Int Surg 2018;**103:**214–221
DOI: 10.9738/INTSURG-D-18-00041.1

Variables Associated to Pathologic Complete Response, Overall Survival and Disease-Free Survival in the Neoadjuvant Setting for Esophageal Cancer: A Retrospective Cohort Analysis

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Objective: The aim of the study was to evaluate prognostic factors during neoadjuvant therapy that can predict pathologic complete response (pCR), overall survival (OS), or disease-free survival (DFS).

Summary of background data: Variables that can predict tumor response to neoadjuvant therapy are required for esophageal cancer management.

Methods: A retrospective cohort was performed with esophageal cancer patients submitted to neoadjuvant therapy. pCR, OS, and DFS were evaluated. Logistic regression was used to evaluate prognostic factors. This study covered 140 patients, 94 squamous cell carcinomas (SCC), and 44 adenocarcinomas. SCC is more often associated with pCR (compared to adenocarcinoma, OR: 8.07, 95% CI: 2.91–22.38); it has higher probability of DFS (HR for death or recurrence was 0.6, 95% CI: 0.37–0.98); and a higher probability of OS (HR for death was 0.59, 95% CI: 0.35–1). Gender, age, grade of cellular differentiation, chemotherapy regimen, and neoplasm circumferential involvement before neoadjuvant therapy are variables that are unrelated to DFS. Relief of dysphagia, and weight gain were also unrelated to the outcomes. In the multivariate analysis, the weight loss during neoadjuvant therapy was related to higher risk for recurrence or death (HR 1.02, 95% CI: 1–

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1.04). SCC histologic type was associated with higher probability of pCR, and higher OS and DFS rates. Gender, grade of cellular differentiation, and chemotherapy regimen are variables that are unrelated to pCR, OS, and DFS. Relief of dysphagia and increased levels of albumin after neoadjuvant therapy were also unrelated to the studied outcomes. Weight loss during neoadjuvant chemotherapy was associated with poor DFS rate in the multivariate analysis.

Key words: Esophageal neoplasms – Neoadjuvant therapy – Prognosis

Adenocarcinoma and squamous cell carcinoma (SCC) comprise the main histologic types of esophageal cancer. Both histologic types usually evidence poor survival rates. About 80% of patients will not survive longer than 5 years.[1] Most of the patients are diagnosed at advanced clinical stages.[2,3]

Concerning advanced stage neoplasms, neoplasm circumferential involvement or even complete esophageal lumen obstruction are common, leading to intense dysphagia, weight loss, and malnutrition.

In locally advanced tumors, neoadjuvant chemoradiotherapy facilitates tumor downstaging, increasing probability for curative intent surgery, and avoiding locoregional recurrence. Tumor shrinking after neoadjuvant therapy may relieve dysphagia and improve patients' nutritional status.[4,5]

Neoadjuvant tumor response varies among patients, and the patient's response to chemoradiotherapy is difficult to evaluate and predict before esophagectomy. Consequently, variables that can predict tumor response to chemoradiotherapy and long-term survival rates after esophagectomy are required for esophageal cancer management.

Objectives

This study aimed to evaluate possible prognostic variables in neoadjuvant therapy that can predict pathologic complete response, overall survival, or disease-free survival.

Methods

A retrospective cohort of patients submitted to neoadjuvant therapy for esophageal carcinoma was performed in a single institution, between 2009 and 2017.

Clinical, demographic, endoscopic, and histopathologic variables were extracted and assessed. Improved nutritional status and dysphagia relief while on neoadjuvant therapy was also recorded. The outcomes evaluated were pathologic complete response (pCR), overall survival (OS), and disease-free survival (DFS).

Statistical Analysis

Quantitative variables were assessed by means and standard deviation. Qualitative variables association to pCR were assessed by Student's t, Mann-Whitney, and Kolmogorov-Smirnov tests. Qualitative variables were assessed by frequency and percentage. Quantitative variables' association with pCR was assessed by Chi-square and likelihood-ratio tests.[6] Odds ratios (OR) using bivariate analysis and simple and multiple logistic regression were applied with 95% confidence interval (95% CI).[7]

Survival analysis was performed by Kaplan-Meier curves and log-rank test. Hazard ratio (HR) and bivariate Cox regression were applied with 95% CI.[8]

The significance level adopted was 0.05. IBM-SPSS 20.0 (Chicago, Illinois) software was used for statistical analysis.

