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Concurrent versus sequential chemoradiotherapy for locally advanced resectable hypopharyngeal carcinoma

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Original Article

Abstract

Purpose: Both concurrent and sequential chemoradiotherapy have been reported to be good alternatives to total laryngectomy in patients with locally advanced hypopharyngeal cancer. We retrospectively reviewed the results of concurrent vs sequential chemoradiotherapy in two institutions for treatment of locally advanced resectable hypopharyngeal cancer in an effort to optimize future laryngeal preservation treatment. **Methods:** Seventy-two patients with locally advanced resectable hypopharyngeal squamous cell carcinoma were reviewed. Arm I included 38 patients treated by concurrent chemoradiotherapy (CCRT) while arm II included 34 patients received sequential chemoradiotherapy. In arm I patients received CCRT of cisplatin 100 mg/m^2 d1, 22 of radiotherapy at dose of 65 Gy/1.8 - 2 Gy/f, 5 days/week. Patients in arm II received 2 cycles of induction chemotherapy consisted of 5 - fluorouracil 1000 mg/m^2 on d1 - 4 on 24 h continuous infusion plus cisplatin 100 mg/m^2 d1; cycle was repeated every 3 weeks followed by radiotherapy as in arm I. **Results:** Demographic data were balanced in both arms. The median age was 50 and 48 years in arm I and II respectively. There was male predominance in both arms. Most of the patients were of ECOGPS of 1and of stage III. No recorded deaths due to treatment toxicities .But as expected CCRT was associated with higher toxicity. In order of frequency; mucositis, anemia were higher in arm I. Significantly higher response rate was observed in arm I (p = 0.04).Three-year survival rates were 74% in arm I and 67.9% in arm II with no significant difference (p = 0.074) but 3 - year PFS rate was significantly higher in arm I (52.6% vs. 47%) (p = 0.03). Laryngeal - preservation rate was 78% in arm I vs. 56% in arm II with significant difference. **Conclusion:** There was higher benefit of concurrent chemo-radiotherapy over sequential chemoradiotherapy. However, larger number of patients and prospective randomized trials are needed to confirm our findings. New strategies that improve organ preservation with less toxicity are needed.

Keywords: Hypopharyngeal Carcinoma, Chemotherapy, Radiotherapy, Sequential Chemoradiotherapy

1. Introduction

Cancer of hypopharynx is uncommon; approximately 2,500 new cases are diagnosed each year in the United States.[1] Locally advanced resectable tumors of hypopharynx may be treated with surgery followed by radiation, sequential or concomitant chemoradiation. In these cases, surgery involves total laryngectomy, partial or total pharyngectomy with neck dissection. Inspite of this radical surgery, there is consequent functional impairment and poor prognosis . Conventional fractionated radiotherapy (RT) up to total dose of 66 - 70 Gy over 7 weeks has been used as definitive treatment for locally advanced tumors instead of surgery. Unfortunately this results in high locoregional relapse (50 - 60% at 2 - years) and overall survival of about 40% at 3 years.[2, 3] For this combined modality therapy has focused on the dual goals of increased survival and functional organ preservation; but it has disadvantage of absence of precise pathologic staging and identification of high risk features that influence prognosis.

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Advantages of induction chemotherapy (IC) followed by definitive radiotherapy (RT) include:1) the potential to decrease the risk of distant failure; 2) rapid reduction in tumor bulk. Nonetheless, this can result in prolonged treatment and additional chemotherapy - related toxicity from systemic doses.[4] Theoretical benefits of delivering concurrent chemoradiotherapy (CCRT) are: 1) radiosensitization of antitumor activity of RT by simultaneous use of chemotherapy; 2) systemic use of chemotherapy may improve survival and eradicate micrometastases outside the irradiated field.

The aim of this study was to review the experience with CCRT versus IC followed by definitive RT (sequential chemoradiotherapy) for treatment of locally advanced resectable hypopharyngeal cancer in an effort to optimize future laryngeal preservation treatment.

2. Methods and Materials

2.1. Study population

Seventy - two consecutive patients treated between January 2000 and December 2010 at two institutions were included in this retrospective study. All patients had stage III - IVA resectable hypopharyngeal squamous cell carcinoma (SCC) according to criteria of the American Joint Committee on cancer 2002.[5] Pre - treatment evaluation included physical examination, panendoscopy and biopsy, computed tomography (CT) or magnetic resonance imaging (MRI) of neck and chest and routine laboratory studies.

Other eligibility criteria were: Eastern Cooperative Oncology Group performance status ECOGPS of 0 - 2, age younger than 70 years, adequate hematological, renal and hepatic functions tests and patients treated by CCRT (arm I) or sequential chemoradiotherapy (arm II).

