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HEAD AND NECK

Transoral laser surgery for recurrent glottic cancer after radiotherapy: oncologic and functional outcomes

La chirurgia transorale nel trattamento del carcinoma glottico dopo fallimento di radioterapia: risultati oncologici e funzionali

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SUMMARY

Primary radiotherapy (RT) has been successfully employed for treatment of early glottic cancer for the past half century. However, local recurrences still occur in 5-35% of patients. Salvage options for persistent/recurrent glottic cancer include total laryngectomy, open neck partial laryngectomies (ONPLs) and transoral laser surgery (TLS). We performed a retrospective chart review of 35 patients with glottic squamous cell carcinoma previously submitted to RT and managed by TLS at the Department of Otorhinolaryngology - Head and Neck Surgery of the University of Brescia, Italy, from 1995 to 2009. Oncologic outcomes were estimated using the Kaplan-Meier method, and separately calculated for the entire cohort of patients (n = 35) and for patients with true persistent/recurrent disease (n = 30), thus excluding the second primary tumours (n = 5). Hospitalization time and complications were obtained by chart review. Functional outcomes of a subgroup of 10 patients in terms of speech and swallowing were analyzed by the Voice Handicap Index (VHI), GRBAS scale, Multi Dimensional Voice Program (MDVP), M.D. Anderson Dysphagia Inventory (MDADI) questionnaire, videoendoscopy (VEES), and videofluoroscopy (VFS) of swallowing (both graded according to Donzelli's scale), and compared to a cohort of 10 patients matched for age, gender and pT category, treated by the same team of surgeons by TLS as a primary treatment. The types of resection used were: 18 Type III, 1 Type IV, and 16 Type V cordectomies. Postoperative staging was 16 rpT1a, 17 rpT2, and 2 rpT3. The 5-year overall survival for the entire series was 91%. Five-year disease-specific survival, local control with laser alone, and organ preservation rates were 94%, 84% and 87%, respectively. Among the variables tested by univariate analysis, for the entire cohort of patients the pT category had a statistically significant impact on local control with laser alone. Anterior transcommissural extension had a borderline statistical impact on disease-specific survival, while it was clearly significant on overall survival. The status of surgical margins and presence of recurrence after TLS statistically influenced both organ preservation and local control with laser alone. The mean values of VHI, MDADI, and MDVP did not show any statistically significant difference between irradiated and non-irradiated patients. The same was true for GRBAS, VEES, and VFS. This series confirms that TLS after RT failure can be considered a successful surgical option in selected early recurrences, with functional outcomes comparable to those observed after TLS as a primary treatment, and much better than those classically described after ONPLs.

KEY WORDS: Laryngeal cancer • Radiotherapy • Salvage surgery • Transoral laser surgery • Oncologic outcomes • Functional outcomes

