Scientific Research Publishing

Journal of Cancer Therapy, 2018, 9, 163-178
http://www.scirp.org/journal/jct
ISSN Online: 2151-1942
ISSN Print: 2151-1934

Clinical Outcome of Definitive Radiotherapy and/or Surgery in T1-2N0M0 Glottic Squamous Cell Carcinoma: A Single Institution Retrospective Report

Dina Ragab Diab Ibrahim[1*], Anas Mohamed Askoura[2], Mohammed Aleem[2]

[1]Clinical Oncology Department, Faculty of Medicine, Ain-Shams University, Cairo, Egypt
[2]Ear, Nose, Throat ENT Department, Faculty of Medicine, Ain-Shams University, Cairo, Egypt
Email: *dibrahi1@gmail.com, anasaskoura@gmail.com, drmaleem2010@gmail.com

How to cite this paper: Ibrahim, D.R.D., Askoura, A.M. and Aleem, M. (2018) Clinical Outcome of Definitive Radiotherapy and/or Surgery in T1-2N0M0 Glottic Squamous Cell Carcinoma: A Single Institution Retrospective Report. *Journal of Cancer Therapy*, **9**, 163-178.
https://doi.org/10.4236/jct.2018.92017

Received: January 15, 2018
Accepted: February 23, 2018
Published: February 26, 2018

Abstract

Background: The current treatment options of early glottic carcinoma are radiotherapy; trans laser microsurgery, and open surgery. However, the best treatment is still controversial due to lack of randomized controlled trials. We aimed to evaluate the treatment results and the prognostic factors of local control of early glottic squamous cell carcinoma patients (GSCC) T1-2N0M0 treated at our institution. **Material and Methods:** We retrospectively studied the charts of 52 patients with early GSCC T1-T2N0M0 from 2010-2015 at the Clinical Oncology Department, Ain-Shams University. 24 patients had T1 and 28 had T2 early glottic carcinoma. The overall survival OS, local control rate, and laryngeal preservation rate were evaluated. Kaplan-Meier method, Cox proportional hazards model were used to analyze the data. **Results:** Median duration of follow-up was 13 months. Thirty-eight patients received radiation treatment alone (73.1%), 7.7% of the patients underwent surgery alone, and 19.2% of the patients had surgery combined with radiotherapy. Local recurrence after radiation failure developed in 6/52 patients, all had T2 disease and were salvaged by total laryngectomy. The ultimate local control rate was 88.5%, and the ultimate laryngeal preservation rate was 77.2% (40/52 patients). The median OS of the 52 patients was 13 months (range 2 - 46 months). Univariate analysis of factors associated with poor local control showed that age > 60 years was the only significant factor ($P = 0.048$). **Conclusion:** Radiotherapy achieves high local control and laryngeal preservation rates for patients with early glottic carcinoma, and is associated with a low rate of severe complications compared to surgery. Salvage surgery is feasible after radiotherapy failure.

Keywords

Larynx, Glottic Squamous Cell Carcinoma, Outcome, Radiotherapy, Surgery

1. Introduction

Early glottic carcinoma includes carcinoma *in situ*, T1, T2 N0 M0 [1]. Glottic SCC represents around 60% - 67% of laryngeal squamous cell carcinoma [2]. The male to female ratio is higher than for supraglottic carcinoma [3]. Stage III and IV disease represent 40% [4].

Glottic SCC has a good prognosis due to early presentation because of voice change and early treatment [5]. Treatment aims at cure, laryngeal function preservation with optimal voice quality, swallowing and breathing functions [6]. Open surgery, transoral laser microsurgery (TLM) and radiation therapy (RT) are successful options for treatment [7]. The treatment choice is not derived from randomized controlled studies making it controversial [8].

RT has less selection criteria, and more laryngeal preservation. Indications of RT are difficult or multiple recurrences after endoscopic excision, and medical inoperability [1]. The 5-year local control rates were 82% - 94% for T1a, 80% - 93% for T1b, 62% - 94% for T2a, and 23% - 73% for T2b [9] [10]. Radiotherapy has a long duration with possible acute side effects [11]. Fractionation schedules included conventional (2 Gy, total dose 60 - 66 Gy) and hypofractionation (2.25 Gy, total dose 60 - 70 Gy) and both were effective [6] [12] [13] [14].

The role of open partial laryngectomy has declined in favor of TLM [15]. Open surgery is considered for selected tumors when radiation or TLM are not technically feasible or available [8]. Salvage surgery after RT failure, is usually total laryngectomy as transoral and partial laryngectomy cause greater risk of chondronecrosis and pharyngocutaneous fistula [1].

Compared to surgery TLM has low morbidity, less need of tracheostomy and nasogastric feeding; no hospital stay, and fewer side effects [16]. A meta-analysis of nine retrospective studies showed similar survival rates of both RT and TLM [17], however, TLM impairs function minimally, is a single day procedure, allows normal diet, and preserves radiotherapy for treatment of recurrences or second malignancies [1]. The National Institute for Health and Care Excellence NICE guidelines advised TLM for T1a tumors, and TLM or RT for T1b-T2 lesions [18]. An update of Cochrane review compared RT, open surgery and TLM, but no randomized trials comparing RT to TLM were found [11].

We analyzed our treatment experience of early glottic carcinoma with radiotherapy and surgery.

2. Material and Methods

We retrospectively studied and analyzed the charts of 52 patients with histologically proven SCC of the glottis stages I and II (T1-T2N0M0) based on the American

Joint Committee on Cancer AJCC 7th edition [19]. The patients were treated at the Ear Nose Throat Department ENT, Ain-Shams University and the Clinical Oncology Department, Ain-Shams University between December 2010 and December 2015. This retrospective study was approved by the Research Ethical Committee at Faculty of Medicine; Ain-Shams University. Minor surgery (vocal cord stripping, cordotomy, excision) or major surgery (vertical hemilaryngectomy, total laryngectomy) was performed. Surgery was done alone or combined with radiotherapy in 14 patients as definitive treatment. Salvage total laryngectomy was performed for all patients who developed local recurrence. The majority of the patients were given radiotherapy as definitive treatment (38 patients) or following surgery in 10 patients. The staging work-up included history and physical examination, video laryngoscopy, routine blood tests, computed tomography of the neck (CT) and chest X-ray. Treatment decisions in the last 3 years of the study duration were discussed at the multidisciplinary meetings taking in account the patient's preferences and explaining the pros and cons.

