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Evidence-based clinical recommendations for hypofractionated radiotherapy: exploring efficacy and safety - Part 2. Lung (non-small cell lung cancer)

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Several recent studies have investigated the use of hypofractionated radiotherapy (HFRT) for various cancers. However, HFRT for non-small cell lung cancer (NSCLC) with or without concurrent chemotherapy is not yet widely used because of concerns about serious side effects and the lack of evidence for improved treatment results. Investigations of HFRT with concurrent chemotherapy in NSCLC have usually been performed in single-arm studies and with a small number of patients, so there are not yet sufficient data. Therefore, the Korean Society for Radiation Oncology Practice Guidelines Committee planned this review article to summarize the evidence on HFRT so far and provide it to radiation oncology clinicians. In summary, HFRT has demonstrated promising results, and the reviewed data support its feasibility and comparable efficacy for the treatment of locally advanced NSCLC. The incidence and severity of esophageal toxicity have been identified as major concerns, particularly when treating large fraction sizes. Strategies, such as esophagus-sparing techniques, image guidance, and dose constraints, may help mitigate this problem and improve treatment tolerability. Continued research and clinical trials are essential to refine treatment strategies, identify optimal patient selection criteria, and enhance therapeutic outcomes.

Keywords: Radiation dose hypofractionation, Carcinoma, Non-small-cell lung

Introduction

Lung cancer is one of the most common types of cancer in Korea and is the leading cause of cancer-related deaths in both men and women [1]. Most lung cancers are non-small cell lung cancers (NSCLC), and definitive concurrent chemoradiotherapy (CCRT) is the cornerstone of treatment for unresectable locally advanced NSCLC (LA-NSCLC). The National Comprehensive Cancer Network guideline suggests a conventionally fractionated regimen of 60–70 Gy in 2 Gy fractions (fx) as the most commonly prescribed dose for definitive radiotherapy (RT) [2].

Many recent studies have investigated hypofractionation regi-

mens for various cancers to reduce the medical resources and patient burden. In breast or prostate cancer, the historical standard fractionation of 1.8–2 Gy per fx can no longer be considered the standard, and the hypofractionated regimen is replacing it [3,4]. However, in the case of NSCLC, despite various technological advances such as intensity-modulated radiotherapy (IMRT), image guidance, and respiratory control, hypofractionated regimens with or without concurrent chemotherapy are not yet widely used because of concerns about serious side effects and the lack of evidence for improving treatment results. In a previous systematic review of 33 studies on radical intent hypofractionated RT (HFRT) for LA-NSCLC, high heterogeneity of published studies was identified, with a wide variety of prescribed doses (ranging from 45 Gy/15 fx to 75 Gy/28 fx) and a correspondingly wide range of survival and toxicity [5]. The 2023 American Society for Therapeutic Radiology and Oncology summary of the American Society of Clinical Oncology guideline also mentions that modest hypofractionation of 2.15–4 Gy per fx can be considered in stage III NSCLC patients receiving definitive RT, but the strength of the recommendation is "weak" and the quality of evidence is judged to be "low" [6].

Biologically, HFRT may achieve better treatment outcomes by increasing the biologically effective dose (BED) and preventing cancer cell repopulation without increasing treatment time [7]. However, investigations of HFRT with concurrent chemotherapy in LA-NSCLC have usually been performed in single arm studies and with a small number of patients; therefore, there are not yet sufficient large-scale data.

HFRT with concurrent chemotherapy has emerged as a promising treatment option for patients with unresectable NSCLC. Therefore, the Korean Society for Radiation Oncology (KOSRO) Practice Guidelines Committee planned this review article to summarize the evidence so far and provide it to radiation oncology clinicians who might find it useful when deciding about the clinical application of HFRT. We will not address perioperative HFRT, which is more unfounded and less frequently used and will only review the case of definitive RT.

We searched PubMed and EMBASE databases using the following keywords: "NSCLC," "radiotherapy" or "hypofraction*." Titles and abstracts were screened for initial study selection, and a full-text review was conducted when the abstracts were inconclusive in determining eligibility. All studies to be mentioned later were selected to satisfy the following conditions: (1) patients with LA-NSCLC, (2) RT for radical aim initial treatment, (3) dose per fx ≥ 2.4 Gy including the simultaneous integrated boost (SIB) or boost techniques, and (4) 10 or more patients in one treatment arm.

The following exclusion criteria were applied (1) irrelevant topic/subject (small cell lung cancer, lymphoma, etc.) or having mixed population, (2) RT for node negative NSCLC, (3) palliative aim RT (total dose under 50 Gy) or for patients with stage IV NSCLC, (4) all doses per fx < 2.4 Gy, (5) a boost regimen after full dose (≥ 60 Gy) radical RT, (6) a re-irradiation study, (7) review article, meta-analysis, case report, editorial, conference abstract only, ongoing clinical trial, or non-human experimental study, and (8) un-interpretable full text or incomplete information.

About 20 studies using HFRT (including fx size ≥ 2.4 Gy) in node-positive NSCLC with or without concurrent chemotherapy were identified. The subsequent descriptions were largely divided according to whether concurrent chemotherapy was administered. The seminal characteristics of the included studies are summarized in Table 1 (HFRT with concurrent chemotherapy) and Table 2 (HFRT alone).

