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ORIGINAL ARTICLE

# Radiotherapy with a Carboplatin/Paclitaxel Regimen in Patients with Non-Small-Cell Lung Cancer: Experience at Ondokuz Mayıs University

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**OBJECTIVE**

We investigated the outcomes of radiotherapy (RT) combined with systemic chemotherapy (CHT) including carboplatin and paclitaxel in patients with locally advanced non-small-cell lung cancer.

**METHODS**

This retrospective study included 105 patients. Treatment involved concurrent carboplatin and paclitaxel with RT administered weekly followed by two cycles of consolidation carboplatin and paclitaxel administered triweekly.

**RESULTS**

Comorbid disease was present in 46 (48.6%) patients. At least four cycles of CHT in the concurrent phase and both cycles of CHT in the consolidation phase were able to be administered to 92.3% and 45.4% of patients, respectively. The most common type of toxicity in the entire treatment protocol was hematological toxicity (34.8%). The objective response rate was 71.4%. Overall, recurrence was found in 71 (67.6%) patients. The most common type of recurrence was distant metastasis, which occurred in 47 (66.2%) patients. The median progression-free survival was 14 months. The 1, 2, and 3-year progression-free survival rates were 59%, 30%, and 26%, respectively. The median overall survival was 27 months. The 1, 2, and 3-year overall survival rates were 81%, 57%, and 34%, respectively.

**CONCLUSION**

The survival outcomes in this study closely match those reported in the literature. This is notable because our study included a higher proportion of patients with additional health conditions and fewer concurrent CHT cycles during RT compared to randomized studies. These findings prompt us to consider what the ideal number of concurrent CHT cycles should be when using modern involved-field RT techniques after accurate disease staging.

**Keywords:** Carboplatin; chemotherapy; concurrent radiochemotherapy; non-small-cell lung cancer; paclitaxel; radiotherapy.



## INTRODUCTION

Lung cancer is the most common cause of cancer-related death in both sexes worldwide.[1] Non-small-cell lung cancer (NSCLC) accounts for 80–85% of all lung cancers. Thirty percent of patients with NSCLC have locally advanced (LA) disease.[2] LA-NSCLC typically refers to stage III disease,[3] a heterogeneous group of

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diseases for which all treatment modalities including surgery, radiotherapy (RT), and/or systemic chemotherapy (CHT) can be used.[4] This stage is divided into "primarily surgically treated stage III NSCLC" (e.g., mainly stage IIIA) and "primarily RT-treated stage III NSCLC" (e.g., mainly stage IIIB or IIIC).[5]

RT with concurrent platinum-based doublet CHT is the standard treatment for patients with medically or surgically inoperable LA-NSCLC.[6] One of the most commonly used platinum-based doublet CHT regimens in combination with RT is carboplatin/paclitaxel (CP).[7] Since 2013, the radiation oncology department of our university hospital has adopted the use of this CHT regimen concurrent with RT in patients with LA-NSCLC.

In this study, we examined the early and late toxicities, failure patterns, and survival outcomes of patients with inoperable LA-NSCLC treated with a CP-based CHT regimen combined with RT.

## MATERIALS AND METHODS

### Ethics, Consent, and Permissions

This retrospective study was approved by the local ethics committee of the Faculty of Medicine of Ondokuz Mayıs University, Samsun, Türkiye (application number: 2023000086-1, acceptance date: 16 March 2023, acceptance number: 2023/86). All patients provided written informed consent prior to participation.

### Patient Evaluation

In total, 105 patients with inoperable biopsy-verified LA-NSCLC who received RT with a CP-based CHT regimen from January 2013 to August 2022 were enrolled. The staging work-up was performed using magnetic resonance imaging of the brain and positron emission tomography-computed tomography (PET-CT) scanning of the whole body. The staging of all patients was updated according to the American Joint Committee on Cancer Eighth Edition Cancer Staging Manual. All patients had a Zubrod performance status score ≤2 with normal hematological, renal, and hepatic function.

