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Treatment Outcomes and Prognostic Factors of Patients with Locally Advanced Non-Small Cell Lung Cancer: A Single Institution Study

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ABSTRACT

Background: Lung cancer is the second most common cancer globally. Non-small cell lung cancer (NSCLC) is the most common pathological type. One third of patients present with locally advanced disease.

Objective: The retrospective study aims to assess prognostic factors and survival outcomes in locally advanced NSCLC patients. **Patients and Methods:** 101 patients, with locally advanced NSCLC registered in the Clinical Oncology and Nuclear Medicine Department, Mansoura University between January 2011 and December 2021, were included.

Results: Mean age of patients was 59 years. The majority were males (83.2%). Most common pathologies were squamous cell carcinoma (47.5 %) and adenocarcinoma (41.6%). All patients were stage III except for 4% with unresectable stage IIB. Thirty-six cases (35.7%) received concurrent chemoradiotherapy (CCRT). Others underwent surgery or received chemotherapy only. Median overall survival (OS) was 9 months. Patients who received CCRT had higher OS (p-value 0.019) and progression free survival (PFS) (<0.001), compared to those who did not. Induction chemotherapy did not affect survival. Radiotherapy (RT) interruption was a statistically significant negative prognostic factor (p-value <0.001). Age of 60 years or above, weight loss, squamous histology, cisplatin-based regimens, and number of cycles were found to be prognostic factors affecting survival on both univariate and multivariate analysis.

Conclusion: CCRT with cisplatin-based chemotherapy remains the superior line of treatment in patients with locally advanced NSCLC.

Keywords: Lung cancer, NSCLC, locally advanced.

INTRODUCTION

Lung cancer is the second most frequently diagnosed cancer and has the highest mortality rate globally [(1)]. According to World Health Organization (WHO) 2015 histological classification of lung cancers, Non-small cell lung cancer (NSCLC) mainly comprises adenocarcinoma, squamous cell carcinoma, and large cell carcinoma [(2)]. Locally advanced NSCLC broadly refers to stage III disease, characterized by primary tumor extension into extrapulmonary structures (T3/4) and lymph node involvement (N1–3), without evidence of distant metastases (M0)[(3)]. Treatment of choice in operable cases is surgery plus adjuvant/neoadjuvant cisplatin-based chemotherapy. Target therapy and immunotherapy have also been recently incorporated into guidelines [(4)]. Clinical guidelines for both R1 and R2 resections recommend either re-resection of the tumor or adjuvant radiotherapy [(5)].

As for unresectable locally advanced NSCLC, the current standard of care is radiation with concurrent platinum-based chemotherapy [(6)]. The standard dose fractionation of RT with chemotherapy for stage III NSCLC remains 60 Gy in 30 daily fractions [(7)]. The consolidation administration of durvalumab after CCRT has demonstrated a survival benefit in unresectable stage III NSCLC and is now recommended in patients whose disease has not progressed following platinum based chemoradiotherapy [(8)].

Although the intent of CCRT is curative, most patients will relapse, with nearly 40% experiencing locoregional recurrence, and approximately 50% or more developing distant metastasis [(9)].

AIM OF WORK

The aim of this study was to better analyze prognostic factors and treatment modalities affecting the modest survival of locally advanced NSCLC patients.

PATIENTS AND METHODS

Study design: Retrospective analysis

Study setting: 101 locally advanced NSCLC patients registered at Clinical Oncology and Nuclear Medicine Department, Mansoura University Hospital, from 2011 to 2021.

Inclusion criteria: 1- Pathologically confirmed NSCLC. 2- Locally advanced disease including irresectable Stage IIB and Stage IIIA, IIIB, IIIC.

Exclusion criteria: 1- Patients with distant metastasis at time of diagnosis. 2- Patients with double malignancy.

Data collected: Patient's age, gender, smoking and weight loss history, and performance status (PS) according to the Eastern Cooperative Oncology Group (ECOG) criteria [(10)]. Radiological assessment was based on CT chest, MRI brain, bone scan or PET/CT. Pathological diagnosis was documented by fibreoptic

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bronchoscopic biopsy and cytology of pleural effusion smear when effusion was present. Molecular testing (EGFR and ALK) was requested in a small number of patients due to scarcity or high cost of the test during the specified 10-year duration.