Key Question 1: What Hypofractionation Regimen Could Be Used for LA-NSCLC Treated with Definitive CCRT?

1. Phase I and II studies

A series of phase I studies have been conducted to explore the optimal fx sizes and total radiotherapy dose to strike a balance between efficacy and safety. This review compiles the results of these studies to gain a comprehensive understanding of the current status of HFRT in NSCLC management. Various phase I studies were analyzed, focusing on patients with unresectable stage IIIA-B NSCLC and some with stage II NSCLC. HFRT was attempted with fx sizes ranging from 2.2–4 Gy and total doses from 58.8–78 Gy. Concurrent chemotherapy regimens consisted of different combinations of cisplatin, docetaxel, carboplatin, and vinorelbine.

In 2013, Bearz et al. [8] conducted a study using HFRT of 60 Gy in 25 fx delivered in 2.4 Gy per fx, alongside concurrent chemotherapy using cisplatin and docetaxel with an escalated docetaxel dose. The median overall survival (OS) and progression-free survival (PFS) were 24 months and 20 months, respectively. The grade ≥ 3 toxicity rate was 3%, involving one patient with grade 3 esophagitis. Regardless of the chemotherapy dose, radiotherapy at 60 Gy in 25 fx is feasible.

A dose escalation study by the Cancer and Leukemia Group B with a total RT dose of 60 Gy delivered in 20–27 fx was reported in 2018 [9]. The 21 enrolled patients were divided into four cohorts with fx sizes of 2.22 Gy (cohort 1), 2.5 Gy (cohort 2), 2.73 Gy (cohort 3), and 3 Gy (cohort 4). The regimen for concurrent chemotherapy consisted of carboplatin and paclitaxel, and all patients were treated with IMRT. With a follow-up of 23 months, the median OS was 19.3 months and PFS was 12.2 months. In cohorts 1–3, six patients were included. However, only three patients were

Table 1. Summary of studies on hypofractionated RT with concurrent chemotherapy in locally advanced non-small cell lung cancer

Study type	Year	Total # of patients	Total RT dose (Gy)	Fraction size (Gy)	# of fraction-ation	RT technique	Median GTV (cm^3)	Median PTV (cm^3)	Chemotherapy	Median follow-up (mo)	OS (mo)	PFS (mo)	Grade ≥ 3 toxicity
Phase I/feasibility trials													
Zhang et al. [16]	2022	25	60	2.5–3 (dose level escala-tion)	20–24	SIB / IMRT	283.5 (159.6–672.0)	473.9 (249.7–1,020.6)	Cisplatin + docetaxel	77.1 (4.3–80.6)	Median: 27.3 1-yr: 84% 3-yr: 44%	Median: 15.4 1-yr: 64% 3-yr: 34%	Total: 20% G3 hematologic: 4% G3 esophagitis: 8% G5 toxicity in 2 pts (8%): 1 upper GI hemorrhage and 1 radiation pneumoni-tis, both in 3 Gy / fx level
Contreras et al. [12]	2022	20	60	3–4 (dose level escala-tion)	15	IMPT	69.7 (12–417.7)	N/A	Carboplatin + paclitaxel	20.3 (1–38)	2-yr: 48%	N/A	Total: 15% G3 pneumonitis: 5% G3 vocal cord paralysis: 5% G3 pleurocutaneous fis-tula: 5% All in 4 Gy/fx group
Glinski et al. [10]	2020	92	58.8	2.8	21	3D-CRT / IMRT	95.6 (2.5–261.4)	464.1 (113.2–787.6)	Cisplatin + vinorelbine	21.5 (1–65)	Median: 38 2-yr: 68% 3-yr: 50%	Median: 25	Total: 35% 7 (7.6%) toxic deaths: 3 fatal hemoptysis, 1 prolonged esopha-geal toxicity, 2 pneu-monitis, and 1 pul-monary abscess
Li et al. [15]	2020	20	78 (GTV) / 60–65 (PTV)	3 (GTV) / 2.3–2.5 (PTV)	26	SIB / IMRT	GTVp: 70.0 (8.7–30.1) GTVn: 36.0 (43.4–139.1)	PTVp: 189.2 (83.9–886.7) PTVn: 148.4 (35.8–405.7)	Cisplatin + docetaxel, paclitaxel, or pemetrexed	N/A	1-yr: 90% 3-yr: 42.6% 5-yr: 35.5%	1-yr: 84.4% 3-yr: 35.5% 5-yr: 28.4%	Total: G3 gastrointestinal toxicity: 1 (5%) G3 hematologic toxici-ty: 5 (25%) G4 hematologic toxici-ty: 4 (20%)
Urbanic et al. (CALGB31102) [9]	2018	21	60	2.22–3 (dose level escala-tion)	20–27	IMRT	158.6 (10.8–437.0)	340.2 (82.9–1,045.4)	Carboplatin + paclitaxel	23 (7.6–30.6)	Median: 19.3	Median: 12.2	Total: 33.3% (7 pts) G3 toxicity: 4 (19.0%) G5 toxicity: 3 (14.3%): 2 hemoptysis, 1 pneumonitis
Jeter et al. [14]	2018	15	72–78	2.4–2.6 (dose level escala-tion)	30	SIB / IMRT / IMPT	72.5 (18.0–392.8)	511.1 (56.4–1,390.3)	Regimen not reported	N/A	Median: 25.3	N/A	Total: 20% G3 esophagitis: 6.7% (72 Gy, IMRT) G3 pneumonitis: 6.7% (78 Gy, IMPT) G5 pneumonitis: 6.7% (78 Gy, IMPT)

