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RESEARCH ARTICLE OPEN ACCESS

Simultaneous Integrated Boost Versus Sequential Boost Chemoradiotherapy Induced Toxicity and Its Association with Oral Candidiasis in Locally Advanced Head and Neck Cancer

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Abstract

Chemoradiotherapy for Locally Advanced Head and Neck Cancer (LAHNC) has varied immensely in the last 20 years with the evolution of conformal Radiotherapy techniques. Whether differences exist in these treatment techniques related to survival and toxicity, remains unanswered. Also, these vulnerable groups of subjects have an enhanced risk of oral Candidiasis, mainly because of immune suppression and mucosal damage. A two-year cross-sectional pilot study was conducted in Barpeta Cancer Centre, Barpeta District, Assam. Two hundred cases with histological confirmation of LAHNC under definitive chemoradiotherapy treatment of 66-70 Gy were included. Sequential boost (SB) was used to treat 130 patients and Simultaneous Integrated Boost (SIB) was used upon 70 patients as separate treatment arms. In both treatment arms Inj. Cisplatin 40 mg/m^2 per week was included as a simultaneous chemotherapeutic. Grading of toxicity was done every week after treatment initiation and during follow-up visits at the end of three (3) months post treatment. Overall survival (OS), Recurrence free survival (RFS) and Disease free survival (DFS) were estimated. Saliva samples were collected from each patient during the first follow up and inoculated on SDA with chloramphenicol. Germ tube test, Dalmau plate culture and Chrom Agar inoculation was used for speciation. The most common subtype was oropharyngeal carcinoma with no treatment-related death in either arm. The OS was estimated to be 70% in SB arm and 62% in the SIB treatment Arm, at the end of 2 years. SIB Arm showed high rates of advanced grade toxicities then SB Arm. Oral candidiasis prevalence was 65%, but was higher in SIB (71.4%) then SB arm (61.5%), and *Candida albicans* (46%) largely outnumbered candida Non-albicans. Significant association was found between high grade mucositis (χ^2 = 17.45, P < 0.001), dysphagia (χ^2 = 28.79, P < 0.001), dermatitis (χ^2 = 42.23, P < 0.001) with Candidal growth. Disease related outcomes showed no changes in both the treating arms. However toxicities and Candidal growth especially *Candida albicans* showed high association, warranting early interventions with oral care and antifungal therapies.

Keywords: Head and Neck Neoplasms, Chemoradiotherapy, Radiotherapy, Intensity-Modulated, Candidiasis, Oral, Radiation Toxicity, Dose Fractionation, Radiation

INTRODUCTION

Radiotherapy for Locally advanced Head and Neck cancer (LAHNC) has varied immensely in the last 20 years with the evolution of conformal Radiotherapy techniques like Intensity-Modulated Radiation Therapy (IMRT), Volumetric Modulated Arc Therapy (VMAT) and Image-Guided Radiation Therapy (IGRT). Whether differences exist in these treatment techniques related to survival and toxicity, remains unanswered.[1] Before the advent of conformal techniques, conventional radiotherapy consisted of a sustained radiation dose per session keeping in mind non cancerous tissue forbearance by consecutive tapering of fields. In the newer conformal methods, treatment involves delivering differential dose to Gross disease (GTV), high-risk subclinical disease (HR-CTV) and low-risk subclinical disease (LR-CTV) maintaining consistent therapeutic load. This method became popular due to its optimized processes (only a one stop inverse-optimised plan is required), and literatures propound enhanced dose homogeneity.[2,3] Hence, this IMRT method, described as Simultaneous Integrated Boost (SIB), has become the new normal when radiotherapy for LAHNCs is concerned. Literature suggests that sustained radiation dose per session to gross disease as more as 2.2 Gy/session with simultaneous chemotherapy[4] and 2.4 Gy/session while using radiotherapy alone,[5] and with integrated boost are innocuous and validated. Moreover, equal tumor control was also documented with a radiation dose-per-session as little as 1.8 Gy to the more conventional 2.0 Gy/fraction.[6] In spite of these dose-per-fraction ranges, variability exists within the SIB plans when outcome profiles and toxicities are concerned.[7]

Improvements in the conformal techniques have reignited interest in sequential boost (SB) planning. Recent narrative reviews and prospective studies in the era of treatment de-escalation continue to highlight mixed toxicity profiles between SIB and sequential techniques, while confirming equivalent tumor control.[8,9] Currently, only a few studies have been found that straightforwardly dealt with the variances among sequential boost (SB) and SIB when LAHNC is concerned. A randomized study from Thailand in 2015 investigated the toxicities and outcomes in a small group of nasopharyngeal carcinoma patients, showing no difference in acute toxicity rates or early outcomes between the two IMRT techniques.[10]

