The Journal of Laryngology & Otology
January 2002, Vol. **116,** pp. 24–28

Squamous cell carcinoma of the hypopharynx treated with surgery and radiotherapy

L. Barzan, M.D., R. Talamini, Sc.D.*, D. Politi, M.D., E. Minatel, M.D.†, C. Gobitti, M.D.†, G. Franchin, M.D.†

Abstract

A series of squamous cell carcinomas (SCC) of the hypopharynx treated with combined surgery and radiotherapy is presented to highlight the results of treatment at an early stage of disease. A retrospective mono-institutional analysis was performed on 153 previously untreated patients with SCC of the hypopharynx, seen between 1980 and 1995 at our institution. Univariate and multivariate analyses were performed using the Cox proportional hazard model. The overall five-year specific, and non-specific, disease survival rates were 68 per cent (95 per cent confidence interval, CI: 60–77) and 47 per cent (95 per cent CI: 39–56), respectively. Compared with other series, this study is characterized by treatment at an earlier stage, better prognosis, and a higher number of multiple malignancies. Twenty-two per cent of hypopharyngeal SCCs were diagnosed during the staging procedures for a different head and neck SCC and 14 per cent during the follow-up for a previous tumour. Multivariate survival analysis of clinical and pathological factors confirmed the clinical class of tumour (T) and node (N) and the nodal capsular rupture as prognosticators of disease.

Key words: Carcinoma; Hypopharynx; Radiotherapy; Surgical Procedure, Operative

Introduction

Among tobacco and alcohol-related squamous cell carcinomas (SCC) of the upper aerodigestive tract, the hypopharyngeal region is often attributed with the poorest prognosis.[1,2] Hypopharyngeal cancer is usually diagnosed in an advanced stage after an asymptomatic beginning, and it is related to a high frequency of lymph node metastases. An eventual bad outcome may occur not only for loco-regional but also for frequent distant failures, other tumours, and associated diseases. The standard treatment of the advanced hypopharyngeal SCC is surgery (encompassing a total laryngectomy) and post-operative radiotherapy; the more recent therapeutic approach with chemo-radiotherapy (aiming at organ-preservation) still remains investigational.[3]

Surprisingly, retrospectively examining the present mono-institutional 15-years-series, a particularly high frequency of early stages and multiple tumours were noted among patients surgically treated for hypopharyngeal SCC. The aims of this paper were to present this series of hypopharyngeal SCC treated with combined surgery and radiotherapy to highlight the results derived from treatment at an earlier stage and to explain how a significant number of early-stage SCCs of the hypopharynx was detected.

Materials and methods

Between 1980 and 1995, 228 previously untreated patients had a histological diagnosis of SCC of the hypopharynx at our institution. Among them, 75 (i.e. 71 men and four women; median age 64; six stage I of disease, 14 stage II, 16 stage III, 31 stage IVA, five IVB, three IVC) were treated with radiotherapy only (i.e. 25 for unresectable loco-regional extension; 24 for poor performance status; 20 for multiple associated unresectable primary tumours; three for distant metatases, and three for refusal of demolitive surgery). Only one of these patients is still alive and free of disease. The other 153 patients (i.e. 86 per cent affected by SCC of the pyriform sinus, eight per cent posterior wall, six per cent postcricoid area), who are the subjects of this paper, underwent surgical treatment (with, or without radiotherapy). Subjects were 149 men and four women with a median age of 57, range 40–78 years.

During the aforementioned period of time, our policy for hypopharyngeal SCC did not change with regard to staging, encompassing computed tomography (CT) scan of the neck and panendoscopy. Whenever possible our approach included surgery, but preserving the larynx, otherwise a total laryngectomy with (partial) pharyngectomy was

From the Otolaryngology Unit, Azienda Ospedaliera 'S. Maria degli Angeli', Pordenone, Italy and the Units of Epidemiology* and Radiotherapy†, Centro di Riferimento Oncologico, IRCCS, Aviano, Italy.
Accepted for publication: 1 August 2001.

considered. However, for pyriform sinus carcinoma, hemithyroidectomy was always performed. The neck dissection was monolateral for T_1N_0 of the pyriform sinus, bilateral in all other cases; and recurrent nodes were always dissected. The dissections were always comprehensive of all the levels of the neck: in case of N_0/mobile nodes the dissection preserved the sternocleidomastoid muscle, internal jugular vein and spinal accessory nerve. In case of a node with impaired mobility a radical neck dissection was performed. For no patient of this series was a bilateral synchronous radical dissection indicated. Thirteen patients with the neck already dissected for a previous different head and neck carcinoma were classified as pN unknown. When suitable, a reconstruction of an adequate calibre food canal, using various flaps (mainly local mucosal flaps or a pectoralis major mucutaneus flap), was performed.

