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LETTER – GASTROINTESTINAL ONCOLOGY

Anti-VEGF Therapy in the Treatment of Unresectable Appendiceal Epithelial Neoplasms

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DEAR EDITOR

We read with interest the article by Choe et al. entitled "Improved Survival with Anti-VEGF Therapy in the Treatment of Unresectable Appendiceal Epithelial Neoplasms" published early online in *Annals of Surgical Oncology*.[1] The authors reported a 34-month improvement in overall survival with addition of anti-vascular endothelial growth factor (VEGF) therapies to cytotoxic chemotherapy (CT) in patients with unresectable appendiceal neoplasms. However, as we noticed in Table 1 (and also stated by the authors in their discussion), 95% of patients who received a biologic agent were treated with doublet chemotherapy (fluoropyrimidine plus oxaliplatin/irinotecan) while only 40% of patients in the "non-biological group" received doublet chemotherapy. Benefit of adding oxaliplatin or irinotecan to a fluoropyrimidine had previously been shown in phase III studies in colorectal cancer in terms of progression-free survival (PFS) or overall survival (OS).[2–4] Therefore, differences in the chemotherapy backbone might also account for such an outstanding difference in PFS and OS between the treatment groups in the present study. The authors state that comparison of CT backbones was not the purpose of this study and that the same treatment principles of colorectal cancer would not be applicable to appendiceal cancer, however such discordance in the frequency of doublet CT use will probably confound the treatment effect of biological agents and should at least be included in the multivariate analysis to refine the benefit of biological agents. The multivariate analyses presented in Tables 2 and 3 are not useful in this sense, as they report neither the effect of the CT regimen (single agent versus doublet) nor, very interestingly, the effect of anti-VEGF therapy. In fact, it is very confusing to not be able to find a mention of the primary study parameter in the tables of a manuscript presenting multivariate analyses.

That being the case, proposing an improvement in OS and PFS with bevacizumab without refining the confounding effect of CT backbone is probably misleading. Addition of the CT regimen type to the multivariate analysis might probably extenuate, if not eliminate, the magnitude of the benefit of anti-VEGF therapy and might provide a better message for readers until randomized trials with bevacizumab are conducted in this patient population.

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