TURKISH JOURNAL of ONCOLOGY

Turk J Oncol 2023;38(2):136–44
doi: 10.5505/tjo.2023.3921

ORIGINAL ARTICLE

Recurrence Patterns in NSCLC Patients Treated with Post-operative Radiotherapy; Turkish Radiation Oncology Society Thoracic Oncology Group Study

Fazilet ÖNER DİNÇBAŞ,[1] Alaattin ÖZEN,[2] Esra KORKMAZ KIRAKLI,[3] Serap AKYÜREK,[4] Fatma SERT,[5] Şule KARABULUT GÜL,[6] Berrin BENLİ YAVUZ,[7] Zafer KOÇAK,[8] Ayşe Nur DEMİRAL,[9] Bekir Hakan BAKKAL,[10] Deniz YALMAN,[5] Funda ÇUKURÇAYIR,[11] Ceren BARLAS,[1] Sevilay ERDEM,[3] Esra GÜMÜŞTEPE,[4] Melek COŞAR YAKAR,[2] Hüseyin TEPETAM,[6] Gül KANYILMAZ,[7] Cenk UMAY,[9] Özlem ELMAS,[10] Gülden BAYIR ANGIN,[11] Şefika Arzu ERGEN,[1] Hasan YILMAZ,[3] Mert SAYNAK[8]

[1]Department of Radiation Oncology, İstanbul University-Cerrahpaşa, Cerrahpasa Faculty of Medicine, İstanbul-*Türkiye*
[2]Department of Radiation Oncology, Eskisehir Osmangazi University Faculty of Medicine, Eskişehir-*Türkiye*
[3]Department of Radiation Oncology, Dr. Suat Seren Chest Disease and Surgery Training Hospital, İzmir-*Türkiye*
[4]Department of Radiation Oncology, Ankara University Faculty of Medicine, Ankara-*Türkiye*
[5]Department of Radiation Oncology, Ege University Faculty of Medicine, İzmir-*Türkiye*
[6]Department of Radiation Oncology, Kartal Dr. Lütfi Kırdar Training and Research Hospital, İstanbul-*Türkiye*
[7]Department of Radiation Oncology, Necmettin Erbakan University Meram Faculty of Medicine, Konya-*Türkiye*
[8]Department of Radiation Oncology, Trakya University Faculty of Medicine, Edirne-*Türkiye*
[9]Department of Radiation Oncology, Dokuz Eylul University Faculty of Medicine, İzmir-*Türkiye*
[10]Department of Radiation Oncology, Bülent Ecevit University Faculty of Medicine, Zonguldak-*Türkiye*
[11]Department of Radiation Oncology, Balıkesir Government Hospital, Balıkesir-*Türkiye*

OBJECTIVE

Post-operative radiotherapy (PORT) in non-small cell lung cancer (NSCLC), especially after complete resection, has long been an unresolved dilemma and debated among therapeutic disciplines. We aimed to evaluate the effects of different radiotherapy volumes and techniques on local-regional recurrence patterns and PORT results in patients with NSCLC.

METHODS

The results of 389 patients who underwent surgery and received PORT at 11 centers were analyzed retrospectively. The surgical margin was positive or closes in 100 (26%) patients. The PORT dose was a median of 50 Gy (36–60 Gy). Intensity-modulated RT methods were used in 68 (17.5%) patients.

RESULTS

The first recurrence of the patients who developed relapse, local recurrence was found in 77 (19.8%) patients, distant recurrence was found in 95 (24%) patients, and both recurrences was found in 30 (8%) patients. The median time to locoregional relapse was 14 months (1.84–59.7 months). Local-regional recurrence was not significantly higher in patients with positive surgical margins than in negative patients (39% vs. 29%, p=0.1), but the dose administered to these patients was also higher. Mediastinal recurrence occurred in 28 (19%) patients who did not receive radiotherapy to the mediastinum; 25 of these recurrences (89%) were just near or outside the field. Cardiac events became 7% in all groups and did not change according to chosen mediastinal radiotherapy volume.

