

IMRT in head and neck cancers: Mapping recurrence to refine radiotherapy in the era of precision oncology

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Abstract. Head and neck squamous cell carcinoma (HNSCC) continues to be associated with substantial rates of locoregional recurrence despite advances in radiotherapy techniques and concurrent chemotherapy. Understanding recurrence patterns following definitive treatment is essential for optimizing treatment strategies and improving disease control. The present study evaluated the incidence and patterns of recurrence in patients with HNSCC treated with intensity-modulated radiation therapy (IMRT) and concurrent chemotherapy and explored factors associated with treatment failure. The present retrospective study included patients with HNSCC treated with definitive IMRT and concurrent chemotherapy. Following eligibility assessment and follow-up availability, 239 patients were analyzed. Patients were followed for up to 3 years, and recurrences were identified through clinical, radiological, and pathological evaluation. Recurrence patterns were classified according to their relationship to the irradiated treatment volumes. During follow-up, 77 of 239 patients (32.2%) developed recurrent disease. In-field recurrence was the predominant pattern of failure, occurring in 48.1% of recurrent cases, followed by marginal recurrence in 29.9%. Local recurrence was the most common form of marginal failure. Midline primary tumors, advanced disease stage and prolonged overall treatment time (≥ 56 days) were associated with an increased risk of recurrence. Cervical lymph nodes represented the most frequent site of recurrence. In conclusion, in-field recurrence remains the most common pattern of failure following definitive IMRT with concurrent chemotherapy for

HNSCC. Advanced-stage disease, midline primary tumors, and prolonged treatment duration were associated with poorer outcomes. These findings underscore the importance of maintaining treatment continuity and highlight the need for further research into biological mechanisms of treatment resistance and strategies to improve local control.

Introduction

Head and neck cancers represent a major oncological burden worldwide, accounting for ~4.5% of all malignancies globally and a disproportionately high 30% of all cancers diagnosed in India, reflecting geographic and lifestyle influences on disease incidence (1,2). Over the past few decades, the incidence of these malignancies has exhibited a steady increase, with some estimates suggesting an annual increase of almost 30% (3). These cancers are more prevalent among the male population, typically presenting at the age of ~60 years, and are strongly associated with lifestyle-related risk factors, such as tobacco use, both smoking and smokeless forms, and chronic alcohol consumption (4,5).

Histologically, the majority of these cancers are squamous in origin and are grouped together as head and neck squamous cell carcinoma (HNSCC). Based on their anatomical origin, they are further subcategorized into cancers of the oral cavity, oropharynx, hypopharynx, nasopharynx, larynx and salivary glands. Each of these subsites exhibits distinct patterns of clinical presentation, lymphatic drainage and metastasis. For instance, tumors of the oral cavity frequently metastasize to levels I, II and III of the cervical nodes, whereas oropharyngeal cancers often metastasize to levels II, III and IV. Similarly, hypopharyngeal cancers tend to spread to levels II-IV, and occasionally to level I, whereas laryngeal tumors predominantly involve levels II and III (6).

The cornerstone of HNSCC treatment is a multidisciplinary approach that incorporates surgery, radiation therapy and chemotherapy, often in combination (4). Early-stage tumors can be treated with a single modality, either surgery or radiation, with a curative intent. However, multimodal therapy is typically required for locally advanced tumors. Surgery with wide local excision and comprehensive cervical lymphadenectomy

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serves not only to remove gross disease, but also to provide vital prognostic information through pathological analysis. Key adverse prognostic factors include tumor diameter, depth of invasion, histological differentiation, perineural invasion (PNI), lymphovascular invasion, nodal metastases and extracapsular extension (ECE) (7). The identification of such features often necessitates the addition of adjuvant radiation therapy, with or without concurrent chemotherapy, to reduce the risk of locoregional recurrence.

Radiation therapy plays a pivotal role in both definitive and adjuvant settings. In patients who are unfit for surgery or when tumors are deemed unresectable due to anatomical constraints, definitive chemoradiation is the preferred strategy. To enhance treatment outcomes, altered fractionation schedules were investigated. Hyperfractionation, which involves delivering smaller doses per fraction more than once daily, aims to increase the total radiation dose without increasing the toxicity. By contrast, accelerated fractionation maintains the total dose, but shortens the overall treatment time (OTT) to counteract tumor repopulation during therapy. Both approaches have shown promise for improving local control, albeit at the cost of increased acute and late toxicities (8-10).

Despite the advancements made in treatment protocols, recurrence remains a persistent and challenging issue, particularly in patients with locally advanced HNSCC. The majority of recurrences tend to occur within the high-dose radiation fields, referred to as 'in-field recurrences'. This suggests the presence of radioresistant tumor cell populations or microenvironmental factors that hinder complete tumor eradication despite adequate dosing. These findings underscore the need for further investigation into recurrence patterns and mechanisms of resistance to radiation therapy. Such insights could inform future strategies, including dose escalation to high-risk volumes, incorporation of radiosensitizers, advanced radiation delivery techniques, such as intensity-modulated radiation therapy (IMRT) or proton therapy, and the development of molecular markers to better predict treatment responses (11).

In summary, HNSCCs represents a heterogeneous and biologically complex group of malignancies with diverse clinical behaviors and treatment responses (12). While multidisciplinary treatment has improved survival outcomes over the years, the challenge of recurrence, particularly within irradiated volumes, necessitates the continuous refinement of therapeutic strategies. Understanding these recurrence patterns and integrating molecular and clinical insights are critical for guiding future innovations for the management of head and neck cancer.

The primary objective of the present study was to assess the incidence of recurrence in patients with HNSCC treated with IMRT. The secondary objective was to examine the pattern of recurrence in patients who received concurrent chemotherapy and associate recurrence with tumor volume and radiation dose distribution.

Patients and methods

Study design and patient selection. The present retrospective observational study was approved by the Institutional Ethics Committee of Kasturba Medical College, Mangalore, India (IEC KMC MLR 07/2022/295) on July 20, 2022. Written

informed consent was obtained from all participants prior to inclusion in the study.

Study-specific access to medical records, data extraction, follow-up data collection and statistical analysis commenced only after ethics approval had been obtained. The study was conducted between July, 2022 and December, 2024. Eligible patients had received definitive treatment for histologically confirmed HNSCC at Kasturba Medical College, Mangalore, India between January, 2017 and February, 2022. Thus, January, 2017 to February, 2022 represented the historical treatment period, whereas July, 2022 to December, 2024 represented the ethics-approved retrospective study and data collection period. Medical records from the historical treatment cohort were reviewed following ethics approval to assess recurrence and recurrence patterns during the predefined 3-year follow-up period.

