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Survival and toxicity outcomes of induction chemotherapy followed by concurrent chemoradiotherapy compared with concurrent chemoradiotherapy alone in inoperable stage III and IVA/B head and neck cancer

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Article Info

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Abstract

Concurrent chemoradiotherapy with or without induction chemotherapy is widely practiced in inoperable stage III and IVA/B head and neck cancer. The aim of this study was to investigate the survival and toxicity outcomes of induction chemotherapy combined with concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in inoperable stage III and IVA/B head and neck cancer patients. From June 2018 to July 2020, 86 patients participated in a quasi-experimental study. Patients were purposively assigned to one of the two arms (arm A or arm B). Arm A got induction chemotherapy and concurrent chemo-radiotherapy, while arm B got only concurrent chemoradiotherapy. According to our findings, the 2-year progression-free survival rate in arm A was 48.8% vs 37.2 % in arm B (p-value=0.042), and the 2-year overall survival rate in arm A was 65.1 % versus 60.5 % in arm B (p-value= 0.416). There were no statistically significant variations in treatment-related toxicities between the two groups (p-value > 0.05). In conclusion, inoperable stage III and IVA/B head and neck cancer patients who got induction chemotherapy plus concurrent chemotherapy had a better progression-free survival rate than those who received concurrent chemoradiotherapy alone.

Introduction

There are several areas within the head and neck where cancer can develop, including the mouth and lips, pharynx, larynx, nasopharynx, nose, sinuses and salivary glands. However, Thyroid cancer, brain cancer, ocular malignancy, and esophageal cancer are not categorized as head and neck cancer (HNC). Squamous cell carcinoma (SCC) and its variations are the most prevalent HNCs.[1] In 2020, there were 9,31,931 new cases of HNC worldwide, with 4,67,125 fatalities.[2] In Bangladesh, 32,337 new cases of HNC were diagnosed in 2020, with 18,145 deaths.[3] Concurrent chemoradiotherapy (CCRT) is the recommended treatment for individuals with inoperable locally advanced HNC.[4] Induction chemotherapy (ICT) is often utilized in clinical practice, although its significance is still debated. In HNC, a number of trials compared the survival advantages of ICT plus CCRT to CCRT alone. Some of them failed to show that ICT plus CCRT had a substantial survival benefit over the CCRT arm.[5-7] However, two earlier trials found that combining ICT with CCRT improved overall and progression-free survival significantly. Furthermore, they observed that the harmful effects of chemotherapy and radiation were nearly same between the two treatment arms.[8,9] In this study, we compared the survival and toxicity outcomes of ICT plus CCRT to CCRT alone in patients with inoperable Stage III and IVA/B HNC.

Methods

From June 2018 to July 2020, a quasi-experimental study was performed on 86 patients with inoperable Stage III and IVA/B HNC in the Department of Clinical Oncology of Bangabandhu Sheikh Mujib Medical University (BSMMU), and the

Department of Radiotherapy of National Institute of Cancer Research and Hospital, Dhaka. Ethical approval was approved from BSMMU Institutional Review Board (IRB). The study was carried out in line with the Helsinki Declaration. Criteria for inclusion was patients with inoperable stage III and IVA/B squamous cell carcinoma of the Head and neck. Criteria for exclusion were age below 18 and above 70 years ; patients with an Eastern Co-operative Oncology Group (ECOG) performance status of three or above; prior head and neck chemotherapy or radiation or surgery; serious concurrent medical condition; and pregnancy or lactating patients. Following the application of inclusion and exclusion criteria, patients were purposively divided between two arms (Arm A and Arm B). Before each patient's involvement in the study, a signed informed consent was obtained from them. To gather information, a data collection sheet was employed. ICT was used with CCRT in Arm A, while CCRT was used alone in Arm B. ICT was administered in arm A with the injection cisplatin 100mg per m2 of body surface area (BSA) with normal saline on day one and injection 5-fluorouracil 1000 mg per m2 of BSA per day with normal saline continuous infusion on days one to five for three cycles.[10] Before and after chemotherapy, adequate hydration and pre and post chemotherapy medicines were maintained. CCRT was used in both arms of the study. Both arms received 66 Gray (33 fractions, 2 Gray/day, 5 days per week over 6.5 weeks) of radiation. During radiation, concurrent chemotherapy was administered weekly with injection cisplatin 30mg per m2 of BSA.[11] Patients were monitored for toxicity every three weeks during ICT and once a week during CCRT. The Radiation Therapy Oncology Group (RTOG) toxicity criteria were used to assess toxicity.[12] Following the end of treatment, patients were evaluated every three months for the treatment responses. RECIST (Response Evaluation Criteria in Solid Tumors) criteria were used to evaluate treatment responses.[13] Patients were evaluated by clinical examination and appropriate investigations during follow-up. The IBM SPSS software application for Windows was used to analyze the data. To compare the toxicity outcomes of the two arms, the Chi-square test was utilized. The log-rank test was performed to compare the two arms in terms of overall and progression-free survival. The Kaplan-Meier curve was generated to compare the survival rates of the two arms. A p-value of less than 0.05 was regarded as significant.