Received: January 06, 2023
Accepted: February 14, 2023
Online: March 01, 2023

Accessible online at:
www.onkder.org

Dr. Alaattin ÖZEN
Eskişehir Osmangazi Üniversitesi Tıp Fakültesi,
Radyasyon Onkolojisi Anabilim Dalı,
Eskişehir-Türkiye
E-mail: dralovettin@gmail.com

CONCLUSION

A clear description of the PORT volumes according to the localization of the primary tumor and the involved lymph nodes would be beneficial in terms of establishing the recurrence/toxicity balance better.

Keywords: Non-small cell lung cancer; postoperative radiotherapy; radiation therapy technique; recurrence patterns.

INTRODUCTION

Lung cancer is still the leading cause of cancer death worldwide. However, a rapid trend of progress has emerged in the last 5–10 years after the treatment instruments have been in a reasonably stable state for a long time. Targeted drugs and immune therapies have started to be included in treatment guidelines at almost every stage. However, the role of postoperative radiotherapy (PORT) in N2 disease with a diagnosis of NSCLC and operated with a negative surgical margin remains an age-old debate.[1,2]

Although the port meta-analysis, which was first published in 1998 and updated twice, was criticized each time for its various shortcomings, it also showed some clues about how this treatment should be applied.[1,3,4] First, the contribution of PORT to local control must be balanced with cardiac and pulmonary toxicity.

When the Lung-ART trial began, it created much excitement because of the goals it aimed to achieve. Consistent with recent evidence in this study, in which many patients had PET/computed tomography (CT) imaging at baseline, and a significant proportion (98%) of patients were treated with chemotherapy, a selective elective lymph node volume was used to reduce the risk of organ toxicity, especially in the heart and lungs. It was expected to increase the importance of local recurrences by controlling the systemic disease. PORT reduced mediastinal recurrences by half, as expected, and disease-free survival, which was the study's primary endpoint, was not significantly different.

Contrary to expectations, severe toxicity was significantly higher in patients who underwent PORT, especially cardiac and pulmonary toxicity. Since the results of this study were published, the dose-volume limitations of the heart and lungs have been criticized. In this group of patients with a long survival expectation, the approach to cardiac dose limits should be low doses, as in breast cancer RT. In addition, also lung dose constraints could be determined more cautiously, especially in patients who had undergone pneumonectomy, by inferring from the mesothelioma data. In this study, perhaps the most important criticism was that the IMRT technique, which has rapidly increased evidence that it is essential in terms of toxicity in curative radiotherapy of locally advanced disease, was used only in 11% of the patients.[5]

In this study, we aimed to evaluate the effects of different radiotherapy volumes and techniques on local-regional recurrence patterns and PORT results in patients with non-small cell lung cancer (NSCLC). For this aim, we analyzed the clinical data of eleven hospitals in Turkey.

MATERIALS AND METHODS

Patient Selection and Treatment Protocol

We retrospectively reviewed electronic medical records for 389 NSCLC patients treated with PORT. Eleven different hospitals participated in the study from Turkey. All patients were treated by the clinicians' practices and department policies. Ethics committee approval was obtained for the Turkish Society of Radiation Oncology (Thoracic Oncology Working Group study 08-009).

Patient and Treatment Characteristics

The characteristics of 389 patients who underwent PORT for surgical margin positivity, N2 Disease, or T4 disease are shown in Table 1. Surgical margins were recorded as positive or close in 26% (n=100) of the patients. 246 (63%) patients received adjuvant chemotherapy, 71 (18%) patients received neoadjuvant chemotherapy, and 38 (10%) patients received both neoadjuvant and adjuvant chemotherapy. While mediastinal RT was not applied to 74 patients, all mediastinal RT was applied to 225 patients, selective elective mediastinal RT was applied to 86 patients, and nodal RT was applied to 4 patients. PORT was administered from 1.8 to 2 Gy per fraction, with a total median of 50 Gy (36 to 66 Gy). Although most patients (82.5%) are treated with 3DRT, intensity-modulated RT methods were used in 68 (17.5%) patients. The patients' treatment, histopathology, and radiotherapy characteristics are given in Tables 2-4.