2.2. Treatment plan

Patients in arm I (38 patients) received CCRT consisted of cisplatin 100 mg/m^2 d1 and 22 concurrent with RT. Radiotherapy was given 5 days a week with conventional RT at 1.8 - 2 Gy/day to total dose of 65 Gy to the primary site and gross lymphadenopathy but to 50 Gy to N0 with cord off after 45 Gy. Cobalt 60 or 6-MV linear accelerator was used for RT sessions.

Patients in arm II (34 patients) were treated by IC consisted of 5 – fluorouracil (5 - FU) 1000 mg/m^2 on days 1 - 4 and cisplatin 100 mg/m^{2}d1 repeated every 3 weeks. Adequate hydration and antiemetics were given before chemotherapy. After 2 cycles of IC, patients received RT sessions as in arm I.

2.3. Assessment of treatment

Toxic effects were graded according to the National Cancer Institute Common Toxicity Criteria, version 3.0,[6] while response evaluation was based on the RECIST criteria.[7] Response was assessed through clinical examination, endoscopy and CT or MRI.

Patients were followed - up after completion of treatment at monthly intervals for first year and every 3 months for second year then at 6-months intervals thereafter.

Overall survival (OAS) rate was defined as the duration between the date of treatment initiation and that of last follow - up or death while disease - free survival (DFS) was defined as the duration between date of initiation of treatment and that of disease progression. Laryngeal – preservation rate was calculated from date of start treatment to date of laryngectomy.

2.4. Statistical methods: Data was analysed by using SPSS (version 15.0), Chi square test used as a test of significance, Kaplan – Meier test was used for survival function (OAS, PFS), and comparison of curves was done by using Log Rank. A p value < 0.05 is statistically significant.

3. Results

We identified 72 patients met the eligibility criteria out of them 38 patients received CCRT (arm I) and 34 received sequential treatment (arm II). Demographic data were balanced in both arms (Table1). The median age was 50 and 48 years in arm I and II respectively. There was male predominance in both arms. Most of the patients were of ECOGPS of 1 and of stage III.

No deaths were recorded due to treatment toxicities. However, as expected CCRT was associated with higher toxicity (Table 2). In order of frequency; mucositis, anemia and tube feeding were higher in arm I (28.9, 18.4 and 15.8%, respectively).

As shown in Table 3; significantly higher response rate was observed in arm I ($p = 0.04$). Three - year survival rates were 74 in arm I and 67.6 in arm II with no significant difference (Figure 1) ($p = 0.074$) but 3 - year PFS rate was significantly higher in arm I (52.6 vs. 47) ($p = 0.03$) (Figure 2). Laryngeal - preservation rate was 78% in arm I vs. 56% in arm II, with significant difference ($p = 0.036$).

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Table 1: Patients demographics

Variable	Arm I (38)		Arm II (34)		P
	N	%	N	%	
Age, years					
Median	50		48		
Range	35-74		33-73		
Sex					
Male	35	92.1	32	94.1	1
Female	3	7.9	2	5.9	1
ECOGPS					
0	13	34.2	10	29.4	0.80
1	19	50	19	55.9	0.45
2	6	15.8	5	14.7	1
Stage					
III	26	68.4	21	61.8	0.62
IVA	12	31.6	13	38.2	0.62

Table 2: Grade 3-4 acute toxic effects

Toxic effects	Arm I		Arm II	
	N	%	N	%
Neutropenia	5	13.2	4	11.8
Thrombocytopenia	3	7.9	2	5.9
Anemia	7	18.4	3	8.8
Nausea/vomiting	5	13.2	5	14.7
Mucositis	11	28.9	6	17.6
Tube feeding	6	15.8	2	5.9
Tracheostomy	2	5.3	2	5.9
Xerostomia	3	7.9	2	5.9

Table 3: Response rate

Response	Arm I		Arm II		P
	N	%	N	%	
Complete response	7	18.4	5	14.7	
Partial response	22	57.8	13	38.2	0.04
Response rate	29	76.2	18	52.9	