A total of 359 patient records were initially screened for eligibility based on the predefined inclusion and exclusion criteria presented in Table I.

Data collection and processing. Patient records were reviewed for demographic data (age and sex), clinical characteristics (tumor site, stage and histology), treatment modalities (radiotherapy dose/fractionation and chemotherapy regimen), and follow-up outcomes (recurrence and survival). All the data were entered into a structured spreadsheet. Patients were classified as 'lost to follow-up' only after three unsuccessful telephone contact attempts via the official hospital line. Data from these patients up to their last follow-up were included in the analysis.

Radiation therapy protocol. The patients received radiation therapy using a linear accelerator (LINAC; Model: Compact, Elekta Ltd.) with 6 MV photon beams. The simulation was performed using contrast-enhanced computed tomography (CECT; Wipro GE, Model: High Speed) from the vertex to the T4 vertebral level. A baseplate and individualized immobilization mold were used. Planning CT images were transferred to a Treatment Planning System (TPS) (Focal Sim, Elekta Ltd.) for IMRT planning. The volumes were delineated according to ICRU Reports 50 and 62.

Conventional fractionation (2 Gy/fraction, five fractions/week) was administered at a total dose of 60-70 Gy. For patients undergoing hyperfractionation, high-risk planning target volume (PTV) received up to 81.6 Gy in 1.2 Gy fractions, administered twice daily with an inter-fraction interval of ≥ 6 h. The prescribed dose was planned so that 99% of the PTV received at least 95% of the prescribed dose.

Chemotherapy protocol. Concurrent chemotherapy was administered using three regimens based on patient performance status and renal function, as follows: Three-weekly cisplatin (100 mg/m² body surface area, calculated using the Du Bois formula) for ECOG 0-1 and creatinine clearance ≥ 60 ml/min (Cockcroft-Gault formula); weekly cisplatin (40 mg/m²) for ECOG 1-2 and creatinine clearance 50-60 ml/min; weekly carboplatin (AUC 1.5-2, calculated using the Calvert formula) for ECOG 1-2 and creatinine clearance 40-50 ml/min; cetuximab was used in cisplatin-ineligible patients (400 mg/m² loading dose followed by 250 mg/m² weekly).

Table I. Pre-defined inclusion and exclusion criteria used in the present study.

Inclusion criteria	Exclusion criteria
1. Patients aged ≥ 18 years	1. Patients who received radiation therapy at institutions other than the authors' center (Department of Radiation Oncology, Kasturba Medical College Mangalore, Manipal Academy of Higher Education, Manipal, India).
2. Histologically confirmed diagnosis of head and neck malignancy	2. Patients who died prior to treatment completion or within 3 months post-treatment
3. Stages I to IVB as per the American Joint Committee on Cancer (AJCC) 8th Edition Tumor Node Metastasis (TNM) staging system	3. Patients who did not complete the prescribed treatment regimen
4. Patients treated with definitive or adjuvant external beam radiation therapy (EBRT) with or without chemotherapy	4. Patients treated with palliative intent

Follow-up and response assessment. The treatment response was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). Monthly clinical assessments were conducted for the first 3 months post-treatment. Imaging (CECT or MRI) was performed 3 months thereafter. Thereafter, patients were followed up every 3 months for the first 3 years. Recurrence was confirmed using appropriate imaging and histopathological evaluation whenever indicated (these data were already available in the medical records of the patients and were obtained as part of the institution's standard post-treatment follow-up protocol. Recurrence status was determined using the clinical, radiological, and histopathological information documented during routine follow-up evaluations. Although some patients continued routine institutional surveillance beyond 3 years according to standard clinical practice, only events occurring within the first 3 years were included in the present analysis).

Statistical analysis. Descriptive statistics were computed using IBM SPSS Statistics for Windows (version 25.0; IBM Corp.). Continuous variables were summarized using the mean $\pm$ standard deviation (SD), or median with inter-quartile range (IQR) based on the data distribution. Categorical variables are expressed as frequencies and percentages. Data analyzed included baseline demographic and clinical characteristics such as age, sex, smoking/alcohol habits, tumor stage, site of primary, histopathological grade and degree of differentiation, sequencing of radiation $\pm$ chemotherapy cycles, as well as patterns of recurrence. The primary outcome was the disease-free survival which was estimated using the Kaplan-Meier method. As no subgroup survival comparisons were performed, log-rank testing was not undertaken.

Factors associated with recurrence were initially evaluated using univariable analyses. Variables considered clinically relevant based on established evidence, as well as variables demonstrating a significance level of $P < 0.20$ on univariable analysis (Chi-squared test or Fisher's exact test where appropriate), were entered into a multivariable logistic regression model. The variables included age, body mass index (BMI),

T stage, N stage, OTT, treatment interruption duration, number of chemotherapy cycles and chemotherapy regimen. Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were calculated to identify independent predictors of recurrence. Comparisons of mean radiation dose among patients with in-field, marginal and out-field recurrence were performed using one-way analysis of variance (ANOVA). A value of $P < 0.05$ was considered to indicate a statistically significant difference.

Of note, minimize bias as much as possible, all data were collected based on predetermined inclusion and exclusion criteria using valid diagnostic methods for identification and standard definitions for data collection.

Results

Patient demographics and tumor characteristics. A total of 359 patients with HNSCC met the initial inclusion criteria. After excluding patients with residual disease ($n=50$), early mortality ($n=63$) and those lost to follow-up ($n=7$), 239 patients were included in the final analysis. The mean age of the patients was 55.5 ± 9.91 years, with a male predominance (82.43%). Common risk habits included smoking (39.5%), alcohol consumption (26.9%) and a combination of both (33.6%) (Table II). The oral cavity was the most common subsite, accounting for 181 of 239 patients (75.73%), followed by the oropharynx [22/239 (9.20%)], larynx [17/239 (7.11%)], and hypopharynx [14/239 (5.86%)]. Within the oral cavity ($n=181$), the buccal mucosa [93/181 (51.38%)] and anterior tongue [82/181 (45.30%)] were the predominant primary sites (Table III). The majority of patients presented with advanced-stage disease, with T4 and N0 being the most common T and N stages, respectively (Table IV).

