Editorial

What's in a (tumor) cavity?

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Cavity formation, or cavitation, is a recognized feature of lung cancer, typically occurring spontaneously in squamous cell carcinomas. One large study found that approximately one-sixth of primary bronchial carcinomas demonstrated cavitation (1). After treatment with angiogenesis inhibitors, other lung cancer types, for example adenocarcinomas, and tumors metastatic to the lung, can also cavitate. The prognostic and therapeutic implications of cavitation are controversial, since some studies have shown a positive association of outcomes with cavitation (2), others not (3,4), whereas others have found a marginal association of cavitation with outcome (5).

The vascular endothelial growth factor (VEGF) family of growth factor receptors have marked effects on vascular endothelium, notably regulating their growth and the proliferation of new vessels (i.e., angiogenesis). Angiogenesis is a cardinal feature and prerequisite of malignant tumor growth, and its inhibition is thus a key therapeutic strategy in oncology. Receptor tyrosine kinase (RTK) inhibitors have shown great efficacy as targeted anticancer agents, including the angiogenesis inhibitors, bevacizumab and apatinib. The former has been more extensively evaluated. In one study of 72 non-small-cell lung cancer (NSCLC) patients treated with bevacizumab, 19% developed tumoral cavitation, but no differences were seen in either progression-free survival (PFS) or overall survival (OS) between those with cavitation or not (4). Other antiangiogenesis agents have also been evaluated in NSCLC; Marom *et al.* [2008] (3) found that 17 of 124 (14%) NSCLC cases developed cavitation after a variety of angiogenesis inhibitors, whereas Crabb *et al.* [2009] (5), observed that 24% of cases receiving an angiogenesis inhibitor and platinum-based chemotherapy developed cavitation.

In a recent study published in *Transl Lung Cancer Res*, Jiang *et al.* [2019] (6) set out to study the relationship between cavitation induced by apatinib and clinical endpoints, in particular locoregional control (LRC), PFS and OS. Additionally, they performed some laboratory experiments aimed at better understanding the mechanism of action of apatinib. They had substantial patient numbers in this retrospective study, including patients with NSCLC and gastric cancer metastatic to the lungs (which they refer to, somewhat confusingly, as metastatic lung cancer patients). Baseline cavitation frequencies nor the percent of apatinib-associated cavitation, were not stated. In both cancer categories, the presence of cavitation was associated with improved outcomes (LRC, PFS and OS). Although a single-institution retrospective study, these data add to a growing body of literature indicating that tumors in the lungs demonstrating cavitation, either *de novo* or after antiangiogenesis therapy, may have prognostic implications (2,5). However, the authors did not put forward a hypothesis as to why cavitation should confer positive anticancer benefits, or whether it was likely to be simply a marker for some biological process that may or may not be linked to tumor behavior.

Commendably, the authors investigated the potential mechanism of action of apatinib, using an innovative *in*

vivo zebrafish angiogenesis system. To do this they utilized two different tumor model cell lines, one, the H1299 line (derived from a NSCLC nodal metastasis), the other, the SCG7901 line (derived from a gastric adenocarcinoma). In both systems, apatinib inhibited vascular growth and mediated some cellular proliferation suppression. These results were not unexpected, since a number of studies have shown that apatinib inhibits cell proliferation and angiogenesis [e.g., (7)]. However, cavitation was not able to be studied in this system, so its direct potential relationship to apatinib exposure remains unclear.

The authors performed some molecular analyses (Western blots), which were not strongly justified nor their rationale explained. Quantitative analyses and mRNA studies would have strengthened this section of the manuscript. Furthermore, in addition to the VEGF2 RTK, apatinib is also an inhibitor, albeit weaker, of c-kit and c-SRC RTKs, and PDGFR-β. It would have been much more informative to observe the effects of apatinib/hypoxia on the levels/activation of these kinases.

The study of Jiang *et al.* [2019] is a very worthwhile addition to the literature on the association between antiangiogenesis agents, in this case apatinib, and cavitation of tumors in the lung. Its main strength is in the clinical outcome findings, which no doubt should be further evaluated prospectively in multicenter biomarker studies with greater follow up durations.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Chaudhuri MR. Primary pulmonary cavitating carcinomas. Thorax 1973;28:354-66.
2. Huang C, Wang X, Wang J, et al. Incidence and clinical implication of tumor cavitation in patients with advanced non-small cell lung cancer induced by Endostar, an angiogenesis inhibitor. Thorac Cancer 2014;5:438-46.
3. Marom EM, Martinez CH, Truong MT, et al. Tumor cavitation during therapy with antiangiogenesis agents in patients with lung cancer. J Thorac Oncol 2008;3:351-7.
4. Nishino M, Cryer SK, Okajima Y, et al. Tumoral cavitation in patients with non-small-cell lung cancer treated with antiangiogenic therapy using bevacizumab. Cancer Imaging 2012;12:225-35.
5. Crabb SJ, Patsios D, Sauerbrei E, et al. Tumor cavitation: impact on objective response evaluation in trials of angiogenesis inhibitors in non-small-cell lung cancer. J Clin Oncol 2009;27:404-10.
6. Jiang M, Zhang C, Liu D, et al. Influence and mechanism of lung cavitation development on antiangiogenic therapy. Transl Lung Cancer Res 2019;8:500-12.
7. Tian S, Quan H, Xie C, et al. YN968D1 is a novel and selective inhibitor of vascular endothelial growth factor receptor-2 tyrosine kinase with potent activity in vitro and in vivo. Cancer Sci 2011;102:1374-80.

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