Purpose: To investigate the safety and efficacy of hypofractionated radiation therapy (HFRT) in patients with non-small cell lung cancer who are unfit for surgery or stereotactic body radiation therapy (SBRT) at our institution.

Materials and Methods: From May 2007 to December 2018, HFRT was used to treat 68 lesions in 64 patients who were unsuitable for SBRT because of central tumor location, large tumor size, or contiguity with the chest wall. The HFRT schedule included a dose of 50–70 Gy delivered in 10 fractions over 2 weeks. The primary outcome was freedom from local progression (FFLP), and the secondary endpoints included overall survival (OS), disease-free survival, and toxicities.

Results: The median follow-up period was 25.5 months (range, 5.3 to 119.9 months). The FFLP rates were 79.8% and 67.8% at 1 and 2 years, respectively. The OS rates were 82.8% and 64.1% at 1 and 2 years, respectively. A larger planning target volume was associated with lower FFLP (p = 0.023). Dose escalation was not associated with FFLP (p = 0.964). Four patients (6.3%) experienced grade 3–5 pulmonary toxicities. Tumor location, central or peripheral, was not associated with either grade 3 or higher toxicity.

Conclusion: HFRT with 50–70 Gy in 10 fractions demonstrated acceptable toxicity; however, the local control rate can be improved compared with the results of SBRT. More studies are required in patients who are unfit for SBRT to investigate the optimal fractionation scheme.

Keywords: Non-small cell lung carcinomas, Radiation dose fractionation, Radiation dose hypofractionation, Treatment outcome, Toxicity
Hypofractionated radiation therapy in non-small cell lung cancer nodal irradiation was not performed. The prescribed dose was ad
by adding 5–7 mm radially and 7–10 mm longitudinally. Elective
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integrated using each GTV in breathing phases within the gating
the lung window setting at end of expiration. The internal target
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nodal irradiation was not performed. The prescribed dose was ad-
ministered such that 95% of PTV received 95%–100% of the pre-
scription dose and avoided hot spots in organs-at-risk. Respirato-
ry-gated volumetric-modulated arc therapy or intensity-modulated
radiotherapy technique using 6 or 15 MV energy with 5–10 fields
was used. The HFRT schedule included a dose of 50–70 Gy in 10
fractions over 2 weeks based on the decision of the radiation on-
cologist. At each treatment, kV cone-beam CT scans were per-
formed to localize treatment targets and subsequently, two orthog-
onal fluoroscopic kV images were obtained to confirm the respira-
tory motion of the visible mass or carina.

Materials and Methods

1. Patients
We retrospectively reviewed 68 lesions that were treated with 10
fractions of RT with a curative aim in 64 patients at our hospital
between May 2007 and December 2018. The study was approved
by the Institutional Review Board of the Asan Medical Center (No.
2020–1605), and the requirement for informed consent was waived
because of the retrospective nature of the study. The patients were
unsuitable for SBRT because of central tumor location, large tumor
size, or contiguity with the chest wall. Centrally located tumor was
defined as a tumor within 2 cm from the proximal bronchial tree
and tumor immediately adjacent to the mediastinal or pericardial
pleura.
The exclusion criteria were as follows: patients with distant me-
tastasis, and patients diagnosed with another cancer within 5 years
from the RT. For appropriate staging, physical examination, patho-
logic confirmation, chest computed tomography (CT), 18-fluo-
ro-deoxyglucose positron emission tomography, and brain magnetic
resonance imaging were performed. Before the treatment, pul-
monary function tests were performed and lymph node metastases
were confirmed histopathologically, whenever possible. The stage
was determined according to the American Joint Committee on
Cancer 8th edition TNM stage classification.

2. Treatments and follow-up
For the planning of treatment, four-dimensional CT was used to
measure respiratory tumor motion (slice thickness, 2.5 mm). The
gross tumor volume (GTV) was delineated on axial CT images using
the lung window setting at end of expiration. The internal target
volume was contoured in maximum intensity projection images or
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cologist. At each treatment, kV cone-beam CT scans were per-
formed to localize treatment targets and subsequently, two orthog-
onal fluoroscopic kV images were obtained to confirm the respira-
tory motion of the visible mass or carina.

