LONG-TERM SURVIVAL OUTCOMES OF RADIATION THERAPY FOR UNRESECTABLE, LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER: A SINGLE-CENTER EXPERIENCE AT HOSPITAL 175

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ABSTRACT

Objective: To evaluate the effectiveness of radiotherapy on overall survival (OS) and identify factors affecting survival outcomes in patients with stage III non-small cell lung cancer (NSCLC) where surgery is not feasible.

Methods: This retrospective study analyzed data from NSCLC patients treated with radiotherapy at Hospital 175 from January 2019 to June 2022. Collected data included patient demographics, pathology, TNM staging, concurrent chemotherapy, PET/CT characteristics, and radiotherapy parameters. Patients received concurrent or sequential chemotherapy with radiotherapy doses equivalent to or exceeding 60Gy, with regular follow-up and re-examination post-radiation to document final patient status.

Results: Among 240 patients (75% male), performance status (PS) scores of 0, 1, and 2 were 15%, 80%, and 5%, respectively. Histopathological subtypes included squamous cell carcinoma (9%), adenocarcinoma (83.5%), and others (7.5%). Stage IIIA, IIIB, and IIIC comprised 32%, 48%, and 20% of cases, respectively. The median follow-up was 16.3 months, with a median OS of 19.5 months. OS rates at 1, 2, and 3 years were 76.2%, 38.8%, and 27.4%, respectively. Patients receiving concurrent

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chemoradiotherapy had better OS compared to those with sequential chemoradiotherapy. Age, histopathological type, and lymph node metastasis significantly impacted overall survival.

Conclusion: The study highlights that OS rates at 1, 2, and 3 years were 76.2%, 38.8%, and 27.4%, respectively. Concurrent chemoradiotherapy provided a better prognosis than sequential therapy. Radiotherapy remains a crucial treatment modality for inoperable NSCLC, with concurrent chemoradiotherapy offering the best survival benefits. Prognostic factors for survival included age, lymph node metastasis, and histopathological type.

**Keywords: radiotherapy, non-small cell lung cancer (NSCLC), concurent chemoradiation, toxicity, immunotherapy*

INTRODUCTION

Lung cancer remains a leading cause of cancer-related mortality globally[1]. Non-small cell lung cancer (NSCLC) is the most prevalent type, accounting for the majority of cases[2, 3]. Patients with unresectable stage III NSCLC often face a dismal prognosis and limited treatment options. While surgery is the primary treatment for early-stage NSCLC, many patients with inoperable, locally advanced disease require alternative treatments and a multimodal approach[4].

Concurrent chemoradiotherapy has become a cornerstone in managing unresectable stage III NSCLC, offering improved outcomes compared to radiotherapy alone[5, 6]. This approach involves simultaneous chemotherapy and radiotherapy to enhance local tumor control and address micrometastatic disease. The synergistic effect of concurrent chemoradiotherapy, where chemotherapy sensitizes tumor cells to radiation, increases treatment efficacy[7]. Numerous clinical trials have demonstrated the superiority of this combined modality over sequential radiotherapy or radiotherapy alone in terms of overall survival, progression-free survival, and local tumor control rates[8, 9]. Efforts to integrate novel biologics, such as tyrosine kinase inhibitors (TKIs) and monoclonal antibodies (mAbs), into the treatment paradigm for inoperable stage III NSCLC are ongoing. However, studies on the addition of maintenance or consolidation therapies post-concurrent chemoradiotherapy have produced mixed results, underscoring the need for further research in this area[10, 11].

This study aims to evaluate long-term survival outcomes and identify factors influencing treatment response in patients with locally advanced, inoperable NSCLC treated with radiotherapy at Military Hospital 175.

PATIENTS AND METHODS

Patient Selection: This retrospective analysis included medical records of patients diagnosed with inoperable stage III NSCLC who received radiotherapy at Military Hospital 175 between January 2019 and June 2022. Patients with a single primary lung tumor and a performance status (PS) score of 0-2 were included. Those with distant metastases or prior treatments, including surgery or radiotherapy, were excluded.

