Impact of combination therapy on disease free survival in hypopharynx cancer

Impacto da associação terapêutica na sobrevida livre de doença no câncer da hipofaringe

Helma Maria Chedid[1]; Sergio Altino Franzi[1]; Abrão Rapoport, ECBC-SP[1]; Otávio Alberto Curioni, TCBC-SP[2]

A B S T R A C T

Objective: To evaluate the disease-free survival in hypopharyngeal tumors submitted to postoperative radiotherapy. Methods: we retrospectively studied 174 patients with the following distribution: two cases of stage I, four stage II, 46 stage III and 122 stage IV. Regarding gender, 163 were male and 11 female; mean age was 56 years. All patients underwent pharyngolaryngectomy; neck dissections were radical in 206 and selective in 16. One hundred six patients underwent postoperative radiotherapy, with a mean dose of 58.2 Gy. Results: Histological examination showed two cases of stage pT1, 15 stage pT2, 100 stage pT3 and 57 stage pT4. As for lymph nodes, 25 patients had no involvement (pN0); 149 presented with lymph node invasion (pN +). Five-year disease-free survival was 40% and the overall survival was 28%. According to the results of histological examination, five-year disease-free survival was 75% in clinical stage III versus 28% in IV. Conclusion: The initial manifestation of squamous cell carcinoma of the hypopharynx happens in advanced stages (III and IV), with superior five-year disease-free survival in clinical stage III.

Key words: Carcinoma, squamous cell. Neoplasms. Hypopharynx. Disease-free survival.

INTRODUCTION

Squamous cell carcinoma of the hypopharynx has initial clinical presentation in advanced clinical stages (III and IV in drinkers and smokers), even in developed countries, accounting for a five-year survival prognosis of 20 to 40%[1,2]. The prognosis is related to age, poor and late presentation of signs and symptoms of the disease and aggressive behavior of locoregional recurrence in the first two years, evolving with distant metastasis at initial presentation or during the disease progression[3]. Distant metastasis is more likely to develop in advanced neoplastic disease and as first manifestation of failure of disease control, rates of 43% of distant metastases being found in patients with squamous cell carcinoma of the hypopharynx and locoregional control of the disease[4].

Among the prognostic factors in squamous cell carcinoma of the hypopharynx, there is neoplastic involvement of lymph nodes. On the first visit to the specialist, 65% to 80% of patients have palpable metastatic nodes. In patients with clinically negative neck (N0), 30 to 40% will be discovered to have positive lymph nodes when submitted to histopathological examination[5-7].

Despite technological advances in the treatment and reconstruction in recent decades, the results in locoregional control of tumors of the hypopharynx showed no changes, especially in advanced stages. Tumors of initial clinical stages (I and II) have favorable results with surgery or radiotherapy alone, whereas clinically advanced ones (stages III and IV) showed better results with resection and associated postoperative radiotherapy[1].The overall survival in histology review ranged from 10% to 50%, with superior results in patients with early clinical stage disease (I and II). However, many of these patients present with advanced disease (III and IV)[2,7-13], in which there was no need for combination therapy. In a retrospective analysis of 94 patients initially treated with resection, disease-free survival at five years was 60% in all clinical stages, lymph node commitment being the main prognostic factor[14].

This study aimed to evaluate the disease-free survival in patients with hypopharyngeal cancer undergoing surgical treatment and postoperative radiotherapy.

Work done at Department of Head and Neck Hospital de Heliopolis - Hosphel, Sao Paulo-BR.
1. Surgeon, Department of Head and Neck Surgery, Hospital de Heliopolis - Hosphel, São Paulo, SP, Brazil; 2. Head, Department of Head and Neck Surgery, Hospital de Heliopolis - Hosphel, São Paulo, SP, Brazil.

METHODS

We conducted a horizontal cohort study based on a retrospective analysis of 174 charts of patients with hypopharynx squamous cell carcinoma who had undergone initial surgical treatment with curative intent from January 1978 to December 2003.

Eligibility criteria were patients without prior cancer treatment and surgical treatment with curative intent. Exclusion criteria were the presence of simultaneous primary tumors, poor clinical conditions with KPS less than 70, unresectable tumors and indication of chemoradiotherapy in organ preservation protocols as initial therapy.

