Comparative Analysis of Tumor Cell Dissemination to the Sentinel Lymph Nodes and to the Bone Marrow in Patients With Nonmetastasized Colon Cancer: A Prospective Multicenter Study

Benjamin Weixler, Carsten T Viehl, Rene Warschkow, Ulrich Gueller, Michaela Ramser, Rafael Sauter & Markus Zuber

Importance
Small nodal tumor infiltrates (SNTI; isolated tumor cells and micrometastases) in sentinel lymph nodes and bone marrow micrometastases (BMM) were independently described as prognostic factors in patients with colon cancer.

Objective
To examine the association between the occurrence of SNTI and BMM as well as their prognostic relevance.

Design, Setting, and Participants
This prospective study was conducted at 3 university-affiliated institutions in Switzerland between May 2000 and December 2006. Statistical analyses were performed in October 2016. A total of 122 patients with stage I to III colon cancer were included. Follow-up time exceeded 6 years, with no patients lost to follow-up.

Interventions
Bone marrow aspiration from the iliac crests and in vivo sentinel lymph node mapping were performed during open standard oncological resection. Bone marrow aspirates were stained with the pancytokeratin marker A45-B/B3. All sentinel lymph nodes underwent multilevel sectioning and were stained with hematoxylin-eosin and the pancytokeratin marker AE1/AE3.

Main Outcomes and Measures
Association of SNTI in sentinel lymph nodes and BMM in patients with stage I to III colon cancer and the prognostic effect on disease-free survival (DFS) and overall survival (OS).

Results
Of the 122 patients, 63 (51.6%) were female, with a mean (SD) age of 71.2 (11.7) years. Small nodal tumor infiltrates and BMM were found in a total of 21 patients (17.2%) and 46 patients (37.7%), respectively. The occurrence of
BMM was not associated with the presence of SNTI by standard correlation ($\kappa$, -0.07; 95% CI, -0.29 to 0.14; $P = .49$) nor by univariate logistic regression analysis (odds ratio, 0.64; 95% CI, 0.22-1.67; $P = .37$) or multivariate logistic regression analysis (odds ratio, 1.09; 95% CI, 0.34-3.28; $P = .88$). The presence of SNTI was an independent negative prognostic factor for DFS (hazard ratio [HR], 2.93; 95% CI, 1.24-6.93; $P = .02$) and OS (HR, 4.04; 95% CI, 1.56-10.45; $P = .005$), as was BMM (HR, 2.07; 95% CI, 1.06-4.06; $P = .04$; and HR, 2.68; 95% CI, 1.26-5.70; $P = .01$; respectively). The combined detection of BMM and SNTI demonstrated the poorest DFS (HR, 6.73; 95% CI, 2.29-19.76; $P = .006$) and OS (HR, 5.96; 95% CI, 1.66-21.49; $P = .03$).

Conclusions and Relevance
This study demonstrates no association between the occurrence of SNTI and BMM in patients with stage I to III colon cancer. However, both SNTI and BMM are independent negative prognostic factors regarding DFS and OS, and the occurrence of both is associated with significantly worse prognosis compared with either one of them.

Trial Registration
clinicaltrials.gov Identifier: NCT00826579.