Post-Chemoradiation Surgical Pathology Stage Can Customize the Surveillance Strategy in Patients With Esophageal Adenocarcinoma

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Abstract

Current algorithms for surveillance of patients with esophageal adenocarcinoma (EAC) after chemoradiation and surgery (trimodality therapy [TMT]) remain empiric. The authors hypothesized that the frequency, type, and timing of relapses after TMT would be highly associated with surgical pathology stage (SPS), and therefore SPS could be used to individualize the surveillance strategy. Between 2000 and 2010, 518 patients with EAC were identified who underwent TMT at The University of Texas MD Anderson Cancer Center and were frequently surveyed. Frequency, type, and timing of the first relapse (locoregional and/or distant) were tabulated according to SPS. Standard statistical approaches were used. The median follow-up time after esophageal surgery was 55.4 months (range, 1.0–149.2 months). Disease relapse occurred in 215 patients (41.5%). Higher SPS was associated with a higher rate of relapse (0/I vs II/III, $P \leq .001$; 0/I vs II, $P = .002$; SPS 0/I vs III, $P \leq .001$; and SPS II vs III, $P = .005$) and with shorter time to relapse ($P < .001$). Irrespective of the SPS, approximately 95% of all relapses occurred within 36 months of surgery. The 3- and 5-year overall

survival rates were shorter for patients with a higher SPS than those with a lower SPS (0/I vs II/III, $P \leq .001$; 0/I vs II, $P \leq .001$; 0/I vs III, $P \leq .001$; and II vs III, $P = .014$). The compelling data show an excellent association between SPS and frequency/type/timing of relapses after TMT in patients with EAC. Thus, the surveillance strategy can potentially be customized based on SPS. These data can inform a future evidence-based surveillance strategy that can be efficient and cost-effective. (*J Natl Compr Canc Netw* 2014;12:1139–1144)

As the eighth most common cancer worldwide and the sixth leading cause of cancer death, esophageal cancer is a global health burden, with approximately 482,000 new cases and 407,000 estimated deaths in 2008.^{1,2} In the West, the incidence of lower esophageal and/or esophagogastric junction adenocarcinoma (EAC) has increased substantially over the past 30 years, and that of squamous cell carcinoma has declined.^{3,4} In the United States, for patients with localized EAC who can withstand surgery, the most common recommendation is chemoradiation followed by surgery, or *trimodality therapy* (TMT).^{5,6} Despite advances in the treatment of localized EAC, the cure rate remains at 30% to 45% for patients with clinical stage II or III, and relapses are common.^{7–10} After TMT, most patients undergo surveillance for at least 5 years; however, the surveillance recommendations vary considerably and are often empiric in nature.^{6,10} Relapses seem to be related to the sensitivity of the primary EAC as determined by the residual cancer in the surgical specimen,^{11,12} particularly after chemoradiation.^{7,13,14} However, more detailed analysis with regard to surgical pathology stage (SPS), type of relapse, and timing of relapse has not been reported and

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may prove useful in developing an evidence-based customized surveillance strategy.

The authors recently reported the timing and frequency of locoregional-only relapses in patients with EAC after TMT, and discussed the low rate of local relapse in the cohort and the outcome of the salvage techniques that were implemented.¹⁵ This article provides a detailed analysis of the type and timing, timing of relapse, and their association with post-TMT SPS. Forming an association between SPS and frequency/timing of relapse could have considerable implications on the cost, frequency/duration, and anxiety associated with surveillance.

Materials and Methods

Patient Selection

Between 2000 and 2010, 518 patients with EAC were identified who underwent TMT at The University of Texas MD Anderson Cancer Center (MDACC). The data were retrieved from a prospectively maintained esophageal cancer database in the department of Thoracic and Cardiovascular Surgery at MDACC. The Institutional Review Board approved this analysis. For this project, patients were selected based on 2 major requirements: (1) they had histologically confirmed EAC and (2) they completed TMT. All patients underwent extensive baseline staging procedures, including a CT, PET, upper gastrointestinal endoscopy, and endoscopic ultrasonography (EUS). Cases were then discussed in a multidisciplinary conference including medical oncologists, thoracic surgical oncologists, radiation oncologists, gastroenterologists, pathologists, radiologists, and many supporting personnel. For the designation of posttherapy (yp) SPS, the AJCC staging system, 7th edition, was used.¹⁶ The surgical specimen was scored using a process proposed by the authors¹² and later validated in a multi-institutional effort.¹¹

Details of TMT

The details of TMT were reported previously.¹⁵ Briefly, preoperative chemoradiation consisted of an intravenous or oral fluoropyrimidine with either a platinum compound or a taxane. The median total radiation dose was 50.4 Gy (range, 39.6–64.8 Gy) in daily fractions of 1.8 Gy. Approximately 5 to 6 weeks after the completion of preoperative chemoradiation, PET and endoscopic studies with biopsy

were performed for preoperative restaging. All patients underwent surgery. Surgical technique (right transthoracic [Ivor-Lewis], transhiatal, 3-field, or minimally invasive esophagectomy) was selected at the discretion of the thoracic surgeon.

