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Original Article

Oncology Section

Comparison of Sequential Boost and Simultaneous Integrated Boost Volumetric Modulated Arc Therapy in Treatment of Head and Neck Carcinoma: A Prospective Interventional Study

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ABSTRACT

Introduction: Volumetric Modulated Arc Therapy (VMAT) is a radiotherapy in head and neck cancer can be delivered by two boost techniques: Sequential Boost (SEQ) and Simultaneous Integrated Boost (SIB). There is still limited data comparing these two techniques.

Aim: To compare SEQ and SIB planning techniques of VMAT in patients of Head And Neck Squamous Cell Carcinoma (HNSCC) in terms of disease response and acute toxicities.

Materials and Methods: A prospective interventional study was conducted at Geetanjali Medical College and Hospital, Udaipur, Rajasthan, India from January 2019 to December 2020. Total of 52 patients of HNSCC planned for radical chemoradiation were enrolled into two study arms SEQ-VMAT and SIB-VMAT. Chemotherapy was given with weekly cisplatin 40 mg/m^2. Dosimetric comparison was done using Dose Volume Histogram (DVH) analysis. Response evaluation was done as per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 at 8-10 weeks follow-up. Acute toxicity evaluation was done as per Radiation Therapy Oncology Group (RTOG) toxicity grading. Statistical analysis was done using Statistical Package for Social Sciences (SPSS) version 20.0 software.

Results: A total of 52 subjects were included in the study, out of which 26 subjects were in each group. No significant difference was observed in demographic data in terms of age 56.2 vs 53.5 years, sex (24 males and 2 females in both the arms), disease site (oropharynx is the most common site 38.5% in both arms) and stage (IVA 69.2% in SEQ arm vs 46.2% in SIB arm and III 30.8% in SEQ arm vs 42.3% in SIB arm). Dosimetric data was comparable between the two arms. SIB-VMAT shows significantly higher incidence of acute dermatitis (grade1 dermatitis at two weeks 69.2% vs 38.5%, p=0.0279 and grade 2 dermatitis at six weeks 84.6% vs 38.5%, p=0.0007) and acute mucositis (grade 1 mucositis at two weeks 84.6% vs 38.5%, p=0.0007) as compared to SEQ-VMAT. SEQ-VMAT shows significantly higher incidence of dysphagia (grade 1 at four weeks 84.5% vs 50%, p=0.0087). No significant differences were observed in terms of xerostomia and laryngeal toxicity. No significant difference in overall response was observed between SIB vs SEQ (complete response 65.4% vs 53.85% p=0.40).

Conclusion: SEQ appears better in terms of acute toxicities but SIB was more convenient as no re-planning was required. For head and neck radiotherapy SIB and Sequential VMAT are comparable in terms of overall response.

Keywords: Chemoradiation, Head and neck, Radiotherapy

INTRODUCTION

With over 2,00,000 cases diagnosed in 2018, HNSCC cancers are one of the most common cancers in the Indian population [1]. In India, these tumours often present at a locally advanced stage [2]. Radiotherapy plays an important role in the treatment of HNSCC cancers, usually as curative treatment in pharyngeal, laryngeal and advanced oral cancer [3]. Radiotherapy for head and neck cancers can be challenging due to the complex anatomy and these tumours often located within close proximity to critical structures which can limit radiation dose [4] VMAT is an advanced technique of Intensity-modulated Radiation Therapy (IMRT) which can achieve high conformity of dosage to target volumes with better sparing of normal tissues [5]. VMAT also has the potential to offer additional advantages, such as reduced treatment delivery time compared with conventional static field Intensity Modulated Radiotherapy (IMRT) [6,7].

VMAT allows treatment delivery by two different approaches: SEQ and SIB [8]. In SEQ technique, radiation dose is delivered in different phases with same dose per fraction. The SIB-IMRT technique is of particular interest because it can be used to increase the fraction dose to the boost volume while, at the same time, keeping the dose to the elective volume at a lower level [9]. SIB technique can also lead to reduction in overall treatment time and increase in both prescribed dose and biological dose [10] There is limited data for normal tissue response in head and neck cancers treated with SIB technique. There is a substantial difference between the radiobiological response of the small high dose areas treated with increased dose per fraction inside intermediate dose volumes. Hence, there is a need to redefine the dosimetric and volumetric relationship for SIB [11]. Farzin M et al., have compared SIB vs. SEQ at other sites of body like high grade glioma of brain [12]. Hence, present study aimed to compare the SEQ and SIB techniques of VMAT in patients of head and neck carcinomas in terms of acute toxicity and treatment response.