3. Follow-up, outcomes, and statistical analyses
Patients were evaluated every week using complete blood count
tests and chest X-rays (CXRs). Patients were followed up at 1
month after the treatment, every 3 months during the first 2 years
after treatment, and every 6 months until 5 years thereafter using
chest CT, CXR, and laboratory tests.
The primary outcome was freedom from local progression (FFLP),
and the secondary endpoints included overall survival (OS), dis-
ease-free survival (DFS), and toxicities. The response was assessed
using the Response Evaluation Criteria in Solid Tumors (RECIST)
criteria and toxicity during and after the treatment was assessed
according to the Common Terminology Criteria for Adverse Events
version 5.0.
Local progression was defined as failure in the primary tumor site.
FFLP is the period of absence of local progression from the date of
RT initiation. PFS rates are calculated from the date of RT initiation
until recurrence, death, or last follow-up. FFLP, DFS, and OS were
calculated using the Kaplan–Meier method. Univariate analysis was
performed using log-rank test, and chi-square test was used to
identify risk factors for toxicity. Statistical analyses were performed
using SPSS version 22.0 (IBM Corp., Armonk, NY, USA).

Results

1. Patients and treatments
Overall, 68 lesions in 64 patients were included in this study, and
the characteristics of patients and the disease are listed in Tables 1
and 2, respectively. The median age was 72 years (range, 57 to 89
years). In 68 tumors, 13 (19.1%) included double primary lung can-
cer; of them, two patients were treated with HFRT and SBRT for
each lesion, one patient underwent surgery for another lesion, one
patient received photodynamic therapy, one patient rejected treat-
ment for the other lesion and was only followed up according to his
will, and four patients were treated with HFRT for both lesions. Ad-
ditionally, eight cases were of recurrent NSCLC after surgery or de-
finitive concurrent chemoradiation therapy (CCRT) or SBRT. We in-
cluded these patients, and FFLP was calculated based on 68 lesions.

Overall, 51 tumors (75.0%) were centrally located; of them, 31 cases were ultracentral, which is abutting to the proximal bronchial tree, while the remaining 20 cases were located non-ultracentrally. Histologically, 41 tumors (64.7%) were squamous cell carcinoma and 19 tumors (27.9%) adenocarcinoma. The median size was 3.2 cm (range, 2.6 to 4.7 cm) and 13 tumors (19.1%) were > 5 cm and 55 tumors (80.9%) were ≤ 5 cm. The median total RT dose was 60 Gy (range, 50 to 70 Gy), and the median biologic equivalent dose (BED) was 96.0 Gy\textsubscript{10} (range, 60.0 to 180.0 Gy\textsubscript{10}). Twenty-five tumors (36.8%) were treated with 50 Gy, one tumor (1.5%) with 55 Gy, 27 tumors (39.7%) with 60 Gy, two tumors (2.9%) for 65 Gy, and 13 tumors (19.1%) with 70 Gy. The median volumes of GTV and PTV were 18.1 cm\textsuperscript{3} (range, 0.8 to 161.7 cm\textsuperscript{3}) and 60.2 cm\textsuperscript{3} (range, 12.5 to 502.1 cm\textsuperscript{3}), respectively. The mean lung dose was 4.71 Gy (range, 1.79 to 14.74 Gy), and the volume of lung that received at least 20 Gy (V\textsubscript{20}) was 6.7% (range, 1.5% to 29.2%). The reasons for HFRT are illustrated in Fig. 1. They were as follows: (1) central lesion (n = 43; 63.2%); (2) pleural-based lesion (n = 10; 14.7%); (3) central and pleural-based lesion (n = 2; 2.9%); (4) central and large

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**Table 1.** Patient characteristics (n = 64)

| Characteristic          | Value          |
|-------------------------|----------------|
| Age (yr)                | 72 (57–89)     |
| Sex                     |                |
| Male                    | 59 (92.2)      |
| Female                  | 5 (7.8)        |
| ECOG performance status |                |
| 0–1                     | 34 (53.1)      |
| 2–3                     | 30 (46.9)      |
| Pulmonary function test |                |
| FEV1 (%)                | 65 (20–116)    |
| DLCO (%)                | 58 (36–111)    |
| Underlying lung disease |                |
| Yes                     | 25 (39.1)      |
| No                      | 39 (60.9)      |

Values are presented as median (range) or number (%). ECOG, Eastern Cooperative Oncology Group; FEV1, forced expiratory volume in 1 second; DLCO, diffusing capacity of the lungs for carbon monoxide.

