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RESEARCH ARTICLE

Efficacy of Induction Chemotherapy with Paclitaxel and Carboplatin in Locally Advanced Squamous Cell Carcinoma of the Hypopharynx: A Descriptive Case Series

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Abstract

Introduction: Head and neck cancer including hypopharyngeal carcinoma is one of commonest malignancies in Pakistan. According to the Pakistan Medical Research Council (PMRC) reports, it was found to be the commonest malignancy in males and was second highest to breast cancer in females. The patients for the management of hypopharyngeal cancer present with locally advanced disease. Induction chemotherapy with paclitaxel and carboplatin is being used for few years but the results have not been documented yet. The aim of this study is to design a protocol in future with improved outcome and acceptable morbidity.

Objective: To determine the efficacy of induction chemotherapy with paclitaxel & carboplatin in locally advanced squamous cell carcinoma of hypopharynx in terms of frequency of complete and partial response.

Settings: This study was conducted at Nuclear Medicine, Oncology and Radiotherapy Institute (NORI), Islamabad.

Study Design: Descriptive case series.

Duration of study: 6 months from 01/08/2017 to 31/01/2018

Material and methods: In this study a total of 59 patients were observed by using World Health Organization sample size calculator where confidence level: 95%, anticipated population proportion: 67%, relative precision: 12%. Moreover, nonprobability consecutive sampling technique was used for sample collection.

Results: Mean age was 60 ± 11.87 years. 40(68%) patients were males while 19(32%) were females. 22(38%) patients had carcinoma of stage III, 32(54%) patients had carcinoma of stage IVA while 5(8%) patients had carcinoma of stage IVB. Moreover, induction chemotherapy was effective in 42(72%) patients and was not effective in 17(28%) patients.

Conclusion: Our study concludes that induction chemotherapy with paclitaxel & carboplatin was 72% effective in locally advanced squamous cell carcinoma of hypopharynx in terms of frequency of complete and partial response.

Introduction:-

Head and neck cancer including hypopharyngeal carcinoma is one of commonest malignancies in Pakistan. According to the Pakistan Medical Research Council (PMRC) reports, it was found to be the commonest

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malignancy in males and was second highest to breast cancer in females. There are multiple treatment modalities available these days but despite that the overall survival of patients has not improved significantly during the past two decades, with the 5-year survival rates between 45- 50%[1]. Hypopharyngeal carcinoma is not very common in developed countries, in United States, approximately 2,500 new cases are diagnosed every year[2]. According to a retrospective cohort study conducted by Kuo et al, there was a decrease in the hypopharyngeal carcinoma incidence in the United States by an average of -2.0% annually between 1973 and 2010[3].

Hypopharyngeal carcinoma affects males more than females with a ratio of 2:1 to 4:1. The incidence rate in males is higher in Hong Kong, France, the Indian subcontinent, central & eastern Europe, Brazil, Spain, Italy & among African Americans in United States[4].

Most patients with hypopharyngeal carcinoma remain symptoms free until their disease gets advanced, at presentation many patients have metastases in lymph nodes (50-70% cases) & distant organs. In approximately 50% of patients, the main presenting complaint is enlarged cervical lymph node. The above-mentioned study conducted by Kuo et al found that 5-year survival rate for hypopharyngeal cancer rose significantly from 1988-1990 but there were no significant changes in survival rates for other years.

The best treatment for hypopharyngeal carcinoma aims for the highest locoregional control rate with the least functional damage. All advanced stage patients of hypopharyngeal cancer should be evaluated by a multidisciplinary team before starting treatment with the goals of educating the patient and family about all the treatment options, their outcome and side effects. With the help of a multidisciplinary team, the management and survival of the patient can be improved[5].

