Distribution of Resistant Esophageal Adenocarcinoma in the Resected Specimens of Clinical Stage III Patients after Chemoradiation: Its Clinical Implications

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Key Words

Esophageal adenocarcinoma · Chemoradiation · Surgery · Treatment decisions

Abstract

Background: We have limited knowledge of the geographic distribution of resistant esophageal adenocarcinoma (EAC) in resected specimens, but its clinical importance can be enormous. **Method:** We selected patients with baseline stage III EAC who had had chemoradiation followed by surgery and had residual EAC (resistant cases only). Outcomes were correlated with various endpoints (percentage of resistant EAC and anatomic distribution). **Results:** A total of 100 clinical stage III patients were studied; 90% had an R0 resection, and 99% had either moderate or poorly differentiated EAC. Twelve percent had >50% residual cancer, 31%

had 11–50% residual cancer, 53% had 1–10% residual cancer, and 3% had positive nodes only. Each compartment was frequently involved: mucosa/submucosa (66%), muscularis propria (76%), and serosa (62%); all compartments were involved in 35% of the cases. Lack of EAC (meaning response) was observed in the mucosa/submucosa (34%), muscularis propria (24%), serosa (38%), and nodes (42%). Although the endoscopic biopsies prior to surgery showed no EAC in 79% of the patients, in the surgical specimens, resistant EAC was frequently occurring in the mucosa/submucosa (66%). **Conclusion:** Contrary to our hypothesis that resistant EAC would be frequent in the nodes, our data show that its distribution is heterogeneous and unpredictable. Most importantly, the postchemoradiation biopsies are misleading, and a decision to delay/avoid surgery based on negative biopsies can be detrimental for the patients.

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Introduction

Esophageal adenocarcinoma (EAC) accounts for 1.1% of all new cancers in the USA. It is estimated that 18,170 new cases and 15,450 deaths from esophageal cancer (EC) will occur in 2014. EAC comprises >67% of all cases of EC in the USA [1]. The treatment of EAC depends on the clinical stage, but the posttreatment surgical stage is a better determinant of prognosis [2–5]. There is interpatient variability in the degree of response to chemoradiation: ~25% of patients achieve a complete response [6], but the remaining have resistant EAC in the surgical specimen. An assessment of histopathologic response after treatment was first proposed for osteosarcoma, using the percentage of residual tumor along with regressive changes, but it was further refined for ovarian cancer [7]. Since then, it has been applied to many solid tumors. The Tumor Regression Grading (TRG) system for EC was first described by Mandard et al. [8]. Chirieac et al. [3] modified the grading system, and this modification has been validated in a multi-institutional setting [2].

The geographic patterns of resistant EAC can be important in developing novel therapeutic strategies and consolidating the current ones; however, this information remains limited. Shapiro et al. [9] reported one noteworthy effort in which 102 consecutive patients with EC (both squamous and adenocarcinoma, including cases that did not have any residual cancer in the specimen) were analyzed for the geographic distribution of EC after chemoradiation. Only 74 patients had EAC (it is not clear how many of these had resistant EAC). Seventy percent of all the EC patients had residual EC, and among these, only 57 patients had baseline T3 EC (maybe most with baseline stage III, but it is unclear how many had EAC).

Our analysis differs from the prior report. We entirely focused on EACs and on baseline stage III patients with resistant EACs. We selected baseline stage III EAC patients (because this is the most prevalent population with localized EAC in the clinics) and compared presurgical parameters (presurgical biopsies) with the findings in the surgical specimens. We also focused on the clinical importance of the distribution of resistant EAC in the surgical specimen. Our results support some of the current trends in the management of localized EAC.

Subjects and Methods

Patient Population

The purpose of this study was to assess the geographic distribution of resistant EAC in the surgical specimen after chemoradia-

tion. We selected patients with baseline stage III EAC according to the 6th edition of the AJCC Cancer Staging Manual [10]. Between the years 2000 and 2013, 100 EAC patients who had had chemoradiation followed by elective surgery at the University of Texas MD Anderson Cancer Center (UTMDACC) were identified. Patients with pathologic complete response were excluded. No other selection criteria were implemented. The Institutional Review Board of the UTMDACC approved this analysis.

Staging and Grading

The pretreatment clinical stage was established by endoscopy and biopsies, endoscopic ultrasonography with fine needle aspiration of suspected lymph nodes, if needed/feasible, computed tomography of the chest and abdomen, and positron emission tomography (PET). All staging data on each patient were reviewed in our multidisciplinary conference.