Data Collection: Data from medical records encompassed demographics (age and sex), histopathology, TNM stage, chemotherapy regimen, PET/CT characteristics, and radiotherapy parameters, such as radiation dose and treatment technique. Patients were monitored for acute adverse events during and post-radiotherapy, with toxicities graded using CTCAE version 5.0.

Treatment Regimen: All patients received radiotherapy using a linear accelerator with photon energy of 6 or 10 MV. Intensity-modulated radiotherapy (IMRT) or 3D-CRT was employed. The target volume included the primary tumor and associated lymph nodes. Patients were prescribed a radiation dose of at least 60 Gy in 30 fractions over six weeks. Concurrent or sequential chemoradiotherapy was administered using cisplatin- or carboplatin-based regimens combined with pemetrexed or paclitaxel. Some patients (12 cases) received consolidation chemotherapy with Durvalumab for 12 months post-treatment (Figure 1, 2).

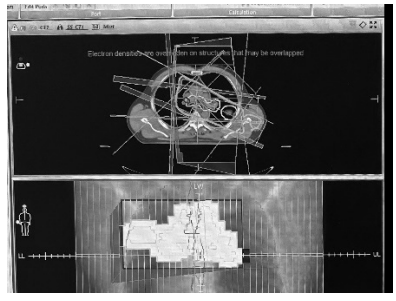
1a)  1b) 

Figure 1: Linac (1a) with immobilization devices, respiratory control system (1b).

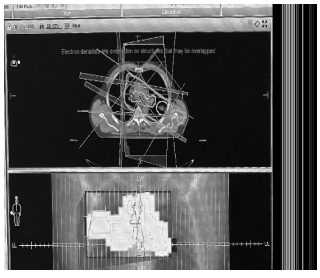
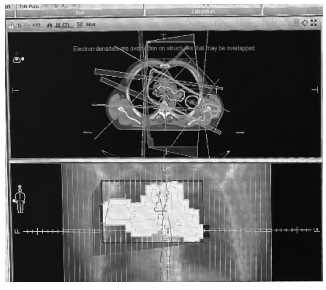
2a)  2b) 

Figure 2: PET/CT images used for target delineation (2a) and planning (2b)

RESULTS

Patient Characteristics: Among the 240 patients, the average age was 64 years (range 26-82), with 19% older than 70 years. Males constituted 75% of the cohort. Performance status scores of 0, 1, and 2 were observed in 15%, 80%, and 5% of patients, respectively. Stage IIIA, IIIB, and IIIC cases were 32%, 48%, and 20%, respectively. Tumor locations were central (36%) and peripheral (64%). Histopathology showed 84% adenocarcinoma, 13% squamous cell carcinoma, and 3% other types. PET/CT max SUV averaged 10.5 ± 7.1 (Table 1).

Table 1: General characteristics of patients

N= 240	Data (%)
clinical	
Average age (min - max); Patients >70 years old	64 (26 – 82); 46 (19%)
Gender: Male: Female	75%: 25%
PS (ECOG): 0, 1, 2	36 (15%), 192 (80%), 12 (5%)
Stage: IIIA, IIIB, IIIC	77 (32%), 115 (48%), 48 (20%)
Tumor location: Central, Peripheral	86 (36%), 154 (64%)
Histopathology: Adeno, Squamous, Others	201 (84%), 31 (13%), 8 (3%)
maxSUV (mean ± standard deviation) with FDG-PET/CT	10.5 ± 7.1
Radiotherapy method: - Sequential chemotherapy (4-6 cycles of prior chemotherapy) - Simultaneous radiation	 197 (82%) 43 (18%)
Consolidation treatment Chemotherapy (2-3 cycles) Targeted therapy (TKI) Immunotherapy (Durvalumab)	 68 (28%) 82 (34%) 12 (5%)

Treatment Results: The median follow-up was 16.3 months. Treatment response per RECIST 4.1 showed 5% complete response (CR), 74% partial response (PR), 17% stable disease (SD), and 4% progressive disease (PD). Median OS was 19 months, with 1-year, 2-year, and 3-year survival rates of 76.2%, 38.8%, and 27.4%, respectively (Table 2, figure 3).

