Hypofractionated Radiotherapy for Locally or Systemically Advanced Non-small Cell Lung Cancer

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Research

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Abstract

**Background:** Palliative thoracic radiotherapy (RT) can improve local control and survival in patients with unresectable locally or systemically advanced non-small cell lung cancer (NSCLC), but the optimal RT dose has not been well-defined. We investigated the survival outcomes of patients with NSCLC who underwent hypofractionated radiotherapy (HFRT).

**Methods:** We retrospectively investigated survival and adverse effects among 74 patients with locally or systemically advanced NSCLC who received HFRT (45 Gy/15 fractions) at our institution.

**Results:** The median overall survival (OS) was 18.7 months, with 1- and 2-year OS rates of 65.9% and 33.9%, respectively. The median local progression-free survival (LPFS) was 7.2 months, with 1- and 2-year LPFS rates of 27.9% and 9.4%, respectively. Sixteen patients (21.6%) developed grade ≤2 pneumonitis and 14 (19%) developed grade ≤2 esophagitis; no grades ≥3 pneumonitis or esophagitis occurred.

**Conclusions:** HFRT is safe, tolerable, and effective for patients with unresectable locally or systemically advanced NSCLC exhibiting poor prognostic factors.

Background

Non-small cell lung cancer (NSCLC) accounts for over 80% of all lung cancers; more than 50% of patients have locally or systemically advanced disease [1, 2]. Concurrent chemoradiotherapy (CCRT) is the recommended treatment for unresectable locally advanced NSCLC [3]. The conventional dose fractionation for radiation administered with concurrent chemotherapy is 60 Gy over 6 weeks [4, 5]. However, in practice, a considerable number of patients are ineligible for curative chemoradiotherapy (CRT) owing to poor performance status, inadequate pulmonary function, advanced age, multiple medical comorbidities, or large tumors. Previous studies have confirmed that palliative thoracic radiotherapy (RT) could improve local control and survival in patients with poor prognostic factors, recurrent tumors, and non-response to chemotherapy, as well as in those who are candidates for potentially toxic drugs [6, 7]. However, currently available data do not support the routine use of chemotherapy with palliative RT for these patients. Although the American Society of Radiological Oncology (ASTRO) published a clinical practice guideline in 2011 and updated it in 2018 [8, 9], the optimal RT dose has not been well-defined. A study performed at the MD Anderson Cancer Center found no statistically significant differences in local control and overall survival (OS) among patients with locally advanced NSCLC treated with hypofractionated radiotherapy (HFRT) (45 Gy at 3 Gy/fraction) and conventional fractionation radiotherapy (CFRT) (60–66 Gy at 2 Gy/fraction) [10]. However, this study mainly focused on patients with stage III disease including a small number of those with stage II, and treatments administered post RT were also unknown. On the other hand, studies have shown that RT produces synergistic effects with targeted therapy [11], antiangiogenic therapy [12] and immunotherapy [13]; however, there remain too few studies on the use of these modalities as consolidation therapy after palliative RT for patients with locally...
or systemically advanced NSCLC. As such, we performed this study to investigate the effect of hypofractionated HFRT in such patients.

**Methods**

**Patient characteristics**

We reviewed the records of 4174 patients with lung cancer treated with RT at Tianjin Medical University Cancer Institute and Hospital between January 2014 and December 2019. We identified 74 patients with unresectable locally or systemically advanced NSCLC who received HFRT (45 Gy/15 fractions). All patients had histologically confirmed disease. Staging was based on the American Joint Committee Classification (AJCC) 7th edition criteria. Pretreatment evaluation consisted of computed tomography (CT) or 18-fluorodeoxyglucose positron-emission tomography (PET/CT). All patients completed their prescribed treatments. This study was approved by the internal review board of our institution.

**Treatment**

CT or PET/CT was used for RT planning. The gross tumor volume (GTV) included the primary tumor and the clinically positive lymph nodes (short axis > 1 cm and/or positive at PET/CT). RT was administered 5 days a week in 15 fractions of 3 Gy/each for 3 weeks. The calculated biologically effective dose (BED) was 58.5 Gy (α/β = 10). RT was delivered using a linear accelerator with 6 MV photon beams with intensity-modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT).

**Follow-up and statistics**

All patients returned for a follow-up (which included CT and PET/CT as necessary) 1–3 months after the completion of RT, every 3–6 months thereafter. The therapy response was assessed as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) according to the Response Evaluation Criteria in Solid Tumors (RECIST) guideline version 1.1 \[14\]. Toxicities were evaluated within 3 months from RT using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Local progression-free survival (LPFS) was defined as the time from RT to relapse inside or within a 1 cm margin around the PGTV on follow-up imaging. OS was defined as the time from RT to death from any cause or to the last follow-up.

Survival was estimated using the Kaplan-Meier method, and used the log-rank test for univariate analysis of LPFS and OS. Multivariate analysis was carried out using the Cox regression method. Variables found to be significant on univariate analysis (p ≤ 0.1) were subjected to multivariate analysis; a p-value < 0.05 was considered statistically significant. SPSS version 24 (IBM Corp., Armonk, NY, USA) and RStudio version 1.2 (RStudio Inc., Boston, MA, USA) were used for Statistical analyses.