Results

Baseline patient's characteristics

This study covered 140 esophageal cancer patients submitted to neoadjuvant therapy followed by esophagectomy. We observed a male predominance (74.3%), and the mean age was 59.5 (±8.1) years. Mean follow-up was 39.1 (±24.8) months. We identified 94 (67.1%) squamous cell carcinomas (SCC); 44 (31.4%) adenocarcinomas; 1 (0.7%) carcinosarcoma; and 1 (0.7%) mixed adenocarcinoma and neuroendocrine carcinoma. Oncologic stage before neoadjuvant therapy was 3.5% for I, 18% for II, 70% for III, 8.5% for IV, according to the 8th edition of American Joint Committee on Cancer (AJCC).[9] The mean percentage increase in body weight was 1.33% (SD: ±12.1) after neoadjuvant therapy. Baseline patient characteristics are reported in Table 1.

Table 1 Patients' baseline characteristics

n	140
N	140
Male (%)	74.3
Age (years; mean ± SD)	59.5 ± 8.1
Histologic type (%)	
Adenocarcinoma	31.4
SCC	67.1
Mixed carcinoma	1.4
Grade of differentiation (%)	
Well	7.9
Moderately	65.4
Poorly	26.8
Radiation dose (%)	
0	14
41.4	55
45	8
50.4	23
Chemotherapy regimen (%)	
CX	6.8
CF	4.5
CI	4.5
CP	84.2
Margins (%)	
Clear	93.5
Compromised	6.5
Pathologic response (%)	
Minimal or absent	24.3
Partial	36.8
Complete	39

CF, cisplatin plus 5-fluoracil; CI, cisplatin plus irinotecan; CP, platin plus paclitaxel; CX, cisplatin plus capecitabine.

Pathologic complete response (pCR)

Association between variables and probability for pCR by univariate analysis are reported in Table 2. SCC is more likely to achieve pCR (compared to adenocarcinoma, OR: 8.07, 95% CI: 2.91–22.38, $P < 0.001$). Gender, age, grade of cellular differentiation, chemotherapy regimen, and neoplasm circumferential involvement before neoadjuvant therapy are variables that are unrelated to pCR. Relief of dysphagia, weight gain, and increased in serum albumin levels after neoadjuvant therapy were also unrelated to pCR.

After multivariate analysis, only SCC was associated with pCR (compared to adenocarcinoma, OR: 9.51, 95% CI: 3.05–29.64, $P < 0.001$).

Overall survival (OS)

By univariate analysis, association between variables and probability for OS are reported in Table 3. SCC was associated with higher probability of OS than other esophageal carcinomas (compared to adenocarcinoma, HR for death was 0.59, 95% CI: 0.35–1, $P = 0.036$). Age was also associated with lower probability of survival (HR 1.05, 95% CI 1.02-1.09, $P = 0.005$). Gender, grade of cellular differentiation, chemotherapy regimen, and neoplasm circumferential involvement before neoadjuvant therapy are variables that are unrelated to OS. Relief of dysphagia, weight gain, and increased serum albumin levels after neoadjuvant therapy were also unrelated to OS. After multivariate analysis, HR for age at diagnosis was 1.05 (95% CI: 1.01–1.08, $P = 0.021$).

Disease-free survival (DFS)

By univariate analysis, association between variables and probability for DFS are reported in Table 4. SCC was associated to higher probability of DFS than other esophageal carcinomas (compared to adenocarcinoma, HR for death or recurrence was 0.6, 95% CI: 0.37–0.98, $P = 0.025$). Gender, age, grade of cellular differentiation, chemotherapy regimen, and neoplasm circumferential involvement before neoadjuvant therapy are variables that are unrelated to DFS. Relief of dysphagia, weight gain, and increased serum albumin levels after neoadjuvant therapy were also unrelated to DFS.

After multivariate analysis, weight loss during neoadjuvant therapy was related to higher risk for recurrence or death (HR 1.02, 95% CI: 1–1.04, $P = 0.047$).

Discussion

Several variables associated with patients' demographics, surgery aspects, and neoplasm status have been used as prognostic factors for esophageal cancer. Large neoplasms and poor cellular differentiation are factors that can predict poor outcomes and, consequently, are usually related to advanced clinical stages.[10]

Regarding locally advanced esophageal cancer, neoadjuvant therapy has been proven to yield better results and is currently considered the standard therapy.[11,12]

In the setting of neoadjuvant therapy, only a few studies examined the relationship between prognostic variables and the change of these variables during neoadjuvant therapy.

