Treatment of carcinoma in situ of larynx: surgery versus radiotherapy

Original Article

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Abstract

Objectives: Evaluate the results of different treatments used in the treatment of *in situ* squamous cell carcinoma of the larynx.
Methods: Observational study that included patients followed in Instituto Português de Oncologia of Lisbon. The study included a group of patients with a diagnosis of in situ squamous cell carcinoma of the larynx, diagnosed between 2006 and 2018, and treated with surgery or radiotherapy.
Results: The study included 59 patients, 46 of these patients were submitted for surgery and 13 patients for radiotherapy. A median follow-up of 63,0 months (30,0-97,0) was made, and it was observed that recurrent disease in 25,4% of the total population, 26,1% of the patients that were submitted to surgery, and 23,1% of the ones that were submitted to radiotherapy. No statistically significant differences were found in recurrent disease between treatments used.
Conclusions: On this study, both treatments allow good local control rates of the disease, without differences between them.

Keywords: Squamous cell carcinoma; Surgery; Larynx; Radiotherapy

Introduction

Traditionally accepted carcinogenesis pathways consisting of a gradual process with progressive accumulation of genetic alterations, differ from those involved in the occurrence of premalignant lesions[1]. However, the clinical risk of malignant transformation increases with increasing grade of dysplasia, albeit in an unpredictable way. A systematic review of the literature to evaluate correlations between grade of dysplasia and the development of laryngeal squamous cell carcinoma (SCC) uncovered very wide ranges for malignant transformation rates: 0%–41.7% for mild dysplasia, 0%–48.0% for moderate dysplasia, 14.3%–44.4% for severe dysplasia, and 11.1%–75% for carcinoma *in situ*[2]. This has hindered the

creation of systems to stratify premalignant lesions that could predict malignant transformation[1,3].

Several scales are used to classify premalignant lesions, whose primary goal is to predict the final clinical outcomes[1]. Carcinoma in situ of the larynx belongs to a spectrum of premalignant lesions. It is histologically characterized as structural and cellular changes (dysplasia) typical of carcinoma that involve the whole mucosa but not the basal membrane (intraepithelial carcinoma)[4,5].

The etiopathogenesis of laryngeal dysplasia and SCC is multifactorial. The most important factors are smoking cigarettes and excessive alcohol consumption, which exert synergistic effects[1].

Laryngeal dysplasia occurs more frequently at the glottic level, when it manifests more frequently as dysphonia. Laryngeal dysplasia occurring either in the supraglottis or subglottis is usually asymptomatic.

The variable and non-specific macroscopic appearance includes hyperkeratosis, leukoplakia, erythroleukoplakia, erythroplakia, and even exophytic lesions[1]. Lesions cannot be definitively diagnosed by laryngeal videostroboscopy, endoscopy using narrow band imaging, or professional image enhancement systems, but these do help to distinguish between non-invasive or low-grade lesions and invasive or high-grade lesions[3]. As no pathognomonic characteristics of dysplasia can be determined by objective examination, a diagnosis can only be confirmed histologically[1,3].

The recommended options for treating laryngeal carcinoma in situ include radiotherapy (RT) and preferred surgical resection[6]. These recommendations are based on the results of several investigations of early-stage invasive carcinoma of the larynx. This is because treatments for premalignant laryngeal lesions differ among studies, and these and post-treatment follow-up regimens are not clear[3]. Some clinicians have achieved good rates of local control of laryngeal carcinoma in situ using either surgery or RT, without statistically significant differences between the treatment modalities[5,7,8]. Surgery remains the first choice for most clinicians, whereas indications for RT remain controversial. The most widely accepted indications are repeated relapse, persistent smoking due to inability to stop, high anesthetic risk, multiple scattered lesions, and patient preferences[3].

The present study aimed to determine the optimal treatment for laryngeal carcinoma in situ and how to achieve good rates of local control. We therefore analyzed demographic data and clinical specificities and compared the effects of surgical approaches with RT on recurrence and survival rates among patients diagnosed with carcinoma *in situ* of the larynx.

Material and Methods

This retrospective observational study included patients followed up at the outpatient clinic of the Instituto Português de Oncologia (IPO; Lisbon, Portugal) between 2006 and 2021.

