Utility of Mucositis Predictive Tools in Patients Receiving Chemo Radiotherapy for Various Indications

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Authors' contributions

This work was carried out in collaboration among all authors. Authors AVSS, SSS, PSD, CHMV contributed for the subject management and content writing and accuracy. Author RS helped in the biostatistics and manuscript complication. All authors read and approved the final manuscript.

Article Information

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ABSTRACT

Background: Mucositis is a debilitating and a common complication in patients receiving Chemo radiotherapy with varying incidence and severity. Certain clinical factors are associated with the incidence and severity of mucositis in different patient populations. Early prediction tools using such clinical factors may help the clinician to adopt various preventive strategies in high risk subjects.
Aim : To assess the utility of two different tools in terms of predicting mucositis of varying severity.
Methods- We conducted a prospective observational (non intervention study) with a total of 438 patients from Jan 2019 till Nov 2020 & followed up-to April 2021 using two published tools for predicting the severity of mucositis.
The population consists of head and neck squamous cell cancer patients , assigned to receive chemoradiotherapy and classified into three risk groups , low , intermediate and high , using the above mentioned tools . They were followed up to determine the incidence and severity of mucositis.

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Results: The study results show that the incidence of grade III/IV mucositis in the low risk group is 9.8% ,the intermediate risk group is 55.2% and the high risk group is 93.3% all of which is consistent with literature as well. There is no difference between the two tools in terms of predicting the incidence and either of them can be used in risk stratifying the subjects.

Conclusion: Identifying high risk patients before the start of chemoradiotherapy for predicting mucositis can help the clinicians adopt strict preventive measures to prevent or reduce the severity of the serious adverse effect and thus improving the quality of life through the treatment and also avoid treatment interruption.

1. INTRODUCTION

Chemoradiotherpay is the mainstay of treatment in the majority of patients with head and neck squamous cell carcinoma. Majority of these patients develop an inflammatory response of the mucosal epithelium, called mucositis, a painful adverse effect , the incidence of which ranges from 40-90% depending on a host of clinical features [1]. Interruption of antineoplastic treatment for high-grade mucositis is attributed in 19% of all cases, which adversely impacts the treatment outcomes in terms of overall and progression free survival [1,2]. It has a varied pathophysiology with conflicting biomarker results published across the globe, making interventions and preventive guidelines difficult to establish and validate [3,4,5,6,7,8,9].

The severity of mucositis varies from a mild presentation of mucosal erythema and a burning sensation to a very severe presentation as confluent, deep, and devastatingly painful ulcerations of oral mucosa. [8] The Mucositis is graded based on CTC criteria [10] and is used to monitor the response to therapeutic interventions .

The established risk factors for mucositis are classically divided into modifiable and non modifiable. The non modifiable risk factors can be further divided into patient related, treatment related and malignancy related as listed below [3,4,5]

In view of the significant impact of mucositis on cancer outcomes, various authors attempted to predict its development based on the genetic markers, biomarkers and simple clinical parameters [3,4,5,6,7,8,9]. While the advanced markers are cumbersome and not universally available, we chose two of the indigenously developed scoring/predicting tools (both done on retrospective data) and validate them on prospective subjects to see the clinical utility in real time.

When we closely take a look into the two different tools, which used the clinical and routinely used labs, there were only subtle differences in the values, and the major difference is in the anatomical site of origin.

According to Attili et al the striking difference in its incidence among different patients receiving same protocol often makes the decision difficult to adopt preventive strategies. Head and neck cancer, being one of the most common malignancy in Indian subcontinent [4], we adopted to choose the tool developed by them for prospective valiadation. We also undertook a similar tool developed by Devaraj eta al [5] for comparison.

Table 1. Factors affecting incidence and severity of mucositis

Patient related	Treatment related	Tumor related
F>M	Dose dense chemotherapy	Head and neck site
Ages<20 and >60	Dose intensive therapy	Stage II and above
Co morbid conditions (especially diabetes)	High dose chemo/ stem cell transplant	Bulky nodal disease
Poor oral hygiene	Radiation doses>60gy	High grade tumors
ECOG performance status	Those involving large RT fields	Those having invasion
BMI or weight	Hypo &Hyper fractionated RT	Squamous etiology
Tobacco use	Conventional 2 D (vs IMRT/ IGRT)	

2. METHODS

The ethics committee permission (central EC, Hyderabad, India) has been taken to conduct this non interventional observational study to determine the utility of the models (developed by Devaraj et al [4] and Attili et al. [5] in predicting mucositis in subjects receiving definitive Chemoradiotherapy for squamous cell carcinoma of head and neck regions.

