

**ORIGINAL RESEARCH****The emerging role of immunotherapy in head and neck squamous cell carcinoma: A controlled clinical trial****<sup>1</sup>Dr. Aditya Kumar Singla, <sup>2</sup>Dr Pardeep Garg, <sup>3</sup>Dr.Raja Paramjeet Singh Banipal**<sup>1</sup>Senior Resident, PGIMER, Chandigarh, India<sup>2</sup>Associate Professor and Incharge, GGS Medical College Hospital, Faridkot, Punjab, India<sup>3</sup>Professor and Head, GMC, Patiala, Punjab, India**Correspondence:**

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**Email:** [drpardeepgarg@gmail.com](mailto:drpardeepgarg@gmail.com)**Abstract**

**Background:** Head and Neck cancer is the most common malignancy among males and 2<sup>nd</sup> most common malignancy overall in India as per Globocan 2020. More than 90% of cases are Squamous cell carcinoma (HNSCC). Treatment requires multidisciplinary approach which includes surgery, radiotherapy and chemotherapy. Despite the various advances in the treatment modalities, the failure rate is still significant high in HNSCC. Various prognostic factors have been explored to explain this high rate of failure. Among all the risk factors, immune suppression which is thought to be a significant contributor towards the poor prognosis of HNSCC. Hence, this study aims to study the role of Immunotherapy as an alternative or adjuvant treatment option for improving treatment outcomes in head and neck cancer.

**Materials and Methods:** This is a prospective study which included 50 patients enrolled between December, 2015 to June, 2016 diagnosed with head and neck squamous cell carcinoma (HNSCC) who were randomized into two arms using odd even formula. Experimental arm received immunotherapy with mycobacterium w vaccine 0.2ml along with conventional chemo-radiotherapy (66Gy/33#/6.5weeks along with cisplatin 40mg/m<sup>2</sup>) while control arm (Arm B) received only conventional chemo-radiotherapy (CRT). All patients were planned for radiotherapy with 2-D technique on cobalt-60. A weekly review of all patients was done for toxicities including hematological, oral mucositis and skin reactions using RTOG criteria. Treatment response was assessed at three months following radiotherapy completion with RECIST criteria. Chi Square tests have been used in the statistical analysis. Follow up was done till six months for every patient.

**Results:** In total, 50 patients were analyzed with 25 patients in each arm. The overall toxicities grade as well as severity was found to be decreased in immunotherapy arm. Oral mucositis severity was found to be statistically decreased with p value of 0.016. None of the patient in Immunotherapy arm presented with grade IV oral mucositis while in conventional CRT arm three patients presented with grade IV oral mucositis. Grades of hematological and skin toxicities were decreased in immunotherapy arm, though not statistically significant with p value 0.283 and 0.183 respectively. As per RECIST scale, there was complete response in 20 patients (80%) in immunotherapy arm while only 8 patients (32%) showed complete response in conventional CRT arm. Hence, treatment response was found to be highly statistically significant in with p value of 0.003.

**Conclusion:** Immunotherapy improves the response as well as decreases the toxic side effects of chemo radiotherapy in locally advanced HNSCC. Though more prospective studies with greater sample size are needed to confirm the role of immunotherapy in HNSCC.