Degree of differentiation. Histopathological grading was unavailable for 40 patients who only underwent fine-needle aspiration cytology (FNAC). The most frequent histological subtype was moderately differentiated squamous cell carcinoma ($n=100$; 41.84%). In total, 3 patients (1.26%) had salivary gland adenocarcinoma.

Table II. Patient demographics.

Characteristic	Value
Mean age $\pm$ SD (years)	55.5 $\pm$ 9.91
Median age (years)	55
Sex	
Male	197 (82.43%)
Female	42 (17.57%)
Median body surface area (m ²)	1.49
Habits	
Smoking	94 (39.5%)
Alcohol consumption	64 (26.9%)
Smoking + alcohol consumption	80 (33.6%)

Table III. Distribution of primary tumor subsites and oral cavity cancers.

A, Distribution of primary tumor subsites among the study population (n=239)

Primary tumor subsite	No. of patients	Percentage of total cohort
Oral cavity	181	75.73
Oropharynx	22	9.20
Larynx	17	7.11
Hypopharynx	14	5.86
Nasopharynx	3	1.26
Unknown primary	2	0.84
Total	239	100.00

B, Distribution of oral cavity cancers (n=181)

Oral cavity subsite	No. of patients	Percentage within oral cavity
Buccal mucosa	93	51.38
Anterior tongue	82	45.30
Other oral cavity subsites	6	3.31
Total	181	100.00

Values are presented as number (%) of patients. Percentages in part A were calculated using the total study population (n=239) as the denominator. Percentages part B were calculated using the oral cavity cohort (n=181) as the denominator.

Sequencing of radiation. The majority of patients received definitive radiation (n=170; 71.13%), whereas the remaining patients received adjuvant radiation. Key pathological risk features were assessed in 67 patients who underwent primary surgery followed by adjuvant radiation (excluding 2 patients with missing data). Lymphovascular space invasion (LVSI)

was identified in 20 patients with oropharyngeal carcinoma (29.85%), 3 patients with oral cavity carcinoma (4.48%) and 4 patients each with laryngeal and hypopharyngeal carcinomas (6.0% each). PNI was observed in 22 patients with oral cavity tumors (32.84%), 4 patients with oropharyngeal tumors (6.0%), and 3 and 4 patients with laryngeal and hypopharyngeal tumors (4.48 and 6.0%, respectively). ECE was present in 7 patients with oral cavity malignancies (10.45%), 4 patients with oropharyngeal malignancies (6.0%), and 1 patient each with laryngeal and hypopharyngeal malignancies (1.5% each). Positive surgical margins were observed in 20 patients (29.9%), including 9 patients with oral cavity tumors (13.43%), 6 with oropharyngeal tumors (9.0%), 3 with laryngeal tumors (4.48%), and 2 with hypopharyngeal tumors (2.99%).

Treatment-related factors: Incidence of recurrence. The present study included 239 patients over a 3-year period. During this time, 77 patients (32.21%) developed recurrences, while 162 patients (67.78%) remained recurrence-free. Notably, no recurrences were observed in tumors originating from the lip, salivary glands, or nasopharynx. The mean time to recurrence was found to be ~17 months (534 days). Kaplan-Meier analysis demonstrated disease-free survival rates of 91.9, 72.2 and 64.4% at 1, 2 and 3 years, respectively. Overall, 77 patients developed recurrence during follow-up, whereas 162 patients were censored. The Kaplan-Meier disease-free survival curve, including censoring marks and numbers at risk, is illustrated in Fig. 1. At 0, 12, 24 and 36 months, the numbers at risk were 239, 216, 146 and 81 patients, respectively. No between-group survival comparisons were performed, and therefore no log-rank test was applied.

Other contributing factors. The analysis of patient characteristics revealed associations between recurrence and lifestyle habits. The majority of the 77 patients with recurrence were male (n=64, 83.12%). However, sex was not statistically significant in predicting recurrence (P=0.984). A strong association was noted between the combined use of tobacco and alcohol, which was present in 60% of the recurrence cases. Smoking alone was observed in 8.51% of the patients. This combined habit was significantly associated with recurrence (P<0.001) (Table V). Only 1 patient with recurrence had no history of smoking or alcohol consumption.

Primary subsite distribution. Among the 77 patients who developed recurrence, the most frequently involved primary sites were the tongue (n=40; 51.95%) and tonsil (n=4; 5.20%) within the oral cavity and oropharynx, respectively.

Clinical stage and recurrence pattern

T stage distribution. Among the 77 patients who developed recurrence, the majority were initially diagnosed with advanced primary tumors. Specifically, T4 disease was the most prevalent stage at presentation and was observed in 44 patients (57.14%) across all subsites. Notably, no recurrence was reported among patients with oropharyngeal, laryngeal, or hypopharyngeal carcinomas who initially presented with T1 stage disease (Table VI). In addition, upon multivariate analysis, a higher T stage independently increased the odds

Table IV. Tumor characteristics.

Subsite	No. of patients								Total
	T1	T2	T3	T4	N0	N1	N2	N3	
Oral cavity	11	60	46	64	81	28	52	20	181
Oropharynx	0	4	9	9	9	3	6	4	22
Larynx	2	2	6	7	6	3	6	2	17
Hypopharynx	0	4	5	5	5	0	8	1	14
Salivary gland	0	0	1	2	1	1	0	1	3
Lip	0	1	0	0	1	0	0	0	1
Nasopharynx (NPC)	0	0	0	1	0	0	1	0	1
Total	13	71	67	88	103	35	73	28	239

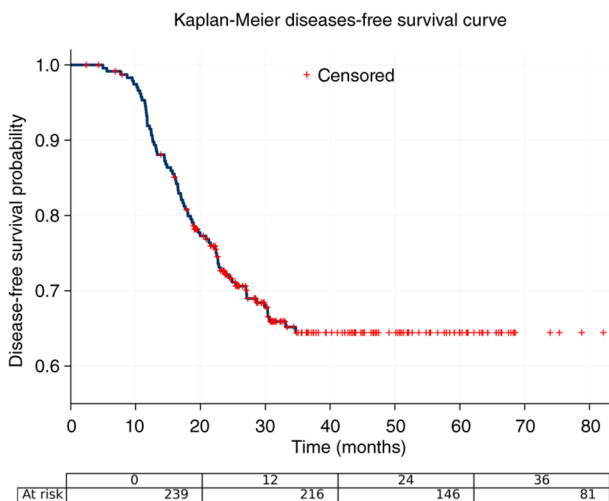


Figure 1. Kaplan-Meier estimate of disease-free survival.

of recurrence by ~72% (adjusted OR, 1.72; 95% CI, 1.09-2.73; $P=0.020$) (Table VII).