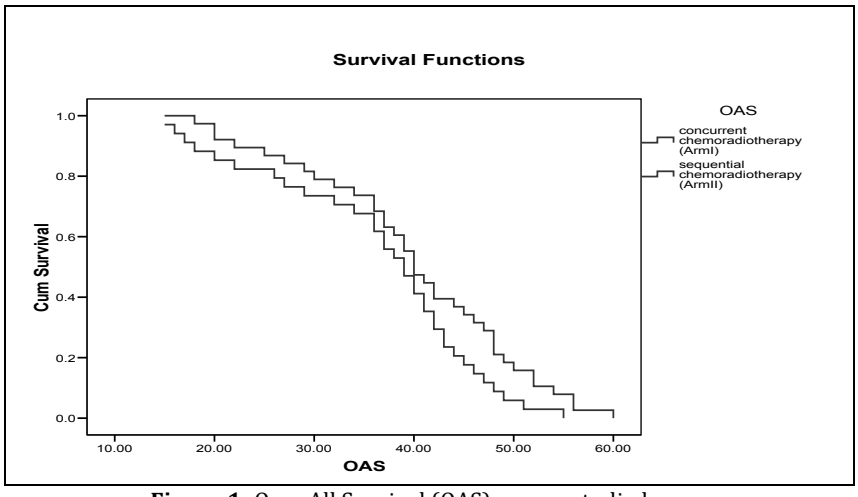

Figure 1: Over All Survival (OAS) among studied cases

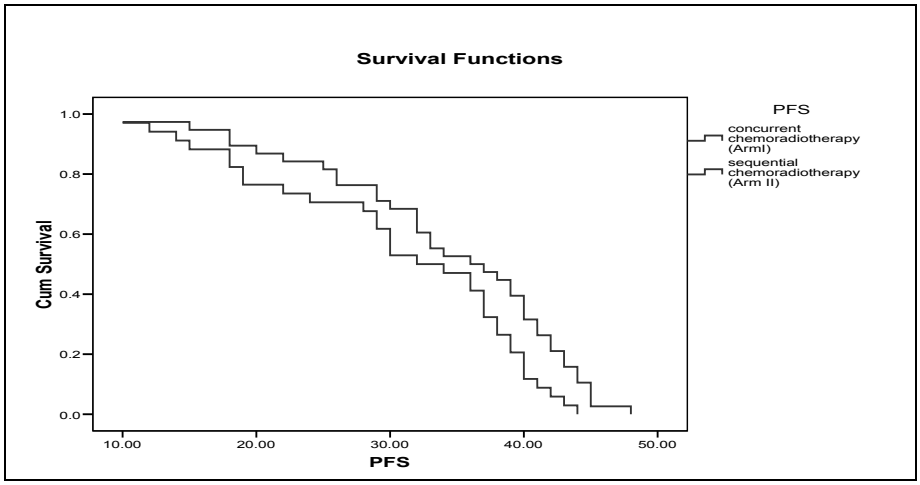

Figure 2: Progression Free Survival (PFS) among studied cases

4. Discussion

Over the last two decades, larynx preservation has been considered one of the most important aims in head and neck oncology. The rationale for CCRT is based on experimental evidence of synergism between chemotherapy and radiation. Theoretically this is mediated by interference with multiple intracellular radiation – induced stress - response pathways involved in apoptosis, proliferation and DNA repair.[8] However; increased toxic effects with CCRT remain major concerns in organ preservation.[9, 10] Cisplatin has the advantage of not having mucositis as toxicity; although as a radiation sensitizer it does increase radiation - induced mucositis. This can explain the higher incidence of mucositis in CCRT arm (28.9 vs 17.6%). Also, increased mucositis lead to higher need for tube feeding and increased anemia due to nutritional deficiency in CCRT. Although the high toxicity rates in CCRT, there was no reported deaths due to complications of treatment.

Advances in diagnostic imaging have contributed in improvement in radiation therapy planning. Both PET and MRI allow better tumor delineation and allow the oncologist to more accurately outline the tumor.[11, 12, 13] Intensity - modulated radiotherapy techniques enables the reduction of dose to normal structures while increasing it to the tumor lead to decreasing toxicity.

There was significantly higher response rate in CCRT arm that was comparable to previous studies.[14, 15, 16] In our study, laryngeal – preservation and PFS rates were significantly higher with CCRT (P = .036, .03, respectively), co - incided with that reported by Forastiere *et al.*[17] and Parades *et al.*[18] A meta - analysis confirmed the overall survival benefit of CCRT.[19, 20] However; in the present study this benefit did not reach statistically significant value.

Trial data have shown TPF (taxotere, platinol, 5-FU) more effective than PF in larynx preservation and have considered it the preferred induction chemotherapy in this setting.[21, 22] Post induction radiotherapy and a targeted agent as epidermal growth receptor inhibitor cetuximab, instead of cisplatin, may help to improve overall tolerability of treatment while retaining activity.[23]

5. Conclusion

There was higher benefit of concurrent chemoradiotherapy over sequential chemoradiotherapy. However, larger number of patients and prospective randomized trials are needed to confirm our findings. New strategies that improve organ preservation with less toxicity are also needed.