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Table 1. Continued

Study type	Year	Total # of patients	Total RT dose (Gy)	Fraction size (Gy)	# of fraction-ation	RT technique	Median GTV (cm^3)	Median PTV (cm^3)	Chemotherapy	Median follow-up (mo)	OS (mo)	PFS (mo)	Grade ≥ 3 toxicity
Liu et al. [11]	2013	26	60–75	3	20–25	3D-CRT	98.1 (30.2–238.7)	248.4 (132.6–396.5)	Carboplatin + vinorelbine	11.5 (4–23)	Median: 13 1-yr: 60.9%	Median: 10 1-yr: 37.0%	G3 esophagitis: 4 (15.4%) G3 pneumonitis: 2 (7.7%) G3/4 neutropenia: 8 (30.8%)
Bearz et al. [8]	2013	33	60	2.4	25	IMRT	N/A	N/A	Cisplatin + docetaxel	N/A	Median: 24	Median: 20	Total 3% G3 esophagitis: 1
Phase II trials													
Ren et al. [18]	2016	12	69	3	23		55.7 (7.9–178.0)	261 (130.3–415.7)	Carboplatin + vinorelbine	10 (5–16)	1-yr: 78.6%	1-yr: 58.3%	G3 esophagitis: 83.3% (5/7 pts) G3 pneumonitis: 28.6% (2/7 pts)
Maguire et al. (SOCCAR) [17]	2014	127	55	2.75	20	3D-CRT	Concurrent: 108.3 (5.7–407.0) Sequential: 119.7 (14.9–1,159.0)	N/A	Cisplatin + vinorelbine	35.2	Median: 24.3 (CCRT) vs. 18.4 (SCRT) 1-yr: 70% (CCRT) vs. 83% (SCRT) 2-yr: 50% (CCRT) vs. 46% (SCRT)	Median: 12.9 (CCRT) vs 12.1 (SCRT) 1-yr: 55% (CCRT) vs. 52% (SCRT) 2-yr: 34% (CCRT) vs. 24% (SCRT)	Total: 32 % (CCRT) vs. 41% (SCRT) Esophagitis: 8.8% (CCRT) vs. 8.5% (SCRT) Pneumonitis: 3.1% (CCRT) vs. 5.2% (SCRT) Neutropenia: 37% (CCRT) vs. 55% (SCRT) G5: 2.9% (CCRT) vs. 1.7% (SCRT)
Phase III trials													
Kim et al. [19]	2023	266	60	2.4	25	SIB / 3D-CRT / IMRT	145.65 (14.0–595.0)	395.05 (95.6–1,017.0)	Cisplatin + paclitaxel	71 (41–128)	Median: 27 2-yr: 50.7% 5-yr: 30.2%	Median: 13 2-yr: 29.7% 5-yr: 23.9%	G ≥ 3 neutropenia: 8.4% G ≥ 3 esophagitis: 2.8% G ≥ 3 pneumonitis: 3.5% G5: 1 (0.7%) esophagitis, 3 (2.1%) pneumonitis
Selective retrospective trials													
Voort Van Zyp et al. [20]	2022	41	66	2.75	24	3D-CRT / IMRT	104 (68–163)	406 (336–509)	Cisplatin + pemetrexed (ADC) Gemcitabine (SCC)	54	Median: 19 1-yr: 66% 2-yr: 37%	N/A	G ≥ 3 total: 21 (51.2%) G5: 5 (12.2%): 4 esophageal fistula/ perforation, 1 hemor-rhage
Iqbal et al. [23]	2019	100	55	2.75	20	3D-CRT / VMAT	N/A	N/A	Cisplatin + vinorelbine	27	Median: 43.4 1-yr: 81% 2-yr: 58%	Median: 23.4 1-yr: 69% 2-yr: 49%	G3/4 esophagitis: 14% G3/4 pneumonitis: 4%

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Table 1. Continued

Study type	Year	Total # of patients	Total RT dose (Gy)	Fraction size (Gy)	# of fraction-ation	RT technique	Median GTV (cm^3)	Median PTV (cm^3)	Chemotherapy	Median follow-up (mo)	OS (mo)	PFS (mo)	Grade ≥ 3 toxicity
Ma et al. [21]	2018	87	65	2.5	26	SIB / IMRT	Esophageal-sparing: 83.7 (25.1–275.3) Standard: 88.2 (22.3–281.4)		Paclitaxel/docetaxel + cis-platin/nedaplatin	18 (1–51)	1-yr: 86.6% 2-yr: 65.4% 3-yr: 43.7%	N/A	No G ≥ 4 esophagitis G3 esophagitis: 15 (17.2%): esopha-gus-sparing group 2, standard group 13
Kerner et al. [22]	2014	318	60	2.4	25	3D-CRT	N/A	N/A	Gemcitabine	N/A	Median: 24.6 5-yr: 26%	Median: 15.5	G ≥ 3 esophagitis: 9.7% G5: 1 hemorrhage, 1 fistula G ≥ 3 pneumonitis: 3% G5: 3 pts