Turk J Oncol 2023;38(2):136–44
doi: 10.5505/tjo.2023.3921

Table 1 Patients' characteristics

	n	%
Age		
Median (Range)	60 (20-81)	
Gender		
Male	345	88.7
Female	44	11.3
Histopathology		
Adenocarcinoma	169	43.4
Squamous cell carcinoma	195	50.1
Large cell carcinoma	6	1.5
Adenosquamous cell carcinoma	7	1.8
Other	12	3.1
Grade		
I	20	5.1
II	131	33.7
III	122	31.4
Unknown	101	26.0
Perioperative surgical mediastinal staging		
Yes	107	27.5
No	281	72.2
Clinical T stage		
T1	71	18.3
T2	133	34.2
T3	123	31.6
T4	62	15.9
Clinical N stage		
N0	121	31.1
N1	96	24.7
N2	156	40.1
N3	15	3.9

Table 2 Treatment characteristics

	n	%
Surgery Type		
Pneumonectomy	93	23.9
Lobectomy	274	70.4
Segmentectomy	1	0.3
Wedge Resection	21	5.4
Mediastinal Evaluation		
No	8	2.1
Dissection	293	75.3
Sampling	88	22.6
Neoadjuvant chemotherapy		
Yes	71	18.3
No	318	81.7
Neoadjuvant chemotherapy protocol		
Platin Based	64	8.1
Other	7	10.9
Neoadjuvant chemotherapy cycle		
Median (Range)	3 (1–6)	
Adjuvant chemotherapy		
Yes	220	56.6
No	169	43.4
Adjuvant chemotherapy protocol		
Platin based	212	96.2
Other	8	3.8
Adjuvant chemotherapy cycle		
Median (Range)	4 (1–7)	

Follow-up

After completion of treatment, all patients were followed by a treating physician such as a radiation oncologist or medical oncologist. The blood sample analyses and chest tomography were made periodically, and additional radiological imaging was performed when necessary. The follow-up period was every 3 months for the first 2 years, every 6 months between the 2nd and 5th years, and annually after that.

Statistical Analysis

All statistical analyses were performed using standard software (SPSS version 22; SPSS Inc., Chicago, IL, USA). The primary outcomes of interest were OS and PFS. Time to death or progression was calculated as the period from the date of diagnosis to the date of death or first clinical or imaging evidence of disease recurrence. Survival analyses were performed using the Kaplan–Meier method and compared using the log-rank test. The $\chi 2$ test or student's t-test was used to analyze the differences in clinical and pathological factors. Univariate analysis was performed via the log-rank test. Multivariate analysis was performed using the Cox proportional hazards model, using covariates with $p<0.1$ based on univariate analysis.

RESULTS

Treatment Outcomes

As a result of the first recurrence site information analysis of the patients who developed relapse, local recurrence was found in 77 (19.8%) patients, distant recurrence was found in 95 (24%) patients, and both local and distant recurrence was found in 30 (8%) patients (Table 5). The locoregional disease was part of the first recurrence in 107 (27.5%) patients. PET/CT was used in 76 patients, and CT was used in 47 patients to detect relapse in 123 patients with local-regional recurrence. Local recurrence was found in 88 (23%) patients, regional recurrence in 87 (22%) patients, and locoregional recurrence in 123 (32%) patients. The relationship between the recurrence sites and the RT field is shown in Table 5. Mediastinal recurrence was devel-

Table 3 Histopathological characteristics

	n	%
Pathological stage		
I	14	3.6
II	83	21.3
III	291	74.8
IV	1	0.3
Pathological T stage		
T0	1	0.3
T1	64	16.5
T2	127	32.6
T3	128	32.9
T4	69	17.7
Pathological N stage		
N0	96	24.7
N1	66	17.0
N2	222	57.1
N3	5	1.3
Surgical margin		
Negative	289	74.3
Positive	100	25.7
Visceral pleural invasion		
Yes	168	43.2
No	210	54.0
Unknown	11	2.8
Chest wall invasion		
Yes	86	22.1
No	303	77.9
Lymphovascular invasion		
Yes	157	40.4
No	94	24.2
Unknown	138	35.5
Perineural invasion		
Yes	83	21.3
No	157	40.4
Unknown	149	38.3