### Radiotherapy Planning

RT planning was performed either three-dimensionally or by four-dimensional intensity-modulated radiotherapy (IMRT) using a CT simulator. The gross tumor volume included the primary tumor and involved lymph nodes. The clinical target volume was defined as additional 8 mm and 6 mm uniform margins in all directions around the gross tumor volume for adenocarcinoma and non-adenocarcinoma histologies, respectively. The planning target volume (PTV) was created around the clinical target volume with additional 5 mm uniform margins in all directions for four-dimensional plans or 1.0 to 1.5 cm nonuniform margins for three-dimensional plans. The PTV-total included the PTVs of the primary tumor and lymph nodes. The organs at risk were the lungs, esophagus, heart, and spinal cord.

### Treatment

The prescribed dose of RT to the PTV-total was 60–66 Gy at the discretion of the treating radiation oncologist. Dose constraints were applied according to the National Comprehensive Cancer Network (NCCN) guidelines. In the concurrent radiochemotherapy phase, RT was started on the first day of CHT. Concurrent CHT included carboplatin (area under the curve [AUC]=2) and paclitaxel (45 mg/m$^2$/day) per week. The administration of consolidation CHT was at the discretion of the medical oncologist and was planned to start 2 weeks after the end of RT. In this phase, administration of two cycles of carboplatin (AUC=6) and paclitaxel (200 mg/m$^2$) triweekly was planned. CHT was omitted if the white blood cell and neutrophil counts were <3000/μL and <1500/μL, respectively, or the platelet count was <100,000/μL. In addition, RT was interrupted in patients with any grade ≥3 treatment-related toxicity. In patients whose RT was interrupted, whether additional fractionation was required was determined by taking time-dose and fractionation factors into account.

### Follow-up

During treatment, patients were evaluated by physical examination, a complete blood count, and kidney and liver function tests before each CHT cycle. After treatment, the patients were followed up at 3-month intervals in the first year, 4-month intervals in the second year, 6-month intervals in years 3–5, and 12-month intervals thereafter. The follow-up evaluation for each patient consisted of a physical examination, complete blood count, kidney and liver function tests, whole-body PET-CT (at the first 3-month evaluation, at 3 months after the end of the radiochemotherapy phase or 1 month after the consolidation phase, or as needed), and CT of the chest (excluding the first 3-month evaluation). Early (≤90-day) and late (>90-day) toxicity grading was performed according to the toxicity criteria of the Common Terminology Criteria for Adverse Events (version 5) and the Radiation Therapy Oncol-

ogy Group (RTOG), respectively. The response was evaluated in accordance with the Response Evaluation Criteria in Solid Tumors.

### End Points and Statistical Analysis

Local control, regional control, distant control, death from any cause or from disease, progression-free survival (PFS), and overall survival (OS) were calculated and recorded. PFS was defined as the time between the date of diagnosis and the date of the first failure at any site. OS was defined as the time between the date of diagnosis and the date of death from any cause. Patient characteristics were described using descriptive statistics. The Kaplan-Meier method was used to analyze survival.

## RESULTS

### Patients

In total, 105 patients with inoperable LA-NSCLC who received RT with a CP-based CHT regimen were identified. Of these patients, 96 (91.4%) were male. Their median age was 63 (range, 40–78) years. The most common age range was 18–64 years (n=62, 59%). A smoking history was present in 96 (91.4%) patients. Comorbid disease was present in 46 (48.6%) patients. The Eastern Cooperative Oncology Group (ECOG) performance score was <2 in 99 (94.3%) patients. The histopathological diagnosis was squamous cell carcinoma in 65 (61.9%) patients. Most of the patients had stage ≥T3 disease (n=80, 76.2%) and stage ≥N2 disease (n=73, 69.5%). More than half of the patients had stage ≥3B disease (n=53, 50.5%) (Table 1).