**Results**

**Patients**
Of the 74 patients, 52 (70.3%) were male and 22 (29.7%) were female; their median age was 62 years (range 28–86 years). Approximately half of the patients (38, or 51.4%) had stage IV disease; 22 had stage B (29.7%) and 14 had stage A (18.9%). Moreover, 40 patients (54.1%) had Karnofsky performance status (KPS) scores ≤ 80. The majority of patients (67, or 90.5%) received at least 1 cycle of chemotherapy before RT, and 17 (23%) underwent surgery. Most patients (49, or 66.2%) had been treated with IMRT while the other 25 (33.8%) received VMAT. Among the 4 patients who were not previously treated, 2 had stage III disease and were unable to undergo CCRT owing to advanced age and complications. Among 37 patients with adenocarcinoma, 5 with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) sensitizing mutations received tyrosine kinase inhibitors (TKIs) post RT. Among 5 patients treated with immunotherapy after RT, 4 received next generation sequencing (NGS) and tumor mutation burden (TMB) test before immunotherapy (Supplementary Table S1). All diagnoses were pathologically confirmed at our institution. The patients’ characteristics and dosimetric parameters are summarized in Tables 1 and 2, respectively.
Table 1
Patient/Treatment characteristics.

| Characteristics (n = 74)       | No. of patients (%) |
|-------------------------------|---------------------|
| Age (y), median(range)        | 62 (28–86)          |
| Gender                        |                     |
| Male                          | 52 (70.3)           |
| Female                        | 22 (29.7)           |
| Smoking status                |                     |
| Current or former             | 25 (33.8)           |
| Never                         | 49 (66.2)           |
| KPS                           |                     |
| 70                            | 6 (8.2)             |
| 80                            | 34 (45.9)           |
| > 80                          | 34 (45.9)           |
| Histology                     |                     |
| ADC                           | 37 (50)             |
| SCC                           | 37 (50)             |
| Stage                         |                     |
| A                             | 14 (18.9)           |
| B                             | 22 (29.7)           |
|                              | 38 (51.4)           |
| Tumor location                |                     |
| Right                         | 41 (55.4)           |
| Left                          | 30 (40.5)           |
| Mediastinum                   | 3 (4.1)             |
| Tumor status                  |                     |
| Primary                       | 4 (5.4)             |
| Recurrence                    | 70 (94.6)           |

KPS, Karnofsky performance status score; ADC, Adenocarcinoma; SCC, squamous cell carcinoma; NLR, neutrophil-to-lymphocyte ratio; RT, radiotherapy; CT, chemotherapy; CCRT, concurrent chemoradiotherapy; IMRT, intensity modulated radiotherapy; VMAT, volumetric modulated arc therapy.
| Characteristics (n = 74) | No. of patients (%) |
|-------------------------|---------------------|
| NLR before RT           |                     |
| < 5                     | 61 (82.4)           |
| ≥ 5                     | 7 (9.5)             |
| Treatment before RT     |                     |
| Surgery                 | 17 (23)             |
| CT +/- RT               | 67 (90.5)           |
| ≥ 2 CT lines            | 20 (27)             |
| EGFR/ALK-TKIs           | 16 (21.6)           |
| Antiangiogenesis         | 8 (10.8)            |
| CCRT                    | 10 (13.5)           |
| Treatment post RT       |                     |
| CT                      | 30 (40.5)           |
| EGFR/ALK-TKIs           | 9 (12.2)            |
| Antiangiogenesis         | 13 (17.6)           |
| Immunotherapy           | 5 (6.8)             |
| Radiation technique     |                     |
| IMRT                    | 49 (66.2)           |
| VMAT                    | 25 (33.8)           |

KPS, Karnofsky performance status score; ADC, Adenocarcinoma; SCC, squamous cell carcinoma; NLR, neutrophil-to-lymphocyte ratio; RT, radiotherapy; CT, chemotherapy; CCRT, concurrent chemoradiotherapy; IMRT, intensity modulated radiotherapy; VMAT volumetric modulated arc therapy.
Table 2
Dosimetric parameters of radiation

| Variables                          | Median GTV volume (range), cc | Median GTV to lungs volume ratio (range) |
|------------------------------------|------------------------------|------------------------------------------|
| Median mean dose (range), cGy      | 726 (33–1437)                | 0.024 (0.002–0.208)                      |
| Median V5 (range), %               | 0.27 (0.01–0.69)             |                                          |
| Median V20 (range), %              | 0.13 (0.0–0.24)              |                                          |
| Median V30 (range), %              | 0.08 (0.0–0.29)              |                                          |
| Heart dose                         |                              |                                          |
| Median mean dose (range), cGy      | 557 (14–2048)                |                                          |
| Median V20 (range), %              | 0.08 (0.0–0.49)              |                                          |
| Median V30 (range), %              | 0.04 (0.0–0.31)              |                                          |
| Esophagus dose                     |                              |                                          |
| Median mean dose (range), cGy      | 872 (52–3283)                |                                          |
| Median max dose (range), cGy       | 4266 (370–5068)              |                                          |
| Median V30 (range), %              | 0.005 (0.0–0.54)             |                                          |
| Trachea                            |                              |                                          |
| Median max dose (range), cGy       | 4697 (34–5204)               |                                          |
| Spinal cord                        |                              |                                          |
| Median max dose (range), cGy       | 2188 (226–3909)              |                                          |

GTV, gross tumor volume; PGTV, planning gross target volume.