Induction chemotherapy followed by definitive radiotherapy offers functional organ preservation in locally advanced hypopharyngeal cancer. The incidence of distant metastases may be decreased with induction chemotherapy compared with radiotherapy alone and it showed a better, although not statistically significant, survival outcome versus concurrent chemoradiotherapy in RTOG 91-11[6].Induction chemotherapy followed by radiotherapy may afford larynx preservation without jeopardizing survival in pyriform sinus region cancer[7].In a study conducted by Frank R. Dunphy, induction chemotherapy with paclitaxel & carboplatin was administered in head and neck cancer patients that was well tolerated by patients & response rate was encouraging considering most patients were stage IV. Overall complete and partial response rate was 67% in hypopharyngeal cancer patients. Organ preservation was also possible. Sample size was calculated from this study, adding up of complete and partial response[8].

At NORI most of the patients diagnosed with hypopharyngeal cancer are present with locally advanced disease. Induction chemotherapy with paclitaxel and carboplatin has been used for a few years but the results have not been documented yet. The aim of this study is to design a protocol in future with improved outcome and acceptable morbidity.

Literature Review:-

Hypopharyngeal Carcinoma

The hypopharynx, or laryngopharynx, is the longest and most inferior portion of the 3 segments of the pharynx and links the oropharynx to the esophagus. It is located posterior to the cartilaginous structures of the larynx[1]. It is superiorly wide and progressively narrows towards the level of the cricopharyngeal muscle. The hypopharynx is a continuous area; the oropharynx is above it and the cervical esophagus through the cricopharyngeal sphincter is below it. This region is known as the pharyngoesophageal junction or postcricoid area. It is bounded anteriorly by the posterior face of the cricoid cartilage.[2] The hypopharynx extends from the hyoid bone to the cricoid cartilage and is further subdivided into the regions of the pyriform sinus, pharyngeal wall, and posterior cricoid.[1, 2]

- **Level I:** The posterior border is defined by the posterior edge of the submandibular gland.
- **Level II:** The superior extent is defined by the mastoid tip and the caudal edge of the lateral C1 process. The inferior extent is defined by the cranial edge of the hyoid bone. The lateral edge is bordered by the sternocleidomastoid muscle.
- **Level III:** This cervical nodal group is bordered anterolaterally by the sternocleidomastoid muscle and begins superiorly at the cranial edge of the hyoid bone. The inferior edge is bordered by the inferior edge of the cricoid cartilage.

- **LevelIV**: This cervical nodal group is bordered by the sternocleidomastoid muscle, begins at the inferior edge of the cricoid cartilage, and extends to 2cm superior to the supraclavicular joint.
- **LevelV**: This posterior neck chain is defined anteriorly by the posterior edge of the sternocleidomastoid and the scalene muscle. It begins superiorly at the cranial edge of the hyoid bone and inferiorly at the transverse cervical vessels.
- **LevelVI**: This nodal group is defined superiorly by the caudal edge of the thyroid gland and inferiorly by the sternal manubrium. It is defined laterally by the medial edge of the sternocleidomastoid muscle and medially by the trachea. It is limited posteriorly by the common carotid artery.[6]

The intimate association between the hypopharynx and the larynx, oropharynx, and esophagus allows for certain dissemination routes of malignant disease. Pyriform sinus carcinomas may spread submucosally into the posterior wall of the hypopharynx, the post cricoid region, or the aryepiglottic fold. Large tumors also extend up into the paraglottic fat, the pre-epiglottic fat, and the base of the tongue. Tumors that arise from the lateral wall or apex of the pyriform sinus often have already invaded the thyroid cartilage. Lesions of the medial wall of the pyriform sinus may spread along the aryepiglottic fold into the false vocal cord and arytenoid cartilage. Medial wall lesions occasionally invade paraglottic and pre-epiglottic fat. They may also grow posteriorly into the postcricoid region and then cross the midline to involve the contralateral pyriform sinus[7,8]

An analysis of the Surveillance Epidemiology and End Results (SEER) database demonstrates that the incidence of hypopharyngeal cancers decreased 35% from 1975 to 2001. [25,26] The mortality rate due to hypopharyngeal cancers also decreased by 30%. This epidemiologic change is believed to be due to a decrease in the initiation of cancer in the hypopharynx and does not necessarily reflect any improvement in survival due to treatment. Cancer that arises in the hypopharynx represents approximately 7% of all cancers of the upper aerodigestive tract. The incidence of laryngeal cancer is 4-5 times that of hypopharyngeal cancer. All pharyngeal subsites accounted for approximately 124,000 cancer cases worldwide in 2002.[27.]