RIASSUNTO

La radioterapia (RT) è stata utilizzata con successo come trattamento del carcinoma laringeo in stadio iniziale per metà del secolo scorso. Ciò nonostante il 5-35% dei casi presenta una recidiva locale. Le opzioni di salvataggio sono rappresentate dalla laringectomia totale, dalle laringectomie parziali a cielo aperto e dalla chirurgia transorale mediante laser (CTL). Abbiamo condotto uno studio retrospettivo su 35 pazienti affetti da recidiva di carcinoma squamoso trattati con RT e sottoposti a CTL di salvataggio presso il Dipartimento di Otorinolaringoiatria e Chirurgia Cervico-Facciale dell'Università degli Studi di Brescia, tra il 1995 ed il 2009. I risultati oncologici sono stati calcolati mediante le curve di Kaplan-Meier sia per l'intera coorte (n = 35), sia per i soli pazienti affetti da persistenza/recidiva di malattia (n = 30), escludendo coloro affetti da un secondo tumore (n = 5). Il tempo di ospedalizzazione e la prevalenza di complicanze sono stati ottenuti mediante l'analisi retrospettiva delle cartelle. In un sottogruppo di 10 pazienti è stata inoltre condotta una valutazione funzionale di voce e deglutizione, sottoponendo i pazienti ad uno studio comprendente il Voice Handicap Index (VHI), la scala GIRBAS, il Multi Dimensional Voice Program (MDVP) ed una valutazione della deglutizione tramite il questionario MD Anderson Dysphagia Inventory (MDADI), una videoendoscopia con studio della deglutizione ed una videofluoroscopia (i cui risultati sono stati classificati secondo la scala di Donzelli). I risultati ottenuti sono stati comparati a quelli di un secondo gruppo di pazienti simili per età, sesso, categoria di T e trattati dallo stesso gruppo di chirurghi tramite CTL come primo trattamento del tumore. Le resezioni endoscopiche sono state: 18 Tipo III, 1 Tipo IV e 16 Tipo V. Lo staging della recidiva è risultato: 16 rpT1a, 17 rpT2 e 2 rpT3. La sopravvivenza globale calcolata a 5 anni è stata del 91%. La sopravvivenza specifica per malattia, il controllo della malattia mediante laser e la preservazione d'organo calcolati a 5 anni sono stati rispettivamente del 94%, 84% e 87%. Tra le variabili prese in considerazione all'analisi univariata per l'intera coorte, la categoria di pT è risultata statisticamente significativa per il controllo locale mediante laser mentre l'estensione transcommissurale anteriore per la sopravvivenza globale, ed in modo "borderline" per la sopravvivenza specifica per malattia. Sono risultati inoltre statisticamente significativi l'impatto dei margini e la presenza di una nuova recidiva dopo CTL sia sul controllo di malattia con laser che sulla preservazione d'organo. I valori medi di VHI, MDADI ed MDVP non hanno mostrato alcuna differenza statisticamente significativa fra i

due gruppi presi in considerazione. Anche il GIRBAS e lo studio oggettivo della deglutizione non hanno mostrato differenze significative fra i due gruppi. In conclusione, per selezionate recidive dopo RT di carcinoma glottico in stadio iniziale, la CTL rappresenta una valida alternativa chirurgica con buoni risultati oncologici e risultati funzionali comparabili a quelli ottenuti in pazienti non irradiati, ed una morbidità di gran lunga minore rispetto ad altre forme di chirurgia di salvataggio.

PAROLE CHIAVE: *Carcinoma laringeo • Radioterapia • Chirurgia di salvataggio • Chirurgia laser transorale • Risultati oncologici • Risultati funzionali*

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Introduction

Primary radiotherapy (RT) has been successfully employed for treatment of early glottic cancer for the past half century [1 2]. However, despite general advances in dose fractionation and RT protocols, local recurrences still occur in 5-35% of cases [3], remaining the most common cause of organ preservation failure [4 5]. State of the art surgical salvage options for persistent/recurrent glottic cancer encompasses a variety of therapeutic strategies ranging from total laryngectomy (TL) to open neck partial laryngectomies (ONPLs) and transoral laser surgery (TLS) [6 7]. In recent years, TLS has been demonstrated to be a minimally-invasive and oncologically-safe surgical technique. Mainly reported in the literature for the primary treatment of early and intermediate glottic tumours (Tis, T1, and T2), it is gradually emerging as an attractive option in the rescue scenario [6 8-12].

The aim of this retrospective study is to describe oncologic and functional outcomes in a cohort of patients homogeneously treated with curative intent by TLS after RT failure for glottic cancer in a single academic institution.

Materials and methods

We performed a retrospective chart review of 35 patients (33 males, 2 females; age range, 46-87 years; mean, 67) with glottic squamous cell carcinoma previously treated by RT and submitted to TLS for persistent/recurrent disease or second laryngeal tumour at the Department of Otorhinolaryngology - Head and Neck Surgery of the University of Brescia, Italy, between February 1995 and February 2009. This group of patients represents less than 5% of the total number of glottic cancers treated by TLS in that time frame at our institution. Pre-RT staging was retrospectively assessed according to the 2010 American Joint Committee on Cancer TNM staging system [13] as reported in Table I.

All patients received RT using cobalt 60, with a mean dose of 68 Gy (range, 64-72), delivered 2 Gy for 5 days per week. The mean disease-free interval between the end of RT and the diagnosis of persistence, recurrence, or second laryngeal tumour for the entire series was 31 months (range, 3-144). Patients with a disease-free interval less than 6 months were defined as persistent tumours, those with an interval ranging between 6 and 60 months were considered as recurrent diseases, and those with lesions diagnosed more than 60 months after RT were defined second laryngeal tumours.

