

Chemoradiotherapy With or Without Surgery for Esophageal Squamous Cancer According to Hospital Volume

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PURPOSE Esophageal squamous cell cancer (ESCC) is still associated with a dismal prognosis. However, surgical series have shown that high-volume hospitals have better outcomes and that the impact of center volume on definitive chemoradiotherapy (dCRT) or CRT plus surgery (CRT + S) remains unknown.

METHODS We performed a retrospective analysis of patients with locally advanced stage II-III (non-T4) ESCC treated with dCRT or CRT + S in São Paulo state, Brazil. Descriptive variables were assessed with the χ^2 test after categorization of hospital volume (high-volume [HV] center, top 5 higher volume, or low-volume [LV] center). Overall survival (OS) was assessed with Kaplan-Meier curves, log-rank tests, and Cox proportional hazards. Finally, an interaction test between each facility's treatments was performed.

RESULTS Between 2000 and 2013, 1,347 patients were analyzed (77% treated with dCRT and 65.7% in HV centers) with a median follow-up of 23.7 months. The median OS for dCRT was 14.1 months (95% CI, 13.3 to 15.3 months) and for CRT + S, 20.6 months (95% CI, 16.1 to 24.9 months). In the multivariable analysis, dCRT was associated with worse OS (hazard ratio [HR], 1.38; 95% CI, 1.19 to 1.61; $P < .001$) compared with CRT + S. HV hospitals were associated with better OS (HR, 0.82; 95% CI, 0.71 to 0.94; $P = .004$) compared with LV hospitals. Importantly, CRT + S superiority was restricted to HV hospitals (dCRT v CRT + S: HR, 1.56; 95% CI, 1.29 to 1.89; $P < .001$), while in LV hospitals, there was no statistically significant difference (HR, 1.23; 95% CI, 0.88 to 1.43; $P = .350$), with a significant interaction test ($P_{\text{interaction}} = .035$).

CONCLUSION Our data show that CRT + S is superior to dCRT in the treatment of ESCC exclusively in HV hospitals, which favors the literature trend to centralize the treatment of ESCC in HV centers.

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INTRODUCTION

Esophageal cancer (EC) is one of the deadliest neoplasms.¹ In 2018, approximately 10,970 cases of EC were expected in Brazil,² which represents the 9th most important oncologic cause of death in the country. EC can be divided into two main subtypes with different presentations and different treatment modalities.³ Esophageal adenocarcinoma (EA) predominates in the distal portion of the esophagus and has an intrinsic relationship with obesity-mediated gastroesophageal reflux disease.³ As a natural consequence of the obesity epidemic, the incidence of EA has consistently increased in the past decade, turning EA into an emergent problem in the developed world.¹ In striking contrast, the predominant type in the middle third of the esophagus is esophageal squamous cell cancer (ESCC). Unlike EA, ESCC has a high incidence in the developing world, where a strong association with tobacco and alcohol consumption preponderates.⁴

Both EA and ESCC represent aggressive diseases, with poor overall survival (OS), even in the initial stages.⁵ Historically, esophagectomy is the main treatment of EC. The results of the CROSS randomized clinical trial⁶ can be considered an important landmark in the treatment of EC. This trial demonstrated the superiority of neoadjuvant chemoradiotherapy (CRT) plus esophagectomy over surgery alone in the OS of esophageal and gastroesophageal junction cancers, which makes trimodal therapy the current standard of treatment of locally advanced EC (both ESCC and EA). Despite these results, 2 European trials showed the possibility of upfront concurrent definitive CRT (dCRT) as a possible treatment of locally advanced ESCC.^{7,8} Currently, this modality has been advocated for patients who decline or who are unsuitable for esophagectomy.⁹

Although esophagectomy is the main pillar of treatment of ESCC, it is an aggressive procedure with high morbidity and mortality.³ Of note, Birkmeyer et al¹⁰ showed that facilities with a high volume (HV) of surgical

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CONTEXT

Key Objective

Could the type of institution influence outcomes of patients with esophageal squamous cell cancer (ESCC) when these patients are treated with regimens containing chemoradiotherapy (CRT)?

