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Salvage surgery after unsuccessful radiotherapy in early glottic cancer

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Abstract. *Salvage surgery after unsuccessful radiotherapy in early glottic cancer*. Surgery is the main therapeutic option to control recurrent laryngeal cancer after radiotherapy (RT) relapse. Most RT-recurred cancer is treated aggressively; although, conservative laryngeal surgery was attempted in selected cases. Here, we report our experiences with salvage laryngeal surgery for early glottic cancers that did not respond to RT. We analyzed files from 1980 to 2006 and selected 173 patients surgically treated for a RT-failed early glottic carcinoma (stage I-II according to 2010 TNM: 114 T1N0, 59 T2N0). Among them, 47 patients (27%) underwent a salvage partial laryngectomy (SPL) and 126 (73%) had a salvage total laryngectomy (STL). When compared with initial T staging, we found 61% of lesions were up-staged, 31% had the same staged lesion, and only 8% were down-staged (according to rTNM). No statistically significant differences were found in terms of disease-free survival and overall survival when SPL and STL patients were compared. Univariate analysis showed that T, rT, and rTNM were prognostic factors for overall survival (p=0.045, p=0.028, and p=0.037, respectively); yet, these significances were lost in multivariate analysis. Our results suggest that salvage surgery is feasible in most cases of RT-recurred early glottic cancer; although, a conservative approach achieves good oncological and functional results only in select RT-recurred patients.

Introduction

Early glottic cancer is a malignant laryngeal neoplasm of the glottic region and is characterized by normal cord mobility.[1] Early lesions are defined as those staged as T1aN0M0, T1bN0M0 (stage I), and T2N0M0 (stage II) (TNM 2010 by American Joint Committee for Cancer (AJCC) and the Union Internationale Contre le Cancer (UICC)).[2-3] The treatment choices for early glottic lesions worldwide are curative radiotherapy (RT) or conservative surgery, which both result in comparable overall survivals. Those patients requiring the best functional voice outcome usually undergo curative RT.[4-5] The RT treatment is characterized by a very limited risk of local recurrence, which is estimated to be as high as 5-10% for T1 lesions and 20-40% for T2 lesions.[6]

Cancers that recur after RT often demonstrate aggressive behavior, arise in a field where lymphatic drainage is unpredictable, and are associated with poor control rates. Thus, most of these cancers have been treated by salvage total laryngectomy (STL); a procedure easy to perform and with good oncologic results.[7] In the late nineties, salvage partial laryngectomy (SPL) was preferred due to some limited recurrence; yet, STL still represents the first choice treatment for salvage surgery. Open partial laryngectomy has a well-defined role in cancer at both the initial presentation and, more recently, in recurrence, but it is used less frequently because of the technical complexity of some procedures, the lack of expertise, and fewer good functional outcomes.[8] Among salvage partial procedures, some reports[6] include supracricoid partial laryngectomy (SCPL, such as cricohyoidopexy, cricohyoidoepiglottopexy, tracheohyoidopexy, and tracheohyoidoepiglottopexy) and endoscopic CO_2 laser cordectomy type IV, as alternatives to STL that preserve laryngeal functions.[9-10] Here, we report on our experience and functional and oncological outcomes from aggressive and conservative salvage surgeries for cases of early glottic cancer that did not respond to RT.

Methods

Between 1980 and 2006, we identified 173 patients who underwent direct laryngoscopy under general anesthesia with histological examination at the ENT Clinic of the University of Florence to confirm

Table I

Clinical data from 173 patients

	Overall (n=173)	SPL (=35)	STL (n=126)	Cordectomy laser (n=11)	FL (n=1)	p value
Age						
group, years <60	54 (31%)	17 (49%)	33 (26%)	3 (27%)	1	0.024
≥60	119 (69%)	18 (51%)	93 (74%)	8 (73%)	1	1
Sex						
Female	12 (7%)	2 (6%)	10 (8%)	0		
Male	161 (93%)	33 (94%)	116 (92%)	11		
Clinical T stage, initial						0.051
1a	67 (39%)	13 (37%)	48 (38%)	6 (55%)	1	
1b	47 (27%)	16 (46%)	28 (22%)	3 (27%)		
2	59 (34%)	6 (17%)	50 (40%)	2 (18%)		
Clinical T stage, salvage						<0.001
1a	25 (14%)	2 (6%)	13 (10%)	10 (91%)	1	
1b	21 (12%)	5 (14%)	16 (13%)	1 (9%)		
2	67 (39%)	17 (14%)	48 (38%)			
3	45 (26%)	8 (49%)	37 (29%)			
4	15 (9%)	3 (8%)	12 (9%)			