RT, radiotherapy; GTV, gross tumor volume; PTV, planning target volume; OS, overall survival; PFS, progression-free survival; SIB, simultaneous integrated boost; IMRT, intensity-modulated radiotherapy; IMPT, intensity-modulated proton therapy; 3D-CRT, three-dimensional conformal radiotherapy; CALGB, Cancer and Leukemia Group B; SOCCAR, sequential or concurrent chemotherapy and hypofractionated accelerated radiotherapy in inoperable stage III NSCLC; VMAT, volumetric modulated arc therapy; GTVp, primary gross tumor volume; GTVn, nodal gross tumor volume; GI, gastrointestinal; CCRT, concurrent chemoradiotherapy; SCRT, sequential chemoradiotherapy; ADC, adenocarcinoma; SCC, squamous cell carcinoma; N/A, not available; G, grade.

treated with 3 Gy per fx doses, because three grade 5 adverse events occurred in cohorts 2 and 3. These included two patients who experienced fatal hemoptysis and one patient who experienced grade 5 pneumonitis. Overall, grade 3 or higher toxicities occurred in seven patients (33%): one in cohort 1, two in cohort 2, two in cohort 3, and two in cohort 4. The maximally tolerated dose suggested in this trial was 60 Gy given at 2.5 Gy/fx.

A relatively large prospective phase I/II study was reported in 2020 by Glinski et al. [10] in 92 patients. Total dose remained at 58.8 Gy, however the fx size was increased up to 2.8 Gy, BED of 75.26 Gy with α/β ratio of 10. RT was delivered using three-dimensional conformal radiotherapy (3D-CRT) and IMRT. These patients received two cycles of concurrent full-dose cisplatin and vinorelbine, with cisplatin 80 mg/m^2 D_1 and D_{22}; and vinorelbine 25 mg/m^2, D_1, D_8, D_{22}, and D_{29}. The survival outcome of this study confirmed the efficacy of HFRT, with a median OS and PFS of 38 and 25 months, respectively. However, the safety of the scheme must be considered. A total of 35% of all patients experienced grade ≥3 toxicities and there were seven (7.8%) toxic deaths due to the following reasons: three from hemoptysis, two from pneumonitis, one from prolonged esophageal toxicity, and one from pulmonary abscess. All patients had centrally located lesions and received a significantly higher median heart dose. Additionally, their planning target volume (PTV) was relatively larger than that of the other studies (median PTV, 464.1 cm^3). The authors emphasize the need to make all efforts to reduce the irradiated volume when using HFRT.

A Chinese group conducted a study on 26 patients treated with 3 Gy/fx, resulting in a total of 60–75 Gy [11]. Both the fx size and total dose were escalated. Carboplatin and vinorelbine were concurrently administered as chemotherapy. The median follow-up time was 11.5 months with median and 1-year OS and PFS of 13 months and 60.9% and 10 months and 37%, respectively. Four cases (15.4%) of grade 3 esophagitis were noted, three of which were treated with 75 Gy, while the remaining one patient was treated up to 69 Gy. Grades 3 and 4 neutropenia were recorded in 30.8% and 7.7% of pneumonitis cases. The median gross tumor volume (GTV) and PTV were relatively small in this study, 72.5 cm^3 and 511.1 cm^3, which could explain the low incidence of severe toxicity, regardless of the large fx size and high total dose.

With the introduction and increased use of proton therapy, a dose-level escalation study using intensity-modulated proton therapy (IMPT) was conducted in 2022 by Contreras et al. [12]. They included 20 patients with a starting dose of hypofractionated proton therapy of 52.5 Gy in 15 fx (3.5 Gy/fx), with the dose per fx escalating by 0.25 Gy, up to a total of 60 Gy. Two-year OS and cancer-specific survival were 48% and 60%, respectively. Severe acute toxicity did not occur, but three cases of late grade 3 toxicity

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Table 2. Summary of studies on hypofractionated RT alone in locally advanced non-small cell lung cancer

Study type	Year	Total # of patients	Total RT dose (Gy)	Fraction size (Gy)	# of fractionation	RT technique	Median follow-up (mo)	OS (mo)	PFS (mo)	Grade ≥ 3 toxicity
Prospective studies										
Sun et al. [33]	2000	43	65	2.5	26	3D-CRT (concomitant boost)	22 (8–46)	N/A	N/A	Total: 0%
Iyengar et al. [34]	2021	50	60	4	15	IGRT	8.7 (3.6–19.9)	1-yr: 37.7% Median: 8.2	Median: 6.4	Total: 36% Dyspnea: 19% (G3 16%, G4 2%, G5 2%) Death NOS: 1% G3 pulmonary toxicity (ARDS 2%, cough 2%, pleural effusion 2%, pneumonitis: 2%)
Selective retrospective studies										
Ghosal et al. [36]	2015	222	52.5–55	2.625–2.75	20	3D-CRT	61.6	Median: 28.6	N/A	N/A
Iocolano et al. [37]	2020	1,112	50–80 (median 58.5)	2.25–4 (median 2.5)	Median: 22	N/A	N/A	1-yr: 42.9% 3-yr: 5.1% Median: 9.9	N/A	N/A
Brada et al. [38]	2022	9,181	55	2.75	20	N/A	N/A	Median: 25	N/A	N/A

RT, radiotherapy; OS, overall survival; PFS, progression-free survival; 3D-CRT, three-dimensional conformal radiotherapy; IGRT, image-guided radiotherapy; NOS, not otherwise specified; ARDS, acute respiratory distress syndrome; N/A, not available.