2.1. Radiotherapy

Radiotherapy was delivered in 48/52 patients using 6 MV LINAC through parallel opposed lateral fields; appropriate wedges were employed to assure homogenous dose distribution in the glottic area as needed. The field borders included the larynx. Elective neck lymph nodes irradiation was not performed. The patients were immobilized in the supine position using a head and shoulders thermoplastic mask. T1 lesions were treated to a total dose of 63 - 66 Gy, and T2 lesions received 66 - 70 Gy using conventional fractionation (2 Gy per faction/day). The patients were examined weekly for acute toxicity.

2.2. Follow-Up Evaluation for the Early Detection of Local Recurrence

The patients were evaluated periodically with disease specific history, neck clinical examination, endoscopy and CT neck. When recurrence was suspected, biopsy was done for confirmation. Patients were regularly seen once every three months during the initial 2 years and then six-monthly till the conclusion of the study period.

2.3. Statistical Analysis

Data were analyzed using the Statistical Package for Social Science (IBM SPSS) version 20. The qualitative data were presented as number and percentages while quantitative data were presented as mean, standard deviations and ranges when their distribution found parametric while non-parametric data were presented as median with inter quartile range (IQR). The comparison between two groups with qualitative data was done by using Chi-square test. The comparison between two independent groups with quantitative data and non-parametric distribution was done by using Mann-Whitney test. Local control was calculated

from the end of treatment to the first occurrence of locoregional failure. Overall Survival was calculated from the date of diagnosis, which is the date of biopsy until the date of death or last follow-up. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following: $P < 0.05$: significant, and $P > 0.05$: non significant.

3. Results

3.1. Patients and Treatment

The patients, tumor and treatment data are depicted in (Table 1 and Table 2). All of the 52 patients were males. T1N0 disease was diagnosed in 24/52 patients versus 28/52 patients who had T2N0. The mean age was 61.85. Most of the patients had stage II disease (53.8%). The median follow-up duration was 13 months. T1 tumor was classified into T1a in 4 patients, T1b in 8 patients and missing subclassification in 12/24 patients. Type of treatment received was radiotherapy alone, combined surgery and radiotherapy and surgery alone. RT was the main type of treatment in 92.3% (48/52 patients) of the cohort; the median radiation dose was 66 Gy. RT was administered, as definitive treatment in 38/52 patients and combined with surgery in 10/52 (19.2%) patients. Surgery alone was performed in (4/52, 7.69%) patients or combined with radiotherapy in 10/52 (19.2%) patients. Tumor excision was the most common type of surgery (6/52, 11.5%).

When considering treatment by stage it was as follows; patients with T1N0 disease (n = 24 patients) received definitive RT in 14/24 patients, excision alone in 4/24, and surgery followed by RT in 6/24 patients. As regards T2N0 glottic SCC (n = 28 patients), 24/28 patients received definitive RT, whereas 4/28 patients had surgery followed by RT. The mean RT total dose was 68.86 Gy (range

Table 1. Patient and tumor characteristics.

		No. = 52
Age	Median (IQR)	57 (54 - 71)
Gender	Male	52 (100.0%)
Subsite	Glottic	52 (100.0%)
Grade	1	14 (26.9%)
	2	36 (69.2%)
	3	2 (3.8%)
Tumor T	1	24 (46.2%)
	2	28 (53.8%)
Lymph Node N	0	52 (100.0%)
Metastasis M	0	52 (100.0%)
Stage	I	24 (46.2%)
	II	28 (53.8%)

Table 2. Treatment characteristics.

		No. = 52
Surgery	No	38 (73.1%)
	Yes	14 (26.9%)
Type of surgery	Bilateral vocal cords stripping	2 (3.8%)
	Excision	6 (11.5%)
	Laser cordectomy	2 (3.8%)
	No	38 (73.1%)
	RT vertical hemilaryngectomy	2 (3.8%)
	Total laryngectomy	2 (3.8%)
Radiotherapy RT	No	4 (7.7%)
	Yes	48 (92.3%)
Indication of RT	Combined surgery and RT	10 (19.2%)
	Definitive	38 (73.1%)
	No	4 (7.7%)
RT dose (Gy)	Median (IQR)	66 (66 - 70)
Both surgery and RT	Radiotherapy	42 (80.8%)
	Surgery & radiotherapy	10 (19.2%)

63 - 70 Gy) in T2 N0 GSCC and 65.4 Gy (range 63 - 66 Gy) in T1N0 disease. The most common type of surgery performed in T1N0 patients was excision (6/24 patients), while for T2N0 disease 2/28 patients had laser cordectomy and 2/28 patients had vertical hemilaryngectomy.

3.2. Local Control

The median duration of local control of T1N0, T2N0 glottic SCC was 14.5 months (range 2 - 46 months), and 10.5 months (2.8 - 30 months) respectively. The local control rate for T1 disease was 100% (24/24 patients) and 78.6% (22/28 patients) for T2 disease. The ultimate local control rate of the studied cohort was 88.5%, where only 6/52 (11.5%) patients developed local recurrence, all had T2N0 disease and were all salvaged by total laryngectomy. None of the patients developed distant metastases.

The patients who received radiotherapy (both combined with surgery and definitive) had local control for a median duration of 13 months and local control rate of 85.7% (36/42 patients), versus the patients who underwent combined surgery and radiotherapy (10/52 patients) who had median local control duration of 12 months and 100% local control rate. 4/52 patients were treated with surgery alone and had 100% local control rate (Table 3).

Univariate analysis of the patient and treatment related factors was performed to assess their prognostic significance of local recurrence, it showed that age > 60 years was the only significant factor affecting incidence of local recurrence (P =

Table 3. Response to treatment by stage T1-T2N0.