Objective:-

To determine the efficacy of induction chemotherapy with paclitaxel & carboplatin in locally advanced squamous cell carcinoma of hypopharynx in terms of frequency of complete and partial response.

Operational Definitions:

Induction Chemotherapy:

Induction chemotherapy refers to the use of chemotherapy for the initial treatment of advanced cancers to make subsequent treatment (as surgery or radiotherapy) more effective.

Methodology:-

Settings:

Study was conducted at Nuclear Medicine, Oncology and Radiotherapy Institute (NORI), Islamabad.

Study Design:

Descriptive case series.

Duration of study:

6 months, 01/08/2017 to 31/01/2018.

Sample size:

Using World Health Organization sample size calculator, where Confidence level: 95%,
Anticipated population proportion: 67%, Relative precision: 12, Sample size was 59 [8]

Sampling technique:

Non–probability consecutive sampling

Sample Selection:

Inclusion criteria: Age 20-70 years
2: Karnofsky performance status > 70%

3: Stage III, IVA & IVB
4: Newly diagnosed histopathological proven squamous cell carcinoma of hypopharynx

Exclusion criteria:

1: Uncontrolled hypertension and diabetes
2: Patients with abnormal RFTs and LFTs.
3: Coexisting second malignancy.
4: Patients with metastatic or recurrent disease

Data Collection Procedure:-

The study was approved by the Hospital Ethical Review Committee on 1st June 2017 and RTMC.A written informed consent was taken from every patient fulfilling the inclusion criteria. Premenopausal patients were explained regarding secondary amenorrhea following treatment.

Patients included in the study were those registered in the Oncology Department of NORI Hospital. They were evaluated in detail by me with history, physical examination, investigations including Hematology, Biochemistry, 24 hours urine for creatinine clearance, Chest X Ray, upper GI endoscopy, CT Scan face & neck and echocardiography. Consultant Radiologist reported all the radiological investigations. Every patient was discussed in multidisciplinary meetings (MDM) involving Oncology Department NORI hospital and Surgery, E.N.T, Radiology and Pathology department of Pakistan Institute of Medical Sciences Islamabad, Federal Govt. Services Hospital and Holy family Hospital. All the patients received injection Paclitaxel 175mg/m^2 I/V 3 hours infusion on Day 1 of chemotherapy with premedication and post medication and injection Carboplatin AUC (GFR+25) I/V 1 hour infusion. The cycle was repeated after every third week. Patients were given 3 cycles of chemotherapy. Toxicity was evaluated according to WHO criteria. At grade 3-4 renal, hematological, or gastrointestinal toxicity, treatment was withheld until complete resolution of toxicity occurred and was resumed later on with dose modification. Final response was evaluated four weeks after completion of the third cycle with the help of clinical examination & CT scan of the head & neck according to RECIST criteria for response assessment. All the data was recorded on the proforma attached in the end. Follow up was ensured by taking contacts of these patients.

Data Analysis:-

The collective data was entered and analyzed using SPSS V 16. Descriptive statistics were calculated for both qualitative and quantitative variables. Qualitative variables include gender, stage and efficacy of induction chemotherapy and these were presented as frequency /percentages. Quantitative variables include age was presented by mean +_SD. Age, gender and stage of carcinoma were controlled by stratification. Post stratification chi-square test was applied and p value ≤ 0.05 was significant. Tables and charts were made for qualitative variables.