Selection criteria for TLS included adequate exposure of the endolarynx (i.e., optimal visualization of the anterior commissure with minimal or no external counterpressure), and lesions staged as glottic rT1, rT2 and rT3 for minimal involvement of the paraglottic space (PGS) but without arytenoid fixation. Therefore, in this series, massive involvement of the PGS and infiltration of the laryngeal framework represented absolute contraindications to TLS.

Every lesion was preoperatively examined using transnasal flexible fibrolaryngoscopy and videolaryngostroboscopy (Kay Digital Strobe 9200, Kay Elemetrics Corporation, Pine Brook, NJ). Moreover, intraoperative rigid endoscopy with 0° and angled telescopes (Karl Storz, Tuttlingen, Germany) was accomplished during microlaryngoscopy under general anaesthesia. Preoperative CT or MRI was performed to exclude infiltration of the laryngeal framework and to quantify the neoplastic involvement of the PGS.

Tumour excision was performed under microlaryngoscopy using a Sharplan 1055 S CO2 laser (Sharplan, Tel Aviv, Israel) from 1995 to 2007 and a Lumenis USA Ultrapulse Encore 60 instrument (Santa Clara, California, USA) with superpulse delivery in continuous mode (1 to 5 W) from 2007 to 2009, coupled to an Acuspot 712 micromanipulator (270 μm spot size) since 1996. Laryngeal exposure was obtained with a wide range of different laryngoscopes ranging from the Dedo to the Dedo-Ossoff (Pilling, Philadelphia, PA) for difficult anatomical conditions. All patients were operated in the Boyce-Jackson position. The Boston University suspension system (Pilling, Philadelphia, PA) was always employed in order to obtain a true suspension laryngoscopy producing elevated-vector forces on the largest diameter laryngoscope available.

Table I. Pre-RT and pT categories after TLS for the entire cohort of patients (n = 35).

	T1a	T1b	T2	T3
Pre-RT	20	3	12	-
After TLS	16	-	17	2

Endoscopic resections were performed applying an "en bloc" or "piece-meal" approach depending on a number of variables such as laryngeal exposure, rT category, tumour site and size. They were subsequently graded according to the European Laryngological Society (ELS) classification [14].
Surgical specimens were sent to a dedicated pathologist after marking one designated edge with black ink. No elective neck dissection was performed in this patient population.
All patients with widely negative margins (R0) were followed by periodic videolaryngostroboscopic examinations or flexible videoendoscopy, scheduled every 2 months in the first year and less frequently thereafter. In case of close (less than 1 mm) or positive superficial surgical margins, watchful endoscopic follow-up with monthly fibre optic controls was chosen. Endoscopic retreatment was performed in all cases with positive multiple superficial or deep margins (R1).
Major postoperative complications (in which surgical treatment was deemed necessary), need and duration of nasogastric feeding tube and tracheotomy, and hospitalization time were also retrospectively analyzed. The last follow-up was obtained in April 2011, with a minimum time of 26 months.