Results

The overall number of participants in the study was 86, with 43 in Arm A and 43 in Arm B. The mean age of Arm A and Arm B patients was 55.27 (±11.23) years and 53.03 (±10.48) years respectively. The majority of patients in both arms have an ECOG score of one (60.50 percent in Arm A and 67.40 percent in Arm B). The oral cavity and larynx were the main sites of disease for the majority of the individuals. More than two-thirds of the patients had tumours that were graded as grade 1 (well differentiated) or grade 2 (moderately differentiated). Only about a third of the patients had grade 3 (poorly differentiated) tumours. 51.2 percent of Arm A patients and 46.5 percent of Arm B patients were in stage III, whereas 48.8 percent of Arm A patients and 53.5 percent of Arm B patients were in stage IVA & B. (Table - I).

Table-I

Baseline and clinical characteristics of the study population (N=110).

Characteristics	Arm A (n=43)	Arm B (n=43)
Age (mean± SD)	55.27±11.23	53.03±10.48
Sex (%)		
Male	28(65.0%)	31(72.0%)
Female	15(35.0%)	12(28.0%)
Clinical stage (%)		
Stage III	22(51.2%)	20(46.5%)
Stage IVA/B	21(48.8%)	23(53.5%)
Differentiation (%)		
Well	13(30.2%)	10(23.3%)
Moderate	19(44.2%)	23(53.5%)
Poor	11(25.6%)	10(23.2%)
Primary sites (%)		
Oral cavity	15(35.0%)	13(30.0%)
Larynx	08(19.0%)	10(23.0%)
Oropharynx	07(16.0%)	06(14.0%)
Hypopharynx	13(30.0%)	14(33.0%)
ECOG Performance (%)		
0	02(04.7%)	03(06.9%)
1	26(60.5%)	29(67.4%)
2	15(34.9%)	11(25.6%)

Oral mucositis, skin reaction, neutropenia, and xerostomia were frequent throughout therapy in both arms of this study. With the exception of xerostomia, all had grade 3 toxicity. Patients in Arm A had grade 2 and 3 oral mucositis, respectively, in 19 (44.2%) and 08 (18.6%) cases. Patients in Arm B had grade 2 and 3 oral mucositis, respectively, in 15 (34.9%) and 06 (14.0%) cases. Patients in Arm A got grade 2 and 3 skin reaction in 20 (45.6%) and 06 (14.0%) of the cases, respectively. In Arm B, 17 (39.5%) and 05 (11.6%) patients, respectively. Regarding xerostomia, 17 (39.5%) and 26 (60.5%) patients in Arm A had had grade 1 and 2 toxicities, respectively. In Arm B, there were 21 (48.8%) and 22 (51.2%) individuals who had grade 1 and 2 toxicity, respectively. In terms of neutropenia, 3 (7%) patients in arm A and 2 (4.7%) patients in arm B had grade 3 neutropenia (Table - II).

Table-II

Distribution of patients by common toxicities

Toxicities	Arm A (n=43)	Arm B (n=43)	p-value
Mucositis (%)			
Grade1	16(37.2%)	22(51.2%)	
Grade2	19(44.2%)	15(34.9%)	0.427
Grade3	08(18.6%)	06(14.0%)	
Skin reaction (%)			
Grade1	17(39.5%)	21(48.8%)	
Grade2	20(45.6%)	17(39.5%)	0.686
Grade3	06(14.0%)	05(11.6%)	
Xerostomia (%)			
Grade1	1739.5%)	21(48.8%)	0.385
Grade2	26(60.5%)	22(51.2%)	
Neutropenia (%)			
Grade1	16(37.2%)	18(41.9%)	
Grade2	06(14.0%)	04(09.3%)	0.742
Grade3	03(07.0%)	02(04.7%)	

According to the survival analysis, 48.8 percent and 37.2 percent of patients in arms A and B, respectively, were progression-free after two years (Figure - 1).