Patient's initial clinical stage was classified according to the TNM AJC UICC, 2002 (Table 1). For statistical analysis, we used the method of Kaplan-Meier.

RESULTS

Regarding the compromised anatomic subsite of the hypopharynx, three patients had a primary tumor with its epicenter on the posterior wall of the hypopharynx and 171 in the pyriform sinus. In 131 patients the tumors did not invade the midline, and in 43 cases this limit was exceeded (Table 2).

The primary tumor size (T) and the presence of lymph node involvement by the neoplasm (N) in the initial clinical presentation are outlined in Table 1. Regarding clinical stage (CS), two patients were stage I, four CS II, 46 CS III and 122 stage IV.

All patients underwent total laryngectomy or pharyngolaryngectomy when they had the primary tumor. When the laryngopharyngeal transit reconstruction was indicated, the pectoralis major musculocutaneous flap was used. One hundred and six (61%) patients underwent postoperative radiotherapy with linear or cobalt accelerator. The radiation dose ranged from 45 to 72Gy, with a mean dose of 52.8 Gy.

Mean follow-up was 31 months after the initial treatment. Regarding gender, 163 were male and 11 female. The average age was 56 years, ranging from 36 to 80.

As for the cervical approach, 222 neck dissections were performed, of which 206 were radical or modified (levels I to V) and the remaining 16 were selective (levels I to III). Of these 222 neck dissections, 48 were bilateral, comprising radical/modified (stages I to V) and selective (levels I to III) ones. Ten patients died within 30 days after surgery due to clinical complications, such as pneumonia, acute myocardial infarction and stroke.

In histopathological examinations, as the primary tumor, two patients were pT1, 15 were pT2, 100 were pT3 and 57 were pT4. Among the 34 N0 patients, 14 (41.2%) were false-negative (pN +) and from the 140 N + patients, seven (5%) were false positive (pN0). Therefore, in relation to lymph node, 27 patients had no lymph nodes involved by cancer (pN0), whereas 149 were node positive (pN +).

The overall survival at five years was 28%. Figure 1 shows the curve of five-year disease-free survival for these patients.

Considering lymph node status on histology, disease-free survival at five years was illustrated in Figure 2 (p=0,001).

As for the clinical stage of the 164 patients with follow-up, two were stage I, three were II, 22 were III and 137 were IV. Five-year disease-free survival is shown in Figure 3, considering the clinical and pathological disease stage (p=0.0004).

Thirty-eight (21.8%) patients referred to postoperative radiotherapy were not submitted to it due to complications in the surgical wound and poor socioeconomic conditions, losing the time frame considered ideal to irradiation.

With regard to recurrences, we observed 15 isolated local recurrences, 15 regional isolated, 18 isolated distant metastases, 13 locoregional and nine locoregional and distant (Figure 4). Apart from these, six patients developed peri-tracheostomy recurrences and one patient developed lymph node recurrence in the retropharyngeal space. We performed 12 rescue surgeries, ten of which for regional recurrences and two for isolated locoregional recurrences. Six patients underwent postoperative radiotherapy. Seven patients were treated with salvage radiotherapy, three for isolated regional recurrences and three for locoregional ones. Only one patient with peri-tracheostomy recurrence underwent resection and radiotherapy. The other patients with locoregional recurrences were directly referred to palliative care. Distant metastasis occurred in 27 cases, and the most frequent sites of involvement were: lung, brain, skin and

Table 1 – Distribution according to the TNM (n = 173).

	T1	T2	T3	T4
N0	2	4	18	10
N1	0	5	23	4
N2	0	7	53	19
N3	0	3	15	10
Total	2	19	109	43

T - size of primary tumor, N - lymph nodes involved by neoplasm. Exclusion of a patient staged as Nx.

Table 2 – Distribution of patients according to anatomical site.