a squamous cell carcinoma of the larynx that recurred after curative RT. The diagnosis was completed using CT (routinely performed after 1995) and chest radiography, to better evaluate laryngeal recurrence and exclude lung metastases. TNM staging was corrected using the 2010 edition, based on the clinical records available. An overview of the clinical series is shown in Table I.

Primary treatment consisted of a median total radiation dose of 6600 cGy (range 5600 to 7200 cGy) administered in 32 fractions (range 27 to 49 fractions) over 47 consecutive days (range 29 to 75 days) at the primary laryngeal site. Follow-up included indirect laryngoscopy at regular intervals, monthly for the first year and every two months from the second year. In addition, after 1995, patients underwent CT scans every six months for the first three years. In cases of suspicion, direct laryngoscopy was performed with biopsies. The diagnosis of local recurrence and restaging were performed using the same criteria used to stage the original laryngeal tumors, which consisted of clinical examination, direct laryngoscopy under general anesthesia with multiple biopsies, and CT of the neck and thorax. Based on these diagnostic procedures, patients with histologically documented laryngeal recurrence after RT were surgically treated at our Institution either by STL or SPL. Table II summarizes the types of salvage surgery performed.

Functional outcomes of salvage SPL were estimated through two parameters: mean time of removal of the nasogastric feeding tube and mean time of decannulation. Disease-free survival (DFS) and overall survival (OS) were calculated using Kaplan-Meier curves. Predictive factors of survival were identified by univariate and multivariate analysis considering the following variables: sex, age, T and N stage, rT and rN stage, field of irradiation (glottic region, larynx or concurrent larynx, and neck), extension of the lesion at first diagnosis and after restaging (glottic, supraglottic, hypoglottic, transglottic), disease-free interval between RT and local recurrence, and type of salvage surgery (STL/SPL/fronto-lateral laryngectomy (FL)/cordectomy). Results were statistically evaluated using the Fisher's exact test. Statistical analysis was performed with STATA statistical software for Windows version 10.0 (Stata Corporation: College Station, Texas USA). A p-value

Table II

Type of salvage surgery performed

Type of salvage surgery	**N=173 (%)**
Endoscopic laser CO_2 cordectomy type IV	11
Frontolateral laryngectomy	1
CHP	23
CHEP	10
THP	1
THEP	1
Total laryngectomy	126 (73%)

Table III
rT-staging of recurrences

T	rT1a	rT1b	rT2	rT3	rT4	Total
1 a	16	1	28	16	6	67
1 b	4	14	16	13	0	47
2	5	6	23	16	9	59
Total	25	21	67	45	15	173

of less than 0.05 was considered statistically significant.

Results

The time of recurrence after primary RT ranged from 3 to 39 months starting from the end of the initial RT treatment, with a median disease-free-interval of 22.8 months. Statistical analysis didn't show a significant association between T stages at the time of the first diagnosis and the time of recurrence (p=0.443). After confirmation of relapse, lesions were rT-staged and the results are shown in Table III. Overall, we documented an up-stage in 105 (61%) RT-recurred cancers, the same stage of primary tumor in 53 (31%) cases, and only 15 (8%) down-staged lesions. As shown in Table II, STL was performed in 126 cases (73%); while, SPL was attempted in only 47 patients (27%) with recurrence. When comparing the period 1980-1995 with 1996-2006, we observed a slightly increased use of SPL in the last decade (15% vs 28%).

Most of the RT-recurred cases were rN0 and only 14 patients presented with clinical N+ disease (8%), which were staged as rcN1 in 12 cases and rcN2 in 2. These patients underwent modified radical neck dissection (mRND type III), except for one patient who underwent selective neck dissection (levels II-IV) for a single ipsilateral node less than 2 cm in size. Of these patients, five were previously irradiated on the larynx and neck, two on the entire larynx, and seven on the glottic region alone. We did not find a significant difference (p=0.47) between the extension of the previous field of radiation and the N+ risk.

