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Original Research Article

A Prospective Observational Study Comparing Simultaneous Integrated Boost Intensity Modulated Radiotherapy (SIB-IMRT) Versus Simultaneous Modulated Accelerated Radiotherapy (Smart) in the Treatment of Locally Advanced Head & Neck Cancer

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Conflict of interest: Nil

Abstract:

Introduction: Locally advanced head and neck squamous cell carcinoma (LAHNSCC) requires optimal radiotherapy strategies to balance efficacy and toxicity. Simultaneous Modulated Accelerated Radiotherapy (SMART) and Simultaneous Integrated Boost Intensity-Modulated Radiotherapy (SIB-IMRT) are two advanced techniques with potential differences in clinical and dosimetric outcomes.

Aims: To compare the dosimetric parameters, acute and late toxicities, and progression-free survival (PFS) between SMART and SIB-IMRT in the treatment of LAHNSCC.

Materials and Methods: This single-institutional prospective observational study was conducted in the Department of Radiotherapy, Medical College and Hospital, Kolkata, from September 2022 to February 2024. A total of 89 biopsy-confirmed LAHNSCC patients were enrolled.

Results: Both arms had comparable baseline characteristics. PTV-HR coverage was excellent in both arms (V95% >99%, p = 0.487). Most dosimetric parameters, including parotid, spinal cord, and brainstem doses, showed no significant differences. However, the mean laryngeal dose was significantly higher in the SMART arm (59.78 ± 7.69 Gy vs. 53.56 ± 9.23 Gy; p = 0.005). PFS at a median 14-month follow-up was 66.7% for SMART and 56.8% for SIB-IMRT. Acute toxicity was significantly higher in the SMART arm with respect to hoarseness of voice and xerostomia. No significant differences were observed in late toxicities or other outcomes.

Conclusion: SMART is a feasible alternative to SIB-IMRT, offering reduced OTT with comparable efficacy. However, increased laryngeal dose and acute toxicities warrant cautious selection and further validation through randomized trials.

Keywords: Head and neck cancer, IMRT, SMART, SIB, radiotherapy, dosimetry, acute toxicity, progression-free survival.

Introduction

Head and neck cancers (HNCs) constitute a significant health burden worldwide, especially in developing countries like India, where they represent a major proportion of cancer morbidity and mortality. Most patients present in advanced stages due to late diagnosis and limited awareness, necessitating aggressive multimodal treatment strategies. Radiation therapy, with or without chemotherapy, remains the cornerstone in the management of locally advanced head and neck cancers (LAHNC), partic-

ularly in patients who are inoperable or medically unfit for surgery. With advances in radiation techniques, there has been a paradigm shift from conventional radiotherapy to highly conformal methods like Intensity Modulated Radiotherapy (IMRT), which enables precise dose delivery to the tumor while sparing surrounding normal tissues. Simultaneous Integrated Boost IMRT (SIB-IMRT) allows differential doses to be delivered to high-risk and low-risk volumes in a single treatment plan, thereby reducing overall treatment time and improving tumor control probability while minimizing toxicity. This technique has gained popularity due to its dosimetric advantages and improved clinical outcomes in several studies [1, 2].

Simultaneous Modulated Accelerated Radiotherapy (SMART), a variation of IMRT, employs accelerated fractionation to reduce tumor repopulation by shortening the overall treatment time. SMART delivers higher fractional doses to gross tumor volumes while limiting doses to organs at risk. Some clinical trials have shown promising results with SMART in terms of locoregional control and acute toxicity profiles [3, 4].

Despite the theoretical and clinical advantages of both SIB-IMRT and SMART, direct comparisons in a prospective observational setting remain limited. It is imperative to evaluate their comparative efficacy, safety, and impact on quality of life, especially in resource-constrained settings. Hence, this study was undertaken to prospectively compare the outcomes of SIB-IMRT and SMART in patients with LAHNC in terms of tumor response, toxicity profiles, and treatment compliance. Aims of the study to compare the dosimetric profiles, locoregional recurrence between the two arms starting from treatment initiation till the end of follow up period.

Materials and Methods

Type of study: Single Institutional Prospective Observational Study.

Place of study: Patients attending the Out Patient Department (OPD) of the Department of Radiotherapy of Medical College and Hospital, Kolkata.

Study duration: September 2022 to February 2024.

Sample size: 89 Patients who are biopsy proven cases of locally advanced Head and neck Carcinoma (LAHNC) and who fulfil the required inclusion and exclusion criteria.