Surveillance Strategy After TMT and Survival Follow-up

As reported previously,¹⁵ a CT or PET/CT with routine blood tests were performed every 3 months for the first year and then every 6 months until the third year, and once a year until at least the fifth year. An endoscopic study to evaluate intraluminal relapse was performed every 6 months in the first 18 months and then once a year until the fifth year. The authors documented the timing and type of first relapse after TMT.

The follow-up data were obtained from the MDACC Tumor Registry, hospital records, or the Social Security database.

Statistical Analyses

Continuous variables were summarized by descriptive statistics, such as means, standard deviations, medians, and ranges. Categorical variables were tabulated by frequency and percentage. Relapse-free and follow-up times were calculated from the date of surgery to the event, overall survival (OS) and relapse-free survival (RFS) outcomes were calculated using Kaplan-Meier estimators, and the log rank test was used to compare the Kaplan-Meier curves. If an event date was not available, the date of the last follow-up was used. Statistical significance was defined as a *P* value less than .05.

Results

Patient Characteristics

The analysis included 518 patients with EAC who received TMT. Patient characteristics of this cohort were reported previously,¹⁵ but briefly, the median age was 61 years (range, 23–79 years) and Caucasian men were the most common patients. Gastroesophageal junction was frequently involved (65.1%). Most patients had clinical stage II (39.0%) or III (51.7%) cancer. Of the 518 patients, 25 (4.8%) had M1a (celiac lymph node metastases) and were designated clinical stage IVa according to the AJCC 6th edition.¹⁷

Type of Surgery

Most of the patients (70.3%) underwent an Ivor-Lewis esophagectomy, and transhiatal, minimally invasive, and 3-fields esophagectomy were performed in 11.2%, 11.0%, and 7.1% of patients, respectively.

Association of Relapse With SPS

At the median follow-up time of 55.4 months (range, 1.0–149.2 months), first relapse occurred in 215 patients (41.5%) after TMT. Among these, 27 (12.6%) had locoregional-only relapse and 188 (87.4%) had distant relapse with or without locoregional relapse. The timing, type, and frequency of first relapse using 12-month intervals after surgery according to the SPS categories are shown in Figure 1. The most common type of relapse was distant in all SPS categories. More relapses occurred in patients with higher a SPS than in those with a lower SPS. In patients with SPS 0 and I, more than 99.0% of all relapses occurred within 36 months of surgery. Irrespective of SPS, 85.1% of all relapses occurred within 24 months of surgery and 94.4% of all relapses occurred within 36 months of surgery.

Table 1 shows comparisons between the types of relapses and the SPS categories. For patients with SPS 0 or I, the overall relapse frequency was similar (P =not significant); therefore, the authors combined SPS 0 and I to compare with the other SPS categories. No difference was noted in the rate of locoregional relapse across all SPSs. However, distant relapses increased with higher SPS. Thus, the risk of relapse was statistically significantly higher for patients with a higher SPS than for those with lower SPS (0/I vs II/II: $P \leq .001$; 0/I vs II: $P = .002$; 0/I vs III: $P \leq .001$; and II vs III: $P = .005$).

Relapses occurred earlier in patients with higher SPS (0/I vs II/III: $P < .001$ [Figure 2A]; 0/I vs II: $P \leq .001$ [Figure 2B]; 0/I vs III: $P \leq .001$ [Figure 2C]; and II vs III: $P \leq .001$ [Figure 2D]). Similarly, OS was shorter for patients with a higher SPS (0/I vs II/II: $P \leq .001$; 0/I vs II: $P \leq .001$; 0/I vs III: $P \leq .001$; and II vs III: $P = .014$ [Table 2]).

Only 30 ($\approx 6\%$) of 518 patients had an R1 resection. The distant metastases rate for these patients was 43% compared with 36% for those who underwent R0 resection.

Figure 1 Visual and numerical demonstration of the type and timing of first relapses according to the surgical pathology stage categories. Orange circles represent locoregional relapses. Green circles represent distant metastases.

Abbreviations: DM, distant metastasis with or without locoregional relapse; LR, locoregional relapse without distant metastasis; pts, patients; SPS, surgical pathology stage.

^aDenominator is all patients at risk.

^bDenominator is all patients with relapse.

