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Key predictors of prolonged overall treatment time in head and neck cancer radiotherapy

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Original Article

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Abstract

Introduction: Prolonged overall treatment time (OTT) in radiotherapy (RT) for head and neck cancer (HNC), particularly beyond 49 days, has been linked to poorer tumour control and survival, primarily due to accelerated tumour repopulation. Identifying modifiable factors contributing to treatment delays may help improve outcomes. This study aimed to evaluate the association between pre-treatment clinical, nutritional and inflammatory factors and prolonged OTT.

Methods: We retrospectively analysed patients with non-metastatic HNC treated with definitive or postoperative RT (with or without chemotherapy) between 2020 and 2022. Pre-treatment factors included Eastern Cooperative Oncology Group (ECOG) performance status, tumour stage, treatment modality, body mass index (BMI), weight loss, sarcopenia (via C3 computed tomography imaging), neutrophil-to-lymphocyte ratio (NLR) and absolute lymphocyte count. Logistic regression was used to identify predictors of prolonged OTT (> 49 days).

Results: Among 465 patients, 287 (61·7%) experienced prolonged OTT. Multivariable analysis identified ECOG status (OR 1·42, $p = 0·004$), significant weight loss > 5% (OR 1·26, $p = 0·036$), concurrent chemotherapy (OR 1·96, $p = 0·005$), NLR (OR 1·03, $p = 0·041$) and sarcopenia (OR 1·18, $p = 0·042$) as independent predictors. Patient-related delays accounted for 53·3% of OTT prolongation, while public holidays contributed to 42·5%.

Conclusions: Several modifiable pre-treatment factors—including poor performance status, pre-treatment weight loss, sarcopenia and systemic inflammation—were independently associated with OTT prolongation. These findings provide evidence to support early, patient-tailored interventions such as prehabilitation and intensive nutritional counselling before and during RT. In addition, system-level strategies, including staffing adjustments and compensatory scheduling during public holidays, may further reduce avoidable treatment delays and enhance care delivery.

Introduction

Head and neck cancer (HNC) is the seventh most common cancer globally and remains among the top five cancers in Thailand.[1] Radiotherapy (RT) is a key treatment modality and can be delivered in radical, postoperative or palliative settings.[2] For curative intent, RT typically requires 5–7 weeks to complete the full prescribed dose. However, treatment-related toxicities frequently lead to unplanned interruptions.[3] These interruptions have been shown to adversely affect treatment outcomes.

From a radiobiological perspective, prolonged overall treatment time (OTT) compromises tumour control through accelerated repopulation of surviving clonogenic cells, typically beginning after the fourth week of RT. In HNC, where tumour cells can double within 4–5 days, treatment interruption allows these clonogens to rapidly repopulate.[4] Recent studies have further reinforced this concept, demonstrating that accelerated repopulation contributes to poorer clinical outcomes, including reduced local control, progression-free survival and overall survival.[5–8] This effect is especially pronounced in nasopharyngeal carcinoma (NPC), where OTT exceeding 49–70 days has been shown to significantly impact survival.[5,9] In our setting, particularly in Thailand, such prolongation is less often caused by the pre-treatment logistical delays or waiting time and more commonly results from unplanned interruptions occurring after RT has already commenced.

One factor contributing to treatment interruption is cancer cachexia, which is highly prevalent among HNC patients.[10] Simple and accessible indicators—such as BMI (using WHO cut-offs for Asians), significant weight loss (> 5% within three months) and pre-treatment weight—can offer useful insights into a patient's nutritional status and their ability to tolerate

intensive therapy.[10–15] Sarcopenia, in particular, has emerged as a key factor associated with treatment tolerance.[16,17] Although traditionally assessed using dual-energy X-ray absorptiometry or whole-body imaging, cross-sectional imaging from RT planning computed tomography (CT) scans can provide practical alternatives. While the skeletal muscle index (SMI) at the L3 level is the standard reference, the cross-sectional area (CSA) at the C3 level—routinely captured in HNC simulation scans—has shown strong correlation with L3-SMI and is increasingly used in clinical practice.[18–21]

In addition, systemic inflammatory markers such as the neutrophil-to-lymphocyte ratio (NLR) and absolute lymphocyte count (ALC), which are easily obtained from routine blood tests, reflect the interplay between systemic inflammation and immune status. Although both NLR and ALC have been associated with prognosis in HNC—including overall survival and disease progression[22–24] —their role in predicting treatment interruptions or prolonged OTT has not been clearly established and remains an area of interest.

