Mini Symposium: Head Neck Cancer

Neo-adjuvant chemotherapy in advanced hypopharyngeal carcinoma

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Abstract

OBJECTIVE: The aim of this retrospective study was to find out the role of neo-adjuvant chemotherapy (NACT) in changing the management and outcome of advanced hypopharyngeal cancer patients. **MATERIALS AND METHODS:** This is a retrospective analysis of 59 treatment naïve, advanced hypopharyngeal cancer patients presenting to our tertiary care center from April 2010 to October 2011. NACT was given as two (platinum with taxane) or three drug with (platinum, taxane with 5-flurouracil [5 FU]) as 3 weekly regimen with cisplatin and docetaxel as 75 mg/m^2 each, 5-FU as 1000 mg/m^2. NACT was either given with the intent of achieving: (1) surgical resection (extensive soft tissue disease, oropharyngeal involvement, extensive disease with cartilage erosion) or (2) organ preservation (Bulky disease with inner cartilage erosion, exolaryngeal disease without cartilage erosion, large N3 nodes). **RESULTS:** The mean age of this population was 55 years. Most (83%) of the patients had pyriform sinus (PFS) involvement. 69% patients had Stage IVa disease, 21% Stage IVb and 10% Stage III. The overall response rate was 66%, including 06% complete responses and 60% partial responses. Following NACT, resectability was achieved in 30% (10/33) and organ preservation protocol was planned after NACT in 73% (19/26) patients. The main toxicities were neutropenia (grade 3, 4, 04%; febrile neutropenia, 4%), mucositis 5%, diarrhea 5%. The median progression free survival was 20 months. **CONCLUSIONS:** NACT can be useful in patients with oropharyngeal involvement to achieve surgical resection and larynx preservation in patients with bulky T3 disease.

Key words: Bulky disease, hypopharyngeal cancers, N3 node, neo-adjuvant chemotherapy, organ preservation, resectability

Introduction

Hypopharyngeal cancers are notorious for poor prognosis. Majority of them present in advanced stages with extensive submucosal disease, large bulky neck nodes and distant metastasis. The treatment is usually multimodal requiring surgery followed by adjuvant treatment or organ preservation in the form of chemoradiotherapy. Neo-adjuvant chemotherapy (NACT) is recommended as one of the modality of treatment for small primary tumor with positive neck nodes like T1N + stage of hypopharyngeal cancer by National comprehensive cancer network (NCCN). Despite chemoradiotherapy being the treatment of choice for advanced hypopharyngeal cancers, there is no level 1 evidence for this or uniform consensus for the same.[1,2] Treatment outcomes for bulky and high volume T3 disease are not satisfactory with chemoradiotherapy.

Extensive T4 lesions which are either unresectable or their resection amounts to positive margin, proper treatment is not yet defined. T4 disease includes a spectrum of situations like exolaryngeal spread through a membrane without cartilage erosion or through cricothyroid space or with extension to oropharynx like tonsil or with involvement of prevertebral fascia, parapharyngeal space. In these situations, it is difficult to achieve free margin of resection if surgery is contemplated. The morbidity associated with extensive resections is also very high.

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The standard of care for large N3 nodes is concurrent chemoradiation but the response rates vary and a large number of patients have residual disease or stable disease (SD). With the increasing nodal size, the chance of regional control decreases with the use of concurrent chemoradiation. Hanna *et al.*,[3] reported a complete cervical remission rate of 69% (all stages) following chemoradiation which was 93% for patients with N1 disease, 62% for N2 disease, and 47% for N3 disease.

Despite multimodality treatment, locoregional control and survival rates are poor. Hence, in this group of patients, NACT may help in selecting patients for organ preservation or make unresectable disease resectable. Hence, in this retrospective analysis we evaluated the impact of NACT to select subsequent definitive therapy and outcome of these patients.

Materials and Methods

This is a retrospective analysis of patients with hypopharyngeal cancers who presented to our Tertiary Health Center from April 2010 to October 2011. The medical records of patients with proven squamous cell carcinoma of the hypopharynx were screened for the study. Cases were selected based on the following eligibility criteria: (1) biopsy confirmed squamous cell carcinoma of the hypopharynx, (2) Patients with extensive and bulky T3 disease or with inner cartilage erosion/T4 disease (3) All patients with N3 nodes or nodes with restricted mobility. Of the total 69 patients who were treated, 59 patients were eligible for analysis. Ten patients did not come for follow up after completion of treatment.