Table 4 Radiotherapy characteristics

	n	%
Radiotherapy planning		
2D Radiotherapy	57	14.7
3D Conformal Radiotherapy (3DCRT)	239	81.4
Intensity Modulated Radiotherapy (IMRT)	60	18.0
3DCRT+IMRT	23	5.9
Postoperative volume		
Whole mediastinal	119	30.6
Bronchial stump	40	10.3
Whole mediastinal+bronchial stump	90	23.1
Bronchial stump+selective nodal	83	8.7
Chest wall alone	34	8.7
Chest wall+selective nodal	3	0.8
Chest wall+whole mediastinal	16	4.1
Bronchial stump+involved nodal	4	1.0
Mediastinal radiotherapy		
No	74	19.0
Whole mediastinal	225	57.8
Selective mediastinal nodal	86	22.1
İnvolved mediastinal nodal	4	1.0
Radiotherapy dose (EQD210)		
Median (Range)	50 (36–70.4)	

Table 5 Relapse patterns

	n	%
Relapse		
Local	77	19.8
Distant	95	24.4
Local+Distant	30	7.7
Local Relapse		
Yes	88	22.6
No	299	76.9
Unknown	2	0.5
Regional Relapse		
Yes	87	22.4
No	300	87.1
Unknown	2	0.5
Locoregional relapse localization		
İnfield	75	61.0
Outfield	40	32.5
Field edge	8	6.5
Ipsilateral lung relapse		
Yes	47	12.1
No	342	87.9
Contralateral lung relapse		
Yes	34	8.7
No	355	91.3

oped in 28 of the patients who did not receive radiotherapy to the mediastinum. These recurrences were within the radiotherapy volume in 3 (10.7%) patients and at the edge of the radiotherapy volume in 2 (7.1%) patients. Regions of mediastinal lymph node recurrence (levels 2–4R, 2–4L, 5 and 6, 7) in patients undergoing selective nodal radiotherapy are shown in Figure 1. Locoregional recurrence developed in 29% of surgical margin-negative patients and 39% of margin-positive patients (p=0.1). However, typically higher RT doses were administered to margin-positive patients. For example, while RT doses of >50 Gy were given to 83% of patients with surgical margin positive, this rate was 23% for margin-negative patients. 5-year locoregional relapse-free survival was 65%, median locoregional relapse-free survival time was 127.6 months (standard error 26.1 months, Kaplan–Meier), and me-

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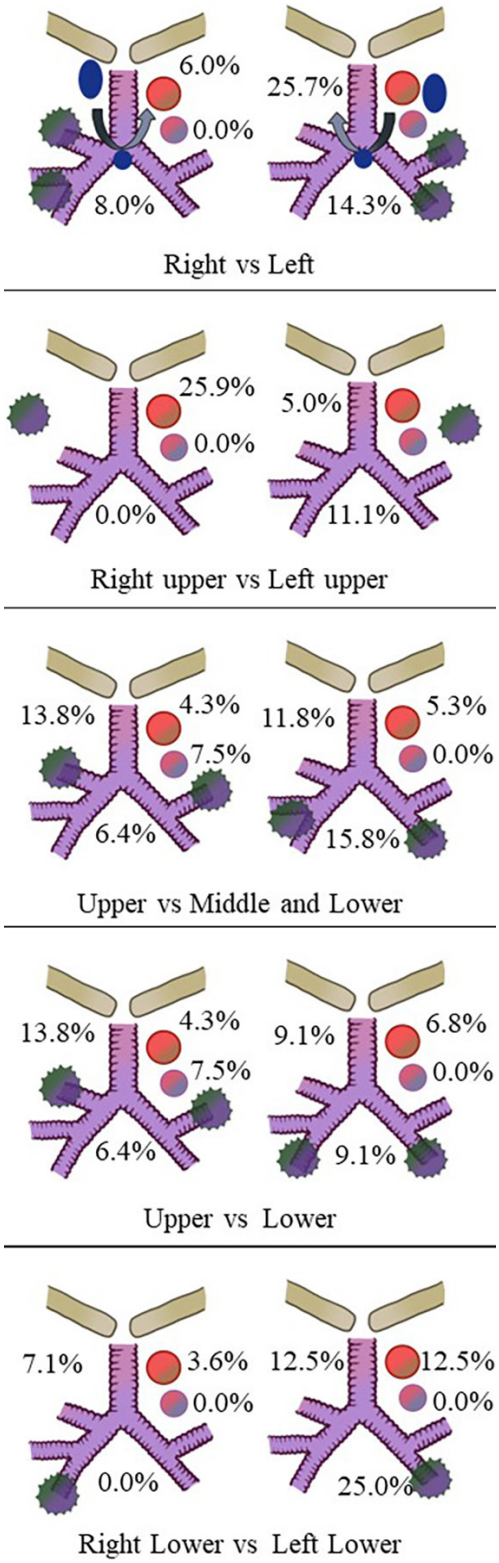