Treatment Modalities

Concurrent Chemoradiotherapy (CCRT): Patients were positioned in supine position with both arms overhead, using immobilization devices as needed. A CT scan, preferably with IV contrast, was done to all patients, with slice thickness 2-3 mm, taken from the cricoid cartilage to L2 vertebra. A 6-10 MV photon beam by a linear accelerator was used.

GTV included primary tumor volume and involved lymph nodes. CTV included GTV plus 8-10 mm isotropic margin, excluding natural barriers like bone and pleura. Another 10 mm was added to define PTV. Elective nodal irradiation was not performed. Organs at risk (OAR) included both lungs, spinal cord, esophagus, heart. Treatment was delivered using anterior oblique, posterior oblique and lateral beam angles. Patients were assigned to 60-66 Gy in 30-33 fractions given in 6-6.5 weeks via conformal 3D technique.

Weekly paclitaxel/carboplatin (Paclitaxel 45 mg/m^2 and carboplatin AUC 2) was used. Two cycles of paclitaxel/carboplatin (Paclitaxel 200 mg/m^2, carboplatin AUC 6 every 21 days) were given as consolidation chemotherapy post CCRT.

Induction Chemotherapy prior to CCRT: Patients not able to start CCRT promptly were started on induction chemotherapy. The induction regimen used was cisplatin/gemcitabine (Cisplatin 75 mg/m^2 on day 1, gemcitabine 1250 mg/m^2 days 1, 8 every 21 days). Carboplatin/gemcitabine (Carboplatin AUC 5 day 1, gemcitabine 1000 mg/m^2 days 1, 8 every 21 days) was used alternatively in cisplatin-ineligible patients. Only 2 cases of non-squamous pathology were given cisplatin/pemetrexed (Cisplatin 75 mg/m^2, pemetrexed 500 mg/m^2 every 21 days).

Surgery plus Perioperative Chemotherapy (± PORT): Surgical candidates underwent lobectomy plus lymphadenectomy. All patients received perioperative chemotherapy (Paclitaxel/carboplatin and gemcitabine/cisplatin in the doses previously mentioned). Only one patient was planned for PORT for infiltrated surgical margins and received 54 Gy/ 30 fractions via conformal technique.

Chemotherapy Only: Some patients received chemotherapy only due to delay in RT, irresectability, or progression/metastasis on neoadjuvant treatment. Regimens given were paclitaxel/carboplatin or gemcitabine/cisplatin every 3 weeks in the doses previously mentioned, or cisplatin/etoposide (Cisplatin 100 mg/m^2 day 1, etoposide 100 mg/m^2 days 1-3 ever 28 days).

Patient Follow Up: Clinical evaluation was done on a weekly basis during CCRT, every three weeks during induction/adjuvant chemotherapy, and once every three months thereafter. CT chest was done as baseline assessment, then at 1 and 3 months after CCRT, then every 3 to 6 months after treatment.

Overall survival (OS) was defined as the time from diagnosis till death or last follow up. Progression-free survival (PFS) was calculated from the date of diagnosis to the date of disease progression.

Ethical Approval:

This study was approved by Medical Research Ethics Committee, Faculty of Medicine, Mansoura University. All the participants gave their written consent after being fully provided with all the necessary information regarding the study. The study was carried out in accordance with Declaration of Helsinki.

Statistical Analysis

Data analysis was conducted using the Statistical Package for the Social Sciences (SPSS) software, version 26.0. Quantitative data were summarized as median, mean and standard deviation, and qualitative data as frequency and percentages. Results were considered significant if p-value was < 0.05 and highly significant if p-value was < 0.001. Survival was displayed by Kaplan-Meier survival curve.

RESULTS

Mean age of patients was 59.12 years (SD ± 9.261) ranging from 31 to 81 years, with 54.5 % of patients aged 60 or more. Majority of patients were males. Smokers represented 76% of patients. Weight loss was documented in 67 patients at presentation. Seventy-three patients presented with performance status 0-1 according to ECOG criteria. Patient characteristics are summarized in **Table 1**.