		T1	T2	Test value	P-value	Sig.
		No. = 24	No. = 28			
Response	CR	22 (91.7%)	24 (85.7%)	0.449*	0.503	NS
	PR	2 (8.3%)	4 (14.3%)			
Local recurrence	No	24 (100.0%)	22 (78.6%)	5.814*	**0.016**	S
	Yes	0 (0.0%)	6 (21.4%)			
Local control duration (months)	Median (IQR)	14.5 (11 - 33)	10.5 (6 - 20)	−2.023ǂ	**0.043**	S
	Range	2 - 46	2.8 - 30			
Metastases	No	24 (100.0%)	28 (100.0%)	-	-	-
Alive or dead at last FU	Alive	20 (83.3%)	26 (92.9%)	1.148*	0.284	NS
	Dead	4 (16.7%)	2 (7.1%)			
ORS months	Median (IQR)	14.5 (11.5 - 33)	12 (9.5 - 22)	−1.545ǂ	0.122	NS
	Range	2 - 46	6 - 30			

ǂ: Mann-Whitney test; *: Chi-square test HS: Highly significant; NS; Non significant; S; Significant.

0.048). Type of treatment whether surgery or radiotherapy or both had no significant effect on local control ($P = 0.401$, $P = 0.661$, $P = 0.485$ respectively). The type of surgical procedure and the median radiotherapy dose also did not influence the incidence of local control ($P = 0.090$, $P = 0.607$ respectively) (Table 4).

3.3. Survival

The median OS of the studied cohort (n = 52 patients) was 13 months (range 2 - 46 months), where the median OS for T1N0 and T2N0 glottic SCC was 14.5 months and 12 months respectively (Table 3, Figure 1, Figure 2). The median OS achieved by radiotherapy (n = 42) and combined surgery and radiotherapy (n = 10) was 16 and 12 months respectively. By the end of follow-up duration 6/52 patients (4 T1N0 patients, and 2 T2N0 patients) died of causes unrelated to the glottic SCC.

3.4. Laryngeal Preservation Rate

Patients with T1N0 had 83.3% preservation rate of the larynx (where 2/24 T1N0 patients had total laryngectomy as the primary treatment). However, the remaining 20/24 patients with T1N0 glottic carcinoma had 100% ultimate laryngeal preservation rate after treatment. The ultimate laryngeal preservation rate of T2N0 disease was 71. 4% where 2/28 patients had vertical hemilaryngectomy as the primary treatment, and 6/28 patients developed local recurrence after the initial treatment and all were salvaged by total laryngectomy. Thus, the ultimate laryngeal preservation rate of the patient cohort was 77.2% (40/52 patients).

Table 4. Univariate analysis of factors predicting poor local control.

		No. = 52	P-value*
Age (<60 vs. >60 years)	Mean ± SD	61.85 ± 10.76	**0.048**
Grade	1	14 (26.9%)	0.604
	2	36 (69.2%)	
	3	2 (3.8%)	
T	1	24 (46.2%)	0.236
	2	28 (53.8%)	
Stage	I	24 (46.2%)	0.236
	II	28 (53.8%)	
Surgery	No	38 (73.1%)	0.401
	Yes	14 (26.9%)	
Type of surgery	No	38 (73.1%)	0.090
	Bilateral vocal cords stripping	2 (3.8%)	
	Excision	6 (11.5%)	
	Laser cordectomy	2 (3.8%)	
	Rt vertical hemilaryngectomy	2 (3.8%)	
	Total laryngectomy	2 (3.8%)	
Radiotherapy (RT)	No	4 (7.7%)	0.661
	Yes	48 (92.3%)	
Indication of RT	Adjuvant	10 (19.2%)	0.607
	Definitive	38 (73.1%)	
	No	4 (7.7%)	
RT dose (Gy)	Median (IQR)	66 (66 - 70)	0.171
Both surgery and RT	Radiotherapy	42 (80.8%)	0.485
	Surgery & radiotherapy	10 (19.2%)	

*Cox Regression Analysis.

4. Discussion

Early stages of glottic SCC T1-2 N0M0 represent 2% of all glottic cancers [20]. They are successfully managed with surgery, radiotherapy, or TLM (endolaryngeal surgery with or without laser) where they all achieve similar local control and survival advantage [11]. Due to the lack of prospective randomized controlled studies, there is no formal proof of the superiority of one treatment modality of early stage GSCC as regards the oncologic outcome or the functional outcome [11] [21]. Choice of treatment modality depends on three factors; local control, voice quality and cost [15] [22] in addition to treatment availability, expertise, and professional need for good voice quality [7]. Prior to 2013 treatment decisions at our institution were not based on the multidisciplinary approach, which explains why some of T1 glottic tumors in our study had surgery (minor surgery and even total laryngectomy in 2 patients) followed by radiation treatment. Currently, all treatment decisions at our institution are made by the

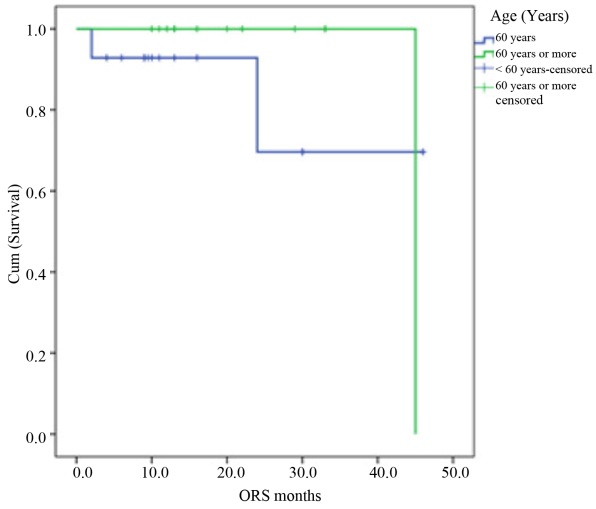

Figure 1. Effect of age on overall survival.