Variable	Category	n	%
Anatomical site	Posterior wall	3	1,8
	Pyriform sinus	171	98,2

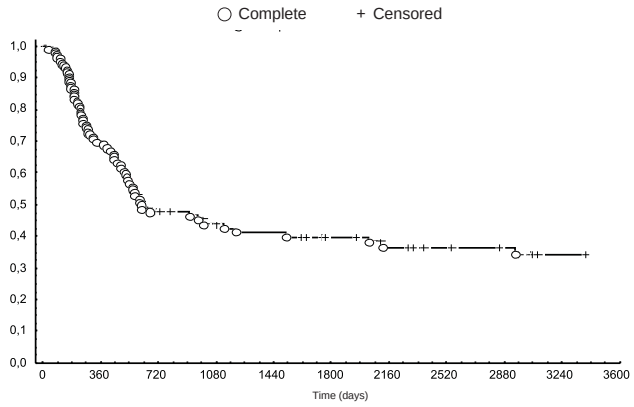

Figure 1 – *Distribution of disease-free survival of 174 patients with squamous cell carcinoma of the hypopharynx.*

n = 174 patients.

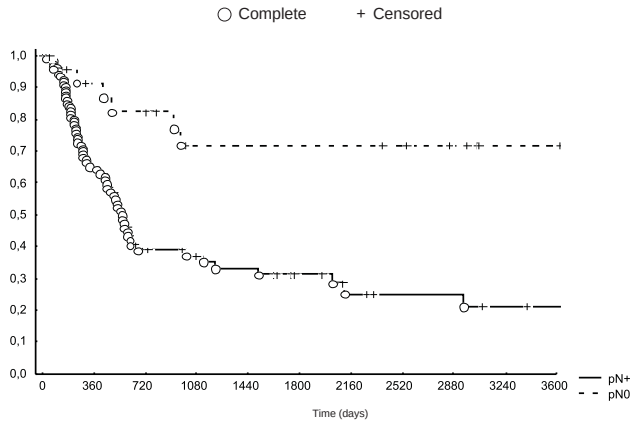

Figure 2 – *Distribution of disease-free survival according to histological lymph node stage (pN) (p=0.001).*

pN0=25 pN+=139.
Exclusion of 10 deaths in the postoperative period.

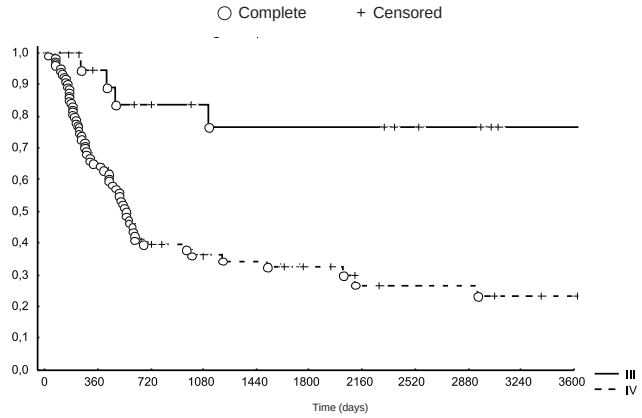

Figure 3 – *Distribution of disease-free survival according to clinical and pathological stage (p = 0.0004).*

pIII=22 pIV=137.
Five cases of stage I or II were excluded.
Excluding 10 deaths in the postoperative period.

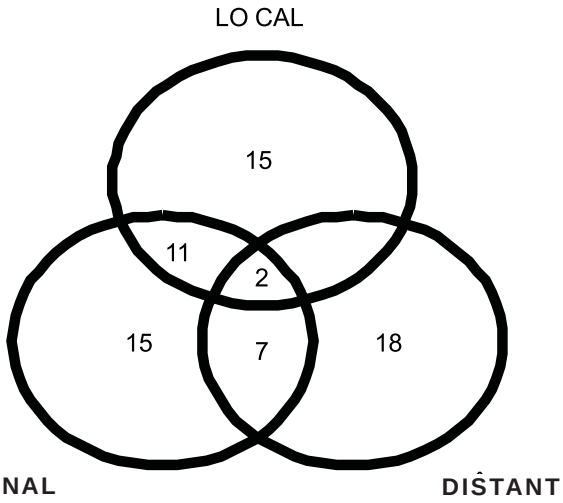

Figure 4 – *Distribution of locoregional and distant recurrences.*

axilla. Fourteen patients developed a second primary tumor, two in the head and neck, such as the mouth floor and tongue edge.

