Treatment Results for Stage III Laryngeal Cancer: Analysis of a Populational Database Using Propensity Scores

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Abstract

Introduction Treatment of stage III laryngeal cancer suffered a major paradigm change with surgery being substituted by radiation therapy with chemotherapy.

Objective To evaluate the oncological outcome of different treatment modalities for stage III laryngeal cancer using a population database.

Methods A population database representing patients treated in the state of São Paulo, Brazil, was analyzed. Demographic, clinical and treatment variables were included, and the outcomes of interest were disease-specific and overall survival. Propensity score with nearest neighbor matching was used to compensate for imbalances in treatment groups.

Results We retrieved data from 1,804 patients. In multivariate analysis, age, female gender, payment source, clinical N stage (cN) stages, and treatment modality were significant for disease-specific and overall survival. Patients submitted to surgery treatment had a significantly better disease-specific ($p < 0.001$) and overall survival ($p < 0.001$) compared with chemoradiation. Propensity score matching was based on cN stage, gender, age, topography, and payment modality, and allowed the pairing of 685 patients from each treatment modality. There was a significant difference in disease-specific survival favoring surgery-based treatment ($p = 0.017$).

Conclusion The treatment choice has a significant impact on survival in patients with stage III laryngeal cancer with surgery-based treatment being superior to chemo-radiotherapy (CRT).

Keywords
- laryngeal neoplasms
- propensity score
- prognosis
- surgery
- radiotherapy

Introduction

The aim of cancer staging is to group patients with similar prognoses and to create categories with maximum separation between them. Clinical stage III laryngeal cancer corresponds to a heterogeneous group of patients with T1-T2 tumors and a single metastatic lymph node < 3 cm and without extracapsular spread (N1), or patients with cT3 primary tumor without lymph node metastases (N0) or staged as N1[1]. Treatment of these patients depends on tumor extent and location, patient characteristics, experience of the

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treating team with the options, and preferences and expectations of the patients.[2]

The usual treatment of laryngeal cancer was primarily surgical until the VA trial was published and caused a major shift in the approach of these patients, with the combination of radiotherapy (RT) and chemotherapy (CT) assuming a major role due to the high rates of larynx preservation reported.[3] The following years made clear that larynx preservation per se was not an adequate endpoint due to the significant rates of laryngoesophageal dysfunction. The preservation of a dysfunctional larynx is not considered adequate.[4,5] The concept of laryngeal function preservation using a nonsurgical treatment was further extended by the RTOG 91–11 trial, which compared sequential to simultaneous chemoradiation (CRT) with a significant advantage for the latter.[6] The results of this trial were updated afterwards and showed a significant improvement in laryngeal preservation with simultaneous CRT, but overall survival was similar between the groups. Deaths not attributed to laryngeal cancer were higher in the simultaneous CRT group.[7]

These results were challenged by the analysis of retrospective and population-based databases. Chen et al. analyzed the National Cancer Database (NCDB) and found similar survival outcomes in stage III patients treated with surgery or CRT, but these were significantly better than exclusive RT.[8] A further analysis of the same database disclosed a worsening survival for patients beginning in the mid-1990s, which was correlated with the shift from surgical to nonsurgical therapy.[9] An analysis from the SEER database also confirmed that surgical treatment was associated with higher survival rates.[10] But in a retrospective series from a single institution, this treatment shift was associated with worse survival in stage IV patients, but not in stage III patients.[11] A meta-analysis of 15 studies showed a significant decrease in overall survival, disease-free survival, and locoregional control in T3 patients treated by laryngeal conservation protocol, but the number of patients enrolled in each study is small.[12] For patients with cT3 laryngeal carcinoma, four options are equally listed in the National Comprehensive Cancer Network: concurrent systemic therapy/RT with isolated RT if the patient is not a good candidate for chemotherapy or surgery with or without adjuvant therapy, induction chemotherapy or participation in clinical trials.[13]

The main object of the present study is to analyze survival results of cT3 cN0–1 laryngeal cancer patients treated by surgery followed or not by adjuvant treatment or CRT in the state of São Paulo, Brazil, using a population-based database.

Materials and Methods

Data for the present report were obtained from the website of the Fundação Oncocentro (www.fosp.saude.sp.gov.br) and were downloaded on September 10th, 2019. These data are provided by several hospitals distributed across the entire state of São Paulo, both public and private, and contain standardized data collected from January 2000 to June 2019.