**Keywords-** Immunotherapy, HNSCC, concurrent chemo-radiotherapy, Treatment Outcome

## Introduction

Head and Neck cancer entity includes malignancies of paranasal sinuses, naso-pharynx, lip, oral cavity, oro-pharynx, hypo-pharynx and larynx. Head and neck cancer is the sixth most common malignancy. <sup>(1)</sup> Globally they account for 4.8% of all cancer cases <sup>(2)</sup> whereas in India they account for 14.3% of all cancer cases. <sup>(2)</sup> Head and neck cancer is a major health problem in Asia, especially in Indian subcontinent. The risk of developing Head and Neck Squamous Cell Carcinoma (HNSCC) increases with age and the majority of HNSCCs occur in patients with age  $\geq 50$  years with males affected more than females (4:1). <sup>(3)</sup> Cigarette-smoking and alcohol consumption are the main reasons for HNSCC in the Western population, whereas the use of smokeless tobacco and areca nut is the most common etiology of HNSCC in India. <sup>(4,5)</sup> The overall prevalence of HPV in HNSCC is around 50%, with the highest prevalence in carcinoma tonsil and base of tongue. <sup>(6)</sup> Multi-disciplinary approach is the standard protocol followed in the treatment of HNSCC. In modern era of organ preservation, for patients with locally advanced head and neck cancer; chemo-radiotherapy has been identified as the cornerstone of treatment. <sup>(7)</sup> Despite advances in radiotherapy and attempts at organ preservation, success rate of treatment has not improved significantly with current regimens. An alternative or adjuvant treatment option being explored now-a-days is immunotherapy. The rationale behind using immunotherapy for head and neck cancers is based on expression of antigens that are selectively expressed on malignant tissues of HNSCC. These antigens include MUC-1, EGFR, the RAGE and GAGE families of tumor antigens. <sup>[8,9,10,11]</sup> Head and neck cancer patients produces several immune- inhibitory mediators including PGE2, TGF- $\beta$ , VEGF, IL-6, IL-8. <sup>[12,13,14]</sup> These mediators are known to be inhibitory towards T cell lymphocytes and functions by decreasing the intra-tumoral levels of T cells in CD-8 T cells. Immunotherapy in the form of Mycobacterium w vaccine which is a live BCG vaccine has been given in this study. It is a TLR2 agonist, a nonspecific immune-modulator and pure Th1 response enhancer. <sup>[15]</sup> Mycobacterium w is a non pathogenic, cultivable, atypical mycobacterium and fast-growing bacterium. Mycobacterium w vaccine enhances both anti-tumor CD4+ T helper and CD8+ responses. Hence, we conducted a study in our department to assess the role of immunotherapy in HNSCC. The primary objective was the response assessment and secondary objective was to assess the various acute toxicities while on radiotherapy.

## Materials and methods

Locally advanced histopathological proven Squamous cell carcinomas with stage III, IVa, IVb were included in this study. Fifty patients were enrolled between December,2015 and June, 2016 and were randomized by odd even formula into two arms. Immunotherapy arm has 25 patients and received conventional chemo-radiotherapy with immunotherapy (66GY/33# with concomitant weekly cisplatin 40mg/m<sup>2</sup> and weekly 0.2 ml intradermal Mycobacterium w vaccine starting 2 weeks prior to treatment) whereas conventional CRT arm received only conventional chemo-radiotherapy(CRT). Chi Square tests have been used in the statistical analysis. The study was conducted for 18 months with follow up of every patient for 6 months.

