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ORIGINAL RESEARCH

Comparison and Assessment of Head and Neck Squamous Carcinoma in Younger and Older Patients Treated with Chemo Radiotherapy

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ABSTRACT

Introduction: Head and neck cancer (HNC) is the 6th most common cancer globally. Unfortunately, even though more than 25% of cancers are diagnosed in people over 60 years, they are often less extensively investigated and undertreated than younger patient and seldom included in clinical trials. The study aimed to compare the profile of younger and elderly patients in terms of compliance, toxicities, and clinical outcomes in head and neck cancers treated with chemo-radiotherapy.

Materials and Methods: Fifty patients were included in the study and patients were distributed in two groups, age ≤ 60 years of age and >60 years of age, and were planned to deliver standard radiotherapy at a dose of 70 Gy in 35 fractions over 7 weeks with concurrent chemotherapy dose Cisplatin 35 mg/m^2 weekly followed by compliance assessment from 3 months of follow up to at least up to 6 months.

Result: In the present study, it was observed that radiotherapy compliance was similar in the elderly group as in younger group. Our study also observed that though chemotherapy compliance in terms of number of the cycle was lower in elderly patients than younger patients due to increase hematological toxicities, they were of grade I/II toxicity. No significant difference in severe Grade III/IV toxicity was observed in elderly group in comparison to the younger group.

Conclusion: The present study suggests that elderly patients should get a complete radical course of concurrent chemo radiotherapy as in younger patients with good supportive care to overcome treatment-related toxicities.

Keywords: Chemoradiation, Head and neck cancer, Old patient, Young patient.

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INTRODUCTION

Head and neck cancers form one of the most common cancers in South and Southeast Asian countries.[1] Oral cancer are predominant forms of head and neck squamous cell cancer (HNSCC) in India, Pakistan, and other Southeast Asian countries; oropharyngeal and tongue cancers are common in the western world.[2] These differences in disease sites may be related to the prevalent habits in the respective regions.[3] Cigarette-smoking, alcohol and smokeless tobacco, areca nut consumption are the main cause of HNSCC in the western population and southeast asia, resepectively.[4,5]

According to the national cancer institute, aging is most important risk factor for cancer. Over last several decades, cancer trends have been changing contemporaneously with knowledge of aging. Furthermore, with improved screening and treatment, many older cancer patients are experiencing long-term survival.

Among all the sites, head and neck cancer incidence, although most of it occurs between the fifth and sixth decades, their onset in patients older than 60 years is not a rare event.[6] As many as 24% of the HNSCCs are found in patients older than 70 years.[7]

Concomitant chemo-radiotherapy is now also being given to patients with locoregionally advanced (AJCC stage III and IVA/IVB) HNSCC. However, the benefit size with concurrent chemo-RT is age-dependent, with the largest benefit in those aged <60 and at the expense of increased acute toxicity (mucosal and hematological) and possibly late toxicity.[9] The current standard chemotherapy regimen for HNSCC is a sequential combination of cisplatin and infusional 5-fluorouracil (5-FU).On the other hand different Studies have also shown that RT is effective and well-tolerated in the elderly patient population and advanced age (>70 years) alone should not be considered a contra indicator for concurrent chemotherapy.[10,11]

Despite similar performance status and co-morbidity burden compared with their younger counterpart, older patients were more commonly treated with less aggressive strategies, including radiation alone.[13] For this reason, understanding about the challenges and points of focus in terms of optimizing cancer treatment planning, supportive care and minimizing toxicity is required in cancer patients of elderly age group, to achieve improved tumor control, better quality of life during and after treatment, and survival with better health.

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Therefore, this study aimed to evaluate the compliance, toxicities, and clinical outcomes of present standard regimen of concurrent chemo-radiotherapy in head and neck cancers, comparing younger and elderly patients.

MATERIALS AND METHODS

The study was conducted at Department of Radiation Oncology at R.R. Cancer Institute and Research Centre, Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly.