Inclusion Criteria: The study included patients with histologically confirmed cases of locally advanced head and neck cancers (Stage III to IVA) who were planned to undergo definitive radiotherapy with concurrent chemotherapy. Eligible participants were aged between 18 and 65 years and demonstrated a good performance status, with a Karnofsky Performance Scale (KPS) score greater than 70 and an ECOG Performance Status of less than 3. All patients underwent baseline hematological and clinical evaluations to establish fitness for chemotherapy and radiotherapy. Inclusion was contingent upon the provision of study-specific informed consent.

Exclusion Criteria: Exclusion criteria encompassed patients with carcinoma involving other subsites of the head and neck, such as the nasopharynx, skin, orbit, salivary glands, paranasal sinuses, as well as those diagnosed with lymphoma. Pregnant and lactating women were excluded, along with patients who had received prior chemotherapy, radiotherapy, or surgery for the current disease. Additional exclusion factors included the presence of uncontrolled comorbid conditions such as uncompensated respiratory, cardiac, hepatic, or renal disease, evidence of systemic metastasis, poor dental hygiene, and significant weight loss exceeding 10% within the three months preceding the initiation of radiotherapy.

Parameters:

- Patient data
- Primary Tumor Assessment
- Dosimetric changes in the target and Organ at Risk
- Toxicity profile
- Response Assessment

Methodology

Biopsy-proven locally advanced head and neck cancer patients presenting to our department's outpatient clinic were screened according to predefined inclusion and exclusion criteria. After obtaining informed consent, a total of 94 patients were enrolled and allocated into two equal groups (n=47 each) following departmental protocols. Pretreatment evaluations including clinical assessment and CT simulation were performed, with data transferred to the treatment planning system (TPS) prior to initiation of therapy. One group received SMART Boost treatment delivering 66/54 Gy in 27 fractions, while the other group received SIB Boost treatment with 70/59.4 Gy in 33 fractions. During the course of treatment, 3 patients in the SMART Boost arm and 2 patients in the SIB Boost arm were lost to follow-up or discontinued treatment. Ultimately, 44 patients in the SMART Boost arm and 45 patients in the SIB Boost arm completed treatment and were included in the endpoint analyses.

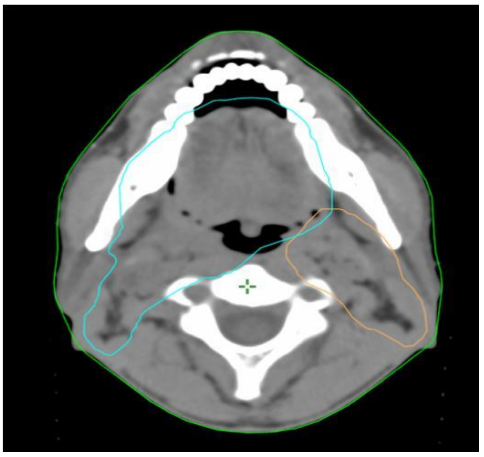

Figure 1: Planning target volume delineation for PTVHR (Cyan) and PTVLR (Red) for SMART Boost technique.