MATERIALS AND METHODS

This prospective interventional study was conducted in Department of Radiation Oncology, Geetanjali Medical College and Hospital, Udaipur, Rajasthan, India. The study was done from January 2019 to December 2020 with a median follow-up of 12.5 months. Total of 52 patients of biopsy proven squamous cell carcinoma of head and neck region were recruited in the study after an approval from

Institutional Ethics Committee (IECNo.GU/HREC/EC/2019/1558) and written informed consent were obtained.

Inclusion criteria: Histopathologically proven primary HNSCC of either sex, who had calorie intake >1500 cal/day were included in the study.

Exclusion criteria: Patients with severe uncontrolled co-morbidities, pregnant and lactating women, those who had received neoadjuvant chemotherapy or prior radiotherapy and postoperative patients were excluded from the study.

Sample size calculation: 95% confidence level, 80% power of study, pooled prevalence=0.27 (Pooled prevalence was calculated by an experienced statistician of the institute) and difference in proportion=0.25. Therefore, sample size was 24 for each group. Considering a 10% dropout rate, the sample size came out to be 24+2 for each study group. Hence, n=26 for each study group.

Procedure

Patients of either sex above the age of 18 years with Eastern Cooperative Oncology Group (ECOG) performance status [13] of less than or equal to two were randomised into two arms, and treated with either SEQ-VMAT or SIB-VMAT. Patients were randomised in two study groups using online randomising software available at www.randomiser.org-

- SEQ-VMAT

-SIB-VMAT

Pre-treatment evaluation including nutritional evaluation was done prior to treatment as per National Comprehensive Cancer Network Guidelines (NCCN) [13]. Assessment of extension of disease and staging was done by American Joint Committee of Cancer (AJCC) criteria along with clinical examination laryngoscopy, Computed Tomography (CT) scan, Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET) scan as required [14].

Treatment planning: All patients were immobilised in the supine position with a tailored head-shoulder four clamp thermoplastic mask to undergo CT simulation with slice thickness of 2.5 mm on GE Optima CT520 simulator. Target volume delineation was performed according to the International Committee for Radiological Units (ICRU) 83 guidelines [15]. Gross Tumour Volume (GTV) was defined as the gross extent of tumour shown by CT, MRI and PET, including all involved (positive) lymph nodes. On the basis of the primary tumour size and involved node, Clinical Target Volume-High Risk (CTV-HR), CTV- Intermediate Risk (CTV-IR) and CTV-Low Risk (CTV-LR) were contoured. Treatment volume definitions and expansions were consistent between SIB and SEQ groups and were individualised as per institutional practice. Normal and avoidance structures were contoured based on their anatomic definitions. Organs at risk included: spinal cord, brain stem, left and right parotids; larynx, oesophagus, trachea, mandible, pharyngeal constrictors and uninvolved oral cavity. Whenever close to the Planning Target Volume (PTV), eyeballs, optic nerves, and optic chiasm were contoured. PTV margin of 3 mm was generated over CTV for all patients. The dose was prescribed to the PTV using 95% isodose line in both the arms. The dose constraints to Organ At Risk (OAR) were prescribed using Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) [16]. Treatment planning was then performed using Monte-Carlo Optimiser on MONACO v5.11. VMAT plans were generated in both the study groups and plans were evaluated using dose-volume histograms. Dosimetric assessment was done using DVH.

Treatment execution: Treatment was executed on Elekta Versa HD Linear Accelerator. Online image guidance in form of X-ray Volumetric Imaging (XVI) version 5.0 was taken daily or alternate days as per institutional practice. In SEQ boost arm, a 2 gray (Gy) dose per fraction was delivered in different phases and for SIB arm, dose ranging from 1.6 Gy to 2.2 Gy per fraction was delivered in a single treatment plan. For SEQ arm, planning was done in a phased manner. Modifications to original plan were made first at the end of fifth week and then at end of sixth week. Dose prescription, specification and reporting were performed according to ICRU 50 and 62 recommendations. All the patients were treated with conventional dose fractionation using a five days per week treatment schedule.