Results:-

In this study age distribution among 59 patients was analyzed as 6 (10%) patients were in age range 40-50 years, 22(37%) patients were in age ranged 51-60 years, 31(53%) patients were in age ranged 61-70 years. Mean age was 60 years with standard deviation ± 11.87. (Table No. 1)

Gender distribution among 59 patients was analyzed as 40(68%) patients were males while 19(32%) patients were females. (Table No. 2)

Stages of carcinoma among 59 patients were analyzed as 22(38%) patients had carcinoma of stage III, 32(54%) patients had carcinoma of stage IVA while 5(8%) patients had carcinoma of stage IVB. (Table No. 3)

Efficacy of induction chemotherapy among 59 patients was analyzed as induction chemotherapy was effective in 42(72%) patients and was not effective in 17(28%) patients. (Table No. 4)

Stratification of efficacy of induction chemotherapy with respect to age, gender and stages of carcinoma is given in table no 5, 6, 7.

Discussion:-

Head and neck cancer including hypopharyngeal carcinoma is one of commonest malignancies in Pakistan. According to the Pakistan Medical Research Council (PMRC) reports, it was found to be the commonest

malignancy in males and was second highest to breast cancer in females. There are multiple treatment modalities available these days but despite that the overall survival of patients has not improved significantly during the past two decades, with the 5-year survival rates between 45- 50%[1]. Hypopharyngeal carcinoma is not very common in developed countries, in United States, approximately 2,500 new cases are diagnosed every year[2]. According to a retrospective cohort study conducted by Kuo et al, there was a decrease in the hypopharyngeal carcinoma incidence in the United States by an average of -2.0% annually between 1973 and 2010[3].

Our study shows that among 59 patients, 40(68%) patients were males while 19(32%) were females. 6(10%) patients were in the age range 40-50 years, 22(37%) patients were in age range 51-60 years, 31(53%) patients were in age range 61-70 years. Mean age was 60 years with SD ± 11.87. 22(38%) patients had carcinoma of stage III, 32(54%) patients had carcinoma of stage IVA while 5(8%) patients had carcinoma of stage IVB. 24(41%) patients had complete response, 18(30%) patients had partial response, 10(17%) patients had stable disease, 7(12%) patients had progressive disease. Induction chemotherapy was effective in 42(72%) patients in terms of frequency of complete and partial response and was not effective in 17(28%) patients.

In a study conducted by Dunphy FR et al[112], induction chemotherapy with paclitaxel & carboplatin was administered in head and neck cancer patients that was well tolerated by patients & response rate was encouraging considering most patients were stage IV. Overall complete and partial response rate was 67% in hypopharyngeal cancer patients. Organ preservation was also possible. Sample size calculated from this study, adding up of complete and partial response[8].

In another study[23] had reported that the median follow-up time of this cohort was 43.4 months (range; 6.9–151.0). The 3-year overall survival, progression-free survival and larynx preservation survival rates were 78.8% (95% confidence interval; 73.0–85.0), 58.4% (95% confidence interval; 51.8–65.9) and 67.5% (95% confidence interval; 61.0–74.7), respectively. Multivariate analyses identified the following significant prognostic factors: an advanced age, the T category and N category for overall survival, the T category and N category for progression-free survival and the T category for larynx preservation survival. Acute toxicities of Grade 3 or higher were observed in 47 patients (23.0%). Two patients (1.0%) had Grade 4 pharyngeal edema. Suspicious treatment-related death due to lethal pharyngeal hemorrhage occurred in 1 (0.4%) patient. The rates of Grade 2 xerostomia in patients treated with intensity-modulated radiotherapy were 28.1, 17.4 and 9.5% at 6 months, 1 and 2 years after the completion of radiotherapy, respectively.

In another study Iqbal H et al[114] had reported that response to induction chemotherapy: complete response (CR) 58 (13%), partial response (PR) 315 (71%), stable disease (SD) 55 (12%) and progressive disease (PD) 18 (4%). Response to RT/CRT; CR 293 (66%) and persistent disease at 3 months post treatment in 153 (34%) patients. Grade 3 and 4 toxicities for induction chemotherapy was anemia 2%/0%, neutropenia 17%/4%, thrombocytopenia 2%/1%, vomiting 5%/1% and diarrhea 5%/1%. Grade 1 transient elevation of ALT/ AST was 17% /11%. Grade 3-4 elevation of creatinine was 2 %/1%. Nine patients (2%) had toxicity related hospital admissions during RT/CRT. The 5- and 10-year OS, DFS and RFS were 56%, 53%, 45%, 41%, 30% and 27% respectively. 149 (33%) patients are alive, disease free and maintaining routine follow up.