Although these pre-RT clinical parameters—BMI, weight loss, inflammatory markers and sarcopenia—are routinely collected in RT centres, their predictive value for prolonged OTT remains uncertain. This study aims to evaluate whether these simple and widely available pre-treatment factors are associated with prolonged OTT in HNC patients. In addition to these biological and nutritional indicators, patient-related (e.g., age, performance status) and disease-related factors (e.g., tumour staging, treatment modality and concurrent chemotherapy) may also contribute to treatment prolongation. Identifying which of these factors are significantly associated with prolonged OTT, particularly those that are modifiable, may support timely interventions such as intensive dietary counselling or prehabilitation to prevent treatment interruption and improve adherence and outcomes.[25]

Materials and Methods

Study design, population and participant recruitment

This retrospective cohort study was conducted at the Faculty of Medicine, Chiang Mai University, to evaluate patients diagnosed with HNC who underwent RT between 2020 and 2022. Eligible patients (aged ≥ 18 years) with histologically confirmed squamous cell carcinoma were included, while those with recurrent or metastatic disease were excluded. Additionally, patients who did not undergo CT simulation for RT planning were excluded.

Treatment protocol

All patients received treatment based on a multidisciplinary tumour board decision. For NPC, radical RT was prescribed at a dose of 70 Gy in 33–35 fractions. Induction chemotherapy, with or without concurrent platinum-based chemotherapy, was administered based on clinical indications. For non-NPC, patients received either postoperative RT (60–70 Gy in 30–35 fractions) or definitive RT (70 Gy in 33–35 fractions), with or without chemotherapy as indicated. All patients were treated with either three-dimensional conformal RT or intensity-modulated RT.

Data collection

Pre-treatment factors were collected from electronic medical records prior to the first fraction of RT. These included age, sex, height, weight, primary tumour site, stage, Eastern Cooperative Oncology Group (ECOG) performance status, treatment modality and complete blood count results. ECOG performance status was assessed using the standard ECOG 0–5 scale.[26] We calculated the NLR as an inflammatory status marker and the ALC as an immune status marker. NLR was determined by dividing the neutrophil count by the lymphocyte count (cells/μL), while ALC was calculated by multiplying the white blood cell count by 1000 and the percentage of lymphocytes.[27]

In this study, we assessed nutritional status using BMI, significant weight loss and sarcopenia status. BMI was calculated using the formula: weight (kg)/height^2 (m^2). Significant weight loss was assessed by reviewing medical records for the patient's weight 3 months before the start of RT and defined as a weight loss of more than 5% within this period[28]. Sarcopenia status was evaluated by using CT simulation CSA at the C3 vertebral level. The CSA was contoured by a radiation oncologist using a fixed Hounsfield unit range of −29 to 150, encompassing the sternocleidomastoid and paravertebral muscles. If a patient had a gross invasion of one sternocleidomastoid muscle, the measurement was duplicated from the contralateral side. However, if the paravertebral muscles were invaded, CSA assessment could not be performed. After contouring, the CSA at C3 was converted into the CSA at L3 and SMI using a specific equation described by Swatz et al.[21] The cut-off value of SMI for diagnosing sarcopenia was set at 43·2 cm^2/m^2.[16,29]

$$CSA\ at\ L3(cm^2) = 27.304 + 1.363 \times CSA\ at\ C3(cm^2) - 0.671 \times Age + 0.640 \times weight(kg) + 26.442 \times Sex$$

$$SMI(cm^2/m^2) = CSAat\ L3\ (cm^2)/height\ (m^2)$$

Overall treatment time was defined as the number of days from the start to the completion of RT. Patients who did not complete RT as scheduled were classified as having a prolonged OTT. The cut-off for OTT was set at 49 days or more, based on studies on NPC.[5]