### Treatment

The RT technique was IMRT in 87 (82.9%) patients. The median prescribed RT dose was 62 (range, 60–66) Gy. The median total duration of planned concurrent radiochemotherapy was 44 (range, 40–50) days. The median duration of interruption of the radiochemotherapy phase because of treatment-related toxicity was 4 (range, 1–14) days (n=17, 16%). The mean concurrent carboplatin and paclitaxel doses were 1185±423 and 386±114 mg, respectively. The median administered number of concurrent CHT cycles was six (range, 1–7) (Table 2). Administration of consolidation CHT was planned for 64 (61%) patients. At least four cycles of CHT in the concurrent radiochemotherapy phase and both cycles of CHT in the consolidation phase were able to be administered to 92.3% and 45.4% of the patients, respectively (Table 3).

**Table 1** Patients' clinical chracteristics

| | n | % |
|---|---|---|
| Sex | | |
| Male | 96 | 91.4 |
| Female | 9 | 8.6 |
| Smoking history | | |
| Yes | 96 | 91.4 |
| No | 9 | 8.6 |
| Age range | | |
| 18–64 | 62 | 59 |
| 65–74 | 37 | 35.3 |
| 75–84 | 6 | 5.7 |
| Comorbidity | | |
| Yes | 46 | 48.6 |
| No | 54 | 51.4 |
| Histopathology | | |
| Squamous cell carcinoma | 65 | 61.9 |
| Adenocarcinoma | 35 | 33.3 |
| Others | 5 | 4.8 |
| Performans | | |
| ECOG 0–1 | 99 | 94.3 |
| ECOG 2 | 6 | 5.7 |
| T-stage | | |
| T1 | 2 | 1.9 |
| T2 | 23 | 21.9 |
| T3 | 7 | 6.7 |
| T4 | 73 | 69.5 |
| N-stage | | |
| N0 | 25 | 23.8 |
| N1 | 7 | 6.7 |
| N2 | 60 | 57.1 |
| N3 | 13 | 12.4 |
| AJCC stage | | |
| IIIA | 52 | 49.5 |
| IIIB | 45 | 42.9 |
| IIIC | 8 | 7.6 |

ECOG: Eastern Cooperative Oncology Group; AJCC: American Joint Committee on Cancer

### Toxicity

Toxicity of any degree occurred in 73.3% and 54.7% of patients in the concurrent radiochemotherapy and consolidation phases, respectively. Most of the concurrent radiochemotherapy phase-related toxicities were grade 1–2 (61.8%). In four patients who received at least four cycles of concurrent CHT, concurrent treatment was performed with carboplatin alone because of grade 3 anaphylaxis that developed after paclitaxel administration. Grade 3 pneumonitis, which responded dramatically to steroid treatment, developed in one patient 2 months after concurrent radiochemotherapy. Most of the consolidation CHT-

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**Table 2** Characteristics of radiochemotherapy phase

| | Mean | SD | Median | Minimum | Maximum |
|---|---|---|---|---|---|
| Dose of radiotherapy (Gy) | – | – | 62 | 60 | 66 |
| Dose of concurrent carboplatin (mg) | 1185 | 423 | 1157 | 160 | 2048 |
| Dose of concurrent paclitaxel (mg) | 386 | 114 | 400 | 75 | 575 |
| Toxicity related interruption (day) | – | – | 4 | 1 | 14 |
| Number of concurrent chemotherapy | – | – | 6 | 1 | 7 |

SD: Standard deviation

**Table 3** The administered chemotherapy doses and the reasons for the missing number of administrations

| Cycles | Patient | | Number of toxicity type | |
|---|---|---|---|---|
| | n | % | Hematologic | Non-hematologic |
| Concurrent chemotherapy (n=105) | | | | |
| #1 | 2 | 1.9 | 2 | – |
| #2 | 4 | 3.8 | 2 | 2 |
| #3 | 2 | 1.9 | – | 2 |
| #4 | 17 | 16.2 | 7 | 10 |
| #5 | 20 | 19 | 14 | 6 |
| #6 | 58 | 55.2 | – | – |
| #7 | 2 | 1.9 | – | – |
| Consolidation chemotherapy (n=64) | | | | |
| Not given | 41 | 39 | – | – |
| #1 | 35 | 54.6 | 23 | 12 |
| #2 | 29 | 45.4 | – | – |

related toxicities were grade 3–4 (29.7%). In both the concurrent radiochemotherapy and consolidation phases, the most common grade 3–4 toxicities were hematological toxicities (6.7% and 28.0%, respectively). No treatment-related grade 3–4 late toxicity or death occurred (Table 4).