Conclusion:-

Our study concludes that induction chemotherapy with paclitaxel & carboplatin was 72% effective in locally advanced squamous cell carcinoma of hypopharynx in terms of frequency of complete and partial response.The study demonstrates that induction chemotherapy with paclitaxel and carboplatin shows a 72% efficacy rate in achieving complete or partial response in patients with locally advanced squamous cell carcinoma of the hypopharynx. These findings suggest that this chemotherapy regimen can be a viable option for reducing tumor size and improving patient outcomes in this specific patient cohort.

Implications

1. **Clinical Practice**: These findings could encourage oncologists to consider this chemotherapy combination as a part of the treatment protocol for similar patient groups, potentially improving initial treatment responses.
2. **Future Research**: The study highlights the need for randomized controlled trials with larger and more diverse populations to confirm these results and assess long-term survival and quality of life.
3. **Patient Education**: Improved patient education regarding treatment options and expected outcomes can be derived from this study, aiding in informed decision-making.

Table1:- Distribution of Involved Lymph Nodes.

Site	Submaxillay (Level I), %	Upper Jugular (Level II), %	Mid Jugular (Level III), %	Lower Jugular (Level IV), %
Pharyngeal wall	20	80	40	40
Pyriform sinus	0	67	33	7
*As found after elective modified neck dissection by Byers et al[6]				

