Importance of residual primary cancer after induction therapy for esophageal adenocarcinoma

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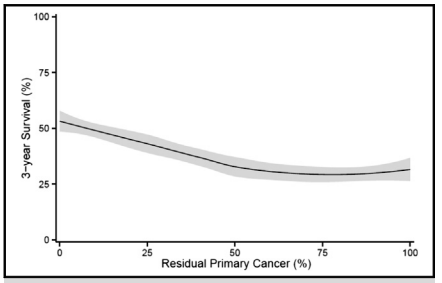
ABSTRACT

Objectives: To (1) assess the continuous distribution of the percentage of residual primary cancer in resection specimens after induction therapy for locally advanced esophageal adenocarcinoma, (2) determine the effects of residual primary cancer on survival after esophagectomy, (3) ascertain interplay between residual primary cancer and *classical* classifications of response to induction therapy (ypTNM), and (4) identify predictors of residual primary cancer.

Methods: From January 2006 to November 2012, 188 patients (78%) underwent accelerated chemoradiotherapy, and 52 patients (22%) underwent chemotherapy alone followed by esophagectomy for adenocarcinoma. Mean age was 61 ± 9.2 years, and 89% were male. Residual primary cancer, assessed as the percentage of residual primary cancer cells in resection specimens, was quantified histologically by a gastrointestinal pathologist. Random Forest technology was used for data analysis.

Results: Twenty-five specimens (10%) had no residual primary cancer (ypT0), 79 (33%) had 1% to 25% residual cancer, 91 (38%) had 26% to 75%, and 45 (19%) had >75%. Survival was worse with increasing residual primary cancer, plateauing at 75%. Greater residual primary cancer was associated with worse survival across the spectrum of higher ypTN. Higher ypT, larger number of positive nodes, and use of induction chemotherapy rather than induction chemoradiotherapy were associated with greater residual primary cancer.

Conclusions: Less residual primary cancer in response to preoperative therapy is associated with a linear increase in survival after esophagectomy for locally advanced esophageal adenocarcinoma; however, survival is poorer than for resected early-stage cancers. Therefore, for patients with poor prognostic indicators, including higher percentage of residual primary cancer, the role of adjuvant therapy needs to be further examined in an attempt to improve survival. (J Thorac Cardiovasc Surg 2016;152:756-61)



Predicted 3-year survival according to percentage of residual primary esophageal adenocarcinoma.

Central Message

Increasing amount of residual primary cancer after induction therapy is associated with worsening survival in esophageal adenocarcinoma.

Perspective

In the 7th edition of the *American Joint Committee on Cancer Staging Manual*, pathologic staging for adenocarcinoma of the esophagus inaccurately predicts survival for responders to induction therapy. This study describes the utility of residual primary cancer as a prognostic indicator for these patients.

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Patients with esophageal adenocarcinoma responding to induction therapy (cancer downstaged) have better survival than nonresponders,[1,2] and those with <50% residual primary cancer in resection specimens are reported to have better survival than those with >50%.[3] However, percentage of residual primary cancer is a continuous variable. Thus, the objectives of this study were to (1) assess the continuous distribution of the percentage of residual primary cancer in resection specimens after induction therapy for locally advanced esophageal adenocarcinoma, (2) determine the effects of residual primary cancer on survival after esophagectomy, (3) ascertain the interplay between residual

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Abbreviation and Acronym
VIMP = variable importance

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primary cancer and *classical* classifications of response to induction therapy (ypTNM), and (4) identify predictors of residual primary cancer.

PATIENTS AND METHODS

Study Population

From January 2006 (when local recording of residual primary cancer was histologically standardized) to November 2012, 240 patients underwent induction therapy followed by esophagectomy for adenocarcinoma; 188 (78%) received accelerated chemoradiotherapy and 52 (22%) chemotherapy alone (Tables 1, 2, and E1). Of note, 17 patients had ypT4 or ypM1 disease. Patients with ypT4a disease had invasion of the diaphragm or direct invasion of the stomach distal to the primary cancer; those with ypT4b had invasion of either the airway or aorta. Patients with M1 disease had peritoneal nodules identified during resection at a point when the procedure could not be aborted; cM1 disease had not been identified. The Cleveland Clinic Institutional Review Board approved use of these data for research, with patient consent waived.