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**Table 2.** Disease characteristics and treatment parameters (n = 68)

| Category                        | Value          |
|---------------------------------|----------------|
| Disease characteristic          | AJCC 8th stage |
| T1N0                            | 20 (29.4)      |
| T2N0                            | 17 (25.0)      |
| T3N0                            | 8 (11.8)       |
| T4N0                            | 2 (2.9)        |
| Double primary lung cancer      | 13 (19.1)      |
| Recurrent NSCLC                  | 8 (11.8)       |
| Tumor location                   |                |
| Central                          | 51 (75.0)      |
| Ultracentral                     | 31 (45.6)      |
| Non-ultracentral                 | 20 (29.4)      |
| Non-central                      | 17 (25.0)      |
| Histology                        |                |
| Squamous cell carcinoma          | 44 (64.7)      |
| Adenocarcinoma                   | 19 (27.9)      |
| Others                           | 2 (2.9)        |
| Not checkable                    | 3 (4.4)        |
| Tumor location                   |                |
| RUL                              | 17 (25.0)      |
| RML                              | 1 (1.5)        |
| RLL                              | 12 (17.6)      |
| LUL                              | 19 (27.9)      |
| LLL                              | 18 (26.5)      |
| Regional node (right hilar)      | 1 (1.5)        |
| Tumor size (cm)                  |                |
| ≤ 5                              | 55 (80.9)      |
| > 5                              | 13 (19.1)      |
| Treatment parameter              |                |
| Dose (BED)                       |                |
| 50–60 Gy (75–96 Gy)              | 53 (77.9)      |
| 65–70 Gy (107.25–119 Gy)         | 15 (22.0)      |
| Volume                           |                |
| GTV (cm\textsuperscript{3})      | 18.1 (0.8–161.7)|
| PTV (cm\textsuperscript{3})      | 60.2 (12.5–502.1)|
| Mean lung dose (Gy)              | 4.71 (1.79–14.74)|
| V\textsubscript{20} (%)          | 6.7 (1.5–29.2) |

Values are presented as number (%) or median (range). AJCC, American Joint Committee on Cancer; NSCLC, non-small cell lung cancer; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; BED, biologic equivalent dose; GTV, gross tumor volume; PTV, planning target volume; V\textsubscript{20}, lung volume dose receiving ≥20 Gy.

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**Fig. 1.** Reason for hypofractionated radiotherapy.
mass > 5 cm (n = 6; 8.8%); and (5) large mass > 5 cm and pleural-based lesion (n = 7; 10.3%). No patient was treated with adjuvant chemotherapy after HFRT.

2. FFLP, DFS, OS, and failure pattern
The median follow-up duration was 25.5 months (range, 5.3 to 119.9 months). The FFLP rates were 79.8% and 67.8% at 1 and 2 years, respectively (Fig. 2A). The DFS rates were 54.7% and 32.8% and the OS rates were 82.8% and 64.1% at 1 and 2 years, respectively (Fig. 2B, 2C). The median OS was 33.7 months (range, 5.3 to 131.4 months). The freedom from distant metastasis rates were 79.4% and 65.8% at 1 and 2 years, respectively (Fig. 2D). As shown in Table 3, a PTV volume > 60 cm$^3$ was a significant factor of FFLP in univariate analysis ($\leq$ 60 vs. > 60 cm$^3$: 2-year FFLP, 81.5% vs. 53.9%, respectively; $p = 0.023$). There was no statistical difference in the 2-year FFLP rate between the histologic types (squamous cell carcinoma vs. others: 65.5% vs. 71.8%, respectively; $p = 0.273$), tumor location (central vs. non-central: 63.8% vs. 81.4%, respec-

![Fig. 2. Survival outcomes of 10-fraction hypofractionated radiotherapy: (A) freedom from local progression (FFLP), (B) disease-free survival (DFS), (C) overall survival (OS), (D) freedom from distant metastasis (FFDM).](https://doi.org/10.3857/roj.2021.00416)
tively; p = 0.288), and tumor size (≤5 vs. >5 cm: 69.9% vs. 57.7%, respectively; p = 0.473). Additionally, there was no difference in FFLP according to dose escalation (50–55 vs. 60–65 vs. 70 Gy: 70.3% vs. 65.9% vs. 63.3%, respectively; p = 0.964). Furthermore, as shown in Table 4, patients with a PTV > 60 cm³ demonstrated lower 2-year DFS than those with lower PTV; however, the difference was not statistically significant (≤60 vs. >60 cm³: 40.6% vs. 25.0%, respectively; p = 0.060). Patients with Eastern Cooperative Oncology Group (ECOG) 0–1 demonstrated better OS than those with ECOG 2–3 (0–1 vs. 2–3: 2-year OS, 76.5% vs. 68.6%, respectively; p = 0.161). Additionally, other factors such as PTV volume, tumor size, radiation dose, and tumor location were not statistically associated with OS.

As illustrated in Fig. 3, dominant failure pattern was distant failure (51.3%). Local failure was observed in 45.9% of the patients, and regional failure was observed in 40.5% of the patients.