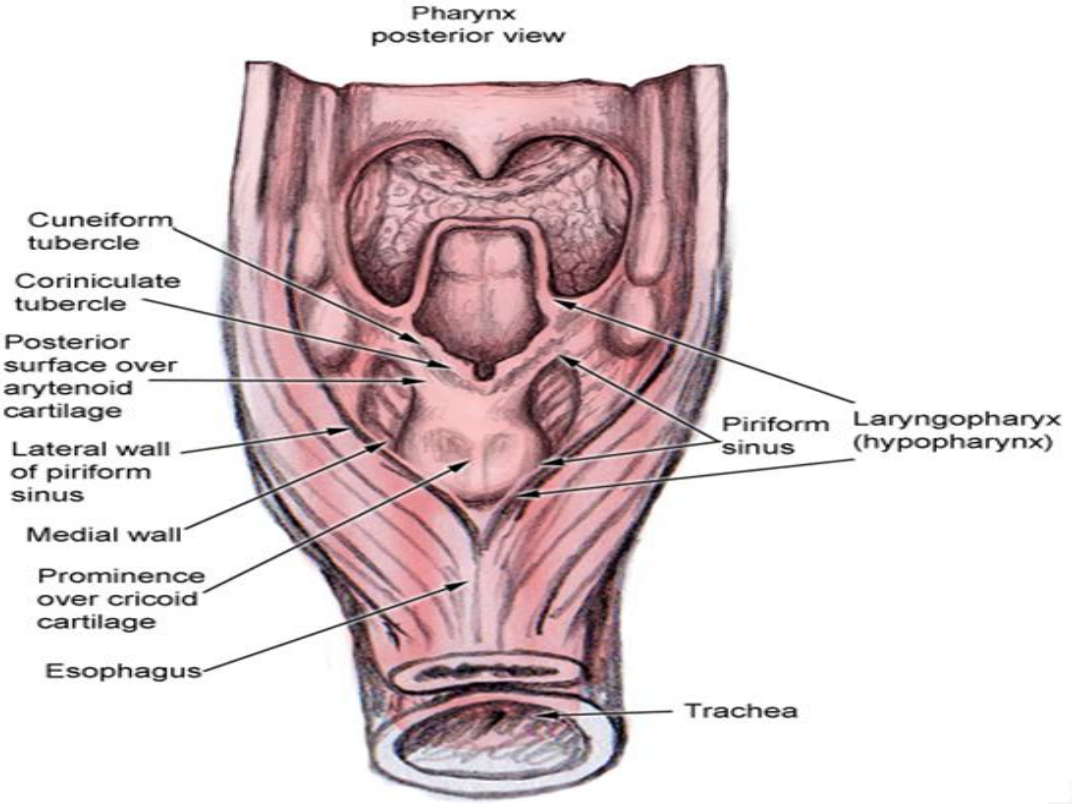

Figure 1:- Source Google **(Posterior View of the Pharynx).**

Table No. 2:-Age Distribution (n=59).

AGE	FREQUENCY	PERCENTAGE
40-50 years	6	10%
51-60 years	22	37%
61-70 years	31	53%
Total	**59**	**100%**

Mean age was 60 years with standard deviation ± 11.87

Table No. 3:-Gender Distribution (n=59)

GENDER	FREQUENCY	PERCENTAGE
Male	40	68%
Female	19	32%
Total	**59**	**100%**

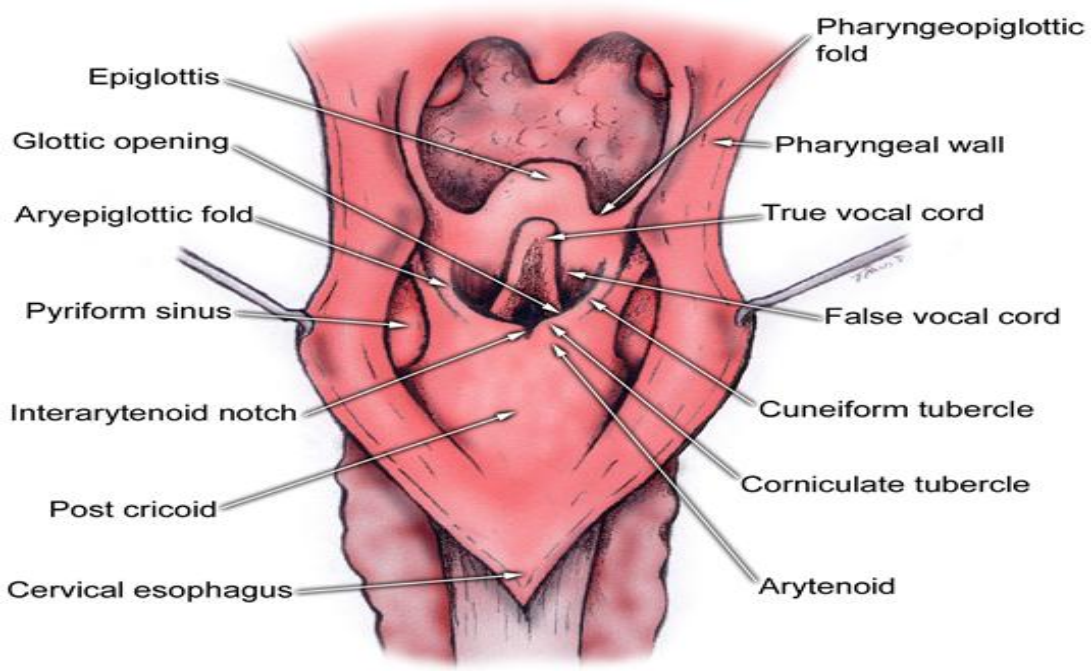

Figure2:- Source Google (**Anterior View of the Larynx and Pharynx**).

Table No. 4:- Stages Of Carcinoma(n=59)

STAGE OF CARCINOMA	FREQUENCY	PERCENTAGE
Stage III	22	38%
Stage IV A	32	54%
Stage IV B	5	8%
Total	**59**	**100%**

Table No. 5:-Follow Up After 4 Weeks (n=59).

Follow up after 4 weeks	FREQUENCY	PERCENTAGE
Complete response	24	41%
Partial response	18	30%
Stable disease	10	17%
Progressive disease	7	12%
Total	**59**	**100%**

Table No. 6:- Efficacy Of Induction Chemotherapy (n=59) .