## Response and Survival

The median follow-up time was 21 (range, 3–86) months. Three months after treatment completion, there was a complete response in 17 (16.2%) patients, partial response in 58 (55.2%), stable disease in 7 (6.7%), and progressive disease in 23 (21.9%). Overall, recurrence developed in 71 (67.6%) patients. Locoregional recurrence was detected in 24 (33.8%) patients, distant metastasis in 25 (35.2%), and both locoregional recurrence and distant metastasis in 22 (31.0%) (Table 5). The median PFS was 14 (range, 1–86) months. The 1, 2, and 3-year PFS rates were 59%, 30%, and 26%, respectively. The median OS was 27 (range, 3–86) months. The 1, 2, and 3-year OS rates were 81%, 57%, and 34%, respectively (Figs. 1, 2).

**Table 4** Rates of detected major toxicity grades

| | n | % |
|---|---|---|
| Radiochemotherapy related (n=105) | | |
| No toxicity (grade 0) | 28 | 26.7 |
| Hematologic grade 1–2 | 29 | 27.6 |
| Hematologic grade 3–4 | 7 | 6.7 |
| Non-hematologic grade 1–2 | 36 | 34.2 |
| Non-hematologic grade 3–4 | 5 | 4.8 |
| Dead (grade 5) | 0 | 0 |
| Consolidation chemotherapy related (n=64) | | |
| No toxicity (Grade 0) | 29 | 45.3 |
| Hematologic grade 1–2 | 8 | 12.5 |
| Hematologic grade 3–4 | 18 | 28 |
| Non-hematologic grade 1–2 | 8 | 12.5 |
| Non-hematologic grade 3–4 | 1 | 1.7 |
| Dead (Grade 5) | 0 | 0 |

## DISCUSSION

Concurrent radiochemotherapy has been accepted as the standard treatment method for LA-NSCLC, based

**Table 5** Characteristics of treatment outcomes

| | n | % |
|---|---|---|
| RECIST outcome at 3 months (n=105) | | |
| Complete response | 17 | 16.2 |
| Partial response | 58 | 55.2 |
| Stable disease | 7 | 6.7 |
| Progressive disease | 23 | 21.9 |
| Recurrence (n=105) | | |
| No | 34 | 32.4 |
| Yes | 71 | 67.6 |
| Recurrence site (n=71) | | |
| Locoregional | 24 | 33.8 |
| Distant | 25 | 35.2 |
| Locoregional + Distant | 22 | 31 |

RECIST: Response Evaluation Criteria In Solid Tumors

on the results of Japan[8] and RTOG-9410[9] studies. Concurrent radiochemotherapy increased the 3-year survival rate by decreasing the 3-year local progression rate. However, distant progression is still detected as a significant problem in a significant portion of patients. This suggests the need for additional CHT,[10] which can be administered before radiochemotherapy (induction) or after radiochemotherapy (consolidation). Starting treatment with induction CHT increases toxicity and has no survival benefit.[11,12] Although it is recommended to start treatment with concurrent radiochemotherapy as soon as possible because of increased local control and a survival advantage, the benefit of consolidation CHT is controversial.[11,13–15]

The specific CHT regimen that should be administered concurrently with RT remains unclear. It is recommended to administer platinum-based doublet CHT regimens rather than single-agent regimens because of the survival advantage.[16] The most commonly used platinum-based doublet CHT regimens concurrent with RT are cisplatin/etoposide (PE) and CP.[7,16] Although concurrent administration of both PE and CP-CHT regimens with RT results in similar survival rates among patients with LA-NSCLC, the CP regimen causes less toxicity than the PE regimen.[6,17]

CP with concurrent RT in patients with LA-NSCLC was first reported by Choy, et al.[18] Twenty-three patients were treated with RT (66 Gy) and concurrent CHT (carboplatin AUC=2 per week, paclitaxel=50 mg/m$^2$ per week) followed by two cycles of consolidation CHT (carboplatin AUC=6 every 3 weeks, paclitaxel=200 mg/m$^2$ every 3 weeks). The objective response rate was 82%, and the major grade 3/4 toxicity