Knowledge Generated

Trimodal therapy with CRT plus surgery (CRT + S) demonstrated a superior overall survival (OS; median, 20.6 months) compared with definitive CRT (dCRT; median, 14.1 months). Only patients treated in the highest-volume institutions seemed to have superior outcomes with trimodal therapy (hazard ratio [HR], 1.56), while those treated in the lowest-volume institutions did not show a difference between dCRT and CRT + S (HR, 1.12).

Relevance

Our findings favor centralization of treatment of patients with ESCC suitable for trimodal therapy and could direct policies of management for these patients in limited-resource countries.

procedures are associated with favorable outcomes, which has launched a trend for the centralization of esophagectomies in some countries.¹¹ Of note, this facility-related pattern has been observed not only in EC but also in rectal, lung, pancreatic, and gastric cancers.¹² Although EC is predominantly a disease of low- and middle-income countries, especially ESCC,³ most observations on how a facility's volume of treatment influences overall mortality come from developed countries.^{11,13-16}

There has been considerable progress in the surgical literature about how hospital resources influence the morbidity of esophagectomy, but analyses of how chemotherapy and radiotherapy could modulate this observation are lacking. Furthermore, how the institutional volume of treated patients can influence treatment of ESCC in a modern scenario, with the incorporation of radiotherapy and chemotherapy, remains an unresolved question. Here, we sought to determine whether the institutions with the highest surgery volume had different outcomes from others in patients with ESCC treated with dCRT or CRT plus surgery (CRT + S) in a developing country.

METHODS

We retrospectively analyzed patients who had undergone treatment for ESCC between 2000 and 2013 in São Paulo (SP) state, Brazil. SP is the biggest state in Brazil and accounts for 21.6% of the entire Brazilian population.¹⁷ We used data from the Fundação Oncocentro de São Paulo (FOSP), an authoritative organization that collects and summarizes information on oncologic treatment in SP, with data from the major public hospitals in SP. Epidemiologic, treatment, and survival information was used. The FOSP has dedicated teams in some of the major hospitals in SP, with the main function to collect information about epidemiology, treatment, survival, and the main cause of death. The FOSP is an institution and is part of the network of hospital-based cancer registries in Brazil, which are coordinated nationally by the National Institute of Cancer. The follow-up was done through an active search of hospital and death records or telephone contact. The data are used by

the Health Ministry of the State of SP for coordination of oncologic activities and programs. All hospitals should promote actions aimed at maintaining and guaranteeing hospital-based cancer registries in accordance with federal law.¹⁸ In our analysis, only analytical cases were used. Analytical cases are defined as the patients who arrived at the institution before any oncologic treatment has been started; thus, their main treatment was planned and performed in the reporting institution (the center responsible for reporting the case to FOSP). However, it is still possible that, for example, a patient would be referred from the reporting institution to another one to perform surgery after neoadjuvant CRT. In this case, the patient will be registered as analytical in the first institution. In our analyses, these patients were not excluded and accounted for the center that started the treatment of ESCC as registered in the FOSP data bank.

The FOSP did not provide information about the sequence of the treatments performed, so those who underwent chemotherapy plus radiotherapy were defined as dCRT, and those who underwent chemotherapy plus radiotherapy plus surgery were defined as CRT + S. Patients with EC were defined as having a confirmed histologic diagnosis on the basis of the International Classification of Diseases, Tenth Revision, codes C15.0-C15.9; in this analysis, we excluded esophagogastric transition cancer. We selected patients with ESCC age > 18 years and with a locally advanced presentation stage (TNM group stages II and III). Until 2005, the 6th edition of the TNM classification was used, and between 2006 and 2013 7th edition was used. We excluded patients in whom initiation of treatment was > 365 days after diagnosis, without T or N definition, or with M1 and T4 lesions. The exclusion of the T4 stage was made because this subset could represent unresectable disease, so patients were consequently not suitable for upfront neoadjuvant treatment. In the Brazilian public health system, positron emission tomography/computed tomography (PET/CT) and endoscopic ultrasound are not available to patients with EC. These patients are staged only with a CT scan of the thorax and abdomen.

We excluded from the analysis patients with early mortality (defined as death that occurred in the first 60 days after diagnosis), with the aim to reduce immortal bias.¹⁹ The FOSP database does not include comorbidity scores; thus, it was not possible to include this variable in the analysis. With the exclusion of early mortality, we expected to reduce the number patients with poor performance. Our primary outcome was OS, which was calculated by estimating the time between treatment initiation to death or censoring date.

