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Key Words: esophageal carcinoma, residual primary cancer, induction therapy, survival

EDITORIAL COMMENTARY

For esophageal cancer, biology is still king

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It has long been known that pathologic response complete (pCR) to induction therapy represents the best scenario for long-term survival in patients with advanced esophageal cancer. In a randomized study published in 2001, Urba and colleagues¹ reported a pCR rate of 28%, with a 64% 3-year survival for those achieving pCR after induction chemoradiation. In this issue of the *Journal*, Raja and colleagues² go further with this concept, reporting a linear trend of worsening survival with increasing residual cancer after induction therapy. The authors also evaluated the predictors of residual cancer and the predictors of survival by using Random Forest technology, a nonparametric analysis that better identifies and handles complex interactions among variables in the study of esophageal cancer. This similar statistical analysis was used to develop

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Central Message

In advanced esophageal cancer, response to induction therapy correlates with survival; however, the biology that determines the degree of this response continues to require study.

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the American Joint Committee on Cancer seventh edition staging for esophageal cancer.³

Readers of this article may question the applicability of this study to their own practice of managing patients with advanced esophageal cancer. The 2 induction treatment

strategies used in this study by Raja and colleagues² are not common regimens, that is, preoperative chemoradiation to only 30 Gy (78% of the cohort) or preoperative chemotherapy alone (22% of the cohort), with both groups also receiving various regimens of postoperative therapy (adjuvant chemoradiation, adjuvant chemotherapy alone, adjuvant radiation alone, or no adjuvant therapy at all).

Readers of this article also may be confused by the data presented, specifically the data showing that tumor response to induction treatment predicts survival and that induction chemoradiation (vs chemotherapy alone) predicts a greater response, however surprisingly the type of induction therapy (chemoradiation vs chemotherapy alone) was not an important predictor of survival. Again, the uncommon induction regimen used in this study may contribute to this discrepancy, because the low pCR rate of 10% is a reflection of the low preoperative radiation dose delivered or no preoperative radiation delivered at all.

Despite the manuscript's limitations, it is not the details of the induction therapy on which one should focus but rather the message delivered from the main finding of this study, that no matter what the induction regimen may be, the increase in response to induction therapy corresponds to a linear increase in survival. This result serves to remind us that we must strive constantly to develop therapeutic strategies that increase response and hence improve survival. Currently for advanced esophageal cancer, triple modality therapy (chemotherapy, radiation to 40-50 Gy, followed by surgery) is viewed by many as the optimal treatment, especially with the publication of the randomized Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) trial in 2012.⁴ Still, the pCR rate from this trial was no greater than 30%, similar to that reported more than 10 years earlier by Urba and colleagues.¹ Thoracic surgeons and oncologists continue

to search for the "Holy Grail," trying to unravel the biologic mystery as to why one tumor may have a superior response to induction therapy over another. Current clinical trials are now examining targeted molecular therapies. The Radiation Therapy Oncology Group (RTOG) 1010 randomizes patients with overexpressed HER2 esophageal adenocarcinoma to triple-modality therapy with or without trastuzumab. Other trials currently under consideration involve the study of immune check point inhibitors.

In his Presidential Statement almost 20 years ago, surgical oncologist Dr Blake Cady⁵ stated, "biology is King, selection is Queen, technical maneuvers are the Prince and Princess; occasionally the Prince or Princess tries to usurp the throne; they almost always fail to overcome the powerful forces of the King and Queen." The results from this study by Raja and colleagues² remind us that our current treatment, the Prince or Princess, continues to lag far behind from the King and that we must constantly strive to close this gap. Then, maybe one day, the Prince and Princess can rise to the level of the King and proclaim cure for this devastating malignancy.

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