Post-operative radiotherapy (6000 cGy/30 fractions by a 6 Mv linear accelerator, using personalizing fixing mask) was used if either of the following were present: microscopically positive surgical margins; intranodal metastases in $\geqslant 2$ lymph nodes; or nodal metastases with capsular rupture. The follow-up examination (i.e. every three months for three years; every six months for the fourth and fifth year; and yearly thereafter) encompassed always a complete upper airway endoscopy and a yearly oesophagoscopy.

The data were retrospectively reviewed to update the Classification of Malignant Tumours (TNM) classification with the fifth edition of the UICC (1997). In the re-evaluation of the margins, those with serious dysplasia/carcinoma *in situ* were considered as 'involved'. The endpoint used to define cause-specific survival was death with active specific cancer.

Information on survival was obtained through an active follow-up based on verifiication of vital status of SCC hypopharynx patients, from disease diagnosis up to the last follow-up on March 1999. Specific disease survival was calculated on deaths from SCC of the hypopharynx (40 patients), and crude survival was calculated on deaths from all causes (91 patients: 40 from specific diseases and 51 from non-specific diseases). In particular, non-specific diseases were 34 patients with secondary primary cancer (16 lung, six stomach, five oesophagus, four colon-rectum, three NHL), and 17 patients with non-cancer diseases (seven other diseases of upper respiratory tract, four acute ischaemic heart diseases, four peripheral vascular diseases, two cerebrovascular diseases). Ninety per cent of our patients died in hospital, therefore causes of death were ascertained, autopsy included (upon family consent), by the attending medical staff.

Univariate and multivariate regression analyses of survival data were performed by the Cox proportional hazard model and 95 per cent confidence interval (CI).[4,5] Covariates to be tested in the multivariate analysis were selected from those which were significant by univariate analysis. Differences between subgroups were assessed by the Wald chi-square test.[5] In all cases, statistical significance was claimed for $p \leqslant 0.05$ (two-tails).

TABLE I

UNIVARIATE AND MULTIVARIATE ANALYSIS OF SPECIFIC DISEASE SURVIVAL OF 153 PATIENTS WITH SQUAMOUS CELL CARCINOMA OF THE HYPOPHARYNX, ACCORDING TO SOME CLINICAL PROGNOSTIC FACTORS AND TREATMENT

Prognostic factor	No.	% survival at 60 months	Univariate* HR (95% CI)§	Multivariate** HR (95% CI)§
Grading				
G1+G2†	81	71	1	
G3+G4	59	63	1.2 (0.6–2.3)	
Not specified	13	–		
Chi-squared			0.32; p = 0.57	
Clinical class of tumour				
T_1†	42	90	1	1
T_2	52	65	4.3 (1.3–14.7)	3.3 (0.8–14.1)
T_3	38	60	4.5 (1.3–16.0)	3.5 (0.7–16.4)
T_4	21	51	7.9 (2.1–30.0)	6.5 (1.3–32.5)
Chi-squared for trend			9.40; $p = 0.002$	4.53; $p = 0.03$
Clinical class of lymph nodes				
N_0†	70	75	1	1
N_1	33	78	1.4 (0.5–3.5)	1.0 (0.4–2.5)
N_2 (a,b,c)-N_3	49	52	3.0 (1.5–6.0)	2.3 (1.1–4.8)
Unknown	1	–		
Chi-squared for trend			9.17; $p = 0.003$	5.44; $p = 0.02$
Surgery of tumour				
With total laryngectomy†	121	63	1	1
Without total laryngectomy	32	88	0.3 (0.1–0.9)	0.9 (0.2–3.8)
Chi-squared			4.23; $p = 0.04$	0.03; $p = 0.87$
Radiotherapy after surgery				
Yes†	104	75	1	
No	49	65	0.6 (0.3–1.3)	
Chi-squared			1.68; $p = 0.19$)	

*Cox-proportional hazard model. **Cox model includes all terms statistically significant at univariate analysis. §Hazard ratio (HR) and 95% confidence intervals (CI). †Reference category.

https://doi.org/10.1258/0022215021910294 Published online by Cambridge University Press