Both treatments were grouped and compared in relation to their baseline variables: sex, age, residence, educational status, time to treatment initiation after histologic diagnosis, treatment and diagnosis performed in the same or different institution, diagnosis year, topography, prognostic group clinical stage, T stage, N stage, facility volume of treatment, and modality of treatment performed. All variables were initially evaluated with a univariable χ^2 test between facilities of HV and low volume (LV).

A center that performs an HV of esophagectomies is commonly defined as one that performs > 8 surgeries per year.¹⁰ With consideration that we have a low number of indications for esophagectomy, we a priori defined an HV center as one that performs > 8 surgical or nonsurgical procedures per year. Specifically, in our study, HV centers performed 8.6-21.9 procedures per year (2.1-5.3 esophagectomies per year), while LV centers performed 1-4.7

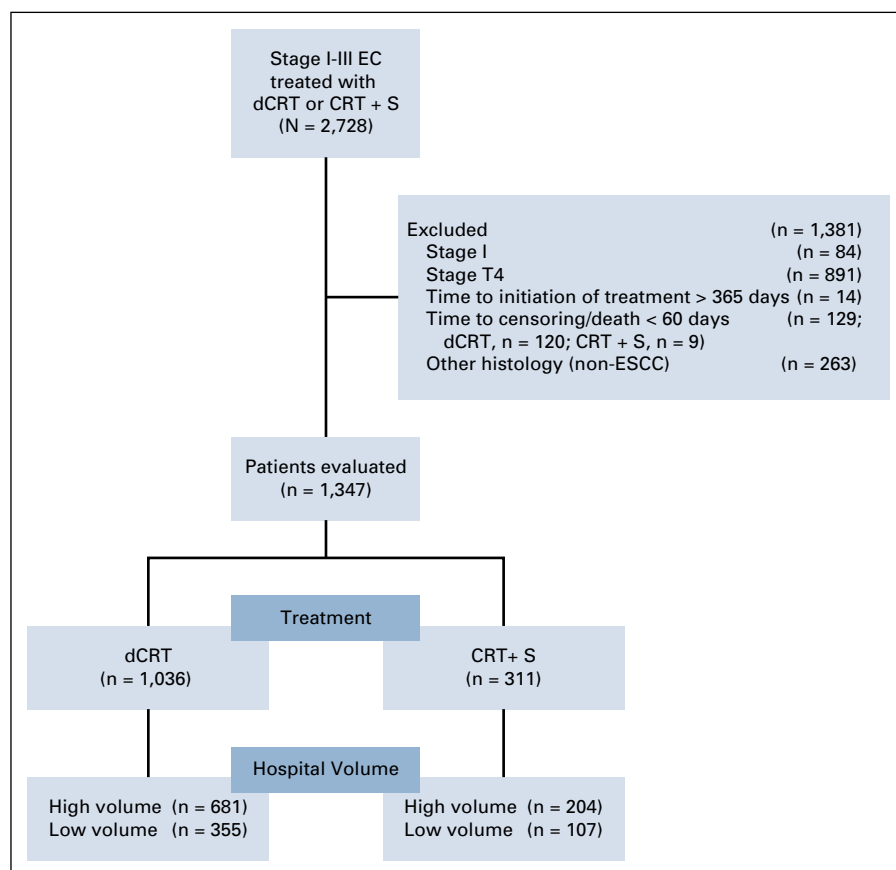
procedures per year (0-1.7 esophagectomies per year). In our data, the 5 HV institutions accounted for approximately two thirds of all performed treatments.

OS was initially assessed through a Kaplan-Meier curve, stratified by the modality of treatment and institution volume, and then we performed a log-rank test. To perform multivariable analysis, we used a Cox proportional hazards regression, with all variables included in the model. We tested for the interaction between the facility volume and treatment modality. Values of significance with 2-sided $P < .05$ were accepted as significant. All data were analyzed and computed using SAS 9.4 software (SAS Institute, Cary, NC). The current study was approved by the Campinas University Ethics Committee, and all analyses were aligned with the GATHER (Guidelines for Accurate and Transparent Health Estimates Reporting) protocol for reporting observational data.²⁰ All data were anonymously analyzed.