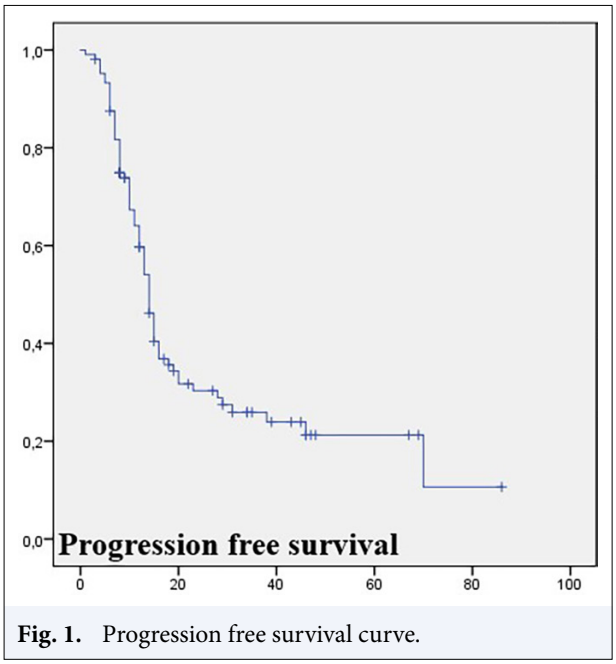


**Fig. 1.** Progression free survival curve.

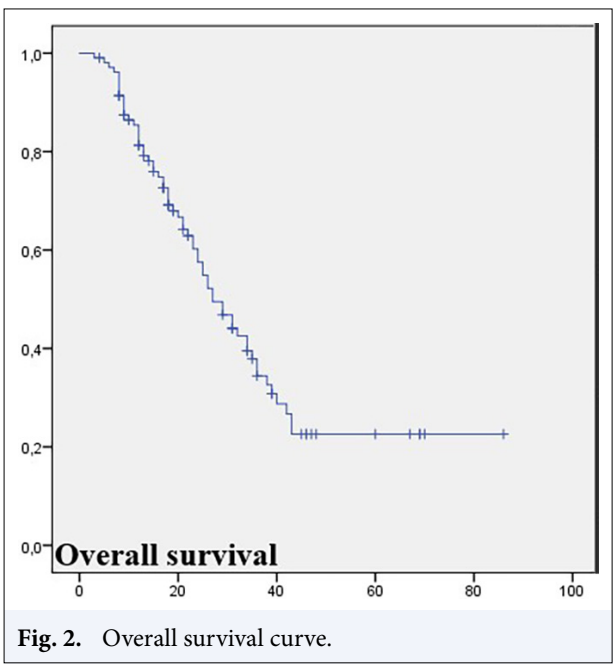


**Fig. 2.** Overall survival curve.

was esophagitis (45%). The authors reported that this protocol had a high response rate with an acceptable and manageable toxicity profile.[18] They subsequently reported the follow-up results of 39 patients. The prescribed dose of RT was administered to 92% of the patients. In the concurrent phase, 94% of the patients received at least six cycles, and in the consolidation phase, 69% of the patients received both cycles. The objective response rate was 75%. The failure rates in