The inclusion criteria were topographical description code of C32 according to the International Disease Classification (IDC), morphological type of squamous cell carcinoma or its variants, lack of previous treatment, and clinical stage **cT3 cN01–1** at diagnosis. Patients with in situ carcinoma or questionable stromal invasion at the morphological description were excluded from the present series. **We also excluded patients treated by exclusive RT or other treatment combinations.**

Statistical analysis was performed using the Stata 16 (Stata Corp., College Station, TX, USA) and R (R Foundation, Vienna, Austria) software. Categorical variables were described by their frequencies and continuous variables, by range, mean and standard deviation (SD). **Proportion comparisons were performed by the chi-squared test, while two means were compared by the Student *t*-test.** Multiple groups means were compared by analysis of variance (ANOVA). Survival analysis was performed by the Kaplan-Meier method followed by the log-rank test and Cox proportional hazard model. To compensate for the nonrandom allocation of patients among different treatments with variable distribution imbalance, a propensity score analysis was performed. Pairing was performed by the nearest neighbor method using a 0.02 calipers. **All tests were considered bicaudal,** and a p-value of 0.05 was considered statistically significant.

Since the data are anonymous and public, no consent from the Ethics Committee for Medical Research was sought.

Results

After application of the inclusion criteria, data from 1,804 patients were retrieved. The demographic, clinical, and treatment variables for the entire cohort are shown in ►**Table 1**. There was a clear temporal trend of increase in nonsurgical treatment in the present series (►**Fig. 1**). The median time of follow-up was 33.5 months. At the last follow-up information, 156 patients (8.7%) were alive with recurrent/persistent cancer, 670 patients were alive without evidence of disease (37.1%), 649 patients (36.0%) were dead from cancer, and 329 patients (18.2%) were dead from other causes. The 5-year overall survival rate was of 45.34% (►**Fig. 2**), and the 5-year disease-specific survival was of 57.09% (►**Fig. 3**).

In the univariate disease specific survival analysis, there were significant differences according to age at diagnosis, gender, cT stage, cN stage, laryngeal topography and treatment modality (►**Table 2**). The same variables remained significant in the multivariate analysis, with laryngeal topography demonstrating a worse prognosis for supraglottic or other laryngeal locations (►**Table 3**). In a comparison of patients treated by surgery with or without adjuvant treatment versus CRT, a significant survival advantage was observed in the second group (hazard ratio [HR]: 1.325; 95% confidence interval [CI]: 1.135–546; $p < 0.001$, ►**Fig. 4**). To evaluate the presence of immortal-time bias, we performed a landmark analysis at the time periods of 3 and 6 months focusing on treatment modalities (unimodal versus

Table 1 Demographic, clinical, and treatment variables summary for the entire cohort

Variable	Categories	Number of patients (frequency)
Gender	Female	237 (13.1%)
	Male	1,567 (86.9%)
Age	Mean (SD)	60.5 years old (9.9 years old)
Insurance	Private insurance	57 (3.2%)
	Public health system	722 (40.0%)
	Self-payment	10 (0.5%)
	Undisclosed	1,015 (56.3%)
Topography	Glottis	540 (29.9%)
	Supraglottis	394 (21.8%)
	Infraglottis	16 (0.9%)
	Transglottic	46 (2.5%)
	Unspecified	808 (44.8%)
cN stage	cN0	1,422 (78.8%)
	cN1	382 (21.1%)
Treatment modality	Surgery	370 (20.5%)
	Surgery + RT	305 (16.9%)
	RT + CT	832 (46.1%)
	Surgery + RT + CT	298 (16.5%)

Abbreviations: CT, chemotherapy; RT, radiotherapy; SD, standard deviation.

multimodal). In the first landmark, 108 patients (5.98%) were excluded from the analysis and, in the second landmark, 357 patients (9.25%) were excluded. The unadjusted and adjusted HRs are shown in ►**Table 4**.

We compared patients with glottic and supraglottic primary tumors. There are significant differences between the two populations regarding gender proportion, cN stage, age at diagnosis, and treatment modality employed (►**Table 5**). After stratification for primary tumor site and using the landmark approach to reduce bias, we get two different survival models (►**Table 6**). Treatment modality and cN stage were significant for both sites, while age was significant only for glottic primaries. Gender was not significant in any model.