Of the rN0 patients, 20 (12%) underwent elective neck dissection (14 selective neck dissection levels II-IV and 6 mRND type III). In rN0 cases, we only performed neck adjuvant treatments in 14 patients (8%) who underwent additional RT and/or chemotherapy due to a higher rT-stage (rT3, rT4) or a histologically documented highly aggressive

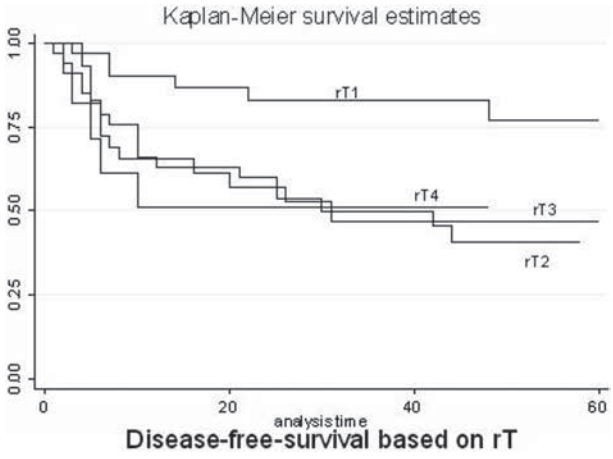

Figure 1
Disease-free-survival based on rT

recurrence (vascular and/or perineural invasion). Figures 1-4 show the DFS and OS according to rT-stage, rTNM, and type of salvage surgery. Most patients who underwent STL had a more advanced disease at the time of recurrence (54 patients, with 31% rT3 or rT4); while, 12 patients (25%) (p=0.108) had higher re-staged cancers in the SPL group. Forty-two (24% of our series) patients experienced a second recurrence after the first salvage surgery, within a median time of 10.3 months (range 4-47 months). In our series, a high rate of unsuccessful salvage surgery was documented in patients treated using salvage endoscopic cordectomy type IV by laser CO_2 (45.5%, 5 out of 11 cases); while, STL and SCPL showed rates of failure of 32% (41 out of 126 cases) and 23% (8 out of 35 cases), respectively. The site of failure was local in 90% (38) and regional in 10% (4) of cases.

For 15 (36%) patients with second recurrences, no further salvage options were possible and patients died from their disease within two months; 13 (33%) were treated with an extra-boost RT and/or chemotherapy, and the remaining 14 (33%)