(pneumonitis, vocal cord paralysis, and pleurocutaneous fistula) occurred, all of which belonged to the 4 Gy/fx group. On the contrary, in another hypofractionated proton therapy study executed by Hoppe et al. [13], which used a similar treatment scheme, 12 of 18 patients experienced a grade ≥ 3 event, including two cases of grade ≥ 4 toxicity (pneumonitis and congestive heart failure). Although only one toxicity event was related to radiotherapy, and the others were attributed to chemotherapy, the authors recommended that 4 Gy/fx should be used with caution in a CCRT setting.

Several studies have attempted HFRT using the SIB technique. In most trials, the PTV dose remained at the conventional fx, whereas the GTV dose was escalated using hypofractionation.

Jeter et al. [14] reported a dose escalation study starting from 72–78 Gy in 30 fx using the SIB technique with IMRT or IMPT. Fifteen patients were enrolled in the study. In the 72 Gy group, six patients were treated with IMRT, and three patients were treated with IMPT. The remaining six patients were in the 78 Gy group, and IMPT was used in all cases. The median overall survival was 25.3 months. Grade ≥ 3 toxicity was reported in three patients (20%): two patients were in the 78 Gy group, including one patient with fatal pneumonitis.

Li et al. [15] used cisplatin-based doublet chemotherapy alongside IMRT using the SIB technique, with 3 Gy/fx to GTV up to 78 Gy and 2.3–2.5 Gy/fx to PTV up to 60–65 Gy. This treatment scheme was efficacious, with 1-year OS and PFS of 90% and 84.4%, and 5-year OS and PFS of 35.5% and 28.4%, respectively. Although grade ≥ 3 esophageal and pulmonary toxicity did not occur, one case each of grade ≥ 3 gastrointestinal and hematologic toxicities were observed.

In a recently published article by Zhang et al. [16], a similar treatment protocol was reported. They used the SIB technique with concurrent administration of cisplatin and docetaxel. Twenty-five patients were included and the radiotherapy dose was escalated in four levels. The first dose level started with conventional fractionation, with 60 Gy/30 fx to the GTV and 54 Gy/30 fx to the PTV. The total radiotherapy dose for the GTV was fixed at 60 Gy and fx size was escalated from 2.5 Gy to 3 Gy, with an increase of 0.25 Gy at each level. The PTV dose was escalated from 50.4 Gy/24 fx to 50 Gy/20 fx. During a follow-up period of 77.1 months, median, 1-year and 3-year OS and PFS were 27.3 months, 84% and 44%, and 15.4 months, 64% and 34%, respectively. Twenty percent of patients suffered grade 3 and higher toxicity. Among them, two patients experienced fatal upper gastrointestinal hemorrhage and radiation pneumonitis; both were in the dose level 4 group (3 Gy/ fx). As a result, the SIB-IMRT protocol with 60.5 Gy in 22 fx to the GTV and 49.5 Gy in 22 fx to the PTV, with concurrent chemotherapy, for unresectable stage III NSCLC was safely achieved.

The aforementioned phase I studies demonstrated the feasibility and efficacy of HFRT with concurrent chemotherapy for unresectable NSCLC. However, the incidence of severe toxicity emphasizes the importance of cautious treatment planning and close patient monitoring to optimize patient outcomes. Two noteworthy phase II studies have been conducted, each exploring a different chemoradiotherapy strategy.

The first study, also known as the sequential or concurrent chemotherapy and hypofractionated accelerated radiotherapy in inoperable stage III NSCLC (SOCCAR) trial, was reported by Maguire et al. [17] in 2014 and compared sequential and concurrent chemoradiotherapy in 127 patients. RT was delivered in a 2.75 Gy/fx up to 55 Gy/20 fx using 3D-CRT. Although the doses were different between groups, both groups were treated with cisplatin and vinorelbine. The treatment-related mortality rates were 2/68 (2.9%) for concurrent and 1/58 (1.7%) for the sequential arms. The rate of grade 3–5 serious adverse events in the concurrent arm was lower (34% vs. 41%). The incidence of grade 3 and above esophagitis and pneumonitis was not different between the groups (concurrent vs. sequential), 8.8% vs. 8.5% and 3.1% vs. 5.2%, respectively. No grade 4 or 5 events were observed. The incidence of grade 3 or above neutropenia was lower in the concurrent arm. The median OS for the concurrent and sequential arms was 24.3 and 18.4 months, respectively ($p = 0.682$). The median PFS was 12.9 and 12.1 months, respectively ($p = 0.463$). The RT parameters required in this study were lung $V_{20} \leq 35\%$ and ≤ 12 cm esophagus within the PTV. This RT regimen of 55 Gy in 20 fx for 4 weeks, either in sequential or concurrent chemotherapy settings, demonstrated the safety and efficacy of a hypofractionated dose schedule commonly used in the UK, emphasizing the importance of optimizing RT protocols.