Table 2: Results of treatment response and overall survival (N = 240)

Result	Data
Median follow-up time (min-max)	16.3 (2-48) (month)
Response rate according to RECIST 4.1	
Complete response (CR)	12 (5%)
Partial response (PR)	178 (74%)
Stable disease (SD)	41 (17%)
Progressive disease (PD)	9 (4%)
Median overall survival (95% confidence interval)	19 (18.9-22.3) (month)
Overall survival rate after 1 year	76.2%
Overall survival rate after 2 years	38.8%
Overall survival rate after 3 years	27.4%

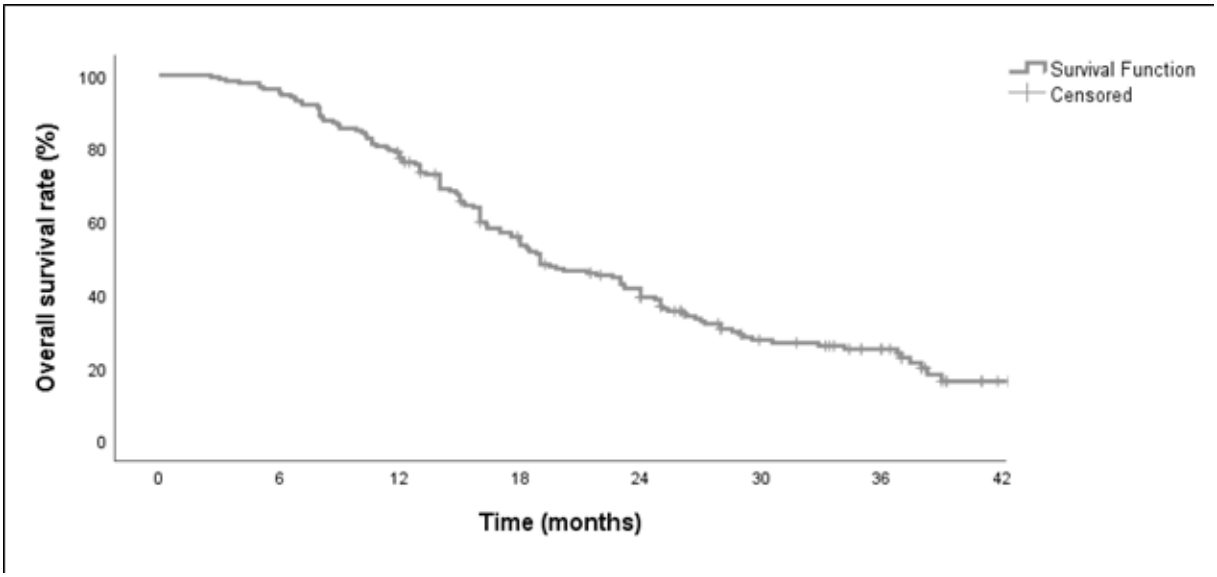


Figure 3: Kaplan Maier plot of overall survival for all patients

Toxicity: Esophagitis (61%), fatigue (46%), and skin reactions (32%) were common, with grade 3 or 4 toxicities primarily esophagitis (10%) (Table 3).

