-CAFs can also be recruited into metastatic lymph nodes and influence the prognosis remains unclear. Methods: We selected 112 patients with pathological N2 stage III lung adenocarcinoma and examined the podoplanin expression of CAFs and their prognostic impact in primary and metastatic N2 lesions. Results: A significant positive correlation was found in podoplanin expression in CAFs between pairs of primary and metastatic lesions ($P < 0.001$). The difference in the overall survival of patients with podoplanin-positive/negative CAFs in their primary lesion was not correlated ($P = 0.927$). In contrast, patients with podoplanin(+)-CAFs in metastatic lymph nodes had a shorter overall survival than those without podoplanin(+)-CAFs ($P = 0.003$). In multivariate analyses, podoplanin(+)-CAFs in metastatic lymph nodes were a significantly independent risk factor for a poor outcome ($P = 0.007$). Conclusions: Our study indicated podoplanin(+)-CAFs in metastatic lymph nodes was a significant prognostic factor for overall survival among pathological N2 stage III adenocarcinoma patients.