**Results (Graph I, II, III, IV)**

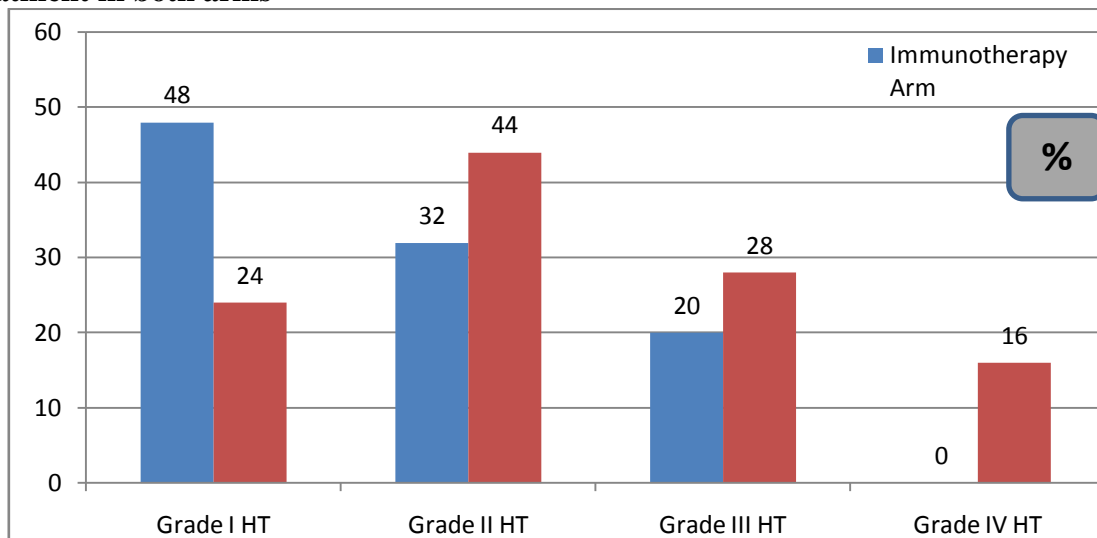
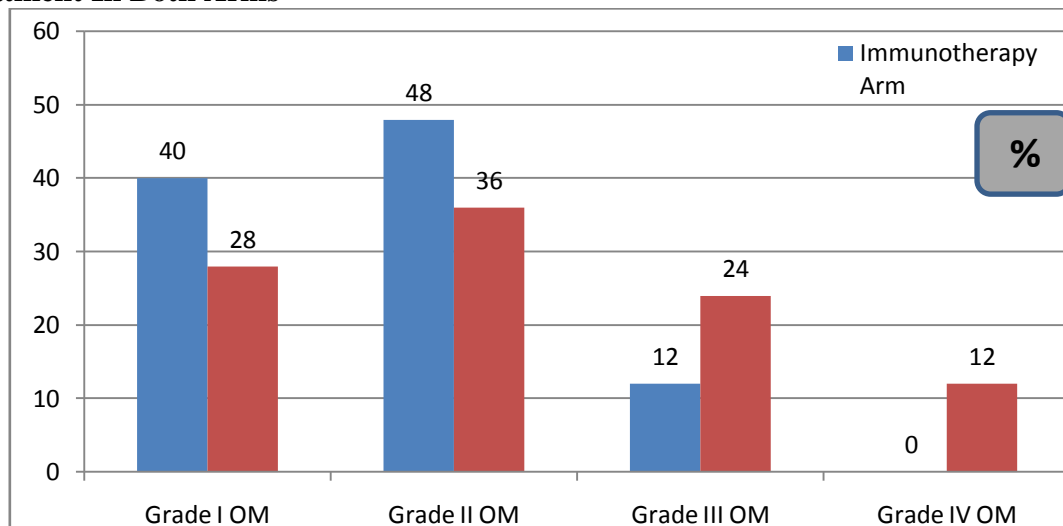
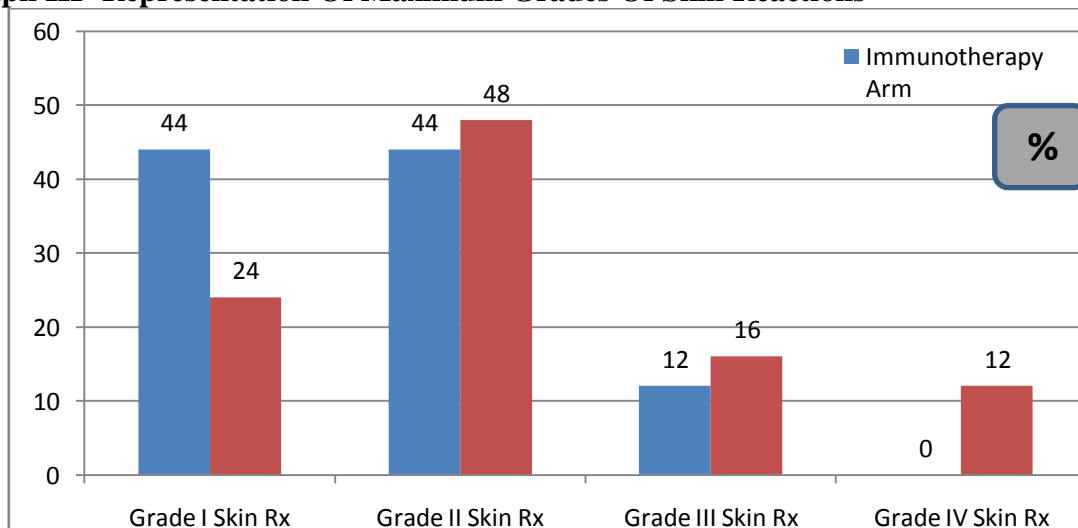
Median age was 52.5 years (range=32-65 years). Majority of the patients in both the arms were male (80%). Overwhelmingly the patients belonged to rural background in both the arms (68% and 76% respectively). All baseline characteristics are comparable in both the arms and tabulated in Table No. 1