Data analysis

Statistical analyses were conducted using Stata version 16. Patient characteristics were analysed based on data type. Continuous variables were evaluated using either the *t*-test or the rank-sum test, while categorical variables were assessed using Fisher's exact test. A two-tailed *p*-value of $< 0{\cdot}05$ was considered statistically significant. To address missing laboratory data and enhance accuracy, predictive capability and statistical power, we employed multiple imputation using the chained equations (MICE) method. Missing values were estimated via predictive mean matching, incorporating diagnosis and patient demographic factors (age, sex, OTT, concurrent chemotherapy and treatment modality) as independent variables. This process generated 20 imputed datasets, which were compared with the original datasets to ensure consistency and reliability. Following imputation, logistic regression coefficients were combined across the 20 datasets using Rubin's rules to calculate odds ratios. Univariable and multivariable analyses were performed to evaluate associations between clinical factors and outcomes, with standard errors clustered by primary diagnosis (NPC vs. non-NPC).

Study size consideration

A retrospective chart review was conducted, and 30 cases were initially contoured as a pilot study to assess five preselected

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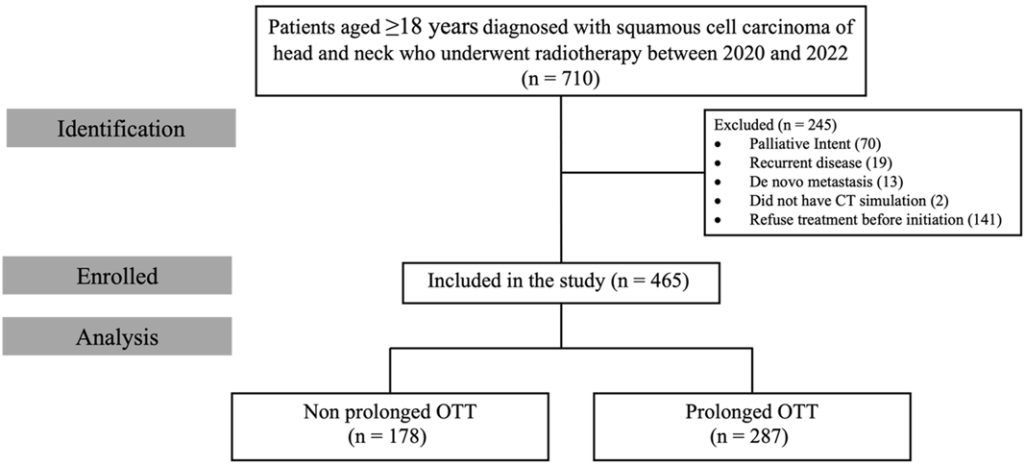

Figure 1. STROBE flow chart.

candidate predictors: ECOG performance status, BMI, NLR, staging, concurrent chemotherapy and sarcopenia. The incidence of prolonged OTT was estimated at 50%, resulting in a 1:1 group distribution. The required sample size was calculated based on either proportion or mean (standard deviation), using an alpha level of 0·05 and 80% power. Given the available data, a minimum of 354 cases were collected.

Results

Of the 465 patients enrolled in the study, 178 (38·3%) completed RT within 49 days (non-prolonged OTT), while 287 (61·7%) experienced delays or incomplete treatment (prolonged OTT), as illustrated in Figure 1, the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) flowchart of this study. Table 1 shows that there were no significant differences in age, sex or ECOG status between the two groups. However, the prolonged OTT group had a lower median weight (50 kg vs. 52 kg, $p = 0{\cdot}010$) and BMI (19·39 kg/m^2 vs. 20·33 kg/m^2, $p = 0{\cdot}015$). A higher proportion of patients in the prolonged OTT group were underweight (41·3% vs. 30·6%), though this difference was not statistically significant ($p = 0{\cdot}070$). In terms of disease characteristics, there were no differences in cancer type distribution, but advanced-stage disease (stage III–IV) was more frequent in the prolonged OTT group (90·9% vs. 78·1%, $p < 0{\cdot}001$). Treatment modalities were similar between the groups, but a higher percentage of patients in the prolonged OTT group received concurrent chemotherapy (80·1% vs. 64·0%, $p < 0{\cdot}001$).