In this study, SCC was associated with better results. The probability for pCR was 8.07 (95% CI: 2.91–22.38) higher than adenocarcinoma; the incidence of death was 0.59 (95% CI: 0.35–1) compared to adenocarcinoma; and the incidence of death or

Table 2 Univariate analysis assessing the variables for the outcome pathologic complete response (pCR)

Variable	pCR		OR	95% CI		*P* value
	No	Yes		Lower	Upper	
Gender, n (%)						0.797
Male	61 (60.4)	40 (39.6)	1			
Female	22 (62.9)	13 (37.1)	0.9	0.41	1.99	
Age			0.98	0.95	1.03	0.610*
Mean ± SD	59.8 ± 8.5	59.1 ± 7.7				
Histologic type, n (%)						<0.001[a]
Adenocarcinoma	37 (88.1)	5 (11.9)	1			
SCC	44 (47.8)	48 (52.2)	8.07	2.91	22.38	
Mixed carcinoma	2 (100)	0 (0)	&			
Grade of differentiation, n (%)						0.218[a]
Well	4 (40)	6 (60)	1			
Moderately	52 (65)	28 (35)	0.36	0.09	1.38	
Poorly	24 (70.6)	10 (29.4)	0.28	0.06	1.2	
Radiation dose, n (%)						0.119[a]
0	11 (84.6)	2 (15.4)	1			
41.4	30 (58.8)	21 (41.2)	3.85	0.77	19.19	
45	3 (42.9)	4 (57.1)	7.33	0.88	61.33	
50.4	10 (47.6)	11 (52.4)	6.05	1.07	34.23	
Chemotherapy regimen, n (%)						0.111[a]
CX	7 (87.5)	1 (12.5)	1			
CF	2 (33.3)	4 (66.7)	14	0.94	207.6	
CI	5 (83.3)	1 (16.7)	1.4	0.77	28.12	
CP	66 (60.6)	43 (39.4)	4.56	0.54	38.39	
Dysphagia after neoadjuvant therapy, compared to previous neoadjuvant therapy, n (%)						0.377[a]
Worse	4 (44.4)	5 (55.6)	1			
Stable	14 (58.3)	10 (41.7)	0.57	0.12	2.68	
Partial improvement	28 (71.8)	11 (28.2)	0.31	0.07	1.39	
Complete improvement	32 (59.3)	22 (40.7)	0.55	0.13	2.28	
Neoplasm circumferential involvement before neoadjuvant therapy, n (%)						0.785[a]
<50% of the circumference	8 (61.5)	5 (38.5)	1			
≥50% of the circumference	6 (50)	6 (50)	1.6	0.33	7.85	
Circumferential involvement	35 (66)	18 (34)	0.82	0.24	2.88	
Complete esophageal obstruction	14 (63.6)	8 (36.4)	0.91	0.22	3.77	
Weight change (%)			0.99	0.96	1.02	0.576*
Mean ± SD	−0.86 ± 12.6	−2.12 ± 11.7				
Serum albumin change			0.88	0.47	1.65	0.691*
Mean ± SD	0.48 ± 0.9	0.4 ± 0.7				

[a]Likelihood-ratio test.

*Student *t* test; and not possible to estimate.

recurrence was 0.6 (95% CI: 0.37–0.98) compared to adenocarcinoma.

Concerning the 5-year OS analysis, Lee *et al* (13) found that patients with SCC had better survival rates than those with adenocarcinomas after trimodal therapy (42% versus 14%; $P = 0.009$).

In their systematic review, Bollschweiler *et al*[14] found that the median probability of pCR is about 24% in the SCC, and 19.5% for adenocarcinoma, with no statistically significant difference. At any rate, tumor response to neoadjuvant therapy has been identified as a prognostic factor. Therefore, the 8th edition of the AJCC staging of epithelial esophageal cancer shows separate classifications for clinical (cTNM), pathologic (pTNM), and post-neoadjuvant (ypTNM) stage groups.[9,14]

Considering neoadjuvant radiation, no significant difference was noted among the different range of doses for the endpoints pCR, OS, and DFS.

Table 3 Univariate analysis assessing the variables for the outcome overall survival (OS)