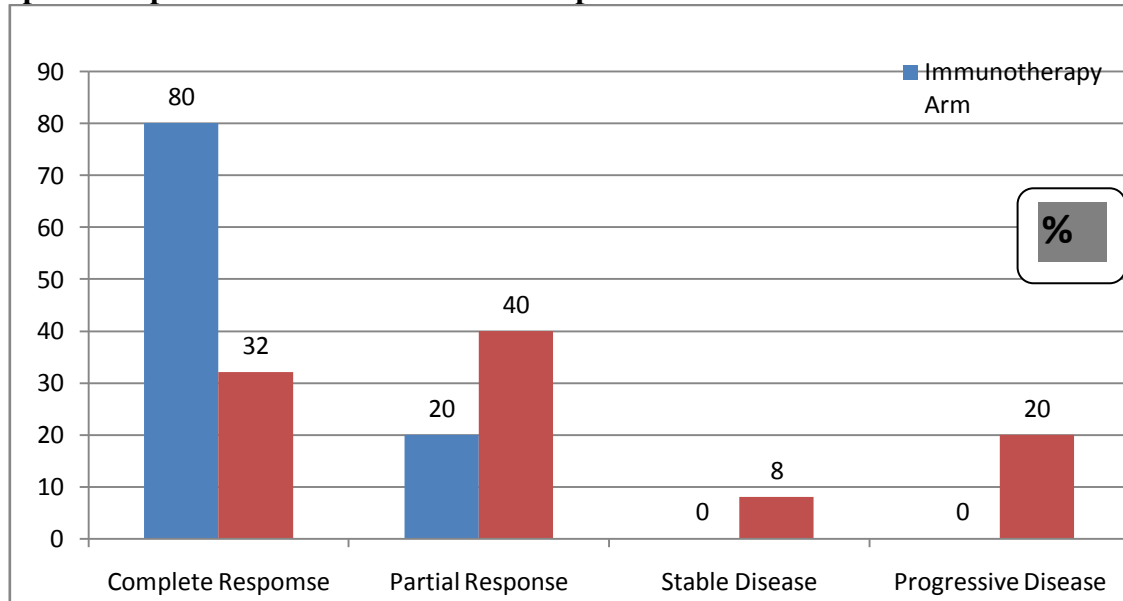
For treatment outcomes, results were assessed for toxicity reactions and treatment response. Patients in immunotherapy arm experienced less severe oral mucositis grades( $p=0.016$ ). Maximum grade III was noticed in immunotherapy arm. Similarly, the incidence of hematological toxicity was also decreased in immunotherapy arm though not significant ( $p=0.283$ ). Skin reactions were more severe in conventional chemo-radiotherapy arm, though the results were not significant ( $p=0.183$ )

CECT head and necks was done at three months to see the treatment response with RECIST criteria. The response was statistically better in immunotherapy arm ( $p=0.003$ ). Complete response was seen in 20 patients (80%) in immunotherapy arm and 8 patients (32%) in conventional CRT arm. The disease progression was not seen in any of the patient in immunotherapy arm but in conventional CRT arm 5 patients (20%) had shown disease progression.