In contrast, the second phase II trial reported by Ren et al. [18] explored a different approach with escalated total and fractional doses of RT along with concurrent carboplatin and vinorelbine administration. However, owing to exceptionally high toxicity, the study was terminated early. The total RT dose was 69 Gy, delivered at 3 Gy/fx, once daily, for 5 fx per week. The median GTV and PTV were 55.7 cm^3 and 261.0 cm^3, respectively, which was relatively small. Twelve patients were enrolled; however, only seven completed the treatment protocol. The other five patients could not complete the treatment due to severe radiation esophagitis. One of the five patients died. Grade 3 radiation pneumonitis occurred in two patients, both of whom developed late lung injury, one grade 2 and one grade 3. After early termination, median follow-up time was 10 months, with 1-year OS and PFS of 78.6% and 58.3%, respectively. According to the results of this study, delivering escalated total and fractional doses simultaneously seems unsafe.

Overall, phase I and II studies collectively support the feasibility and potential benefits of HFRT for inoperable stage III NSCLC. Although these studies have provided encouraging results, it is essential to recognize their limitations, including a small number of patients, variations in treatment protocols, and potential biases in patient selection.

2. Phase III studies

The Korean Radiation Oncology Group 09-03 conducted a randomized multicenter phase III study comparing conventional fractionated radiotherapy (CFRT) with HFRT in a CCRT setting in patients with inoperable stage III NSCLC [19]. The study included 266 patients, with 124 allocated to the CFRT (arm 1) and 142 allocated to the HFRT (arm 2) groups. Arm 1 received CFRT with a total dose of 60 Gy delivered in 30 fx to the GTV and 44 Gy delivered in 22 fx to the PTV. In contrast, arm 2 used the SIB technique, delivering 45 Gy to the PTV and 60 Gy to the GTV in 25 fx, with the GTV receiving 2.4 Gy/fx. Both groups received concurrent weekly cisplatin (20 mg/m^2 intravenously over 1 hour) and paclitaxel (50 mg/m^2 intravenously over 1 hour). More than 90% of patients in both groups completed the planned treatment.

The treatment outcomes in both groups were comparable. The median follow-up period for the surviving patients was 71 months (range, 41 to 128 months). The median OS and PFS of all the patients were 26 and 11 months, respectively. The median OS for arm 1 was 26 months and that for arm 2 was 27 months. At 2 years, OS rates were 50.4% in arm 1 and 50.7% in arm 2. The median PFS for arm 1 was 10 months and that for arm 2 was 13 months. The 2-year PFS rates were 29.3% in arm 1 and 29.7% in arm 2.

Regarding adverse events, there were no fatal grade 5 hematologic adverse events. The incidence of grade ≥ 3 neutropenia did not significantly differ between the two groups: seven patients (5.6%) in arm 1 and 12 patients (8.4%) in arm 2. However, grade ≥ 3 radiation esophagitis occurred in 11 patients (8.4%). In arm 1, five patients experienced grade 3 esophagitis and two patients had grade 4 esophagitis. In arm 2, three cases of grade 3 esophagitis occurred, and one fatal grade 5 esophagitis was reported. A total of 14 patients (10.7%) experienced grade ≥ 3 radiation pneumonitis, with nine patients in arm 1 and five in arm 2. There were nine cases of grade 5 toxicity: six in arm 1 and three in arm 2, with acute respiratory distress syndrome in six patients, one case of massive hemoptysis, one of aspiration pneumonia, and one bronchial fistula. The rates of grade ≥ 2 radiation dermatitis were significantly lower in the HFRT group (16.9% vs. 7.0%). IMRT was more frequently applied in arm 2, likely because of concerns about the toxicity of larger fractions.

This major randomized study could not confirm the superiority of accelerated hypofractionated 2.4 Gy/fx. However, with comparable

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efficacy and safety, this study supports the use of hypofractionated IMRT as a reasonable option for patients with inoperable stage III NSCLC undergoing CCRT.

3. Selective retrospective studies

Several retrospective studies have evaluated different treatment regimens for patients with stage III NSCLC. These studies explored various RT techniques and dosing schedules to achieve optimal efficacy while minimizing treatment-related toxicities.

In 2022, a retrospective observational study conducted by Van der Voort et al. [20] analyzed the outcomes of patients with stage III NSCLC. Patients were treated with concurrent platinum doublet chemotherapy, and RT was delivered at doses up to 66 Gy in 24 fx. A total of 41 patients were analyzed. Among these, 17% was treated with 3D-CRT and 83% with IMRT. Constraints for the esophagus were as follows: D_{max} esophagus + 0.5 cm ≤66 Gy and length of esophagus in the radiation field <12 cm. However, the D_{max} esophagus + 0.5 cm was exceeded in 90% of patients, and the length of esophagus in the PTV <12 cm was exceeded in 39%. The median follow-up period was 4.7 years and the median OS was 19 months with 1-year and 2-year OS of 66% and 37%, respectively. Grade ≥3 toxicity occurred in 21 patients (51.2%). Of these, 16 patients (39%) experienced esophageal toxicity. Grade 5 esophageal toxicity occurred in five patients (12.2%): four cases with esophageal fistula/perforation and one due to hemorrhage. All these patients had centrally located bulky tumors. Due to the excessive occurrence and severity of esophageal toxicity, the authors stopped using this regimen.