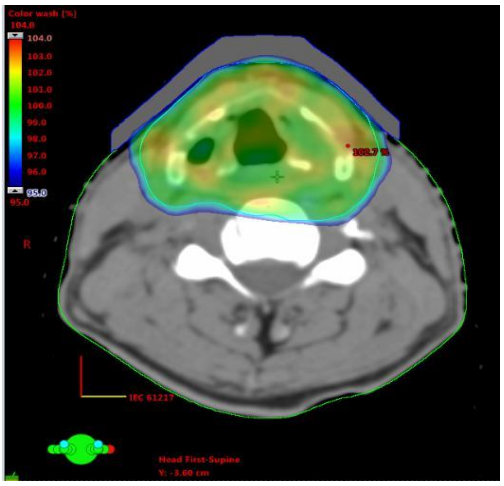

Figure 2: Dose colour wash showing 95% coverage

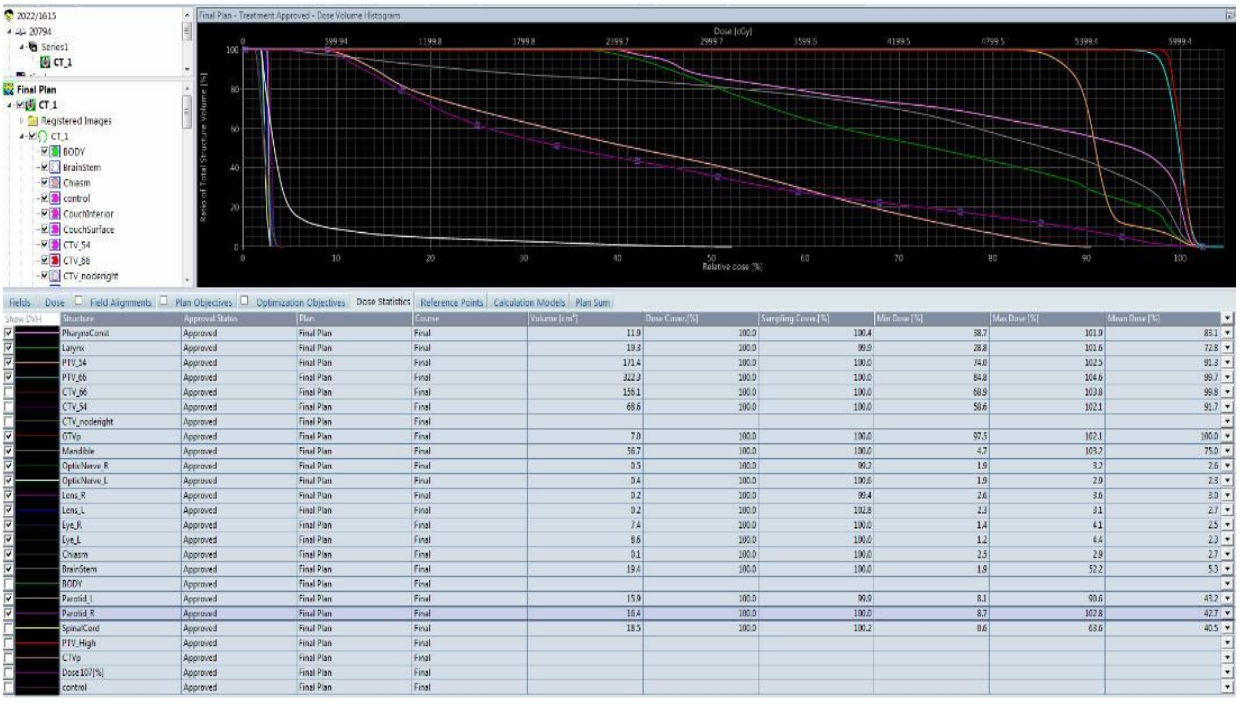

Figure 3: Dose volume histogram with dose statistics obtained during plan approval

Statistical Analysis: The collected data were tabulated using Microsoft Office 365. Descriptive statistics (counts and percentages) were used.

Numerical and categorical variables were compared between groups using the unpaired t-test and chi-square test, respectively. Volumetric and dosimetric parameters were compared using the Wilcoxon test. Acute and late toxicities were analyzed using the chi-square or Fisher's exact test, with toxicity scores coded as binary. Progression-free survival (PFS) was assessed using Kaplan-Meier analysis and compared with the log-rank test. A p-value < 0.05 was considered statistically significant.

Univariate Cox proportional hazards models were used to analyze clinical, pathological, survival, and treatment-related variables. All analyses were performed using IBM SPSS version 29.

Results

Table 1: Distribution of patient particulars between the treatment arms

Category	Variables	Study Arm (n = 45)	Control Arm (n = 44)	P-value
Gender	Male	29 (64.4%)	27 (61.6%)	0.195
	Female	16 (35.6%)	17 (38.4%)	
Residence	Urban	16 (35.5%)	17 (38.7%)	0.432
	Rural	29 (64.5%)	27 (61.3%)	
ECOG Performance Status	PS0	5 (11.1%)	7 (15.9%)	0.317
	PS1	23 (51.1%)	24 (54.5%)	
	PS2	17 (37.8%)	13 (29.6%)	
Age Group	Age(years, Mean±SD)	53.73 ± 11.47	54.06 ± 11.89	0.112
	<50yrs	16 (35.5%)	20 (45.4%)	0.063
	≥50yrs	29 (64.5%)	24 (54.6%)	