Evaluation of treatment efficacy and patient outcomes

Among the 68 patients who were included in the analysis of efficacy, 2 (2.9%) achieved CR, 25 (36.8%) achieved PR, 35 (51.5%) achieved SD, and 6 (8.8%) developed PD. The objective response rate (ORR) was 16% and the disease control rate (DCR) was 91.2%.

As of the most recent follow-up, 54 patients (73%) had died; the median OS was 18.7 months, while the 1- and 2-year OS rates for all patients were 65.9% and 33.9%, respectively. Univariate analysis revealed that
undergoing < 2 previous lines of chemotherapy ($p = 0.008$), TKIs treatment post RT ($p = 0.003$), and GTV-to-lung ratio ($p = 0.002$) were significantly associated with OS (Table 3, Fig. 1). Cox regression analysis indicated that patients with poorer therapy response had worse prognoses (Table 4).
Table 3  
Univariate analyses for overall survival (OS) and local progression-free survival (LPFS).

| Variables | OS (months) | LPFS (months) |
|-----------|-------------|---------------|
|           | Median      | 95% CI        | p Value | Median      | 95% CI        | p Value |
| All patients | 18.7        | 13.935–23.465 | -       | 7.2        | 5.811–8.589 | -       |
| Gender     |             |               |         |             |               |         |
| Male       | 21.0        | 15.145–26.855 | 0.832   | 7.2        | 4.723–9.677 | 0.798   |
| Female     | 17.7        | 9.443–25.957  |         | 7.2        | 4.916–9.484 |         |
| Age        |             |               |         |             |               |         |
| ≤ 70       | 18.7        | 11.925–25.475 | 0.820   | 7.2        | 5.927–8.473 | 0.843   |
| > 70       | 22.7        | 12.306–33.094 | 8.4     | 1.680–15.120 |               |         |
| Smoking status |             |               |         |             |               |         |
| Current or former | 20.9            | 14.012–27.788 | 0.274  | 7.3        | 4.917–9.683 | 0.753   |
| Never      | 18.7        | 8.592–28.808  |         | 7.2        | 5.618–8.782 |         |
| KPS        |             |               |         |             |               |         |
| 70         | 18.3        | 4.378–32.222  | 0.877   | 7.8        | 3.074–12.526 | 0.425   |
| 80         | 21.0        | 12.574–29.426 |         | 7.2        | 6.143–8.257 |         |
| > 80       | 18.7        | 5.727–31.673  | 8.4     | 5.443–11.357 |               |         |
| Histology  |             |               |         |             |               |         |
| Adenocarcinoma | 18.7            | 9.306–28.094 | 0.303   | 8.2        | 7.202–9.198 | 0.158   |
| SCC        | 18.3        | 11.362–25.238 |         | 6.4        | 5.501–7.299 |         |
| Stage      |             |               |         |             |               |         |

CI, confidence interval; KPS, Karnofsky performance status score; SCC, squamous cell carcinoma; NLR, neutrophil-to-lymphocyte ratio; CT, chemotherapy; CCRT, concurrent chemoradiotherapy; RT, radiotherapy; GTV, gross tumor volume; PGTV, planning gross target volume; IMRT, intensity modulated radiotherapy; VMAT, volumetric modulated arc therapy.
| Variables                  | OS (months) |                         |      | LPFS (months) |                         |      |
|----------------------------|-------------|--------------------------|------|---------------|--------------------------|------|
|                            | Median      | 95% CI                   | p    | Median        | 95% CI                   | p    |
|                            |             |                          |      |               |                          |      |
| OS (months)                |             |                          |      |               |                          |      |
|                           | 20.9        | 16.075–25.725            | 0.268| 6.7           | 5.135–8.265              | 0.170|
|                           | 17.7        | 8.552–26.848             |      | 7.8           | 6.348–9.252              |      |
| Tumor location             |             |                          |      |               |                          |      |
| Right                      | 16.7        | 10.786–22.614            | 0.813| 6.2           | 3.917–8.423              | 0.231|
| Left                       | 20.9        | 15.518–26.282            |      | 8.6           | 6.642–10.558             |      |
| Mediastinum                | 24.5        | -                        |      | 9.1           | -                        |      |
| NLR before RT              |             |                          |      |               |                          |      |
| < 5                        | 20.9        | 16.136–25.664            | 0.144| 8.2           | 6.553–9.847              | < 0.001|
| ≥ 5                        | 13.0        | 2.222–23.778             |      | 3.6           | 1.213–5.987              |      |
| No. of previous CT lines   |             |                          |      |               |                          |      |
| < 2                        | 22.7        | 17.207–28.193            | 0.008| 8.2           | 6.670–9.730              | 0.140|
| ≥ 2                        | 12.8        | 7.847–17.753             |      | 5.1           | 2.236–7.964              |      |
| TKIs before RT             |             |                          |      |               |                          |      |
| Yes                        | 53.6        | 16.530–25.270            | 0.691| 7.8           | 4.506–11.094             | 0.251|
| No                         | 20.9        | -                        |      | 6.9           | 5.171–8.629              |      |
| CCRT                       |             |                          |      |               |                          |      |
| Yes                        | 16.7        | 7.183–26.217             | 0.323| 5.2           | 0.598–9.802              | 0.130|
| No                         | 20.9        | 14.996–26.804            |      | 7.3           | 5.851–8.749              |      |
| CT post RT                 |             |                          |      |               |                          |      |
| Yes                        | 21.0        | 14.345–27.655            | 0.798| 8.2           | 5.287–11.113             | 0.844|