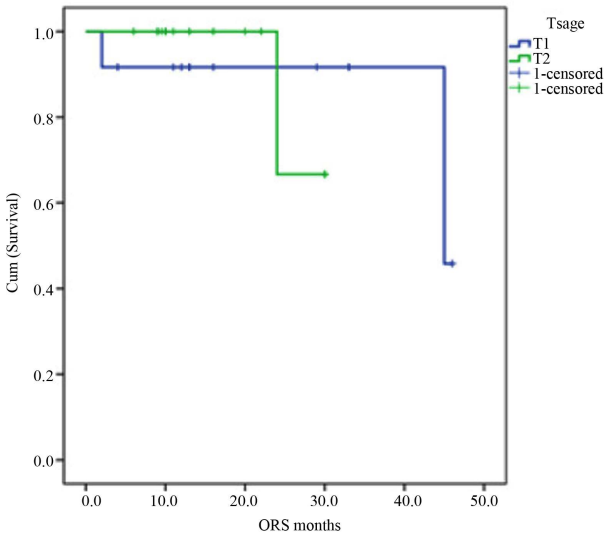

Figure 2. Effect of T stage on ORS.

multidisciplinary team, patients with early GSCC are offered the choice between RT and surgery. In this study we aimed to analyze the effect of radiotherapy and surgery on the treatment outcome of early glottic carcinoma at our institution.

In western countries the use of TLM is expanding, while open surgery is less frequently performed [23]. Compared to the conventional open partial laryngectomy, endolaryngeal surgery has the advantages of less need of tracheostomy, and/or nasogastric feeding, short hospital stay, inexpensive, and few side effects [16]. Similar to RT, endolaryngeal surgery is voice-sparing, but can be easily repeated which makes it more available retreatment for local recurrence where it could be followed by RT [24]. There are limitations for TLM mainly the inadequate exposure on suspension microlayngoscopy, limited exposure of the glottis due to trismus, protruding teeth, anatomical variations of the upper and lower jaw, bulky tongue, cervical spondylosis, and previous surgery or radiotherapy to

the neck [7]. The ENT-UK Head and Neck group reached a consensus that endoscopic excision is generally the preferred treatment for T1a GSCC, and suggested that it should be offered to GSCC tumors up to stage 2a [23]. The literature reports local control rates 71% - 100% for T1a GSCC treated with endoscopic laser surgery versus local control rates from 73% - 95% for patients who received RT [21]. A meta-analysis of 7600 patients in nine retrospective studies which compared objective voice quality in GSCC patients treated with RT versus laser microsurgery. Although non-significant the results trended towards favoring radiotherapy [17]. In our study only 2 patients with T2N0 disease had laser cordectomy followed by radiotherapy.

Conservative open laryngeal surgery includes a range of techniques from a laryngofissure approach with cordectomy to supracricoid laryngectomy. However, the oncologic and functional advantages of TLM reduced the indications of open partial laryngectomy which is reserved as salvage for patients with local recurrence after RT [25]. A systematic review analyzed the outcome of open partial laryngectomy for all stages of laryngeal cancer, it showed excellent outcome; local control rate was 89.8% at 24 months, the overall survival rate was 79.7%, and the pooled mean disease-free survival rate was 84.8% [26]. Dinapoli N *et al.* [27] reported on 143 patients with T1 glottic SCC; 73 underwent surgery and 70 underwent radiotherapy. The authors showed non-statistical significance of OS and disease-free survival DFS between the two treatment groups with better voice quality for patients treated with RT. In the current study 10/52 patients underwent surgery followed by RT, and only 4 patients had surgery alone. The local control and OS were better for patients treated with RT although it did not reach statistical significance.

Radiotherapy offers laryngeal preservation but has a prolonged course and may be associated with side effects such as oral mucositis, dysphagia, radiation skin burns and xerostomia [11]. The progress in radiotherapy delivery techniques led to better definition of target volumes and preservation of normal surrounding structures [22]. Different fractionation schedules have been used in various institutions varying from conventional fractionated schemes to hypofractionated and hyperfractionated schedules [10].

Hypofractionated radiotherapy has the advantage of reduced both overall treatment time, number of fractions, thus decreasing the cost, the burden of treatment upon institutions, and less visits by the patients. In the series by Ermis *et al.* [28] , the authors demonstrated their 10-year experience of using of 55Gy in 20 fractions, 2.75 Gy per fraction over 4 weeks offered high rates of local control with acceptable long term toxicity for both T1 and T2 glottic carcinoma. The ultimate local control rates (including successful salvage treatment) were overall 97.3%, T1a 100%, T1b 93.8% and T2% 95.8%. The disease-free survival was 23 months (range 5-73 months) then 20/132 patients developed recurrence. Currently, our policy is to treat T1N0 and selected cases of T2N0 glottic carcinoma are with hypofractionated RT 2.25 Gy per fraction.

Hyperfractionation is an alternative approach to accelerate treatment schedules. Hyperfractionated RT for T2 due to the relatively poor outcome-particularly T2b may be considered to a total dose of 74.4 Gy at 1.2 Gy twice per day with possibility of addition of concomitant weekly cisplatin 30 mg/m^2 for unfavorable T2 lesions [29]. Mendenhall *et al.* 2010 [29] demonstrated that the 5-year rates of ultimate local control with larynx preservation were 95% for T1a, 94% for T1b, 81% for T2a, and 74% for T2b. Trotti *et al.* [12] reported non-significant improvement of 5-year local control using hyperfractionated RT ($P = 0.11$). Harada *et al.* [30] retrospectively studied the treatment outcome of early glottic SCC patients treated with radiotherapy as initial treatment and salvaged by surgery for radiation failure. 79 patients were treated with conventional RT, and 36 patients were treated with hyperfractionated RT (1.2 Gy per fraction at 6 h intervals). The median total doses were 66 Gy for T1a, 70 Gy for T1b, and 74.4 Gy for T2 glottic SCC. The 5-year local control rates by initial RT al were 92% in patients with T1a disease, 83% in patients with T1b disease, 86% in patients with T2 disease and 88% in patients with all T stage (T1-T2).