Table 2: Distribution of tumor parameters between the treatment arms

Category	Parameters	Smart Arm (n = 45)	Control Arm (n = 44)	P-value
Tumor Site	Oral Cavity	22 (48.9%)	19 (43.1%)	0.923
	Oropharynx	10 (22.2%)	12 (26.7%)	
	Hypopharynx	04 (8.9%)	03 (6.7%)	
	Larynx	09 (20.0%)	10 (22.7%)	
Histological Grade	Well Differentiated	6 (13.3%)	8 (18.1%)	0.527
	Moderately Differentiated	34 (75.5%)	32 (72.7%)	
	Poorly Differentiated	5 (11.1%)	4 (9.0%)	
AJCC (8th Edition)	Stage III	28 (62.2%)	25 (56.8%)	0.608
	Stage IV (Non-metastatic)	17 (37.8%)	19 (43.2%)	
Tumor (T) Stage	T2	14 (31.1%)	16 (36.3%)	0.71
	T3	20 (44.4%)	18 (40.9%)	
	T4	11 (24.4%)	10 (22.8%)	
Nodal (N) Stage	N0	06 (13.3%)	06 (13.6%)	0.514
	N1	24 (54.5%)	22 (50.0%)	
	N2a	07 (15.6%)	06 (13.6%)	
	N2b	08 (17.6%)	10 (22.8%)	

Table 3: Target Volume Dosimetry

Category	Dosimetric Parameter	SMART Arm (Mean ± SD)	SIB Arm (Mean ± SD)	P-value
PTV-HR	V95 (%)	99.24 ± 0.61	99.14 ± 0.72	0.487
	Dmean (Gy)	66.09 ± 1.16	69.93 ± 0.55	0.406
	Volume (cc)	289.29 ± 79.53	281.24 ± 101.49	0.679
PTV-LR	V95 (%)	98.99 ± 0.83	98.68 ± 1.43	0.204
	Dmean (Gy)	54.77 ± 1.07	60.02 ± 0.51	0.138
	Volume (cc)	199.35 ± 127.38	228.82 ± 152.98	0.327
Organs at Risk	Right Parotid Dmean (Gy)	28.61 ± 8.50	28.68 ± 8.61	0.971
	Left Parotid Dmean (Gy)	26.87 ± 7.30	27.52 ± 8.63	0.699
	PRV Spine Dmax (Gy)	43.43 ± 4.38	43.58 ± 4.64	0.882
	PRV Brainstem Dmax (Gy)	42.46 ± 11.37	43.15 ± 10.23	0.773
	PCM Dmean (Gy)	52.62 ± 4.59	53.43 ± 4.25	0.389

	Mandible Dmax (Gy)	67.83 ± 2.10	67.74 ± 2.72	0.868
	Larynx Dmean (Gy)	59.78 ± 7.69	53.56 ± 9.23	0.005

Table 4: showing Means and Medians for Survival Time

Treatment Arm	Mean Estimate	Std. Error (Mean)	95% CI (Mean)	Median Estimate	Std. Error (Median)	95% CI (Median)
SIB	14.238	0.866	12.542 – 15.935	18.67	0	Not Estimable
SMART	15.532	0.762	14.039 – 17.026	18.67	1.412	15.902 – 21.438
Overall	14.896	0.575	13.769 – 16.024	18.67	1.055	16.603 – 20.737