Table 1 Relationship Between the Pattern of Recurrence and Surgical Pathology Stage

		Locoregional Recurrence Rate	P Value	Distant Metastases Rate	P Value	Total Recurrence Rate	P Value
0/I vs II/III	0/I	4% (7/191)	.226	24% (46/191)	<.001	28% (53/191)	<.001
	II/III	6% (20/327)		43% (142/327)		50% (162/327)	
0/I vs II	0/I	4% (7/191)	.594	24% (46/191)	.003	28% (53/191)	.002
	II	5% (9/189)		38% (72/189)		43% (81/189)	
0/I vs III	0/I	4% (7/191)	.09	24% (46/191)	<.001	28% (53/191)	<.001
	III	8% (11/138)		51% (70/138)		59% (81/138)	
II vs III	II	5% (9/189)	.232	38% (72/189)	.023	43% (81/189)	.005
	III	8% (11/138)		51% (70/138)		59% (81/138)	

To assess associations between categorical data, the chi-square test was performed using IBM SPSS software, Version 22.0 (Cary, NC).

Discussion

The rates of locoregional-only relapses and outcomes of salvage strategies in this cohort were reported previously.¹⁵ This article reports on all relapses (locoregional and distant) observed and their significant association with SPS. SPS, particularly after chemoradiation, is a reflection of the biology of EAC.^{11,12,14} The higher the SPS, reflecting the resistance of the primary tumor to chemoradiation, the higher the metastatic potential of EAC. The present data show that distant metastases are much more frequent than locoregional-only relapses and that a higher SPS leads to higher rates of relapses. In addition, patients with a higher SPS tend to develop metastases not only more frequently but also sooner than those with a lower SPS (eg, within the first 12 months of surgery, the fraction of all relapses in various SPS categories were as follows: SPS 0=41%; SPS I=42%; SPS II=61%; and SPS III=68%). Thus, the frequency of relapses based on timing could be exploited in formulating future surveillance strategies. For SPSs 0 and I, all relapses occurred (with the exception of 1 locoregional relapse in year 5 in a patient with SPS I disease) within 36 months of surgery. This observation could be used to principally terminate surveillance in patients with SPS 0 or I after 3 years. The quandary is whether it is reasonable to recommend any surveillance (and what the frequency should be and what tests should be performed) for SPS II or

III. Based on the present data (Figure 2), one could question the benefit of surveillance in patients with SPS III, because approximately 60% of patients are likely to experience relapse and 86% of these relapses are anticipated to be metastatic. Considerable discussion would be necessary to establish guidance for patients with SPS II. No specific strategy may be needed to detect a locoregional relapse for a specific SPS category, because the locoregional relapse rate is similar across the SPS. OS data are consistent with the overall relapse data, in that the higher the SPS, the shorter the survival of those patients. The authors believe a serious national dialogue is needed to restructure the overall surveillance strategy for EAC (and this can be extended to a few other solid tumors). Such a dialogue may lead to the launch of a prospective trial to establish a firm evidence-based strategy.

The limitations of this study are that it was a single-institution experience, it was a retrospective analysis, and the results may not be generalizable. The strengths of the study are that it involved a large cohort (>500 patients) and focused only on adenocarcinoma; an aggressive surveillance strategy was used, and therefore the data are reliable; and it is the first report to provide the detailed timing, type, and frequency of EAC relapses in the context of SPS. Some of the limitations and strengths of this analysis were published previously.¹⁵

Esophageal Adenocarcinoma Surveillance Strategy

Figure 2 The Kaplan-Meier plot of recurrence-free survival according to (A) surgical pathology stage (SPS) 0/I vs II/III, (B) SPS 0/I vs II, (C) SPS 0/I vs III, and (D) SPS II vs III.

Abbreviations: E, events; N, denominator.

These results have important implications on the development of efficient and customized surveillance strategies. Chemoradiation resistance and metastatic progression remain significant problems in patients with localized EAC, and future efforts should focus on full characterization of molecular and immune biology of EAC. Newer strategies to overcome these obstacles will be immensely helpful.

Conclusions

The present data show a significant association between SPS after chemoradiation in EAC and the timing, type, and frequency of relapses after surgery. These data raise many questions about who should be surveyed (and how) and for how long, and can be useful in developing a rational surveillance strategy for patients with EAC who undergo TMT.

Table 2 Relationship Between Overall Survival and Surgical Pathology Stage				
	Median OS (95% CI)	3-y OS Rate	5-y OS Rate	P Value by Log Rank
O/I vs II/III				<.001
O/I	89.9 mo (–)	71%	60%	
II/III	29.6 mo (23.7–35.6)	46%	35%	
O/I vs II				<.001
O/I	89.9 mo (–)	71%	60%	
II	37.1 mo (26.0–48.1)	51%	40%	
O/I vs III				<.001
O/I	89.9 mo (–)	71%	60%	
III	22.4 mo (17.9–27.0)	39%	28%	
II vs III				.014
II	37.1 mo (26.0–48.1)	51%	40%	
III	22.4 mo (17.9–27.0)	39%	28%	

Abbreviations: OS, overall survival.

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