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## Antiangiogenic therapy elicits malignant progression of tumors to increased local invasion and distant metastasis.

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### Abstract

Multiple angiogenesis inhibitors have been therapeutically validated in preclinical cancer models, and several in clinical trials. Here we report that angiogenesis inhibitors targeting the VEGF pathway demonstrate antitumor effects in mouse models of pancreatic neuroendocrine carcinoma and glioblastoma but concomitantly elicit tumor adaptation and progression to stages of greater malignancy, with heightened invasiveness and in some cases increased lymphatic and distant metastasis. Increased invasiveness is also seen by genetic ablation of the Vegf-A gene in both models, substantiating the results of the pharmacological inhibitors. The realization that potent angiogenesis inhibition can alter the natural history of tumors by increasing invasion and metastasis warrants clinical investigation, as the prospect has important implications for the development of enduring antiangiogenic therapies.

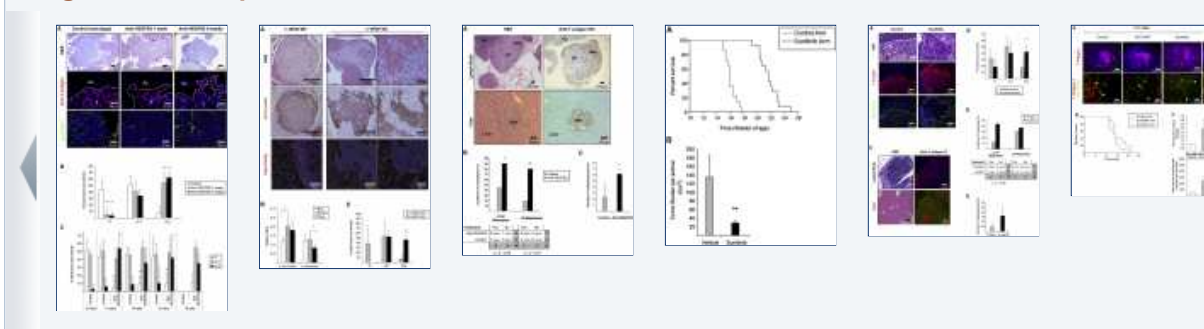
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