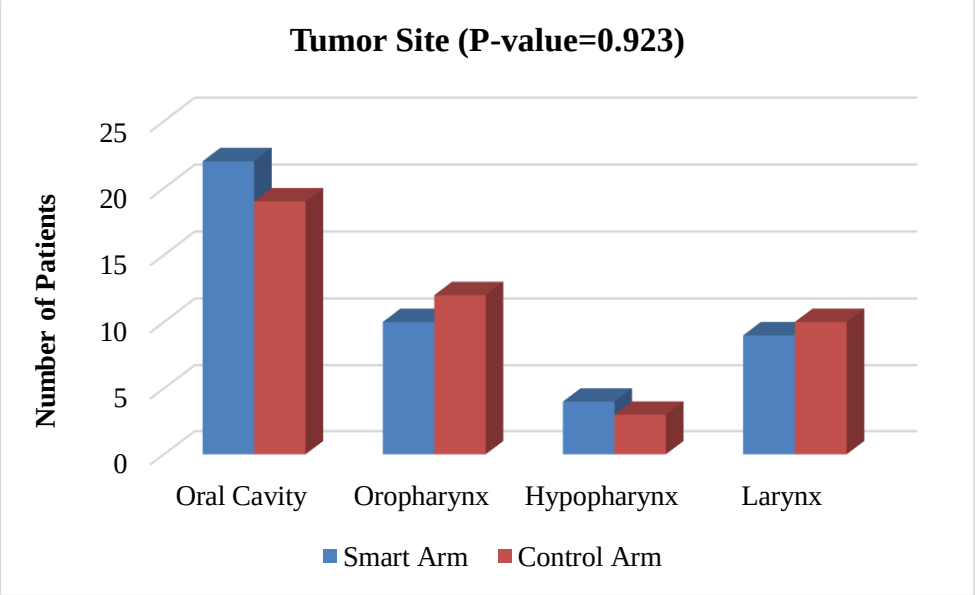

Figure 4: Distribution of Tumor Site

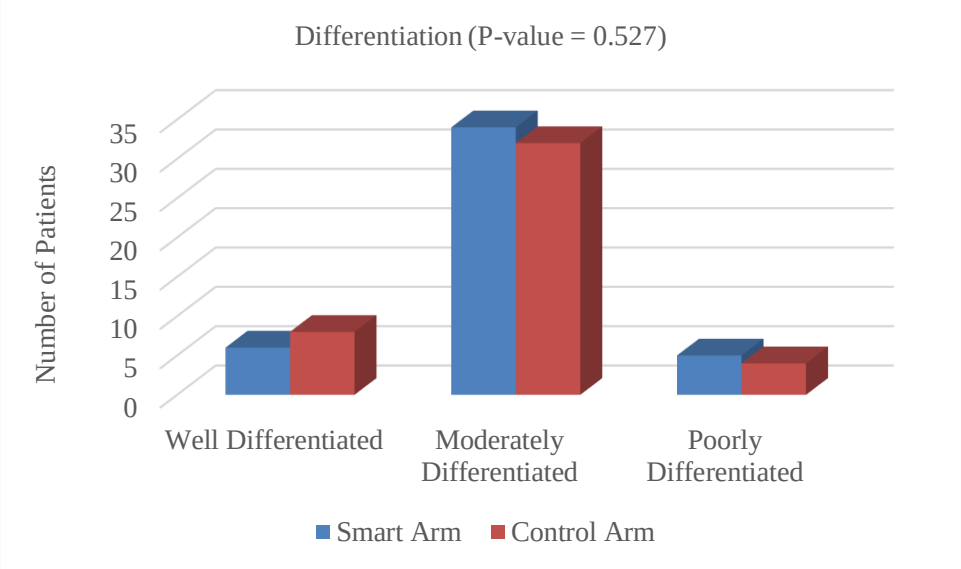

Figure 5: Distribution of Differentiation

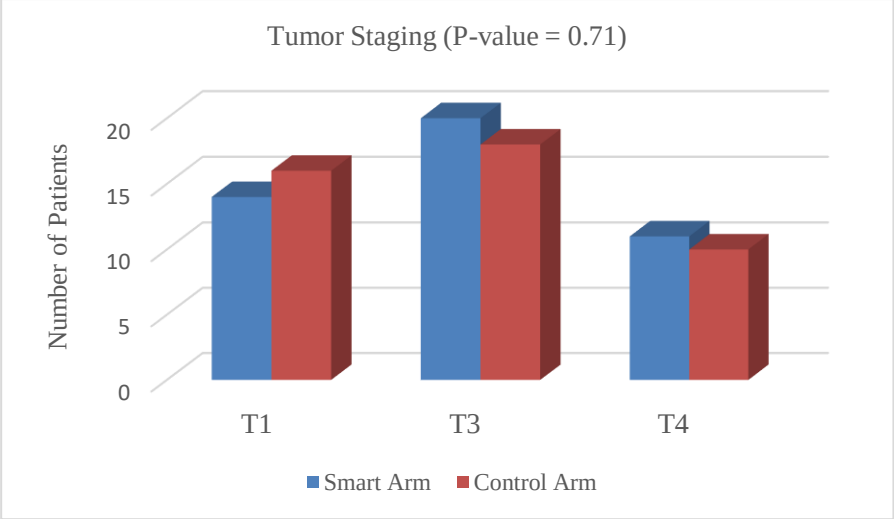

Figure 6: Distribution of Tumor Staging

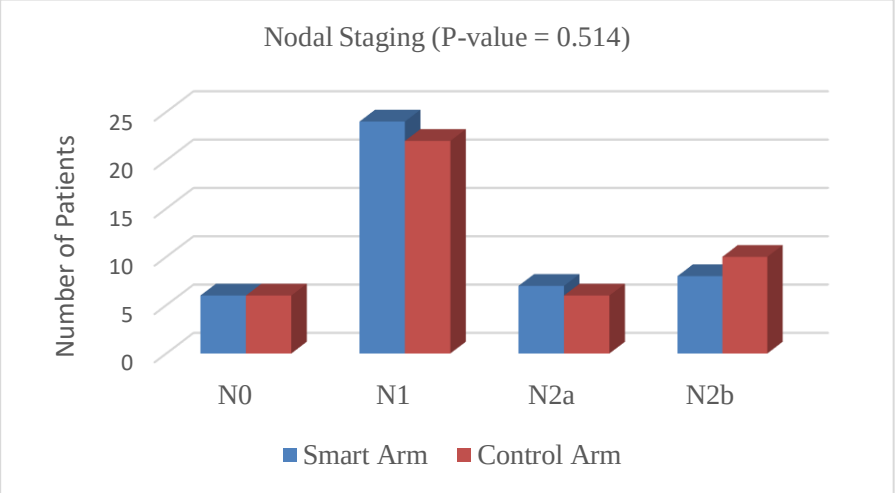

Figure 7: Distribution of Nodal Staging

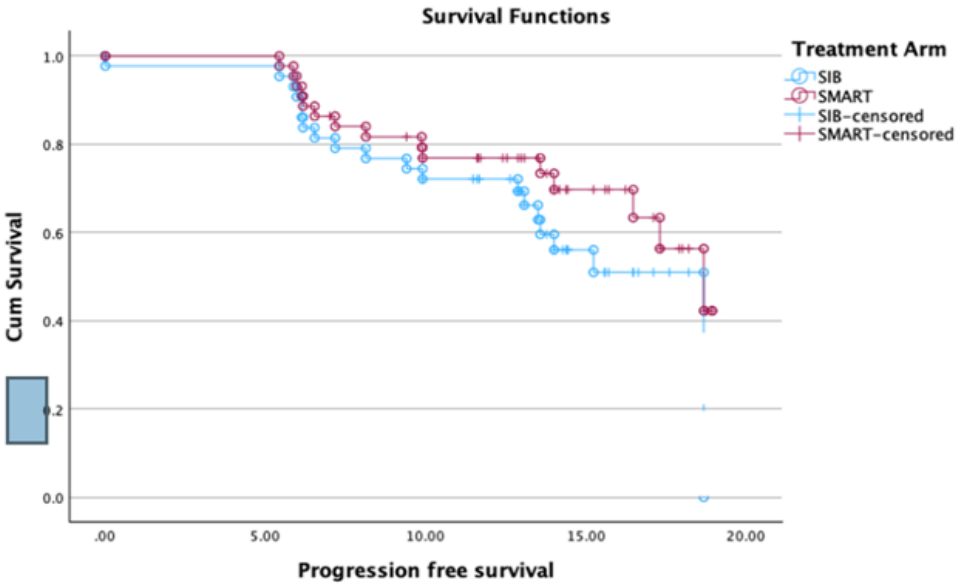

Figure 8: Kaplan Meier curve showing similar Progression free survival for SMART arm and SIB IMRT arm (p=0.212)

The present study enrolled a total of 89 patients with locally advanced head and neck cancer, with 45 patients in the Study Arm (SMART) and 44 in the Control Arm (SIB-IMRT). The mean age of patients in the Study Arm was 53.73 ± 11.47 years, while that in the Control Arm was 54.06 ± 11.89 years, with no statistically significant difference observed (p = 0.112). In terms of age distribution, 35.5% of patients in the Study Arm and 45.4% in the Control Arm were below 50 years of age, while the remaining 64.5% and 54.6% respectively were 50 years or older (p = 0.063).

Regarding gender, males predominated in both groups, comprising 64.4% of the Study Arm and 61.6% of the Control Arm, while females accounted for 35.6% and 38.4%, respectively. The gender distribution between the two arms was comparable (p = 0.195). In terms of residence, 35.5% of patients in the Study Arm and 38.7% in the Control Arm were from urban areas, while the majority, 64.5% and 61.3%, respectively, were from rural regions. This difference was not statistically significant (p = 0.432).