Fig. 1. Regions of mediastinal lymph node recurrence (levels 2-4R, 2-4L, 5 and 6, 7) in patients undergoing selective nodal radiotherapy.

dian time to relapse in patients with locoregional relapse was 14 months (1.84–59.7 months). At the end of the median follow-up period, 134 patients were alive without disease, and 21 were alive with disease. The relationship between the location of the primary disease and the location of lymph node metastasis is given the Table 6 as a percentage.

Toxicity

We know the lung and heart dose values in 309 patients (Table 7). Median Mean Heart Dose was 6.8 Gy (0–56), the median V25 was 10% (0–100), and the median V30 was 6% (0–98). Median Mean Lung Dose (MLD) was 11 Gy (0.8–27), the median V20 value was 17.5% (0.8–55.81), and median V5 value was 39% (0–81). In 65 patients with pneumonectomy, the median MLD was 7.5Gy (1.5–28.4), the median V20 value was 8.7% (0–39.9), and the median V5 value was 33% (0–72). Considering the patients who developed Grade 3 radiation pneumonia, it was understood that pneumonectomy was performed in 2 patients, lobectomy in 2 patients, and wedge resection in 1 patient. The characteristic of the patient who developed Grade 5 toxicity is the patient treated with lobectomy and postoperative 50 Gy/25 fr 3DRT. T20, V5 for lung, and MLD values were reported as 12.5%: 51%, and 9.4 Gy, respectively. Cardiac events were reported in 7% of the patients, and 127 (33%) patients had no cardiac event information. Coronary artery disease in 19 patients, arrhythmia in four patients, pericarditis in three patients, valve disease in one patient, and arrhythmia and coronary disease in one patient were reported as cardiac events.

DISCUSSION

A positive surgical margin is generally accepted as a marker for an increased risk of local-regional recurrence. Unfortunately, although complete gross resection does not guarantee local/regional control, PORT is often considered for patients with a positive surgical margin. In patients with completely resected NSCLC, PORT has never been used for pN0 and N1 disease. PORT has been a topic of debate for many years in patients with mediastinal nodal involvement (pN2), as a 1998 meta-analysis cast doubt on its associated benefits. However, it is considered that RT can increase local control in patients who have had resection for lung cancer.[1] In our series, the local recurrence rate was 21.3% in 83 fully resected patients with N2 disease. This rate may be relatively high in a group of patients who have received radiotherapy. However, patients

Table 6 The relationship between the location of the primary disease and the location of lymph node metastasis in patients treated with 3D Conformal Radiotherapy and/or Intensity Modulated Radiotherapy