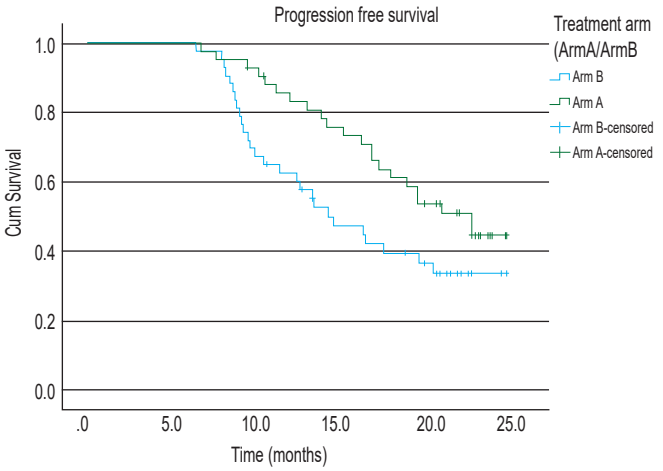

Figure 1: Kaplan–Meier plot of progression-free survival (PFS) in inoperable Stage III and IVA/B HNC patients treated with ICT + CCRT vs. CCRT alone.

Overall survival was 65.1 percent in arm A and 60.5 percent in arm B after two years (Figure - 2).

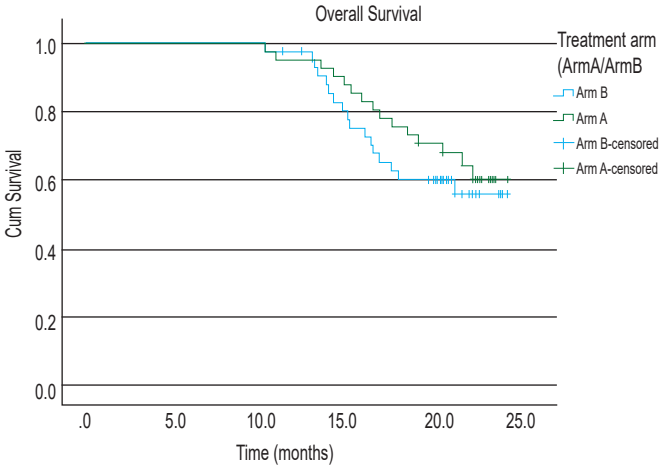

Figure - 2: Kaplan–Meier plot of overall survival (OS) in inoperable Stage III and IVA/B HNC patients treated with ICT + CCRT vs. CCRT alone.

Discussion

In locally advanced head and neck cancer, CCRT was found to be the best therapeutic choice in a meta-analysis of chemotherapy in head and neck cancer (MACH-NC).[14] The effectiveness of induction chemotherapy is still debatable. Several investigations on the effect of ICT in locally advanced HNC have been conducted. Two of them found that combining ICT with CCRT improves overall and progression-free survival.[8,9] The goal of this study was to investigate the survival and toxicity of ICT plus CCRT against CCRT alone in inoperable stage III and IVA/B HNC patients.

In several clinical studies, TPF (docetaxel, cisplatin, and fluorouracil) outperformed PF (cisplatin plus fluorouracil) in terms of ICT scheduling. [15,16] Our study, on the other hand, was done in government institutions with low-income patients who couldn't afford TPF regimen with granulocyte-colony stimulating factor (G-CSF) assistance. As a result, instead of using the TPF schedule, we utilized a less expensive cisplatin plus fluorouracil regimen.

The participants in this study were diagnosed with inoperable stage III and IVA/B HNC. The patients' toxicities were assessed both during and after therapy. During this time, oral mucositis, skin reactions, neutropenia, and xerostomia were all common. In Arm A, eight patients (18.6%) had grade 3 oral mucositis, while in Arm B, six patients (14.0%) developed grade 3 oral mucositis. Six (14.0%) patients in arm-A experienced grade 3 skin toxicity, while 05 (11.6%) patients in Arm B developed grade 3 skin toxicity. Three patients (7%) in arm A and 2 (4.7%) in arm B had grade 3 neutropenia. These

differences were not statistically significant (p > 0.05), which is consistent with the findings of Paccegnella et al.[9] Toxicities, on the other hand, were well tolerated and easily managed.