On the other hand, disruption of the oral microbiota and an impaired immune system due to chemotherapy and radiotherapy increases the risk of oral fungal infections, like candidiasis.[11] Also radiotherapy (RT) alone may cause xerostomia, oral mucositis, dysgeusia, dysphagia, and ulcerations which can be precursors for candidal colonization and proliferation in conjunction with an immunocompromised state.[12] *Candida* species most implicated in such conditions may be attributable to the following 5 *Candida* spp., as revealed by long-term global surveillance studies: *Candida albicans*, *Candida tropicalis*, *Candida glabrata*, *Candida krusei*, and *Candida parapsilosis*. Among these, *Candida albicans*, a diploid, polymorphic yeast, causes severe form of Candidiasis generating yeast cells, pseudohyphae, and real hyphae, three distinct morphologic forms.[13,14] Moreover, antifungal resistance is on the rise among *Candida* species, with resistance being documented to the azoles and echinocandins in *Candida glabrata,*[15] intrinsic resistance to fluconazole in *Candida krusei,*[16] and *Candida auris* being multidrug-resistant.[17]

Literatures equating therapeutic results and toxicities amid subjects under treatment of different conformal methods are minimal. The originality of the current study is bestowed upon its comprehensive estimation of *Candida* species prevalence, and their association with the conformal treatment modalities along with their toxicities in head and neck cancer patients in a specific region of India (Assam).

The purpose of this study is to analyse SB versus SIB chemoradiotherapy induced toxicity and its association with oral candidiasis in Head and Neck cancer patients.

MATERIALS AND METHODS

This cross-sectional pilot study was conducted in Barpeta Cancer Centre in Barpeta District, Assam, from October 2021 to September 2023 as a hospital-based. Approval was taken from the Institutional Ethical Committees of VISTAS, Chennai (Letter No. VISTAS-SPS/IEC/I/2022/05) and Fakhruddin Ali Ahmed Medical College & Hospital, Assam (Letter No. FAAMC&H/P. Est./I.E.C./26/2021/346). Dual approvals complied with the ethical requirements of the academic institution (VISTAS, Chennai) and the clinical site (Barpeta Cancer Centre, Assam), thereby adhering to regional and institutional ethical standards. Informed consent from all participants was obtained.

This cross-sectional study was carried out in a tertiary care hospital as a pilot study by randomly selecting a cohort of two hundred (200) cases with histological confirmation of squamous cell LAHNC under definitive chemoradiotherapy treatment of 66 Gy-70 Gy.

Inclusion criteria of participants were patients with histologically confirmed squamous cell LAHNC who were scheduled to receive conformal radiotherapy technique and who provided written informed consent.

Exclusion criteria consisted of participant refusal, current use of antifungal drugs, use of immune altering drugs, and documented baseline candidiasis.

Sequential boost was used to treat 130 patients and Simultaneous Integrated Boost (SIB) was used upon 70 patients using VMAT/IMRT/IGRT as separate treatment arms. Radiotherapy for sequential Arm was implemented in three (3) Stages, Stage I: 46 Gy-50 Gy, Stage II: 10 Gy -14 Gy, and Stage III: 10 Gy, whereas SIB Arm as 66 Gy (High risk), 60 Gy (Intermediate risk), and 54 Gy (Low risk). In both treatment arms Inj. Cisplatin 40 mg/m^2 per week was included as a simultaneous chemotherapeutic. There are no significant differences pertaining to chemo cycles. Both groups received weekly chemo 5-6 cycles and B/L neck nodal RT.

Toxicities were graded in conformity to the latest criteria laid down in the Common Terminology Criteria for Adverse Events. Dermatitis, mucositis, xerostomia and dysphagia were separately graded numerically every week after treatment initiation and during follow-up visits at the end of three (3) months post treatment. Recurrence free survival (RFS), Disease free survival (DFS) and Overall survival (OS) were also calculated.

All statistical analyses were performed using SPSS software for Windows, version 26.0. Descriptive statistics are presented as frequencies and percentages for categorical variables and as medians with ranges for continuous variables. Categorical variables were compared between groups using the Pearson χ^2 test or Fisher's exact test (when any expected cell frequency <5). Survival outcomes (OS, DFS, RFS) were estimated by the Kaplan–Meier method and compared between arms using the log-rank test. Two-sided P <0.05 were considered statistically significant. 95% confidence intervals were reported.