N stage distribution. The initial nodal staging revealed that N2 disease was the most common nodal status among patients who experienced recurrence (29/77, 37.66%). Among the recurrent oral cavity cancers ($n=60$), N2 disease was present in 21 patients (35.0%), followed by N0 disease in 19 patients (31.67%). Among recurrent oropharyngeal cancers ($n=8$), N2 and N3 disease were each observed in 2 patients (25.0%). In recurrent laryngeal cancers ($n=6$), N2 disease was the predominant nodal stage, occurring in 3 patients (50.0%). All recurrent hypopharyngeal cancers ($n=3$) initially presented with N2 disease. The distribution of initial nodal stage among patients who developed recurrence is summarized (Table VIII).

Patterns of recurrence. Among the 77 patients who developed recurrence, 33 (42.86%) experienced recurrence in other head-and-neck regions, while 30 patients (38.96%) developed cervical nodal recurrence. Although other head-and-neck sites collectively accounted for a slightly larger proportion of recurrences, the cervical lymph nodes represented the most

common single anatomical site of recurrence. Recurrence at the primary surgical site and distant metastatic sites occurred in 8 (10.39%) and 6 (7.79%) patients, respectively. Among the cervical nodal recurrences, oral cavity cancers were the most commonly implicated primary sites ($n=22$, 73.33%). The distribution of cervical nodal recurrence according to primary site is presented in Table IX.

OTT and treatment gaps. The median OTT for the entire cohort of 239 patients was 52 days. Among the patients who developed recurrence, the most common OTT was 56-60 days ($n=21$), whereas among the patients without recurrence, the most frequently observed OTT was 45-50 days ($n=78$). Unplanned treatment interruptions were defined as a continuous interruption in radiotherapy of ≥ 4 days. Among the patients who developed recurrence, 47 (61.03%) experienced unplanned treatment interruptions, compared with 57 (35.18%) of patients who did not develop recurrence. This difference was statistically significant ($P<0.001$, Chi-squared test). This finding suggests that prolonged treatment interruptions were more common among patients who subsequently experienced disease recurrence (Table X). Notably, upon multivariate analysis, a longer OTT was independently associated with a significantly increased risk of recurrence (adjusted OR, 1.37; 95% CI 1.23-1.52; $P<0.001$). Treatment interruptions (gap duration) were also an independent predictor of recurrence (adjusted OR, 1.45; 95% CI, 1.23-1.71; $P<0.001$) (Table VII).

Degree of differentiation. The majority of recurrences occurred in tumors initially classified as moderately differentiated, accounting for 35 cases (45%).

Pathological features. Among the patients who underwent primary surgical treatment and subsequently developed recurrence ($n=31$, 40.26%), ECE was the most frequently observed pathological feature. ECE was present in 3 of 4 recurrent oropharyngeal cancers (75%), 5 of 20 recurrent oral cavity cancers (25%), and 1 of 5 recurrent laryngeal cancers (20%).

Positive surgical margins were observed in 7 of 20 recurrent oral cavity cancers (35%), all 4 recurrent oropharyngeal cancers (100%), 3 of 5 recurrent laryngeal cancers (60%), and 1 of 2 recurrent hypopharyngeal cancers (50%). Among

Table V. Association of demographic and lifestyle factors with recurrence.

Variable	Recurrences (n=77) (%)	No. of recurrences (n=162) (%)	P-value
Sex			
Male	64 (83.12)	133 (82.10)	0.984
Female	13 (16.88)	29 (17.90)	
Habits			
Alcohol + smoking	46 (60.00)		<0.001
Smoking	31 (8.51)		

Table VI. Distribution of T stage among patients with recurrence (n=77).

T stage	Oral cavity (n)	Oropharynx (n)	Larynx (n)	Hypopharynx (n)	Total recurrences, n (%)
T1	2	0	0	0	2 (2.59)
T2	10	0	0	0	10 (13.00)
T3	14	5	1	1	21 (27.27)
T4	34	3	5	2	44 (57.14)
Total	60	8	6	3	77 (100)

Table VII. Multivariable logistic regression analysis of factors associated with recurrence.

Variable	Adjusted odds ratio (aOR)	95% Confidence interval	P-value
Age (years)	0.99	0.94-1.03	0.580
BMI (kg/m ²)	1.10	0.97-1.26	0.133
T stage	1.72	1.09-2.73	0.020
N stage	1.34	0.88-2.05	0.173
Overall treatment time	1.37	1.23-1.52	<0.001
Treatment interruption (gap duration)	1.45	1.23-1.71	<0.001
Number of chemotherapy cycles	1.23	0.92-1.66	0.165
Chemotherapy regimen (cisplatin vs. carboplatin)	0.85	0.39-1.88	0.694
Cetuximab vs. carboplatin	1.28	0.28-5.82	0.746

Variables included in the multivariable logistic regression model were selected based on clinical relevance and univariable screening ($P < 0.20$). The results of the univariable analyses are not shown. Adjusted odds ratios with 95% confidence intervals are presented. Statistical significance was defined as $P < 0.05$.

Table VIII. Initial N-stage distribution among patients who developed recurrence (n=77).

N stage	Oral cavity, n (%)	Oropharynx, n (%)	Larynx, n (%)	Hypopharynx, n (%)	Total, n (%)
N0	19 (31.67)	3 (37.50)	1 (16.67)	0 (0.00)	23 (29.87)
N1	10 (16.67)	1 (12.50)	0 (0.00)	0 (0.00)	11 (14.29)
N2	21 (35.00)	2 (25.00)	3 (50.00)	3 (100.00)	29 (37.66)
N3	10 (16.67)	2 (25.00)	2 (33.33)	0 (0.00)	14 (18.18)
Total	60 (100.00)	8 (100.00)	6 (100.00)	3 (100.00)	77 (100.00)

Table IX. Distribution of cervical nodal recurrences by primary site.

Primary site	No. of cases (n)	Percentage
Oral cavity	22	73.33
Oropharynx	3	10.00
Larynx	4	13.33
Hypopharynx	1	3.34
Total	30	100.00

Table X. Association of overall treatment time and treatment interruptions with recurrence.