The results of all prior studies were either 3-year or 5-year survival rates. Only a 2-year survival rate was shown in our study. According to our data, the 2-year PFS rate in the IC plus CCRT arm was 48.8%, while it was 37.2 % in the CCRT alone arm. This difference between the two arms is statistically significant (p-value=0.042). Ghi et al also observed in their study that the ICT plus CCRT arm had a significantly higher PFS than the CCRT arm.[8] On the other hand, The 2-year OS rate in the IC plus CCRT arm was 65.1 percent compared to 60.5 percent in the CCRT alone arm (p = 0.416). This finding differs with Ghi et al., although it is in line with Haddad et al.[6;8]

Conclusion

In terms of progression-free survival, ICT coupled with CCRT is more effective than CCRT alone in inoperable stage III and IVA/B HNC with comparable toxicity. At the same time, the overall survival is slightly higher in the ICT arm, but the difference is not statistically significant between the two treatment groups.

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References

1. Symonds P, Deehan C, Mills J, Meredith C. Walter and Miller's textbook of radiotherapy. 7th ed. Edinburgh: Elsevier Churchhill Livingstone; 2012. 342-343 p.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries CA: Cancer J. Clin. 2021; 71(3): 209-49.
3. International Agency for Research on Cancer. Globocan 2020 Bangladesh Fact Sheet [Internet]. gco.iarc.fr. The Global Cancer Observatory; 2021 [cited 2021 Jul 17] p. 1–2. Available from: https:// gco.iarc.fr/ today/data/ factsheets/populations/50-bangladesh-fact-sheets.pdf
4. Gregoire V, Lefebvre JL, Licitra L, Felip E, EHNS-ESMO-ESTRO guidelines working group. Squamous cell carcinoma of head and neck: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010; 21(5): 184-185.
5. Zhang L, Jiang N, Shi Y, Li S, Wang P, Zhao Y. Induction chemotherapy with concurrent chemoradiotherapy versus concurrent chemoradiotherapy for locally advanced squamous cell carcinoma of head and neck: a meta-analysis. Sci Rep. 2015; 5(1): 10798.
6. Haddad R, O'Neill A, Rabinowits G, Tishler R, Khuri F, Adkins D, et al. Induction chemotherapy followed by concurrent chemoradiotherapy (sequential chemoradiotherapy) versus concurrent chemoradiotherapy alone in locally advanced head and neck cancer (PARADIGM): a randomised phase 3 trial. Lancet Oncol. 2013; 14(3): 257–64.
7. Hitt R, Grau JJ, López-Pousa A, Berrocal A, García-Girón C, Irigoyen A, et al. A randomized phase III trial comparing induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as treatment of unresectable head and neck cancer. Ann Oncol. 2014; 25(1): 216–25.
8. Ghi M, Paccagnella A, Ferrari D, Foa P, Alterio D, Codecà C, et al. Induction TPF followed by concomitant treatment versus concomitant treatment alone in locally advanced Head and Neck Cancer. A phase II-III trial. Ann Oncol. 2017; 28(9): 2206-12.
9. Paccagnella A, Ghi M, Loreggian L, Buffoli A, Koussis H, Mione C, et al. Concomitant chemoradiotherapy versus induction docetaxel, cisplatin and 5 fluorouracil (TPF) followed by concomitant chemoradiotherapy in locally advanced head and neck cancer: a phase II randomized study. Ann Oncol 2009; 21(7): 1515-22.
10. Chu E, DeVita VT Jr. Physicians' cancer chemotherapy drug manual 2020. 20th ed. Sudbury, MA: Jones and Bartlett; 2019. 567 p.
11. Dobbs J, Barrett A, Morris SL. Practical radiotherapy planning. 4th edition. London: Hodder Education; 2009. 88 p.
12. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the radiation therapy oncology group (RTOG) and the European organization for research and treatment of cancer (EORTC). Int J Radiat Oncol Biol Phys. 1995; 31(5): 1341–6.
13. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst. 2000; 92(3): 205–16.
14. Pignon JP, Bourhis J, Domenge C, Designe L. 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. Cancer Radiother. 2001; 5(2): 201–2.
15. Posner MR, Hershock DM, Blajman CR. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med. 2007; 357(17): 1705-15.
16. Pointreau Y, Garaud P, Chapet S, Sire C, Tuchais C, Tortochaux J, 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(7): 498–506.