Pathologic complete response after esophagectomy following neoadjuvant chemoradiation therapy for esophageal carcinoma: A cure sometimes?

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Central Message

A pathologic complete response after esophagectomy following neoadjuvant chemoradiation therapy for locally advanced esophageal carcinoma is not synonymous with cure.

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A pathologic complete response after esophagectomy following neoadjuvant therapy for locally advanced esophageal carcinoma is not synonymous with a cure. Although a pathologic complete response is associated with improved overall and disease-free survival rates, about 20% to 40% of patients will have a recurrence,¹⁻³ most within the first 2 years.⁴ To paraphrase Hippocrates, although we often treat, we only sometimes cure.

In this edition of the *Journal*, Barbetta and colleagues¹ report a single-institution retrospective review of 233 patients with stage II or III esophageal cancer who underwent esophagectomy after neoadjuvant chemoradiation therapy during a 10-year period and were found to have had a pathologic complete response. This is an important study, with relevance to the everyday clinical practice of esophageal surgeons. Although the recurrence and disease-free survival rates are similar to those in other studies, there are several unique, salient findings of this study worth discussing.

First, as shown by the Kaplan-Meier curves, risk is not constant – it changes throughout the course of follow-up. Indeed, although 26.2% of patients in this study had a recurrence, most (73%) recurrences were within the first 2 years. Although simply hypothesis generating and neither the intent of the study nor supported by its data, perhaps patients with a pathologic complete response should undergo a more intensive surveillance program, such as cross-sectional surveillance imaging every 3 months, for the first 2 years after esophagectomy. Further studies are needed to ascertain whether early detection of recurrence in such patients affects survival.

Second, few studies have examined risk factors for recurrence after a pathologic complete response. Barbetta and colleagues⁵ found that poor tumor differentiation is independently associated with an increased risk of recurrence. Similar to other studies, most (72%) of the recurrences were distant metastases, implicating a need for better

systemic tumor control. The only cohort of patients proven to benefit from adjuvant chemotherapy after esophagectomy following neoadjuvant chemoradiation therapy are those patients with residual nodal disease.⁶ Perhaps consideration should also be given to placing patients with poorly differentiated tumors that had a pathologic complete response to neoadjuvant therapy on a course of standard systemic therapy or single-agent maintenance therapy after esophagectomy to mitigate this risk. A clinical trial to test this hypothesis is needed.

Finally, this and other recent studies have demonstrated a surprising number (25%-30%) of patients with a pathologic complete response develop brain metastases. Although not currently included in National Comprehensive Cancer Network guidelines for posttreatment surveillance, this study suggests that routine cross-sectional brain imaging should be considered for patients with esophageal adenocarcinoma who have had a pathologic complete response.

Outcomes after esophagectomy have been “the tale of men repeatedly losing to a stronger adversary yet persisting in an unequal struggle until the nature of the problem became apparent and the war was won.”⁷ Indeed, despite numerous contemporaneous improvements in patient care, survival for patients with esophageal cancer has improved little during the past several decades. The knowledge that we gain from studies such as that of Barbetta and

colleagues⁵ should help us to evolve our patient care strategies and make strides against this disease.

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