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Commentary: Circulating tumor components: Does surgical manipulation increase the risk of metastasis?

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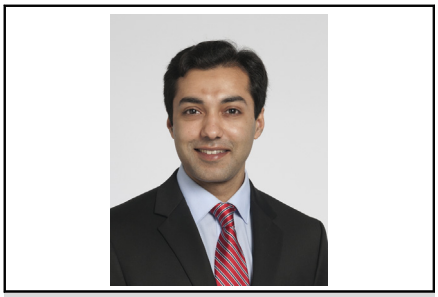

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Detection of circulating tumor components has gained significant traction over the last several years. The utility of circulating tumor DNA (ctDNA) has allowed for tumor detection and longitudinal surveillance after treatment, leading to the concept of liquid biopsy.[1] The role of ctDNA in disease management continues to evolve and will likely hold significant importance as the technology advances.

This is in contrast to study of circulating tumor cells, which has gone in and out of favor over the last 2 decades due in part to the rarity of circulating tumor cells as well as difficulty in detection. There is increasing evidence that the presence and burden of circulating tumor cells has been associated with progression-free survival and overall survival in patients with lung cancer.[2] In addition, the presence of circulating tumor cells in the pulmonary veins at the time of resection has been associated with a high risk of recurrence.[3]

Nonetheless, it remains unclear whether surgical manipulation of the tumor or organ increases the risk of metastases or, in other words, alters disease biology and progression. Wei and colleagues[4] tested the presence of circulating tumor cells in arterial circulation in patients who underwent lung resection. They compared the tumor cell burden in patients who underwent pulmonary inflow ligation first and patients who had pulmonary outflow ligation as the first step. In their study population, the overall circulating tumor cell burden was relatively low compared with what others have reported.

CENTRAL MESSAGE

Whether or not surgical manipulation of a tumor increases the risk of shedding tumor components into the bloodstream, their detection has the potential to alter clinical management.

Whether this is a function of the testing method or of the sampling method, with samples taken from peripheral arterial circulation, is unclear, making interpretation of the results more challenging. It is interesting to note that this study included patients with nodal disease, the effect of which likely overshadows the effect of tumor manipulation. Dr Wakeam and colleagues have provided an in-depth review of the findings of the study along with its shortcomings.[5] Any future study addressing this particular question should take their critique into account.

The idea of decreasing surgical manipulation of tumors in order to avoid risk of metastases or the so-called "no touch" technique has been part of surgical mantra for a long time. The concept studied by Wei and colleagues goes a step further and proposes outflow ligation before manipulation or resection. Although in theory this is a viable concept and "couldn't hurt," it is not really supported by the existing evidence. In the study of resectable lung cancer, surgical resection has never been identified as a risk factor for local or systemic recurrence, as would be the case if surgical manipulation led to increased viable micrometastases. Moreover, in a dynamic organ like the lung, tumor manipulation may theoretically occur with any vigorous change in fluid movements through the organ and tumor. Exercise-induced pulmonary arterial pressure elevation, manipulation during biopsy, and deflation of the lung during resection could potentially have effects similar to surgical manipulation of the tumor. How much effect, if any, these manipulations have on mobilizing tumor components into

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systemic or lymphatic circulation is of unknown clinical significance.

Regardless of the degree of manipulation during resection, the more clinically relevant question is how to reliably detect persistent or recurrent disease. Circulating tumor DNA found after resection of the primary tumor can be used to monitor radiographically undetectable residual disease or what is known as minimal residual disease.[6] The presence of minimal residual disease has been shown to correlate with clinical radiographic recurrence at a later stage and perhaps can be used to guide adjuvant therapy. In the current area of targeted therapy and individualized cancer care, it is important to agree on a reliable and reproducible circulating tumor marker, be it tumor cells or their representative components.

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