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'SMART'-Simultaneous Modulated Accelerated Radiotherapy:Do we have a feasible alternative for managing locally advanced head and neck cancer during the COVID19 Pandemic?

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Abstract

Background: *The global COVID19 pandemic has created immense strain on the radiotherapy community for delivering optimal care for patients with Locally Advanced Head and Neck Cancer (LAHNC). Departments require contingency plans to mitigate the damage caused by prolonged waiting lists, compromised workforce, availability of machines and more importantly risking infection to immunocompromised cohort of cancer patients.*

Objectives: *Interval analysis of a study evaluating the potential of 'SMART' in providing an effective shorter radiotherapy protocol with manageable toxicity when compared to the standard conventional fractionation of 70Gy in 35 fractions over 7 weeks at 2Gy per fraction along with concurrent chemotherapy.*

Materials and Methods: *Thirteen patients randomised to receive 'SMART' treatment of 60Gy in 25 fractions versus IMRT with Simultaneous integrated Boost (SIB) 70Gy in 35 fractions with concurrent platinum based chemotherapy.*

Conclusion: *'SMART' may provide a potentially effective protocol to manage LAHNC with a safe and shorter treatment when limitations towards delivering concurrent chemoradiation exist.The 'SMART' protocol showed comparable cytoreduction and toxicity in terms of grade3 mucositis and dysphagia to the standard arm. There was no interval break due to toxicity in the 'SMART' arm and all patients could complete treatment within 5weeks.*

Keywords: *Hypofractionation, COVId-19, Head and neck cancer*

Introduction

As the COVID19 pandemic widens its outreach, the burden on the oncology community to provide optimal cancer care is also escalating. Head and Neck Squamous Cell Carcinoma (HNSCC) provides several unique problems. The immunocompromised [1]state and associated comorbidities associated with long years of tobacco[2] exposure put these patients at higher risk for COVID19 infection as well as life threatening respiratory complications[3]. The standard of care for inoperable Head and Neck Cancer is concurrent chemoradiation with platinum based chemotherapy[4]. The problems involved in providing this would be the 7 weeks of risk of exposure to the oncologist and health care providers.

The need for Concurrent chemotherapy can also compromise the patient's immunity and increase the pre existing risk of infection (1). Most international and national associations including ASTRO, ESTRO and NHS have recommended the use of hypofractionated schedules when clinically feasible to mitigate the situation. However the scope for hypofractionation in the radical management of LAHNC is limited[5]. As a part of a planned research project, a randomised trial to evaluate the efficacy of a shorter more intense treatment with 'SMART'[6] Simultaneous Modulated Radiotherapy compared to the standard of care concurrent chemoradiation with IMRT[4] was initiated in october 2019. The study arm was planned to receive 60Gy in 25 fractions over a period of 5weeks, that is 2 weeks more condensed than the standard of care which received conventional fractionation of 70Gy in 35 fractions over 7 weeks. In the current COVID19 such a protocol had the potential to provide a temporary expedient to mitigate the long waiting list and acute shortage of manpower and treatment machines. The authors in the article look into the efficacy and safety profile of this shorter regimen compared to standard chemoradiation.

Materials and Methods

Patient selection

This was a randomised open labelled clinical study approved by the Clinical Ethics Board.Random allocation made using computer designed random numbers. The study was proposed to evaluate 40 patients to be randomised to receive 60Gy in 25 fractions with 'SMART or Intensity modulated radiotherapy [IMRT] of 70Gy in 35 fractions. Both regimens would employ simultaneous integrated boost(SIB)[7] and concurrent chemotherapy with a weekly platinum based regimen. The inclusion criteria

considered patients with locally advanced non metastatic, stage III/IV Head and Neck Cancer between 18-70years of age, ECOG[8] performance status of ≤ 2 and no prior history of malignancies.

Response assessment by contrast enhanced CT scan was scheduled at mid treatment, end of treatment and 6 weeks post treatment in the both arms. The authors have done an interval analysis of thirteen patients enrolled in this study to evaluate the efficacy, toxicity and practical utility of considering this shorter protocol as a clinical option during COVID19 scenario.