RESULTS

Initially, we assessed 2,728 patients with locally advanced EC who underwent dCRT alone or CRT + S. After exclusion according to the defined criteria, 1,347 patients with ESCC were included in this analysis; 1,036 (77%) of 1,347 patients underwent dCRT, while 311 (33%) received CRT + S. [Figure 1](#) shows the flow of patient inclusion in this analysis; 462 (34%) of 1,347 patients were treated in LV facilities, while 882 (65.7%) were treated in HV facilities. [Figure 2](#)

FIG 1. CONSORT diagram. CRT + S, chemoradiotherapy plus surgery; dCRT, definitive chemoradiotherapy; EC, esophageal cancer; ESCC, esophageal squamous cell cancer.



shows the number of treatments performed per institution, which are sorted in descending order by the total volume of treatments in the institutions analyzed.

The patients who had dCRT had a median OS of 14.1 months (95% CI, 13.3 to 15.3 months), while those who had CRT + S had a median OS of 20.6 months (95% CI, 16.1 to 24.9 months; Fig 3), with a significant difference by log-rank test ($P < .001$). We found that more patients initiated treatment within 60 days of diagnosis in the LV facilities compared with the HV facilities (285 [39.0%] of 462 ν 345 [61.7%] of 885; $P < .001$). In all, 189 (21.4%) of 885 patients in HV centers had their diagnosis and treatment in the same institution ν 184 (36.8%) of 462 in LV centers ($P < .001$). There was more stage III cancer in LV centers compared with HV centers (213 [46.1%] of 462 ν 304 [34.4%] of 885; $P < .001$). We did not observe differences in the rate of CRT + S according to facility volume (204 [23.1%] of 885 in HV centers ν 107 [23.2%] of 462 in LV centers; $P = .96$; Table 1).

The mean follow-up was 24.7 months for HV facilities and 22.1 months for LV facilities. In all cohorts, the mean follow-up time was 23.7 months. The median OS for patients who underwent dCRT was 14.7 months (95% CI, 13.7 to 16.2 months) in HV centers and 13.1 months (95% CI, 11.2 to 14.6 months) in LV centers (Fig 4). Those who underwent CRT + S in HV hospitals had a median OS of 24.9 months (95% CI, 19.8 to 29.8 months), whereas it was 15.1 months (95% CI, 11.6 to 20.2 months) for LV hospitals (Fig 4). There was a significant difference ($P_{\text{log-rank}} < .001$) for OS in relation to treatment modality (Fig 4). As listed in Table 2, female sex (HR, 0.76; 95% CI, 0.64 to 0.90; $P = .002$) and treatments performed between 2011 and 2013 (HR, 0.80; 95% CI, 0.68 to 0.94; $P = .009$) were both associated with better outcomes, while unspecified topography was related to worse survival (HR, 1.25; 95% CI, 1.02 to 1.53; $P =$

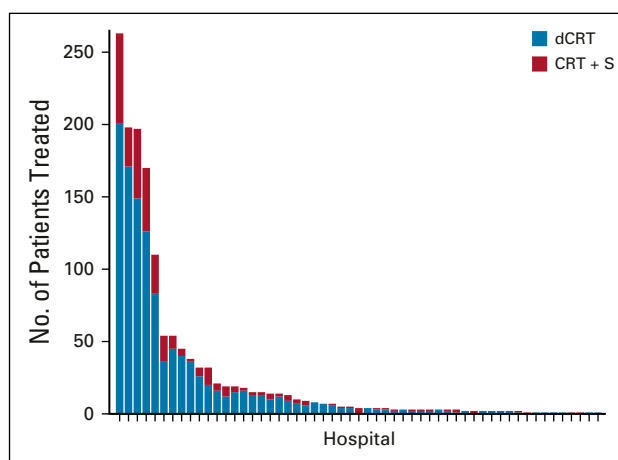


FIG 2. Treatments performed per institution ranked in descending order. Every hospital included in this analysis corresponds to a single bar. CRT + S, chemoradiotherapy plus surgery; dCRT, definitive chemoradiotherapy.