Performance status as measured by ECOG criteria was also similar across both groups. In the Study Arm, 11.1% of patients had a PS of 0, 51.1% had a PS of 1, and 37.8% had a PS of 2. In comparison, the Control Arm had 15.9% with PS 0, 54.5% with PS 1, and 29.6% with PS 2. No statistically significant difference was found between the two groups in terms of ECOG performance status (p = 0.317).

The distribution of primary tumor sites was comparable between the two groups. In the SMART Arm, the most common tumor site was the oral cavity (48.9%), followed by oropharynx (22.2%), larynx (20.0%), and hypopharynx (8.9%). Similarly, in the Control Arm, oral cavity tumors accounted for 43.1%, followed by oropharynx (26.7%), larynx (22.7%), and hypopharynx (6.7%). The overall distribution of tumor sites did not differ significantly between the arms (p = 0.923).

Histological grading showed that moderately differentiated tumors were predominant in both groups, with 75.5% in the SMART Arm and 72.7% in the Control Arm. Well-differentiated tumors were seen in 13.3% and 18.1% of cases, while poorly differentiated tumors were observed in 11.1% and 9.0% of patients, respectively. There was no statistically significant difference in histological grade between the groups (p = 0.527).

Based on the AJCC 8th edition staging system, a majority of patients in both arms presented with Stage III disease — 62.2% in the SMART Arm and 56.8% in the Control Arm. The remaining patients had non-metastatic Stage IV disease (37.8% and 43.2%, respectively), with no significant difference in stage distribution (p = 0.608). Tumor (T) staging showed that T3 tumors were the most common in both groups, accounting for 44.4% in the SMART Arm and 40.9% in the Control Arm. T2 tumors were present in 31.1% and 36.3% of patients, respectively, and T4 tumors in 24.4% and 22.8%, respectively. The distribution of T stages was statistically similar (p = 0.710).

Regarding nodal (N) staging, N1 nodes were most frequently involved — 54.5% in the SMART Arm and 50.0% in the Control Arm. N0 status was noted in 13.3% and 13.6% of patients, while N2a involvement occurred in 15.6% and 13.6%, and N2b in 17.6% and 22.8% of patients, respectively. These differences were not statistically significant (p = 0.514).

The analysis of dosimetric parameters revealed that both treatment techniques achieved excellent target coverage for high-risk planning target volume (PTV-HR), with V95% being 99.24 ± 0.61% in the SMART Arm and 99.14 ± 0.72% in the SIB Arm, showing no statistically significant difference (p = 0.487). The mean dose (Dmean) to the PTV-HR was 66.09 ± 1.16 Gy in the SMART group and 69.93 ± 0.55 Gy in the SIB group (p = 0.406). The mean volume of PTV-HR was comparable between the arms: 289.29 ± 79.53 cc (SMART) and 281.24 ± 101.49 cc (SIB), with no significant difference (p = 0.679).

For the low-risk planning target volume (PTV-LR), V95% was 98.99 ± 0.83% in the SMART Arm versus 98.68 ± 1.43% in the SIB Arm (p = 0.204). The Dmean was slightly lower in the SMART group (54.77 ± 1.07 Gy) compared to the SIB group (60.02 ± 0.51 Gy), though this was not statistically significant (p = 0.138). The PTV-LR volumes were also comparable (199.35 ± 127.38 cc vs. 228.82 ± 152.98 cc; p = 0.327).

Regarding organs at risk (OAR), the mean dose to the right parotid was 28.61 ± 8.50 Gy in the SMART Arm and 28.68 ± 8.61 Gy in the SIB Arm (p = 0.971), while the left parotid received 26.87 ± 7.30 Gy and 27.52 ± 8.63 Gy respectively (p = 0.699). The maximum dose to the PRV spinal cord and PRV brainstem was also similar between both arms (Spine Dmax: 43.43 ± 4.38 Gy vs. 43.58 ± 4.64 Gy, p = 0.882; Brainstem Dmax: 42.46 ± 11.37 Gy vs. 43.15 ± 10.23 Gy, p = 0.773).

Further, the PCM (pharyngeal constrictor muscle) received a mean dose of 52.62 ± 4.59 Gy in the SMART Arm compared to 53.43 ± 4.25 Gy in the SIB Arm (p = 0.389). The maximum dose to the mandible was almost identical in both arms (67.83 ± 2.10 Gy vs. 67.74 ± 2.72 Gy; p = 0.868). However, a statistically significant difference was noted in the mean dose to the larynx, which was higher in the SMART Arm (59.78 ± 7.69 Gy) compared to the SIB Arm (53.56 ± 9.23 Gy), with a p-value of 0.005, indicating increased laryngeal dose in the SMART group.