All patients were assessed by direct laryngoscopy with incisional or excisional biopsy under general anesthesia between 2006 and 2018. A diagnosis of laryngeal carcinoma *in situ* was established through pathological reviews of slides at the IPO in Lisbon. All patients were treated by surgical excision or RT. Patients who underwent excisional and incisional biopsies followed by surgery with cold instruments or a CO2 laser comprised the surgically treated group. A subgroup of patients who underwent incisional biopsies of lesions spread over wide areas and had specific anatomic factors (poor glottic exposure), high anesthetic risk, or a personal preference were treated by RT.

The inclusion criteria comprised a diagnosis of carcinoma *in situ* established by biopsy, reassessment of slides by a pathologist at the IPO, surgical or RT treatment, regular follow-up with records of laryngoscopy in otorhinolaryngology consultations at the IPO, and at least 36 months of follow-up.

The exclusion criteria comprised a history of premalignant or malignant laryngeal lesions, a history of neck RT, carcinoma *in situ* ruled out by reassessment of biopsy slides at the

IPO, and refusal to accept treatment or loss to follow-up.

All data were statistically analyzed using SPSS v. 26 (IBM Corp., Armonk, NY, USA). The results are expressed as medians (25th–75th percentiles). Groups were compared using Mann-Whitney and chi-squared tests. Values with $p < 0.05$ were considered significantly different.

Results

The study included 59 patients. Of these, 52 were men (88.1%), and seven were women (11.9%) with a median age of 65.5 years (range: 58.8–70.0 years). The percentage of smokers was 84.6%, with a median smoking rate of 45.0 packs-year (range: 20.0–70.0), and 82.5% of patients consumed alcohol.

The site of the larynx most affected by carcinoma in situ was the glottis in 96.6% of the patients, followed by the supraglottis (3.4%). The macroscopic appearance of carcinoma in situ widely varied, with leukoplakia being the most frequent (35.8%), followed by exophytic lesions (33.9%), erythroleukoplakia (13.2%), hyperkeratosis (9.4%), and erythroplakia (7.5%). Among patients with carcinoma in situ in the glottis, an anterior commissure was involved in 25.0%, and both vocal cords were involved in 32.1%.

Among the 44 (74.6%) patients treated by surgery, a CO2 laser and cold instruments were used for 24 (54.5%) and 20 (45.5%) patients, respectively. The 15 (25.4%) patients treated with RT received a median dose of 63.0 (63.0–65.8) Gy.

Table 1 shows the demographics and characteristics of the patients, locations of carcinoma *in situ*, and type of treatment.

Smoking habits and alcohol consumption significantly differed between the groups. Significantly more patients treated with

Table 1
Demographics, characteristics, location of carcinoma *in situ*, and types of treatment

Variable	n	Ratio of total (%)
Sex		
Female	7	11,9
Male	52	88,1
Habits		
Cigarette smoking	50	84,6
Alcohol	49	82,5
Both	40	67,5
Macroscopic appearance		
Erythroplakia	4	7,5
Erythroleukoplakia	8	13,2
Hyperkeratosis	6	9,4
Leukoplakia	21	35,8
Exophytic lesion	20	33,9
Location: larynx		
Supraglottis	2	3,4
Glottis	57	96,6
Location: glottis		
Anterior commissure	15	25,0
Both vocal cords	19	32,1
Treatment		
Surgery	44	74,6
Cold instruments	20	33,9
CO2 laser	24	40,7
RT	15	25,4

Carbon dioxide; RT, radiotherapy

surgery than those treated with RT consumed alcohol (90.0% vs. 60.0%; p = 0.033) and consumed alcohol and smoked cigarettes (76.7% vs. 40.0%; p = 0.034). Demographic data, characteristics, and location of carcinoma *in situ* did not significantly differ between the groups (Table 2).

The median follow-up was 63.0 (30.0–97.0), months and 15 patients relapsed, among whom 27.3% and 20.0% were respectively treated with surgery and RT. The median time to relapse was 22.0 (14.0–27.0) months and rates of local disease control at three and five years were 78.2% and 71.4%, respectively, with no significant differences between surgery and RT. None of the patients developed regional or distant recurrence. Figures 1 and 2 show three and five year disease-free survival curves, respectively, according to the type of treatment.