Whole mediastinal radiotherapy	Selective mediastinal radiotherapy (n=174)					Metastatic lymph node station (n=85)				
	RUL (n=46) %	RML (n=15) %	RLL (n=44) %	LUL (n=43) %	LLL (n=26) %	RUL (n=20) %	RML (n=17) %	RLL (n=14) %	LUL (n=26) %	LLL (n=8) %
Right supraclavicular	0.0	0.0	0.0	2.3	0.0	10.0	0.0	0.0	7.7	0.0
Left supraclavicular	0.0	0.0	0.0	4,6	0.0	0.0	0.0	0.0	3.8	0.0
Right upper paratracheal	4.3	13.3	0.0	0.0	0.0	10.0	17.6	0.0	15.4	12.5
Left upper paratracheal	0.0	0.0	0.0	0.0	0.0	5.0	0.0	0.0	3.8	12.5
Retrotracheal	0.0	0.0	0.0	0.0	0.0	5.0	0.0	0.0	3.8	0.0
Perivascular	0.0	6.6	0.0	0.0	0.0	10.0	5.8	0.0	0.0	0.0
Right lower paratracheal	13.0	13.3	0.0	2.3	7.7	20.0	11.7	14.3	11.5	12.5
Left lower paratracheal	0.0	6.6	0.0	6.9	3.8	0.0	5.8	7.1	7.7	12.5
Aortopulmonary	0.0	6.6	0.0	6.9	3.8	0.0	0.0	0.0	15.4	0.0
Paraaortic	0.0	6.6	0.0	4.6	0.0	0.0	0.0	0.0	11.5	0.0
Subcarinal	10.9	40.0	7.0	6.9	3.8	0.0	23.5	0.0	11.5	25.0

RUL: Right upper lobe; RML: Right middle lobe; RLL: Right lower lobe; LUL: Left upper lobe; LLL: Left lower lobe

who undergo radiotherapy are usually in the group of patients considered risky in terms of recurrence in that center. This situation creates a bias for the radiotherapy series from the beginning.

Data show that mortality is tightly correlated with treatment volume in patients treated with PORT, and this negative contribution to local control negates the survival benefit. For example, RT applied to large mediastinal volumes can cause mortality up to 15% (≥7%).[6] Firstly, Kelsey et al.[7] conducted a study to identify possible relapse localizations, and similar studies followed that study. Our group series includes 2D and 3D radiotherapy plans. Due to its multicentricity, the preferred irradiation areas in small-volume irradiations varied from center to center. In our study, it was seen that the irradiation of selected regions of lymph nodes in the application of PORT might be a factor that increases the risk of recurrence. Therefore, it has been understood that the volume of RT must be carefully planned. For this reason, the issue of which regions will be irradiated in the elective selective approach should be initiated.

Trodella et al.[8] published a study containing 102 patients with T1–2N0 disease randomized to PORT or surgery alone. These patients were treated with a conventional fractionation of 1.8 Gy/fx and received 59.4 Gy radiotherapy from small areas targeting the bronchial stump and ipsilateral hilum using three-dimensional conformal planning. Although not much

Table 7 Main dose levels for lung and heart

Lung V20 (cc)	
Mean (Range)	18.487 (0.00–55.81)
Lung V5 (cc)	
Mean (Range)	39.311 (0.00–80.55)
Mean Lung Dose (Gy)	
Mean (Range)	10.517 (0.80–28.40)
Heart V25 (cc)	
Mean (Range)	15.988 (0.00–100.00)
Heart V30 (cc)	
Mean (Range)	13.442 (0.00–98.00)
Mean Heart Dose (Gy)	
Mean (Range)	9.791 (0.00–48.54)

discussed, PORT improved overall survival and local control rates in this study.[9] However, today, systemic treatment is applied in addition to surgery in early-stage diseases with risk factors. Therefore, considering other local therapy addition to treatment management is a long shot.

After the surgery of stage II to IIIA NSCLC, adjuvant chemotherapy with cisplatin-based regimens has been the standard treatment based on phase 3 randomized trials.[9] Therefore, it became imperative to reassess the usefulness of post-operative radiation therapy using limited spaces and modern techniques. Based on this randomized trial, PORT is not currently routinely recommended for patients with lung cancer. The optimal PORT dose in patients with lung cancer is unclear.

Turk J Oncol 2023;38(2):136–44
doi: 10.5505/tjo.2023.3921

In the Lung-ART study, the 54 Gy dose prescribed for the entire volume was high and a matter of discussion.[5] Postoperatively applying 54 Gy RT to the whole treatment volume may be a factor that increases cardiopulmonary toxicity. In our series, there was no advantage for local control in patients who received doses higher than 50.4 Gy. However, 83% of these patients were surgical margin-positive patients.