DISCUSSION

When treating squamous cell carcinoma of the hypopharynx, one should consider the preservation of voice, swallowing without aspiration and impact of these functions to the patient's quality of life. In this context, early clinical stage diseases (I and II) showed good survival and functional outcome following surgical treatment or radiotherapy as the initial treatment[14,15]. Moreover, the disease in advanced clinical stages (III and IV) has encouraging results with the combination of resection with radiotherapy in addition to being the standard treatment at this point[16].

The present study demonstrated a high rate of 21.8% of patients with advanced disease without radiotherapy after surgery. Sixty-eight patients were not irradiated in the initial treatment. Ten cases died within 30 days after surgery and 58 patients did not undergo postoperative irradiation in the absence of histopathological criteria established in the literature for complementation with postoperative radiotherapy, such as lymph node involved and capsular rupture, margin compromised by neoplasia, pT4 tumors and perineural invasion. Postoperative complications caused the considered optimal period for adjuvant radiotherapy to be exceeded, such as wound infection and necrosis, wide pharyngo-cutaneous fistulae and lack of adherence to treatment, usually by poor socioeconomic conditions.

Still, during the 20 years included in the study, the wound complication rates suffered interference, such as the surgeon formation time (learning curve), developments in the preoperative prophylaxis of infections and the emergence of wide-spectrum antibiotics and measures of asepsis and antisepsis. However, the biological behavior of these tumors

deserves special attention, as it determines an insidious onset and diagnosis in advanced stages.

The absence of postoperative radiotherapy is associated with lower rates of overall survival and disease-free survival. Comparing the results of this study with a series of 104 patients initially treated surgically, 80% were in advanced stage (T3 and T4), 62% had cervical metastases and 66% underwent postoperative radiotherapy. Locoregional recurrences occurred in 38 (37%) patients, with 47% overall survival and 62% five-year disease-free survival[17].

The results are corroborated in a retrospective population study conducted in Canada with patients with squamous cell carcinoma of the hypopharynx, where the primary tumor size was a significant prognostic factor for survival along with lymph node status[18].

Differences in disease-free survival in clinical stages III and IV observed in this study can be attributed to the presence of T4 tumors of greater size and degree of infiltration, causing no detectable subclinical disease.

Some authors demonstrated that the failure of initial treatment was related to regional recurrence and distant metastasis, with better rates of disease local control[17,19]. In that series, similar and superior results were shown for hematogenous metastases, with 26% of patients with distant dissemination.

Lymph node status is an independent prognostic factor in several series, which unanimously show, by univariate and multivariate analyses, the worst results of disease-free survival in the presence of lymph node involvement[14,19,20]. We demonstrated similar results on five-year disease-free survival in patients with tumors of the hypopharynx in the presence of lymph node involvement by cancer, exceeding 70% in pN (0) versus 30% in pN (+) cases.

Depending on the type of initial therapy, the rates of local disease control in the literature are variable, such as survival of 16% in initial tumors and 18% in advanced tumors with association of resection and complementary radiotherapy[21]. Discordant results were observed in this study, local recurrences presenting rates around 53%. Local failure can be related to the prevalence of advanced tumors (T3 and T4) and the absence of additional postoperative radiotherapy in 21.8% of induviduals. The isolated use of radiotherapy in the primary tumor resulted in a survival rate of 6%[16]. Although this study did not focus on the initial radiotherapy or chemoradiotherapy for tumors of the hypopharynx, the worst results of organ preservation are found in advanced tumors with deep infiltration and involvement of the neck soft tissues[22].

The guidelines of our department advocate surgical treatment for tumors of the hypopharynx in association with postoperative radiotherapy. Disease-free survival after initial surgical treatment with or without postoperative radiotherapy was 40% and 96.5% of the tumors presented as advanced disease at the time of manifestation (clinical stages III and IV).

In the face of a disease with advanced initial manifestation, clinical-pathological stages III and IV represent 91.4% of the histopathology findings. When comparing the curves of disease-free survival between these two clinical stages, this study showed 75% disease-free survival in stage III and 30% in stage IV. This difference is related to primary tumor size (T3 and T4), given that local recurrence alone is rarely capable of salvage therapy, being the main cause of failure in controlling the disease.