Table 3: Common types of toxicity due to radiotherapy (N=240)

Type of radiation toxicity (according to CTCAE 5.0, 2018)	Any grade Number of patients (%)	Grade 3, 4 Number of patients (%)
Esophagitis	146 (61%)	24 (10%)
Tired	110 (46%)	15 (6%)
Skin reactions	76 (32%)	22 (9%)
Pneumonia	64 (27%)	17 (7%)
Pericarditis	15 (6%)	2 (1%)
Hematology (anemia)	86 (36%)	14 (6%)
Liver function (increased AST/ ALT)	33 (14%)	10 (4%)
Renal function (increased serum urea nitrogen or creatinine)	19 (8%)	8 (3%)

Radiotherapy Plans: Nearly half used PET/CT for planning, with 3D-CRT or IMRT techniques. The average percentage of PTV receiving at least 95% of the total dose was 96.92%. Mean lung dose was 14.6 Gy, indicating low risk for radiation-induced lung toxicity (Table 4).

Table 4: Information about radiotherapy plans (N=240)

Total radiation therapy dose (Gy), dose fractionation	60Gy – 64 Gy (2Gy/ fraction)
Use PET/CT for simulation and planning	42.1%
Simulation technique (free breathing): 3D versus 4D	82% vs. 18%
Tool to control respiratory movements (breathing monitoring system, body fix, chest mask)	100%

Time from simulation to radiation: average (min-max)	4.5 (3 – 10) days
Radiotherapy techniques	
Conformable radiotherapy (3D-CRT)	78 %
Intensity modulated radiotherapy (IMRT)	22 %
Take a check of the projection field immediately before irradiation (Iview)	
Conformable radiotherapy (3D-CRT)	Every Monday
Intensity modulated radiotherapy (IMRT)	Every day (Monday-Friday)
Tumor volume (cc):	
3D simulation (mean ± sd)	31.33 (24.5 ± 41.6)
4D simulation (mean ± sd)	36.7 (28.9 ± 52.4)
Number of projection fields	
Conformable radiotherapy (3D-CRT)	3 - 5
Intensity modulated radiotherapy (IMRT)	5 - 7
% PTV receiving at least 95% of total radiation dose (57 Gy)	96.92% ± 8.9%
V20 of both lungs (mean ± sd)	25.7 % ± 6.9 %
Mean lung dose (mean ± sd):	
Both lungs	14.6 Gy ± 3.4 Gy
Ipsilateral lung	24.4 Gy ± 7.4 Gy
Contralateral lung	6.9 Gy ± 3.4 Gy
Mean dose to the heart (mean ± sd)	8.9 Gy ± 6.6 Gy
Mean dose to esophagus (mean ± sd)	20.9 Gy ± 7.7 Gy
Maximum spinal dose (mean ± sd)	45.2 Gy ± 0.6Gy

Prognostic Factors: Multivariate analysis showed age, histopathology, and N stage significantly influenced survival, while concurrent chemoradiotherapy reduced mortality risk.

Table 5: Multivariate analysis of prognostic factors according to the Cox regression model

Prognostic factors	Hazard ratio	95% confidence interval	p-value
Age (standardized) (age-mean)/ standard deviation	1.27	1.06 - 1.52	*0.013*
Gender (female vs male)	0.93	0.66 - 1.47	0.937
PS-ECOG (0 vs 1 vs 2)	0.80	0.54 - 1.18	0.227
Histopathology (adeno, squamous, other)	0.62	0.41 - 0.95	*0.026*
T (T1 vs T2 vs T3 vs T4)	0.86	0.69 - 1.07	0.191
N (N0 vs N1 vs N2 vs N3)	1.24	1.01 - 1.53	*0.039*
Treatments (concurrent radiotherapy vs sequential radiotherapy)	0.33	0.14 - 0.74	*0.015*
Meets RECIST (CR vs PR vs SD vs PD)	0.76	0.49 - 1.16	0.180