EFFICACY	FREQUENCY	PERCENTAGE
Effective	42	72%
Not effective	17	28%
Total	**59**	**100%**

Table No. 7:-Stratifications Of Efficacy Of Induction Chemotherapy W.R.T Age Distribution (n=59).

EFFICACY	40-50 years	51-60 years	61-70 years	Total
Effective	4	16	22	42
Not effective	2	6	9	17
Total	**6**	**22**	**31**	**59**

Chi square test was applied in which P value was 0.9579

Table No. 8:- Stratifications Of Efficacy Of Induction Chemotherapy W.R.T Gender Distribution (n=59).

EFFICACY	Male	Female	Total
Effective	28	14	42
Not effective	12	5	17
Total	**40**	**19**	**59**

Chi square test was applied in which P value was 0.7703

Table No. 9:- Stratifications Of Efficacy Of Induction Chemotherapy W.R.T Stage Of Carcinoma.(n=59)

EFFICACY	Stage III	Stage IVA	Stage IVB	Total
Effective	16	23	3	42
Not effective	6	9	2	17
Total	**22**	**32**	**5**	**59**

Chi square test was applied in which P value was 0.8445

Limitations

1. **Sample Size**: The study involved a relatively small number of patients, which may limit the generalizability of the findings to a wider population.
2. **Short Follow-Up Period**: The follow-up duration was limited, preventing assessment of long-term efficacy and survival rates.
3. **Observational Data**: The study's reliance on observational data may introduce biases, such as selection bias and reporting bias.

Conflict of Interest Statement

The authors declare that there is no conflict of interest regarding the publication of this paper. There are no financial or personal relationships with other individuals or organizations that could inappropriately influence or bias the content and findings of this work. This disclosure aims to uphold the integrity of the scientific record, ensuring that all decisions and interpretations of the research are free from any undue influence.

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References:-

1. Alamgir M, Jamal Q, Jafarey NA, Mirza T. Clinicopathological parameters of 50 oral squamous cell carcinoma cases in Karachi. Pak J Med Dentistry. 2013;2(2):3-8.
2. Mendenhall WM, Werning JW, Pfister DG. Treatment of head and neck cancers. Cancer: Principles and Practice of Oncology. 9th ed. Philadelphia, Pa: Lippincott Williams & Wilkins. 2011;729-80.
3. Kuo P, Chen MM, Decker RH, Yarbrough WG, Judson BL. Hypopharyngeal cancer incidence, treatment, and survival: temporal trends in the United States. Laryngoscope. Sep 1 2014;124(9):2064-9.
4. Bray F, Ren JS, Masuyer E, Ferlay J. Global estimates of cancer prevalence for 27 sites in the adult population in 2008. Int J Cancer. Mar 1 2013;132(5):1133-45.
5. Kelly SL , Jackson JE, Hickey BE, Szallasi FG, Bond CA. Multidisciplinary clinic care improves adherence to best practice in head and neck cancer. Am J Otolaryngol. Feb 28 2013;34(1):57-60.
6. Lefebvre JL, Andry G, Chevalier D, Luboinski B, Collette L, Traissac L, De Raucourt D, Langendijk JA. Laryngeal preservation with induction chemotherapy for hypopharyngeal squamous cell carcinoma: 10-year results of EORTC trial 24891. Ann Oncol. Oct 1 2012;23(10):2708-14.
7. Vokes EE.Competing roads to larynx preservation. J Clin Oncol. 2013;31(7):833.
8. Dunphy FR, Dunleavy TL, Harrison BR, Trinkaus KM, Kim HJ, Stack BC, et al. Induction paclitaxel and carboplatin for patients with head and neck carcinoma. Cancer. Mar 1 2001;91(5):940-8.
9. Vaiman M, Complex Evaluation of Pain After Tonsillectomy. Acta Otolaryngol. 2007;127(9):957-65.
10. Huebner WW, Schoenberg JB, Kesley JL. Oral and pharyngeal cancer and occupation: a case control study. Epidemiology. 1992;3:300–9.