Inclusive Criteria

Fifty patients with histologically proven head and neck region malignancies, age ≥18 years, karnofsky performance scale above 70 and all patients have Normal Haemogram, Normal Renal Function Tests, Normal Liver function Tests and Normal ECHO.

Exclusion Criteria

Patients have metastatic disease and any previous prior and synchronous malignancies.

All patients were planned and delivered standard radiotherapy at a dose of 70 Gy in 35 fractions over 7 weeks with concurrent chemotherapy injectable Cisplatin 35 mg/m^2 weekly. Patients were randomized into two groups (twenty-five each) and Group A comprises young patients (age up to 60 year), whereas Group B have elder patients (above 60 years).

Radiotherapy planning includes all patients were immobilized with 5 point thermoplastic cast. Patients were conventionally planned by three fields (two opposing lateral fields and a lower anterior neck field). Spinal cord was shielded after 44 Gy in 22 fractions in lateral fields. Total Dose prescribed was 70 Gy in 35 fractions over 7 weeks.

During chemotherapy, patients were received Cisplatin 35 mg/m^2 weekly and were adequately hydrated with 2 to 2.5 litres of fluids and supplemented with injectable KCL and $MgSO_4$. Radiotherapy was delivered within 30 minutes of administration of Cisplatin. Before administering chemotherapy, proper antiemetic therapy with 5-HT3 antagonist, dexamethasone, and ranitidine was given.

During treatment assessment of a heamogram was done weekly. Radiation toxicity (skin, mucosal and salivary gland) was assessed by RTOG (Radiation Therapy Oncology Group) acute and late morbidity scoring criteria. Late radiation reactions were assessed using RTOG late morbidity criteria from 3 months of follow up to at least 6 months.

Clinical response was assessed during radiotherapy and every month after radiotherapy for at least 6 months. The patients were assessed for objective tumour response according to WHO criterion, including complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD).

Significance is assessed at 5% level of significance. Chi-square has been used to find the significance of study parameters on a categorical scale between two or more groups. Student t-test (two-tailed, dependent) has been used to find the significance of study parameters like correlation between various clinical, treatment and toxicity parameters on continuous scale within each group.

RESULTS

In both study groups, the male population was predominant (88% and 96%). There were only three females in group A and one patient in group B. Median age in group A was 54 years and median age in group B was 65 years. Overall comorbid conditions were higher in group B patients at time of presentation. Diabetic (20% vs. 16%), Hypertension (16% vs. 20%) and tuberculosis (16% vs. 28%). No statistical significance was observed in two groups shown in Table 1.

Group A and B had equal numbers of oral cavity carcinoma patients. More than two third of patients in both the groups were in stage III (80% vs. 72%) shown in Table 2.

Table 1: Patient related factors

Gender	*Group A n (%)*	*Group B n (%)*	*P value*
Male	22 (88%)	24 (96%)	
Female	3 (12%)	1 (4%)	
Median age	54 years	65 years	
Co morbid conditions			
Diabetes	5(20%)	9(36%)	0.20
Hypertension	4(16%)	5(20%)	0.71
Tuberculosis	4(16%)	7(28%)	0.30

Table 2: Tumor related factors

Cancer Site	*Group A n (%)*	*Group B n (%)*
Oral cavity	7 (28%)	7 (28%)
Oropharynx	8 (32%)	9 (36%)
Larynx	10 (40%)	9 (36%)
T Stage		
T1	1 (4%)	2 (8%)
T2	10 (40%)	8 (32%)
T3	11 (44%)	15 (60%)
T4a	1 (4%)	0 (0%)
T4b	2 (8%)	0 (0%)
Stage		
Stage III	20 (80%)	18 (72%)
Stage IVa	4 (16%)	4(16%)
Stage IVb	1(4%)	3 (12%)

Radiotherapy dose > 66 Gy up to 70 Gy was received by most of the patients in both the groups and higher in the younger population (96% vs. 88%), although compared between two groups, it is found to be statistically not significant. Compliance for concurrent chemotherapy was significantly poor in Group B patients (p = 0.041). The cumulative dose of cisplatin is higher in Group A (Table 3).