Chemoradiation and Surgery

All patients received concurrent chemotherapy [fluoropyrimidine (i.v. or oral) with either a platinum compound or taxane as the second agent] with a total radiation dose of 45–50.4 Gy delivered in daily fractions of 1.8 Gy. Approximately 6 weeks after chemoradiation, all patients underwent a presurgical evaluation including endoscopic biopsies and repeat PET within 7 weeks after the end of chemoradiation. The patients then proceeded to surgery, the type of which was selected by the primary surgeon.

Evaluation of the Surgical Specimen

Our validated method of surgical specimen examination has been in implementation [2, 3]. In brief, each case was assessed for the percentage of resistant EAC, yp staging according to the 7th edition of the AJCC Cancer Staging Manual [11], tumor differentiation, and tumor distribution. The geographic distribution was categorized into 4 compartments: (1) mucosa/submucosa, (2) muscularis propria, (3) serosa, and (4) nodes. Certain specimens were re-reviewed if the original pathology report was not comprehensive. We did not purposely re-review each specimen, so that we could present the information in accordance with the normal flow of medical information (real time) in our system that leads to current patterns of treatment decisions. Re-review not being the standard of care could have introduced biases; thus, going forward, re-reviews would not have been practical.

Statistical Analysis

Univariate Cox proportional hazards regression was used to identify any association between each factor and each survival outcome. For each factor, medians, HR, their 95% CI, and proportional hazards regression p values were established. Statistical analysis was performed using STATA/SE version 13.1 statistical software (StataCorp LP, College Station, Tex., USA).

Results

Baseline Patient Characteristics

The patient characteristics are shown in table 1.

Table 1. Summary statistics of the clinical and demographic patient characteristics

	Patients, n (%)
Age	
<60 years	48 (48)
≥60 years	52 (52)
Gender	
Female	3 (3)
Male	97 (97)
Baseline stage	
IIIA	86 (86)
IIIB	11 (11)
IIIC	3 (3)
Tumor grade	
G1	1 (1)
G2	45 (45)
G3	54 (54)
Surgical stage	
I	13 (13.5)
II	41 (42.7)
III	42 (43.8)

Surgical Pathology

ypT0 was noted in 3 patients (these 3 had positive nodes), ypT1 in 22, ypT2 in 13, ypT3 in 62, and ypN0 in 42 patients. The surgical pathology stage was I in 14 and II in 41 patients. Stage III EAC was most frequent and was observed in 45 cases. Resection was R0 in 90 patients and R1 in 10. The tumor grade was undetermined in 11, well differentiated in 1, moderately differentiated in 18, and poorly differentiated in 70 patients. The degrees of residual EAC were as follows: 1–10% (n = 53), 11–50% (n = 31), and >50% (n = 12). The median number of examined lymph nodes was 23 (range: 3–52). The median number of positive lymph nodes was 1 (range: 0–20).

Geographic Distribution of Resistant EAC

Residual EAC was frequently found in more than 1 anatomic compartment. Mucosal and submucosal involvement was found for 66 EACs (with 20 EACs not overlapping other compartments), the muscularis propria was involved in 76 EACs (with 4 EACs not overlapping), the serosa was affected in 62 patients, and the nodes were involved in 58 EACs (with 3 not overlapping). In 35 EACs, all anatomic compartments were involved.

The relative response rate was calculated by the absence of residual EAC in a given compartment, and it was as follows: 34% in the mucosa/submucosa, 24% in the muscularis propria, 38% in the serosa, and 42% in the nodes.

Presurgical Biopsy and Residual EAC

In all, 79% of the patients did not have EAC in the endoscopic biopsy specimens prior to surgery; however, 66% of the resected specimens had EAC in the mucosa/submucosa. Biopsy-positive EACs had a median of 30% residual EAC, in contrast with biopsy-negative EACs, which had a median of 7% of residual EAC ($p < 0.001$). Positive biopsy results did not correlate with the presence of positive nodes, which is unlike what we had previously reported based on a smaller number of patients [12].

Survival and Recurrence

The median duration of follow-up was 33 months (range: 6–129); 47 patients died. The median overall survival (OS) and relapse-free survival (RFS) periods were 50 and 23 months, respectively. For the entire cohort, the 5-year OS rate was 47%. In the univariate analysis for OS, age, the number of positive lymph nodes, residual tumor score, baseline TNM stage, tumor grade, and margin status were significant. In the multivariate analysis, only tumor grade, baseline TNM stage, and margin status were independent for survival. The multivariate analysis is presented in table 2. Additionally, the percentage of residual EAC-influenced survival (fig. 1) was as anticipated. A positive presurgical biopsy conferred poor survival (median: 24 months) as compared to a negative biopsy (56 months), but this was not significant ($p = 0.089$) – even though this finding has previously been reported by others [13, 14]. The trends were similar for RFS. Higher tumor grade, as reflected in the primary diagnostic biopsy, was related to shorter RFS ($p < 0.001$).