To compensate for differences in patient allocation, propensity score matching was performed. Using cN stage, gender, age, topography, and payment modality, it was possible to match 685 patients from each group. The distribution of the propensity scores according to treatment is shown in ►**Fig. 5**. The comparison of the survival curves by the log rank test showed a significant difference favoring the surgical group ($p = 0.017$, ►**Fig. 6**).

With overall survival as the outcome of interest, a univariate analysis disclosed as significant the treatment modality, cN stage, primary tumor topography, payment modality, gender, and age (►**Table 7**). Multivariate analysis showed the same variables as being significant (►**Table 8**).

Discussion

We analyzed a public database containing information regarding stage III laryngeal cancer diagnosed in the state of São Paulo, Brazil. Since contribution to the database is voluntary, it does not represent the whole population, but a significant sample of it. Our major outcome of interest is survival, both disease-specific and overall. Since we have data focusing on a period of major transition from treatment modality, our major point of analysis is to compare surgery isolated or followed by adjuvant treatment versus chemoradiation.

In the present series, gender, age at diagnosis, tumor topography, cN stage, insurance status, and treatment modality were significantly associated with differences in survival rates. This finding correlates with a previous population-based series.[8] Unfortunately, insurance status was missing from a significant number of patients, but its prognostic impact possibly relates to comorbidity and general health status, including differences in housing and nutrition, rather than quality of care or treatment facilities. In a series from the Ontario Cancer Registry, socioeconomic status was significant for survival in patients with glottic, but not with supraglottic laryngeal cancer with more advanced T stage, explaining 3 to 23% of this effect.[14]

Patients with cT3 cN0–1 stage III laryngeal cancer in this sample treated by primary surgery fared significantly better than those treated by CRT, and this difference remained after adjustment for nonrandom allocation by propensity score. This finding is unlike the VA trial[3] but similar to those reported by Chen et al., whose patients treated by surgery followed or not by adjuvant treatment fared better than the CRT group.[8] Another prospective randomized trial demonstrated similar disease-specific survival in patients treated by surgery and RT versus CRT with salvage surgery (60% versus 50%), and considers CRT a valid larynx preservation strategy.[15] This finding demonstrates that our results are much closer to those reported by previous population-based analyses than those of prospective randomized trials conducted at tertiary centers. But a variable not recorded in the present series that significantly impacts survival is tumor volume. Patients with low volume (up to 3.5 cm3) cT3 tumors had higher survival rates when treated by exclusive RT.[16] It calls attention that a careful patient selection using restrictive criteria may have a significant impact on the prognosis. In general, the overall survival for cT3 laryngeal cancers treated by exclusive RT ranges from 52[17] to 83%.[18] A significant limitation of these series are the not very clear inclusion criteria and the therapeutic selection bias. The nonrandom allocation of patients for different treatments was shown in a recent article using the NCDB. In patients with cT3/T4 laryngeal cancer, initial treatment with total laryngectomy or chemoradiation was more frequent in patients with low comorbidity index. Both modalities had comparable overall survival in patients with cT3cNx primary

Fig. 1 Percentage of patients submitted to nonsurgical treatment according to year of treatment initiation.