Lei et al.[10] published a meta-analysis evaluating modern phase 3 studies, including the Lung ART study, and reported that PORT contributed to local recurrence and disease-free survival. In a national analysis from the USA, 505 patients received 3D conformal RT, and 88 patients received PORT with IMRT from N2 patients who underwent lobectomy after induction chemotherapy. In that study, PORT applied with IMRT was not found to be a factor associated with survival.[5]

Microscopically incomplete (R1) resection hurts survival, regardless of the stage of the disease. The value of PORT in R1-resected NSCLC must be clarified and debatable, as there are no prospective comparative data.[6] Ethical problems due to the primary treatment principle in this direction and limited accumulation possibility to such a study in question some difficulties are planning a randomized study. However, recent evidence from large retrospective series has demonstrated the role of PORT in these patients.

Wang et al.[9] examined the data of 3395 patients with either R1 or R2 resection who underwent lobectomy at least between 2003 and 2011. 1207 (35.6%) patients received PORT, and 1758 (52%) received ChT. 1892 patients (56%) had R1, 129 patients (4%) had R2, and 1374 patients (40%) had R1 or R2 resection. The 5-year overall survival was better in the entire PORT group and patients with individual N0, N1, and N2 diseases.

Verma et al.[11] analyzed the records of 4921 patients, 29% of whom were positively operated on with surgical margins. About 54% of the patients had concomitant chemoradiotherapy (ChRT), and 46% had sequential ChRT. They found median OS among the sequential ChRT and concurrent ChRT groups in patients who were margin negative was 54.6 versus 39.5 months, respectively ($p<0.001$), and after the propensity score matching analysis, statistical differences found persisted ($p<0.001$). In the microscopic and macroscopic positive margin subgroups, no differences in OS were seen between cohorts ($p=0.368$ and 0.553, respectively). Our series consists of patients who have undergone PORT. Eighty-five patients had surgical margin positivity in our series, but the local recurrence rate was not higher in these patients.

Optimal sequencing of PORT and ChT after surgery is a topic to discuss and study prospectively. With today's knowledge, concurrent therapy can only be performed in exceptional cases because of the high mortality risk reported in the studies. Since the risk of at least metastasis is closely related to survival, systemic therapy prioritizes the treatment of N2 disease, radiotherapy followed by ChT. Shen et al.[12] evaluated the advantage of concurrent ChRT to "ChT alone" in the post-operative management of completely resected N2 disease. Five years of disease-free survival was significantly better in the ChRT arm (30.3% vs. 18.8%, $p=0.04$). In terms of overall survival, a trend favored the ChRT arm in terms of overall survival ($p=0.07$).

To define the optimal timing of radiotherapy in the postoperative setting, Sura et al.[13] recently analyzed the records of 1622 patients treated between 2004 and 2012 in the National Cancer Database. If ChT and RT were administered concurrently, "RT applied before or after 8 weeks" did not affect the results. However, if ChT and RT were applied consecutively, overall survival was better when RT was performed 8 weeks later. However, there is a concern about an increase in toxicity with concomitant chemotherapy. Toxicity may be very important in this group of patients. The fact that concomitant ChRT was not used in our series may also be speculated to be related to the fact that the risk of toxicity remains at this relative level.

It is essential to recognize that due to the physics of therapeutic radiation, incidental dose to normal tissue is unavoidable, irrespective of the technique. Lateral fields dramatically increase the volume of irradiated lung tissue, which is generally considered the pivotal factor in predicting radiation pneumonitis.[14] The non-randomized quality of life analysis derived from RTOG 0617 provides indirect evidence supporting the routine use of IMRT in this setting.[15]

In the Lung ART study, the target volume contains the resected clinical tumor volume, involved lymph node stations, the bronchial stump, the ipsilateral hilar node region, and the probable extension to the mediastinal pleura adjacent to the resected tumor bed. And also, because of the frequent involvement of subcarinal and ipsilateral paratracheal lymph nodes, these stations were systematically included in the CTV. Routine irradiation of the contralateral mediastinum is not recommended for tumors located in the right lung in the Lung-ART study.[5] In our study, we observed that in patients with tumors located in the left lung, if all

mediastinal irradiation was applied, right paratracheal nodal recurrence was much less common (no upper paratracheal recurrence) than selective nodal irradiation in patients who were planned for conformal RT at least. This situation suggests that it would be reasonable to include the right paratracheal region in the PORT volume in left lung tumors if selective nodal irradiation is to be performed. On the other hand, our results support the treatment volumes in the Lung-ART study because of the high rate of subcarinal and ipsilateral paratracheal lymph node metastases.