Radiotherapy treatment plan

All patients were contoured so as to have the clinical target volume [CTV1]to include the gross tumour volume[GTV] and 5mm margin for primary disease cropped to anatomical borders. The CTV2 included high risk areas and was separately created with a 1 cm margin for primary disease. The CTV2 and CTV3 for nodal regions represented areas of high risk and low risk microscopic disease respectively.The standard treatment arm(control) would receive a model dose prescription of 70, 63 and 56Gy to the high risk (CTV1),intermediate risk(CTV2) and low risk(CTV3). For the study arm the corresponding values for CTV1,CTV2 and CTV3 were 60Gy,55Gy and 50Gy respectively.Patients were planned with Monaco treatment planning systems version:5.11.02 and treated on Elekta Infinity/Versa HD machine.

Scientific rationale

Accelerated repopulation of tumor clonogens have been postulated as a possible cause of treatment failure[9][10][11]. This anticipated event usually occurs around the 3rd to 5th week[9][12] and by addressing this period with treatment intensification may provide us with a window of opportunity to improve local control. This could either be done with timed dose escalation or reduction in the overall treatment time. The study arm with 'SMART'[6]hopes to achieve this through the latter, while still providing a radiobiologically equivalent dose to the high risk tumor volumes[13][14] After inclusion of anticipated repopulation in Linear Quadratic model the BED of both the study and control arm were comparable (65.9-76.2Gy)versus (66.1-73Gy)[13][14]

Efficacy and Toxicity Evaluation

The focus of interval analysis was comparison of tumor cytoreduction as a surrogate of response and tolerance as well as the need for supportive care to assess suitability of the study arm protocol to be a temporary expedient. As the numbers are too small to conduct a statistical programme,we have used proportion and ratio analysis with frequency tables and graphs to relate the differences between the two arms.

Results

The patients in both the study arm(A) and control arm(B) were comparable in terms of site distribution,stage and volume of disease.Patient characteristics are given in table1.

PATIENT CHARACTERISTICS		
Gender	**Study**	**Control**
Male	6	5
Female	2	0
Stage		
II	0	0
III	2	2
IV	6	3
T Status		
T1,T2	0	0
T3,T4	8	5
N Status		
<-N2a	5	3
<-N2b	7	4
Nodal involvement		
Node absent	2	1
Node present	6	3
Site		

Oropharynx	8	3
Hypopharynx	0	0
Larynx	2	0
Comorbidities		
Nil	8	2
Present	1	2
Pathology		
Grade 1	1	1
Grade 2	4	1
Grade 3	1	1
Grade not specified	2	2
Substance abuse		
Chewed tobacco		
Yes	3	1
No	5	4
Smoking		
Yes	6	5
No	2	0
Alcohol		
Yes	6	5
No	2	0
Atleast 5 cycles of CT(200mg/m2)	3	4
Medial tumor volume including nodal volume		
Total	259.67	191.12
Oropharynx	247.95	185.51
Larynx	11.72	5.61