Table 1: Patient Characteristics

Factor		N (101)	Percentage
Age	< 60 years	46	45.5 %
	≥ 60 years	55	54.5 %
Sex	Male	84	83.2 %
	Female	17	16.8 %
PS	0-1	73	72.3 %
	2	28	27.7 %
Smoking	Smokers	77	76.2 %
	Non-smokers	24	23.8 %
Weight Loss	Yes	67	66.3 %
	No	34	33.7%

The two most common pathologies were squamous cell carcinoma (48 cases) and adenocarcinoma (42 cases). Around 75 % of cases were of high grade (Grade 3). As per local staging, the most common stage was stage IIIB. The majority of patients were node positive, with 46.5% with N2 disease. Tumor characteristics are shown in **Table 2**.

Table 2: Tumor Characteristics

Factor		N (110)	Percentage
Pathology	Squamous Cell Carcinoma	48	47.5 %
	Adenocarcinoma	42	41.6 %
	Large Cell Carcinoma	11	10.9 %
Grade	Grade 1	3	3 %
	Grade 2	23	22.8 %
	Grade 3	75	74.3 %
Stage	Stage IIB	4	4 %
	Stage IIIA	43	42.6 %
	Stage IIIB	46	45.5 %
	Stage IIIC	8	7.9 %
Tumor Size	T4	51	50.5 %
	T2, T3	50	49.5 %
Nodal Stage	N0	23	22.8 %
	N1	25	28.8 %
	N2	47	46.5 %
	N3	6	5.9 %
EGFR	Wild	15	14.9 %
	Mutant	2	2%
ALK	Wild	9	8.9 %
	Mutant	0	0%

Regarding molecular testing, 9 patients underwent ALK testing, but all were found to be of wild type. Seventeen patients underwent EGFR testing, out of which only two were mutant. None, however, received any target therapy. PD-L1 testing was not done to any of the patients.

Regarding modalities of treatment, 8 patients were candidates for surgery. All 8 patients underwent lobectomy plus lymphadenectomy and had at least one of 3 risk factors postoperatively: accidental mediastinal lymph nodes (6 cases), infiltrated surgical margins (3 cases), and positive lymphovascular embolization (LVE) (5 cases). All patients received perioperative chemotherapy, but only one patient received postoperative radiotherapy (54 Gy / 30 Fx / 6 weeks).

Thirty-six cases (35.7%) received CCRT, of which 31 had received induction chemotherapy prior to starting radiotherapy. Sixteen patients suffered interruption of radiotherapy sessions.

The remaining 57 cases (56.4%) unfortunately received chemotherapy only, either due to poor general condition, or due to unavailability of immediate or nearby radiation therapy.

Responses to CCRT and chemotherapy alone after around 1.5 months of ending treatment according to response evaluation criteria in solid tumors (RECIST)[11] were documented (**Table 3**). Around 55% of cases showed good response after CCRT varying between regression (14 cases), stationary disease (4 cases), and complete response (3 cases). On the other hand, only 6 patients showed regression post chemotherapy alone, while the majority (60%) progressed under chemotherapy.

Table 3: Responses to CCRT and Chemotherapy According to RECIST Criteria

	N (36)	Percentage %
Lost follow up	8	22.2%
Progressive Disease	7	19.4%
Regressive Disease	14	38.9%
Stationary Course	4	11.1%
Complete Response	3	8.4%
Response to Chemotherapy	**N (58)**	**Percentage %**
Lost follow up	18	31.1%
Progressive Disease	34	58.6%
Regressive Disease	6	10.3%

Median follow-up period was 2 years. Mean overall survival was 13.446 ± 1.418 and median overall survival was 9 months. Progression free survival mean was 22.581 ± 4.201 with a median of 10 months. OS and PFS curves are shown in **Figures 1 and 2**.