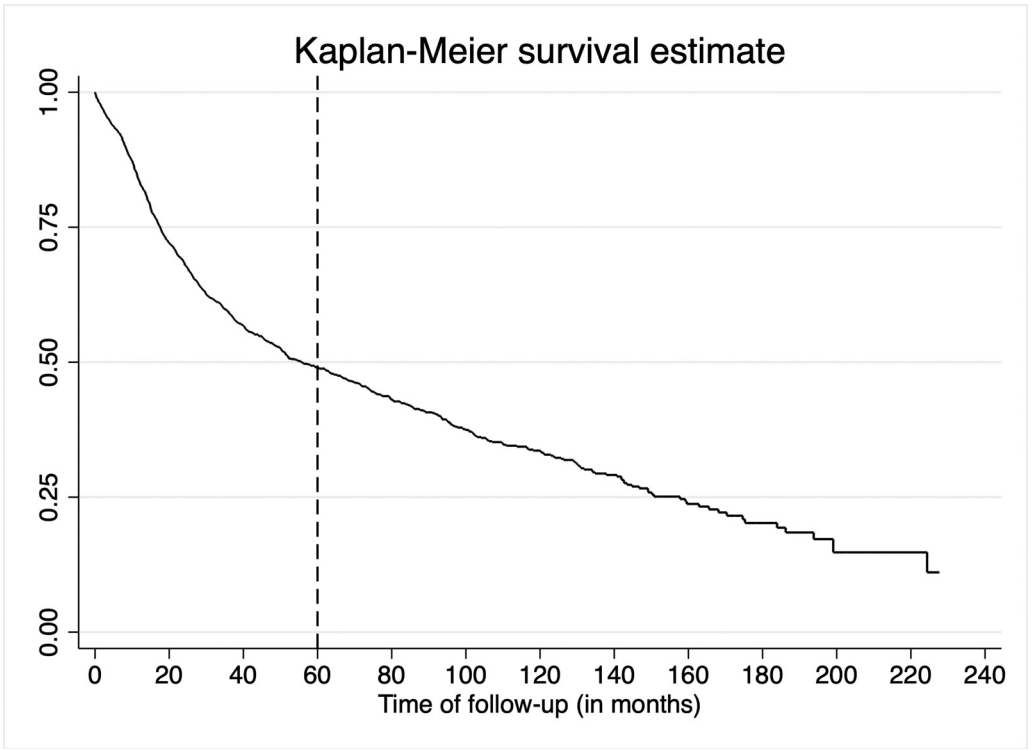

Fig. 2 Overall survival for patients included in the present series. The 5-year interval is indicated by the vertical dotted line.

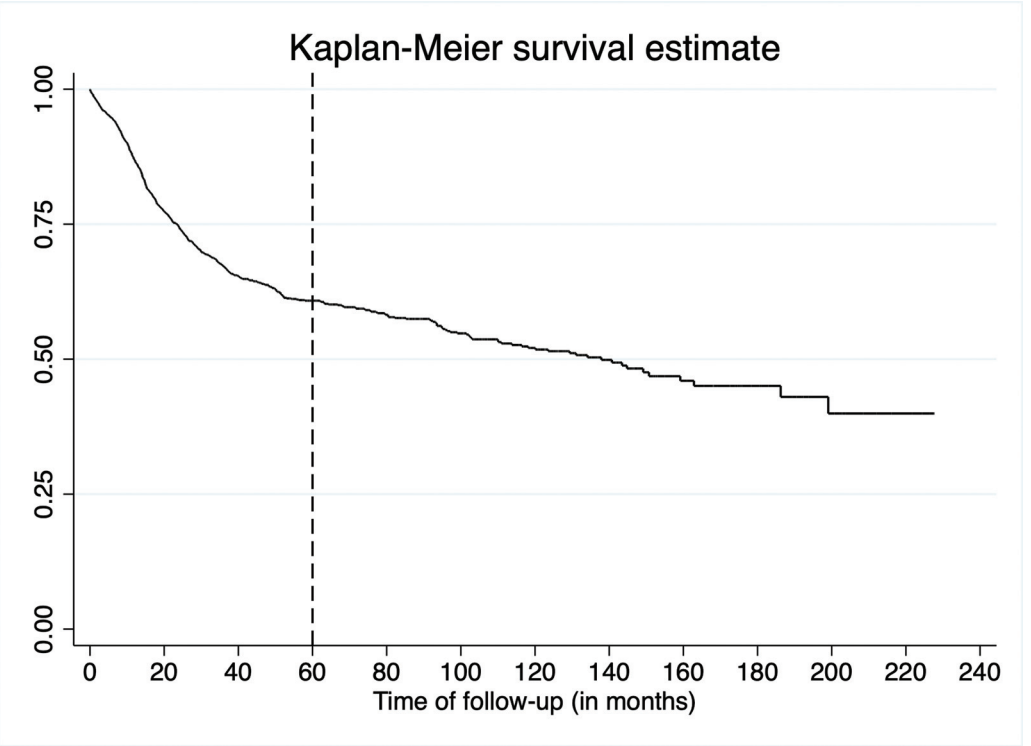

Fig. 3 Disease-specific survival for patients in the present series. The 5-year interval is indicated by the vertical dotted line.