CI, confidence interval; KPS, Karnofsky performance status score; SCC, squamous cell carcinoma; NLR, neutrophil-to-lymphocyte ratio; CT, chemotherapy; CCRT, concurrent chemoradiotherapy; RT, radiotherapy; GTV, gross tumor volume; PGTV, planning gross target volume; IMRT, intensity modulated radiotherapy; VMAT, volumetric modulated arc therapy.
| Variables                                      | OS (months) | LPFS (months) | p Value | OS (months) | LPFS (months) | p Value |
|------------------------------------------------|-------------|---------------|---------|-------------|---------------|---------|
|                                                | Median      | 95% CI        |         | Median      | 95% CI        |         |
| No                                             | 18.7        | 8.632–28.768  |         | 6.9         | 6.209–7.591   |         |
| TKIs post RT                                   |             |               |         |             |               |         |
| Yes                                            | 46.0        | 10.986–22.414 | 0.003   | 25.9        | 0.000–61.962  | 0.005   |
| No                                             | 16.7        |               |         | 6.7         | 5.375–8.025   |         |
| Antiangiogenesis post RT                       |             |               |         |             |               |         |
| Yes                                            | 17.7        | 2.701–32.699  | 0.768   | 8.2         | 4.651–11.749  | 0.366   |
| No                                             | 18.7        | 13.663–23.737 |         | 7.2         | 5.971–8.429   |         |
| Immunotherapy post RT                          |             |               |         |             |               |         |
| Yes                                            | 23.1        | 6.617–39.583  | 0.927   | 6.1         | 4.992–7.268   | 0.510   |
| No                                             | 18.3        | 13.710–22.890 |         | 7.8         | 6.277–9.323   |         |
| GTV                                            |             |               |         |             |               |         |
| ≤ 76 cc                                        | 24.3        | 17.369–31.231 | 0.002   | 9.0         | 7.270–10.730  | 0.053   |
| > 76 cc                                        | 13.0        | 8.531–17.469  |         | 6.1         | 4.842–7.358   |         |
| GTV-to-lungs ratio                              |             |               |         |             |               |         |
| ≤ 0.024                                        | 23.2        | 14.601–31.799 | 0.014   | 8.2         | 5.238–11.162  | 0.117   |
| > 0.024                                        | 15.2        | 9.182–21.218  |         | 6.13        | 5.093–7.167   |         |
| Therapy response                               |             |               |         |             |               |         |
| CR/PR/SD                                       | 18.7        | 13.077–24.323 | 0.094   | 8.2         | 6.628–9.772   | 0.011   |
| PD                                             | 13.1        | 0.000–30.264  |         | 4.6         | 1.856–7.344   |         |

CI, confidence interval; KPS, Karnofsky performance status score; SCC, squamous cell carcinoma; NLR, neutrophil-to-lymphocyte ratio; CT, chemotherapy; CCRT, concurrent chemoradiotherapy; RT, radiotherapy; GTV, gross tumor volume; PGTV, planning gross target volume; IMRT, intensity modulated radiotherapy; VMAT, volumetric modulated arc therapy.
Variables | OS (months) | LPFS (months) |
|---------|------------|---------------|
|         | Median | 95% CI | p Value | Median | 95% CI | p Value |
| IMRT    | 18.3   | 9.016–27.584 | 0.612 | 6.8   | 5.836–7.764 | 0.300- |
| VMAT    | 23.1   | 7.768–38.432 | 8.4 | 6.574–10.226 |

CI, confidence interval; KPS, Karnofsky performance status score; SCC, squamous cell carcinoma; NLR, neutrophil-to-lymphocyte ratio; CT, chemotherapy; CCRT, concurrent chemoradiotherapy; RT, radiotherapy; GTV, gross tumor volume; PGTV, planning gross target volume; IMRT, intensity modulated radiotherapy; VMAT, volumetric modulated arc therapy.

Table 4
Multivariate analysis for overall survival (OS) and local progression-free survival (LPFS).

| Variables | OS | LPFS |
|-----------|----|------|
|           | HR (95% CI) | p Value | HR (95% CI) | p Value |
| No. of previous CT lines | 1.755 (0.905–3.407) | 0.096 | - | - |
| ≥ 2 vs < 2 | | | | |
| GTV-to-lung ratio | 2.004 (0.794–5.057) | 0.141 | - | - |
| ≤ 0.024 vs > 0.024 | | | | |
| GTV | 0.999 (0.995–1.004) | 0.802 | 1.188(0.607–2.327) | 0.615 |
| > 76 vs ≤ 76, cc | | | | |
| TKIs post RT | 0.228 (0.052–1.005) | 0.051 | 0.506 (0.148–1.734) | 0.279 |
| Yes vs No | | | | |
| Therapy response | 2.987 (1.117–7.989) | 0.029 | 3.718 (1.306–10.583) | 0.014 |
| PD vs CR/PR/SD | | | | |
| NLR before RT | - | - | 4.894 (1.901–12.598) | 0.001 |
| < 5 vs ≥ 5 | | | | |

HR, hazard ratio; CI, confidence interval; CT, chemotherapy; GTV, gross tumor volume; PGTV, planning gross target volume; NLR neutrophil-to-lymphocyte ratio.