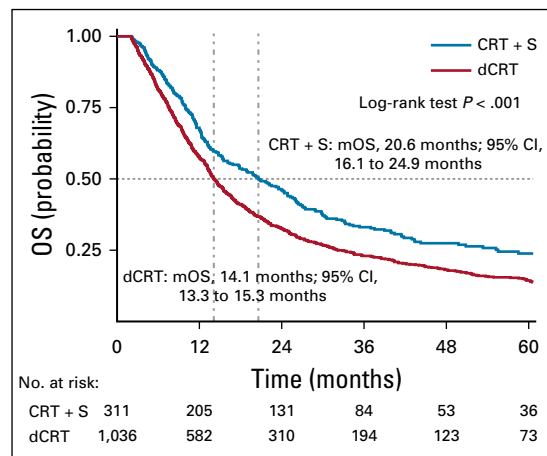


FIG 3. Kaplan-Meier estimates of overall survival (OS) according to treatment. CRT + S, chemoradiotherapy plus surgery; dCRT, definitive chemoradiotherapy; mOS, median overall survival.

.031). In the multivariable analysis, HV centers were associated with better outcomes than LV centers (HR, 0.82; 95% CI, 0.71 to 0.94; $P = .004$). In addition, the patients who underwent dCRT presented with significantly worse survival than those who received CRT + S (HR, 1.38; 95% CI, 1.19 to 1.61; $P < .001$; Table 2).

We also reported a significant interaction between treatment modality and hospital volume (Fig 4). The benefit of being treated with CRT + S was exclusive of HV centers (HR, 1.56; 95% CI, 1.29 to 1.89; $P < .001$), while in LV centers, we observed no differences between treatment modalities (HR, 1.23; 95% CI, 0.88 to 1.43; $P = .350$) ($P_{\text{interaction}} = .035$). In an explorative fashion, we performed interaction tests on sex, volume, year of diagnosis, and treatment received. We observed no other statistically significant interactions in this additional analysis.

DISCUSSION

Our study is the first to our knowledge to compare the relationship between the type of facility (volume of treatment) and treatment modality in the management of ESCC in Latin America. Our findings show that aggressive treatments (ie, CRT + S) are best managed in HV centers. Despite recent advances in the treatment of ESCC, such as the advent of neoadjuvant CRT and trimodal therapy, it remains a disease with a poor prognosis. Even those who underwent intensive treatments, represented by CRT + S, had a median OS of 24.9 months, which was far from the 81.6 months reported in the ESCC group of the CROSS study⁶ and highlights the differences between real-life and trial scenarios. Our data also show that patients treated with CRT + S had superior OS compared with those treated with dCRT, but this difference was significantly affected by the type of institution where the treatment was performed. This demonstrates that the gain with trimodal therapy has been

TABLE 1. Patient Characteristics According to Institution Treatment Volume

Variable	High Volume, No. (%)	Low Volume, No. (%)	Total	P
Mean follow-up, months	24.7	22.1	23.7	^a
Sex				
Male	749 (84.6)	395 (85.5)	1,144	.67
Female	136 (15.4)	67 (14.5)	203	
Age, years				
18-50	170 (19.2)	101 (21.9)	271	.30
51-65	494 (55.8)	238 (51.5)	732	
> 65	221 (25.0)	123 (26.6)	344	
Residency				
São Paulo state	807 (91.2)	458 (99.1)	1,265	< .001
Outside São Paulo	78 (8.8)	4 (0.9)	82	
Educational status				
Elementary education incomplete	555 (62.7)	166 (35.9)	721	< .001
Elementary education complete	129 (14.6)	72 (15.6)	201	
High school	80 (9.0)	33 (7.1)	113	
Ignored	121 (13.7)	191 (41.3)	312	
Time to start of treatment, days				
≤ 60	345 (39.0)	285 (61.7)	630	< .001
> 60	540 (61.0)	177 (38.3)	717	
Diagnosis and treatment				
Same hospital	189 (21.4)	184 (36.8)	373	< .001
Different hospital	696 (78.6)	278 (60.2)	974	
Year of diagnosis				
2000-2005	193 (21.8)	130 (28.1)	323	.03
2006-2010	375 (42.4)	174 (37.7)	549	
2011-2013	317 (35.8)	158 (34.2)	475	
Tumor location				
Upper	117 (13.2)	53 (11.5)	170	< .001
Middle	386 (43.6)	135 (29.2)	521	
Inferior	106 (12.0)	52 (11.3)	158	
Not specified	276 (31.2)	222 (48.1)	498	
Clinical stage				
II	581 (65.7)	249 (53.9)	830	< .001
III	304 (34.4)	213 (46.1)	517	
T stage				
1	17 (1.9)	7 (1.5)	24	< .001
2	134 (15.1)	108 (23.4)	242	
3	734 (82.9)	347 (75.1)	1,081	
N stage				
0	529 (59.8)	218 (47.2)	747	< .001
1	356 (40.2)	244 (52.8)	600	
Treatment				
CRT + S	204 (23.1)	107 (23.2)	311	.96
dCRT	681 (77.0)	355 (76.8)	1,036	