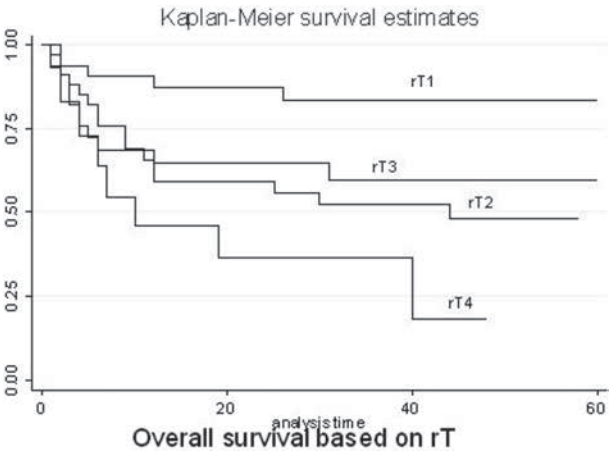

Figure 2
Overall survival based on rT

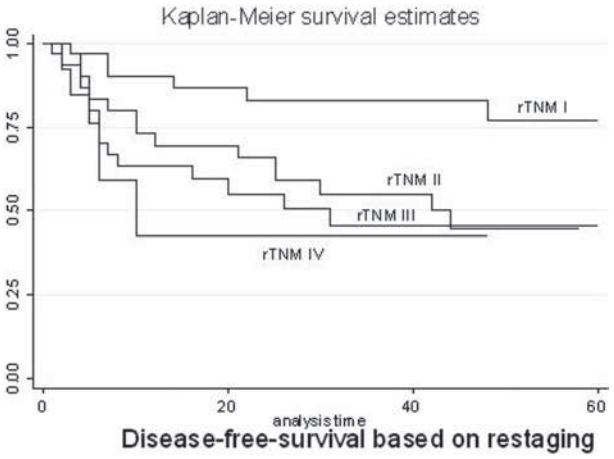

Figure 3
Disease-free-survival based on restaging

underwent a second salvage surgery (94.5% STL, 5.5% SPL was successfully attempted). Univariate analysis showed T, rT, and rTNM staging were prognostic factors only for OS (p=0.045, p=0.028, and p=0.037, respectively), but these significances were lost in multivariate analysis. In SPL patients, the median time to remove the nasogastric tube was 28.9 days and for decannulation was 40 days. Among these patients, statistical analysis did not show a significant difference in terms of functional results between the group of patients where both arytenoids were spared versus those who required surgical sacrifice of one arytenoid (p=0.78).

For patients who underwent STL, the mean time to remove the nasogastric feeding tube was 43 days (min 9, max 230) and the mean time to remove the tracheal cannula was 56 days (min 4, max 450). We

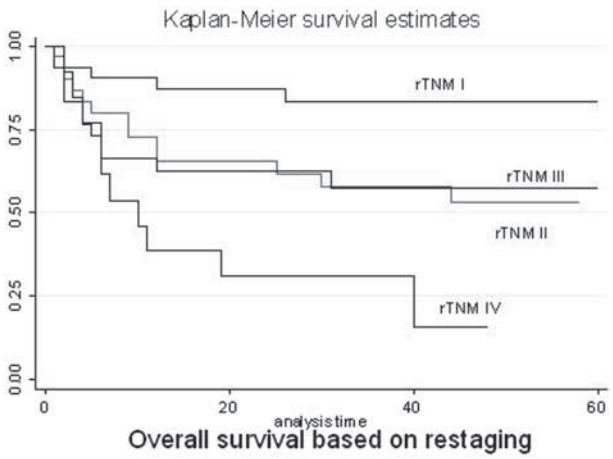

Figure 4
Overall survival based on restaging

also analyzed the influence of neck surgery (mRND type III or selective neck dissection) on restoration of physiological functions. The mean time to remove the nasogastric feeding tube and tracheal cannula in neck dissected patients were 24 days (min 14 max 55) and 63 days (min 4 max 240), respectively, compared with 42 days (min 4 max 230) and 53 days (min 5, max 450), respectively (p=0.573 and p=0.463), for patients who didn't undergo additional neck surgery.

Postoperative complications after salvage surgery are summarized in Table IV. The overall rate of complication was 36%. The most common complication was pharyngocutaneous fistula (54 patients, 31%), which is typical for patients undergoing STL (52 patients, 41% of STLs). The management of fistula was conservative in most cases, with compressive dressings and daily medications, and hyperbaric therapy when available, as well as instructing the patient to expectorate saliva instead of swallowing it. In four STL patients (7%), closure of the fistula required additional surgery with a pectoralis major myocutaneous flap; while, five more patients (10%) underwent reparative surgery with local flaps. Definitive closure of the fistula was confirmed by contrast-enhanced transit x-ray.

Patients who experienced a pharyngocutaneous fistula had longer mean times of decannulation and removal of nasogastric feeding tubes compared with patients without this complication (101 days versus 28 and 76 days versus 20, respectively, p<0.05 for both). Pharyngocutaneous fistula is a significant negative prognostic factor in the

Table IV
Complications according to type of post-RT salvage surgery

	Overall (n=173)	SPL (n=35)	STL (n=126)	Endoscopic laser CO_2 cordectomy type IV (n=11)	FL	P value
Overall complication						0.138
No	109	30	68	10	1	
Yes	64	5	58	1	0	
Local wound complication						**0.01**
No	117	33	72	11	1	
Yes	56	2	54			
Swallowing complications						**0.03**
No	167	32	123	11	1	
Yes	6	3	3			
Airway complications						0.620
No	163	33	118	11	1	
Yes	10	2	8			
Systemic/metabolic complications						1
No	168	35	121	11	1	
Yes	5		5			
Pharyngocutaneous fistula	54	2	52			**0.005**

restoration of normal physiological functions in terms of swallowing and respiration ($p<0.0001$ both). We also tried to identify, using logistic regression analysis, potential factors predictive of pharyngocutaneous fistula. We identified age and type of salvage surgery as factors potentially responsible for a higher rate of pharyngocutaneous fistula ($p=0.004$ and $p=0.041$, respectively).