Conflict of interest

The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Mendenhall WM, Werning JW, Pfister DG: Treatment of head and neck cancer. In: DeVita VT Jr, Lawrence TS, Rosenberg SA: Cancer: Principles and Practice of Oncology. 9th ed. Philadelphia, Pa: Lippincott Williams & Wilkins, 2011: 729-80.
2. Brizel DM, Albers ME, Fisher SR, *et al.* Hyperfractionated irradiation with or without concurrent chemotherapy for locally advanced head and neck cancer. N Engl J Med. 1998;338:1798-804.
3. Calais G, Alfonsi M, Bardet E, *et al.* Randomized trial of radiation therapy versus concomitant chemotherapy and radiation therapy for

advanced–stage oropharynx carcinoma. J Natl Cancer Inst. 1999;91:2081-6.
4. Jain P, Kumar P, Pai VR, *et al*. Neoadjuvant chemotherapy or chemoradiotherapy in head and neck cancer. J India Cancer 2008;45:83-9.
5. Greene FL, Page DL, Fleming ID, *et al*. AJCC Cancer Staging Manual. 6th ed, New York, NY, USA: Springer, 2002:157-164.
6. Trotti A, Colevas AD, Setser A, *et al*. CTCAE v3.0:development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol. 2003;13:176-81.
7. Therasse P, Arbuck SG, Eisenhauer EA, *et al*. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2009;92:205-16.
8. Dent P Yacoub A, Contessa J, Caron R, *et al.* Stress and radiation –induced activation of multiple intracellular signaling pathways. Radiat Res. 2003;159:283-300.
9. Lee WT, Akst LM, Adelstein DJ, *et a*l. Risk factors for hypopharyngeal/upper esophageal stricture formation after concurrent chemoradiation . Head Neck. 2006;28:808-12.
10. Hanna E, Alexiou M, Morgan J, *et al*. Intensive chemoradiotherapy as a primary treatment for organ preservation in patients with advanced cancer of the head and neck: efficacy, toxic effects and limitations. Arch Otolaryngol Head Neck Surg. 2004;130:861-7.
11. Frank SJ, Chao KS, Schwartz DL, *et al*. Technology insight :PET and PET/CT in head and neck tumor staging and radiation therapy planning. Nat Clin Pract Oncol. 2005;2:526-33.
12. Perez CA, Bradley J, Chao CK, *et al*. Functional imaging in treatment planning in radiation therapy: a review. Rays. 2002;27:157-73.
13. Manavis J, Sivridis L, Koukourakis MI. Nasopharyngeal carcinoma: the impact of CT scan and of MRI on staging, radiotherapy treatment planning, and outcome of the disease. Clin Imaging. 2005;29:128-33.
14. Forastiere AA, Goepfert H, Maor M, *et al*. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med. 2003;349:2091-98.
15. Ang KK, Harris J, Garden AS, *et al*. Concomitant boost radiation plus concurrent cisplatin for advanced head and neck carcinoma: radiation therapy oncology group phase II trial 99-14. J Clin Oncol. 2005;23:3008-15.
16. Adelstein DJ, Li Y, Adams GL, *et al.* An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol. 2003;21:92-8.
17. Forastiere AA, Zhang Q, Weber RS, *et al*. Long–term results of RTOG 91-11: A comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced laryngeal cancer. J Clin Oncol. 2013;31:845-52.
18. Prades JM, Lallemant B, Garrel R, *et al*. Randomized phase III trial comparing induction chemotherapy followed by radiotherapy to concomitant chemoradiotherapy for laryngeal preservation I T3M0 pyriform sinus carcinoma. Acta-Otolaryngol. 2010;130(1):150-55.
19. Pignon JP, Bourhis J, Domenge C, *et al*. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. Lancet. 2000;355:949-55.
20. Pignon JP, le Maître A, Maillard E, *et al.* MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomized trial and 17,346 patients. Radiother Oncol. 2009;92:4-14.
21. Pointreau Y, Garaud P, Chapet S, *et al*. Randomized trial of induction chemotherapy with cisplatin and 5-fluorouracil with or without docetaxel for larynx preservation. J Natl Cancer Inst. 2009;101:498-506.
22. Posner MR, Norris CM, Wirth LJ, *et al*. Sequential therapy for the locally advanced larynx and hypopharynx cancer subgroup in TAX 324:Survival,surgery and organ preservation. Ann Oncol. 2009;20:921-7.
23. Lefebvre JL, Pointreau Y, Rolland F, *et al*. Induction chemotherapy followed by either chemoradiotherapy or bioradiotherapy for larynx preservation: The TREMPLIN randomized phase II study. J Clin Oncol. 2013;31:853-9.