Variable	Recurrences (n=77) (%)	No Recurrences (n=162)(%)	P-value
Overall treatment time (days)			0.001
45-50	18 (23.38)	78 (48.15)	
51-55	19 (24.68)	77 (47.53)	
56-60	21 (27.27)	7 (4.32)	
>60	19 (24.68)	0 (0.00)	
Treatment interruptions			<0.001
Gap ≥4 days	47 (61.04)	57 (35.18)	
Gap <4 days	28 (36.36)	64 (39.51)	
No gap	2 (2.60)	41 (25.31)	
Total	77 (100)	162 (100)	

recurrent oral cavity cancers, negative surgical margins were documented in 8 of 20 patients (40%), while margin status was unavailable in 5 patients (25%).

LVSI was identified in 11 of 20 recurrent oral cavity cancers (55%), 3 of 5 recurrent laryngeal cancers (60%), 1 of 4 recurrent oropharyngeal cancers (25%), and 1 of 2 recurrent hypopharyngeal cancers (50%). Univariate analysis demonstrated that LVSI was not significantly associated with recurrence ($P=0.504$). PNI was present in 14 of 20 recurrent oral cavity cancers (70%), 2 of 4 recurrent oropharyngeal cancers (50%), 2 of 5 recurrent laryngeal cancers (40%), and 1 of 2 recurrent hypopharyngeal cancers (50%). The presence of PNI exhibited a trend toward significance in the univariate analysis ($P=0.144$). As these pathological factors were not statistically significant predictors of recurrence, the pathological features in patients with recurrence following primary surgery are presented descriptively in Table XI.

Radiation. The most common recurrence pattern was in-field recurrence, observed in 37 patients (48.05%), followed by marginal recurrence in 23 patients (29.87%). Of note, no differences were noted in the dose distribution that caused patients to have a higher chance of recurrence based on the three recurrence patterns. Thus, the pattern of recurrence

was not significantly associated with the delivered radiation dose (ANOVA, $P=0.294$). Furthermore, in-field recurrences occurred at a slightly lower mean dose (60.6 Gy) than marginal or out-field recurrences (~63.8 Gy); however, this difference was not deemed statistically significant (Table XII).

Chemotherapy. Of the 77 patients who experienced recurrence, 71 (92.21%) received chemotherapy as part of their treatment, while 6 patients (7.79%) did not receive chemotherapy owing to poor general condition and were treated with radiation therapy alone. In comparison, among the 162 patients without recurrence, 122 (75.31%) received chemotherapy, whereas 40 (24.69%) were managed with radiation alone. Cisplatin was the most commonly used chemotherapeutic agent in both groups and was administered to 41 patients with recurrence (53.25%) and 77 patients without recurrence (47.53%). Among those treated with cisplatin, 3-weekly regimens were used in 12 patients with recurrence and 26 patients without recurrence, whereas weekly regimens were more commonly employed (29 and 51 patients, respectively). Carboplatin was administered to 24 patients with recurrence (31.17%) and to 38 patients without recurrence (23.46%). Cetuximab was administered to 6 patients in the recurrence group (7.79%) and 7 patients without recurrence (4.32%). A total of 6 patients with recurrence (7.79%) and 40 patients without recurrence (24.69%) received no chemotherapy. Of the 118 patients treated with cisplatin-based chemoradiation, 41 developed recurrences, corresponding to a recurrence rate of 34.75%. By contrast, 24 of the 62 patients treated with carboplatin developed recurrence, yielding a higher recurrence rate of 38.71%. These findings suggest that cisplatin-based regimens, particularly the 3-weekly schedule, may be associated with a lower recurrence rate than carboplatin (Table XIII). Among the patients who received systemic therapy, recurrence rates were 34.75% for cisplatin, 38.71% for carboplatin and 46.15% for cetuximab. Univariate analysis demonstrated no significant association between chemotherapy regimen and recurrence (Pearson's Chi-squared test, $P=0.670$; Table XIV).

Notably, in the multivariable logistic regression using recurrence as the dependent variable, the use of cisplatin did not differ significantly from carboplatin with respect to recurrence risk (adjusted OR 0.85; 95% CI, 0.39-1.88; $P=0.694$). Cetuximab demonstrated a non-significant trend toward inferior outcomes compared with carboplatin (adjusted OR, 1.28; 95% CI, 0.28-5.82; $P=0.746$). Independent predictors of recurrence were evaluated separately using multivariable logistic regression analysis, the results of which are presented in Table VII.

Recurrence relative to dose distribution, T and N stage. In the cohort of 77 patients, the most common type of recurrence across all head and neck subsites was in-field recurrence, observed in 37 patients (48.05%). This was followed by marginal recurrence in 23 patients (29.87%), and outfield recurrence in 15 patients (19.48%). A total of 6 patients (7.79%) developed distant metastases, most frequently in the lungs ($n=5$), and 1 patient had skeletal metastases.

The incidence of in-field recurrence was highest among patients with T4 tumors (24/77, 31.2%), particularly in the oral

Table XI. Pathological features of patients with recurrence following primary surgery.

Pathological feature	Oral cavity (n=20)	Oropharynx (n=4)	Larynx (n=5)	Hypopharynx (n=2)
LVSI	11 (55%) Present 9 (45%) Absent	1 (25%) Present 3 (75%) Absent	3 (60%) Present 2 (40%) Absent	1 (50%) Present 1 (50%) Absent
PNI	14 (70%) Present 6 (30%) Absent	2 (50%) Present 2 (50%) Absent	2 (40%) Present 3 (60%) Absent	1 (50%) Present 1 (50%) Absent
ECE	5 (25%) Present 15 (75%) Absent	3 (75%) Present 1 (25%) Absent	1 (20%) Present 4 (80%) Absent	0 Present 2 (100%) Absent
Positive margins	7 (35%) Positive 8 (40%) Negative 5 (25%) Data unavailable	4 (100%) Positive 0 Negative	3 (60%) Positive 2 (40%) Negative	1 (50%) Positive 1 (50%) Negative

LVSI, lymphovascular space invasion; PNI, perineural invasion; ECE, extracapsular extension.

Table XII. Association between recurrence pattern and delivered radiation dose (n=77).

Recurrence Pattern	No. of patients, n (%)	Mean radiation dose (Gy)
In-field recurrence	37 (48.05)	60.6
Marginal recurrence	23 (29.87)	63.8
Out-field recurrence	17 (22.08)	63.8
ANOVA P-value		0.294

Table XIII. Chemotherapeutic agents used in patients with and without recurrence.