Functional outcomes

Excluding patients who died for disease or other causes, those subsequently salvaged by further TL or ONPLs, and subjects refusing a comprehensive functional evaluation, this protocol was performed on a subgroup of 10 patients (all males; mean age, 64 years; range, 50-80) (Group A). This group of patients was retrospectively compared with a cohort of selected patients matched for age, gender and pT category treated by the same team of surgeons with TLS as primary treatment (Group B). Functional evaluation of voice and swallow was carried on by a panel of 3 dedicated laryngologists and 2 speech pathologists, blinded to the type of surgery and/or previous RT status.
At least 2 years after surgery, we evaluated both Groups A and B using a protocol including a comprehensive voice assessment with subjective analysis using the Voice Handicap Index (VHI) [15], perceptual voice evaluation (GRBAS scale) [16], and objective analysis with the Multidimensional Voice Program (MDVP) [17].
The VHI questionnaire scores were grouped in 5 different categories: score 0 (normal voice), score 1-30 (slight dysphonia), score 31-60 (moderate dysphonia), score 61-90 (severe dysphonia), and score 91-120 (very severe dysphonia) [15].
Perceptual evaluation was accomplished on a current conversational speech sample digitally recorded, with a sampling frequency of at least 20,000 Hz, in a quiet room, with a mouth-to-microphone distance of 10 cm as suggested by the Committee on Phoniatrics of the ELS [18]. These samples were subsequently graded according to the GRBAS scale that consists of 5 domains: grade (G), rough (R), breathy (B), asthenic (A), and strained (S) voice [16]. Each patient was rated in all 5 domains on a grading scale ranging from 0 to 3. Score 0 corresponded to a normal voice, score 1 to slight, score 2 to moderate and score 3 to severe voice problem.
An objective analysis including jitter%, shimmer%, noise to harmonic ratio (NHR), and maximum phonation time (MPT) was performed by the MDVP on the sustained vowel /a/ uttered three times, with pitch and loudness held as constant as possible for at least 3 sec (recording and technical aspects herein followed were identical to those previously described for perceptual evaluation) [17 18].
Swallowing was assessed by a comprehensive evaluation protocol including the M.D. Anderson Dysphagia Inventory (MDADI) [19], videonasal endoscopic examination of swallowing (VEES) with blue dyed semi-solid food colouring, and videofluoroscopy (VFS) during barium swallow [20 21].
MDADI is a subjective evaluation of dysphagia based on a self-administered questionnaire with a score ranging from 0 (extremely low functioning deglutition) to 100 (high functioning deglutition) [19].
We performed VEES with a flexible digital videonasolaryngoscope. Patients never received topical anaesthesia and were evaluated during swallowing of blue dyed semi-liquid food. All examinations were video recorded and graded according to Donzelli's classification, which is a 3-point scale distinguishing: Level 1, no laryngeal food entering; Level 2, laryngeal vestibule food entering, without penetration or aspiration; Level 3, tracheal aspiration [22].
VFS was performed by oral administration of liquid and semiliquid contrast medium (barium or iso-osmolar water soluble contrast medium) in the right lateral and antero-posterior projections with rapid digital registration of swallowing (30 frames/second) using a Siregraph CF (Siemens, Forchheim, Germany). In order to obtain a clear correlation between VEES and VFS outcomes, the 3 level classification proposed by Donzelli was also applied to radiologic examinations [23].

Statistical analysis

The SPSS statistical package was used for statistical analysis. Five-year survival curves were estimated using the Kaplan-Meier method and separately calculated for the entire cohort of patients (n = 35) and for patients with true persistent/recurrent disease (n = 30), thus excluding the second primary tumours (n = 5). The entry point was the date of beginning of RT. The end point for overall survival was the date of death or the date of last consultation for patients alive at the end of the study (censored observations). For analysis of disease-specific survival, patients who died for unrelated causes were considered as cen-

sored observations at the date of death. The end point of the organ preservation rate was the date of TL. Patients who died with their larynx were considered as censored observations at the date of death.

The prognostic value on disease-specific survival, local control and organ preservation rate was tested by univariate analysis with the long-rank test for the following variables: pT category, involvement of the anterior commissure, subglottis, anterior transcommissural extension, PGS, the presence of a recurrence after TLS and status of margins.

Statistical analysis was performed with the Mann-Whitney U test for comparison of continuous variables (VHI questionnaire, objective analysis with MDVP, and MDADI questionnaire). The Pearson chi-square test was applied to compare categorical variables (i.e., GRBAS, VEES, and VFS scores). A p value < 0.05 was considered statistically significant for both tests.

Results

According to our temporal criteria, 5 patients had persistent, 25 recurrent and 5 second laryngeal tumours. The types of resection performed, according to the ELS classification, were as follows: 18 Type III, 1 Type IV, and 16 Type V cordectomies. Patients were classified as: 16 rpT1a, 17 rpT2, and 2 rpT3. All patients had been staged as cN0 by palpation and/or neck ultrasonography. When comparing the pre-RT staging with the postoperative one, we observed a shift toward higher T categories in 7 (20%) patients (Table I). According to the status of surgical margins, patients were subdivided into 29 R0 (safe or close margins) and 6 R1 cases (multiple superficial or deep positive margins).

