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Scientific paper

Accuracy of pathologic examination in detection of complete response after chemoradiation for esophageal cancer

Eugene Y. Chang, M.D.[a], Christina A. Smith, M.D.[b], Christopher L. Corless, M.D., Ph.D.[b], Charles R. Thomas Jr, M.D.[c], John G. Hunter, M.D.[a], Blair A. Jobe, M.D.[a,*]

[a]*Department of Surgery, Oregon Health & Science University, Mail Code L223A, 3181 SW Sam Jackson Park Rd, Portland, OR 97239, USA*
[b]*Department of Pathology, Oregon Health & Science University, Mail Code L223A, 3181 SW Sam Jackson Park Rd, Portland, OR 97239, USA*
[c]*Department of Radiation Medicine, Oregon Health & Science University, Mail Code L223A, 3181 SW Sam Jackson Park Rd, Portland, OR 97239, USA*

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Abstract

Background: Although a substantial proportion of patients undergoing neoadjuvant chemoradiation for invasive esophageal cancer develop a pathologic complete response (pCR), these patients nonetheless have a poor 5-year survival rate. We hypothesized that routine pathologic examination fails to identify some residual cancer.

Methods: Patients undergoing esophagectomy for cancer at 2 tertiary care centers were identified. Archived tumor blocks were retrieved for patients with pCR, sectioned at 50-μm intervals and reexamined for residual cancer.

Results: Seventy patients underwent neoadjuvant chemoradiation. Tumor blocks were available for 23 of 26 complete responders. A total of 159 blocks were reexamined. One patient was found to have a possible focus of residual invasive adenocarcinoma versus high-grade dysplasia. The remaining 22 patients had no residual disease.

Conclusions: A more aggressive examination protocol for postchemoradiation esophagectomy specimens may not result in significant upstaging. Inadequate pathologic examination is likely not a major factor in the suboptimal survival in patients with pCR.

Keywords: Esophageal cancer; Neoadjuvant chemoradiation; Pathologic complete response; Staging

Although esophageal cancer is a relatively rare malignancy, with an incidence of approximately 14,000 per year in the United States, it is highly lethal, with a relative 5-year overall survival rate of under 20% [1–4]. A number of studies have shown that the administration of neoadjuvant chemoradiation produces a survival advantage in patients with esophageal cancer, particularly those with stage III disease [5,6]. In patients with a partial response, the percentage of tumor reduction correlates directly with survival [7]. These data have led to the adoption of neoadjuvant chemoradiation as a de facto standard of care for patients with clinical stage II and stage III disease in North America. A substantial proportion of patients receiving neoadjuvant therapy are found to have no residual tumor on pathologic examination of the esophagectomy specimen [5,6]. These patients are deemed to have a pathologic complete response (pCR) and, in uncontrolled studies, carry an improved survival compared with patients with residual malignancy [5,8–14]. Nevertheless, the majority of patients with pCR are not cured and ultimately die of distant disease.

The presence of a complete response is established by pathologic examination of resected specimens using routine methods. Under current standards of care, portions of tissue approximately 3 mm in thickness are taken from grossly identified areas of interest in the specimen, processed through organic solutions, and embedded into paraffin "blocks." Only one or two 5-μm sections from these blocks are then mounted onto glass slides for histologic examination. The remainder of the paraffin block is archived. Thus, only a minute fraction of the paraffin-embedded tissue is actually examined under a microscope. Because tumor may be present in the unexamined tissue, patients who are considered complete pathologic responders may have had undetected residual tumor in their resected specimens. We hypothesized that a number of patients deemed to have pCR

* Corresponding author. Tel.: +1-503-494-8372; fax: +1-503-494-8884.
E-mail address: jobeb@ohsu.edu

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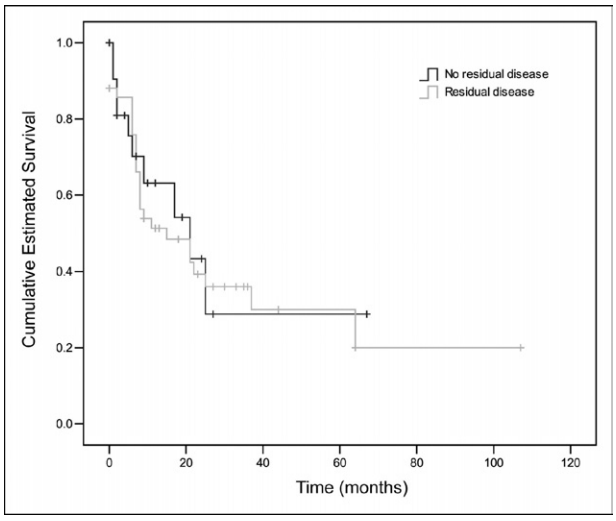

Fig. 1. Kaplan-Meier curves showing overall survival among patients with and without pathologic complete response to neoadjuvant chemoradiation (by the standard pathologic examination protocol).

may actually harbor residual disease that the pathologic examination has failed to detect.