During the first 3 monthly follow up, the spitting technique was used to collect 5 ml of saliva samples from all the study participants into sterile wide-mouthed sample containers. Saliva samples are a non-invasive collection method and have the reliability of reflecting microbial colonisation of the oropharynx. The samples were then inoculated on Sabouraud dextrose agar slants with chloramphenicol. Gram stain was performed for morphological identification of budding yeast cells. Using germ tube assays, *C. albicans* was quickly identified morphologically. The generation of blastoconidia and chlamydospores was measured using cornmeal agar. It was followed by inoculation into Chrom Agar medium for the differentiation and identification of *Candida* spp., since the medium contains chromogenic substrates that change colour in response to specific enzymes produced by different *Candida* spp. The isolates on the SDA media were cultured for 48 hours at 37 °C in the dark. To satisfy the requirements, a number of biochemical tests were also carried out, including fermentation and sugar assimilation.

Table 1. Patient Demographics: N = 200 (SB = 130/ SIB = 70)

Characteristics	Sequential Boost (SB) (n_1 = 130)	SIB (n_2 = 70)
Sex		
Male	95 (73%)	58 (83%)
Female	35 (27%)	12 (17%)
Age		
Median age	55 (30-80)	52 (32-70)
Tobacco/Tobacco Related Products		
Yes	110 (84.6%)	60 (86%)
No	20 (15.4%)	10 (14%)

RESULTS

In this cross-sectional pilot study, 200 cases with histological confirmation of carcinoma of the squamous cell type in the head and neck region were enrolled, with 130 patients treated using sequential boost (SB) chemoradiotherapy and 70 using simultaneous integrated boost (SIB). Patient/Case profiles are summarized in Table 1. The major chunk of cases were male (74% in SB arm and 83% in SIB arm), with median age being 55 years (range 30-80) in the SB arm and 52 years

Table 2. Site/Stage/Treatment Profile/Performance score (ECOG) of LAHNC patients: N = 200 (SB = 130/ SIB = 70)

Characteristics	Sequential Boost (SB) (n_1 = 130)	SIB (n_2 = 70)
Site		
Oropharynx	65 (50%)	42 (60%)
Larynx	32 (24.6%)	12 (17%)
Hypopharynx	20 (15.3%)	10 (14%)
Oral cavity	12 (9.4%)	3 (4.5%)
MUO neck	1 (0.7%)	3 (4.5%)
Stages		
II	5 (4%)	7 (10%)
III	25 (19%)	13 (18.5%)
IVA	70 (54%)	35 (50%)
IVB	30 (23%)	15 (21.5%)
Treatment		
CCRT	98 (75.5%)	49 (70%)
RT	32 (24.5%)	21 (30%)
Performance Score (ECOG-ideal score being 0)		
0	50 (38.5%)	35 (50%)
1	60 (46%)	30 (42.5%)
2	20 (15.5%)	5 (7.5%)

(range 32-70) in the SIB arm. Tobacco or related product use was prevalent in both arms (84.6% in SB and 86% in SIB).

Tumor site, stage, treatment modality, and performance status are detailed in Table 2. Oropharyngeal carcinoma was the highest encountered anatomical location in both treating arms (50% in SB and 60% in SIB), followed by laryngeal (24.6% in SB and 17% in SIB) and hypopharyngeal (15.3% in SB and 14% in SIB) primaries. Most patients presented with advanced disease (Stage IVA: 54% in SB and 50% in SIB; Stage IVB: 23% in SB and 21.5% in SIB). Concurrent chemoradiotherapy (CCRT) was administered to 75.5% of SB patients and 70% of SIB patients, with the remainder receiving radiotherapy alone. OAR'S achieved as per Quantac and ALARA principle. But case to case variation was observed in both groups, but within tolerance. Eastern Cooperative Oncology Group (ECOG) performance scores were generally favorable, with ECOG 0-1 in 84.5% of SB patients and 92.5% of SIB patients.

Table 3. Prevalence and profile of *Candida* spp. isolated: N = 200 (SB = 130/SIB = 70)

Species Isolated	Sequential Boost (SB) (n_1 = 130)	SIB (n_2 = 70) (N = 200)	Prevalence rate
Candida albicans	55	37	92 (46%)
Candida krusei	15	9	24 (12%)
Candida tropicalis	10	4	14 (7%)
Total isolates	80 (61.5%)	50 (71.4%)	130 (65%)

Oral candidiasis was detected in 130 patients (65% overall prevalence), with a higher rate in the SIB arm (71.4%, 50/70) compared to the SB arm (61.5%, 80/130), which was found to be numerically significant. *Candida albicans* was the mostly encountered species (46% of the culture positives), then by *Candida krusei* (12%) and *Candida tropicalis* (7%). The prevalence and species profile are depicted in Table 3.