At the time of data cutoff, 55 patients (74.3%) showed disease progression. The median LPFS was 7.2 months, while the 1- and 2-year LPFS rates were 27.9% and 9.4%, respectively. Univariate analysis showed that the pretreatment neutrophil-to-lymphocyte ratio (NLR) (p < 0.001), TKIs treatment post RT (p
= 0.005), and therapy response ($p = 0.011$) were significantly associated with LPFS (Table 3, Fig. 1). Cox regression analysis indicated that therapy response and NLR before RT were significantly related to LPFS (Table 4).

**Toxicity**

Treatment was generally well-tolerated in all patients. Overall, 16 patients (21.6%) experienced pneumonitis (6 with grade 1 and 10 with grade 2) while 14 patients (19%) developed esophagitis (5 with grade 1 and 9 with grade 2); no grades ≥ 3 pneumonitis or esophagitis among the patients was found.

**Discussion**

We found HFRT to be effective; the median OS was 18.7 months (with 1- and 2-year OS rates of 65.9% and 33.9%, respectively) while the median LPFS was 7.2 months (with 1- and 2-year LPFS rates of 27.9% and 9.4%, respectively). The adverse effects were tolerated given that no grade ≥ 3 toxicities occurred; this was also the case in the study by Amini et al. [15].

Studies at the MD Anderson Cancer Center used HFRT (45 Gy/15 fractions) to treat patients with unresectable NSCLC who could not tolerate the CFRT; no significant differences in local recurrence and OS were observed between the 2 regimens. The 1- and 2-year OS rates of patients who received HFRT were 53% and 12%, respectively [10, 15, 16]. In a study by Abratt et al., the median OS of patients with stage III NSCLC who received palliative RT (45 Gy/15 fractions) was 8.5 months [17]. The patients in our study had better survival than did those in previous studies, which might be due in part to the innovations in cancer therapeutics (including targeted therapy, antiangiogenic therapy, immunotherapy, combination therapy, and technological improvements in other modalities).

A previous analysis demonstrated that an absolute OS benefit was observed that ranged from 0.36–0.7% for every 1 Gy increase in BED [16]. Machtay et al. also found that an increase of 1 Gy BED could improve survival by approximately 4%, along with greater acute toxicity [18]. A meta-analysis by Fairchild et al. found that patients received higher dose schedules (BED ≥ 35 Gy, $\alpha/\beta = 10$) achieved a significantly better survival than those received lower dose schedules, with 2-year OS rates of 26.5% vs. 21.7% for well-performing patients, albeit at the cost of greater esophageal toxicity. While there was no advantage in administering high dose schedules for poorly performing patients [19]. However, a higher total dose appeared not to benefit palliative patients with lung cancer (50 Gy/20 fractions vs. 25 Gy/5 fractions) [20].

The traditional approach to increase BED is to increase the number of fractions. CFRT is usually not well-tolerated among patients with poor performance or advanced disease. Hypofractionation, on the other hand, enables the delivery of higher BED, as HFRT involves significantly fewer fractions with higher doses per fraction compared to standard modalities. Large fractions are an effective way of ablating tumors, likely owing in part to the reduced rate of tumor cell repopulation; and may be more convenient and cheaper than conventional fractionation [21, 22]. Compared with other studies of palliative RT regimens
with lower BED, patients in our study achieved higher survival benefits by increasing the dose per fraction to obtain higher a BED (58.5 Gy, α/β = 10) while adverse events remained tolerable.

Many studies comparing the efficacy of HFRT and stereotactic body radiation therapy (SBRT) for the palliative treatment of patients with advanced lung cancer showed that HFRT appeared to provide a greater survival benefit. Lewis et al. investigated the effects of fraction schedules (30 Gy/10 fractions, 20 Gy/5 fractions, and 10 Gy/1 fraction) on the survival of lung cancers treated with palliative RT and found that increasing the total dose was associated with better survival regardless of performance status [23].

Moreover, SBRT is generally not suitable for tumors that are central (i.e., close to the trachea or heart), those that are accompanied by necrosis or mediastinal lymph node metastases, or those that are large in size.

In the past decade, the use of molecularly targeted therapy has led to significantly longer survival in patients with EGFR or ALK sensitizing mutations [24]. However, previous studies focused mainly on concurrent administration of these therapies with RT as first-line treatment for patients with advanced disease, which maybe place them at a higher risk of adverse effects. In our study, 9 patients who were treated with TKIs after RT achieved significantly longer LPFS and OS with no obvious adverse effects observed. Okamoto et al. found that 2 of 9 patients with unresectable stage II NSCLC exhibiting EGFR mutations who were treated with gefitinib and concurrent RT survived for more than 5 years, although the study was stopped owing to a high incidence of adverse events [25]. In the RECEL trial that compared erlotinib versus etoposide/cisplatin with concurrent RT for patients with unresectable stage III NSCLC carrying EGFR mutations, the erlotinib/RT arm had significantly improved PFS compared to the CRT with the same incidence of adverse effects [26]. The SINDAS study showed that first-line TKI with upfront SBRT to all sites significantly improved both PFS and OS compared with TKI alone in previously untreated patients with oligometastatic NSCLC (≤ 5 lesions) carrying EGFR mutations [27].