Discussion

The most important message from our results, which has not been previously reported, is that one should not make a decision to delay or avoid surgery based on negative endoscopic biopsies after chemoradiation. Doing so can jeopardize trimodality therapy-eligible patients who are likely to benefit from surgery. Our results also confirm the previously reported finding that the degree of residual cancer correlates with the OS of EAC patients. In this context, we investigated the geographic distribution of resistant EAC in clinical stage III EAC patients treated with chemoradiation and surgery. Our results are complementary to other findings, extend the observations of others meaningfully, and paint a more succinct picture of this phenomenon. A greater knowledge of where residual EACs reside should influence the clinical decision-making.

Fig. 1. Kaplan-Meier OS plots according to the degree of residual EAC in the resected specimen.

Table 2. Full and reduced multivariate analyses for OS

	Full model			Reduced model		
	HR	95% CI for OS	p value	HR	95% CI for OS	p value
Number of positive lymph nodes	1.06	0.92–1.23	0.410			
Age						
<60 years						
≥60 years	1.45	0.54–3.89	0.463			
Tumor grade						
G1/G2						
G3	7.50	2.03–27.72	0.003	9.66	3.14–29.73	<0.001
Residual tumor score						
TRG2: score 1–10						
TRG3: score 11–50	1.30	0.37–4.65	0.682			
TRG4: score >50	3.32	0.63–17.52	0.158			
Margins						
Free						
Involved	36.61	2.08–645.913	0.014	81.66	6.58–1,012.637	0.001

ing process and also help develop novel clinical strategies. At times, when a complete clinical response is achieved, patients (and sometime physicians) are tempted to delay/avoid surgery. However, based on our results and those of others [9], it is clear that EAC is a highly resistant cancer, and in 70% of the cases, residual cancer is found. Our data also contradict the conclusions made by Shapiro et al. [9] that we can implement a wait-and-see approach for

some trimodality therapy-eligible patients. We have previously reported on >300 patients who had a complete clinical response (meaning that the presurgical biopsies were negative and the PET results were physiological), and 70% of them had resistant EAC in the surgical specimen [15]. The fact that we have no reliable tools for recommending a delay in or avoidance of surgery for EAC patients is further emphasized by our current results sug-

gesting that a negative postchemoradiation biopsy result is frequently misleading.

Additionally, our findings are contrary to what we anticipated: the lymph node compartment turned out to be the most sensitive of the 4 compartments. Resistant EAC can be widely distributed in all 4 compartments, and the heterogeneity of the patterns of its geographic distribution is intriguing. Presurgical biopsy results highly correlate with the degree of residual EAC to be found in the surgical specimen. Our data also suggest that clinical stage III (A, B, and C) EAC patients should be encouraged to undergo surgery because there is considerable resistant EAC in the surgical specimens of these patients. Our previous report also suggests benefits from surgery for this particular group of patients [16].

Our study is retrospective in nature; therefore, it has its limits and does not provide guidance for individualizing therapy. It simply adds to our understanding of the geographic distribution of resistant EAC. The shortcomings of our staging evaluations prior to surgery are evident and provide another glimpse into the complexity of treating EAC. The strength of this report is that it is the largest study on clinical stage III (A, B, and C) EAC. We made the novel observation of a discrepancy between pre-

surgical biopsy results and what is found in the resected specimen; finally, the degree of residual EAC correlates with the results of presurgical biopsy.

In conclusion, resistant EAC after chemoradiation is widely distributed in various anatomic compartments in an unpredictable manner. Postchemoradiation (i.e. presurgical) biopsy is misleading and should not be used as the basis for a recommendation on whether or not to delay or avoid surgery.

Acknowledgements

The authors received generous support from the Caporella, Dallas, Sultan, Park, Smith, Frazier, Oaks, Vanstekelenberg, and Cantu Families; from the Schecter Private Foundation, Rivercreek Foundation, Kevin Fund, Myer Fund, Dio Fund, and Milrod Fund, as well as a Multidisciplinary Grant provided by the UTMDACC. The study was supported in part by RO1CA129906 and RO1CA172741 from the National Cancer Institute (to J.A.A.).

Disclosure Statement

The authors declare that they have no conflicts of interest.

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