Abbreviations: dCRT, definitive chemoradiotherapy; CRT + S, chemoradiotherapy plus surgery.

^aStatistical test was not performed because of data characteristic.

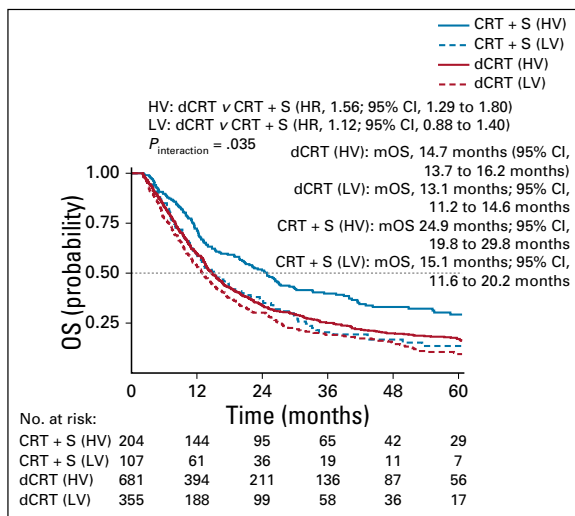


FIG 4. Kaplan-Meier estimates of overall survival (OS) according to treatment and facility volume. Strata 1, 2, 3, and 4 represent definitive chemoradiotherapy (dCRT) in high-volume (HV) hospitals, dCRT in low-volume (LV) hospitals, chemoradiotherapy plus surgery (CRT + S) in HV hospitals, and CRT + S in LV hospitals, respectively. HR, hazard ratio; mOS, median overall survival.

restricted to HV institutions, a result that possibly reflects the experience of the institution's treatment team.

In a Brazilian cohort,²¹ the 5-year OS of ESCC was 22.8%, regardless of clinical stage and age, which was similar to our study. The poor 5-year OS reported in this study is not exclusive to Brazil, as similar outcomes have been reported in other observational studies.^{22,23} Along this line, Chen et al²⁴ reported a 5-year OS of 20% for patients with locally advanced ESCC treated with dCRT. Similar outcomes have been reported by the WECC esophageal study group, with a 5-year OS of 30% in patients with clinical stage II and III ESCC.²⁵ These findings probably represent the complexity of the treatment of this population, even in high-resource countries. Of note, the standard of care for treatment of ESCC, even before the results of the CROSS trial, already includes trimodality therapy, but our data show that relatively few patients received CRT + S. Some factors may have contributed to the infrequent use of trimodality. First, limited access to the health care system, as indicated by the deferment in treatment initiation, may have contributed to the presence of more-advanced unresectable disease in our cohort. Second is the low capacity of the health system to perform surgeries. Altogether, these data suggest that Brazil needs improvements in its EC care line.

Our data are concordant with most of the literature that evaluated how institutional experience can influence the outcome of treatment.²⁶ In some countries, for instance, it has been advocated that esophagectomy should be performed only by more experienced teams.¹¹ Of note, these findings can also be influenced by factors such as the availability of human and physical resources. For example,

radiology, medical support, and intensive care can directly influence early and late mortality.²⁷⁻³⁰ Furthermore, not only the number of surgeries per se but also the frequency and proficiency of the surgeon affect surgical outcomes.³¹ Also of note, there is a growing enthusiasm for investigating the feasibility of active surveillance in patients with EC who have achieved a complete clinical response after neoadjuvant CRT.³² Therefore, it is important to be aware that the institution's expertise may influence the outcomes of these clinical trials.