Table 2 Univariate survival analysis with disease specific survival as the outcome of interest

Variable	Values	Hazard ratio	95%CI	*p-value*
Gender	Male	1		
	Female	0.7422	0.578–0.952	0.019
Age		1.018	1.009–1.026	<0.001
Payer	Private Insurance	1		
	Public system	1.959	1.039–3.695	0.038
	Self-paid	1.804	0.395–8.235	0.446
	Not specified	2.234	1.192–4.187	0.012
Topography	Glottis	1		
	Supraglottis	2.044	1.321–3.163	0.001
	Subglottis	1.191	0.489–2.902	0.699
	Other locations	1.293	1.033–1.617	0.025
cN	cN0	1		
	cN1	1.573	1.321–1.874	< 0.001
Treatment	Surgery	1		
	Surgery + RT	0.725	0.552–0.952	0.021
	RT + CT	1.232	1.001–1.517	0.050
	Surgery + RT + CT	1.080	0.839–1.391	0.547

Abbreviations: CI, confidence interval; CT, chemotherapy; RT, radiotherapy.

Table 3 Multivariate survival analysis with disease specific survival as the outcome of interest

Variable	Values	Hazard ratio	95%CI	*p-value*
Gender	Male	1		
	Female	0.742	0.576–0.956	0.021
Age		1.019	1.011–1.028	< 0.001
Payer	Private Insurance	1		
	Public system	2.116	1.187–3.770	0.011
	Self-paid	2.813	0.903–8.765	0.074
	Not specified	2.701	1.521–4.798	0.001
cN	cN0	1		
	cN1	1.551	1.294–1.861	< 0.001
Treatment	Surgery	1		
	Surgery + RT	0.739	0.577–0.946	0.016
	RT + CT	1.163	0.953–1.418	0.137
	Surgery + RT + CT	1.052	0.831–1.332	0.671
Topography	Glottis	1		
	Supraglottis	1.284	1.057–1.559	0.012
	Subglottis	0.633	0.571–3.397	0.467
	Other locations	2.072	1.333–3.220	0.001

Abbreviations: CI, confidence interval; CT, chemotherapy; RT, radiotherapy.

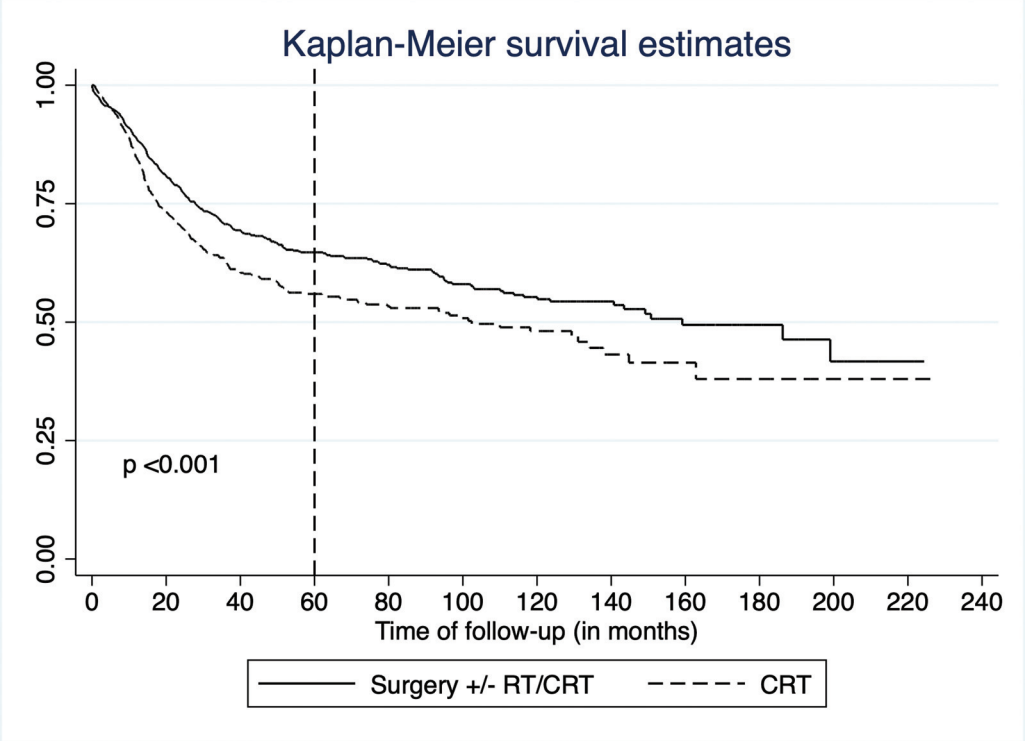

Fig. 4 Kaplan-Meier curves comparing single versus multimodal treatment. A significant survival advantage for patients submitted to surgery +/− adjuvant treatment is visible.