TABLE II

UNIVARIATE AND MULTIVARIATE ANALYSIS OF SPECIFIC DISEASE SURVIVAL OF 153 PATIENTS WITH SQUAMOUS CELL CARCINOMA OF THE HYPOPHARYNX, ACCORDING TO SOME PATHOLOGICAL PROGNOSTIC FACTORS

Prognostic factor	No.	% survival at 60 months	Univariate* HR (95% CI)§	Multivariate** HR (95% CI)§
Pathological class of tumour				
pT1†	41	94	1	1
pT2	38	63	7.2 (1.6–31.5)	2.8 (0.5–14.6)
pT3	36	59	6.9 (1.5–31.4)	2.6 (0.5–13.2)
pT4	38	56	9.4 (2.1–41.6)	2.7 (0.5–14.3)
Chi-squared for trend			9.00; $p = 0.003$	0.30; $p = 0.59$
Pathological class of lymph nodes				
pN_0†	39	89	1	1
pN_1	18	84	1.6 (0.3–9.6)	1.6 (0.2–13.3)
pN_2 (a,b,c)-N3	83	48	8.1 (2.5–26.5)	1.5 (0.2–9.2)
Unknown	13	–		
Chi-squared for trend			14.71; $p \leqslant 0.001$	0.12; $p = 0.73$
Margins				
Free†	138	67	1	
Involved	14	80	0.5 (0.1–2.2)	
Unknown	1	–		
Chi-squared			0.81; $p = 0.37$	
pN+ without capsular rupture				
0†	65	74	1	1
1	27	84	0.5 (0.1–1.5)	0.3 (0.1–1.1)
2	18	56	1.9 (0.8–4.5)	0.8 (0.3–2.1)
⩾3	30	43	2.4 (1.2–5.0)	1.4 (0.6–3.5)
Unknown	13	–		
Chi-squared for trend			7.15; $p = 0.007$	1.13; $p = 0.29$
pN+ *with capsular rupture*				
0+	69	89	1	1
1	28	44	6.3 (2.3–17.1)	5.5 (1.5–20.9)
2	23	36	11.7 (4.4–31.1)	7.9 (1.9–31.9)
⩾3	20	39	8.4 (3.0–23.2)	4.7 (1.2–18.7)
Unknown	13	–		
Chi-square for trend			25.06; $p \leqslant 0.001$	3.96; $p = 0.05$

Results

Overall five-year specific disease survival (calculated on deaths from SCC of the hypopharynx) was 68 per cent (95 per cent CI: 60–77), disease-free survival 67 per cent (95 per cent CI: 59–76), and crude survival (calculated on deaths from all causes) 47 per cent (95 per cent CI: 39–56) (not shown). Median follow-up was 37 months, range: 15–19.9 months. Univariate and multivariate survival analyses, assessed by the Cox proportional hazard model, according to some clinical prognostic factors and treatment, are reported in Table I. No gender or age-related differences were found in the five-year survival (not shown). Multivariate analysis showed that the clinical prognostic factors such as clinical class of tumour and clinical class of lymph nodes were the major factors influencing survival. The hazard ratios (HRs) for clinical class were 3.3 (95 per cent CI: 0.8–14.1), 3.5 (95 per cent CI: 0.7–16.4), and 6.5 (95 per cent CI: 1.3–32.5) for T_2, T_3, T_4, respectively, compared with T_1, with a significant Chi-squared for trend ($p = 0.03$). For clinical class of lymph nodes the HRs were 2.3 (95 per cent CI: 1.1–4.8) for N_2-N_3 in comparison to N_0 ($p = 0.02$).

Table II shows the univariate and multivariate survival analyses for some pathological factors. At the multivariate analysis, pN+ with capsular rupture resulted as a major factor influencing survival. HRs for 1,2 ⩾3 lymph nodes with capsular rupture were 5.5 (95 per cent CI; 1.5–20.9), 7.9 (95 per cent CI: 1.9–31.9), and 4.7 (95 per cent CI: 1.2–18.7), respectively ($p = 0.05$).