Chemotherapy agent	Recurrences (n=77)	%	No recurrence (n=162)	%
Cisplatin (total)	41	53.25	77	47.53
3-weekly	12	-	26	-
Weekly	29	-	51	-
Carboplatin	24	31.17	38	23.46
Cetuximab	6	7.79	7	4.32
No chemotherapy	6	7.79	40	24.69
Total no. of patients	77	-	162	-

cavity. By contrast, patients with early stage T1 tumors had the lowest recurrence rate, with only two in-field failures and no marginal or out-of-field recurrences. This difference in the recurrence pattern according to the T stage was statistically significant ($P<0.001$). The association between T stage and recurrence pattern is shown in Table XV.

Similarly, N2 stage was most frequently associated with all recurrence types, particularly in-field and distant failures. Among patients with N2 disease, 3 patients developed distant lung metastases and 1 patient developed bone metastasis.

Furthermore, a significant association was observed between N stage and in-field recurrence ($P=0.034$). The association between N stage and recurrence pattern is shown in Table XVI.

Patients with advanced nodal disease ($\geq N2$) accounted for the majority of distant failures, representing 4 of the 6 patients (66.7%) who developed distant recurrence. Distant recurrences were most commonly observed in patients with T3-T4 disease. The distribution of distant recurrences according to T stage and N stage is summarized in Table XVII.

Marginal recurrences and site analysis. Among the 23 patients who developed marginal recurrences, the most common site of failure was local recurrence, occurring in 9 patients (39.13%). Regional nodal marginal recurrences were observed in 8 patients (34.78%), while surgical-site marginal recurrences occurred in 6 patients (26.09%). Local marginal recurrences were predominantly observed in the oral cavity, and notably all local marginal recurrences within the oral cavity were localized to the tongue. Among the regional nodal marginal recurrences, the contralateral level IV cervical lymph node was the most frequently involved nodal site, accounting for 4 of the 8 cases. Marginal recurrences at the surgical site most commonly originated from primary tumors of the oral tongue (n=3) and buccal mucosa (n=2). Of note, 1 patient with a tumor arising from the floor of mouth also developed a surgical-site recurrence. Additional sites of marginal recurrence included the base of tongue, pyriform fossa, supraglottis and retromolar trigone. The patterns of recurrences within the head and neck region, at the surgical site and at distant metastatic sites are depicted in Fig. 2.

Cervical lymph node levels in marginal recurrences. The analysis of the cervical nodal levels involved in marginal recurrences revealed that level IV was the most frequently affected, with 5 out of 8 nodal recurrences (62.5%) occurring at this level. Of these, 4 cases were contralateral to the primary tumor site and 1 case was ipsilateral. Contralateral level IV involvement was primarily associated with tumors originating in the tongue, buccal mucosa and tonsils. Additionally, 1 case of contralateral

Table XIV. Association between chemotherapy regimen and recurrence among patients receiving systemic therapy (n=193).

Chemotherapy regimen	Recurrence (n=71) (%)	No recurrence (n=122) (%)	Total	Recurrence rate (%)
Cisplatin	41 (57.75)	77 (63.11)	118	34.75
Carboplatin	24 (33.80)	38 (31.15)	62	38.71
Cetuximab	6 (8.45)	7 (5.74)	13	46.15
Total	71 (100)	122 (100)	193	
P-value				0.670

Table XV. Association between T stage and type of recurrence (n=77).

Location	Infield				Marginal				Outfield				Total patients, n (%)	P-value
	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4		
Oral cavity	2	6	6	20	0	3	5	7	0	1	3	7	60 (77.92)	≤0.001
Oropharynx	0	0	1	0	0	0	2	2	0	0	2	1	8 (10.40)	
Hypopharynx	0	0	0	1	0	0	0	1	0	0	1	0	3 (3.89)	
Larynx	0	0	1	3	0	0	0	2	0	0	0	0	6 (7.79)	
Total no. of patients	2	6	8	24	0	3	7	12	0	1	6	8	77 (100)	

Table XVI. Association between N stage and type of recurrence (n=77).

Location	Infield				Marginal				Outfield				Total patients, n (%)	P-value
	N0	N1	N2	N3	N0	N1	N2	N3	N0	N1	N2	N3		
Oral cavity	13	3	9	6	1	6	7	2	5	1	5	2	60 (77.92)	0.034
Oropharynx	0	0	0	1	2	0	1	1	1	1	1	0	8 (10.39)	
Hypopharynx	0	0	1	0	0	0	1	0	0	0	1	0	3 (3.90)	
Larynx	0	0	2	2	1	0	1	0	0	0	0	0	6 (7.79)	
Total non. Of patients	13	3	12	9	4	6	10	3	6	2	7	2	77 (100)	

Table XVII. Distant recurrences in relation to N stage and T stage (n=6).

T stage	N0	N1	N2	N3	Total distant recurrences
T1	0	0	0	0	0
T2	0	0	0	0	0
T3	0	1	3	0	4
T4	1	0	0	1	2
Total	1	1	3	1	6

level III involvement was observed in a patient with a tonsillar primary tumor, and 2 cases of level V involvement were noted, corresponding to the supraglottic and oral tongue tumors.

Histological differentiation and nodal recurrence. The histopathological findings of nodal recurrences were obtained from pathology reports available in the medical records of the patients demonstrated that 6 of the 8 patients (75%) had well-differentiated squamous cell carcinoma (W.D. SCC) on biopsy. Notably, among these cases, the primary tumor histology at initial diagnosis was moderately differentiated squamous cell carcinoma (M.D. SCC) in 4 patients and W.D. SCC in 1 patient. Of note, 1 additional patient was diagnosed with SCC without further sub-classification. In 1 patient, only FNAC was performed, precluding the assessment of the histological grade of the tumor.

As regards the radiation doses, the majority of the patients who developed marginal recurrences underwent adjuvant radiation (n=15; 65.22%) (Fig. 3), while the majority of patients underwent a single phase of radiation (n=6) and only 2 patients underwent phased radiation therapy.

