B-ENT, 2005, **1**, 107-111

Salvage surgery after radiation failure in squamous cell carcinoma of the larynx

G. Mercante, A. Bacciu*, L. Banchini*, E. Moretto**, G. Oretti* and T. Ferri**

*Department of Otorhinolaryngology, University of Parma, Italy, **Department of Economy, University of Parma, Italy

Key-words. Larynx; squamous cell carcinoma; salvage surgery; radiation failure

Abstract. *Salvage surgery after radiation failure in squamous cell carcinoma of the larynx. Aim and background*: To investigate patients treated with radiotherapy (RT) for laryngeal squamous cell carcinoma (SCC) in order to estimate the recurrence rate and treatment used as salvage surgery. The survival rate in the group of patients treated with salvage surgery was compared to that of patients who had chemotherapy rather than surgery or who refused any treatment.
Methods: From 1989 to 1999, 185 patients came to our institution for laryngeal SCC. All of them underwent RT as primary treatment. Only patients with a minimum of three years follow-up (n = 143) were included in the study group.
Results: The 143 cases included 22 loco-regional recurrences (15.3%) during the minimum three years of follow-up. Recurrence was observed in the larynx in eighteen cases (81.8%), in cervical nodes in one case (4.55%) and in both the larynx and cervical nodes in one case (4.55%). There was peristomal recurrence in two cases (9.1%). Recurrence was observed after an average of 16.3 months. Fourteen patients (63.6%) out of the twenty-two cases of recurrence underwent salvage surgery. Surgery was not performed on the remaining eight patients (36.4%). The global survival rate was 92.3% after three years and 66.6% after five years in the group of patients treated with surgery. The actuarial survival rate was 100% after three years and 83.3% after five years. The global and actuarial survival rate was 20% after three years and 0% after five years in the group of patients who received chemotherapy rather than surgery or who refused any kind of treatment.
Conclusion: The RT seems to play an important role in the loco-regional control of laryngeal SCC (especially in glottic T1). Salvage surgery for recurrence results in a good survival rate.

Introduction

Data from the International Agency for Research on Cancer[1] confirm that the incidence of laryngeal squamous cell carcinoma (SCC) is lower in southern Europe than in the rest of the continent. Nevertheless, if diagnosis is early, small tumours can be managed easily and part of the larynx can be saved with a near-total laryngectomy, laser therapy or radiotherapy (RT). RT can also be used when the tumours are large and/or index for the performance status of the patient is low.

In the present study, patients treated with RT for laryngeal SCC were investigated retrospectively in order to determine the recurrence rate and assess the treatment used as salvage surgery. The survival rate in the group of patients treated with salvage surgery was compared to that of patients who underwent chemotherapy rather than surgery or who refused any treatment.

Patients and methods

From 1989 to 1999, 185 patients with laryngeal SCC were observed at our institution and all of them received RT. There were 174 men (94.1%) and 11 women (5.9%). Mean age was 66.5 years (range 42-88, SD 9.87). All patients underwent haematological and urinary examination, chest X-ray, ultrasonography (US) and CT scan of the cervical region, endoscopy of the upper aero-digestive system (oesophageal-gastro-duodenoscopy and bronchoscopy) and spirometry in order to exclude other synchronous tumours. All patients underwent biopsy during the microlaryngoscopy to confirm the diagnosis. The tumour site was supraglottic in 33 cases (17.8%), glottic in 124 cases (67%), subglottic in three cases (1.6%) and glottic extending to supraglottis and/or subglottis in 25 cases (13.6%). Table 1 shows the T and N stages classified according to the UICC classification.[2]

Patients were only included in the study group if they had received follow-up lasting at least three years. The patients were all treated with planned continuous-course radiotherapy. Five fractions were delivered a week in single daily fractions of 200 cGy using megavoltage equipment. The treatment volume depended on the site of the tumour. For patients with palpable neck nodes or a high probability of infraclini-