tumors.[19] In a single institution series, the authors demonstrate equivalent survivals for cT3 patients treated by primary surgery or CRT, but emphasize the role of strict selection criteria to achieve these results.[20]

The tumor primary site was significant for overall survival when comparing glottis with supraglottis and other locations in our series. This finding contrast with the analysis of a Norwegian series that demonstrated similar prognosis for

Table 4 Landmark analysis of patients at the 3- and 6-month time points

		Unadjusted models		Adjusted models	
Survival model	Patients analyzed	HR (CI)	*p-value*	HR (CI)	*p-value*
Base model	1,804	0.804 (0.696–0.928)	0.003	1.297 (1.111–1.514)	0.001
Landmark at 3 months	1,696	1.426 (1.213–1.678)	< 0.001	1.401 (1.191–1.649)	< 0.001
Landmark at 6 months	1,637	1.377 (1.166–1.628)	< 0.001	1.354 (1.145–1.601)	< 0.001

Abbreviations: CI, confidence interval; HR, hazard ratio.
The covariates were fixed at the lowest level, if categorical, or at the mean, if continuous. Surgery with or without adjuvant treatment was considered as reference.

Table 5 Comparison between the patients with glottic and supraglottic primary tumors

Variable	Values	Glottic primary	Supraglottic primary	*p-value*
Gender	Female	49 (9.1%)	82 (20.8%)	< 0.001
	Male	491 (90.9%)	312 (79.2%)	
Age	Mean (SD)	61.35 (9.89)	59.94 (9.03)	0.025
cN	0	487 (90.2%)	276 (70.1%)	< 0.001
	1	53 (9.8%)	118 (29.9%)	
Treatment	Surgery +/− RT/CRT	244 (45.2%)	253 (64.2%)	< 0.001
	CRT	296 (54.8%)	141 (35.8%)	

Abbreviations: CI, confidence interval; CRT, chemoradiotherapy; RT, radiotherapy; SD, standard deviation.

Table 6 Survival models according to primary tumor site (glottis versus supraglottis) with disease-specific survival as the outcome of interest

Variables	Values	HR	95%CI	*p-value*
Glottic primary tumor				
Age		1.034	1.018–1.051	< 0.001
Gender	Male	1		
	Female	1.061	0.613–1.838	0.832
cN	0	1		
	1	1.541	0.940–2.527	0.086
Treatment modality	Surgery +/− RT/CRT	1		
	CRT	1.249	1.027–1.701	0.015
Supraglottic primary tumor				
Age		1.001	0.983–1.1019	0.892
Gender	Male	1		
	Female	0.761	0.492–1.175	0.218
cN	0	1		
	1	1.448	1.029–2.038	0.034
Treatment modality	Surgery +/− RT/CRT	1		
	CRT	1.125	1.012–1.589	0.041

Abbreviations: CI, confidence interval; CRT, chemoradiotherapy; HR, hazard ratio; RT, radiotherapy.

both glottic and supraglottic cancers only in cT3 patients.[21] In our series, CRT decreased disease-specific survival in glottic and supraglottic tumors.

A meta-analysis of 25 studies on treatment outcomes for T3 glottic carcinomas demonstrated that disease-specific and overall survival were comparable in the surgery, RT and CRT arms, but with an improved local control in the surgery and CRT arms.[22] The data from the NCDB support the use of RT-based larynx preservation strategy. In a series of 2,622 patients, overall and disease-specific survival were