Radiation-induced toxicity is the perpetrator of the fact that the advantage of local control in all stages of RT is not reflected in the survival results.[16] Pertinently, cardiac and pulmonary rehabilitation is essential for this group of patients with a relatively long life expectancy. In the early stages of IMRT use, by giving PORT to "The patients who underwent pneumonectomy," there were impoverished experiences in terms of toxicity.[16] In a mesothelioma series, which underwent radiotherapy with IMRT technique and uses relatively high lung dose-volume limitations, 6 of the 13 patients died due to fatal pneumonia. For this reason, the QUANTEC analysis published in 2010 was cautious and recommended values of V5 <55–60%, V20 <4–10%, and MLD <8 Gy for a single lung.[13] In the Lung-ART study, the "V20 value for the lung" was limited to 31% in patients who underwent lobectomy and 22% in patients with pneumonectomy and, the V30 value for the heart is limited to 35%.[17] The importance of cardiac doses in patients with a long-life expectancy has been known for a long time. In our study, the heart doses in the groups with and without mediastinal irradiation were very close and within the recommended limits. Cardiac events were similar in these two groups of patients. Sequelae have not had severe levels of late lung toxicity. The fact that post-operative doses are relatively low than curative doses may also play a role in this. Available data demonstrated those field arrangements should not include lateral fields PORT is administered.[18] The increasing use of 3D and IMRT methods toward the last period has also provided better confinement of high-dose regions other than the target volume, and this may have contributed to the relatively low toxicity results. In our series, 23% of patients had IMRT as part of the RT plan.

The use of conventional fraction doses is recommended to avoid toxicity. The alpha/beta ratio was calculated to be 4±0.9 for radiation pneumonia and about 3.5 for radiation fibrosis.[19] In a randomized study by the Groupe d'Etude et de Traitement des Cancers Bronchiques, patients were treated with daily doses ranging from <2 Gy to 2.5 Gy. Non-cancer-related deaths occurred in 7% of patients in the control arm, 16–18% of patients who received ≤2 Gy per fraction, and 26% of patients who received >2 Gy per fraction. Therefore, it may be inconvenient to use fraction doses greater than 2 Gy. In the modern period, PORT is not performed a hypofractionated fashion. Doses of >2 Gy per fraction were not used in our series either.

CONCLUSION

The probability of lymphatic recurrence is ~20% if no mediastinal radiotherapy was applied in patients who underwent PORT due to surgical margin positivity and irradiation of selected lymph node regions in PORT application might be a factor that increases the risk of recurrence. Our findings support the need to avoid large volumes to cause lethal toxicity or too small to miss a significant portion of sites of relapse when setting the target volume for radiotherapy. A clear description of the PORT volumes according to the localization of the primary tumor and the involved lymph nodes would be beneficial in terms of establishing the recurrence/toxicity balance better.

Peer-review: Externally peer-reviewed.

Conflict of Interest: All authors declared no conflict of interest.

Ethics Committee Approval: The study was approved by the Trakya University Faculty of Medicine Scientific Research Ethics Committee (no: 12/03, date: 31/05/2021).

Financial Support: None declared.

Authorship contributions: Concept – S.A., M.S., F.Ö.D.; Design – S.A., M.S., F.Ö.D.; Supervision – S.A., F.Ö.D., M.S.; Materials – E.K.K., S.A., M.S., F.Ö.D.; Data collection and/or processing –F.Ö.D., A.Ö., E.K.K., S.A., F.S., Ş.K.G., B.B.Y., Z.K., A.N.D., B.H.B., D.Y., F.Ç., C.B., S.E., E.G., M.C.Y., H.T., G.K., C.U., Ö.E., G.B.A., Ş.A.E., H.Y., M.S.; Data analysis and/or interpretation – A.Ö., E.K.K., A.N.D.; Literature search – A.Ö., A.N.D., F.S., M.S.; Writing – A.Ö., M.S.; Critical review – S.A., M.S., F.Ö.D.

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