Variable	Mean time (months)	95% CI		HR	95% CI		Death			*P* value
		Lower	Upper		Lower	Upper	N	N	%	
Gender										0.352
Male	75.8	65	86.7	1			44	104	42.3	
Female	78.7	60.7	96.8	0.757	0.421	1.363	15	36	41.7	
Age				1.051	1.015	1.089				0.005*
Histologic type										0.036
Adenocarcinoma	49.7	37.9	60.8	1			23	44	52.3	
SCC	83.6	71.4	95.9	0.592	0.348	1.004	35	94	37.2	
Mixed carcinoma	18.7	18.8	18.7	3.401	0.446	25.966	1	2	50	
Grade of differentiation										0.312
Well	61.4	28.9	94	1			6	10	60	
Moderately	69.8	58.9	80.7	0.563	0.233	1.356	32	83	38.5	
Poorly	59.6	45.2	73.9	0.782	0.304	2.015	16	34	47.1	
Radiation dose										0.904
0	67.7	49.4	86.1	1			5	14	35.7	
41.4	46.7	39.9	53.6	1.401	0.524	3.75	20	53	37.7	
45	57.6	34.5	80.8	1.127	0.267	4.753	3	7	42.8	
50.4	62	46.1	77.7	1.392	0.485	3.993	12	21	57.1	
Chemotherapy regimen										0.58
CX	48.5	35.7	61.4	1			3	9	33.3	
CF	76.7	55.7	97.7	0.612	0.101	3.689	2	6	33.3	
CI	50.5	24.4	76.7	1.737	0.387	7.796	4	6	66.7	
CP	63	53.4	72.7	1.417	0.441	4.548	50	111	45	
Dysphagia after neoadjuvant therapy, compared to previous neoadjuvant therapy, n (%)										0.957
Worse	65.9	33.7	98.2	1			4	9	44.4	
Stable	63.3	47.6	79	0.999	0.306	3.263	9	24	37.5	
Partial improvement	56.5	45	67.6	1.1	0.374	3.241	20	41	48.7	
Complete improvement	65.1	53.5	76.6	0.924	0.317	2.699	22	55	40	
Neoplasm circumferential involvement before neoadjuvant therapy, n (%)										0.275
<50% of the circumference	65.2	51.8	78.7	1			3	13	23.1	
≥50% of the circumference	62.4	45	79.7	1.697	0.379	7.594	4	12	33.3	
Circumferential involvement	59.3	46.4	72.3	2.869	0.87	9.46	28	56	50	
Complete esophageal obstruction	67.6	41.2	74.2	2.462	0.675	8.982	10	22	45.5	
Weight change (%)				1.02	0.998	1.043				0.081*
Serum albumin change				1.406	0.799	2.474				0.238*
Margins										0.002
Clear	78.7	68	89.5	1			51	129	39.5	
Compromised	27.3	15	39.5	3.234	1.457	7.177	7	9	77.8	
Recurrence										<0.001
No	103	91.3	114.8	1			17	82	20.7	
Yes	35.2	28.21	42.2	5.635	3.147	10.092	42	58	72.4	
Pathologic complete response										0.003
No	53.7	43.7	63.6	1			44	83	53	
Yes	92	77.4	106.5	0.413	0.229	0.746	15	53	28.3	
Pathologic staging										<0.001
0/I/II	88	76.4	99.5	1			34	104	32.7	
III/IV	33.8	27.2	40.3	2.968	1.748	5.037	25	36	69.4	
Total	76.6	66.3	86.7				59	140	42.1	

Kaplan-Meier and log-rank test.

*Bivariate Cox Regression; and not possible to estimate.

Table 4 Univariate analysis assessing the variables for the outcome disease-free survival (DFS)

Variable	Mean time (months)	95% CI			95% CI		Recurrence or death			
		Lower	Upper	HR	Lower	Upper	N	N	%	*P* value
Gender										0.322
Male	31	3.7	58.3	1			55	102	53.9	
Female	51.4	1	105.4	0.765	0.448	1.303	18	36	50	
Age				1.029	0.998	1.062				0.068*
Histological type										0.025
Adenocarcinoma	24.5	20.9	22.1	1			27	42	64.3	
SCC	85	31.6	138.3	0.602	0.372	0.975	44	94	46.8	
Mixed carcinoma	13.8			2.385	0.562	10.123	2	2	100	
Grade of differentiation										0.186
Well	17.5	16.9	18.1	1			5	9	55.6	
Moderately	58.1	24.5	91.6	0.754	0.296	1.921	40	82	48.8	
Poorly	24.5	22.3	26.7	1.209	0.457	3.202	23	34	67.7	
Radiation dose										0.669
0	&			1			6	14	42.8	
41.4	42.1	19.3	64.9	1.483	0.609	3.612	26	52	50	
45	&			0.728	0.146	3.618	2	6	33.3	
50.4	51.3	3.3	99.5	1.368	0.517	3.621	13	21	61.9	
Chemotherapy regimen										0.787
CX	&			1			4	9	44.4	
CF	58.1			0.795	0.177	3.582	3	6	50	
CI	23.9	11	36.8	1.423	0.355	5.712	4	6	66.7	
CP	26.9	11	42.8	1.326	0.482	3.647	62	109	56.7	
Dysphagia after neoadjuvant therapy, compared to previous neoadjuvant therapy, n (%)										0.953
Worse	26.4	20.2	32.6	1			5	9	55.6	
Stable	24.4			1.064	0.373	3.034	12	23	52.2	
Partial improvement	26.2	12.6	39.7	1.143	0.434	3.007	24	41	58.5	
Complete improvement	51.4	19.1	83.6	0.978	0.377	2.538	29	55	52.7	
Neoplasm circumferential involvement before neoadjuvant therapy, n (%)										0.211
<50% of the circumference	&			1			5	13	38.4	
≥50% of the circumference	&			1.265	0.366	4.371	5	12	41.7	
Circumferential involvement	24.4	21.2	27.6	2.346	0.917	6.003	35	55	63.6	
Complete esophageal obstruction	28.9	10.7	47.1	1.932	0.687	5.432	13	22	59.1	
Weight change (%)				1.017	0.997	1.037				0.096*
Serum albumin change				1.456	0.912	2.324				0.116*
Margins										0.063
Clear	43.3	5.63	81	1			65	128	50.8	
Compromised	14	12.3	15.8	2.172	0.938	5.025	6	8	75	
Pathologic complete response										<0.001
No	24.3	22.7	25.9	1			54	81	66.7	
Yes	&			0.389	0.227	0.666	18	53	33.9	
Pathologic staging										<0.001
0/I/II	85			1			43	103	41.7	
III/IV	19.2	12.4	25.9	3.075	1.91	4.951	30	35	85.7	
Total	36.8	13.3	60.3				73	138	52.9	