The purpose of this study was to evaluate whether a more rigorous examination would yield a higher detection rate for residual disease. Patients who are previously considered to be complete responders and found to have residual tumor on further examination would be considered upstaged. Because patients with residual disease are expected to have a shorter survival rate compared with complete responders, the finding of residual tumor on further examination would explain the low rate of long-term survival among patients currently classified as complete responders.

Methods

Under an institutional review board–approved protocol, tumor registries, discharge databases, surgeon databases, and pathology databases at the Portland VA Medical Center and at Oregon Health & Science University were reviewed to identify patients with esophageal cancer from 1990 to 2005. Patients who underwent neoadjuvant chemoradiation for adenocarcinoma and squamous-cell carcinoma were identified. Age, gender, histology, stage of disease, and length of survival were recorded from hospital records. Patients who were reported to have no residual tumor in esophagectomy specimen were identified, and archived microscopic slides and tumor blocks were retrieved. The previously reviewed microscopic slides were rereviewed to confirm that no residual disease had been previously overlooked. From each tumor block, 3 additional sections were taken at 50-μm intervals for microscopic examination by two pathologists looking for evidence of residual disease. Tissue from lymph nodes and margins of esophagectomy were excluded from analysis. Kaplan-Meier curves of overall survival were generated of patients with and without pCR. Survival curves were compared by using the log-rank test by using SPSS 13 (SPSS Inc, Chicago, IL). A Student *t* test was used to compare mean ages between groups. A Fisher exact test was used to compare the distribution of categorical variables (gender, histology, and stage). A *P* value of .05 was used as the threshold for statistical significance.

Results

Screening of registries and databases identified 70 patients who underwent chemoradiation for esophageal cancer. Of these, 42 had residual tumor in the esophagectomy specimen, and 2 patients had areas suspicious for residual microscopic disease. No residual tumor was found in the remaining 26 patients. Of these 26 patients, archived specimens were available for 23 patients whose specimens are included in this study. The mean age of the patients was 60.6 years. Most patients had stage II or III disease, although 2 patients had stage IVa disease. Previously viewed slides were available for 22 patients. Reexamination of these slides did not identify any overlooked areas containing tumor. A total of 159 archived tissue blocks were available for further processing. Upon taking additional slides from archived tissue and examination under the more stringent protocol, 22 of the 23 patients had no evidence of residual disease. In 1 patient, a small focus of residual adenocarcinoma was seen, although this was indistinguishable from high-grade dysplasia extending into an esophageal gland. The specimen showed increased architectural complexity, with small, fused glands and a large, central lumen. The glandular cells had an increased nuclear to cytoplasmic ratio, with enlarged, pleomorphic nuclei, loss of nuclear polarity, and prominent nucleoli. A lack of desmoplasia around the gland, however, argued against adenocarcinoma, whereas the incomplete nature of the gland suggested adenocarcinoma.

The mean length of follow-up was 16 months. One patient with stage IIa disease developed a local recurrence. Three patients with stage IIb, III, and IVa disease developed distant disease (M1B) after R0 resection. Kaplan-Meier survival curves were generated for the 22 patients with confirmed pCR and the 42 with residual disease (Fig. 1). Those with a complete response did not have a better survival than those with residual disease ($P = .802$). The 5-year survival rate for complete responders was 28.8% compared with 30.0% for partial or nonresponders. Similarly, no difference in survival was seen when patients with stage II disease ($P = .462$) or stage III disease ($P = .850$) were examined separately. No significant differences were seen between complete responders and partial or nonresponder in age, gender, or stage of disease (Table 1).

Table 1
Characteristics of patients who developed a complete pathologic response to neoadjuvant chemoradiation and those who did not

	Partial and nonresponders (n = 44)	Complete responders (n = 23)	*P* value
Mean age	59.1	60.6	.563
Males	40 (90.9%)	20 (87.0%)	.413
Stage 1	1 (2.3%)	0 (0.0%)	.565
Stage 2	19 (43.2%)	11 (47.8%)	
Stage 3	23 (52.3%)	10 (43.5%)	
Stage 4	1 (2.3%)	2 (8.7%)	
Adenocarcinoma	40 (90.9%)	16 (69.6%)	.072