Univariable and multivariable analysis

Univariable analysis (Table 2) identified significant associations with prolonged OTT: ECOG status (OR 1·27, $p = 0{\cdot}001$), underweight (OR 1·65, $p = 0{\cdot}045$), advanced stage (OR 2·81, $p = 0{\cdot}048$), concurrent chemotherapy (OR 2·27, $p < 0{\cdot}001$), NLR (OR 1·04, $p = 0{\cdot}013$), ALC (OR 0·99, $p = 0{\cdot}025$), sarcopenia (OR 1·19, $p = 0{\cdot}036$) and postoperative treatment (OR 1·28, $p = 0{\cdot}010$). Age, sex and weight loss were non-significant. Multivariable analysis confirmed independent predictors: ECOG status (OR 1·42, $p = 0{\cdot}004$), weight loss (OR 1·26, $p = 0{\cdot}036$), concurrent chemotherapy (OR 1·96, $p = 0{\cdot}005$), NLR (OR 1·03, $p = 0{\cdot}041$) and sarcopenia (OR 1·18, $p = 0{\cdot}042$).

Among the 287 patients who experienced prolonged RT treatment, the most common causes of delay were patient-related factors (53·3%), which included severe acute toxicity (grade ≥ 3), fatigue and the need for re-planning due to anatomical changes. Public holidays accounted for 42·5% of delays, while COVID-19 infection or risk of exposure contributed to 3·1%. Only 1·0% of delays were related to machine malfunction (Table 3).

Discussion

Prolonged OTT has long been recognized as a critical factor influencing treatment outcomes in HNC RT. In our cohort, only 38·3% of patients completed RT within the recommended 49-day period, which is markedly lower than previously reported rates.[7] We found that 53·3% of the delays were attributable to patient-related factors, followed by 42·5% due to public holidays. In contrast, COVID-19-related disruptions and machine malfunctions were infrequent. While some delays may reflect systemic issues, such as scheduling around holidays, a substantial proportion stemmed from patient-level challenges—many of which may be modifiable. These findings underscore the importance of identifying contributing factors early, with the goal of minimizing treatment interruptions and preserving the therapeutic benefit of RT.

Among disease-related factors, concurrent chemoradiotherapy was independently associated with prolonged OTT, likely due to its known toxicity burden.[30,31] While it remains standard for curative treatment in locally advanced HNC, this finding highlights the importance of early supportive intervention in vulnerable patients. ECOG performance status also showed a significant association with treatment delay. Notably, even a small shift from ECOG 0 to 1, indicating only mild restriction in physically strenuous activity, was associated with a 1·5-fold increase in the risk of prolonged OTT. In clinical settings, differentiating between ECOG scores can be subjective, yet this finding highlights that even subtle reductions in functional capacity may meaningfully impact treatment continuity. Functional status, however, may be improved with interventions such as prehabilitation or symptom management.

Systemic inflammation and nutritional status also showed meaningful associations with treatment duration. Pre-treatment NLR was an independent predictor of prolonged OTT, suggesting that elevated baseline inflammation may impair treatment tolerance. Although ALC was not significant in multivariable analysis, it remains a relevant marker of immune competence and has been previously linked to survival outcomes in HNC.[22,23,32–34] Regarding nutrition, both significant weight loss (> 5% within

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Table 1. Baseline characteristics of the overall cohort