Kaplan-Meier and log-rank test.

*Bivariate Cox Regression; and not possible to estimate.

The CROSS (ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study) trial[15] used a dose of 41.4 Gy in 23 fractions, yielding a pCR rate of 29%, with locoregional recurrence rate of 14%. These rates are comparable to doses of 50.4 or even higher.[16] Consequently, 41.4 Gy dose has been increasingly being used, avoiding radiation toxicity, and CROSS trial is currently the basis for National

Comprehensive Cancer Network (NCCN) guidelines for esophageal cancer management.[17]

None of the chemotherapy regimens was found to lead to better outcomes. Nevertheless, Li *et al*[12] reported that taxane-incorporated chemotherapy is associated to higher OS rate; and there was a nonsignificant trend toward increased progression-free survival rate for taxane-incorporated group compared to patients receiving traditional cisplatin and 5-fluorouracil.

Dysphagia relief after neoadjuvant therapy is not a valuable predictor of pCR, OS, and DFS. Strandby *et al*[18] found similar results for adenocarcinoma of the gastroesophageal junction. Relief from dysphagia may not be linked only to the neoplasm shrinkage. Besides the neoplasm mechanical obstruction, neoplasm encircling lower esophageal sphincter or infiltration of myenteric plexus branches or vagus nerves may theoretically contribute to dysphagia symptoms.[18,19]

Esophageal cancer patients usually evidence poor nutritional status due to intense dysphagia. Weight gain after neoadjuvant therapy was not significantly associated with pCR, OS, or DFS. After multivariate analysis, weight loss during neoadjuvant therapy was related to higher risk for recurrence or death (HR 1.02, 95% CI: 1–1.04). Forshaw *et al*[20] reported that weight gain and improved swallowing after chemotherapy are not sufficiently sensitive to identify pathologic responders from nonresponders.

Serum albumin level change during neoadjuvant therapy was unrelated to any of the outcomes. However, critical albumin levels before or after neoadjuvant therapy may impact survival.[21]

As limitations of this work, we would like to mention that this is retrospective, single institutional study, and data were missing in some of the studied analyses. Also, we only investigated a few groups of chemotherapy regimens, and some regimens consisted of only a few patients. A recent cohort reported promising results for biweekly docetaxel plus cisplatin and fluorouracil for advanced esophageal cancer, particularly for elderly patients and patients with moderate organ disorders. Biweekly docetaxel plus cisplatin and fluorouracil showed lower toxicity rates than traditional docetaxel plus cisplatin and fluorouracil regimen, with high clinical efficacy.[22]

Conclusions

The SCC histologic type was associated with higher probability of pCR, and higher OS and DFS rates. Gender, grade of cellular differentiation, chemotherapy regimen, and neoplasm circumferential involvement before neoadjuvant therapy are variables that are unrelated to pCR, OS, and DFS. Relief of dysphagia and increased serum albumin levels after neoadjuvant therapy were also unrelated to the studied outcomes. Weight loss during neoadjuvant chemotherapy was associated with poor DFS rate in the multivariate analysis.

Acknowledgments

This study did not receive any financial support. This study was approved by the local Ethics Committee (ICESP). All authors read and approved the final manuscript. The authors declare that they have no competing interests.

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