Despite these intricacies, the value of dCRT seems to be undervalued in these analyses. Similarly to our study, Naik et al³³ showed that trimodal therapy (v dCRT) and type of institution are associated with different outcomes, with patients treated in academic facilities having the best OS. On the other hand, Hsu et al¹³ retrospectively evaluated patients with ESCC treated without surgical procedures and reported that LV hospitals had the best outcomes. In striking contrast, our analysis showed that there was no OS difference between HV and LV institutions for patients who underwent dCRT. One possible reason for this discrepancy is that there were clear imbalances in the proportion of patients who underwent surgery in the Hsu et al study by the institutional volume. Besides that the patients in our study lacked comorbidities and basal performance status, we showed a similar proportion of patients being treated with surgical modalities in HV and LV institutions, which raises a question of whether there could be a better selection of patients more suitable for surgery in HV institutions.

The treatment schedule is one of the major limitations of our work. The FOSP data do not specify the treatment details, mainly whether it was concurrent or sequential dCRT and whether it was performed before (neoadjuvant) or after (adjuvant) surgery. Our data do not exclude the notion that factors associated with the treatment itself could influence these outcomes too. The fact that our data did not include radiation fields, doses, and fractionation; type of chemotherapy; and surgical techniques limited the analysis of how much these variables could have influenced the analyzed outcomes. Along this line, reports have shown that Brazil is in the midst of a serious radiation therapy access crisis.³⁴

In our analysis, although deferment of the initiation of treatment was not associated with the worst outcomes, it is important to highlight that our work was not powered to account for the impact of delayed time in OS outcomes. Of note, Tustumi et al²¹ reported a high proportion of patients who received delayed treatment; specifically, more than one half of the patients received treatment 4 months after their diagnoses. These findings are in concordance with ours and reflect the difficulties in treatment access that patients with EC face in Brazil. Thus, we do not exclude that this factor may be associated with the inferior OS compared with other series in high-income countries.

TABLE 2. Multivariable Analysis of the Relationship Between Epidemiologic Characteristics and Outcome in Patients With Esophageal Squamous Cell Cancer

Variable	HR	P
Sex		
Male		
Female	0.76	.002
Age, years		
18-50		
51-65	1.07	.435
> 65	0.97	.785
Residency		
São Paulo state		
Outside São Paulo	0.98	.880
Educational status		
Elementary education incomplete		
Elementary education complete	0.98	.835
High school	0.85	.171
Ignored	0.85	.056
Time to start of treatment, days		
≤ 60		
> 60	0.99	.902
Diagnosis and treatment		
Same hospital		
Different hospital	0.99	.846
Year of diagnosis		
2000-2005		
2006-2010	0.88	.104
2011-2013	0.80	.009
Tumor location		
Upper		
Middle	1.17	.120
Inferior	1.24	.095
Not specified	1.25	.031
Clinical stage		
II		
III	1.17	.428
T stage		
1	0.88	.666
2		
3	1.03	.750
N stage		
0		
1	1.12	.523

(Continued in next column)

TABLE 2. Multivariable Analysis of the Relationship Between Epidemiologic Characteristics and Outcome in Patients With Esophageal Squamous Cell Cancer (Continued)

Variable	HR	P
Facility volume		
Low		
High	0.82	.004
Treatment		
CRT + S		
dCRT	1.38	< .001

Abbreviation: dCRT, definitive chemoradiotherapy; CRT + S, chemoradiotherapy plus surgery; HR, hazard ratio.

Our study has other limitations, the first of which is the lack of patients' initial performance status in our data. This could lead to a subgroup of patients in the dCRT group who received a palliative treatment instead of a definitive one. It is worth noting that in contrast to treatment with isolated chemotherapy or radiotherapy, the indication of combination regimens demands a minimum of performance status. Second, the unavailability of PET/CT and endoscopic ultrasound is a limitation to adequate staging but reflects the reality of treatment of ESCC in the Brazilian public health system, where only CT is accepted as a reimbursable image examination in patients with EC. Finally, the retrospective nature of our work significantly limits the generalizability of our findings.

In conclusion, our analysis shows that patients with ESCC treated in HV facilities had better outcomes than those treated in LV facilities. This influence is associated with those who underwent CRT + S in HV facilities. Our data would support the need to centralize the treatment of ESCC suitable for a surgical procedure. We also highlight the importance of the FOSP database as a way to evaluate the efficiency of the Brazilian health system. Furthermore, our work represents an important advance in the use of oncologic hospital records in Brazil to improve the management of patients with ESCC.

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Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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