



Pathologic complete response is not equivalent to cure in esophageal cancer

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We thank the authors of the editorial commentary entitled “*Recurrence in complete responders after trimodality therapy in esophageal cancer*”, for their thoughtful review and critical appraisal of our manuscript. Our study examined recurrence in patients with esophageal cancer (EC) that achieved pathologic complete response (pCR) following trimodality therapy, with the aim of evaluating potential predictors of recurrence.

The first question presented by this editorial was the role of signet ring cell (SRC) histology in esophageal adenocarcinoma (EAC), as it has been shown to be an important predictor of poor prognosis in patients with advanced stage gastric adenocarcinoma (1). SRC is a rare histological subtype of EAC, and while the role of SRC remains controversial, several studies have shown that it is associated with a higher tumor grade, lower incidence of pCR, and worse prognosis (2-5). Our results did not find statistically significant difference in rate of recurrence when examining EAC patients with SRC as compared to those without SRC. Although not reported in the manuscript, we evaluated the variable SRC as a risk factor for recurrence in our univariate and multivariate analysis and the rate of recurrence was not significantly higher among the 29 patients with SRC histology (12.4%). However, our results may be limited by small study numbers, which may be confounded by the fact that patients with SRC are less likely to achieve pCR. More research is needed in this area to determine if patients with SRC in EAC require different

treatment strategies.

Regarding the radiation dose used, we completely agree with the authors that high doses of radiation only increase the risk of complications without any advantage for local control or cure rates. This is well described by Radiation Therapy Oncology Group (RTOG) 94-05 (6). For this reason, we mainly use 5,040 cGy as an induction as well as definitive dose. However, we included this variable in our multivariate analysis, even if not significant in the univariate analysis, because we considered the dose of radiation a clinically relevant variable that might have affected recurrence rate. While our group did not specifically examine specific doses of radiation in this study, recent publications have shown comparable results in terms of survival and pCR even with lower dose of radiation, suggesting that the optimal dose of radiation maybe be lower than current clinical guidelines (7).

Due to the rapid increase of EAC incidence in the US, this editorial highlighted the importance of predicting recurrence in this population. Further research by our group examining incidence of brain metastasis suggests that pCR may be a risk factor for isolated brain metastasis following curative resection. Mirroring our findings, a recent cohort study published by MD Anderson Cancer Center also report data suggesting that pCR may be a risk factor for brain metastasis (4). While surgical resection of isolated brain metastasis is well described in lung cancer, this has not been well described in EC. Recently a

systematic review examining isolated organ recurrence in EC suggested that there may be a survival benefit to surgical resection of isolated brain metastasis with the caveat that additional research is needed in this area (8).

We appreciated the clear and concise summary of the central message of our study by Bouabdallah *et al.* The histology of EC is of vital importance, such that moving forward, we believe that EAC and esophageal squamous carcinoma (ESCC) should no longer be considered together in research studies and clinical trials. EC is an aggressive disease and a more intensive surveillance paradigm (and perhaps treatment) might improve outcomes. Quadrimodal therapy consisting of induction chemotherapy followed by concurrent chemoradiotherapy and then surgery may be indicated for select patients, as several studies examining the role of induction chemotherapy in EC have shown increased rates of pCR and improved disease-free survival in high risk patients (9,10). Induction treatment cannot make up for bad surgical resection and we agree that extended lymphadenectomy (especially but not only for ESCC) improves the likelihood for long term survival.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are 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.

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