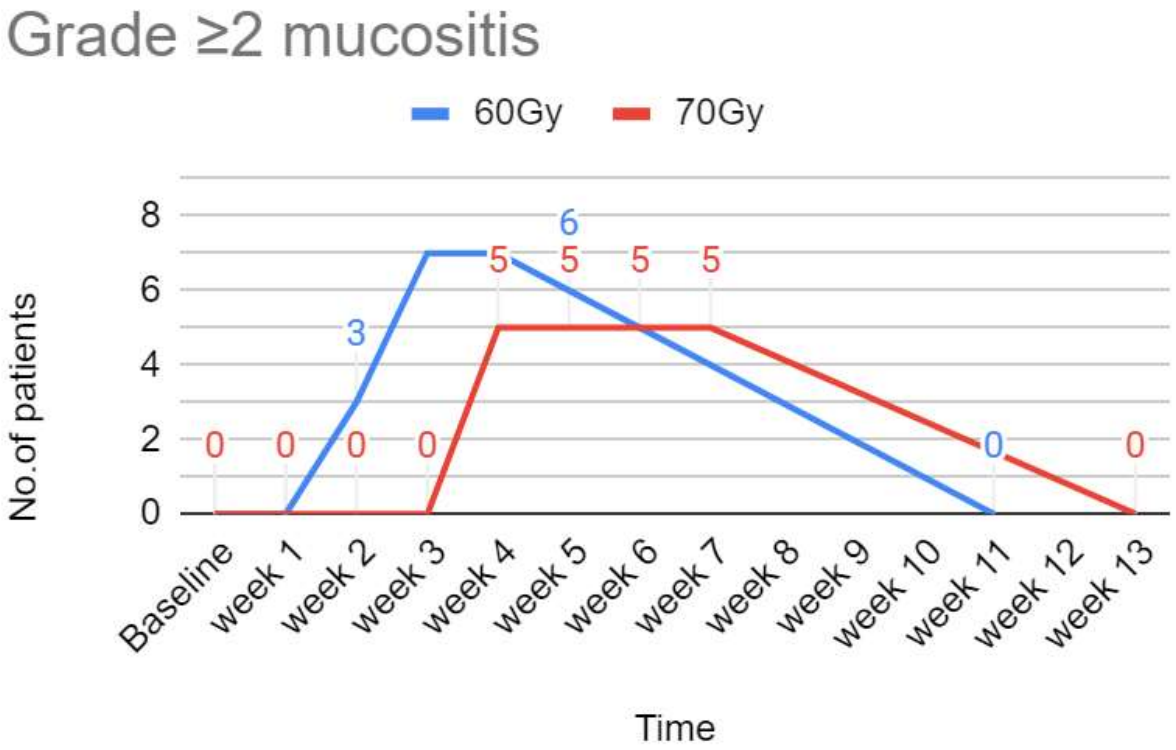
Table 01

Eight patients were randomised to receive 60Gy in 25 fractions with GTV tumor and nodes receiving 2.4Gy/fraction. Five patients received treatment in the control arm (70Gy), however one patient discontinued treatment midway due to social reasons unrelated to toxicity and was excluded from the analysis.

The study cohort completed treatment in a time frame of 34 to 51 days ,median 34 days which was 2 weeks earlier than the control cohort(48-55), median of 51 days. The overall time benefit was 15 days.

All patients were planned to receive weekly Cisplatin of 40mg/m2 concurrent with IMRT. Fifty percent of the study arm and ninety percent of the control arm were able to receive a cumulative dose of at least 200mg/m2of cisplatin. The main toxicities of concern when using a shorter more intense treatment protocol would be acute mucositis, dermatitis, dysphagia and resultant loss of weight. Toxicities were graded with CTCAE version 4**[**15**]**

There was no interruption of treatment in either arm as a result of toxicity.The study arm and control arm had comparable rates of grade2 and grade3 mucositis however it was shown that the onset of grade3



mucositis was earlier in the study arm, beginning at around the 3rd week of treatment. However it was also seen to resolve earlier and did not require assisted feeding dependence as shown in Figure 1.

Figure 01

The most promising aspect of this interim assessment was the pattern of volumetric cytoreduction. The mean mid treatment percentage reduction of GTVp was 80.15% in the study group versus 50.2% in the control. The percentage shrinkage of right and left parotids at mid treatment was almost identical in both groups. The average of the mean shrinkage of parotids in the study group was 29.7% versus 33.65% in the control group.The pattern of dermatitis as well as weight loss were also similar in both arms with no grade3 dermatitis or weight loss greater than 3Kgs. We did observe that the onset of dysphagia was earlier in the study arm and logically correlated to the pattern of mucositis. Interestingly both dysphagia and fatigue also resolved earlier by 2 weeks. As a result the recovery of weight loss was faster and at first follow up the study cohort had a more favorable toxicity profile for all three parameters.The pattern of toxicities are shown in figure 2-5.