Because the incidence and severity of esophageal toxicity are major concerns when treating with large fx sizes, Ma et al. [21] investigated an esophagus-sparing technique using IMRT. This retrospective study included 87 patients with stage IIIA-B NSCLC. RT was delivered in a median of 26 fx, and the total doses for PTV for GTV and PTV for clinical target volume were 65 Gy and 45–50 Gy, respectively. The patients were treated with SIB-IMRT and concurrent chemotherapy, and were divided into two groups: one with and the other without the esophagus-sparing technique. The esophagus-sparing technique included (1) a margin of 3 mm was added to the esophagus; (2) maximum dose to esophagus <65 Gy and V_{50} <30%; (3) minimum dose to GTV >60 Gy; and (4) image guidance with daily cone-beam computed tomography. No grade 4 or 5 radiation esophagitis was reported in any of the 87 patients. Patients in the esophagus-sparing group showed significantly lower incidence of grade 3 radiation-induced esophagitis, 4.5% vs. 30.2%. With a median follow-up of 18 months, the OS ($p = 0.301$) and local recurrence free survival ($p = 0.871$) were comparable between the two groups. This study demonstrated the feasibility of HFRT using an esophagus-sparing technique without compromising treatment efficacy.

Another retrospective study by Kerner et al. [22] assessed the outcomes of concurrent gemcitabine and HFRT in 318 patients with unresectable stage III NSCLC patients. Hypofractionated accelerated radiotherapy (60 Gy) was delivered over 5 weeks using 3D-CRT. Two cycles of induction chemotherapy comprising cisplatin and gemcitabine were administered. The median OS and PFS were 24.6 and 15.5 months, respectively. For the 244 patients who completed CCRT, the median OS was 26.3 months. Grade ≥3 esophagitis was observed in 9.7% with two grade 5 events. One patient had esophageal ulcerative stenosis that led to massive hemorrhage, and the other patient developed an esophageal-bronchial fistula after receiving a stent for esophageal stenosis. Grade ≥3 radiation pneumonitis was seen in 3% (10 patients). Among them, three patients experienced a grade 5 event. The emergence of grade ≥3 esophagitis and radiation pneumonitis highlighted the significance of balancing treatment intensity and patient tolerability.

A retrospective analysis using the same radiotherapy scheme as in the SOCCAR trial (55 Gy/20 fx) was published in 2019 by Iqbal et al. [23]. One hundred patients were treated at a single institution. The 3D-CRT was performed in 73 patients, of whom 27 were treated with volumetric arc therapy. Cisplatin and vinorelbine were administered concurrently during the first and last weeks of RT. Adjuvant chemotherapy was administered 4 weeks after the completion of concurrent therapy. With a median follow-up of 27 months, median PFS and OS were 23.4 and 43.4 months, respectively. One-year PFS and OS were 69% and 81%, and 2-year PFS and OS were 49% and 58%, respectively. The incidence of grade ≥3 esophagitis was 14% and radiation pneumonitis was 4%. These data also demonstrate acceptable morbidity and outcomes.

These retrospective studies shed light on the potential challenges associated with HFRT. The incidence and severity of esophageal toxicity have emerged as major concerns, particularly in the treatment with large radiation fractions. Strategies, such as esophagus-sparing techniques, image guidance, and dose constraints, may help mitigate these toxicities and improve treatment tolerability. Although these studies provide valuable information, it is crucial to recognize the limitations of retrospective designs and the need for further investigations through prospective randomized trials.

Key Question 2: What Hypofractionation Regimen Could Be Used for LA-NSCLC Treated with Definitive RT Alone without Chemotherapy?

The number of frail patients who cannot receive concurrent chemotherapy owing to medical comorbidities is increasing. However,

few prospective studies have evaluated radical hypofractionated regimens in the setting of RT alone without chemotherapy. In addition, many retrospective studies included heterogeneous patients with stages I–IV, or used varied RT regimens, including hyperfractionation or mixed modalities with or without chemotherapy, making it difficult to draw clear conclusions [24–32]. As mentioned previously, stereotactic body radiotherapy (SBRT)-like studies including patients with node-negative NSCLC (especially hypofractionation for a central lesion which is not amendable for SBRT) and studies using a palliative dose (< 50 Gy) for patients with poor performance status have not been covered in the present review.