Many studies have shown that antiangiogenic agents could produce significant survival benefits for patients with advanced NSCLC. However, previous efforts have focused more on concurrent antiangiogenic agents with RT, and few investigators have used such agents as maintenance therapy post-RT. The ECOG 4599 study showed that the addition of bevacizumab to paclitaxel/carboplatin for treating recurrent or advanced NSCLC produced a significant survival benefit [28]. The ALTER0303 trial showed that anlotinib administered as the third-or-greater-line treatment prolonged PFS and OS in patients with advanced NSCLC [29]. Moreover, patients in the HELPER study who received continuous infusion of endostar combined with CCRT for unresectable stage III NSCLC achieved favorable PFS and OS with tolerable toxicities [30]. In our current study, no survival benefit was found among 13 patients (17.6%) who were treated with antiangiogenetic therapy after RT; this may partly be due to the most of these patients (10, or 80%) having stage IV disease while 5 patients (38%) were still alive as of the last follow-up.

The recent development of immune checkpoint inhibitors (ICIs) has essentially changed the treatment profiles of patients with advanced NSCLC [31]. A network meta-analysis by Almutairi et al. that compared
the efficacy and safety of PD-1/PD-L1 inhibitors in patients who were previously treated for advanced NSCLC found significant benefits of pembrolizumab and nivolumab in terms of PFS, OS, and in pairwise comparisons to docetaxel [32]. Another meta-analysis by Schulz et al. found that PD-L1/PD-1 inhibitors as second-or-later-line treatments for advanced NSCLC demonstrated greater survival benefits, producing the highest expected 5-year OS rates compared to other treatments [33]. PACIFIC study showed that, compared to placebo, durvalumab demonstrated significant PFS improvements for patients with unresectable stage III NSCLC without progression after CRT, the 3-year OS was 66.3% versus 43.5% [34, 35]. In our study, 5 patients (17.6%) received immunotherapy after RT among whom 1 was lost to follow-up and 1 was still alive after 10 months (with 5.1 months of LPFS) as of the last follow-up; the LPFS times for the other 3 patients were 6.1, 21.1, and 6.7 months, respectively, while their OS times were 23.1, 29.6 and 12.8 months, respectively. Although the sample size was small, these data preliminarily suggested that ICIs after HFRT can provide a promising survival benefit.

Previous studies have shown that the combination of RT and either TKIs, antiangiogenetic therapy, or ICIs could improve survival in patients with locally or systemically advanced NSCLC, usually at the cost of a high incidence of toxicity, although the optimal RT dose remains uncertain. In contrast, we found that patients who received TKIs, antiangiogenetic therapy, or ICIs as maintenance therapy after HFRT achieved improved survival with no obvious adverse effects.

Recent studies also found that the NLR, well-known as a marker of host inflammation, may be a useful predictor of poor prognosis in patients with NSCLC. Scilla et al. found that baseline NLR was a significant prognostic indicator in patients with locally advanced NSCLC who received definitive CRT with or without surgery [36]. A retrospective multicenter study indicated that patients with NSCLC who have high pretreatment NLR (i.e., > 5) may experience inferior PFS and OS treated with nivolumab [37]. A meta-analysis by Zhang et al. also showed that a high NLR was associated with poor PFS and OS in patients with NSCLC treated with ICIs [38]. Similar results were obtained in our study, in which patients with low NLRs had better prognoses.

Our study’s finding that patients with larger tumor sizes and greater tumor-to-lung volume ratios had poorer prognoses were similar to the conclusions of Werner-Wasik et al. [39] and Bradley et al. [40]. Strøm et al. found that patients with NSCLC tumors > 7 cm appeared to benefit notably from palliative CRT, but with an increased risk of radiation-induced esophagitis and pneumonia[41]. As such, it is possible that a larger tumor volume might not be a limitation for RT, as the incidence of adverse effects could be reduced by administering HFRT alone or sequential CRT.

Moreover, we found that patients who underwent ≥ 2 previous chemotherapy lines may experience inferior survival; as such, we posit that administering RT earlier may improve the survival of these patients.

In conclusion, our findings suggest that HFRT is safe and effective for treating patients with unresectable locally or systemically advanced who have poor prognostic factors. However, this study was limited by its retrospective design as well as its relatively short follow-up time. Further investigations using novel
hypofractionated regimens combined with TKIs, antiangiogenic therapy, or immunotherapy are warranted.

**Abbreviations**

OS: overall survival; LPFS: local progression-free survival; RT: radiotherapy; HFRT: hypofractionated radiotherapy; CT: chemotherapy; CCRT: concurrent chemoradiotherapy; IMRT: intensity modulated radiotherapy; VMAT: volumetric modulated arc therapy; GTV: gross tumor volume; PGTV: planning gross target volume; KPS: Karnofsky performance status score; ADC: Adenocarcinoma; SCC: squamous cell carcinoma; NLR: neutrophil-to-lymphocyte ratio.

**Declarations**

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**Authors’ contributions:**

All authors contributed to review and revision. NBL and LJZ: developed the main concept and designed the study. DH, SYC and JFS: were responsible for collection of clinical data. DH and JJZ: performed data analysis and interpretation. JJZ and ZNQ: drafted the paper. JW, LJZ and NBL: contributed to editing and critical revision for important intellectual contents.

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**Ethics approval and consent to participate:**

The requirement of patients’ consent was waived because this was a retrospective study.

**Consent for publication:**

The requirement of patients’ consent was waived because this was a retrospective study.