Hemoglobin and platelet toxicities were higher in group B, which was statistically significant (0.04 and 0.036). Grade II creatinine toxicity was higher in Group B patients, although statistically not significant (P = 0.073) shown in Table 4.

When compared in two study groups, no difference was found in acute skin toxicity. Grade III/IV toxicity was higher in group B (44% vs. 32%) but not statistically significant. One patient of group B had acute grade II xerostomia. In group B, no acute xerostomia was observed (Tables 5 and 6).

No statistical significance was observed in tern of clinical response in 6 months stage response evaluation between two groups (Table 7).

DISCUSSION

A longer life expectancy will lead to a higher cancer burden for elderly people in the coming decades. Presently, under-representation and under-treatment of elderly cancer patients is an alarming issue that has not been investigated sufficiently till date, particularly in Indian cancer patients. This study aimed to assess profiles of elderly patients of head and neck cancer and compare these profiles with younger patients of head and neck cancer in terms of compliance, toxicities, and outcome.

Table 3: Compliances of radiotherapy and chemotherapy

Radiotherapy dose	*Group A n (%)*	*Group B n (%)*	*P value*
< 66 Gy	1 (4%)	3 (12%)	0.29
66–70 Gy	24 (96%)	22 (88%)	
Number of concurrent chemotherapy cycle			
≤ 5 cycles	6 (24%)	13 (52%)	0.041
6–7 cycles	19 (76%)	12 (48%)	
Mean Cumulative Dose	225.4 mg	200 mg	0.77

Table 4: Hematological toxicities

	Group A n (%)	*Group B n (%)*	*P value*
Anaemia			
Grade I/II	9(36%)	16 (64%)	0.04
Grade III/IV	0 (0)	0 (0)	-
Neutropenia			
Grade I/II	3 (12%)	0 (0%)	0.07
Grade III/IV	0 (0%)	1 (4%)	0.31
Thrombocytopenia			
Grade I/II	0(0%)	4 (16%)	0.036
Grade III/IV	0 (0%)	0 (0%)	-
Nephrotoxicity (serum creatinine) toxicity			
Grade I/II	0 (0%)	3 (12%)	0.07
Grade III/IV	0 (0%)	0 (0%)	-
Hepatotoxicity (Serum Bilirubin)			
Grade I/II	0	0	-
Grade III/IV	0	0	-

Patient-related Factors

Gender

In study of Augusta *et al*.. patients were mostly males, 77.4% within the geriatric group and 91.4% among younger patients group.[12] In a retrospective study of Wasil *et al*.. on a total of 183 patients, the male to female ratio was 1:1.[13] Kuriakose *et al*. in his study found that in patients younger than 35 years old, oral SCC occurred

Table 5: Acute radiotherapy reactions

	Group A n (%)	*Group B n (%)*	*P value*
Skin Reactions			
Grade I/II	24 (96%)	24 (96%)	1.0
Grade III/IV	1 (4%)	1 (4%)	1.0
Mucosal Reactions			
Grade I/II	17 (68%)	14 (56%)	0.38
Grade III/IV	8 (24%)	11 (44%)	0.38
Xerostomia			
Grade I/II	0 (0%)	2 (8%)	0.41
Grade III/IV	0 (0%)	0 (0%)	-

Table 6: Late reaction (Mild to moderate vs. Severe)

	Group A n (%)	*Group B n (%)*	*p-value*
Laryngeal toxicity			
Grade I/II	4 (16%)	1 (4%)	0,15
Grade III/IV	0 (0%)	0 (0%)	-
Skin toxicity			
Grade I/II	2 (8%)	0 (0%)	0.14
Grade III/IV	1 (4%)	2(8%)	0.54
Mucosal toxicity			
Grade I/II	11 (44%)	5 (20%)	0.068
Grade III/IV	0 (0%)	2 (8%)	0.14
Xerostomia			
Grade I/II	8 (32%)	4 (8%)	0.18
Grade III/IV	0 (0%)	1 (4%)	0.31