A complete medical history was obtained and tumor assessment was performed at baseline. Complete pre-operative evaluation was done in all patients including a direct laryngoscopy, imaging with contrast enhanced computed tomography (CT) scans and barium swallows.

The primary objectives of the study were resectability and organ preservation and secondary objectives were response rate of the tumor to NACT, side effects, progression free survival, overall survival. Resectability was defined as tumors which surgeon considered as resectable with adequate margins post two cycles NACT and which were considered un-resectable at baseline. Similarly, organ preservation was defined as treatment with chemoradiotherapy with preservation of larynx for patients who were not fit for organ preservation at baseline. NACT was either given with the intent of achieving

Resectability (surgical resection) - extensive soft tissue disease, oro-pharyngeal involvement, extensive disease with cartilage erosion or

Organ preservation - Bulky disease with doubtful inner cartilage erosion, exolaryngeal disease without cartilage erosion, large N3 nodes or nodes with restricted mobility.

NACT was given as two (platinum with taxane) or three drug (platinum, taxane and 5-fluorouracil [5-FU]) as 3 weekly regimen with cisplatin and docetaxel as 75 mg/m^2 each on day 1 and 5-FU as 750 mg/m^2 as 24 h iv infusion for 5 days for three cycles. Patients receiving 3 drug regimen were given granulocyte-colony stimulating factor prophylactically from day 6 to day 12. Tablet levofloxacin 500 mg once daily was given for the same duration as primary prophylaxis for bacterial infections. Carboplatin as area under curve 6 was given to older individuals or those with compromised glomerulo-filtration rate of less than 60 ml/min. Only those patients who at least completed 2 cycles of NACT were included in the study.

Response to NACT was assessed with response evaluation criteria in solid tumors (RECIST) criteria 1.1. All CT scans were evaluated by a senior radiologist pre and post NACT. Side effects were assessed with common toxicity criteria version 4. Dose reduction was done for any grade 3 or grade 4 toxicity. Dose response was assessed after two cycles of chemotherapy. Those with stable disease (SD) were treated with radical radiotherapy/chemoradiotherapy or surgery. Those with partial response (PR) or complete response (CR) were given III cycle and then were either operated or treated with chemoradiation/radiation. Patients with progressive disease (PD) or extensive disease received palliative radiotherapy. One patient developed hemiplegia while taking second cycle of docetaxel + cisplatin + 5-FU; hence the chemotherapy was stopped immediately.

Tumor responses were assessed by clinical evaluation and imaging studies like positron emission tomography CT scan done 12 weeks after the completion of chemoradiotherapy. Patients were monitored every 3 monthly for recurrence for first 2 years by clinical examination or imaging. In our study, the follow-up varied from 2 months to 21 months.

Statistical analysis was done using the software SPSS 20.0 (IBM, NY, USA). *P* values were calculated using Chi-square or *t*-tests. A *P* value of less than 0.05 was considered significant. Survival was calculated with Kaplan-Meier analysis.

Results

The mean age of the population was 55 years ranging from 22 years to 80 years. Majority of these lesions (49/59) involved the PFS. Extension to larynx was noticed in 95% of the patients (55/59). While the majority of the tumors were T4a (54%), only 5% were T4b. The tumor, nodal status and stage of the disease and European cooperative oncology group (ECOG) scale are described in [Table 1]. The median hemoglobin of the population was 12.35 g/dl (8.9-17.2 g/dl) and median albumin was 4 mg/dl (2.7-4.7 mg/dl).

Twelve (20%) of our patients received three drug regimen while 47 (80%) received two drug regimen. Fifty patients (85%) received two cycles and 9 (15%) patients received three cycles of NACT. In all the patients, docetaxel was used. According to RECIST criteria 1.1, the overall response rate was 66% with 06% CR and 60% PR rate. Thirty percent patients had SD and 4% had PD. The response assessment when done separately for primary and nodes was 76% and 65% respectively.

All patients were assigned to receive chemoradiotherapy beginning 3-6 weeks after the start of the third cycle of induction chemotherapy (second cycle when received two cycles only). Weekly cisplatin at a dose of 30 mg/m^2 was given as an intravenous infusion for the 1-hour period for 6-7 weekly doses during the course of radiotherapy. The definitive curative radiation dose administered to the primary tumor was between 66 Gy and 70 Gy, administered as fractions of 2 Gy per day 5 days/week. The dose administered to uninvolved lymph nodes was at least 50 Gy. Involved lymph nodes were to receive 60-70 Gy. Surgery was done for those patients who had resectable residual disease at the primary site or in the neck post neoadjuvant treatment.