The key eligibility criteria include :

a) Age 18-65 years
b) Patients with proven Squamous cell head and neck malignancy
c) Clinically assigned by the treating physician for "curative intent" and planned for the chemoradiation (cisplatin 40 mg/m2 /week along with local radiation of 60-70 Gy depending on primary site) or high dose chemotherapy.
d) Adequate renal, hepatic and bone marrow reserves.
e) ECOG PS <3

The flow of the selected patients is described in Fig. 1 to elaborate the above selection criteria.
The scoring system recommended by the respective authors , in their publication was followed. To elaborate, the criteria included were as follows:

Age>40years, ECOG PS > 2 ,WBC < 3000/μl, elevated ESR, Albumin<3gm/dl, stage III disease or more, presence of more than one co morbid conditions. A score of 1 was assigned for the above mentioned risk factors. [4,5] Subjects were prospectively classified into Low risk (score less than 3), Intermediate risk (score of 4-6) and high risk (score of more than 6).

A total of 438 patients were enrolled for initial screening with a study period of 18 months from Jan 2019 till Nov 2020 & were followed up till April 2021.

The sample size was determined to look for the non inferiority of the two tools among each other, which was 312. However later we continued to recruit as many subjects till the Nov 2020. We used both the tools to predict the severity of mucositis and the results were compared. P value of <0.05 was considered to be significant

3. RESULTS AND DISCUSSION

The demographics of the subjects were detailed in Table 2. To summarize, there were more males, which is in lines with existing incidence pattern of India [11], the stage distribution, tobacco consumption and co morbidities are also in lines with the national reported data hence we feel that the sample may be a true representation of the disease presentation pattern and further sub setting was not performed.

The selection of the patients and the outcomes are delineated in the Fig. 1 as mentioned below
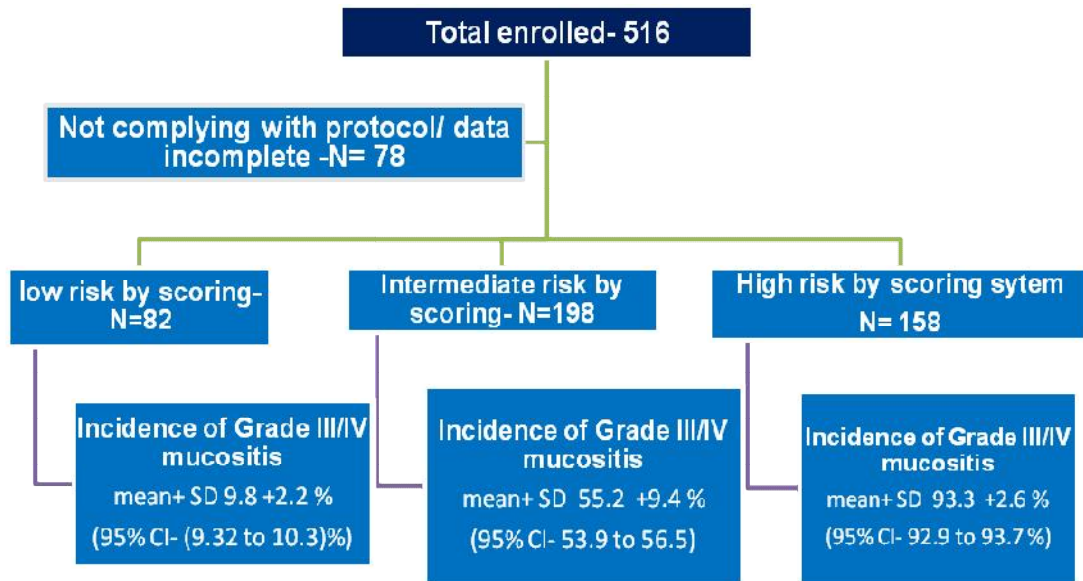

Fig. 1. Flow of the selected patients with scores

Table 2. demographic data of the subjects

Age (mean ± SD)	48 ± 12 years
Ratio men: women	3.29 : 1 (336:102)
Stage of disease, n (%)	
I	11.4% (50/438)
II	23.3 % (102/438)
III	41.6% (182/438)
IV (A)	23.7% (104/438)
ESR (mean ± SD)	28 ± 12 in 1st hour
WHO performance status, n (%)	
1	46.3% (203/438)
2	40.1% (176/438)
3	9.1 % (40/438)
4	4.3 % (19/438)
Serum albumin (mean ± SD)	3.1 ± 1.3 g/dL
Tobacco use, (%)	50.6 %(222/438)
Co morbid conditions, n (%)	46% (202/438)