Table 1

UICC T and N stages in patients

	N0	N1	N2	N3	**TOT**
T1a	107	1	0	1	109
T1b	21	0	0	0	21
T2	21	3	0	0	24
T3	14	9	1	1	25
T4	1	1	3	1	6
TOT	164	14	4	3	**185**

Table 2

UICC T and N stages in patients with follow-up

	N0	N1	N2	N3	**TOT**
T1	90	1	0	1	92
T2	13	3	0	0	16
T3	11	4	0	0	15
T4	0	0	1	0	1
TOT	133	8	1	1	**143**

Table 3

UICC T and N stages in patients with glottic localisation

	N0	N1	N2	N3	**TOT**
T1a	86	0	0	0	86
T1b	19	0	0	0	19
T2	7	0	0	0	7
T3	1	0	0	0	1
T4	0	0	0	0	0
TOT	113	0	0	0	**113**

Table 4

UICC T and N stages in patients with supraglottic localisation

	N0	N1	N2	N3	**TOT**
T1	4	1	0	1	6
T2	6	3	0	0	9
T3	1	1	0	0	2
T4	0	0	1	0	1
TOT	11	5	1	1	**18**

cal nodal involvement, the treated volume included both side nodes, including node levels II, III and IV. Patients received once-daily treatment with a mean total dose of 65 ± 6.6 Gy (64-75; median 66 Gy) over a mean treatment period of 44 ± 6 days. The doses delivered were 65 Gy for T1a, 66 Gy for T1b, 67 Gy for T2, and 72 Gy for T3 and T4 tumours. Patients with palpable nodes received 65 Gy to the neck.

Loco-regional recurrences, recurrence treatment, survival rates and complications were studied retrospectively.

The Fisher exact test was used to compare the recurrence rates depending on T stage and T localisation.

The Kaplan-Meier method was used to calculate the global and actuarial survival rates.

Results

One hundred and forty-three patients were followed-up for periods of between three and five years. The TNM distribution of the study group is shown in Tables 2, 3 and 4. Forty-two patients were excluded from the study because they failed to complete the follow-up. A loco-regional recurrence was observed in 22 patients (15.3%). T localisation before RT was as follows: supraglottic in four cases (18.2%), one T1 and three T2; glottic in fourteen cases (63.6%), ten T1a, two T1b and two T2; glottic extending to supraglottis and/or subglottis in four cases (18.2%), all T3. One hundred and thirty-four patients were N0, eight N1, one N2 and one was N3.

Recurrences were observed at the site of the primitive tumour in eighteen patients (81.8%), in the cervical nodes in one patient (4.55%), in both sites in one patient (4.55%) and in the stoma in two patients (9.1%). These two were tracheotomised for dyspnoea during or at the end of RT.

The recurrence rates in patients with T1, T2 and T3 tumours were 14.1% (13/92 patients), 31.3% (5/15 patients) and 26.6% (4/15 patients) respectively.

The recurrence rates were 22.2% (4/18 patients) in patients with a supraglottic tumour and 12.3% (14/113 patients) in patients with a glottic tumour.

The average time between the end of RT and recurrence was 16.3 months (range 0-48; DS 14.6). Table 5 shows the TNM classification before RT and at the moment of recurrence, and the pTNM classification for those cases submitted to surgery.

Salvage surgery was performed in fourteen patients (63.6%) out of 22: laryngofissure with chordectomy was used in one case (7.1%); total laryngectomy in four cases (28.6%), total laryngectomy with neck dissection in nine cases (64.3%), five of whom underwent a pectoralis major myocutaneous flap reconstruction for defect repair. Eight patients did not undergo surgery: six refused any kind of treatment and two were treated with chemotherapy for a second metachronous tumour. At the moment of recurrence a pulmonary metastasis was also observed in two out of six patients who refused any treatment.

During RT, two out of four tracheotomised patients developed a peristomal recurrence.

Fisher's exact test was used to assess differences between the groups. The null hypothesis was that stage (T1, T2 or T3) did not affect recurrence (YES or NO), i.e. that stage and recurrence were independent. The p-value was 0.1408 so the null hypothesis cannot be rejected. Statistical analysis showed that there was no correlation between stage and recurrence.

Table 5
TNM classification of patients before and at the moment of recurrence. pTNM classification is reported for surgery cases

Patient	Age	T localisation	TNM before RT	pTNM/TNM after recurrence
O E	57	Supraglottis	T1 N0 M0	T3 N0 M1
C.C.	66	Glottis	T1a N0 N0	PT1a N0 M0
B.V.	69	Glottis	T1a N0 M0	T3 N0 M0
R.A.	78	Glottis	T1a N0 M0	T3 N0 M0
C.U.	65	Glottis	T1a N0 M0	PT3 N0 M0
R.G.	75	Glottis	T1a N0 M0	PT2 N0 M0
C.G.	78	Glottis	T1a N0 M0	PT3 N0 M0
Z.G.	54	Glottis	T1a N0 M0	PT4 N0 M0
E.G.	64	Glottis	T1a N0 M0	T3 N0 M1
B.A.	66	Glottis	T1a N0 M0	PT4 N0 M0
Z.C.	68	Glottis	T1a N0 M0	PT3 N0 M0
C.G.	55	Glottis	T1b N0 M0	PT3 N0 M0
F.G.	60	Glottis	T1b N0 M0	PT4 N0 M0
P.R.	78	Supraglottis	T2 N0 M0	T1 N3 M0
V.B,	70	Supraglottis	T2 N0 M0	PT4 N0 M0
P.S.	73	Glottis	T2 N0 M0	PT4 N0 M0
M.G.	79	Supraglottis	T2 N0 M0	T0 N3 M0
T.Q.	51	Glottis	T2 N0 M0	PT3 N0 M0
F.V.	57	Supraglottis-Glottis-Subglottis	T3 N0 M0	T4 N0 M0
T.O.	58	Glottis-Supraglottis	T3 N0 M0	PT3 N0 M0
S.G.	77	Glottis-Subglottis	T3 N0 M0	PT4 N0 M0
L.D.	77	Supraglottis-Glottis-Subglottis	T3 N0 M0	T4 N0 M0