**Table No.1 (Basic Characteristics) n=50**

Parameter	Arm A (N=25) N(%)	Arm B (N=25) N(%)
<b>Age</b>		
< 50 Years	15 (60)	13 (52)
>50 Years	10 (40)	12 (48)
<b>Sex</b>		
Male	20 (80)	20 (80)
Female	5 (20)	5 (20)
<b>Area</b>		
Rural	17 (68)	19 (76)
Urban	8 (32)	6 (24)
<b>Site</b>		
Oral Cavity	11 (44)	11 (44)
Oropharynx	4 (16)	3 (12)
Hypopharynx	4 (16)	3 (12)
Larynx	6 (24)	2 (8)
<b>Addiction</b>		
Alcohol	15 (60)	20 (80)
Smoking	21 (84)	19 (76)
Tobacco Chewing	19 (76)	17 (58)
Opium	5 (20)	3 (12)
<b>Stage</b>		
III	10 (40)	9 (36)
IVA	11 (44)	10 (40)
IVB	4 (16)	6 (24)

**Graph I: Representation of maximum hematological toxicity grades throughout the treatment in both arms****Graph II- Representation Of Maximum Oral Mucositis Grades Throughout The Treatment In Both Arms****Graph III- Representation Of Maximum Grades Of Skin Reactions**

**Graph IV-Representation Of Treatment Response At 6 Weeks In Both Arms**

### Discussion

Despite advances in surgery, radiotherapy, and chemotherapy, the overall survival rates for patients with HNSCC have not changed over the last decades. Because patients with HNSCC are frequently immunocompromised due to the elimination or dysfunction of critical effector cells of the immune system, it might be necessary to restore these immune functions to allow for the generation of more effective antitumor host responses. This creates the space for an additional intervention besides conventional treatment in HNSCC and immunotherapy is one of them. The comparison in this study was in terms of acute toxicities and response evaluation at three months after completion of treatment. The hematological toxicity is expected when cytotoxic chemotherapy agents are administered and if they are used concomitantly along with the radiotherapy then there will be an synergist effect and incidence of myelosuppression will be increased as shown in the study conducted by Lone M Maqbool et al.<sup>(188)</sup> In our study, hematological toxicity was noticed weekly. 20 patients (80%) suffered from grade I and II hematological toxicity with no grade IV toxicity in immunotherapy arm while in conventional CRT arm 8 patients (32%) presented with grade III and IV hematological toxicities. The patients who developed toxicity were given blood transfusions for anemia, growth factors (G-CSF) for neutropenia and platelet rich plasma for thrombocytopenia. The grades of hematological toxicity were less severe in immunotherapy arm though the results were not significant (p=0.283)

Oral mucositis (OM) grades were also compared in both the arms. None of the patient in immunotherapy arm presented with grade 4 OM while in conventional CRT arm three patients presented with grade IV oral mucositis. Till grade III no interruption was done in the radiation, patient was managed on outpatient basis but grade IV patients were admitted and radiotherapy (RT) was stopped. RT was started only when oral mucositis grade reduced by at least one grade. The hospitalized patients were managed by intravenous fluids and supportive therapy. They were advised to maintain proper hygiene and to do saline gargles every 4 hourly. Local paste was also prepared for the patient for local application in the oral cavity with constitution of anti-fungal, local anesthetic and tetracycline. Our study results have clearly shown statistically significant reduction in oral mucositis in immunotherapy arm (p=0.016)

Immunotherapy arm had reported grade III skin reactions as the maximum grade whereas conventional CRT arm had three patients (12%) with grade IV skin reactions. Though the results were not statistical significance ( $p$  value=0.183).

The response to the treatment, in our study, was assessed at three months after therapy according to RECIST criteria. No patient had defaulted from the treatment. There was complete response in 20 patients (80%) in immunotherapy arm while only 8 patients (32%) showed complete response in conventional CRT arm. 5 patients (20%) shown partial response in immunotherapy arm while 10 patients (40%) shown partial response in CRT arm. None of the patient reported with progressive disease in immunotherapy arm while 5 patients (20%) reported with progressive disease in CRT arm. These results were statistically significant with  $p$  value of 0.003 in favour of immunotherapy arm.

### Conclusion

The observation made in our study helped us to arrive at a conclusion that mycobacterium w vaccine with conventional chemo radiotherapy arm administers a better response than only conventional chemo radiotherapy with considerable reduction in the grades of acute toxicities during the radiation. Hence, the addition of mycobacterium w vaccine weekly with conventional chemo radiotherapy is a promising option to improve the results and quality of life for the patient.

But the need of the hour is that more studies should be done with larger sample sizes and longer follow up should be instituted for further validation of this treatment option.

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