Airway complications such as stomal stenosis occurred in 10 patients (6%). All of these patients successfully underwent revision surgery with stomaplasty. Only three patients in our series were affected by aspiration pneumonia. All patients underwent SCPL, two were successfully treated with antibiotic therapy with no further episodes of aspiration, while the other required total laryngectomy because of functional problems. Two SPL patients (6% of 35 SCPL) underwent percutaneous gastrostomy because of persistent difficulty in swallowing. Three patients (2%) died perioperatively because of myocardial infarction.

Discussion

Recently, SPL has been proposed as a valid alternative to STL as a salvage procedure after RT failure in selected cases of early glottic cancer; however, this was proposed based on only a few cases from single institutions.[11-12] This is mainly due to the difficulty in correctly restaging the tumor, which is useful for planning SPL, as well as the technical complexity of open conservation procedures, the lack of experts in this field, and the need for dedicated rehabilitation equipment for good functional recoveries. More accurate imaging and endoscopic technologies have provided the ability to better define the limits of RT-recurrence in the larynx, which has prompted several surgeons to successfully attempt conservative surgical approaches. Our series began in 1980; thus, most of the patients with laryngeal recurrence after RT were treated by STL (72%), while the number of SPLs increased after the mid-nineties. We found DFS and OS varied in relation to the salvage surgical technique employed and were generally in agreement with similar published studies.

An endoscopic laser CO_2 cordectomy type IV represents a feasible treatment mostly for T1a and T1b lesions. There are published reports of satisfactory functional results in terms of deglutition and quality of voice for this endoscopic procedure, while the 5-year DFS was extremely variable, ranging from 38 to 88%.[13] This study included a limited number of RT-recurred lesions treated endoscopically; of these, 54.5% of cases had loco-regional control at 5 years and the 5-year OS rate was 72.7%. Among those patients who experienced a second recurrence, only 16.7% underwent a second salvage conservative surgery, consistent with previous studies.[10] We observed that salvage

endoscopic laser CO_2 cordectomy seems to present a high risk for a second laryngeal recurrence when compared with open partial laryngectomy approaches (usually up to 70%, according to a review by Agra *et al.*).[6] It is likely that the direct view of the neoplasia together with a more extended excision of the involved and irradiated larynx in the open approaches provides better local control after RT relapse than endoscopic approaches.

Among patients treated by SCPL, we found a 5-year DFS rate of 85.5% and an OS rate of 75%.[6] These data are consistent with previous reports and show a better prognosis for these patients versus those undergoing STLs, for which we found 5-year DFS and OS rates of 63.3% and 60%, respectively. The apparent discrepancy is justified by the selection criteria for SPL (rT1-rT2 and selected rT3), which makes it a dedicated procedure for less aggressive or extended recurrences. These results support the use of SPL as an oncologically sound and functionally conservative surgical procedure for rT2 and rT3 upstaged lesions, reserving STLs for the treatment of rT4 lesions or second (post salvage surgery) recurrences, as previously reported.[14-15] The actuarial survival rate for patients treated by STL was 60% in our study, in agreement with other reports.

During follow-up, we diagnosed a second recurrence in 24% of patients, with only 5.5% able to be surgically treated by SPL. As previously reported, we confirmed in our study that the prognosis in these patients with a second recurrence is extremely negative and the only treatment option is STL with adjuvant treatment. When we compared the DFS and OS of patients who underwent STL with those who underwent total laryngectomy as a primary surgery, the DFS and OS of the first group were 71% and 47.5%, respectively, in contrast with 76% and 82%, respectively, for the second group.[16] A worse prognosis was also reported for SPL as a salvage procedure rather than primary surgery, with a DFS of 100% and OS of 94% for the first-treatment group and 87.5% for both in the salvage group.