1. Prospective studies

Sun et al. [33] carried out an early clinical trial between 1994–1998, in which chemotherapy was refused or deemed unsuitable. The experimental arm received 65 Gy/26 fx using concomitant boost technique (CBT) to gross disease with a small margin, and the control arm received 70.8 Gy/38 fx of conventional treatment technique (CTT). No grade 3 lung or esophageal toxicities were observed in the CBT group. The response rates were 69.8% and 48.1% for the CBT and CTT patients, respectively. Multivariate analysis showed that CBT group (odds ratio [OR] = 3.03, p = 0.022), good performance status (OR = 5.33, p < 0.001), and severity of acute toxicity (OR = 0.33, p = 0.019) affected the response rate. This study demonstrated that CBT is tolerable and produces a superior response rate compared to conventional RT in patients not receiving chemotherapy.

A more aggressive regimen of 4 Gy/fx using image-guided RT was tested in a phase 3 randomized trial [34]. Iyengar et al. [34] reported data of 96 patients with Zubrod performance status ≥ 2, with greater than 10% weight loss in the previous 6 months, and/or who were ineligible for CCRT. Patients were randomized to receive either HFRT (60 Gy/15 fx; n = 50) or conventional RT (60 Gy/30 fx; n = 46). This trial was closed early after a planned interim analysis demonstrated failure of the survival benefit of HFRT. One-year OS was 37.7% for HFRT and 44.6% for conventional RT (p = 0.29). There were also no significant differences between the two groups in median OS, PFS, time to local recurrence, time to distant metastasis, and toxic effects of grade ≥ 3. Although they did not prove the superiority of the hypofractionated regimen, they suggested that additional research was required to prove its equivalence.

2. Selective retrospective studies

Accelerated RT for patients with poor performance status (PS) is an attractive option because it shortens the treatment period and may not compromise efficacy; however, few retrospective studies have included homogeneous populations. Although the European Society for Medical Oncology guidelines mention hypofractionation (66 Gy/24 fx) as an option for patients receiving sequential chemotherapy and RT, or RT alone [35], high-level clinical evidence to support this recommendation is lacking.

Ghosal et al. [36] reported their experience with 222 patients treated with 52.5–55 Gy/20 fx which is the most commonly used schedule in the UK. With a median follow-up of 61.6 months, median OS was 28.6 months including stages I, II, and III in 28%, 18%, and 53% of cases, respectively. They believed that the increasing evidence supporting this regimen, with survival outcomes comparable to historical results, was sufficient to support its future application in inoperable NSCLC.

Iocolano et al. [37] performed an analysis using the National Cancer Database to evaluate the practice patterns and outcomes of HFRT (50–80 Gy in 2.25–4 Gy/fx, median 58.5 Gy in 2.5 Gy/fx) vs. CFRT (60–80 Gy in 1.8–2 Gy/fx, median 66 Gy in 2 Gy/fx) in United States patients with stage III NSCLC undergoing definitive RT alone. HFRT use was associated with older age, lower BED, academic facility type, higher T stage, and lower N stage. In the univariate analysis, HFRT was associated with inferior OS (median 9.9 vs. 11.1 months; p < 0.001), but it was no longer significant after adjusting for covariates. The authors suggest that HFRT could be an option for patients with LA-NSCLC who are not candidates for chemotherapy or surgical resection.

Using a national-level database, Brada et al. [38] analyzed 12,898 cases treated with radical RT from the Public Health England dataset and showed inferior outcomes with HFRT (55 Gy/20 fx) compared to CFRT (OS: 25 months vs. 28–29 months), unfortunately without details about concurrent chemotherapy due to the limitations of the database. Interestingly, the authors highlighted that even if the suboptimal results of HFRT are acknowledged, it can still be a reasonable option in specific situations. This is particularly true when the need for frequent visits is sufficiently burdensome to warrant a shorter treatment duration. Additionally, HFRT may be preferred when the potential risks associated with daily visits are deemed too significant, such as during a pandemic.

In the absence of robust evidences, KOSRO Practice Guidelines Committee cannot recommend HFRT as routinely applicable schedules for patients with LA-NSCLC treated definitive RT with or without chemotherapy. However, it may be considered for selected patients according to the current review of the literature. The encouraging results of several studies was noted but the usefulness of HFRT should be further investigated in the future.

Conclusion

Although conventional dose/fractionation remains the standard of

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care, the choice of a hypofractionated regimen has been decided in many clinical situations irrespective of the combination of chemotherapy in patients with LA-NSCLC. As there is still a lack of high-level evidence, further prospective trials are needed to evaluate the toxicity and tumor control. The application of HFRT has both advantages and disadvantages, and decision on use should follow discussion between the patient and doctor.

In summary, HFRT, particularly when combined with concurrent chemotherapy, has shown promising results in the treatment of LA-NSCLC. The reviewed data support the feasibility, comparable efficacy, and potential to improve treatment tolerability. Continued research and clinical trials are essential to refine treatment strategies, identify optimal patient selection criteria, and enhance therapeutic outcomes.

Statement of Ethics

Because this study did not involve any human subjects, Institutional Review Board approval and informed consent were not required.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Author Contributions

Conceptualization, BHK, YKK. Investigation and methodology, BHK, YKK. Project administration, YSK, BHK. Resources & Writing of the original draft, BHK, YKK. Data curation, BHK, YKK. Writing of the review and editing, BHK, YKK, YSK, SYS, JHS, GSY, HKB, YJK, KSK. All the authors have proofread the final version.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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