Acute toxicities were graded weekly during treatment. In the SB arm (Table 4), Grade 3-4 mucositis occurred in 65% of patients, dysphagia in 50%, dermatitis in 42%, and xerostomia in 15%. In the SIB arm (Table 5), rates of Grade 3-4 toxicities were higher for mucositis (80%), dysphagia (75%), and dermatitis (70%), but lower for xerostomia (5%).

Survival outcomes at 2 years are presented in Table 6. Overall survival (OS) was 70% (95% CI: 56%-79%) in SB arm followed by 62% (95% CI: 50%-74%) in SIB arm. Disease-free survival (DFS) was 76% (95% CI: 68%-83%) in SB and 70% (95% CI: 55%-79%) in SIB. Local recurrence-free survival (RFS) was 89.5% (95% CI: 78.5%-95.5%) in SB and 85.5% (95% CI: 78%-92%) in SIB, with similar regional RFS (90% vs. 91%) and distant DFS (88% vs. 89%). Disease related outcomes showed no changes in both the treating arms.

Associations between high-grade (Grade 3+) acute toxicities and the presence of oral candidiasis are summarized in Table 7. Candidiasis prevalence was significantly higher in patients with Grade 3+ mucositis (74.5% vs. 42.4% in low-grade; $\chi^2 = 17.45$, $P < 0.001$), dysphagia (80.5% vs. 42.7%;

Table 4. Acute Toxicity: SEQUENTIAL BOOST (SB) arm (n_1 = 130)

Toxicity/Grade	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Dermatitis	0%	3%	55%	40%	2%
Mucositis	1%	4%	30%	60%	5%
Xerostomia	10%	50%	25%	15%	0%
Dysphagia	3%	12%	35%	50%	0%

Table 5. Acute Toxicity: SIB arm (n_2 = 70)

Toxicity/Grade	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Dermatitis	0%	10%	20%	50%	20%
Mucositis	2%	8%	10%	55%	25%
Xerostomia	0%	50%	45%	5%	0%
Dysphagia	0%	10%	15%	60%	15%

Table 6. Overall Performance of patients treated with Sequential vs SIB arm

Parameter	Sequential boost Arm	SIB Arm
OS	70% (56-79)	62% (50-74)
DFS	76% (68-83)	70% (55-79)
Local RFS	89.5% (78.5-95.5)	85.5% (78-92)
Regional RFS	90% (80-95)	91% (84-94)
Distant DFS	88% (76-92)	89% (78-95)

χ^2 = 28.79, P < 0.001), and dermatitis (86.5% vs. 41.7%; χ^2 = 42.23, P < 0.001). No significant association was found with xerostomia (75.0% vs. 63.6%; χ^2 = 0.75, P = 0.386).

DISCUSSION

This pilot study compared SB and SIB chemoradiotherapy in LAHNC, revealing no major changes in oncologic consequences, with 2-year

Table 7. Association Between High-Grade Acute Toxicities (Grade 3+) and Presence of Oral Candidiasis (Overall, N = 200)

Toxicity	Grade Level	No Candidiasis (n = 70)	Candidiasis (n = 130)	Prevalence of Candidiasis (%)	χ^2	P-value
Mucositis	Low (0-2, n = 59)	34	25	42.4	17.45	<0.001
	High (3+, n = 141)	36	105	74.5		
Dysphagia	Low (0-2, n = 82)	47	35	42.7	28.79	<0.001
	High (3+, n = 118)	23	95	80.5		
Dermatitis	Low (0-2, n = 96)	56	40	41.7	42.23	<0.001
	High (3+, n = 104)	14	90	86.5		
Xerostomia	Low (0-2, n = 176)	64	112	63.6	0.75	0.386
	High (3+, n = 24)	6	18	75.0		

OS at 70% (SB) versus 62% (SIB), DFS at 76% versus 70%, and comparable RFS rates. These results match with Mani et al.,[18] who outlined equivalent OS and DFS in a randomized trial of 68 LAHNC patients, and Jiang et al.[19] meta-analysis showing no differences in OS (HR 0.94) or recurrence metrics between SIB and sequential IMRT. Also neutropenia was not experienced in either arm, because the chemotherapy protocol used was weekly and not 3 weekly.