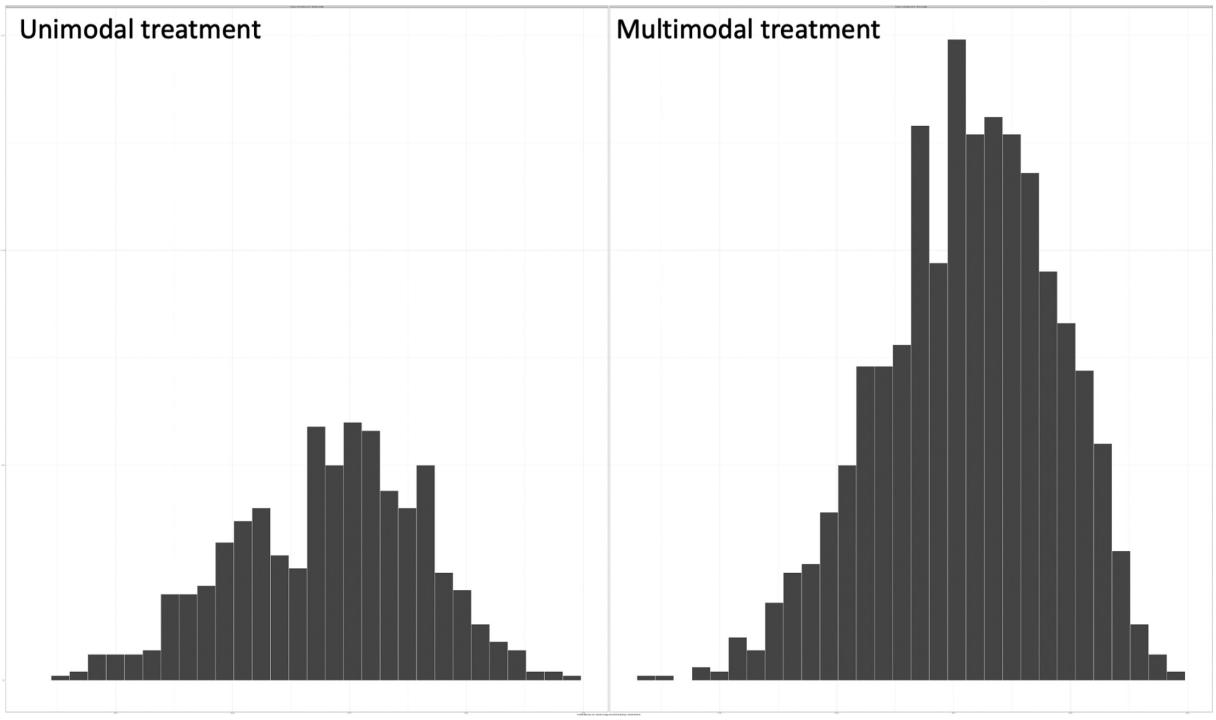

Fig. 5 Distribution of propensity score estimates according to treatment status.