Table III shows the distribution of 84 patients with hypopharyngeal SCC and multiple tumours, according to anatomical sites and chronology of the second

TABLE III

DISTRIBUTIONS OF 84 PATIENTS WITH SQUAMOUS CELL CARCINOMA OF THE HYPOPHARYNX WITH MULTIPLE PRIMARY TUMOUR, ACCORDING TO ANATOMICAL SITES AND CHRONOLOGY OF SECOND TUMOUR

	Second primary tumour		
Anatomical site	Previous No ()	Synchronous No. ()	Subsequent No. ()
Head and neck	16 (2)	31 (1)	7 (7)
Oesophagus	2	2 (2)	9 (1)
Lung	1	1	8 (1)
Other (non-head and neck)	2	–	5 (6)
Total	21 (2)	34 (3)	29 (15)

() No. of patients with third tumour.

https://doi.org/10.1258/0022215021910294 Published online by Cambridge University Press

TABLE IV

PER CENT OF SURVIVAL PROBABILITY (SPECIFIC AND NON-SPECIFIC DISEASE) AT 60 MONTHS OF 153 PATIENTS WITH SQUAMOUS CELL CARCINOMA OF THE HYPOPHARYNX, ACCORDING TO SECOND PRIMARY TUMOUR

Second primary tumour	No.	% Survival probability at 60 months	
		Specific disease	Non-specific disease
None	69	51	43
Previous	21	73	53
Synchronous	34	73	45
Subsequent	29	100	57
All patients	153	68	47

primary tumours. Only 45 per cent of patients in our series had a single tumour. In fact, 22.2 per cent of hypopharyngeal SCC were diagnosed during the staging procedures for a synchronous different head and neck SCC, and 13.7 per cent during the follow-up for a previous tumour of the upper aerodigestive tract.

A further analysis of the data showed that patients with either a previous or synchronous cancer had an increased risk of growing a second, early stage SCC of the hypopharynx. Moreover, in patients with SCC of the hypopharynx, the probability of growing a synchronous second cancer was not influenced by gender, clinical, pathological stage of N, or recurrences (not shown).

Table IV shows the percentage of survival probability (specific and non-specific of disease) at 60 months of 153 patients with hypopharyngeal SCC, according to secondary primary tumour. The patients without a second tumour displayed the lowest difference between specific and non-specific survival. In fact, death was usually due to (more advanced) hypopharyngeal SCC. When the hypopharyngeal SCC was diagnosed during the staging or the follow-up for a different tumour, it was often detected in an early asymptomatic stage; therefore, the specific disease prognosis was more favourable. When a second tumour was diagnosed during the follow-up of a successfully treated hypopharyngeal SCC, the hypopharynx-related survival rate resulted as the highest since the patient would have been more likely to die from the new tumour.

Discussion

This is a retrospective mono-institutional review of all patients firstly diagnosed with an hypopharyngeal SCC and treated with surgery with/without radiotherapy. Diagnosis and treatment were accomplished in Friuli-Venezia Giulia, one of the Italian regions with higher tobacco and alcohol consumption and with an incidence of upper aerodigestive tract tumours among the highest in Europe.[6,7] Compared with others in the recent literature,[2,8–10] the present series are characterized by earlier stages (with more favourable prognoses), and a high number of multiple malignancies. When compared with the meta-analysis of Haughey[11] (i.e. 12.7 per cent of second tumours for hypopharynx), the frequencies of other primary tumours appeared particularly high. The majority of these endoscopically detected hypopharyngeal SCC were asymptomatic, early-stage lesions and were treated with a curative aim. Probably due to these reasons, our patients had a greater specific disease survival than other series.[2,9,12]

We cannot agree, however, with Dhooge's[13] theory of equivalent prognostic significance of a second tumour and of a recurrence, since the dismal prognosis of our patients who relapsed was quite different from patients with multiple malignancies. The early stage of the hypopharyngeal SCC was considered and the related possibility of a radical treatment have been determinant for the increased survival rate. On the other hand, the patients who did not undergo a panendoscopy during the staging or the follow-up of a different SCC, had the diagnosis of the otherwise asymptomatic hypopharyngeal SCC in more advanced stage with, therefore, a less favourable prognosis. Paradoxically, the presence of an other SCC would act as protective factor in the specific disease survival of the hypopharyngeal SCC.

In the present study the treatment factors did not seem significant for survival, this is in contrast to Czaja's series,[12] where patients treated with larynx-sparing surgery had a worse prognosis. In fact, the functional surgery, if correctly indicated and accurately carried out may have the same oncological radicality as the approach with total laryngectomy and a better local outcome due to the early stages of the tumour.

The present series has some of the inconveniences related to all retrospective studies. The true statistical significance of some prognostic factors may be flattened by the treatments, more aggressive for the unfavourable cases. Although the prognostic factor such as clinical class of T and N emerged as significant for both univariate and multivariate analyses, the pathological classes of T and N remained non-significant at multivariate analysis. The mobility of the lymph nodes, subjective parameter not recognized as criterion for the classification by the last two editions of the UICC's TNM, displayed in this series a prognostic statistical significance only with the univariate analysis. With respect to capsular rupture, the pathological status of the lymph nodes resulted as a significant prognosticator.