Table 7: Disease status at the end of 6 months

	Group A n (%)	*Group B n (%)*	*p-value*
Complete response	15 (52%)	13 (52%)	0.28
Partial response	4 (16%)	8 (32%)	0.18
Stable disease	0 (0%)	0 (0%)	-
Progressive disease	6 (24%)	4 (16%)	0.23

more commonly in females.[14] In the present study, 46 patients were male (92%), and only 4 were female (8%). Individually in both the Groups male patients are predominant (88% vs. 96%). However female: male ratio is slightly higher in younger group. No significant correlation was found between age and gender in clinical outcome.

In contrast to study of Augusta *et al..*,[12] we had fewer females in elderly group in comparison to younger group. This skewered male to female ratio can be explained by the very low incidence of tobacco products intake in the women of the region, lack of awareness, literacy and negligence about women health in families. All four females in our study had oral cancer.

Symptoms

Infante-Cossio *et al.* in their study they observed that patients < 65 years showed more clinical symptoms and In patients >65 years, fatigue and constipation and dry mouth and sticky saliva obtained the highest scores.[15] Derks *et al.* found that at the base line of 3 months there was no association between pain and age.[16] In present study, we observed that pain was the commonest symptom in both the groups. However, in the younger population, pain was the more common symptom while hoarseness of voice and difficulty in swallowing was the more common in elderly group. Presenting symptoms were higher overall in the elderly group of the study group as per literature mentioned above. This scenario can be due to late presentation of the elderly group.

Co-morbidity

Bøje *et al*. observed that co-morbidity did not influence cancer-specific death in elderly patients.[17] In a study of Sarini *et al*.,[18] there were no differences in co-morbidities between younger and elderly groups of the study. In a study of Marc *et al*., more co-morbidity showed to be independent prognostic factors for mortality.[19] In our study, the elderly group had overall higher co-morbidities. (Diabetic = 36% vs. 20%) (Hypertension= 20% vs. 16%) (Tuberculosis = 28% vs. 16%). No significant correlation was found between age and co-morbidity in terms of clinical outcome in our study. In contrast to Sarini *et al*.[18] co-morbidities were higher in elderly group of our study group, this is due to poorer metabolic activity and relative functional impairment in elderly patients.

Personal History

Jeffrey *et al.* showed that smoking and drinking were lower in young when compared with older adults.[20] Kuriakose *et al*., in their study, found that in patients older than 60 years of age, oral carcinoma was always seen associated with smoking, alcohol or pan chewing.[14] In the present study, in comparison to a younger group, elderly group had a higher frequency of smoking (72% vs 60%) tobacco addiction (84% vs 72%), and alcohol consumption (24% vs. 20%) singly or in combinations. Our study found no significant correlation between age and co-morbidity in clinical outcomes. The results of our study were similar to the studies mentioned above it may be due to more stress or more social and emotional burden on elderly group.

Site

Jeffrey *et al.* observed that the young group had a higher proportion of oral tongue cancer, unspecified oral cavity/ oropharynx cancer, and a lower proportion of larynx cancer than older adult cases.[20] Augusta *et al.* found that the most frequent tumor locations were similar in both younger and elderly group: larynx, oral cavity, and oropharynx - base of the tongue.[12] Kuriakose *et al.* found that the tumors manifested predominantly as invasive lesions affecting the tongue in young females <35 years.[14] In the current study, site wise distribution was almost equal in both the groups. Oral cavity (28% vs. 28%), oropharynx (32% vs. 36%) and larynx (40% vs. 36%). Hypopharyngeal carcinoma was not present in either of the group coincidentally. Our study found no significant correlation between age and primary site in terms of clinical outcome. In contrast to the above study, laryngeal carcinoma was slightly more common in younger group in our study group, it may be due to the frequency of gutka chewing is higher in this study area.