Surgery was the preferred treatment of recurrence and was performed in 14 of the 15 patients who relapsed (93.3%); in other words, all patients submitted to RT as the initial treatment and 91.7% of those primarily submitted to surgery. One patient who was initially treated by surgery relapsed and then underwent RT.

Disease-specific and overall survival rates at five years were 100.0% and 82.2%, respectively, and did not significantly differ between the groups. Second primary tumors were diagnosed in 8 (13.6%) patients; four were located in the lungs, two in the oral cavity, and one each in the oropharynx and colon.

Discussion

The larynx is the most frequent location of carcinoma in situ within the head and neck region, and its incidence is increasing[9,10].

Table 2
Demographic data, characteristics, location of carcinoma *in situ*, relapse rates of all patients and of two subgroups according to treatment with surgery or RT

Variable	Total patients n= 59	Surgery n= 44	RT n= 15	p-value
Sex				
Female (%)	11,9	11,4	13,3	0,064
Male (%)	88,1	84,1	86,7	
Age (y)	65,5 (58,8-70,0)	65,0 (58,0-69,0)	70,0 (63,0-78,0)	0,886
Habits				
Smoking (%)	84,6	87,8	72,7	0,223
Drinking (%)	82,5	90,0	60,0	0,033
Smoking + drinking (%)	67,5	76,7	40,0	0,034
Macroscopic appearance				
Erythroplakia (%)	7,5	10,0	0,0	0,166
Erythroleukoplakia (%)	13,2	10,0	23,1	
Hyperkeratosis (%)	9,4	12,5	0,0	
Leukoplakia (%)	35,8	37,5	30,8	
Exophytic lesion (%)	33,9	30,0	46,2	
Location in the larynx				
Supraglottis (%)	3,4	2,3	6,7	0,421
Glottis (%)	96,6	97,7	93,3	
Location in the glottis				
Anterior commissure (%)	25,0	20,5	38,5	0,200
Both vocal cords (%)	32,1	25,0	53,8	0,055
Relapse (%)	25,4	27,3	20,0	0,580
Elapsed time to relapse (m)	22,0 (14,0-27,0)	23,0 (14,75-27,0)	20,0 (11,0-60,0)	0,885

m, months; RT, radiotherapy; y, years

Figures 1 and 2
Disease-free survival at three and five years after surgery or RT

Figure 1

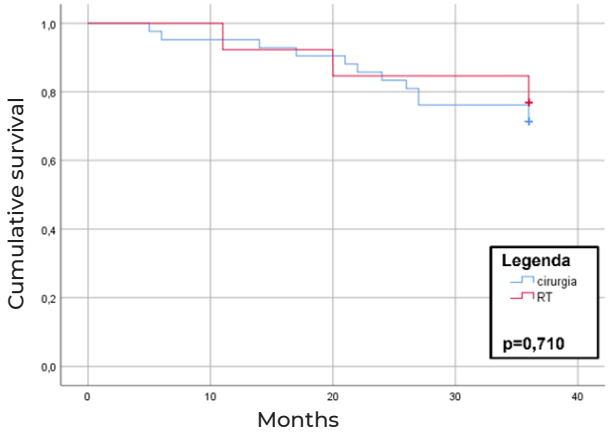
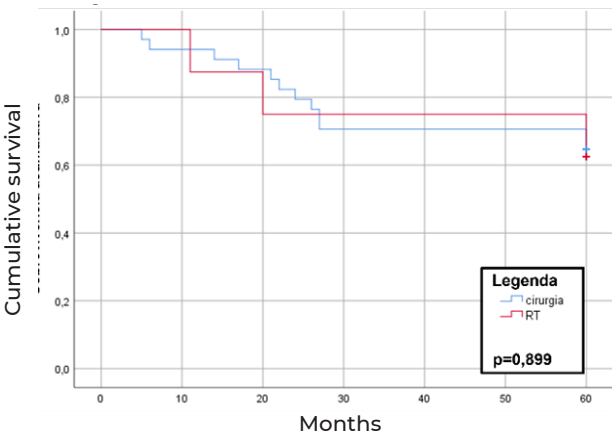


Figure 2



The present findings showed that the incidence of laryngeal carcinoma *in situ* was higher among males than females at a ratio of 7.4:1. These results are in line with previous findings that the incidence of carcinoma in situ is 5.2- and 6-fold higher in men in the USA and Germany, respectively[9,10]. This might be associated with different exposure to carcinogens, especially tobacco smoke and alcohol[11,12]. The median age of our patients (65.5 [58.8–70.0]) y was similar to that in previous studies[5,10].