Chemotherapy as indicated in both the study groups, consisted of weekly cisplatin 40 mg/m^2 with a ceiling dose of 70 mg. All patients had consultation with dietician and whenever required nasogastric feeding tube was placed, if patient was unable to maintain nutrition. The acute toxicities were documented as per the RTOG Toxicity Criteria included skin, mucosa, salivary glands, pharynx/oesophagus and larynx. Response Evaluation Criteria In Solid Tumours (RECIST) v1.1 [17] was used for response evaluation at the end of 8-10 weeks after the completion of radiotherapy. Patients were assessed clinically, laryngoscopic examination and imaging with CT/MRI/PET CT scan as required.

STATISTICAL ANALYSIS

Data was presented as mean, standard deviation, median (range), or percentage. Statistical Analysis was done using the SPSS version 20.0 (Chicago, IL). Chi-square test and t-test were used for comparison of qualitative and quantitative variables respectively. The p-value less than 0.05 were considered significant.

RESULTS

Total of 52 patients (26 patients in SEQ VMAT group and 26 patients in SIB VMAT group) were included and data was collected for analysis. Demographic data showed no significant difference in both treatment arms in terms of age (56.2 years in SEQ vs 53.5 years in SIB arm, p-value=0.41), sex (24 males and 2 females in both the arms), disease site{oropharynx is the most common site 38.5% (10/26) in both arms} and stage at presentation {stage IVA constitutes 18(69.2%) patients in SEQ arm vs 12 (46.2%) patients in SIB arm and stage III constitutes 8 (30.8%) patients in SEQ arm vs 11 (42.3%) in SIB arm} [Table/Fig-1]. Majority of the patients were males {24(92.3%) in both the arms}.

Characteristics	Total (N=52)	SEQ (n=26)	SIB (n=26)	p-value
Age (years) Mean±SD	54.85±11.7	56.2±12.6	53.5±10.8	0.4107
Sex				
Male	48 (92.3%)	24 (92.3%)	24 (92.3%)	0.99
Female	4 (7.7%)	2 (7.7%)	2 (7.7%)	
Primary site				
Oral cavity	12 (23.0%)	8 (30.8%)	4 (15.4%)	0.32
Paranasal sinus	01 (1.9%)	1 (0.38%)	0	0.99
Oropharynx	20 (38.5%)	10 (38.5%)	10 (38.5%)	0.99
Larynx & Hypopharynx	19 (36.5%)	7 (26.9%)	12 (46.2%)	0.25
AJCC stage grouping				
II	3 (5.7%)	0	3 (11.5%)	0.097
III	19 (36.5%)	8 (30.8%)	11 (42.3%)	
IVA	30 (57.7%)	18 (69.2%)	12 (46.2%)	

[Table/Fig-1]: Patient Demographic Data (N=52).
AJCC: American joint committee of cancer; SEQ: Sequential Volumetric Modulated Arc Therapy (VMAT) arm; SIB: Simultaneous integrated boost VMAT arm

Toxicity assessment showed that 10 (38.5%) patients in SEQ arm experienced grade 1 acute dermatitis as compared to 18 (69.2%) patients in SIB arm at the end of 2 weeks. Similarly, Grade 2 Dermatitis was observed in 10 (38.5%) patients in SEQ arm vs 22 (84.6%) patients in SIB arm at the end of six weeks [Table/Fig-2]. Patients experiencing grade 1 acute mucositis were 10 (38.5%) patients in SEQ arm vs 22 (84.6%)SIB arm at the end of week-2

[Table/Fig-3]. Most of the patients observed either grade 1 or grade 2 acute xerostomia. Grade 3 or 4 acute xerostomia was observed in none of the patients [Table/Fig-4]. No major differences were observed in terms of dysphagia and acute laryngeal toxicity in both the study arms [Table/Fig-5,6]. Complete response was observed in 14 (53.8%) in SEQ arm vs 17 (65.4%) patients in SIB arm, p-value=0.40 while a partial response was observed in 12 (46.1%) patients in SEQ arm vs 9 (34.6%) patients in SIB arm, p-value=0.40 when assessed at 8-10 weeks post-treatment [Table/Fig-7].