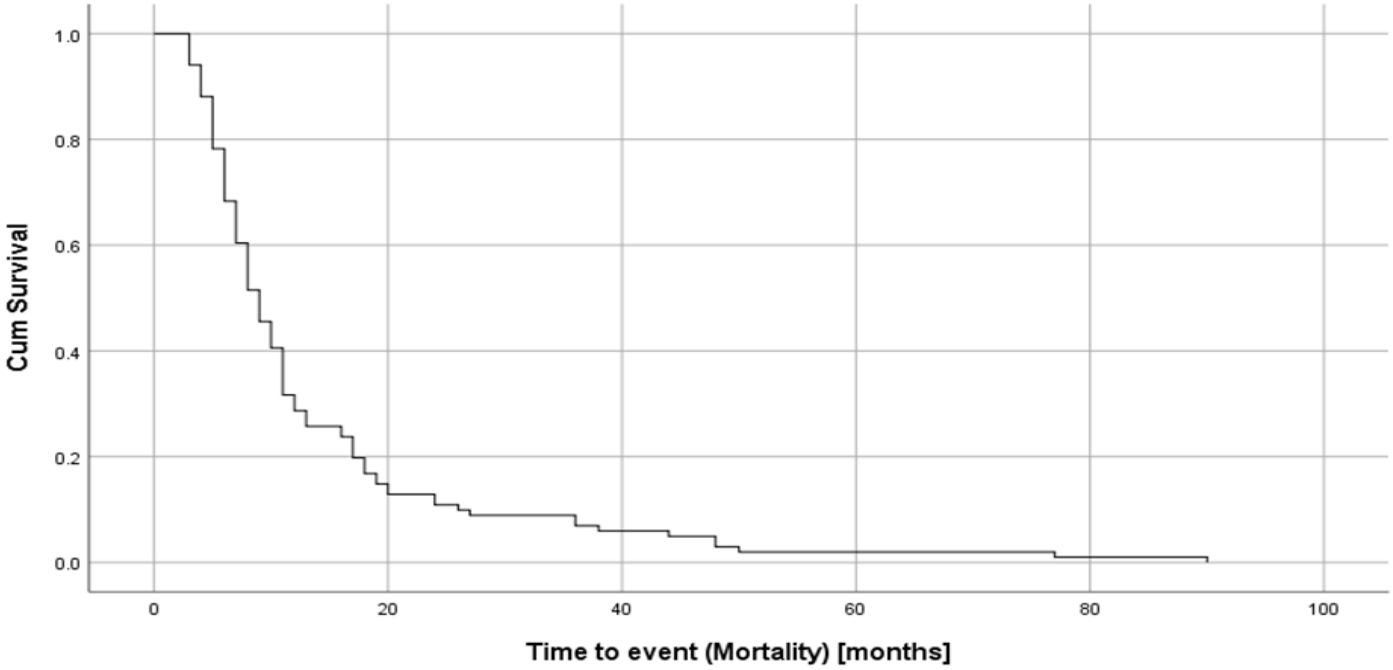

Figure 1: Overall Survival Kaplan Meier curve

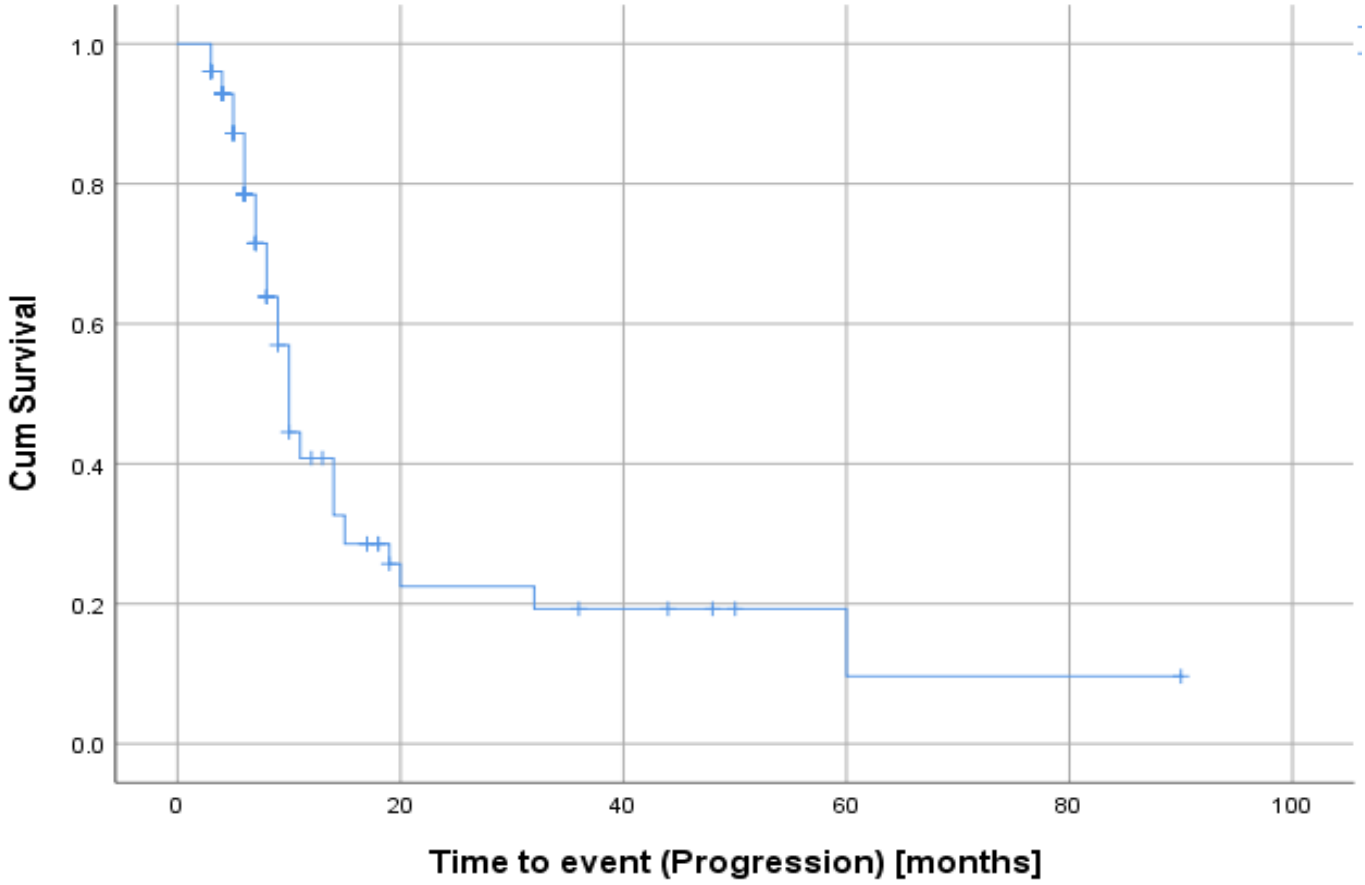

Figure 2: Progression Free Survival Kaplan Meier Curve.

Univariate Analysis of Overall Survival and Progression Free Survival

Univariate analysis, shown in **Tables 4-5,** revealed that age and pathological type were statistically significant in terms of OS.

Regarding PFS, weight loss and EGFR mutation were found to be statistically significant. Patients presenting with weight loss and those with EGFR mutations had significantly lower progression free survival.

Patients who received CCRT had statistically significant higher overall and progression free survivals compared to those who underwent surgery or received chemotherapy only.

Whether patients received induction chemotherapy or not prior to CCRT was non-significant. Interruption of radiotherapy was found to be a statistically significant predictor of time to death. Patients who suffered interruption of RT sessions had median OS of 7 months, compared to 17 months in patients who had no interruption. Interruption also led to median PFS of 11 months compared to 32 months in cases with no interruption.

Patients who received chemotherapy only had statistically significant lower OS and PFS compared to patients who received combined treatment modalities.

Postoperative positive lymphovascular embolization (LVE) was found to be the only statistically significant surgical risk factor.

Regarding chemotherapy regimens, univariate analysis results revealed that use of cisplatin-based chemotherapy and the number of cycles were two statistically significant predictors of time to death. Patients who received cisplatin-based chemotherapy exhibited median OS of 11 months, compared to 7 months in patients who received other chemotherapy lines. Patients who received more than 4 cycles of chemotherapy, regardless of chemotherapy regimen, exhibited higher median OS (12 months) compared to those who received 4 cycles or less (7 months).