The main etiopathogenic factors of laryngeal carcinoma *in situ* are cigarette smoking and excessive alcohol consumption, which exert synergistic effects[1]. Over 80% of our patients smoked cigarettes or consumed alcohol, which were both habitual in 67.5% of them.

Carcinoma *in situ* in the supraglottis or subglottis is often asymptomatic. This explains why direct observation of the larynx is frequently delayed until symptoms appear, when lesions can already be extensive/malignant[1]. In contrast, laryngeal carcinoma in situ is far more frequently diagnosed in the glottis, which is often associated with dysphonia; hence, patients tend to seek assistance earlier[1,10]. The present study found that 96.6% of carcinoma *in situ* was located in the glottis.

The most prevalent macroscopic appearance was leukoplakia (35.8%), followed by exophytic lesions (33.9%), erythroleukoplakia (13.2%), hyperkeratosis (9.4%), and erythroplakia (7.5%). Carcinoma *in situ* does not have a specific macroscopic appearance and includes hyperkeratosis, leukoplakia, erythroleukoplakia, erythroplakia, and exophytic lesions[1].

Although carcinoma *in situ* often appears as leukoplakia, the histological characteristics might differ. A histological analysis of 2,188 samples of laryngeal leukoplakia revealed no, mild/moderate dysplasia, and carcinoma in situ in 53.6%, 33.5%, and 15.2% of samples, respectively[13].

The choice of treatment for premalignant laryngeal lesions that include carcinoma *in situ* remains controversial. Most treatment for such lesions is based on knowledge gained from early-stage invasive laryngeal carcinomas (T1–T2). Therefore, until more data about the treatment of premalignant laryngeal lesions are accumulated, the recommended treatment remains the same as that for early-stage invasive carcinoma, with the expectation of a similar result[3]. The clinical guidelines of the National Comprehensive Cancer Network (NCCN) recommend treating carcinoma *in situ* of the larynx by surgical resection of the lesion or RT, with a preference for the former. This is based on studies on the effects of treating T1–T2 carcinomas of the larynx[6,14,15]. Two reports have described similar results of surgical resection and RT

for laryngeal carcinoma *in situ*[5,7]. Most (74.6%) of our patients were treated by surgery per the NCCN recommendations. Patients with lesions covering a larger area, anatomical factors (poor glottic exposure), high anesthetic risk, or a personal preference underwent RT. The demographic characteristics (sex and age), location of the carcinoma (larynx or glottis), macroscopic appearance of lesions, rates of relapse, and time to relapse did not significantly differ between the two groups. These results are in line with previous findings[3,5,7].

The survival rate for laryngeal carcinoma *in situ* is fairly high. Mortality appears to be associated with malignant transformation[5,7]. Most patients with this type of premalignant lesion are heavy smokers who consume alcohol, and some also have other associated comorbidities, which explains the higher overall, than disease-specific mortality.

Therefore, on the one hand, these patients probably have a higher anesthetic risk, which is an important factor to consider before choosing surgical resection for such patients. On the other hand, they are more likely to have second primary head and neck tumors, and undergoing RT as the primary treatment for laryngeal carcinoma *in situ* might limit its subsequent use for second tumor[7].

Conclusions

The present study found that both RT and surgical resection of laryngeal carcinoma *in situ* with lasers or cold instruments resulted in good three- and five-year rates of local disease control, with no significant differences between the two treatment modalities. Considering this, selection of the primary treatment should be based on contraindications, potential adverse effects, and the personal preferences of patients.

Conflicts of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

Data Confidentiality

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

Protection of humans and animals

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the 2013 Helsinki Declaration of the World Medical Association.

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Availability of scientific data

There are no datasets available, publicly related to this work.

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