Conventional RT was studied by several reports. Chera *et al.* [10] reported on 585 patients with T1-T2N0 SCC of the glottis all treated with definitive RT. Conventional RT dose for T1-T2a GSCC was 63 Gy in 28 fractions and 65.25 Gy in 29 fractions for T2b disease). The authors demonstrated that the 5-year rates of ultimate local control with larynx preservation were 95% for T1a, 94% for T1b, 81% for T2a, and 74% for T2b. Mendenhall *et al.* [31], reported on local control of T2 lesions by conventional RT to be approximately 71% - 85% and salvage rate for local radiation failure of 88 -95%. In the current study, RT was the main type of treatment in 92.3% of the cohort (definitive RT in 38/52 patients and RT following surgery in 10/52 patients). In agreement, the mean total conventional RT doses in our study were 65.40 Gy (range 63 - 66 Gy) for T1N0 glottic SCC and 68.86 Gy (range 63 - 70) for T2N0 disease.

As regards results of local control rates by conventional radiotherapy, different studies reported local control rates for T1 glottic SCC treated with RT at a range from 80% - 95% and with surgical salvage the ultimate local control rates vary between 90% - 100% [10] [32]. We observed better 100% local control rate by conventional radiation for T1N0 patients (RT alone in 14 patients and combined RT and surgery in 6 patients). Local control rates for T2N0 SCC of the glottis treated with conventional radiation was around 65% - 85% and salvage rate for local recurrence was 88% - 95% [10] [31] [32] comparably we reported 71.4% local control for T2N0 glottic SCC. Despite the high cure rate associated with radiotherapy of early glottic carcinoma, where the 5-year overall and disease specific survival rates are approximately 79% and 96%, respectively [6], still around 10% - 41% may have RT failure [33]. According to the series by Medenhall *et al.* [6], the site of RT failure in early glottic carcinoma was mostly local, while the regional failure rates were 5-20%. In the current study, failure was local and occurred in patients with T2N0 who all received RT (RT alone in 24 patients

and adjuvant RT in 4 patients). We detected treatment failure rate of 21.4% similar to other reports. The overall survival for T1N0 and T2N0 glottic SCC was 83.3% (dead patients 4/24) and 92.9% (dead patients 2/28 patients) respectively.

Studies compared the treatment outcome of the endoscopic laryngeal surgery, radiotherapy and open surgery. The local recurrence rate ranges from 8-20.75% for patients treated by 70 Gy radiotherapy [9] [10] 0% - 9% for patients treated with endoscopic laryngeal surgery [34], and 11% for those treated by open partial laryngectomy [35].The laryngeal preservation rate varies from 73% - 95% after 70 Gy radiation treatments [36] and 91% - 100% after endoscopic surgery and open surgery [35]. The laryngeal preservation rate for T1 disease is better than T2 [37]. Similarly, the laryngeal preservation rate in our study was better for radiotherapy alone treated T1N0 glottic SCC patients at 100% versus 71.4% after initial radiotherapy for T2N0 disease. According to Argawal and Ha [38], regarding the transoral laser resection the final local control rate including salvage therapy was 97% - 98%, laryngeal preservation rate 90% - 99%, and the 5-year disease specific survival 90% - 98%. As for radiotherapy, the final control rate including the salvage therapy 90% - 96%, laryngeal preservation 83% - 95%, and the 5-year disease specific survival 95% - 98%.

The prognostic factors which affect local control by radiotherapy are patient and tumor-related and radiotherapy related. Patient-tumor factors include tumor grade, pre-treatment hemoglobin, p53 expression, T-stage, anterior commissure involvement, vocal cord mobility, and tumor extension [39]. Tong CC *et al.* [40] evaluated the radiotherapy outcome of 56 patients with T1-2 N0 glottic SCC. Multivariate analysis of parameters that have had prognostic impact on T1 disease showed worse control with poorly differentiated grade (p 0.035), anterior commissure involvement (p 0.011), faction size 2 Gy (p 0.035), and tumor dose tumor BED $Gy_{15} < 65.0\ Gy_{15}$ ($p = 0.017$). For T2N0 disease, multivariate analysis showed adverse local control by poorly differentiated grade (p 0.22), hemoglobin < 13.0 (p 0.031), subglottic extension (p 0.027), and tumor BED $Gy_{15} < 65.0\ Gy_{15}$ (p 0.038). Groome *et al.* [9] identified age and smoking to be associated with worse locoregional control. In agreement, our study showed that age (mean 61.85 years) was the only significant factor affecting local control by both radiotherapy and/or surgery (p 0.048). Among The radiation related factors of recurrence two are very important and closely related the duration of RT, and fraction size [14] [15]. It is well documented that prolonged overall radiation treatment time as well as interrupted radiation negatively impacts survival and loco-regional control [9]. In early stage glottic carcinoma, radiotherapy completed within 42 days resulted in 100% local control rate [41], while treatment completed in more than 50 days was associated with lower control rate [42]. Fraction size more than 2 Gy resulted in better local control [43], while fraction size more than 3 Gy leads to higher complications rate [44]. Tong CC *et al.* [40], recommend using a fraction size 2.5 Gy for T1 disease, but for T2 disease the authors prescribe 70 Gy in 35 fractions, 2 Gy per fraction, 5 daily per week.

Surgery is the main salvage treatment after unsuccessful radiotherapy. Proper restaging of radiation recurred laryngeal carcinoma is crucial in planning salvage surgical treatment to achieve good functional and oncological results. The exact staging of recurrence in the irradiated larynx may help to avoid total laryngectomy [45]. Santaro *et al.* [44] retrospectively studied 173 patients with early glottic SCC who were surgically treated after RT recurrence, 47 patients were salvaged by partial laryngectomy and 126 patients underwent salvage partial laryngectomy. The authors could not identify significant results of DFS and OS between both types of surgery. They concluded possibility of conservative surgery only in select RT-relapsed patients and salvage total laryngectomy is still preferred. Endoscopic CO_2 laser cordectomy type IV, is an alternative to total laryngectomy that preserve laryngeal functions [46]. In their series, Pontes P *et al.* [47] showed high rate of recurrences after RT, patients underwent open partial laryngectomy or endoscopic surgery with control rates of 77.7% and 25% respectively. The authors reported that open partial laryngectomy without neck dissection is effective in treating RT-failures in patients who remain in stages T1a or T1b. Salvage total laryngectomy was performed in all RT recurrences in our study.