Patient characteristics	Missing data *n* (%)	Prolonged OTT (*n* = 287, 61·72%)	Non-prolonged OTT (*n* = 178, 38·28%)	*p*-value
Age, mean (SD)	0 (0)	59·09 (13·91)	59·53 (13·96)	0·740
Sex, *n* (%)	0 (0)			
Male		217 (75·61)	130 (73·03)	0·584
Female		70 (24·39)	48 (26·97)	
ECOG performance status, *n* (%)	1 (0·22)			
0		232 (81·12)	152 (85·39)	0·427
1		50 (17·48)	23 (12·92)	
2		3 (1·05)	3 (1·69)	
3		1 (0·35)	0 (0)	
Weight at start RT (kg), median (IQR)	2 (0·44)	50 (43–59·8)	52 (46–63·5)	0·010*
Primary cancer, *n* (%)	0 (0)			
NPC		68 (23·69)	42 (23·60)	1·000
Non-NPC		219 (76·31)	136 (76·40)	
Stage grouping (AJCC 8th)	2 (0·44)			
I		7 (2·46)	20 (11·24)	< 0·001*
II		19 (6·67)	19 (10·67)	
III		55 (19·30)	47 (26·40)	
IV		204 (71·58)	92 (51·69)	
Radiotherapy approach, *n* (%)	0 (0)			
Postoperative RT		123 (42·86)	87 (48·88)	0·214
Radical RT		164 (57·14)	91 (51·12)	
Concurrent chemotherapy	0 (0)			
No		57 (19·86)	64 (35·96)	< 0·001*
Yes		230 (80·14)	114 (64·04)	
ALC (cells/μL), median (IQR)	20 (4·30)	1648 (1211–2221)	1730 (1192–2326)	0·854
NLR, median (IQR)	18 (3·87)	2·35 (1·63–3·62)	2·39 (1·67–3·16)	0·853
BMI (kg/m^2), median (IQR)	9 (1·94)	19·39 (16·76–22·22)	20·33 (17·78–22·66)	0·015*
BMI classification[a]	9 (1·94)			
Underweight		118 (41·26)	52 (30·59)	0·070
Normal weight		115 (40·21)	79 (46·47)	
Overweight		53 (18·53)	39 (22·94)	
Significant weight loss[b]	8 (1·73)			
No		140 (49·12)	97 (56·40)	0·147
Yes		145 (50·88)	75 (43·60)	
Sarcopenia status[c]	9 (1·94)			
No		132 (46·15)	87 (51·18)	0·333
Yes		154 (53·85)	83 (48·82)	

Abbreviations: ALC, absolute lymphocyte count; BMI, body mass index (kg/m^2); ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; kg, kilograms; NLR, neutrophil-to-lymphocyte ratio; NPC, nasopharyngeal carcinoma; RT, radiotherapy; SD, standard deviation.
* Statistically significant (*p*-value <0.05).
[a]BMI classification according to the WHO criteria for Asian populations.
[b]Significant weight loss is defined as a weight loss of more than 5% in the past 3 months.
[c]Sarcopenia status was determined by converting C3 measurements to the skeletal muscle index (SMI), with a cut-off value of 43·2 cm^2/m^2 for defining sarcopenia.

3 months prior to RT) and CT-defined sarcopenia were independently associated with treatment prolongation. We assessed muscle mass using CSA at the C3 vertebral level, a validated surrogate for L3 skeletal muscle index in HNC patients. Despite variation in diagnostic cut-offs, sarcopenia has consistently been associated with impaired treatment adherence and survival.[35,36] Together, these findings underscore the interconnected roles of inflammation, malnutrition and physical deconditioning—all of which are potentially modifiable through early interventions.

Multimodal prehabilitation, incorporating physical exercise, nutritional support and psychosocial interventions, has been proposed as a comprehensive approach to improve treatment tolerance in HNC.[37,38] Structured programmes that combine aerobic, resistance and flexibility training have shown potential benefits in preserving skeletal muscle mass and function.[39] Immune-enhancing nutrition, as well as intensive nutritional counselling by dietitians, has been associated with improved adherence and attenuated rises in inflammatory markers such as the NLR during RT.[27,40] Although fully integrated multimodal prehabilitation remains in the feasibility-testing phase, initial findings suggest it may offer synergistic benefits across physical, nutritional and psychological domains.[41] Further prospective trials are warranted to confirm its clinical impact.