Hospitalization time ranged from 3 to 9 days (mean, 4). No perioperative mortality was encountered. Major postoperative bleeding needing endoscopic revision occurred in 1 (2.9%) patient. Three (8.7%) patients experienced late thyroid cartilage chondritis (n = 1) or chondronecrosis (n = 2), which were successfully treated by hyperbaric oxygen therapy. One (2.9%) patient needed a nasogastric feeding tube for persistent dysphagia, which was removed 1 week later after swallow rehabilitation. No patient needed tracheotomy. No aspiration pneumonia or laryngeal stenosis was observed.

Thirteen (37%) patients developed a recurrence between 6 and 60 months after TLS. Salvage included a second TLS in 6, ONPL in 1 and TL with or without neck dissection in 6. Two (15%) patients developed a second local recurrence salvaged by a third TLS and TL, respectively.

At the last follow-up, 2 (5.7%) patients died of laryngeal cancer, 7 (20%) for unrelated causes (2 lung cancer, 2

Table II. Univariate analysis for the entire cohort of patients (n = 35).

	Overall survival	Disease specific survival	Organ preservation rate	Local control with laser alone
pT category				
pT1	93	100	100	100
pT2	88	88	75.5	75
pT3	100	100	100	50
p	NS	NS	NS	0.01
Anterior commissure				
No	90	95	95	95
Yes	92	92	73	67
p	NS	NS	NS	NS
Transcommissural extension				
No	94	97	89	86
Yes	67	67	67	67
p	0.01	0.05	NS	NS
Subglottis				
No	93	96	89	88.5
Yes	80	80	75	60
p	NS	NS	NS	NS
Paraglottic space				
No	88	91.5	92	91.5
Yes	100	100	73	65
p	NS	NS	NS	NS
Recurrences after TLS				
No	100	100	100	100
Yes	77	82.5	63.5	58
p	NS	NS	0.0001	0.0001
Margins				
Negative/Superficial	93	96	96	93
Deep/Multiple	83	83	50	50
p	NS	NS	0.0001	0.0002

NS, not statistically significant (p > 0.05).

cardio-vascular disease, 2 non-head and neck tumours, and 1 other disease), and 26 (74.3%) were alive without evidence of disease.

The 5-year overall survival for the entire series was 91%. Five-year disease-specific survival, local control with laser alone and organ preservation rates were 94%, 84% and 87%, respectively. When considering only persistent/recurrent tumours (n = 30), 5-year overall and disease-specific survivals, local control with laser and organ preservation rates were 89%, 93%, 81% and 84.5%, respectively.

Among the variables tested at univariate analysis, for the entire cohort of patients, the pT category had a statistically significant impact on the local control with laser alone. Anterior transcommissural extension had a borderline statistical impact on disease-specific survival, while was clearly significant on overall survival. The status of the surgical margins and presence of recurrence after TLS statistically influenced both organ preservation and local control with laser alone (Table II) (Fig. 1a). When considering only persistent/recurrent diseases, pT category maintained a statistically significant impact on local control with laser alone, while the transcommissural extension became significant only for determinate survival. Lateral subglottic extension showed a significant impact on local control. The presence of recurrence after TLS statistically influenced every end point, while the status of surgical margins continued to be significant on local control and organ preservation (Table III) (Fig. 1b).

Seven (20%) patients received TL as a final salvage treatment. Among these, 57% initially showed an involvement of the anterior commissure, while 71% presented positive deep margins or multiple positive margins (R1) after TLS. Furthermore, two of the 7 patients that had undergone TL died for disease due to stomal recurrences. Involvement of the anterior commissure by local recurrence was evident in 13 patients. Among these, 4 (57%) underwent TL, while among those with a preserved larynx the anterior commissure was involved in 32% of cases. However, anterior commissure involvement by itself did not affect either local control or organ preservation rates.

The mean values of VHI, MDVP, and MDADI did not show any statistically significant differences between Groups A and B (Table IV). The GRBAS score was not statistically different between the two groups. Swallowing examination by VEES in Group A, according to Donzelli's scale, was normal in 50% of patients (Level 1), showed vestibule penetration without aspiration in 30% (Level 2), and tracheal aspiration in 20% (Level 3). On the other hand, the same examination in Group B showed Level 1 deglutition in 78%, Level 2 in 11% and Level 3 in 11% of

Table III. Univariate analysis for persistent/recurrent diseases (n = 30).