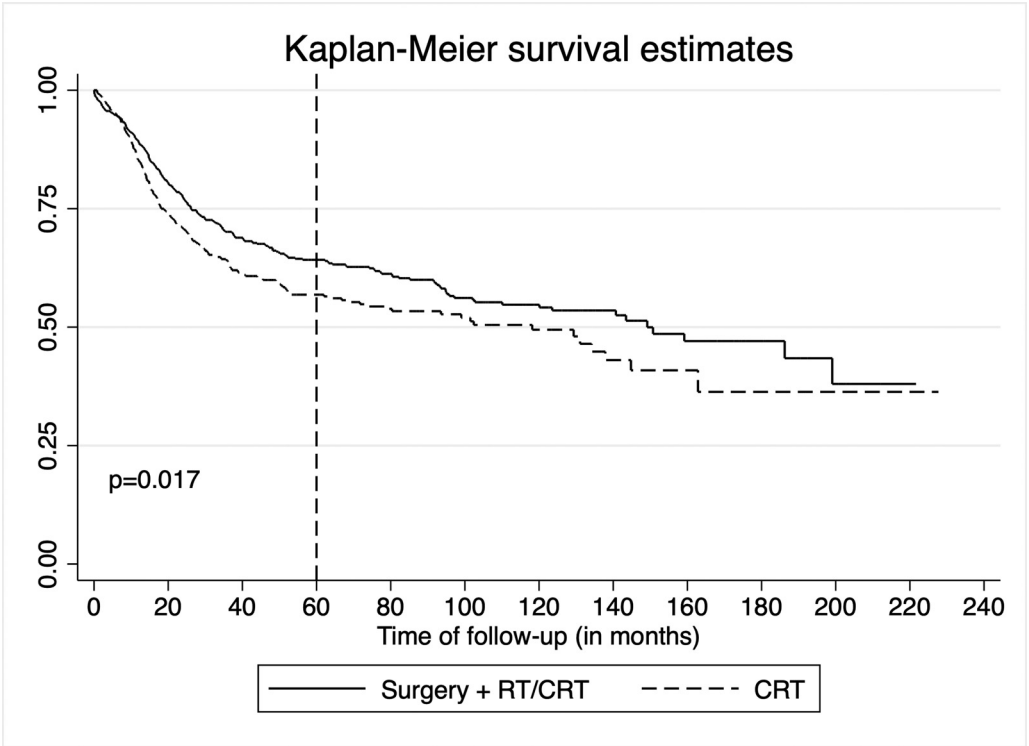

Fig. 6 Comparison of survival curves according to treatment modality after pairing by propensity score. In this cohort, a significant advantage for surgery-based treatments remains.

comparable between surgical and nonsurgical approaches.[23] A more recent analysis of the same database reported that patients treated by CRT had a significant better survival than those submitted to primary surgery in univariate analysis, but this advantage was not retained in multivariate analysis.[24] This may be related to nonrandom patient selection. But a retrospective series analyzing RT or CRT for cT3 cNx laryngeal carcinoma showed improved local control and laryngectomy-free survival with minimal increase in toxicity for patients submitted to CRT.[25] Interestingly, Timmermans

Table 7 Univariate survival analysis using overall survival as the outcome of interest

Variable	Values	Hazard ratio	95%CI	*p-value*
Gender	Male	1		
	Female	0.699	0.552–0.886	0.003
Age		1.025	1.018–1.033	< 0.001
Payer	Private Insurance	1		
	Public system	2.387	1.227–4.641	0.010
	Self-paid	2.230	0.497–10.648	0.287
	Not specified	2.716	1.403–5.255	0.003
Topography	Glottis	1		
	Supraglottis	1.808	1.218–2.685	0.003
	Subglottis	1.123	0.529–2.388	0.762
	Other locations	1.292	1.056–1.582	0.013
cN	cN0	1		
	cN1	1.394	1.182–1.644	< 0.001
Treatment	Surgery	1		
	Surgery + RT	0.725	0.552–0.953	0.021
	RT + CT	1.232	1.000–1.517	0.050
	Surgery + RT + CT	0.979	0.839–1.391	0.547

Abbreviations: CI, confidence interval; C**R**T, chemor**adio**therapy; RT, radiotherapy.

Table 8 Multivariate survival analysis using overall survival as the outcome of interest

Variable	Values	Hazard ratio	95%CI	*p-value*
Gender	Male	1		
	Female	0.742	0.576–0.956	0.021
Age		1.019	1.011–1.028	< 0.001
Payer	Private Insurance	1		
	Public system	2.030	1.074–3.837	0.029
	Self-paid	2.044	0.446–9.360	0.357
	Not specified	2.371	1.261–4.461	0.007
cN	cN0	1		
	cN1	1.552	1.294–1.861	< 0.001
Treatment	Surgery	1		
	Surgery + RT	0.702	0.534–0.925	0.012
	RT + CT	1.212	0.977–1.504	0.081
	Surgery + RT + CT	1.111	0.860–1.434	0.420
Topography	Glottis	1		
	Supraglottis	2.072	1.333–3.220	0.001
	Subglottis	1.393	0.571–3.397	0.467
	Other locations	1.152	0.912–1.456	0.235

Abbreviations: CI, confidence interval; CT, chemotherapy; RT, radiotherapy.

et al. reported on the results from the Netherlands Cancer Institute showing no survival difference between T3 and T4 tumors. The treatment option, as dictated by institutional protocols, was nonsurgical for T3 patients and surgical for T4 patients. The authors suggest that the lack of a survival difference may be related to the treatment option.[26] Our results show that surgery alone or associated with adjuvant treatment is superior to CRT. This result is in line with that reported by Chen et al., who favor surgery over nonsurgical approaches.[8]

Conclusion

The treatment choice has a significant impact on survival in patients with stage III laryngeal cancer, with surgery-based treatments having improved outcome when compared with CRT. In this population, the results of the previously reported prospective randomized trials are not reproduced.

Conflict of Interests
The authors have no conflict of interests to declare.

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