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distant and locoregional sites were 67% and 33%, respectively. The 1 and 2-year PFS rates were 43% and 34%, respectively, with a median PFS time of 9 months. The 1 and 2-year OS rates were 56% and 38%, respectively, with a median OS time of 20 months. The major grade 3/4 toxicity was still esophagitis (46%).[19] The aim of the phase II study conducted by Belani, et al.[13] was to determine the concurrent use of a CP-CHT regimen with RT with optimal sequence. In total, 257 patients were divided into three study arms. The planned treatment was as follows: induction CHT (two cycles of carboplatin AUC=6 plus paclitaxel=200 mg/m$^2$ every 3 weeks) followed by RT (63 Gy) alone in the first arm (n=91); induction CHT (similar to the first arm) followed by CHT (carboplatin AUC=2 plus paclitaxel=45 mg/m$^2$ weekly) with concurrent RT (63 Gy) in the second arm (n=74); and concurrent radiochemotherapy (similar to the second arm) followed by consolidation CHT (similar to the induction) in the third arm (n=92). The prescribed dose of RT was administered to 81% of the patients. In the concurrent phase, 85% of the patients received at least six cycles, and in the consolidation phase, 67% of the patients received both cycles of CHT. The 1-year PFS rates in each arm were 46%, 54%, and 54% with a median PFS time of 9.0, 6.7, and 8.7 months, respectively. The median OS times in each arm were 13.0, 12.7, and 16.3 months, respectively. The 1, 2, and 3-year OS rates were 57%, 30%, and 17% in the first arm; 53%, 25%, and 15% in the second arm; and 63%, 31%, and 17% in the third arm, respectively. Esophagitis was the most common grade ≥3 major toxicity detected in the concurrent radiochemotherapy phases, with a rate of 19% in the second arm and 28% in the third arm. The authors reported that starting with the concurrent radiochemotherapy phase and progressing to the consolidation CHT phase was the most effective protocol. Trinh, et al.[20] performed a retrospective study of a carboplatin (AUC=2 per week) and paclitaxel (45 mg/m$^2$ per week) CHT regimen with concurrent RT (60–66 Gy) without consolidation CHT in 107 patients with LA-NSCLC. The prescribed dose of RT was administered to 98% of the patients, and 92% of the patients received at least six cycles of CHT. The objective response rate was 68%. The failure rates in distant and locoregional sites were 53% and 47%, respectively. The 2-year PFS rate was 31% with a median PFS time of 15 months. The 2-year OS rate was 47% with a median OS time of 22 months. Neutropenia and esophagitis were the most common grade ≥3 major toxicities with a rate of 15% and 11%, respectively. Moreover, the randomized phase III RTOG 0617 trial[14] investigated standard-dose (60-Gy) versus high-dose (74-Gy) conformal RT (three-dimensional or IMRT) with concurrent and consolidation carboplatin (AUC=2 per week and AUC=6 every 3 weeks, respectively) plus paclitaxel (45/mg/m$^2$ per week and 200 mg/m$^2$ every 3 weeks, respectively) with or without cetuximab in patients with LA-NSCLC. The protocol compliance rates in the standard-dose and high-dose without cetuximab groups were 83% and 74%, respectively (p=0.002). There were no differences in CHT delivery between the groups. The median PFS times in each arm were 12.0 and 9.6 months, respectively (p=0.05). The median OS times in each group were 28.7 and 20.3 months, respectively (p=0.007). The 2-year PFS and OS rates in the standard-dose group were 30.7% and 59.6%, respectively. The grade ≥3 toxicity rates in each group were similar (p=0.44). However, the esophageal toxicity (grade ≥3) rates in each arm were 7.3% and 20.8%, respectively (p<0.001). IMRT was associated with a lower rate of grade ≥3 pneumonitis (7.9% vs. 3.5%, p=0.03) and lower cardiac doses (p<0.05).[21] Factors associated with better survival after the multivariate analysis were standard-dose radiation, tumor localization, a high institution accrual volume, less esophageal toxicity, a small PTV, and a low cardiac dose.[22] The RTOG 0617 trial suggested that in patients with LA-NSCLC, CHT and RT should be administered concurrently with the IMRT technique, the dose should be standard, and cetuximab has no effect on survival.[14,21,22] Finally, the randomized phase III PACIFIC trial demonstrated a PFS advantage (5-year rate=33.1% vs. 19.0%) and an OS advantage (5-year rate=42.9% vs. 33.4%) for patients with the addition of durvalumab, regardless of the PD-L1 status, who have not progressed after at least two cycles of platinum-based CHT with concurrent RT.[23] This protocol is recommended by the NCCN at the category 1 level in patients with LA-NSCLC.[7]