The rate of distant metastasis is higher in squamous cell carcinoma of the hypopharynx, fact related to the presence of disease in an advanced clinical stage at the time of diagnosis[21]. Distant metastasis of hypopharynx neoplasia is also related to the first clinical manifestation of failure in controlling the disease, with rates of 16% and 20%[23,24]. Our study showed similar data, with detection of 15.5% of distant metastasis during follow-up; in 66.7% of cases distant metastasis was the first manifestation of disease recurrence.

Therapeutic planning in hypopharynx cancer should be preceded by careful assessment of imaging methods, such as Pet-CT, in all clinical stages, focusing on the detection of subclinical disease.

Squamous cell carcinoma of the hypopharynx has its initial manifestation predominantly in advanced clinical stages III and IV (96.5%), with findings of five-year disease-free survival higher in patients with clinical stage III and no lymph node involvement on histological examination.

R E S U M O

Objetivo: *Avaliar a sobrevida livre de doença nos tumores de hipofaringe submetidos ao tratamento operatório e à radioterapia pós-operatória.* ***Métodos:*** *Estudo retrospectivo de 174 pacientes com distribuição, de acordo com o estádio clínico em: dois casos de estádio clínico I; quatro II; 46 III e 122 IV. Quanto ao gênero, 163 eram masculinos e 11 femininos, com idade média de 56 anos. Todos os casos foram submetidos à faringolaringectomia e realizados 206 esvaziamentos cervicais radicais e 16 seletivos. Cento seis pacientes foram submetidos à radioterapia pós-operatória, com dose média de 58,2 Gy.* ***Resultados:*** *O exame histológico demonstrou dois casos de estádio clínico pT1, 15 pT2, 100 pT3 e 57 pT4. Quanto aos linfonodos, 25 pacientes apresentavam ausência de linfonodos comprometidos pela neoplasia (pN0) e 149 com linfonodos comprometidos pela neoplasia (pN+). A sobrevida livre de doença há cinco anos foi de 40% e a global de 28%. A sobrevida livre de doença há cinco anos foi de 75% no estádio clínico III* versus *28% no IV, de acordo com o resultado do exame histológico.* ***Conclusão:*** *A manifestação inicial do carcinoma epidermóide de hipofaringe ocorre na fase avançada (estádios III e IV), com sobrevida livre de doença a cinco anos superior no estádio clínico III.*

Descritores: *Carcinoma de células escamosas. Neoplasias. Hipofaringe. Sobrevivência livre de doença.*