Preoperative and Postoperative Therapy

One hundred and eighty-eight patients received accelerated preoperative (induction) chemoradiotherapy, consisting of 4 days of cisplatin (20 mg · m^{-2} · d^{-1}) and fluorouracil (1000 mg · m^{-2} · d^{-1}), and concurrent hyperfractionated radiation therapy (1.5 Gy twice daily to a total dose of 30 Gy).[4] Of these, 127 received a similar course of postoperative (adjuvant) chemoradiotherapy; 1 patient received adjuvant chemotherapy alone, 2 adjuvant radiotherapy alone, and 58 no adjuvant therapy.

Fifty-two patients received 3 courses of induction chemotherapy, consisting of epirubicin (50 mg · m^{-2}) and oxaliplatin (130 mg · m^{-2}) on day 1 and fluorouracil (200 mg · m^{-2} · d^{-1}) as a continuous intravenous infusion for 21 days.[5] Cycles were repeated every 3 weeks. Of these, 39 received adjuvant chemoradiotherapy, consisting of 2 cycles of cisplatin (80 mg · m^{-2}) and fluorouracil (4000 mg · m^{-2}), and concurrent radiation therapy to a total dose of 50-55 Gy; 1 patient received adjuvant chemotherapy alone and 12 no adjuvant therapy.

Follow-up

Median follow-up was 1.1 years. Median follow-up for surviving patients was 1.7 years, with 25% followed more than 3.0 years and 10% more than 4.8 years. Median potential follow-up, if there were no deaths, was 2.3 years (25% more than 3.5 years and 10% more than 5.8 years).[6]

Pathologic Analysis

Residual primary cancer was measured by percentage of residual primary cancer cells in the resection specimen. Esophagectomy specimens were examined by pathologists specializing in gastrointestinal pathology. Specimens were evaluated using light microscopy after hematoxylin and eosin staining. A minimum of 4 blocks of the primary cancer were examined, but this number increased with increasing cancer size. Percentage of residual primary cancer cells was scored in accordance with previously published histologic criteria that were standardized by a gastrointestinal pathologist (J.R.G.),[7] but using 1% increments for values 0% to 5% and then 5% increments for the remainder. Regional lymph nodes were not scored for residual primary cancer.

TABLE 1. Patient characteristics (total n = 240)

Variable	n*	Number (%) or mean ± SD
Demographics		
Age (y)	240	61 ± 9.0
Male	240	214 (89)
White	240	229 (95)
Body mass index (kg · m^{-2})	195	28 ± 5.6
Comorbidities		
Diabetes	196	35 (18)
Coronary artery disease	232	34 (15)
Hypertension	196	96 (49)
Peripheral arterial disease	232	6 (2.6)
Smoking history	176	135 (73)
FEV_1 (% of predicted)	236	93 ± 16
FVC (% of predicted)	236	98 ± 14
Creatinine (μmol · L^{-1})	142	79 ± 22
Bilirubin (μmol · L^{-1})	188	5.1/6.8/12†

SD, Standard deviation; *FEV_1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity. *Patients with data available. †15th/50th/85th percentiles.

Data Analysis

Random Forest analysis. We used Random Forest technology as the analytic strategy in part to avoid restrictive parametric modeling assumptions, given no prior knowledge of what relationships might exist, and in part because we previously demonstrated with this method that there is a complex interplay between esophageal cancer characteristics and survival.[8] A Random Forest is a collection of decision-tree analyses, wherein a variable is chosen to optimally split the population to improve prediction. This process is applied recursively to create a tree (recursive partitioning,[9] classification and regression trees[10]). Individual trees "grown" by this method are inherently unstable, but this can be mitigated by creating a collection of trees from bootstrap samples of the original dataset (the bootstrap dataset is formed by random sampling of patients with replacement until a dataset of equal size is generated; some patients will be duplicated, and an average of 37% will not be sampled). Subsequently, an ensemble average can be formulated across this forest of individual trees. The validity of the forest is evaluated by assessing outcomes of patients who were not selected in the bootstrap process, resulting in internal multifold cross-validation. This transforms variables associated with an outcome of interest into predictors of that outcome.

Because values were missing for some variables, Random Forest imputation was used to maximize use of available data.[11]

Variable selection. Rather than *P* values, 2 metrics of prediction accuracy are generated. The first ranks the importance of each variable in predicting the outcome of interest (variable importance, or VIMP) based on the patients not selected (called the "out-of-bag" or holdout samples).[12] The second quantifies the average number of branches before a variable is split (called "minimal depth"): The closer to the trunk of the tree a variable is split, the more important that variable is to prediction accuracy.[13]

In summary, predictors of outcome using Random Forest technology are identified in 2 steps: (1) building the forest based on residual primary cancer and other patient characteristics and the outcome of interest, and (2) using the resulting forest to discover the importance of variables to