Tumor ' T ' Stage

Jones *et al.* found that older patients tended to have significantly more advanced diseases at the primary site. They also observed that tumor-specific 5 years survival of patients with head and neck cancer was higher in the younger group.[21] In the present study Group A, 4% of patients had T1 lesion, 40% of patients had T2 lesion, 44% of patients had T3 lesion, 4% of patients had T4a lesion, 8% of patients had T4b lesion, and in Group B, 8% of patients had T1 lesions 32% of patient had T2 lesion, 60% of patient had T3 lesion. T4a and T4b lesion were not present in Group B. There was no significant difference between elderly and younger patients in our study in terms of T staging. Our study found no significant correlation between age and early or late tumor 'T' stage in terms of clinical outcome. In contrast to the above study, patient withT4 stage is presented only in the younger group. It may be due to the aggressive pathology of those patients.

Nodal Status

Jones *et al.* found that older patients tended to have significantly more advanced disease at the primary site

and fewer neck node metastases when compared with younger patients at presentation.[21] In this study, Group A 32% of patients had N0 lesion, 36% of patients had N1 lesion, 28% of patients had N2 lesion, 4% of patients had N3 lesion, and in Group B, 52% of patients had N0 lesions, 20% of patients had N1 lesion,16% of patients had N2 lesion, and 12% of patients had N3 lesion. No significant correlation was found between age and nodal status at presentation in terms of clinical outcome in our study. Our study observed that node-negative patients were more in elderly patients at presentation, as mentioned in the above study, which can be due to the slow progression of disease in elderly patients.

AJCC Stage

As per Marc *et al*., higher tumor stages showed to be independent prognostic factors for mortality in an elderly group of their study.[19] Sarini *et al*. found no differences in TNM stage grouping between the two groups.[18] Barzan *et al*. revealed that stage appeared to be the most important prognostic factor concerning survival.[22]

In our study Group A, no patient had 80% of patients had stage III lesion, 16% of patients had stage IVa lesion, and 4% had stage IVb lesions. In Group B, 72% of patients had stage III lesion, 16% of patients had stage IVa lesion, and 12% had stage IVb lesions. No significant correlation was found between age and nodal status at presentation in terms of clinical outcome in our study. As per Sarini *et al*., there is no significant difference is present in terms of stage of presentation between elderly and younger group in our study.[18]

Compliances

Radiotherapy Compliances

Derks *et al.* observed that the age itself independently influences treatment choice. Wasil *et al.* concluded that radiation therapy could be safely administered to an elderly population with both curative and palliative intent with the expectation of completion in more than 80% of patients.[23] Bourhis at el in his study told that There was a benefit on locoregional control in favor of altered fractionation versus conventional radiotherapy more in younger patients but not in older patients.[24]

In our study, radiotherapy seems to be well tolerated by younger as well as an elderly group of patients. In Group A, 96% of patients and in Group B, 88% of patients received ≥66 Gy of RT dose. There was no significant correlation between age and clinical outcome at radical RT dose delivered to both groups. Compared with Wasil *et al*., in our study, 88% of elderly groups completed planned radiotherapy in our study.[13]

Overall Treatment Time

José *et al.* in his extensive bibliographic search observed a strong significant relationship between OTT delay and LRC and/or OS exists, and delays in RT may result in an average loss of LRC ranging from as low as 1.2% per day to as high as 12–14% per week.[25] In the present trial, overall treatment time for Group A and Group B was 52 days and 54 days, respectively. In our study, the correlation between OTT and clinical response observed that complete response was decreased when OTT>51 days (67% vs.56%). No significant correlation was found between differences in the clinical outcome based on age between both groups.