Acute dermatitis		Grade 0	Grade 1	Grade 2	Grade 3
At 2 weeks	SEQ	16 (61.5%)	10 (38.5%)	0	0
	SIB	8 (30.8%)	18 (69.2%)	0	0
	p-value	0.0279	0.0279	-	-
At 4 weeks	SEQ	2 (7.7%)	19 (73.1%)	5 (19.2%)	0
	SIB	0	24 (92.3%)	2 (7.7%)	0
	p-value	-	0.0699	0.2288	-
At 6 weeks	SEQ	0	15 (57.7%)	10 (38.5%)	1 (3.8%)
	SIB	0	3 (11.5%)	22 (84.6%)	1 (3.8%)
	p-value	-	**0.0005**	**0.0007**	1.00

[Table/Fig-2]: Dermatitis (N=52).
Grade 1: Faint erythema or desquamation; Grade 2: Moderate to brisk erythema or patchy, moist desquamation confined to skin folds and creases; Moderate swelling; Grade 3: Confluent, moist desquamation greater than 1.5 cm diameter, which is not confined to the skin folds

Acute mucositis		Grade 0	Grade 1	Grade 2	Grade 3
At 2 weeks	SEQ	14 (53.8%)	10 (38.5%)	2 (7.7%)	0
	SIB	4 (15.4%)	22 (84.6%)	0 (0%)	0
	p-value	0.0039	0.0007	-	-
At 4 weeks	SEQ	2 (7.7%)	19 (73.1%)	5 (19.2%)	0
	SIB	2 (7.7%)	13 (50%)	11 (42.3%)	0
	p-value	1.0	0.0900	0.0739	-
At 6 weeks	SEQ	0	10 (38.5%)	12 (46.1%)	4 (15.4%)
	SIB	0	5 (19.2%)	16 (61.6%)	5 (19.2%)
	p-value	-	0.1282	0.2828	0.7198

[Table/Fig-3]: Mucosal reactions (N=52).
Grade 0: no signs and symptoms; Grade 1: painless ulcers, edema, or mild soreness; Grade 2: painful erythema, edema, or ulcers but able to eat; Grade 3: painful erythema, edema, or ulcers but unable to eat

Acute xerostomia		Grade 0	Grade 1	Grade 2
At 2 weeks	SEQ	13 (50%)	13 (50%)	0
	SIB	13 (50%)	13 (50%)	0
	p-value	1.0	1.0	-
At 4 weeks	SEQ	3 (11.5%)	18 (69.2%)	5 (19.2%)
	SIB	6 (23.1%)	18 (69.2%)	2 (7.7%)
	p-value	0.2735	1.0	0.2288
At 6 weeks	SEQ	0	13 (50%)	13 (50%)
	SIB	1 (3.8%)	12 (46.2%)	13 (50%)
	p-value	-	0.7860	1.0

[Table/Fig-4]: Xerostomia (N=52).
Grade o: no symptoms; Grade 1: Mild Symptomatic -dry or thick saliva without advise of significant dietary alteration; Grade-2: Moderate Symptomatic and significant oral intake alteration advised; Grade 3: Severe Symptoms leading to inability to adequately aliment orally or parenteral nutrition indicated

Dosimetric analysis was done comparing the mean doses to organs at risk for both the study groups and Planning Target Volume (PTV) coverage. No difference was observed in terms of target coverage for both techniques. Mean dose to larynx was 44.31±8.72 Gy in SEQ arm and 43.57±8.17 Gy in SIB arm, p-value=0.79. Similarly, dose to left and right parotid gland were 24.4±1.94 Gy and 24.81±2.54 Gy in SEQ arm and 24.71±3.23 and 27.75±7.93 Gy in SIB arm respectively, p-values 0.75 and 0.07 [Table/Fig-8].