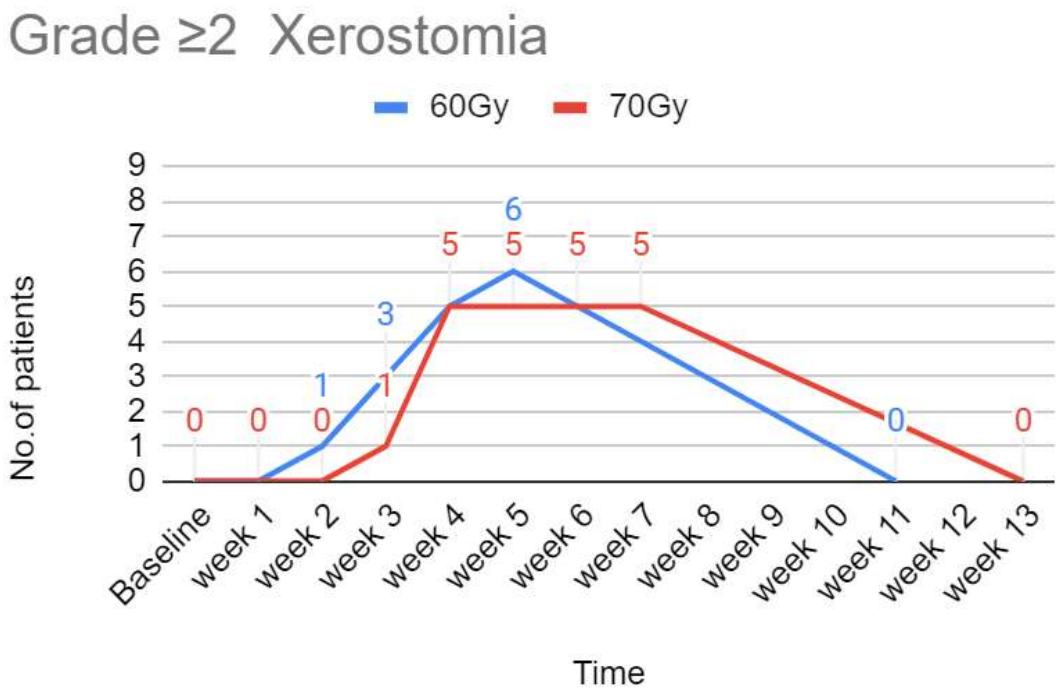


Figure 02

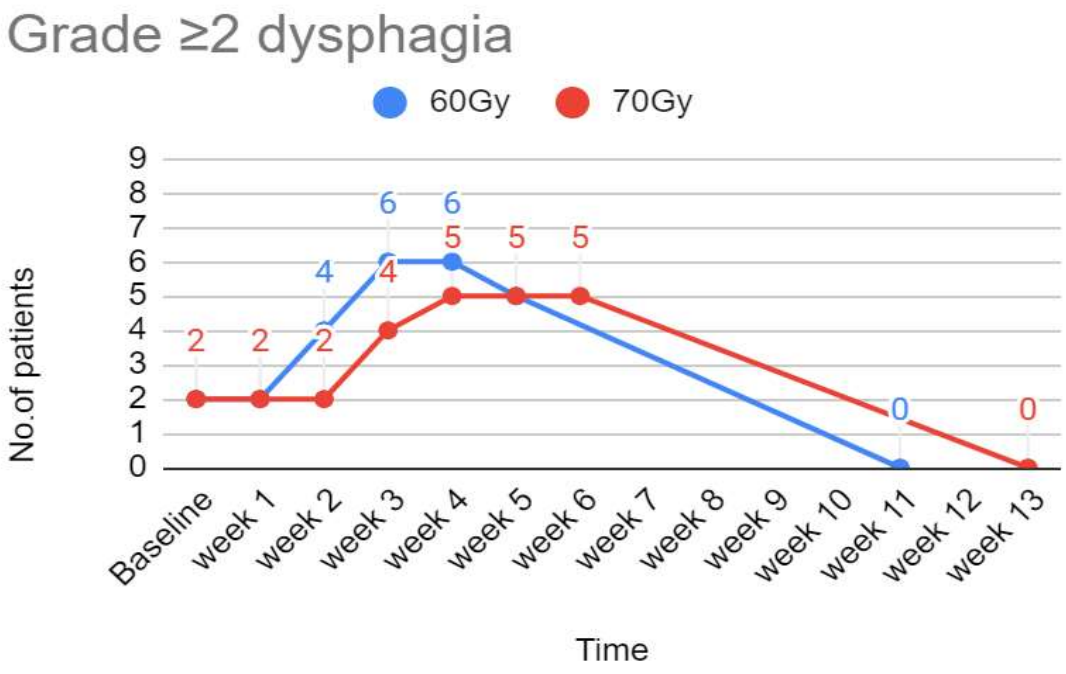


Figure 03

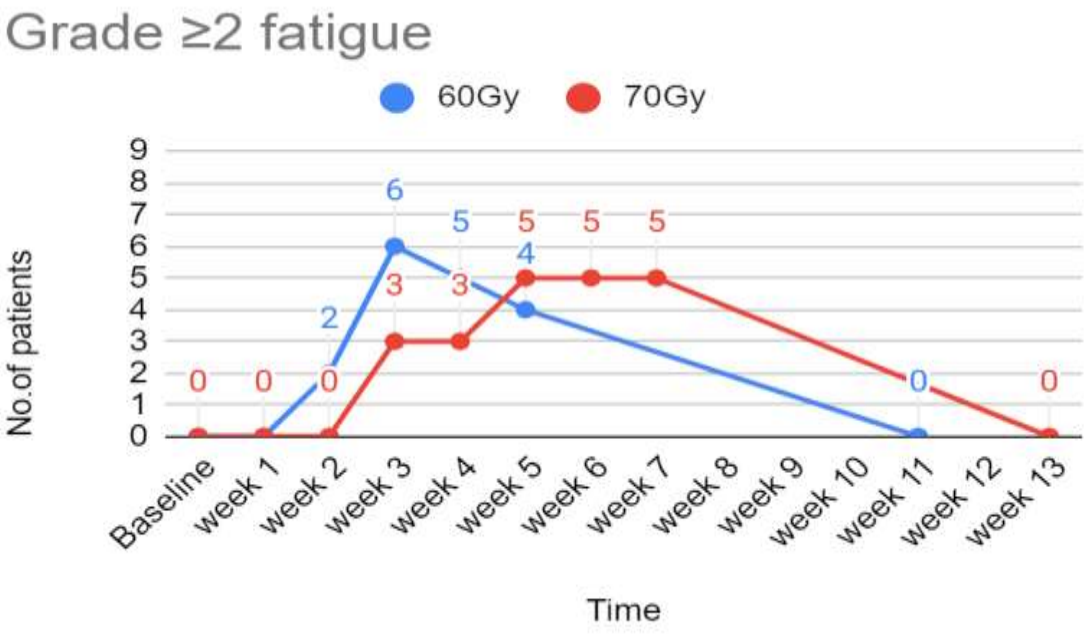


Figure 04

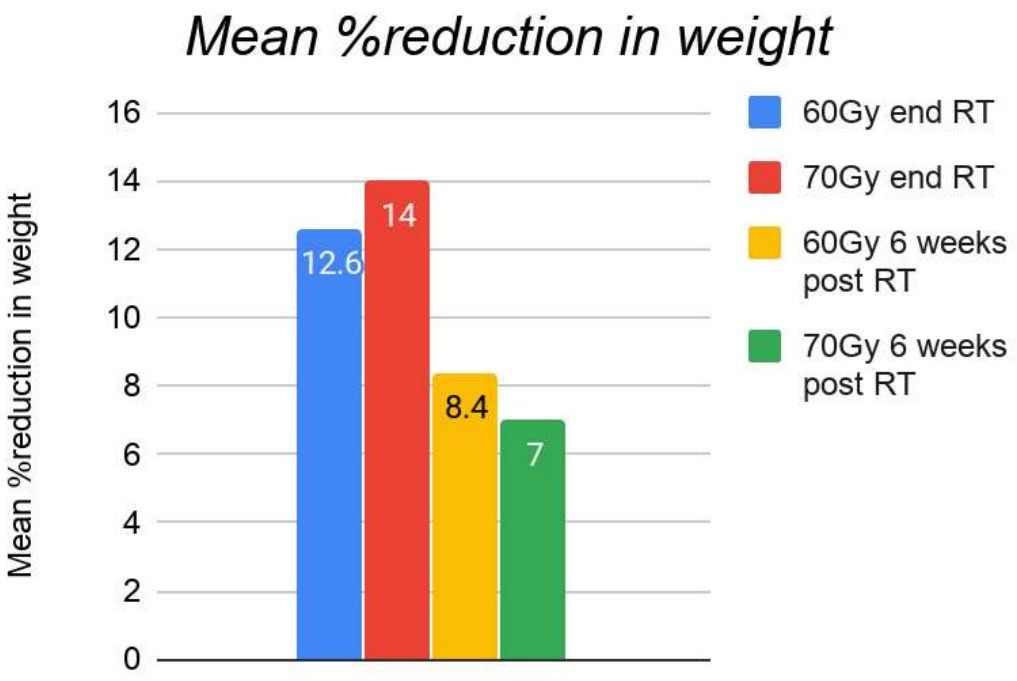


Figure 05

In addition to evaluation of the toxicities, authors have also looked into the tumour response in terms of volumetric cytoreduction at mid-treatment and 6 weeks post treatment in both arms. Even though statistically non-significant, 60 Gy arm showed a numerically greater cytoreduction in both mid (80.15% vs 50.2%) and post treatment scans (90.9% vs 60.45%) as shown in figure6-7.