Overall, in our study, 35% of our patients died as a consequence of the post-RT recurrence and this was due to a second recurrence in 75% of these cases despite attempting STL (82%). As shown in literature[16] and confirmed in our study, the prognosis for these patients is extremely negative and the only option suitable is STL followed by adjuvant treatment or curative/palliative RT and chemotherapy. Minor causes of death were documented: 8% experienced a second primary extra-laryngeal cancer, 2% had pulmonary metastases, and 2% experienced fatal perioperative bleeding.

In our series, we recorded a 36% overall rate of postoperative complications and a 2% incidence of postoperative mortality. A similar, previous report found a postoperative complication rate of 20% and no postoperative mortality.[4] There was a lower rate of postoperative complications for SPL than STL (14% vs 46%, p=0.138). In comparison, Pellini *et al.*[14] reported the incidence of complications for patients who underwent SPL was 14% and 38.5%, respectively, while perioperative mortality was 0% and 1.3%. One of the most common complications in this study was aspiration pneumonia (8.6%), and a similar incidence was found in Pellini's study (8.9%). All cases were treated with medical therapy except for one, which is a better result than found in Makeieff's work where 8.7% of patients with aspiration pneumonia died.[15] In our study the incidence of early postoperative complications was 1%, which consisted of one case of bleeding and a neck abscess, which was also reported in Pellini's work (6.4%). These two other studies also showed the incidence of late complications, such as granuloma of the subglottis or edema of the arytenoids, was estimated around 17.9%, while it was around 32% in our series.

Among the 35 patients who underwent SPL restoration, oral feeding was achieved in all patients with a mean time of 29 days. In other studies[17] the mean time to restore normal feeding was 25 days and it was less than one month for 61.5% of patients in Pellini's study.[14] In previous reports, the time for removal of the feeding tube ranged from 10-96 days[18] to 12-90 days;[17] while, it was 4-230 days in our study. Only two patients (6%) weren't able to restore normal swallowing functions and required percutaneous endoscopic gastrostomy, which was similar to the findings by Makeieff *et al.*[15] (4.4%) and Pellini *et al.*[14] (7.7%).

In our study, the mean time of decannulation was 22.5 days (range 18-35 days) and previous findings ranged from 14-90[17] to 12-365 days.[18] Our results, when compared with previous studies, are characterized by a lower incidence of pneumonia and higher time of decannulation. This is mainly due to our approach, which better protects the airways during swallowing rehabilitation by main-

taining the tracheal cannula for a longer time. This may explain the higher time of decannulation but lower risk of aspiration pneumonia, even if this usually delays restoration of normal swallowing.

In our study, STL was associated with higher rates of postoperative complications (46%), which is consistent with many reported series, especially after previous RT (from 29.4% to 21.9%[5]) and chemoradiotherapy (from 41.2% to 50%).[18] The incidence of complications, such as stomal stenosis, is estimated in literature to be about 9%;[4] while, it was 6% in our case study with all patients requiring surgical re-intervention. The most common complication was pharyngocutaneous fistula, which had an incidence of 41% in our study, 11.9% in Ganly's, and 30% in Weber's[16]. The rate of pharyngocutaneous fistula following STL in irradiated patients is higher than after total laryngectomy as a primary treatment (ranges from 68% to 8.69%[19-23]). Our series included only early glottic cancer, with no patient treated with a laryngeal preservation protocol for advanced disease; thus, we found a higher rate of fistulas than reported previously. In our institute, fistula is usually treated with a conservative approach using a scopolamine patch and medications for good functional results but longer hospitalizations. Only 8% underwent reparative surgery with a pectoralis major myocutaneous flap.

Conclusion

Correct restaging of RT-recurred laryngeal cancer is crucial in planning salvage surgery and, thus, in achieving good functional and oncological results. The possibility to avoid total laryngectomy is strictly linked to an exact staging of recurrence in the irradiated laryngeal area. To date, imaging procedures still show low accuracy, while clinical experience and multiple biopsy procedures are helpful in this setting. This difficulty is related to structural alterations of laryngeal mucosa due to previous RT treatment, alterations which are often macroscopically indistinguishable from local recurrence. Therefore, an accurate evaluation of a RT-recurred laryngeal carcinoma is mandatory to plan the surgical salvage treatment in early glottic cancer treated unsuccessfully with RT and is not limited to STL. Our experience suggests that conservative approaches are still feasible with good oncologic results, but only in selected RT cancer patients with recurrences.

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