After the end of RT, the global survival rate in people with recurrence was 70.6% after three years and 35.7% after five years.

The global and actuarial survival rate for those operated on was 20% after three years and 0% after five years.

Global survival in the group treated with surgery was 92.3% after three years and 66.6% after five years; the actuarial survival rate was 100% after three years and 83.3% after five years.

After surgery, a mucocutaneous fistula occurred in one laryngectomee patient (7.1%), and it was resolved using dressings.

In two laryngectomee patients, a metachronous carcinoma (one pulmonary and one oesophageal) was diagnosed after 31 and 50 months respectively. The patient with oesophageal carcinoma died from that pathology, while the patient with pulmonary tumour underwent a lobectomy. He is still alive.

Discussion

The study reports a recurrence rate for laryngeal SCC after radiation failure. The treatment of choice for tumours classified as glottic T1 (86 T1a and 19 T1b) and selected T2 (7 T2N0) was radiotherapy. For tumours classified as supraglottic (18 cases) and T3 (13 cases) or T4 (6 cases) the choice of RT was the result of a surgery refusal by nine patients, low performance status in fourteen cases and high anaesthesiological risk in eight cases. Twenty-two (15.3%) out of 143 patients developed a loco-regional recurrence after radiation failure.

The recurrence rates reported in the literature after both radiation and surgical failures do not differ from those of this study. Vitraniemi *et al.*[3] observed a rate of 22% for local recurrences in T1 and T2 patients after radiation failure. In a similar population, McLaughlin *et al.*[4] observed a recurrence rate of 11%; Schwaab *et al.*[5] found that recurrence rates differed for T1a, T1b and T2, being 14%, 16% and 36% respectively. In T3 and T4 Johansen *et al.*[6] observed a recurrence of 32% after RT; in an analogous group of patients Leon *et al.*[7] reported a recurrence rate of 31%. Parsons *et al.*[8] observed a loco-regional recurrence in 22% of supraglottic tumours treated with RT. Puxeddu *et al.*[9] reported a rate of 10% for local recurrence three years after primary surgery in the T1 group and 15% in the T2 group.

The results of the present study do not differ from those in the literature: the recurrence rates for patients with tumours classified as T1, T2 and T3 were 14.1%, 31.3% and 26.6% respectively. The recurrence rates were 22.2% in patients with supraglottic tumours and 12.3% in patients with glottic tumours.

In our study one patient suffered a recurrence both in the larynx and in the neck; the regional recurrence was probably due to a recurrence in the larynx that was not diagnosed previously. The T2N0 case with a neck failure (T0 N3) can probably be explained as a micrometastasis not respondent to therapy. The primary tumour was in the supraglottis and it is well known that there is a high risk of occult micrometastasis in levels II and III in carcinomas located in this part of the larynx, even when they are classified clinically as N0 in the early stages.

The average time between the end of RT and the observation of recurrence was 16 months. It would be correct to classify recurrence before 6 months of follow-up as persistence.

No patient underwent a near-total laryngectomy because of the T extension or the performance status of the patient. Some authors[10-13] advocate partial laryngectomy as salvage surgery after radiation failure; crico-hyoidopexy (CHP) and crico-hyoido-epiglottopexy (CHEP) lead to good results both in term of voice quality and survival rates. Quer *et al*.[14] propose endoscopic laser surgery in cases of radiation failure in early laryngeal carcinoma. Close follow-up during and after RT would seem to be important because only early diagnosis allows conservative surgery. In our study, only one patient underwent a laryngofissure with chordectomy, while in the others the treatment was a total laryngectomy with neck dissection when necessary and, where appropriate, pectoralis major myocutaneous flap reconstruction. It was not possible for the study to include patients treated with near-total laryngectomy because of a lack of follow-up; however, when there is recurrence, both tumour extension and performance status limit the indication.

The only complication observed was a mucocutaneous fistula, which was treated with good results using daily dressing. Two out of four patients tracheotomised during RT for dyspnoea had peristomal recurrence. We therefore suggest a total laryngectomy within 48 hours when it is necessary to tracheotomise a patient during or immediately after RT for dyspnoea. This procedure can prevent recurrences in the subglottis or in the stoma, the sites with the highest risks of recurrence after tracheotomy. The survival rate for these patients was worse than for the others.