Table 4: Univariate Analysis of OS and PFS

Factor		Median OS (months)	Median PFS (months)	P-value (OAS)	P-value (PFS)
Age	< 60 years	10	10	**0.031***	0.471
	≥ 60 years	8	11		
Gender	Male	8	10	0.529	0.180
	Female	11	19		
PS	0-1	10	10	0.160	0.721
	2	6	9		
Smoking	Smoker	8	10	0.497	0.646
	Non-smoker	10	11		
Weight Loss	Yes	9	9	0.709	**<0.001****
	No	8	-		
Pathology	AC	11	10	**0.043***	0.924
	SCC	8	10		
	LCC	10	10		
Grade	Grade 1	4	20	0.809	0.829
	Grade 2	8	10		
	Grade 3	9	10		
Stage	IIIA	9	11	0.181	0.352
	IIIB	8	9		
	IIIC	6	10		
	IIB	17	14		
EGFR	Wild	13	8	0.856	**0.002***
	Mutant	8	3		

Table 5: Univariate Analysis of OS and PFS (continued)

Factor		Median OS (months)	Median PFS (months)	P-value (OAS)	P-value (PFS)
Treatment Modalities					
• **Surgery + Perioperative Chemotherapy**		11	10	0.217	0.681
• **CCRT**		12	32	**0.019***	**<0.001****
• **Chemotherapy Only**		8	7	**0.001***	**<0.001****
Surgical Prognostic Factors					
PORT	Yes	77	60	0.105	0.127
	No	11	10		
Accidental Mediastinal LNs	Yes	6	8	0.265	0.307
	No	11	10		
Infiltrated Margins	Yes	10	9	0.784	0.869
	No	11	10		
Positive LVE	Yes	10	9	**0.015***	**0.020***
	No	36	14		
CCRT Prognostic Factors					
Induction Chemotherapy	Yes	12	-	0.949	0.106
	No	17	-		
Interruption of RT	Yes	7	11	**<0.001****	**0.048***
	No	17	32		
Chemotherapy Regimens					
• **Cisplatin Based Chemotherapy**		11	10	**0.003***	0.388
• **Non-Cisplatin-Based Chemotherapy**		7	10		
Number of Cycles					
• **≤ 4 cycles**		7	10	**0.001***	0.972
• **> 4 cycles**		12	10		

Multivariate Analysis of Overall Survival and Progression Free Survival

Based on cox regression analysis, participants aged 60 years or older and those with squamous histology showed hazard ratios (HR) of 1.4- and 1.8- times, respectively, to exhibit mortality. Patients who did not receive CCRT exhibited 1.3 times higher risk of mortality compared to those who received CCRT. Patients who received chemotherapy only also exhibited 2.8- times higher hazard ratio compared to those who received combined treatment modalities. Patients who did not receive cisplatin, and those who received 4 cycles or less had 1.7- and 2.1- higher hazard ratio to exhibit mortality, respectively.

Moreover, weight loss at presentation was a statistically significant independent predictor of time to progression, with hazard ration 2.7-. Participants did not receive CCRT had 1.7-times higher hazard ratio to exhibit progression compared to those who received CCRT.

DISCUSSION

Predominance of males and smokers in this study population was concordant with several studies. However, no difference in outcomes were observed between sexes, nor between smokers and non-smokers [12, 13].

According to recent studies [14,15], weight loss led to worse outcomes for NSCLC patients independent of other variables. This study demonstrates similar results as weight loss, present in 66% of patients, proved to drastically affect PFS with p-value <0.001.

In **Itaya *et al.*** [15] and **Shen *et al.*** [9], histological subtype was a significant prognostic factor of OS, and in multivariate analysis, OS differed significantly in

adenocarcinoma versus other histologies (P= 0.0017). This study proves the same results; adenocarcinoma histology had statistically significant better prognosis (P value 0.04), while squamous histology was a statistically significant independent bad prognostic factor with HR 1.8.

Older patients tend to have poor PS and higher rate of treatment adverse effects, and therefore lower OS and PFS, as presented by **Ahmed *et al.*** [16]. In this study, patients less than 60 years had statistically significant higher OS compared to patients above 60 (p-value 0.031).

As for EGFR mutation, due to the scarcity of such testing and corresponding anti-EGFR therapy throughout the duration of our study, only 17 patients were tested for EGFR mutation. Two patients were EGFR mutant but did not receive anti-EGFR. EGFR wild patients had statistically significant higher PFS than mutant ones. These results might show discrepancy compared to studies with bigger sample size or involving patients who actually received anti-EGFR therapy. But results of the current study are in concordance with multiple studies, which documented that EGFR over-expression is associated with poor prognosis [17-19].

In this study median age of the studied patients was 59 years. Median OS of all patients was 9 months. Median PFS was around 10 months. Patients who received CCRT without interruption had the highest OS (17 months) and highest PFS (32 months). Patients who received chemotherapy only had the lowest OS (8 months) and PFS (7 months) in comparison to other treatment modalities.