Chemotherapy Compliance

Meta-analysis of chemotherapy in head and neck cancer (MACH NC) There was a significant OS advantage for patients up to 70 years old, but not for patients 71 and older.[26] Argiris *et al*. suggested benefit of concurrent chemo-radiotherapy was age-dependent, with the largest benefit in patients younger than 60 years of age.[8] Jasenka *et al*. concluded that the ability of older patients to cope with chemotherapy is comparable to younger ones, particularly when adequate supportive care is provided.[27]

In our trial, there was a significant difference found between elderly and younger group regarding chemotherapy compliance (P = 0.041). In Group A, 24% of patients and Group B, 52% of patients failed to receive ≥5 cycles of concurrent chemotherapy during treatment. The cumulative dose of concurrent chemotherapy was less in group B than longer patients. Increased chemo-related toxicities can explain it in group B. As same mentioned in above literature in our study clinical complete response was decreased in younger patients (33% vs. 68%) but in contrast to literature it was increased in elderly group (58% vs. 62%). It can be due to increased chemo-induced toxicities in patients, leading to increased overall treatment time.

Hematological Toxicities

Argiris *et al.* analyzed combined data and concluded that higher incidence of grade 3 to 4 thrombocytopenia.[8] Balducci *et al.* concluded that elderly patients were more susceptible to chemotherapy-induced myelotoxicity.[6] In our study, grade I/II anemia and thrombocytopenia was observed as higher hematological toxicity. Grade II amenia was significantly higher (20% vs. 48%; p = 0.036) in elderly group. Grade II thrombocytopenia is also significantly higher (0% vs 16%; p-value = 0.036) in elderly group. Grade III/IV anemia and thrombocytopenia were absent in both groups. It is because of supportive care provided during treatment as soon as toxicities were noticed. Otherwise, Grade I/II could eventually lead to

higher toxicity observed in group B. As mentioned in the literature, hematological toxicities were higher in elderly patients in our study group.

Nephrotoxicity

Sekine *et al*.[28] reported that patients with nephrotoxicity are older than those without nephrotoxicity and concluded age as a risk factor for nephrotoxicity. Argiris *et al.* found that elderly patients had a higher incidence of grade 3 to 4 renal complications.[8] In our study nephrotoxicity was observed only in elderly patients (12% vs 0%). However, it was statistically non-significant (p=0.07). The differences in clinical Outcomes were also non-significant statistically. As the literature mentioned, nephrotoxicity was higher in the elderly group in our study.

Skin Toxicity

Machtay *et al.* observed significant variables correlated with the development of severe late toxicity were older age.[29] Ortholan *et al.* concluded that in elderly population, radiotherapy of oral cavity might have a high acute and chronic toxicity.[9] In our study, there was no difference in acute skin toxicity between Group A and Group B. Grade III/IV late skin reaction was found slightly more in the elderly group (8% vs.4%) as mentioned in the above literature.

Mucositis and Laryngeal Toxicity

Argiris *et al.* found that elderly patients with head and neck carcinoma treated with chemotherapy had a higher incidence of grade 3 to 4 stomatitis than younger patients.[8] Elderly patients with recurrent or metastatic head and neck cancer sustained increased toxicities with cisplatin-based doublets. However, they had comparable survival outcomes compared with younger patients.[8] As same as the above study, our study also observed grade III/IV toxicity was higher in elderly group (44% vs.32%). Late oral mucositis is more in group A (20% vs. 16%). Late laryngeal toxicities were higher in group A (16% vs 4%) in our study.

Xerostomia

Dirix *et al.* have concluded that they found most patients (93%) suffered from a dry mouth, and 65% had moderate to severe xerostomia.[30] In contrast to the above study, acute xerosomia was present in only one patient of group B and late toxicity was observed in both groups A and B (32% vs. 20%). Our study observed that radiotherapy compliance was similar in the elderly group as in the younger group. Our study also observed that though chemotherapy compliance in terms of the number of cycles was lower in elderly patients than younger patients due to increase hematological toxicities, they were of grade I/II. No significant difference of sever Grade III/IV toxicity was observed in elderly group in comparison to younger group.

CONCLUSION

Overall, Increase toxicities were seen in elderly group. Optimization of the treatment plan and increased supportive care may help decrease toxicities and unwanted hospitalization of elderly patients, ultimately improving the clinical outcome of treatment. We suggest that elderly patients can be treated with concurrent chemo-radiotherapy if good supportive care is supplemented to overcome treatment-related toxicities.

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