The global survival rate in the study group was 70.6% after three years of follow-up and 35.7% after five years. The global survival rate in the group treated with surgery was 92.3% after three years and 66.6% after five years, while the actuarial survival rate was 100% after three years and 83.3% after five years. The survival rate in the operated patients was lower because of the death of the tracheotomised patients with recurrence. Patients treated only with chemotherapy (two cases) or patients who refused any kind of treatment (six cases) had a survival rate of 20% after three years and 0% after five years.

Conclusion

Meticulous follow-up is required in patients treated with RT in order to diagnose any recurrence at an early stage and to conduct salvage surgery that is as conservative as possible.

Surgical technique is more difficult in a neck previously treated with RT. Nevertheless, reconstruction with a flap reduces the number of complications.

Local control of the disease after radiation and a good survival rate after salvage surgery for recurrence do not contra-indicate a first approach with RT for T1 and selected T2 laryngeal SCC.

Acknowledgments

Our special thanks go to Professor Sergio Zani for his assistance with statistical analysis.

Biblography

1. Esteve J, Kricker A, Ferlay J, Parkin DM. Facts and figures of cancer in the European Community. *International Agency for Research on Cancer.* 1993:Lyon, France.
2. Sobin LH, Wittekind C, Ed. *TNM Classification of malignant tumours, sixth edition.* John Wiley & Sons, Inc., New York;2002:36-42.
3. Virtaniemi JA, Hirvikoski PP, Kumpulainen EJ, Johansson RT, Kosma VM. Surgical management of irradiation failures in T1-T2 squamous cell carcinoma of the glottic larynx. *Anticancer Res.* 2001;21: 4185-4188.
4. McLaughlin MP, Parsons JT, Fein DA, *et al*. Salvage surgery after radiotherapy failure in T1-T2 squamous cell carcinoma of glottic cancer. *Head Neck*. 1996;18:229-235.
5. Schwaab G, Mamelle G, Lartigau E, Parise O Jr, Wibault P, Luboinski B. Surgical salvage treatement of T1/T2 glottic carcinoma after failure of radiotherapy. *Am J Surg.* 1994;168: 474-475.
6. Johansen LV, Grau C, Overgaard J. Glottic carcinoma-patterns of failure and salvage treatement after curative radiotherapy in 861 consecutive patients. *Radiother Oncol*. 2002;63: 257-267.
7. Leon X, Quer M, Orus C, Lopez M, Gras JR., Vega M. Results of salvage surgery for local or regional recurrence after larynx preservation with induction chemotherapy and radiotherapy. *Head Neck*. 2001;23:733-738.
8. Parsons JT, Mendenhall WM, Stringer SP, Cassisi NJ, Million RR. Salvage surgery following radiation failure in squamous cell carcinoma of the supraglottic larynx. *Int J Radiat Oncol Biol Phys*. 1995;32:605-609.
9. Puxeddu R, Argiolas F, Bielamowicz S, Satta M, Ledda GP, Puxeddu P. Surgical therapy of T1 and selected cases of T2 glottic carcinoma: cordectomy, horizontal glottectomy and CO2 laser endoscopic resection. *Tumouri*. 2000;86:277-282.
10. Laccourreye O, Weinstein G, Naudo P, Cauchois R, Laccourreye H, Brasnu D. Supracricoid partial laryngectomy after failed laryngeal radiation therapy. *Laryngoscope*. 1996;106:495-498.

11. Bron L, Brossard E, Monnier P, Pasche P. Supracricoid partial laryngectomy with cricohyoidoepiglottopexy and cricohyoidopexy for glottic and supraglottic carcinomas. *Laryngoscope*. 2000;110:627-634.
12. Spriano G, Pellini R, Romano G, Muscatello L, Roselli R. Supracricoid partial laryngectomy as salvage surgery after radiation failure. *Head Neck*. 2002;24:759-765.
13. Rodriguez-Cuevas S, Labastida S, Gonzalez D, Briseno N, Cortes H. Partial laryngectomy as salvage surgery for radiation failures in T1-T2 laryngeal cancer. *Head Neck*. 1998;20:630-633.
14. Quer M, Leon X, Orus C, Venegas P, Lopez M, Burgues J. Endoscopic laser surgery in the treatment of radiation failure of early laryngeal carcinoma. *Head Neck*. 2000;22:520-523.

Mercante Giuseppe, M.D.
Department of Othorhinolaryngology
University of Parma
Via Gramsci 14
43100 Parma, Italy
Tel.: +39(0)521702715
Fax: +39(0)521290157
E-mail: giuseppe.mercante@wanadoo.fr