Following NACT, patients were assessed by the joint clinic and final decision of resection was taken by the surgeon. Ten patients underwent total laryngectomy and thus, following NACT, resectability was achieved in 30% (10/33) patients when the intent of giving NACT was resectability. Of the operated 10 patients, three patients had no residual tumor post NACT and two patients had close margins of resection. However, Organ preservation protocol was planned after NACT in 73% (19/26) patients where intent was to select patient for organ preservation.

All 10 patients who underwent surgery received adjuvant chemoradiotherapy or radiotherapy. Six patients who had PD with NACT received palliative radiotherapy. Two patients denied further treatment as they had relief of symptoms with NACT and did not consent for radical treatment. One patient died of disease and other was alive with disease at follow up of 3 months. This patient had PR to NACT. Rest of the 41 patients either received definitive radiotherapy or chemoradiotherapy. One patient underwent total laryngectomy and one patient radical neck dissection post chemoradiotherapy. Both were disease free at follow-up of 12 and 8 months respectively.

Twenty seven percent (9/33) patients were disease free in surgery followed by chemoradiotherapy group when the intent of giving NACT was resectability and 62% (15/24) were disease free at a median follow up of 12 months in patients where the intent of receiving NACT was organ preservation. The mean overall survival for the whole population was 22 months

Table 1: Demographic details

Demographic details (*N*=59)		
Age mean	55 years	
Median	55 years	
Range	22-80 years	
	Number of patients	**Percent**
Sex		
Male	55	93
Female	04	07
Site of the disease		
Pyriform sinus	49	83
Post cricoid	07	12
Posterior pharyngeal wall	03	05
Tumor status		
T2	04	6.8
T3	20	34
T4a	31	52.5
T4b	04	6.8
Nodal status		
N0	17	28.8
N1	09	15.3
N2a	07	11.9
N2b	10	16.9
N2c	08	13.6
N3	08	13.6
Staging		
Stage III	06	10
Stage IVa	41	69
Stage IVb	12	21
ECOG performance status		
0	04	07
1	51	86
2	04	07
3	0	0
4	0	0

ECOG: European cooperative oncology group

and median duration was not reached. The mean and median progression free survival was 18 and 20 months respectively. Two patients who did not take treatment post NACT were excluded from survival analysis.

The pattern of failure was mostly regional followed by locoregional and distant metastasis. Patients who did not receive definitive treatment post NACT were excluded from this analysis. The pattern of failures is described in detail in [Table 2].

The main toxicities of NACT were neutropenia (grade 3, 4) 04%, febrile neutropenia 4%, mucositis 5% and diarrhea 5%. Other side effects included nausea, anorexia, renal dysfunction and failure, hypokalemia, hyponatremia as described in [Table 3].

Table 2: Failures by treatment given*

Treatment given (*n*=57)	Number of patients	Failures	Residual/ recurrence
Surgery followed by chemoradiation	10	01	1 Regional+ distant metastasis
Radical chemoradiation	30	10 (2 died)	2 local
			4 regional
			2 locoregional
			2 locoregional+ distant metastasis
Radical radiation	11	03 (1 died)	1 local
			1 regional
			1 distant
Palliative radiotherapy	06	06 (all died)	6 died

*2 patients who did not receive any treatment post neo-adjuvant chemotherapy were not included in the analysis

Table 3: Side effects of chemotherapy

Side effects of chemotherapy	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	None (%)
Nausea	02	02	0	0	96
Vomiting	27	19	3	0	51
Mucositis	24	27	03	02	42
Diarrhea	17	31	03	02	47
Neutropenia	08	02	02	02	86
Febrile neutropenia			02	02	96
Thrombocytopenia	02	02	0	0	96
Peripheral neuropathy	03	02	0	0	95
Anorexia	02	02	0	0	96
Hyponatremia	04	0	10	02	84
Hypokalemia	04	02	02	0	08
Renal dysfunction	06	0	0	01	07

Discussion

Hypopharyngeal cancers present in advanced stages due to late and non-specific symptoms and thus have poor overall survival. Recently, chemotherapy has widened its application in the treatment of head and neck cancer. NACT combined with subsequent radiation therapy has emerged as one of the possible treatment options for advanced, but resectable head and neck cancer.[4] Several multi-institutional studies have shown that use of NACT can be helpful in avoiding extensive surgeries and achieving organ preservation with survival rates comparable to standard surgery and post-operative radiation.[5] This is particularly important in hypopharyngeal cancers, which undergo extensive laryngeal and pharyngeal resection with significant morbidity. A significant number of these patients retain their larynx, which otherwise would have been removed without the use of organ preservation treatment.