REFERENCES

1. Shah JP. Hypopharynx and cervical esophagus. Head and Neck Surgery. London: Mosby-Wolfe; 1996.
2. Wei WI. The dilemma of treating hypopharyngeal carcinoma: more or less: Hayes Martin Lecture. Arch Otolaryngol Head Neck Surg. 2002;128(3):229-32.
3. Chu PY, Wang LW, Chang SY. Surgical treatment of squamous cell carcinoma of the hypopharynx: analysis of treatment results, failure patterns, and prognostic factors. J Laryngol Otol. 2004;118(6):443-9.
4. Alvi A, Johnson JT. Development of distant metastasis after treatment of advanced-stage head and neck cancer. Head Neck. 1997;19(6):500-5.
5. Carpenter RJ 3rd, DeSanto LW, Devine KD, Taylor WF. Cancer of the hypopharynx. Analysis of treatment and results in 162 patients. Arch Otolaryngol. 1976;102(12):716-21.
6. Shah JP, Shaha AR, Spiro RH, Strong EW. Carcinoma of the hypopharynx. Am J Surg. 1976;132(4):439-43.
7. Lefebvre JL, Castelain B, De la Torre JC, Delobelle-Deroide A, Vankemmel B. Lymph node invasion in hypopharynx and lateral epilarynx carcinoma: a prognostic factor. Head Neck Surg. 1987;10(1):14-8.
8. Barzan L, Talamini R, Politi D, Minatel E, Gobitti C, Franchin G. Squamous cell carcinoma of the hypopharynx treated with surgery and radiotherapy. J Laryngol Otol. 2002;116(1):24-8.
9. Ho CM, Lam KH, Wei WI, Yuen PW, Lam LK. Squamous cell carcinoma of the hypopharynx - analysis of treatment results. Head Neck. 1993;15(5):405-12.
10. Spector JG, Sessions DG, Emami B, Simpson J, Haughey B, Harvey J, Fredrickson JM. Squamous cell carcinoma of the pyriform sinus: a nonrandomized comparison of therapeutic modalities and long-term results. Laryngoscope. 1995;105(4):397-406.
11. Wahlberg PC, Andersson KE, Biörklund AT, Möller TR. Carcinoma of the hypopharynx: analysis of incidence and survival in Sweden over a 30-year period. Head Neck. 1998;20(8):714-9.
12. Godballe C, Jørgensen K, Hansen O, Bastholt L. Hypopharyngeal cancer: results of treatment based on radiation therapy and salvage surgery. Laryngoscope. 2002;112(5):834-8.
13. Pingree TF, Davis RK, Reichman O, Derrick L. Treatment of hypopharyngeal carcinoma: a 10-year review of 1,362 cases. Laryngoscope.1987;97(8):901-4.
14. Chu PY, Li WY, Chang SY. Clinical and pathologic predictors of survival in patients with squamous cell carcinoma of the hypopharynx after surgical treatment. Ann Otol Rhinol Laryngol. 2008;117(3):201-6.
15. Shah JP, Lydiatt W. Treatment of cancer of the head and neck. CA Cancer J Clin. 1995;45(6):352-68.
16. Baclesse F. Roentgentherapy in cancer of the hypopharynx. JAMA. 1949;140:525-9.
17. Chu PY, Wang LW, Chang SY. Surgical treatment of squamous cell carcinoma of the hypopharynx: analysis of treatment results, failure patterns, and prognostic factors. J Laryngol Otol. 2004;118(6):443-9.
18. Hall SF, Groome PA, Irish J, O'Sullivan B. Towards further understanding of prognostic factors for head and neck cancer patients: the example of hypopharyngeal cancer. Laryngoscope. 2009;119(4):696-72.
19. Vandenbrouck C, Eschwege F, De la Rochefordiere A, Sicot H, Mamelle G, Le Ridant AM, et al. Squamous cell carcinoma of the pyriform sinus: retrospective study of 351 cases treated at the Institut Gustave-Roussy. Head Neck Surg. 1987;10(1):4-13.
20. Gilbert H, Kagan R. Recurrence patterns in squamous cell carcinoma of the oral cavity, pharynx, and larynx. J Surg Oncol. 1974;5(6):357-80.
21. Lalanne CM, Cachin Y, Juillard G, Lefur R. Telecobalt therapy for carcinoma of laryngopharynx. Am J Roentgenol Radium Ther Nucl Med. 1971;111(1):78-84.
22. Lefebvre JL, Chevalier D, Luboinski B, Kirkpatrick A, Collette L, Sahmoud T. Larynx preservation in pyriform sinus cancer: preliminary results of a European for Research and Treatment of Cancer phase III trial. EORTC Head and Neck Cancer Cooperative Group. J Natl Cancer Inst. 1996;88(13):890-9.
23. León X, Quer M, Orús C, del Pardo Venegas M, López M. Distant metastases in head and neck patients who achieved loco-regional control. Head Neck. 2000;22(7):680-6.
24. Vikram B, Strong EW, Shah JP, Spiro R. Failure at distant sites following multimodality treatment for advanced head and neck cancer. Head Neck Surg. 1984;6(3):730-3.

Received 03/10/2009
Accepted for publication 14/12/2009
Conflict of interest: none
Source of funding: none

How to cite this article:
Chedid HM, Franzi AS, Rapoport A, Curioni AO. Impact of combination therapy on disease free survival in hypopharynx cancer. Rev Col Bras Cir. [periódico na Internet] 2010; 37(6). Disponível em URL: http://www.scielo.br/rcbc

Correspondence to:
Abraham Rapoport
E-mail: arapoport@terra.com.br