In a comparable Canadian retrospective study [20], median age was 70 years. Median OS of all stage III patients was 14 months. Survival was longest in patients who received CCRT, whose median OS was around 23 months. Patients who received systemic therapy alone had low OS of about 15 months. The higher rates of OS compared to our study could be attributed to bigger sample size, patient characteristics including PS or comorbidities, delivery of RT with better techniques, and administration of target therapies to some patients.

In NSCLC patients with unresectable N2 disease or with N3 lymph nodes, definitive concurrent chemo–radiotherapy has been the standard-of-care treatment, as demonstrated by the EORTC 08941 [21] and ESPATUE trials [22] and by a meta-analysis of six randomized trials by **Aupérin *et al.*** [23].

Overall mortality is significantly higher in stage III NSCLC patients who undergo surgery compared to radiotherapy [24]. This is explained by the increased risk of postoperative mortality associated with the complex surgical interventions often required in locally advanced cases. Therefore, chemoradiotherapy remains the preferred approach in many institutions [25].

Expectedly, the results of this study showed statistically significant difference in OS (p value 0.019) and PFS (p value <0.001) in favor of patients who received CCRT compared to those who underwent surgery or received chemotherapy only.

Studies on RT interruption are scarce. The most recent data are derived from studies during the COVID pandemic era. In one study by **Ying *et al.*** [26], interruption of definitive radiotherapy led to disease progression and patient death (p value 0.008). Our study was able to highlight the impact of RT interruption on survival and disease progression. Of 36 patients who received CCRT, 16 cases suffered interruption. These patients had significantly lower OS of 7 months compared to 17 months in patients who finished CCRT without interruption (p value <0.001). They showed significant reduction in PFS as well (p value 0.048).

Induction chemotherapy prior to CCRT, given to 31 out of the 36 patients who received CCRT in our study, did not yield statistically significant results in terms of OS and PFS, similar to several other studies [27-29].

Regarding surgical prognostic factors in patients who underwent surgery, positive LVE was found to be a statistically significant poor prognostic factor, adversely affecting OS (p value 0.015) and PFS (p value 0.02). This was documented in **Higgins *et al.*** [30], which associated LVE with the development of regional LN and distant metastasis.

Other postoperative prognostic factors like accidentally discovered mediastinal lymph nodes or positive surgical margins did not result in significant difference in survival. However, it is important to note that this insignificance can be attributed to small sample size.

Only 1 out of 8 patients received PORT after R1 resection. Two large contemporary clinical trials failed to demonstrate a better outcome with postoperative radiotherapy (PORT) after complete resection [31, 32].

Platinum based chemotherapy is the mainstay of first line for advanced NSCLC. We tried to demonstrate survival benefit of cisplatin-based chemotherapy over non-cisplatin regimens. We found that cisplatin-based regimens had a statistically significant benefit on OS (p value 0.003) compared to non-cisplatin ones, but there was no significant difference in PFS. Previous meta-analyses showed no difference in OS between carboplatin- and cisplatin-based chemotherapy, but showed a benefit in response rate for cisplatin [33]. Also, in the setting of concurrent chemoradiation, cisplatin containing regimen was found superior to weekly paclitaxel/carboplatin in terms of OS [34].

In terms of optimal number of chemotherapy cycles, current evidence emphasizes that the optimal number of first-line platinum cycles should be four for any NSCLC histology. Our results showed that patients who received more than 4 cycles had higher median OS than those who received 4 cycles or less (p value 0.001). However, the two groups showed equivalent PFS.

Number of cycles was an independent prognostic factor of OS in the cox regression analysis. One study concluded that the total platinum dose given affected survival, and that higher platinum dose delivery was important in maintaining the efficacy of adjuvant chemotherapy [35].

CONCLUSION

CCRT with cisplatin-based chemotherapy remains the superior line of treatment in patients with locally advanced NSCLC. Median OS was 9 months. Patients who received CCRT had statistically significant higher OS and PFS compared to those who received other modalities of treatment. Induction chemotherapy did not affect survival. Age of 60 years or above, weight loss, squamous histology, and RT interruption were proven to be negative prognostic factors affecting survival on both univariate and multivariate analysis.

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