We acknowledge the limitations of the study; the drawbacks of retrospective studies, the small number of patients and the relatively short duration of follow-up. Some of the studied patients had their treatment decisions before starting the multidisciplinary meetings at our institution.

5. Conclusion

Our results indicated the efficacy of radiotherapy in treatment of T1-T2 N0 glottic carcinoma in agreement with the literature. Radiotherapy is associated with laryngeal preservation and it is a good alternative to surgery. Both surgery and radiotherapy achieve similar overall survival and local control rates. Large scaled prospective randomized controlled studies are needed to study the potential risk factors of radiation failure and to identify patients who may benefit from upfront surgery. We emphasize the importance of multidisciplinary approach for appropriate treatment decisions taking in consideration patient preferences.

Conflict of Interest

The authors have no conflict of interest to declare.

References

[1] Lin, J.R. and Prisman, E. (2014) Transoral Laser Microsurgery for Early Glottic Carcinoma. *Surgery Current Research*, **4**, 5.

[2] Ahn, S.H., Hong, H.J., Kwon, S.Y., Kwon, K.H., Roh, J.L., Ryu, J., *et al.* (2017) Guidelines for the Surgical Management of Laryngeal Cancer: Korean Society of Thyroid-Head and Neck Surgery. *Clinical and Experimental Otorhinolaryngology*, **10**, 1-43. https://doi.org/10.21053/ceo.2016.01389

[3] Coughlin, A.M. (2016) Glottic Cancer. Head and Neck Surgery, University of Nebraska Medical Center. Medscape.

[4] Myers, E.N., Suen, J.Y., Myers, J.N. and Hanna, E. (2003) Cancer of the Head and Neck. 4th Edition, Saunders, Philadelphia, PA.

[5] Peng, Z., Li, Y., Jin, L., Tao, X., Cai, X., Feng, J., *et al.* (2016) Retrospective Analysis of Therapeutic Effect and Prognostic Factors on Early Glottic Carcinoma. *Photodiagnosis and Photodynamic Therapy*, **15**, 167-171. https://doi.org/10.1016/j.pdpdt.2016.06.008

[6] Mendenhall, W.M., Amdur, R.J., Morris, C.G. and Hinerman, R.W. (2001) T1-T2N0 Squamous Cell Carcinoma of the Glottic Larynx Treated with Radiation Therapy. *Journal of Clinical Oncology*, **19**, 4029-4036. https://doi.org/10.1200/JCO.2001.19.20.4029

[7] Hakeem, A.H., Hakeem, I.H. and Wani, F.J. (2015) Treatment for Early Glottic Carcinoma. *Journal of Otolaryngology and Reconstructive Surgery*, **1**, 102. https://doi.org/10.19104/jors.2015.102

[8] Pfister, D.G., Laurie, S.A., Weinstein, G.S., Mendenhall, W.M., Adelstein, D.J., *et al.* (2006) American Society of Clinical Oncology Clinical Practice Guidelines for the Use of Larynx Preservation Strategies in the Treatment of Laryngeal Cancer. *Journal of Clinical Oncology*, **24**, 3693-3704. https://doi.org/10.1200/JCO.2006.07.4559

[9] Groome, P.A., O'Sullivan, B., Mackillop, W.J., Jackson, L.D., Schulze, K., Irish, J.C., *et al.* (2006) Compromised Local Control Due to Treatment Interruptions and Late Treatment Breaks in Early Glottic Cancer: Population-Based Outcomes Study Supporting Need for Intensified Treatment Schedules. *International Journal of Radiation Oncology • Biology • Physics*, **64**, 1002-1012. https://doi.org/10.1016/j.ijrobp.2005.10.010

[10] Chera, B.S., Amdur, R.J., Morris, C.G., Kirwan, J.M. and Mendenhall, W.M. (2010) T1N0 to T2N0 Squamous Cell Carcinoma of the Glottic Larynx Treated with Definitive Radiotherapy. *International Journal of Radiation Oncology • Biology • Physics*, **78**, 461-466. https://doi.org/10.1016/j.ijrobp.2009.08.066

[11] Warner, L., Chudasama, J., Kelly, C.G., Loughran, S., McKenzie, K., Wight, R., *et al.* (2014) Radiotherapy versus Open Surgery versus Endolaryngeal Surgery (with or without Laser) for Early Laryngeal Squamous Cell Cancer. *Cochrane Database of Systematic Reviews*, Issue 12, Art. No.: CD002027. https://doi.org/10.1002/14651858.CD002027.pub2

[12] Trotti 3rd, A., Zhang, Q., Bentzen, S.M., Emami, B., Hammond, M.E., Jones, E., *et al.* (2006) Randomized Trial of Hyperfractionation versus Conventional Fractionation in T2 Squamous Cell Carcinoma of the Vocal Cord (RTOG 9512). *International Journal of Radiation Oncology • Biology • Physics*, **66**, S15. https://doi.org/10.1016/j.ijrobp.2006.07.1339

[13] Williams, M.V., James, N.D., Summers, E.T., Barrett, A. and Ash, D.V., Audit Sub-Committee, Faculty of Clinical Oncology, Royal College of Radiologists (2006) National Survey of Radiotherapy Fractionation Practice in 2003. *Clinical Oncology* (*R Coll Radiology*), **18**, 3-14. https://doi.org/10.1016/j.clon.2005.10.002

[14] Yamazaki, H., Nishiyama, K., Tanaka, E., Koizumi, M. and Chatani, M. (2006) Radiotherapy for Early Glottic Carcinoma (T1N0M0): Results of Prospective Randomized Study of Radiation Fraction Size and Overall Treatment Time. *International Journal of Radiation Oncology • Biology • Physics*, **64**, 77-82. https://doi.org/10.1016/j.ijrobp.2005.06.014