**Competing interests:**

The Authors declare that they have no competing interests.

**References**

1. Torre LA, Siegel RL, Ward EM, Jemal A. Global Cancer Incidence and Mortality Rates and Trends--An Update. Cancer Epidemiol Biomarkers Prev. 2016;25:16-27.
2. Morgensztern D, Ng SH, Gao F, Govindan R. Trends in stage distribution for patients with non-small cell lung cancer: a National Cancer Database survey. J Thorac Oncol. 2010;5:29-33.

3. Yoon SM, Shaikh T, Hallman M. Therapeutic management options for stage III non-small cell lung cancer. World J Clin Oncol. 2017;8.

4. Perez CA, Stanley K, Rubin P, Kramer S, Brady L, Perez-Tamayo R, et al. A prospective randomized study of various irradiation doses and fractionation schedules in the treatment of inoperable non-oat-cell carcinoma of the lung. Preliminary report by the Radiation Therapy Oncology Group. Cancer. 1980;45:2744-53.

5. Bradley JD, Paulus R, Komaki R, Masters G, Blumenschein G, Schild S, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol. 2015;16:187-99.

6. Stevens R, Macbeth F, Toy E, Coles B, Lester JF. Palliative radiotherapy regimens for patients with thoracic symptoms from non-small cell lung cancer. Cochrane Database Syst Rev. 2015;1:CD002143.

7. Toy E, Macbeth F, Coles B, Melville A, Eastwood A. Palliative thoracic radiotherapy for non-small-cell lung cancer: a systematic review. Am J Clin Oncol. 2003;26:112-20.

8. Rodrigues G, Videtic GM, Sur R, Bezjak A, Bradley J, Hahn CA, et al. Palliative thoracic radiotherapy in lung cancer: An American Society for Radiation Oncology evidence-based clinical practice guideline. Pract Radiat Oncol. 2011;1:60-71.

9. Moeller B, Balagamwala EH, Chen A, Creach KM, Giaccone G, Koshy M, et al. Palliative thoracic radiation therapy for non-small cell lung cancer: 2018 Update of an American Society for Radiation Oncology (ASTRO) Evidence-Based Guideline. Pract Radiat Oncol. 2018;8:245-50.

10. Nguyen LN, Komaki R, Allen P, Schea RA, Milas L. Effectiveness of accelerated radiotherapy for patients with inoperable non-small cell lung cancer (NSCLC) and borderline prognostic factors without distant metastasis: a retrospective review. Int J Radiat Oncol Biol Phys. 1999;44:1053-6.

11. Jiang L, Meng X, Zhao X, Xing L, Yu J. Perspective on treatment for unresectable locally advanced non-small cell lung cancer with oncogene-driven mutation: a narrative review. Transl Lung Cancer Res. 2020;9:2137-44.

12. Hamming LC, Slotman BJ, Verheul HMW, Thijsen VL. The clinical application of angiostatic therapy in combination with radiotherapy: past, present, future. Angiogenesis. 2017;20:217-32.

13. Herrera FG, Bourhis J, Coukos G. Radiotherapy combination opportunities leveraging immunity for the next oncology practice. CA Cancer J Clin. 2017;67:65-85.

14. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-47.

15. Amini A, Lin SH, Wei C, Allen P, Cox JD, Komaki R. Accelerated hypofractionated radiation therapy compared to conventionally fractionated radiation therapy for the treatment of inoperable non-small
cell lung cancer. Radiat Oncol. 2012;7:33.

16. Kaster TS, Yaremko B, Palma DA, Rodrigues GB. Radical-intent hypofractionated radiotherapy for locally advanced non-small-cell lung cancer: a systematic review of the literature. Clin Lung Cancer. 2015;16:71-9.

17. Abratt RP, Shepherd LJ, Salton DG. Palliative radiation for stage 3 non-small cell lung cancer–a prospective study of two moderately high dose regimens. Lung Cancer. 1995;13:137-43.

18. Machtay M, Bae K, Movsas B, Paulus R, Gore EM, Komaki R, et al. Higher biologically effective dose of radiotherapy is associated with improved outcomes for locally advanced non-small cell lung carcinoma treated with chemoradiation: an analysis of the Radiation Therapy Oncology Group. Int J Radiat Oncol Biol Phys. 2012;82:425-34.

19. Fairchild A, Harris K, Barnes E, Wong R, Lutz S, Bezjak A, et al. Palliative thoracic radiotherapy for lung cancer: a systematic review. J Clin Oncol. 2008;26:4001-11.

20. Schröder C, Ivo M, Buchali A. Does high-dose radiotherapy benefit palliative lung cancer patients? Strahlentherapie und Onkologie. 2013;189:771-6.

21. Abratt RP, Bogart JA, Hunter A. Hypofractionated irradiation for non-small cell lung cancer. Lung Cancer. 2002;36:225-33.

22. Fowler JF, Chappell R. Non-small cell lung tumors repopulate rapidly during radiation therapy. Int J Radiat Oncol Biol Phys. 2000;46:516-7.

23. Jumeau R, Vilotte F, Durham A-D, Ozsahin E-M. Current landscape of palliative radiotherapy for non-small-cell lung cancer. Transl Lung Cancer Res. 2019;8:S192-S201.

24. Giustini NP, Jeong A-R, Buturla J, Bazhenova L. Advances in Treatment of Locally Advanced or Metastatic Non-Small Cell Lung Cancer: Targeted Therapy. Clin Chest Med. 2020;41:223-35.

