**WSA Discussion of 2022-334**

**Colorectal Liver Micrometastases: Association with *RAS/TP53* Co-Mutation and Prognosis after Surgery**

**DR VALENTINE NFONSAM** (Tucson, AZ): This is a good manuscript addressing a very important topic regarding colorectal metastasis: micrometastases and their association with co-mutations of the specific genes *RAS* and *TP53*. We all know the liver is the most common site of metastasis for colorectal cancer. About 15%–25% of patients have synchronous metastasis and another 18%–25% develop it after initial presentation. Patients have significantly poorer survival if they have liver metastasis; about 11% in 5 years without liver resection. That is why this study is very interesting.

This study was conducted in 2 institutions. Only the largest tumors were sectioned and analyzed. Because there is primary tumor heterogeneity, which is reflected in the varied response to chemotherapy, what do you think of the validity of your results? And how could that be explained? Since you are sectioning only the large tumor and there is tumor heterogeneity, the response to chemotherapy is different.

How did the authors ensure that the 2-cm margin was achieved by all surgeons? How was that standardized? In addition, considering that more aggressive tumors tend to metastasize in a more aggressive manner, was there any consideration in correlating the tumor biology, which means the tumor differentiation, with micrometastases?

**DR YUN SHIN CHUN** (Houston, TX): You are correct that for patients with multiple tumors, we only evaluated the largest metastasis, which is a limitation of our study. Earlier studies have shown that the larger the tumor, the higher the incidence of micrometastases. Thus, by evaluating the largest tumor, we believe we have reasonably captured the presence of micrometastases surrounding smaller tumors.

Regarding tumors that do not have a 2-cm circumferential resection margin, we enrolled patients in whom we anticipated a 2-cm circumferential margin, and in situations where that was not possible, we cut the resected specimen as far out radially as we could. Earlier studies have shown that micrometastases tend to occur close to the gross tumor, within millimeters. Therefore, we believe our method identified most micrometastases.

As to correlating tumor biology with micrometastases, we did not specifically look at tumor grade. Our previous study on resection of colorectal liver metastasis showed that *RAS/TP53* co-mutation was a surrogate marker of tumor biology and stronger predictor of survival compared with other clinical and pathologic factors.

**DR ERNEST MOORE** (Denver, CO): My recent reading suggests that there is ongoing work to determine the regulation of the so-called tumor microenvironment, and specifically suppression of T cells via expression of the PD-L1 ligand. What is the status of immunotherapy with respect to tumor recurrence?

**DR YUN SHIN CHUN** (Houston, TX): Immunotherapy has not been effective for colorectal cancer that is not microsatellite instability (MSI)-high for various reasons we are learning more and more about. We are conducting clinical trials for non-MSI high patients where we are trying to regulate the tumor immune environment to render immunotherapy more effective.

**DR SKYE MAYO** (Portland, OR): I think in hepatobiliary oncology, we have this problem of under-staging our patients and this micrometastatic disease burden that exists; when we take the patient to the operating room and say that they “have a recurrence,” where it is just progression of this micrometastatic disease that you see. With more sensitive modalities coming out, PET/MRI with Eovist, etc, do you think this will improve our ability to detect metastases and better risk stratify these patients? We have 2 Phase III randomized trials, EORTC 40983 and the recently reported JCOG 06 trial, showing no overall survival benefit of chemotherapy for patients who have resectable colorectal liver metastasis, just progression-free survival. So how do we incorporate your findings with this? Should these patients be selected for liver-directed therapy like hepatic artery infusion to help treat this micrometastatic disease burden? Should they be profiled up front with this for selection?

**DR YUN SHIN CHUN** (Houston, TX): I think one of the issues with randomized trials is how one defines “resectable.” Much of our patient population is borderline resectable, and for those patients, I do not think there is a debate around administering neoadjuvant chemotherapy.

Regarding better ways to stage patients and identify micrometastases preoperatively, we currently do not have radiologic studies that can detect micrometastases, but we are using more and more circulating tumor DNA. That may be a very promising method in the future to identify patients who have more disease than we think we see on CT scans.

**DR C MAX SCHMIDT** (Ann Arbor, MI): The survival rate was dramatically different between the micrometastatic and non-micrometastatic. How variable was survival in the micrometastatic group? Often, you will see a lot of variability. If it was homogeneous and not variable, in terms of re-resection strategies, we are often asked to consider re-resection in these patients who have a recurrence. Should we say “no,” if they had micrometastatic disease in the first resection?

**DR YUN SHIN CHUN** (Houston, TX): It was homogeneous. If you had micrometastases, the recurrence rate was high across the board. We have not looked at patients with micrometastases who develop recurrent liver metastases, as to whether any of them have had re-resection. That would be very interesting to look at.

**DR DAVID NAGORNEY** (Rochester, MN): Have your findings changed your post-resection treatment strategies?

**DR YUN SHIN CHUN** (Houston, TX): That is an excellent question, do we need to rethink intrahepatic arterial chemotherapy for patients with micrometastases?