[15] Mendenhall, W.M., Werning, J.W., Hinerman, R.W., Amdur, R.J. and Villaret, D.B. (2004) Management of T1-T2 Glottic Carcinomas. *Cancer*, **100**, 1786-1792. https://doi.org/10.1002/cncr.20181

[16] Remacle, F., Nest, M. and Levine, R.D. (2007) Laser Steered Ultrafast Quantum Dynamics of Electrons in LiH. *Physical Review Letters*, **99**, Article ID: 183902. https://doi.org/10.1103/PhysRevLett.99.183902

[17] Higgins, K.M., Shah, M.D., Ogaick, M.J. and Enepekides, D. (2009) Treatment of Early-Stage Glottic Cancer: Meta-Analysis Comparison of Laser Excision versus Radiotherapy. *Journal of Otolaryngology—Head & Neck Surgery*, **38**, 603-612.

[18] National Institute for Clinical Excellence (2016) Cancer of the Upper Aerodigestive Tract: Assessment and Management in People Aged 16 and over; NICE Guidelines [NG36]. http://www.nice.org.uk/NG36

[19] Edge, S.B., Byrd, D.R., Compton, C.C., Fritz, A.G., Greene, F.L. and Trotti, A. (2010) AJCC Cancer Staging Manual. Springer, New York, Vol. 7, 87-96.

[20] Jones, D.A., Mendenhall, C.M., Kirwan, J., Morris, C.G., Donnan, A., Holwerda, *et al.* (2010) Radiation Therapy for Management of t1-t2 Glottic Cancer at a Private Practice. *American Journal of Clinical Oncology*, **33**, 587-590. https://doi.org/10.1097/COC.0b013e3181beaab0

[21] Remmelts, A.J., Hoebers, F.J., Klop, W.M., Balm, A.J., Hamming-Vrieze, O. and van den Brekel, M.W. (2013) Evaluation of Laser Surgery and Radiotherapy as Treatment Modalities in Early Stage Laryngeal Carcinoma: Tumor Outcome and Quality of Voice. *European Archives of Oto-Rhino-Laryngology*, **270**, 2079-2087. https://doi.org/10.1007/s00405-013-2460-x

[22] Cuny, F., Gery, B., Florescu, C., Clarisse, B., Blanchard, D., Rame, J.P., *et al.* (2013) Exclusive Radiotherapy for Stage T1-T2N0M0 Laryngeal Cancer: Retrospective Study of 59 Patients at CFB and CHU de Caen. *European Annals of Otorhinolaryngology, Head and Neck Diseases*, **130**, 251-256. https://doi.org/10.1016/j.anorl.2012.04.013

[23] Bradley, P.J., Mackenzie, K., Wight, R., Pracy, P., Paleri, V. and ENT-UK Head & Neck Group (2009) Consensus Statement on Management in the UK: Transoral Laser Assisted Microsurgical Resection of Early Glottic Cancer. *Clinical Otolaryngology*, **34**, 367-373. https://doi.org/10.1111/j.1749-4486.2009.01944.x

[24] Higgins, K.M. (2011) What Treatment for Early-Stage Glottic Carcinoma among Adult Patients: CO_2 Endolaryngeal Laser Excision versus Standard Fractionated External Beam Radiation Is Superior in Terms of Cost Utility? *Laryngoscope*, **121**, 116-134. https://doi.org/10.1002/lary.21226

[25] Mendenhall, W.M., Takes, R.P., Shah, J.P., Bradely, P.J., Beitler, J.J., Strojan, P., *et al.* (2015) Current Treatment of T1N0 Squamous Cell Carcinoma of the Glottic Larynx. *European Archives of Oto-Rhino-Laryngology*, **272**, 1821-1824. https://doi.org/10.1007/s00405-014-3388-5

[26] Thomas, L., Drinnan, M., Natesh, B., Mehanna, H., Jones, T. and Paleri, V. (2012) Open Conservation Partial Laryngectomy for Laryngeal Cancer: A Systematic Review of English Language Literature. *Cancer Treatment Reviews*, **38**, 203-211. https://doi.org/10.1016/j.ctrv.2011.05.010

[27] Dinapoli, N., Parrilla, C., Galli, J., Autorino, R., Micciche, F., Bussu, F., *et al.* (2010) Multidisciplinary Approach in the Treatment of T1 Glottic Cancer. The Role of Patient Preference in a Homogenous Patient Population. *Strahlentherapie und Onkologie*, **186**, 607-613. https://doi.org/10.1007/s00066-010-2142-1

[28] Emris, E., Teo, M., Dyker, K.E., Fosker, C., Sen, M. and Prestwich, R.J. (2015) Definitive Hypofractionated Radiotherapy for Early Glottic Carcinoma: Experience of 55Gy in 20 Fractions. *Radiation Oncology*, **10**, 203. https://doi.org/10.1186/s13014-015-0505-6

[29] Mendenhall, W.M., Riggs, C.E., Vaysberg, M., Amdur, R.J. and Werning, J.W. (2010) Altered Fractionation and Adjuvant Chemotherapy for Head and Neck Squamous Cell Carcinoma. *Head Neck*, **32**, 939-945. https://doi.org/10.1002/hed.21261

[30] Harada, A., Sasaki, R., Miyawaki, D., Yoshida, K., Nishimura, H., Ejima, Y., *et al.* (2015) Treatment Outcomes of the Patients with Early Glottic Cancer Treated with Initial Radiotherapy and Salvaged by Conservative. *Japanese Journal of Clinical Oncology*, **45**, 248-255. https://doi.org/10.1093/jjco/hyu203

[31] Mendenhall, W.M., Parsons, J.T., Millon, R.R. and Fletcher, G.H. (1988) T1-T2 Squamous Cell Carcinoma of the Glottis Larynx Treated with Radiation Therapy: Relationship of Dose Fractionation Factors to Local Control and Complications. *International Journal of Radiation Oncology*, *Biology*, *Physics*, **15**, 1267-1273. https://doi.org/10.1016/0360-3016(88)90220-9