The margins (free/involved) of the surgical specimen and the post-operative radiotherapy (yes/no) are apparently without prognostic significance. However, radiotherapy has probably been effective, bringing patients with some less favourable theoretical factors to the same prognosis as those with

https://doi.org/10.1258/0022215021910294 Published online by Cambridge University Press

better factors, who did not undergo radiotherapy. In fact, only one patient with microscopically involved margins experienced a recurrence at primary site.

In conclusion, in our experience, the systematic endoscopy of the upper aerodigestive tract during the staging and the follow-up of a primary head and neck SCC has allowed the detection of many asymptomatic hypopharyngeal SCCs at an early stage. Treating these patients by surgery with, or without radiotherapy, and treating all hypopharyngeal SCCs by an aggressive approach (i.e. radical surgery researching the microscopically free margins, bilateral neck dissection, recurrent dissection, and, if indicated, post-operative radiotherapy) may result in a more favourable prognosis than previously reported.

Acknowledgements

This work was supported by the Ministero della Sanità, Ricerca Finalizzata, grant number ICS.060.2/RF97/52. The authors wish to thank Mrs Luigina Mei for language and editorial assistance.

References

1 Pingree TF, Davis RK, Reichman O, Derrick L. Treatment of hypopharyngeal carcinoma: a 10-year review of 1362 cases. *Laryngoscope* 1987;**97**:901–4
2 Hoffman HT, Karnell LH, Shah JP, Ariyan S, Brown GS, Fee WE, *et al.* Hypopharyngeal cancer patient care evaluation. *Laryngoscope* 1997;**107**:1005–17
3 Lefebvre JL. Larynx preservation: the discussion is not closed. *Otolaryngol Head Neck Surg* 1998;**118**:389–93
4 Cox DR. Regression models and life tables. *J Roy Stat Soc B* 1972;**34**:187–220
5 Allison PD. *Survival Analysis using the SAS System: a Practical Guide.* Cary, NC: SAS Institute Inc., 1995
6 Negri E, La Vecchia C, Levi F, Franceschi S, Serra-Majem L, Boyle P. Comparative epidemiology of oral and oesophageal cancers in Europe. *Eur J Cancer Prev* 1996;**5**:267–80
7 Macfarlane GJ, Macfarlane TV, Lowenfels AB. The influence of alcohol consumption on worldwide trends in mortality from upper aerodigestive tract cancers in men. *J Epidemiol Comm Health* 1996;**50**:636–9
8 Kowalsky LP, Santos CR, Magrin J, Scopel A. Factors influencing controlateral metastasis and prognosis from pyriform sinus carcinoma. *Am J Surg* 1995;**170**:440–5
9 Kraus DH, Zelefsky MJ, Brock HAJ, Huo J, Harrison LB, Shah JP. Combined surgery and radiation therapy for squamous cell carcinoma of the hypopharynx. *Otolaryngol Head Neck Surg* 1997;**116**:637–41
10 Elias MM, Hilgers FJM, Keus RB, Gregor RT, Hart AAM, Balm AJM. Carcinoma of the pyriform sinus: a retrospective analysis of treatment results over a 20-year period. *Clin Otolaryngol* 1995;**20**:249–53
11 Haughey BH, Gates GA, Arfken CL, Harvey J. Meta-analysis of second malignant tumors in head and neck cancer: the case for an endoscopic screening protocol. *Ann Otol Rhinol Laryngol* 1992;**101**:105–12
12 Czaja JM, Gluckman JL. Surgical management of early-stage hypopharyngeal carcinoma. *Ann Otol Rhinol Laryngol* 1997;**106**:909–13
13 Dhooge IJ, de Vos M, Van Cauwenberge P. Multiple primary malignant tumors in patients with head and neck cancer: results of a prospective study and future perspectives. *Laryngoscope* 1998;**108**:250–6

Address for correspondence:
Luigi Barzan, M.D.,
Otolaryngology Unit,
Azienda Ospedaliera 'S. Maria degli Angeli',
Via Montereale, 24,
33170 Pordenone,
Italy.

Fax: +39-0434-399753
E-mail: luigibarzan@libero.it

Dr L. Barzan takes responsibility for the integrity of the content of the paper.
Competing interests: None declared