	Overall survival	Disease specific survival	Organ preservation rate	Local control with laser alone
pT category				
pT1	93	100	100	100
pT2	84	84	67	67
pT3	100	100	100	50
p	NS	NS	NS	0.02
Anterior commissure				
No	88.5	94	94	94
Yes	91	91	67	61
p	NS	NS	NS	NS
Transcommissural extension				
No	93	96	87	84
Yes	50	50	50	50
p	NS	0.02	NS	NS
Subglottis				
No	92	95.5	87	86
Yes	75	75	67	50
p	NS	NS	NS	0.02
Paraglottic space				
No	86	90	91	90
Yes	75	100	62.5	54
p	NS	NS	NS	NS
Recurrences after TLS				
No	100	100	100	100
Yes	70	78	49	43
p	0.01	0.04	0.0001	0.0001
Margins				
Negative/Superficial	92	96	95.5	91.5
Deep/Multiple	80	80	40	40
p	NS	NS	0.0001	0.002

NS, statistically not significant (p > 0.05).

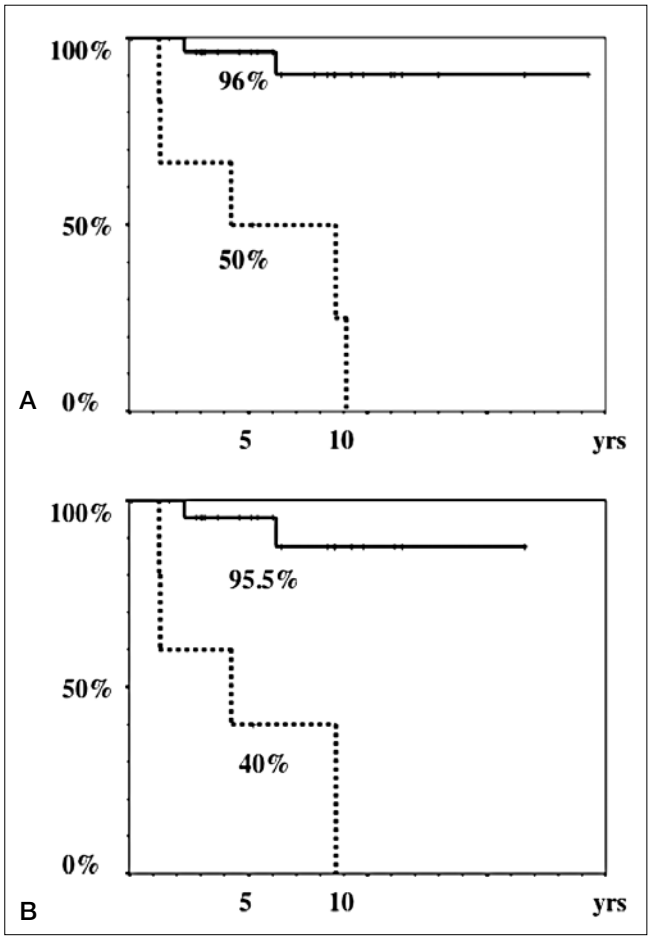

Fig. 1. Kaplan-Meier curves showing the impact of the status of surgical margins on organ preservation rate in: a, entire cohort of patients (p = 0.0001) and, b in persistent/recurrent disease (p = 0.0001). The continuous line indicates R0 patients, while the dotted line indicates R1 cases.