[32] Khan, M.K., Koyfman, S.A., Hunter, G.K., Reddy, C.A. and Saxton, J.P. (2012) Definitive Radiotherapy for Early (T1-T2) Glottic Squamous Cell Carcinoma: A 20 Year Cleveland Clinic Experience. *Radiation Oncology*, **7**, 193. https://doi.org/10.1186/1748-717X-7-193

[33] Al-Mamgani, A., van Rooij, P.H., Woutersen, D.P., Mehilal, R., Tans, L., Monserez, D., *et al.* (2013) Radiotherapy for T1-2N0 Glottic Cancer: A Multivariate Analysis of Predictive Factors for the Long-Term Outcome in 1050 Patients and a Prospective Assessment of Quality of Life and Voice Handicap Index in a Subset of 233 Patients. *Clinical Otolaryngology*, **38**, 306-312. https://doi.org/10.1111/coa.12139

[34] Burke, L.S., Greven, K.M., McGuirt, W.T., Case, D., Hoen, H.M. and Raben, M. (1997) Definitive Radiotherapy for Early Glottic Carcinoma: Prognostic Factors and Implications for Treatment. *International Journal of Radiation Oncology*, *Biology*, *Physics*, **38**, 37-42. https://doi.org/10.1016/S0360-3016(96)00613-X

[35] Spector, J.G., Sessions, D.G., Chao, K.S., Hanson, J.M., Simpson, J.R. and Perez, C.A. (1999) Management of Stage II (T2N0M0) Glottic Carcinoma by Radiotherapy and Conservation Surgery. *Head Neck*, **21**, 116-123. https://doi.org/10.1002/(SICI)1097-0347(199903)21:2<116::AID-HED4>3.0.CO;2-8

[36] Cellai, E., Frata, P., Magrini, S.M., Paiar, F., Barca, R., Fondelli, R., *et al.* (2005) Radical Radiotherapy for Early Glottic Cancer: Results in a Series of 1087 Patients from Two Italian Radiation Oncology Centers. I. The Case of T1N0 Disease. *International Journal of Radiation Oncology*, *Biology*, *Physics*, **63**, 1378-1386. https://doi.org/10.1016/j.ijrobp.2005.05.018

[37] Jones, A.S., Fish, B., Fenton, J.E. and Husband, D.J. (2004) The Treatment of Early Laryngeal Cancers (T1-T2 N0) Surgery or Irradiation? *Head Neck*, **26**, 127-135. https://doi.org/10.1002/hed.10361

[38] Agrawal, N. and Ha, P.K. (2008) Management of Early-Stage Laryngeal Cancer. *Otolaryngologic Clinics of North America*, **41**, 757-769. https://doi.org/10.1016/j.otc.2008.01.014

[39] Kim, T.G., Ahn, Y.C., Nam, H.R., Chung, M.K., Jeong, H.S., Son, Y.I., *et al.* (2012) Definitive Radiation Therapy for Early Glottic Cancer: Experience of Two Fractionation Schedules. *Clinical and Experimental Otorhinolaryngology*, **5**, 94-100. https://doi.org/10.3342/ceo.2012.5.2.94

[40] Tong, C.C., Au, K.H., Ngan, R.K., Cheung, F.Y., Chow, S.M., Fu, Y.T., *et al.* (2012) Definitive Radiotherapy for Early Stage Glottic Cancer by 6 MV Photons. *Head & Neck Oncology*, **4**, 23. https://doi.org/10.1186/1758-3284-4-23

[41] Rudoltz, M.S., Benammar, A. and Mohiuddin, M. (1993) Prognostic Factors for Local Control and Survival in T1 Squamous Cell Carcinoma of the Glottis. *International Journal of Radiation Oncology*, *Biology*, *Physics*, **26**, 767-772. https://doi.org/10.1016/0360-3016(93)90490-M

[42] Fein, D.A., Lee, W.R. and Hanlon, A.L. (1996) Do Overall Treatment Time, Field Size, and Treatment Energy Influence Local Control of T1-T2 Squamous Cell Carcinomas of Glottic Larynx? *International Journal of Radiation Oncology*, *Biology*, *Physics*, **34**, 823-831. https://doi.org/10.1016/0360-3016(95)02205-8

[43] Short, S., Krawitz, H., Macannn, A., West, T., Morton, R.P., McIvor, N.P., *et al.* (2006) T1N0/T2N0 Glottic Carcinoma: A Comparison of Two Fractionation Schedules. *Australasian Radiology*, **50**, 152-157. https://doi.org/10.1111/j.1440-1673.2006.01559.x

[44] Van der Voet, J.C., Keus, R.B., Hart, A.A., Hilgers, F.J. and Bartelink, H. (1998) The Impact of Treatment Time and Smoking on Local Control and Complications in T1 Glottic Cancer. *International Journal of Radiation Oncology*, *Biology*, *Physics*, **42**, 247-255. https://doi.org/10.1016/S0360-3016(98)00226-0

[45] Santaro, R., Bini, B., meccriello, G., Paiar, F. and Gallo, O. (2014) Salvage Surgery after Unsuccessful Radiotherapy in Early Glottic Cancer. *B-ENT*, **10**, 113-120.

[46] Piazza, C., Peretti, G., Cattaneo, A., Garrubba, F., De Zinis, L.O. and Nicolai, P. (2007) Salvage Surgery after Radiotherapy for Laryngeal Cancer: From Endoscopic Resections to Open-Neck Partial and Total Laryngectomies. *Archives of Otolaryngology—Head & Neck Surgery*, **133**, 1037-1043. https://doi.org/10.1001/archotol.133.10.1037

[47] Pontes, P., Brasil, O., Filho, F., Moraes, B., Pontes, A. and Neto, J. (2011) Radiotherapy for Early Glottic Cancer and Salvage Surgery after Recurrence. *Brazilian Journal of Otorhinolaryngology*, **77**, 299-302. https://doi.org/10.1590/S1808-86942011000300005