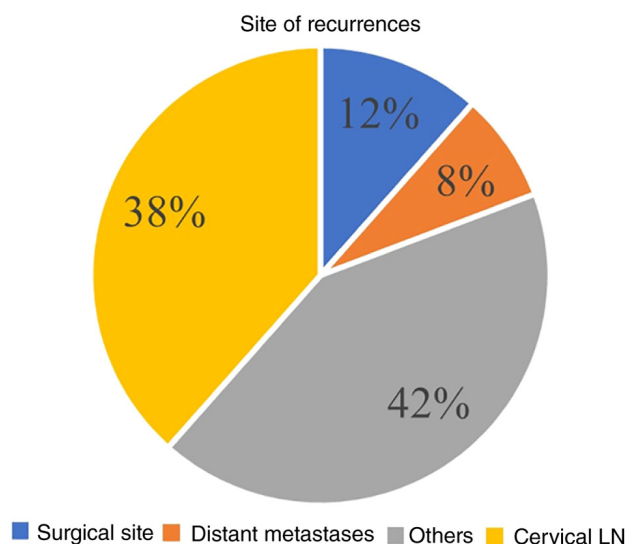


Figure 2. Distribution of recurrence sites.

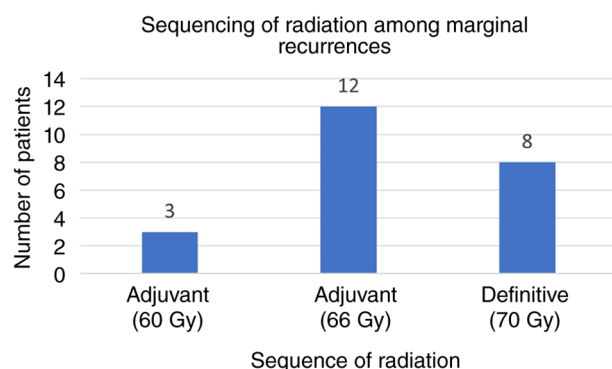


Figure 3. Sequencing of radiation among marginal recurrences.

Discussion

The present study evaluated the recurrence patterns and clinicopathological predictors of treatment failure in patients with squamous HNSCC treated with curative-intent IMRT, with or without concurrent chemotherapy. Approximately one-third of patients developed recurrence during follow-up, with almost half of these failures occurring within the high-dose treatment volume. These findings demonstrate that despite advances in conformal radiation delivery, locoregional recurrence remains the predominant mode of treatment failure and is influenced more by tumor biology than by geographical target miss.

In the present study cohort, the mean time to recurrence was 1 year and 5 months, with 32.21% of recurrences occurring within this period after completion of treatment. This finding indicates that the majority of treatment failures occur relatively early during follow-up, underscoring the importance of intensive surveillance during the first 2 years after therapy. These observations are consistent with those of previous reports demonstrating that the majority of HNSCC recurrences develop within the first few years following treatment, with several occurring during the first year following definitive or adjuvant therapy (13-15).

Regional recurrence was the predominant pattern of failure in the present study cohort, occurring in 30 patients (38.96%), which is comparable to the locoregional recurrence rates reported by Haring *et al* (42.5%) (16). The principal finding of the present study was the predominance of in-field recurrences, accounting for almost half of all failures. Similar recurrence patterns have been reported by Johansen *et al* (15), Raktoe *et al* (17), and Popovtzer *et al* (11), who likewise observed that the majority of failures following IMRT occurred within the high-dose planning target volume. These consistent observations across different cohorts suggest that treatment failure following contemporary IMRT is less likely to result from inadequate target coverage or geographical miss and more likely to reflect underlying tumor biology. Notably, the recurrence pattern was not significantly associated with delivered radiation dose in the present study, and patients with in-field recurrence received radiation doses comparable to those who developed marginal or out-of-field failures ($P=0.294$). This finding further supports the hypothesis that biological resistance rather than dosimetric inadequacy is the dominant mechanism underlying a number of recurrences. Advanced-stage tumors frequently harbor hypoxic sub-volumes, radioresistant cancer stem cell populations, and substantial intratumoral heterogeneity, all of which can reduce radiosensitivity despite adequate dose delivery. In addition, accelerated repopulation of surviving clonogens during treatment may contribute to persistent disease, particularly in patients with prolonged treatment duration. From a clinical perspective, these observations suggest that the further expansion of treatment volumes or uniform dose escalation alone may provide limited benefit, while increasing normal tissue toxicity. Instead, future IMRT strategies should focus on biologically guided treatment adaptation, including functional imaging-guided target delineation, hypoxia-directed dose painting, adaptive radiotherapy, and the integration of molecular and radiomic biomarkers to identify patients at greatest risk of in-field failure. Such approaches may permit selective intensification of treatment to resistant tumor sub-regions, while preserving normal tissue sparing, thereby maintaining the therapeutic advantages of IMRT.

In the present study cohort, distant recurrence was observed in 6 patients, with the oral cavity being the most common primary site. The majority of patients who developed distant metastases also had advanced nodal disease and extranodal extension (ENE), suggesting that a higher regional tumor burden may predispose to systemic dissemination. This observation is consistent with previous studies demonstrating an association between advanced nodal stage, ENE, and an increased risk of distant metastasis in HNSCC (18,19).

Herein, the multivariable analysis demonstrated that an advanced T stage, a prolonged OTT and treatment interruptions were independent predictors of recurrence, whereas age, BMI, nodal stage and chemotherapy cycles were not independently associated with recurrence following adjustment for other variables. The association between an advanced T stage and recurrence is biologically plausible. Larger tumors contain a higher burden of clonogenic cells, exhibit greater intratumoral hypoxia, and demonstrate increased molecular heterogeneity, all of which reduce radiosensitivity and increase the probability of residual microscopic disease

after treatment. These findings are consistent with previous reports from Yao *et al* (20) and Geretschlager *et al* (21), which demonstrated inferior local control in patients presenting with bulky T3-T4 disease.

Treatment duration emerged as one of the strongest predictors of recurrence. Each prolongation in OTT was associated with an increased risk of treatment failure. The accelerated repopulation of squamous cell carcinoma is considered to begin ~4 weeks following the initiation of radiotherapy, with tumor clonogens proliferating rapidly during treatment interruptions. The classical radiobiological studies by Skladowski *et al* (22) and Cannon *et al* (23) demonstrated that each day of unnecessary prolongation may reduce local control by ~1-2%. The findings of the present study reinforce the importance of maintaining uninterrupted treatment schedules and suggest that aggressive supportive care, prompt management of toxicities and the minimization of machine-related delays remain essential quality indicators in head and neck radiotherapy.