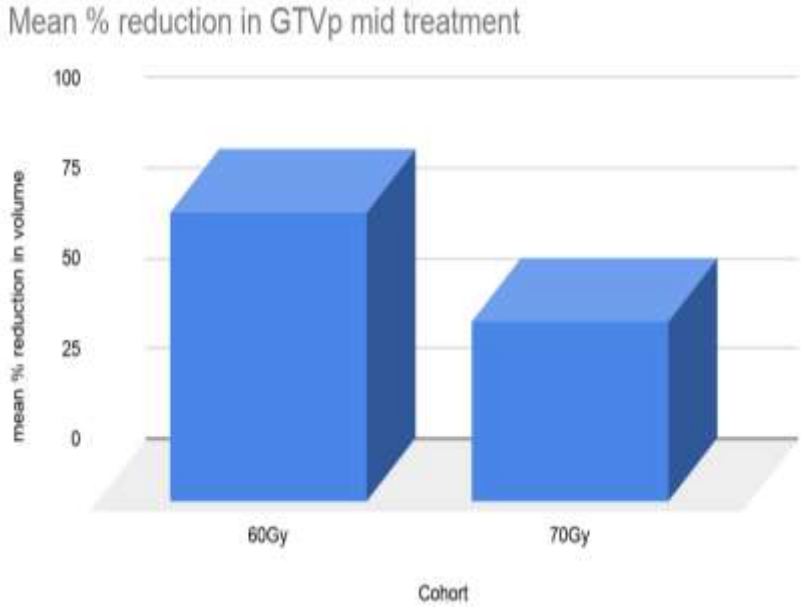


Figure 06

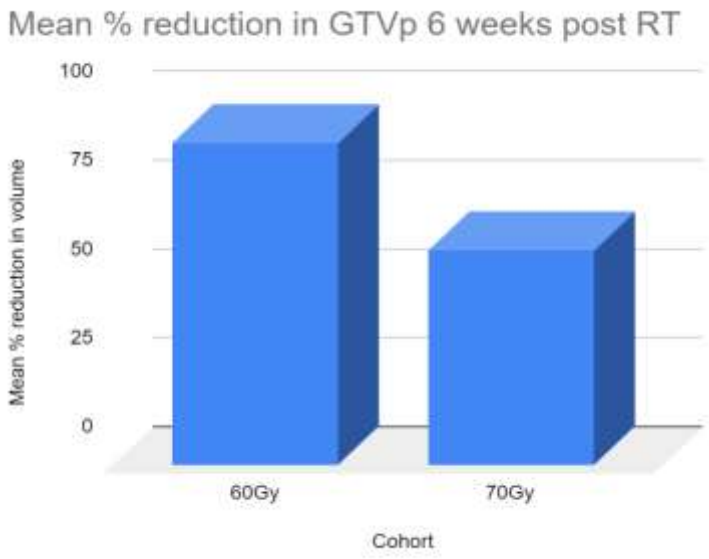


Figure 07

Discussion

In the background of COVID19 pandemic it is vital that we modify our approach to the treatment of patients with considering the risk benefit ratio of the treatment protocol to the risk of infection due to the increased burden of long waiting lists of patients with delayed and interrupted treatment as well as sudden shortage of healthcare resources. This scenario has resulted in many global organisations including ASTRO, ESTRO and NHS recommending the use of shorter treatment protocols whenever feasible. The purpose of this study was to evaluate whether 'SMART'**[**6**]** could safely fit into this recommendation.

Concurrent chemoradiation has been established as the standard of care for the radical management of Locally Advanced Head and Neck Cancer by several meta analysis and is the primary treatment of choice for inoperable stageIII and IV Locally Advanced Head and Neck Cancer**[**4**][**16**][**17**]**. However even with optimal care LAHNC is generally associated with a poor outcome,with 3 year overall survival rates of 40-50%**[**18**][**19**][**20**]**.The past decade has seen considerable advances in head and neck cancer care in terms of wider availability of advanced technology and biology tailored treatment. The current protocol was designed to counter the anticipated accelerated repopulation towards the 4th to 5th week of treatment by reducing the overall treatment time**[**21**]**. Butler et al**[**6**]**were the first to evaluate the efficacy and toxicity of the 'SMART' protocol. The response roles were impressive with 90% of patients showing a complete response and other toxicity parameters comparable with historical controls. Another more recent trial by Sarthak Tandon et al**[**13**]** considered 'SMART'**[**6**]** technique with concurrent chemotherapy. They