Acute dysphagia		Grade 0	Grade 1	Grade 2	Grade 3
At 2 weeks	SEQ	19 (73.1%)	7 (26.9%)	0	0
	SIB	15 (57.7%)	11 (42.3%)	0	0
	p-value	0.2477	0.2477	-	-
At 4 weeks	SEQ	3 (11.5%)	20 (84.5%)	3 (11.5%)	0
	SIB	7 (26.9%)	13 (50%)	6 (23.1%)	0
	p-value	0.1627	0.0087	0.2735	-
At 6 weeks	SEQ	0	10 (38.5%)	13 (50%)	3 (11.5%)
	SIB	0	13 (50%)	8 (30.8%)	5 (19.2%)
	p-value	-	0.4084	0.1624	0.4456

[Table/Fig-5]: Dysphagia (N=52).
Grade 0: normal; Grade 1: within functional limits- abnormal oral or pharyngeal stage but able to eat a regular diet without modifications or swallowing precautions; Grade 2: mild impairment- mild dysfunction in oral or pharyngeal stage, requires a modified diet without need for therapeutic swallowing precautions; Grade 3: mild-to-moderate impairment with need for therapeutic precautions-requires a modified diet and therapeutic precautions to minimise aspiration risk

Acute laryngitis		Grade 0	Grade 1	Grade 2	Grade 3
At 2 weeks	SEQ	13 (65%)	7 (35%)	0	0
	SIB	13 (68.4%)	6 (31.6%)	0	0
	p-value	0.7967	0.7967	-	-
At 4 weeks	SEQ	5 (25%)	12 (60%)	3 (15%)	0
	SIB	3 (16.7%)	14 (77.8%)	1 (5.6%)	0
	p-value	0.4657	0.1697	0.2695	-
At 6 weeks	SEQ	1 (5%)	10 (50%)	7 (35%)	2 (10%)
	SIB	0	9 (50%)	8 (44.4%)	1 (5.6%)
	p-value	-	1.0	0.4927	0.5580

[Table/Fig-6]: Laryngeal toxicity.
Grade 0: no symptoms; Grade 1: mild hoarseness and dryness; Grade 2: Moderate hoarseness and dryness; Grade 3: Severe hoarseness with dyspnoea, moderate odynophagia and dysphagia
Total is different in all toxicities as some patients did not have the toxicities. One patient who had grade 0 toxicity at 2 weeks was managed conservatively, did not report any toxicity on 4th and 6th weeks

Response at 8-10 weeks	CR		PR	
	N	%	N	%
SEQ	14	53.85	12	46.15
SIB	17	65.4	9	34.6
p-value	0.4006			

[Table/Fig-7]: Response evaluation (N=52).
CR: Complete response; PR: Partial response

DMean	SEQ			SIB			p-value* of Dmean
	Mean	SD	N	Mean	SD	N	
Dmean Larynx	44.31	8.72	20	43.57	8.16	18	0.7921
Dmean Trachea	33.23	7.25	26	32.59	6.87	26	0.9302
Dmean Oesophagus	28.84	6.03	26	29.5	4.35	26	0.8011
Dmean Parotid Left	24.4	1.94	26	24.71	3.23	26	0.7543
Dmean Parotid Right	24.81	2.54	26	27.75	7.93	26	0.0778
Dmean Mandible	50.38	4.79	26	47.86	5.74	26	0.0918
Dmax SC	34.17	3.26	26	34.69	4.25	26	0.944
Dmax Brain Stem	6.06	4.69	26	4.94	2.14	26	0.1815

[Table/Fig-8]: Dosimetric comparison.
SC: Spinal cord; *t-test

DISCUSSION

The present prospective study evaluated and compared the acute toxicities and disease response between SEQ-VMATvs SIB-VMAT for HNSCC. To our best knowledge, this is the first randomised trial comparing SIB and SEQ boost using VMAT in non nasopharyngeal head and neck carcinoma. SEQ-VMAT and SIB-VMAT treatment in head and neck cancer are comparable in terms of overall response. Higher incidence of grade 1-2 acute dermatitis, mucositis and dysphagia was observed in SIB arm. No patient had treatment interruption due to acute toxicities. Toxicities were managed

conservatively with use of topical anaesthetics, analgesics and opioids. Nutrition and hydration were maintained using dietician advised diet and i.v. fluids. There was no difference in the incidence of xerostomia and laryngeal toxicity. There was a trend towards higher incidence of grade 3 dysphagia in SIB arm but this was not found to be statistically significant. In present study, SEQ and SIB had comparable target coverage and dose to organs at risk. This was similar to the dosimetric studies done by Chen SW et al., and Nesrin D et al., comparing the target volume coverage and normal tissue sparing of SIB-IMRT versus SEQ-IMRT for nasopharyngeal carcinoma [18,19].