25. Okamoto I, Takahashi T, Okamoto H, Nakagawa K, Watanabe K, Nakamatsu K, et al. Single-agent gefitinib with concurrent radiotherapy for locally advanced non-small cell lung cancer harboring mutations of the epidermal growth factor receptor. Lung Cancer. 2011;72:199-204.

26. Xing L, Wu G, Wang L, Li J-C, Wang J, Yuan Z, et al. A multicenter, randomized, open-label, phase II trial of erlotinib versus etoposide plus cisplatin with concurrent radiotherapy in unresectable stage III non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) activating mutation. J Clin Oncol. 2017;35:8531-.

27. Wang X, Zeng M. First-line tyrosine kinase inhibitor with or without aggressive upfront local radiation therapy in patients with EGFRm oligometastatic non-small cell lung cancer: Interim results of a randomized phase III, open-label clinical trial (SINDAS) (NCT02893332). J Clin Oncol. 2020;38:9508-.

28. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med. 2006;355:2542-50.

29. Han B, Li K, Wang Q, Zhang L, Shi J, Wang Z, et al. Effect of Anlotinib as a Third-Line or Further Treatment on Overall Survival of Patients With Advanced Non-Small Cell Lung Cancer: The ALTER 0303 Phase 3 Randomized Clinical Trial. JAMA Oncol. 2018;4:1569-75.
30. Zhai Y, Ma H, Hui Z, Zhao L, Li D, Liang J, et al. HELPER study: A phase II trial of continuous infusion of endostar combined with concurrent etoposide plus cisplatin and radiotherapy for treatment of unresectable stage III non-small-cell lung cancer. Radiother Oncol. 2019;131:27-34.

31. Evans T, Ciunci C, Hertan L, Gomez D. Special topics in immunotherapy and radiation therapy: reirradiation and palliation. Transl Lung Cancer Res. 2017;6:119-30.

32. Almutairi AR, Alkhatib N, Martin J, Babiker HM, Garland LL, McBride A, et al. Comparative efficacy and safety of immunotherapies targeting the PD-1/PD-L1 pathway for previously treated advanced non-small cell lung cancer: A Bayesian network meta-analysis. Crit Rev Oncol Hematol. 2019;142:16-25.

33. Schulz C, Gandara D, Berardo CG, Rosenthal R, Foo J, Morel C, et al. Comparative Efficacy of Second- and Subsequent-line Treatments for Metastatic NSCLC: A Fractional Polynomials Network Meta-analysis of Cancer Immunotherapies. Clin Lung Cancer. 2019;20:451-60.e5.

34. Hui R, Özgüroğlu M, Villegas A, Daniel D, Vicente D, Murakami S, et al. Patient-reported outcomes with durvalumab after chemoradiotherapy in stage III, unresectable non-small-cell lung cancer (PACIFIC): a randomised, controlled, phase 3 study. Lancet Oncol. 2019;20:1670-80.

35. Gray JE, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Three-Year Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC-Update from PACIFIC. J Thorac Oncol. 2020;15:288-93.

36. Scilla KA, Bentzen SM, Lam VK, Mohindra P, Nichols EM, Vyfhuis MA, et al. Neutrophil-Lymphocyte Ratio Is a Prognostic Marker in Patients with Locally Advanced (Stage IIIA and IIIB) Non-Small Cell Lung Cancer Treated with Combined Modality Therapy. Oncologist. 2017;22:737-42.

37. Russo A, Russano M, Franchina T, Migliorino MR, Aprile G, Mansueto G, et al. Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), and Outcomes with Nivolumab in Pretreated Non-Small Cell Lung Cancer (NSCLC): A Large Retrospective Multicenter Study. Adv Ther. 2020;37:1145-55.

38. Zhang N, Jiang J, Tang S, Sun G. Predictive value of neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in non-small cell lung cancer patients treated with immune checkpoint inhibitors: A meta-analysis. Int Immunopharmacol. 2020;85:106677.

39. Werner-Wasik M, Swann RS, Bradley J, Graham M, Emami B, Purdy J, et al. Increasing tumor volume is predictive of poor overall and progression-free survival: secondary analysis of the Radiation Therapy Oncology Group 93-11 phase I-II radiation dose-escalation study in patients with inoperable non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2008;70:385-90.

40. Bradley JD, leumwananonthachai N, Purdy JA, Wasserman TH, Lockett MA, Graham MV, et al. Gross tumor volume, critical prognostic factor in patients treated with three-dimensional conformal radiation therapy for non-small-cell lung carcinoma. Int J Radiat Oncol Biol Phys. 2002;52:49-57.

41. Strøm HH, Bremnes RM, Sundstrøm SH, Helbekkmo N, Aasebø U. Poor prognosis patients with inoperable locally advanced NSCLC and large tumors benefit from palliative chemoradiotherapy: a subset analysis from a randomized clinical phase III trial. J Thorac Oncol. 2014;9:825-33.
Figures

Figure 1

Kaplan-Meier survival analysis of overall survival (OS) and local progression-free survival (LPFS) for all patients. RT, radiotherapy; CT, chemotherapy; GTV, gross tumor volume; NLR, neutrophil-to-lymphocyte ratio.

Supplementary Files

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- HFRTSupplementaryTableS1.xlsx