Table 3. Comparison of tools for predicting the mucositis

Comparison of tools				P value
Group	Score	Mucositis prediction - tool 1	Mucositis prediction - tool 2	
High	6–8	Grade I/II-(10/158)-6.3%	Grade I/II-(12/158)-7.6%	NS
		Grade III -(41/158)-25.9%	Grade III-(36/158)-22.8%	
		Grade IV -(107/158)-67.8%	Grade IV-(110/158)-69.6%	
Intermediate	3–5	Grade I/II-(89/198)-44.9%	Grade I/II-(88/198)- 44.4%	NS
		Grade III -(77/198)- 38.8%	Grade III-(81/198)-40.9%	
		Grade IV-(32/198)- 16.2%	Grade IV-(29/198)- 14.6%	
Low	<3	Grade I/II-(74/82)-90.2%	Grade I/II (73/82)- 89%	NS
		Grade III (6/82)- 7.3%	Grade III (7/82)-8.5%	
		Grade IV (2/82)- 2.5%	Grade IV-(2/82) -2.5%	

3.1 Discussion

There were few literatures which had a deeper look into the management strategies of the mucositis in head and neck cancer patients reported [12], but none of them looked into the predicting tools, excepting a few [4,5]. There is an immense need for the clinicians to have one handy tool for the same and we undertook this study to verify which one is netter

In the present study patients had a mean age of 48 years and majority were males, wich is higher compared to tose of Attili et al, where the median age was 34 years. [4]. This might be due to tobacco consumption habits which typically starts in the teenage in the earlier study, which was conducted in a RCC, which see more patients from lower socio economic strata compared to the present study, which was done at privates setting. The co morbid conditions of the present population is higher than those reported by other authors, probably owing to the median age being older age [4,5]

The study results show that in subjects where the score is less than 3, the incidence of gradeI III/IV mucositis is 9.8 +2.2 % (mean+ SD) with a 95% CI- (9.32 to 10.3)%. And there is no large difference in either of the tools used to stratify the subjects

For those subjects who were classified into intermediate risk by either of the scoring systems, which again have practically no difference in the predictions only 55.2 % of the subjects have grade III/IV mucositis, mean+ SD 55.2 +9.4 % and 95% CI- 53.9 to 56.5, which though is a good marker, but the clinical decision making may sometimes be challenging in adopting the aggressive prophylaxis for these cases.

However for those who were classified as high risk by either of the scoring system, have truly higher incidence of Grade III/IV mucositis with mean+ SD values of 93.3 +2.6 % and 95% CI- 92.9 to 93.7 %

Though our tool is not very discriminative for predicting the Grade III/IV, it can surely classify the patients into Grade I/II vs. Grade III/IV, which itself is quite useful in clinical practice

In lines with the results from Attili et al who found a positive correlation between the markers of local immunity (total WBC counts, co morbid conditions, tobacco use, nutritional status as reflected by the albumin levels), markers of inflammation (ESR which indicate ongoing damage) and markers of healing capacity (performance and nutritional status and co morbid conditions) with the severity and incidence of mucositis, our results were also in the similar lines re-confirming the hypothesis of the tool being accurate [4]

4. CONCLUSION

The positive and negative predictive values are more than 90% making either of the tools equally useful in clinical practice to risk stratify the patients prone to develop treatment related mucositis which would help clinicians to adopt preventive strategies and the planned interruptions of therapy without compromising on the oncology outcomes.

Between the two tools used, we could not find any difference in terms of predicting mucositis making both equally efficacious for clinical use. The results of the present study suggested that we could successfully validate the clinical utility of the existing tools in predicting mucositis in patients receiving either high dose chemotherapy or on chemoradiotherapy.

LIMITATIONS

While it is accepted that biomarkers and genetics may be better predictive tools, the scant availability of these tests makes their clinical utility limited universally [6,7]. The present tools are a simple combination of physical and widely available routine lab tests and an App/calculator would be handy for the oncologists in their daily practice.

CONSENT

All authors declare that 'written informed consent was obtained from the patient for publication of this case report and accompanying images.

ETHICAL APPROVAL

"All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki."

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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