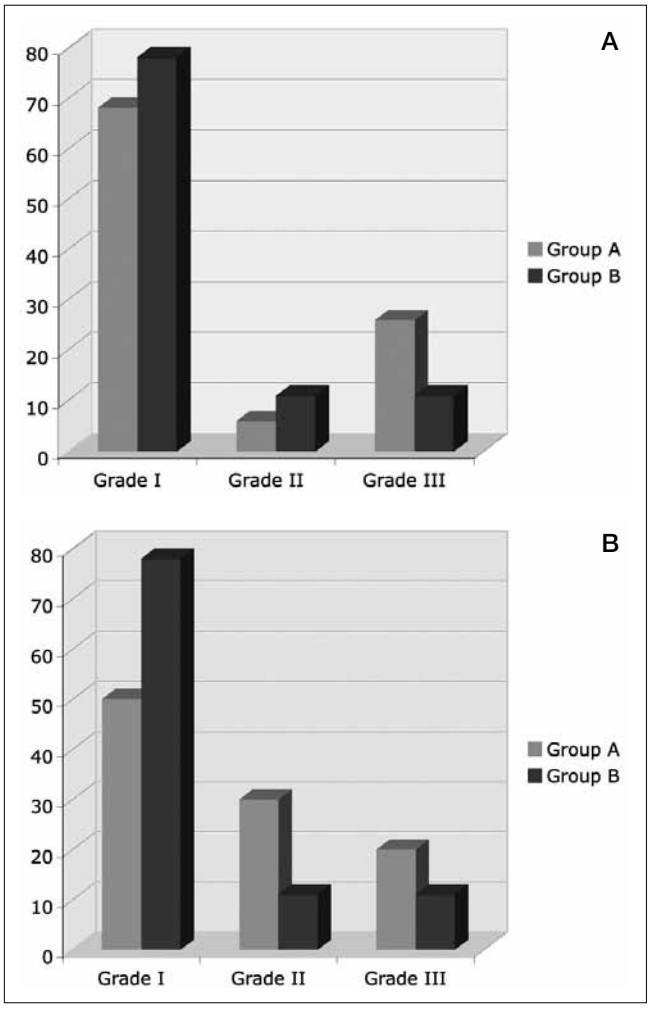

Fig. 2. a, VEES and b, VFS outcomes classified according to the 3-point scale proposed by Donzelli et al. [22] in Groups A and B.

patients. VFS showed Level 1 outcome in 68%, Level 2 in 6% and Level 3 in 16% of Group A, while it was 88%, 11% and 11%, respectively, for patients in Group B. No statistically significant difference was observed between the groups for either VEES or VFS (Fig. 2a, b).

Discussion

The heterogeneity of studies reporting salvage outcomes for recurrent laryngeal cancer after RT makes comparative analysis difficult. Nowadays, approximately one-third of patients with local glottic recurrence after RT undergo conservative surgery [5 6 8 24-26], achieving local control rates of 65% and 77% with ONPL and TLS, respectively [27].

For T1-T2 glottic tumours, local control rates with ONPL after RT failure have been reported to be between 65% and 96% [24 28 29], with a 5-year disease-specific survival of 93% [26 30]. In spite of acceptable disease control, ONPLs are expensive procedures, with long hospitalization and somewhat unpredictable functional results, with reported decannulation times between 3 and 30 days [30 31] and long-term swallowing problems. The latter represents the main functional morbidity encountered in 17-40% of patients [25 31], with an average time needed to return to "normal swallow" ranging from 9 to 55 days [25 31 32]. For this reason, both Laccourreye [31] and Makaieff [25] proposed percutaneous gastrostomy in all cases of salvage ONPL. Long-term severe diet restrictions with major aspiration and possible pneumologic complications are limited to about 10% of supracricoid partial laryngectomies, with a minority (2.5%) requiring TL for functional reasons or permanent feeding tube [33 34].

Table IV. Statistical analysis by the Mann-Whitney U test for comparison of continuous variables.

	Group A	Group B	p
VHI	25 (SD ± 25)	14 (SD ± 10)	NS
MDADI	88.3 (SD ± 10.6)	80.1 (SD ± 28.7)	NS
Jitter%	3.61 (SD ± 3.4)	3.26 (SD ± 4.1)	NS
Shimmer%	8 (SD ± 8)	15.3 (SD ± 7.8)	NS
NHR	0.29 (SD ± 0.25)	0.36 (SD ± 0.19)	NS
MPT	8.57 (SD ± 7.57)	5.28 (SD ± 2.99)	NS

Moreover, elderly patients (over 70 years of age) and those with chronic obstructive pulmonary diseases, typically associated with several other comorbidities in laryngeal cancer patients, may present even longer decannulation times, swallowing normalization times and hospitalization after ONPLs [33 35]. Furthermore, the violation of the integrity of the laryngeal cartilaginous framework, especially in a previously irradiated organ, favours delayed wound infection [36] and severe postoperative complications, such as chondritis, chondronecrosis and salivary fistula [37]. In this respect, the literature reports overall complication rates and fistula formation after RT failure in 8-20% of cases [26 29 30].