At the system level, public holidays falling on weekdays accounted for a substantial proportion of delays. Addressing this issue may involve scheduling staff coverage or applying altered fractionation in cases where continuity is disrupted. Even short unplanned treatment gaps, particularly those occurring after the onset of accelerated repopulation, may warrant compensatory dosing of approximately 0·8 Gy per missed day to maintain tumour control, as recommended in recent radiobiological guidelines.[42]

This study has several limitations. First, its retrospective design may introduce selection bias and limit causal inference. Second, although we included a range of pre-treatment variables, unmeasured confounding factors—such as comorbidities, socio-economic status and patient motivation—could influence treatment

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Table 2. Factors significantly associated with prolonged overall treatment time, clustered by primary cancer site (NPC vs. non-NPC)

	Univariable		Multivariables	
Factors	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age	0·99 (0·99–1·01)	0·700	1·00 (0·99–1·01)	0·562
Sex	0·88 (0·75–1·03)	0·091	0·89 (0·74–1·07)	0·207
ECOG	1·27 (1·11–1·45)	0·001*	1·42 (1·13–1·79)	0·004*
Staging				
I–II	1	0·048*	1	0·066
III–IV	2·81 (1·01–7·81)		2·09 (0·96–4·56)	
Treatment regimen				
Postoperative RT	1	0·010*	1	0·316
Definitive RT	1·28 (1·07–1·54)		1·25 (0·82–1·92)	
Concurrent chemotherapy	2·27 (1·98–2·60)	< 0·001*	1·96 (1·23–3·14)	0·005*
ALC	0·99 (0·99–1·00)	0·025*	1·00 (1·00–1·01)	0·283
NLR	1·04 (1·01–1·07)	0·013*	1·03 (1·01–1·05)	0·041*
Significant weight loss[a]	1·34 (0·98–1·83)	0·068	1·26 (1·02–1·55)	0·036*
BMI underweight[b]	1·65 (1·02–2·70)	0·045*	1·33 (0·98–1·79)	0·072
Sarcopenia[c]	1·19 (1·02–1·39)	0·036*	1·18 (1·01–1·37)	0·042*

Abbreviations: 95% CI, 95% confidence interval; ALC, absolute lymphocyte count; ECOG, Eastern Cooperative Oncology Group; NLR, neutrophil-to-lymphocyte ratio; NPC, nasopharyngeal carcinoma; OR, odds ratio; RT, radiotherapy.
* Statistically significant (*p*-value <0.05).
[a]Significant weight loss is defined as a weight loss of more than 5% in the past 3 months.
[b]BMI classification according to the WHO criteria for Asian populations.
[c]Sarcopenia status was determined by converting C3 measurements to the skeletal muscle index (SMI), with a cut-off value of 43·2 cm^2/m^2 for defining sarcopenia.

Table 3. Causes of radiotherapy prolongation ($n = 287$ patients)

Cause of prolongation	*n* (%)
Patient-related factors	153 (53·30)
Public holiday	122 (42·51)
COVID-19 risk/infection	9 (3·14)
Machine malfunction	3 (1·05)

adherence. Third, the use of ECOG performance status and sarcopenia cut-offs may be subject to inter-observer variability and population-specific differences. Lastly, as this was a single-centre study, the generalizability of our findings may be limited. Further validation in multi-institutional cohorts and prospective settings is warranted.

In conclusion, prolonged OTT remains a critical issue in head and neck RT. This study identifies several modifiable pre-treatment factors—including poor performance status, systemic inflammation, weight loss and sarcopenia—that are independently associated with treatment delay. These findings support integrating early nutritional and functional interventions into routine care. In parallel, system-level strategies such as improving scheduling around public holidays may help reduce avoidable interruptions and improve treatment outcomes.

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Competing interests. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical consideration. The study protocol was reviewed and approved by the Faculty of Medicine, Chiang Mai University Institutional Review Board (EXP-2566–0172–000300) in accordance with the Declaration of Helsinki. The requirement for informed consent was waived due to the retrospective analysis of anonymized clinical data, with all patient information handled.

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