11. Shih-Kai H, Hung-Li C, Chen-His H. Treatment of Advanced Hypopharyngeal Cancer — Comparison of Two Modalities Tzu Chi Med J. 2006;18:1-9
12. Schwartz DL, Ford E, Rajendran J. Imaging for preradiotherapy staging of head-and-neck squamous cell carcinoma. Int J Radiat Oncol Biol Phys. 2006;61:129-36.
13. Robbins KT. The evolving role of combined modality therapy in head and neck cancer. Arch Otolaryngol Head Neck Surg. 2000;**126**:265-9.
14. Psyrri A, Kwong M, DiStasio S. Cisplatin, fluorouracil, and leucovorin induction chemotherapy followed by concurrent cisplatin chemoradiotherapy for organ preservation and cure in patients with advanced head and neck Cancer: Long-term follow-up. J Clin Oncol. 2004;22:3061-9.
15. Hsu LP, Chen PR: Distant metastases of head and neck squamous cell carcinomas- experience from eastern Taiwan. Tzu Chi Med J. 2005;17:99-104.
16. Baatenburg de Jong RJ, Hermans J, Molenaar J, Briaire JJ, le Cessie S: Prediction of survival in patients with head and neck cancer. Head Neck. 2001;23:718-24.
17. Robson A. Evidence-based management of hypopharyngeal cancer. Clin Otolaryngol. 2002;27:413–20.
18. Sewnaik A, Hoorweg J, Knegt P. Treatment of hypopharyngeal cancer: analysis of nation-wide study in the Netherlands. Clin Otolaryngol. 2005;30:52–7.
19. Koshy M, Paulino AC, Howell R. F-18 FDG PET-CT fusion in radiotherapy treatment planning for head and neck cancer. Head Neck. 2005;27:494-502.
20. Groome P, Schulze K, Keller S. Explaining socioeconomic status effects in laryngeal cancer. Clin Oncol. 2006;18:283–92.
21. Hussain N, Karnath B. GI consult: Dysphagia. Emergency Medicine. 2003;35(9):14-9
22. Postma GN, McGuirt WF. Laryngopharyngeal abnormalities in hospitalized patients with dysphagia. Laryngoscope. 2007;117:1720-2.
23. Castell DO, Hila A. Upper gastrointestinal disorders. In: Hazzard W, Blass JP, Halter JB, Ouslander JG, Tinetti ME. Eds. Principles of Geriatric Medicine and Gerontology. 5th edition. New York, McGraw-Hill. 2003.p.613-40
24. Piccirillo JF, Tierney R, Costas I. Prognostic importance of comorbidity in a hospital based cancer registry. JAMA. 2004;291:2441–7.
25. Hall SF, Boysen M, Groome PA. Squamous cell carcinoma of the head and neck in Ontario, Canada and southeastern Norway. Laryngoscope. 2003;113:695–701.
26. Barbera L, Groome PA, Mackillop W. The role of computed tomography in the T classification of laryngeal carcinoma. Cancer. 2001;91:394–407.
27. Pen-Yuan Chu, Shyue-Yih Chang Reconstruction of the Hypopharynx After Surgical Treatment of Squamous Cell Carcinoma J Chin Med Assoc. 2009;7:7-67
28. Robb GL, Lewin JS, Deschler DG, Haughey BH, Brown DH, Langmore SE, Lewin JS. Speech and swallowing outcomes in reconstructions of the pharynx and cervical esophagus. Head Neck. 2003;25:232–44.
29. Alam DS, Vivek PP, Kmiecik J. Comparison of voice outcomes after radial forearm free flap reconstruction versus primary closure after laryngectomy. Otolaryngol Head Neck Surg. 2008;139:240–4.
30. Kim JG, Sohn SK, Kim DH. Phase II study of concurrent chemoradiotherapy with capecitabine and cisplatin in patients with locally advanced squamous cell carcinoma of the head and neck. Br J Cancer. 2005,93:1117-21.