evidenced a survival advantage in the study with accelerated treatment: the 2 year PFS was 53.3% versus 80%(p=0.028) and overall survival 60% versus 86.7%(p=0.02)**[**13**]**. No difference in acute toxicities were observed in both arms except for fatigue which was significantly higher in the protracted treatment arm.

The current study was to determine the efficacy and feasibility of using this protocol for reducing the treatment time by 2 weeks while allowing for manageable toxicities. The results of this interim analysis shows that this is possible with the advantage of showing a favourable pattern of enhanced cytoreduction at mid treatment. Hopefully this would herald better outcomes in terms of local control and survival parameters on longer follow up. But most importantly the current treatment may not compromise response compared to the standard of care. The toxicities reported were manageable and did not mandate a treatment break or increase the need for enteral support. The study arm even showed a faster recovery of grade 3 mucositis and weight loss.The comparable shrinkage of parotids in both treatment protocols may act as a surrogate to predict non inferior outcomes in terms of late toxicities.The limitation of small numbers and follow up preclude any inferences in terms of comparison between 'SMART'**[**6**]** and the standard of care of 70Gy in 35fractions**[**4**]**

However the interim analysis suggests the possibility of an effective alternative regimen with scope for further evaluation and future studies.

Conclusion

The 'SMART' radiotherapy technique may provide a shorter clinically effective and safe alternative treatment protocol that can serve as a temporary expedient in managing locally advanced head and neck cancer during the COVID19 pandemic.

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