In a single institutional retrospective study by Vlacich G et al., performed matched cohort analysis on patients of locally advanced head and neck carcinoma treated with chemoradiation to 69.3 Gy in 33 fractions [20]. Out of 209 patients evaluated for analysis, 68 patients were treated with SEQ and 141 were treated with SIB. No significant difference was observed between SEQ versus SIB in disease free survival (63% vs 69%; p=0.27) and overall survival (69.3% vs 76.8%; p=0.13). They observed a significantly higher incidence of grade 3 or 4 acute dysphagia (82% vs 55%) and acute dermatitis (78% vs 58%), whereas present study shows no difference in the incidence of grade 3 dysphagia SEQ (11.5%) vs SIB (19.2%), p-value=0.44.

A randomised study by Songthong A et al., compared SEQ boost vs SIB IMRT in nasopharyngeal carcinoma on a total of 122 patients [21]. Similar to the present study, this study showed no statistically significant difference in grade 3 mucositis, dysphagia and xerostomia. Also, there was no statistically significant difference in clinical response between SEQ-IMRT and SIB-IMRT in both the studies.

Scorsetti M et al., reported their early clinical experience in radiotherapy of different sites of head and neck cancer treated by volumetric modulated arcs [22]. Similar to present study, percutaneous gastrostomy or feeding tube was not required in any of the patients. The most common acute grade 3 toxicities in this study were reported as mucositis (28%), dermatitis (14%) and dysphagia (7%). Whereas in present study, the most common grade 3 acute toxicities were mucositis (17%), dysphagia (15%) and laryngeal toxicity (6%). On sub-group analysis, patients treated with cetuximab had the majority of grade 3 toxicities, while the patients treated with cisplatin mainly had grade 1 toxicities. Whereas cisplatin was used as concurrent chemotherapy in all patients.

Jiang L et al., performed a meta-analysis of seven studies to compare the treatment outcome and severe acute side effects between SIB-IMRT and SEQ-IMRT [23]. A total of 1049 patients were evaluated. This meta-analysis showed no significance difference in overall survival (Hazard Ratio, HR=0.94; 95% CI, 0.70-1.27; p-value=0.71), progression free survival (HR 1.03; 95% CI, 0.82-1.30; p-value=0.79), locoregional recurrence free survival (HR 0.98; 95% CI, 0.65-1.47; p-value=0.91) and distant metastasis free survival (HR 0.87; 95% CI, 0.50-1.53; p-value=0.63). Similarly, the present study shows no significant difference in the tumour response. The present study needs longer follow-up to compare overall survival and recurrence free survival.

In this study, SIB VMAT shows significantly higher incidence of acute dermatitis (grade1 dermatitis at two and four weeks; grade 2 dermatitis at six weeks) and acute mucositis (grade 1 mucositis at two weeks and grade 2 mucositis at four weeks) as compared to SEQ-VMAT. This difference in acute toxicities in SIB arm can be attributed to the higher dose per fraction to the high-risk volumes. SIB has an advantage of being convenient requires one plan as compared to two or more plans in SEQ. Simultaneous boost also reduces overall treatment duration. As the main aim of radiotherapy treatment is to provide the best tumour control in the target and non target lesions. Similar to other studies, in this study no significant difference was observed in the overall response to treatment. Both arms have equivalent dose prescription to the target volumes in terms of biological effective dose. Disease progression was observed in two patients in SIB arm and four in SEQ arm. No distant failure was seen in this study.

Limitation(s)

Lack of assessment of late toxicities, disease free survival and overall survival analysis because of short follow-up. Lack of blinding of the study participants and of the investigator was another limitation of this study.

CONCLUSION(S)

For head and neck cancers, radical radiotherapy by SIB-VMAT and Sequential-VMAT planning are comparable in terms of overall response. But SIB arm had higher rates of acute dermatitis and mucositis. Dosimetric data was comparable between the two arms but SIB-VMAT was more convenient as no replanning was required as compared to SEQ-VMAT.

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