A transoral approach to recurrent glottic carcinoma after RT failure has been reported in a small number of publications [6 9 10 38]. Nonetheless, it has demonstrated efficacy for early recurrent or persistent glottic lesions, with oncologic outcomes comparable to those obtained by ONPLs, with disease-specific survival and organ preservation rates ranging from 68% to 86%, and from 50% to 79%, respectively [8 10 28 39 40]. Therefore, our oncologic results are in agreement with those mentioned above.

Accurate selection of patients suitable for TLS after RT failure should take into account several factors such as site, size and biological behaviour of the tumour, overall health status and the possibility to obtain adequate laryngeal exposure, which is usually more difficult in a post-RT scenario. The difficulty in identifying tumour boundaries, even under rigid endoscopy and operating microscopes, is higher after RT and requires extensive previous experience in primary TLS. Furthermore, resection within free-margins may be more challenging due to the presence of fibrosis, oedema, inflammation and associated patterns of multifocal and submucosal neoplastic spread [39 41]. In such a scenario, ultra-narrow margin resections (Type I and II cordectomies) should be avoided in favour of wider cordectomies with a more comprehensive compartmental approach. In fact, our series clearly shows how incomplete resection with multiple superficial and/or deep positive margins negatively influences both local control and organ preservation rates. For this reason, substantial effort should always be made to obtain a complete resection with clear surgical margins at the first attempt.

Although superficial involvement of the anterior commissure limited at the glottic plane in our experience does not represent a contraindication to TLS, the anterior transcommissural extension above and below the vocal cords can hide the persistence of deep nests of neoplastic cells invading visceral compartments or focally involving the laryngeal framework. This has been shown to statistically influence the determinate survival rate especially when dealing with true persistent/recurrent diseases (96% *vs*. 50%). Moreover, we found a higher rate of salvage TL after failure of TLS in case of transglottic recurrence involving the anterior commissure (57% *vs*. 32%). The same consideration should be taken into account when dealing with T3 recurrent/persistent disease after RT. Even though a minimal involvement of the PGS can be successfully managed by TLS, great caution should be paid in order to exclude any massive involvement of this visceral space, crico-arytenoid fixation or tumour encroachment on the laryngeal framework at the thyroid cartilage level.

For patients developing a second recurrence after salvage TLS, local control with laser alone and organ preservation rates appear to be unfavourable. This should prompt the surgeon to shift immediately to an ONPL (when not to a TL) after a first TLS salvage attempt.

Concerning organ preservation, our data are similar to those reported in the literature [9 38], with a rate of 87% for the entire cohort and 84.5% when excluding second primary tumours. Nonetheless, the 5-year determinate survival of 94% emphasizes the importance of strict follow-up with regular fibreoptic examinations and periodic imaging by MR, allowing early detection and treatment of further recurrences without a negative impact on survival.

The main advantage of TLS is based on its functional aspects. In all reports dealing with TLS after RT failure, no long-term swallowing disorders were encountered and voice quality was satisfactory. Apart from subjective evaluation obtained by the VHI questionnaire, both perceptual and objective voice examinations underline that there are no significant differences between patients submitted to Type III-V cordectomies after RT compared to matched non-irradiated patients.

Swallowing functions are slightly impaired after TLS due to the fact that endoscopic surgery minimizes the resection of uninvolved tissues, speeding up compensatory deglutition mechanisms. Moreover, physiologic laryngeal elevation, essential in adequate bolus progression, remains unchanged after TLS. The results of both VEES and VFS after TLS did not show any significant difference between irradiated and non-irradiated patients, clearly confirming the reduced impairment of swallowing after such a surgical approach even in the post-RT scenario. Moreover, our complication rate, hospitalization time, need and duration of nasogastric feeding tube and tracheotomy clearly demonstrate a reduced burden in terms of perioperative morbidity for patients treated by TLS.

Conclusions

In conclusion, issues such as quality of life, cost-effectiveness ratio and global social burden of any given treatment cannot be ignored. In the post-RT scenario, due to the fact that TLS and ONPL for selected early stage glottic recurrences appear to be associated with comparable oncologic outcomes, the least aggressive and morbid procedure should always be chosen as the first-line treatment modality.

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