Acute toxicities were higher in SIB, with Grade 3-4 mucositis (80% vs. 65%), dysphagia (75% vs. 50%), and dermatitis (70% vs. 42%), consistent with Sharma et al.[20] reporting elevated dermatitis in SIB-VMAT, and Mani et al.[18] observing similar trends. This pattern is further corroborated by recent 2025-2026 prospective and comparative analyses showing often elevated acute dermatitis, mucositis, and dysphagia with SIB/VMAT approaches, although survival metrics remain comparable.[8,9,21] Late toxicities were also more frequent in SIB, as reported by Vlacich et al.[1] Moreover, patients in SIB arm had treatment break due to higher grades of toxicity and candidiasis compared with sequential arm.

Oral candidiasis prevalence was 65% overall, higher in SIB (71.4% vs. 61.5%), with the predominance of *Candida albicans* (46%). This matches Chitapanarux et al.[22] at 53.5%-65.9% during RT, and Pereira-Riveros et al.[23] at 64.6% in irradiated Head and Neck Cancer. Recent prospective observational data (2026) have reinforced the high colonization rates during radiotherapy (rising to >60% by treatment completion) and demonstrated a clear correlation between Candida positivity and worsening mucositis severity.[24]

Significant associations linked candidiasis to high-grade mucositis (74.5% prevalence; χ^2 = 17.45, P < 0.001), dysphagia (80.5%; χ^2 = 28.79, P < 0.001), and dermatitis (86.5%; χ^2 = 42.23, P < 0.001), but not xerostomia. Kawashita et al.[25] and Saito et al.[26] reported similar ties to severe mucositis and dysphagia (OR 2.75), while Deng et al.[27] noted candidiasis, worsening soreness and swallowing. Recent studies confirm this

bidirectional relationship, where severe mucosal injury facilitates fungal overgrowth, which in turn exacerbates symptoms and may prolong recovery.[24,28,29] The higher toxicity burden in the SIB arm is biologically plausible because larger daily fractional doses to the gross tumour volume intensify acute mucosal and dermal injury, thereby creating a more favourable environment for fungal overgrowth.

Clinically, these results highlight the importance of proactive supportive care. Implementation of standardised oral care protocols, prophylactic or early therapeutic antifungals (e.g., fluconazole or nystatin in patients developing Grade 2+ mucositis), and close monitoring of dysphagia may reduce candidiasis incidence, improve treatment tolerance, and enhance quality of life. Contemporary evidence supports proactive strategies including standardized oral care protocols and early antifungal use in patients developing Grade 2+ mucositis to improve treatment tolerance.[24,30,31] Although both techniques yielded similar oncologic outcomes, the more favourable toxicity profile of sequential boost (SB) regiment in the current study which even though is in contrast to other studies,[32] may be preferable in resource-constrained settings where intensive supportive care is limited.

Strengths of the present study include prospective saliva sampling with gold-standard phenotypic speciation (germ-tube test, ChromAgar, Dalmau culture), simultaneous evaluation of toxicity and mycological outcomes in the same cohort, and the first such data from the North-Eastern region of India.

Limitations include the pilot nature of the study, unbalanced treatment arms (130 SB vs. 70 SIB), single-centre design, and 2 year follow-up, which limit assessment of late toxicities and long-term survival. Future multicentre randomised controlled trials with longer follow-up, health-related quality-of-life endpoints, and cost-effectiveness analyses are warranted.

CONCLUSION

No difference was noted in disease linked consequences among both the treatment arms. An increased rate of acute toxicity like Grade III/IV Radiation dermatitis, mucositis and associated oral candidiasis and dysphagia emphasizes the need for integrated oral care, including early antifungal intervention, to improve treatment tolerance and patient outcomes.

Limitation

1. Needs long term follow up to understand the recurrence pattern and late toxicity.
2. Pilot nature.
3. Unbalanced treatment arms.

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None.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

RC carried out the study. AKK and GG supervised the study. TS supported the study by providing clinical and treatment history and assisted with sample processing. DB contributed by ensuring adherence to laboratory standard operating procedures (SOPs) and validating the data. SB compiled the data and wrote the manuscript. All authors read and approved the final manuscript for publication.

FUNDING

None.

DATA AVAILABILITY

All datasets generated or analyzed during this study are included in the manuscript.

ETHICS STATEMENT

This study was approved by the Institutional Ethics Committees of VISTAS, Chennai (Approval No. VISTAS-SPS/IEC/I/2022/05), and Fakhruddin Ali Ahmed Medical College & Hospital, Barpeta, Assam (Approval No. FAAMC&H/P. Est./I.E.C./26/2021/346).

INFORMED CONSENT

Written informed consent was obtained from the participants before enrolling in the study.

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