Figure 2: Kaplan Maier plot of overall survival by treatment

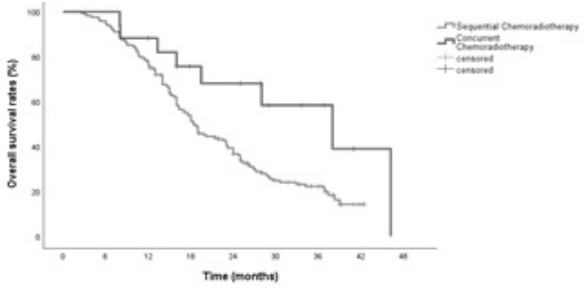
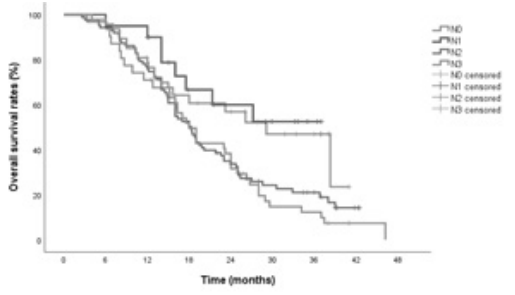


Figure 3: Kaplan Maier plot of overall survival according to lymph node metastasis status



DISCUSSION

The management of unresectable stage III non-small cell lung cancer (NSCLC) presents considerable challenges due to the heterogeneity of the disease and the typically poor prognosis associated with advanced stages. The findings of this study align with existing literature, demonstrating the significant role of concurrent chemoradiotherapy in improving overall survival (OS) outcomes for patients with locally advanced NSCLC. Our results indicate that patients receiving concurrent chemoradiotherapy had superior OS compared to those receiving sequential therapy, with median survival rates of 19 months and one-, two-, and three-year OS rates of 76.2%, 38.8%, and 27.4%, respectively.

The superiority of concurrent chemoradiotherapy observed in this study is consistent with prior research, which has established this approach as the standard of care for unresectable stage III NSCLC. The synergistic effect of combining chemotherapy and radiotherapy is thought to result from chemotherapy's ability to sensitize tumor cells to radiation, thereby enhancing local control and reducing the risk of distant metastasis[12-14]. However, it is essential to recognize the increased toxicity associated with concurrent regimens, as evidenced by the higher incidence of grade 3 or 4 esophagitis observed in our cohort. This underscores the need for careful patient selection and management of adverse effects to optimize outcomes.

The analysis of prognostic factors in our study highlights the importance of age, histopathological subtype, and lymph node involvement in determining survival outcomes. Older age was associated with poorer prognosis, likely due to decreased physiological reserves and increased comorbidities that complicate treatment tolerance and recovery. Histopathological analysis revealed that adenocarcinoma was the predominant subtype, consistent with global epidemiological trends[15, 16]. Notably, patients with squamous cell carcinoma had worse survival outcomes compared to those with adenocarcinoma, aligning with previous studies that have reported similar findings[17]. The presence of lymph node metastasis (N stage) was another critical factor, with higher nodal involvement correlating with reduced OS, emphasizing the aggressive nature of the disease and the importance of effective locoregional control.

The role of advanced imaging techniques, such as PET/CT, in radiotherapy planning was evident in our study, with nearly half of the cases utilizing this modality. PET/CT provides superior delineation of tumor boundaries and metastatic nodes, facilitating more precise targeting and potentially improving treatment outcomes. The use

of intensity-modulated radiotherapy (IMRT) and three-dimensional conformal radiotherapy (3D-CRT) further contributed to optimizing dose distribution while minimizing exposure to surrounding healthy tissues, as indicated by the low mean lung dose (14.6 Gy) and the high percentage of the planning target volume (PTV) receiving at least 95% of the prescribed dose[18].

In conclusion, this single-center experience underscores the pivotal role of concurrent chemoradiotherapy in managing unresectable stage III NSCLC, with significant improvements in overall survival compared to sequential therapy. Age, histopathological subtype, and lymph node involvement are crucial prognostic factors influencing survival outcomes. Continued research and clinical trials are essential to refine treatment strategies and incorporate novel therapies to enhance the prognosis for this challenging patient population.

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