

The effect of time interval on esophagectomy after neoadjuvant treatment

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Abstract: “Esophagectomy timing after neoadjuvant therapy for distal esophageal adenocarcinoma” published in the *Annals of Thoracic Surgery* (doi: 10.1016/j.athoracsur.2015.09.044) states that 30- and 90-day mortality after esophagectomy for adenocarcinoma in patients with neoadjuvant chemoradiation, is significantly higher in patients with a postradiation interval of 9 weeks or more. The authors suggest that a “wait and see” approach after neoadjuvant therapy for esophageal adenocarcinoma may not be safe.

Keywords: Esophageal cancer; adenocarcinoma; neoadjuvant therapy; esophagectomy

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The optimal time interval of esophagectomy after neoadjuvant therapy for locally advanced esophageal adenocarcinoma remains largely unknown. Several prospective randomized trials describe a time interval of 3–8 weeks between neoadjuvant therapy and esophagectomy (1-3). Extremely prolonged observation after neoadjuvant therapy may lead to salvage esophagectomy which was reported to have a 3-fold increase in perioperative mortality (4). Esophagectomy timing after neoadjuvant therapy has been examined in a few retrospective analyses, with divergent conclusions (5-8).

This study investigated the influence of esophagectomy timing in patients with invasive distal esophageal adenocarcinoma undergoing neoadjuvant therapy.

From the National Cancer Data Base (NCDB) 4,284 cases of invasive distal esophageal adenocarcinoma (invasive adenocarcinoma, mucinous adenocarcinoma and signet ring cell carcinoma) treated within 26 weeks after neoadjuvant chemoradiation and diagnosed between 2003 and 2011 were included. Primary outcome measures were 30- and 90-day postintervention mortality and overall survival. Secondary objectives were rates of ypT0, ypN0, and margin-negative resections.

The average postradiation interval until esophagectomy was 7.8±3.4 weeks (median, 7.1 weeks; interquartile range,

5.7–9 weeks). The group was divided in quartiles at several clinically meaningful cutoff levels: 5 weeks (approximately 25th percentile), 7 weeks (50th percentile), and 9 weeks (75th percentile).

Thirty- and 90-day mortality were respectively 2.9% (n=127) and 7.8% (n=336). A postradiation interval of 9 weeks or longer, the highest household income quartile, and age were significantly associated with the odds of 30- and 90-day mortality.

Overall median survival was 33.5 months after diagnosis (95% CI, 32–34.7 months), and the 5-year survival rate was 31.6% (95% CI, 29.5–33.8%). Individual median survival was 35.5, 35.2, 34.1, and 28.2 months for those with postradiation intervals <5, ≥5 and <7, ≥7 and <9, and 9 weeks or longer, respectively. Corresponding 5-year overall survival rates were 35.0%, 32.3%, 30.9% and 29.1%, respectively.

Dichotomization of the Kaplan-Meier curves of the entire study population at 9 weeks resulted in a univariate hazard ratio of 1.21 (P<0.001) in favour of the shorter time interval.

In the multivariate analysis comorbidity, clinical nodal status and a postradiation interval of 9 weeks or longer were significantly associated with higher risk of death and patients with a median annual household income of more than \$63,000 with a lower risk of death.

The proportion of patients with complete histologic

response of the primary tumor increased with a longer waiting period. Negative resection margins did not differ according to the length of postradiation delay.

Based on these results in this very large sample size, the authors correctly warn for “watch and wait” regimens for distal esophageal adenocarcinoma although they also found that longer waiting periods were associated with an increased incidence of ypT0 and ypN0. Similar findings were described in a recently published meta-analysis on 1,016 patients (squamous cell and adenocarcinoma) with time interval cutoff of 7–8 weeks: non-significant trend toward increased postoperative mortality, significantly worse 2-year overall survival and non-significant trend toward worse 5-year overall survival in the longer time interval. However, this study did not find a difference in ypT0N0) (9).

The authors conclude that perioperative mortality and overall survival among patients with distal esophageal adenocarcinoma undergoing neoadjuvant therapy and esophagectomy are associated with the length of the interval between chemoradiation and esophagectomy, but causality cannot be evaluated. Indeed the role of the reason of a longer time interval (e.g., physical and nutritional status and recovering from neoadjuvant therapy and its possible adverse events) needs to be further investigated in prospective studies.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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