The indications for NACT are not well defined yet. NACT is used as it helps in control of micrometastasis and might downstage the tumor and hence making the lesions operable.[6,7] In a study by Paccagnella,[8] the 5 and 10 year survival data of operable and inoperable patients showed benefit in terms of reduction in distant metastasis in those who received induction chemotherapy followed by radiotherapy when compared with radiotherapy alone. However, none of the randomized trial has shown any benefit in the overall survival. This might be attributed to the sample size of each trial, which could be too underpowered to demonstrate any positive results.

The Head And Neck Tumors Italian Study Group clinical trial[8] showed that NACT given in patients who were inoperable and hence went for radical RT were benefitted in term of disease free survival and overall survival. This benefit was observed 10 years after the treatment also.

The 10 year update of European organization for research and treatment of cancer 24891[9] trial has shown the induction followed by radiotherapy arm to be similar to surgery followed by radiotherapy arm in terms of overall and disease free survival. The 10-year overall survival rate was 13.8% in the surgery arm and 13.1% in the chemotherapy arm. The 10-year progression-free survival rates were 8.5% and 10.8%, respectively. In the chemotherapy arm, the 10-year survival with a functional larynx rate was 8.7%. These results are especially important as all these patients had hypopharyngeal cancers only. Though the group of

patients were not entirely similar to those of our study; however, they still included advanced tumor and nodal stage as in our study; thus, giving a good evidence for the role of induction chemotherapy as useful as surgical management in terms of overall and disease free survival.

Volume of the disease is a strong predictor of outcome for hypopharyngeal cancers when radiotherapy is used for treatment. Those patients with tumor volume less than 40 ml on CT scan should be considered for organ preservation.[10] Thus, in our study also, those patients who had bulky or high volume disease were given NACT followed by radical chemoradiation. Though, the volume of disease was not calculated objectively, it was based on joint decision by a radiologist, and treating medical oncologist, surgical oncologist and radiation oncologist.

Newer drugs like platinum, taxanes and 5-FU have very good efficacy and response rates. In our series, the overall response rate was 66%, including 06% CR and 60% PR rate which is comparable with 72% and 64% response rates with Taxane, cisplatin and 5-Fluorouracil and cisplatin and 5-Fluorouracil respectively in TAX 324

(Cisplatin and fluorouracil with or without docetaxel as induction treatment for locally advanced SCCHN trial).[11] Toxicity was acceptable with the NACT in our series with grade 3 and 4 neutropenia in 08% patients and with no grade 3 and 4 thrombocytopenia. This is in sharp contrast with TAX 324 where the grade 3 and 4 neutropenia was 83% in TPF and 56% in PF and the grade 3 and 4 thrombocytopenia was 11% and 4% respectively. This could be attributed to reduction of dose of chemotherapy in those patients who had side effects and use of 2 drugs in the majority of patients. This also highlights that two drug combination of taxane with platinum needs to be investigated further to replace three drug combination.

Recently, two new randomized trials,[12,13] of neoadjuvant followed by chemoradiotherapy versus chemoradiotherapy in advanced head and neck cancers have shown that the overall survival and disease free survival were similar in both arms. However, there results need to be taken with caution as they have certain flaws with the design and interpretation of the results. In both these studies, majority of the patients were oropharynx which otherwise also have a good prognosis and the accrual of patients was not sufficient to detect the statistical significant difference between the two arms. But the incidence of distant metastasis was statistically lower in the NACT group.

Conclusion

Role of NACT in hypopharyngeal cancer is evolving. With the use of NACT, resection could be achieved in more than one fourth of the patients particularly in those with oropharyngeal involvement. Larynx could be preserved in more than half of patients with bulky and extensive disease, which otherwise would have undergone surgery. Our present study though a retrospective analysis without a control group dictates the important role of NACT in achieving organ preservation and resectability in otherwise unresectable and advanced lesions where it is difficult to aim for cure.

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