Herein, although advanced nodal stage was associated with recurrence in the univariate analysis, its significance diminished following adjustment for other clinical variables. Nevertheless, patients with N2 disease demonstrated the highest frequency of regional and distant failure, particularly when extranodal extension was present. This observation supports existing evidence that nodal disease reflects aggressive tumor biology and increased metastatic potential. Rather than functioning as an isolated prognostic marker, nodal stage may interact with tumor burden, extranodal extension and treatment-related factors to influence the risk of recurrence.

An additional key observation was the predominance of cervical nodal recurrence, particularly involving level IV lymph nodes, with several failures occurring contralateral to the primary tumor. This finding is clinically relevant because contemporary consensus contouring guidelines generally consider level IV to be a lower-risk region for several oral cavity tumors. Although the present study cannot justify routine expansion of elective nodal volumes, it suggests that patients with advanced-stage oral tongue cancers, midline lesions, extensive nodal disease, or extranodal extension may warrant more individualized target volume selection. Future studies incorporating deformable image registration and recurrence mapping could determine whether these marginal failures represent true geographical misses or biological failures occurring despite adequate dose coverage.

Among surgically treated patients, extranodal extension, positive margins and perineural invasion were frequently observed in recurrent disease. PNI was identified in 60% of oral cavity recurrences and 65% of laryngeal recurrences in the present study cohort, suggesting its association with an increased risk of treatment failure. PNI is a well-recognized adverse pathological feature that facilitates tumor spread along neural pathways and has been associated with poorer oncological outcomes, including recurrence, even in early-stage, node-negative HNSCC (24). Lubov *et al* (25) and Cassidy *et al* (26) identified extranodal extension and positive margins as major indications for adjuvant chemoradiotherapy. While several pathological variables including LVSI, PNI, ECE and positive surgical margins did not retain statistical significance, largely due to the limited sample size, their clinical importance should not be underestimated the lack of

statistical significance in our cohort likely reflects insufficient power rather than absence of biological effect.

The chemotherapy regimen did not independently influence recurrence in the present study. Patients receiving carboplatin or cetuximab demonstrated numerically higher recurrence rates than those treated with cisplatin; however, these differences were not statistically significant after adjustment. Xiang *et al* (27) found cancer-specific mortality to be lower with cisplatin (27%) than with carboplatin (30%). This finding should be interpreted cautiously, as treatment allocation was determined by performance status, renal function and comorbidities, introducing unavoidable selection bias. Accordingly, the results of the present study should not be interpreted as evidence of equivalent efficacy between chemotherapy regimens.

The present study possesses several strengths. It represents one of the larger single-institution analyses evaluating recurrence mapping following IMRT in a contemporary Indian cohort and combines detailed clinicopathological assessment with recurrence pattern analysis. Unlike a number of previous studies that reported treatment outcomes and recurrence primarily as an endpoint without detailing anatomical mapping of failure patterns (19,20), the present study characterizes the anatomical distribution of failure, identifies nodal levels at greatest risk and examines treatment-related factors contributing to recurrence.

Beyond identifying the anatomical distribution of treatment failure, these findings provide insight into the underlying mechanisms driving recurrence after IMRT. The predominance of in-field failures despite adequate dose delivery suggests that recurrence in numerous patients may be primarily related to intrinsic tumor biology rather than deficiencies in radiation planning or target coverage. Advanced T-stage tumors, which constituted the majority of recurrent cases in the present study cohort, are more likely to harbor hypoxic regions, increased clonogenic cell burden, and greater molecular heterogeneity, factors known to reduce radiosensitivity and promote treatment resistance. Furthermore, the high proportion of recurrences arising from oral tongue and other midline lesions may reflect complex lymphatic drainage patterns and occult microscopic disease crossing anatomical boundaries. The frequent occurrence of contralateral level IV nodal failures supports this hypothesis and indicates that recurrence risk in such patients may not be fully explained by conventional staging alone.

These findings also have direct implications for clinical practice. The strong association between a prolonged OTT, treatment interruptions and recurrence highlights the importance of maintaining uninterrupted radiotherapy schedules. From a quality-assurance perspective, minimising treatment gaps through proactive nutritional support, early toxicity management, and timely machine maintenance may represent one of the most immediately actionable strategies to improve outcomes. Similarly, the observed pattern of cervical nodal recurrence suggests that patients with advanced oral cavity tumors, midline primaries, or significant nodal burden may benefit from careful individualization of nodal target volumes and more intensive post-treatment surveillance. Collectively, these observations suggest that further gains in local control are likely to come not only from technical advances in

radiation delivery but also from biologically informed treatment adaptation and optimization of treatment execution.

The present study has several limitations which should be acknowledged. The retrospective design introduces the potential for selection and information bias. HPV testing was not conducted in many patients as it had not been integrated into the institutional testing schema at the time of patient treatment (2017-2022) and was thus not included in the statistical analysis. Pathological variables such as LVSI, PNI, extranodal extension and margin status were available only in surgically treated patients, reducing statistical power for multivariable modelling. Furthermore, recurrence mapping was performed using clinical imaging rather than deformable image registration onto the original planning CT, preventing precise dosimetric assessment of recurrence relative to delivered dose.

Future studies should incorporate deformable image registration, radiomic and genomic biomarkers, and prospective multicenter validation to more effectively distinguish biological radio resistance from technical treatment failure. The integration of functional imaging, adaptive radiotherapy and artificial intelligence-based risk stratification may permit selective treatment intensification for patients at greatest risk of in-field recurrence, while minimizing toxicity for lower-risk populations.

In conclusion, the present study demonstrates that locoregional in-field recurrence remains the dominant pattern of failure following IMRT for HNSCC. Advanced primary tumor stage, prolonged overall treatment time and treatment interruptions were the principal independent predictors of recurrence, underscoring the importance of treatment continuity and timely completion of radiotherapy. These findings suggest that future improvements in outcomes are more likely to arise from biologically guided treatment intensification and the optimization of treatment delivery than from simple expansion of radiation target volumes.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

RSA and AMS conceived and designed the study. RSA, AMS, SB, DL, AK, JS and PS collected the patient data. CS and DL contributed to data collection or analysis tools, such as SPSS software utilization. RSA, AMS, SB, AK, JS and PS performed the analysis and identification of significant contributory factors. RSA and AMS wrote the manuscript. All

authors have read and approved the final manuscript. RSA and AMS confirm the authenticity of all the raw data.

Ethical approval and consent to participate

The present retrospective observational study was approved by the Institutional Ethics Committee of Kasturba Medical College, Mangalore, India (IEC KMC MLR 07/2022/295) on July 20, 2022. Written informed consent was obtained from all participants.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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