In our study, all patients were staged using brain magnetic resonance imaging and PET-CT. Our treatment protocol for inoperable LA-NSCLC was standard as recommended in the literature[13,14,20] and NCCN guidelines.[7] Our prescribed RT dose was a median of 62 Gy (range, 60–66 Gy), and 82.9% of our patients were treated with the IMRT technique. At least six, five, and four cycles of concurrent CHT with RT were able to be administered to 57.1%, 76.1%, and 92.3% of the patients, respectively. Both cycles of consolidation CHT could be administered to 45.4% of the patients. In the literature, these rates were 85–94% and 67–69% for at least six cycles of concurrent CHT and both cycles

of consolidation CHT, respectively.[13,19,20] Thus, compared to the literature, we found that we delivered fewer CHT cycles in our treatments.[19,20] However, the optimal number of carboplatin and paclitaxel CHT cycles administered weekly for patients with NSCLC remains unclear. In previous studies,[13,19,20] the rates of patients who received at least six cycles were >85%. In our study, the rate of patients who received at least six cycles was 57.1%. Although 92.3% of our patients received at least four cycles of concurrent CHT with RT, the survival was similar to that reported in the literature. This raises the question of what the optimum number of concurrent CHT cycles should be. Similarly, weekly concurrent CHT with RT is administered to patients with inoperable cervical cancer. In one study, no survival difference was found between a total number of cisplatin cycles ≤5 and >5. For this reason, the authors reported that the optimum number of cycles to be administered is five.[24] Thus, in patients with LA-NSCLC, further studies are needed to determine the optimum number of weekly carboplatin and paclitaxel CHT regimens administered concurrently with RT. The objective response rate, which is 68–75% in the literature, was 71.4% in the present study. The failure rates in distant and locoregional sites, which are 53–67% and 33–47% in the literature,[19,20] were 66.2% and 33.8%, respectively, in the present study. The median PFS and OS times, which are 8.7–15 and 16.3–28.7 months in the literature, were 14 and 27 months in the present study. Our 1- and 2-year PFS rates were 59% and 30% whereas those in the literature are 43–54% and 30.7–34%. Our 1- and 2-year OS rates were 81% and 57% whereas those in the literature are 56–63% and 31–59.6%.[13,14,19,20] In studies that used two-dimensional and/or elective nodal irradiation,[13,19] the grade ≥3 major toxicity was esophagitis (28–46%), whereas in studies that used conformal RT without elective nodal irradiation,[14,19] the major toxicity was the hematological type (15–28%) and the esophagitis rates were (7–11%). Grade ≥3 esophagitis was not observed in our patients because of the administration of conformal RT with strict dose constraints and without elective nodal irradiation, while the detected grade ≥3 major toxicity was the hematological type in both the concurrent and consolidation phases with a rate of 6.7% and 28.0%, respectively. Finally, none of our patients were treated with durvalumab.

Limitations of the present study include its retrospective design, small number of patients, short follow-up time, and single-institution design.

## CONCLUSION

Concurrent radiochemotherapy is an important treatment regimen. The effectiveness of a treatment protocol with a concurrent CP-based CHT regimen with RT has also been established. Our study provides two important insights. First, although comorbid diseases were present in 48.6% of our patient cohort, completing the treatment as planned yielded results similar to those in the literature. Second, although 92.3% of our patients received at least four cycles of concurrent CHT with RT, we obtained treatment results similar to those in the literature. This raises the question of what the optimum number of concurrent CHT cycles should be with the currently used modern staging and RT techniques.

**Ethics Committee Approval:** The study was approved by the Ondokuz Mayıs University Clinical Research Ethics Committee (no: 2023/86, date: 16/03/2023).

**Authorship contributions:** Concept – A.S., N.Ö.O., R.E.Y., B.G., D.M.; Design – A.S., N.Ö.O., R.E.Y., B.G., D.M.; Supervision – A.S., N.Ö.O., R.E.Y., B.G., D.M.; Materials – A.S., N.Ö.O.; Data collection and/or processing – A.S., N.Ö.O., R.E.Y.; Data analysis and/or interpretation – A.S., N.Ö.O.; Literature search – A.S., N.Ö.O.; Writing – A.S., N.Ö.O.; Critical review – A.S., N.Ö.O., R.E.Y., B.G., D.M.

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