The mean survival time was slightly higher in the SMART group (15.53 months) compared to the SIB group (14.24 months). Median survival time was the same (18.67 months) across all groups, but confidence intervals were estimable only for SMART (15.90–21.44 months) and Overall (16.60–20.74 months), not for SIB due to censoring.

Discussion

In the present prospective study involving 89 patients with locally advanced head and neck squamous cell carcinoma (LAHNSCC), we compared SMART (Simultaneous Modulated Accelerated Radiotherapy) and SIB-IMRT (Simultaneous Integrated Boost Intensity-Modulated Radiotherapy) techniques in terms of patient demographics, dosimetric profiles, and short-term treatment outcomes. The baseline characteristics including age, gender, residence, performance status (ECOG), tumor site, histology, and TNM staging were well balanced between the two treatment arms, with no statistically significant differences observed, ensuring comparability.

Dosimetric analysis revealed excellent target coverage in both groups, with PTV-HR V95% exceeding 99% in both arms. The mean dose delivered to the PTV-HR and PTV-LR was slightly higher in the SIB-IMRT arm, though not statistically significant. Organ-at-risk (OAR) sparing was comparable, except for a significantly higher mean dose to the larynx in the SMART arm (59.78 ± 7.69 Gy vs. 53.56 ± 9.23 Gy; $p = 0.005$), indicating a potential limitation of the SMART technique in sparing this critical structure. Our study demonstrated a progression-free survival (PFS) of 66.7% at a median follow-up of 14 months in the SMART arm and 56.8% in the SIB-IMRT arm, though long-term outcomes such as overall survival (OS) remain to be assessed due to limited follow-up. These findings are comparable to prior studies. Among SIB-IMRT studies, Chao et al. (2003)[5] reported a 24-month PFS of 85%, while Spiotto et al.[6] (2014) observed 68.7% PFS and 66.9% OS at 24 months. Studer et al. [7](2006) reported 80% PFS and 82% OS, and Gupta et al.[1] (2012) noted 80.5% PFS and 68% OS. In contrast, our SIB-IMRT arm showed a lower 14-month PFS of 56.8%, potentially attributable to shorter follow-up and patient-related factors.

In the SMART arm, historical studies by Butler et al. [9](1999) showed a complete response (CR) rate of 95%, while Schwartz et al. [10](2007) reported 83% PFS and 80% OS at 36 months. Chan et al.[11] (2011) observed 79.1% PFS and 74.3% OS, and Tandon et al. [12](2018) reported 80% PFS and 86.7% OS at 24 months. Our SMART arm demonstrated a modest 66.7% PFS at 14 months, which, though lower than earlier studies, still appears favourable compared to the SIB arm in our cohort. The variation in outcomes between studies may be attributed to differences in radiation dose per fraction, patient selection, staging distribution, use of concurrent chemotherapy, and duration of follow-up. Our study used a dose of 2.4 Gy/# in the SMART arm and 2.12 Gy/# in the SIB arm, consistent with the regimens employed in previous trials.

Overall, SMART appears to provide comparable, if not superior, target coverage and clinical outcomes within a shorter treatment duration. However, the increased dose to the larynx in SMART warrants further attention to mitigate potential toxicity. Longer follow-up is needed to assess the impact of each technique on locoregional control, survival outcomes, and late toxicities. In this study, the SMART group showed a slightly higher mean survival time (15.53 months) than the SIB group (14.24 months). Median survival time was equal (18.67 months) across all groups. Confidence intervals for the median were only estimable in SMART and overall groups due to censoring in SIB. Similar findings were reported by Lee et al. [13](2018) and Kim et al.[14] (2020), favouring SMART. These results support the potential survival benefit of SMART over SIB.

Conclusion

The study concludes that the SMART boost technique is a feasible alternative to SIB-IMRT for treating locally advanced head and neck cancer, offering reduced overall treatment time (OTT) without compromising dosimetry, progression-free survival (PFS), or late toxicity.

Although acute toxicity—specifically hoarseness of voice and xerostomia—was significantly higher in the SMART arm, other outcomes were comparable between groups. Given the potential benefits for high-volume cancer centers, further randomized studies with larger sample sizes, longer follow-up, and inclusion of radiobiological endpoints are recommended to validate these findings and assess overall survival (OS).

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