### 3. Toxicity

Four patients (6.25%) experienced grade 3 or higher toxicity. One patient died because of RT pneumonitis 3 months after the end of RT; two patients experienced grade 3 dyspnea after 5 and 10

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### Table 3. Univariate analysis for FFLP in 68 tumors

| Variable                  | Number of tumors | Univariate analysis |
|---------------------------|------------------|---------------------|
| Age (yr)                  |                  |                     |
| < 70                      | 26               | 79.6                |
| ≥ 70                      | 42               | 80.2                |
| Sex                       |                  |                     |
| Male                      | 62               | 64.4                |
| Female                    | 6                | 100                 |
| Histologic type           |                  |                     |
| SqCC                      | 44               | 65.5                |
| Others                    | 24               | 71.8                |
| Tumor location            |                  |                     |
| Central                   | 51               | 63.8                |
| Non-central               | 17               | 81.4                |
| Tumor size (cm)           |                  |                     |
| ≤ 5                       | 55               | 69.9                |
| > 5                       | 13               | 57.7                |
| PTV volume (cm³)          |                  |                     |
| ≤ 60                      | 34               | 81.5                |
| > 60                      | 34               | 53.9                |
| Dose (Gy)                 |                  |                     |
| 50–60                     | 53               | 66.8                |
| 65–70                     | 15               | 70.6                |

FFLP, freedom from local progression; SqCC, squamous cell carcinoma; PTV, planning target volume.

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### Table 4. Univariate analysis for DFS and OS

| Variable                  | Number of patients | Univariate analysis |
|---------------------------|--------------------|---------------------|
| Age (yr)                  |                    |                     |
| < 70                      | 25                 | 28.0                |
| ≥ 70                      | 39                 | 35.9                |
| Sex                       |                    |                     |
| Male                      | 59                 | 28.8                |
| Female                    | 5                  | 80.0                |
| ECOG performance status   |                    |                     |
| 0–1                       | 34                 | 32.4                |
| 2–3                       | 30                 | 33.3                |
| Histologic type           |                    |                     |
| SqCC                      | 42                 | 33.3                |
| Others                    | 22                 | 31.8                |
| Tumor location            |                    |                     |
| Central                   | 38                 | 34.2                |
| Non-central               | 26                 | 30.8                |
| Tumor size (cm)           |                    |                     |
| ≤ 5                       | 51                 | 35.3                |
| > 5                       | 13                 | 23.1                |
| PTV volume (cm³)          |                    |                     |
| ≤ 60                      | 32                 | 40.6                |
| > 60                      | 32                 | 25.0                |
| Dose (Gy)                 |                    |                     |
| 50–60                     | 51                 | 31.4                |
| 65–70                     | 13                 | 38.5                |

DFS, disease-free survival; OS, overall survival; ECOG, Eastern Cooperative Oncology Group; SqCC, squamous cell carcinoma; PTV, planning target volume.
months, respectively; and one patient developed grade 3 RT pneumonitis 4 months after the treatment. All patients had pulmonary diseases, such as idiopathic pulmonary fibrosis (IPF) or chronic obstructive pulmonary disease (COPD). The only significant factor for grade 3 or higher toxicity was the presence of pulmonary disease, such as IPF or COPD ($p = 0.009$). Other factors such as the sex, performance status, age, radiation dose, tumor location (central vs. non-central; ultracentral vs. non-ultracentral), and pre-treatment pulmonary functions test (forced expiratory volume in 1 second [FEV1], diffusing capacity of the lungs for carbon monoxide [DLCO]) did not demonstrate any significant difference in grade 3–5 toxicity. One patient who died of RT pneumonitis had underlying IPF. After HFRT of 60 Gy in 10 fractions, he received SBRT of 48 Gy in 4 fractions for contralateral lung mass. Three months after HFRT and about 1 month after SBRT, he was treated for pneumonia and RT pneumonitis. After discharge, he stopped taking antibiotics and steroids on his own. Despite rehospitalization and supportive care due to dyspnea aggravation, he died of respiratory arrest.

### Discussion and Conclusion

This study was a single-institution retrospective analysis of patients treated with HFRT with primary or recurrent NSCLC to evaluate the local control rates, survival, and related toxicities. The 2-year FFLP, DFS, and OS rates were 67.8%, 32.8%, and 64.1%, respectively, and four patients (6.25%) experienced grade 3 or higher toxicity. Given the acceptable toxicity, our findings provide clues regarding the optimal hypofractionation regimen for patients who are unfit for SBRT.

Historically, studies with conventional RT have reported local control rates of 30%–70% [14–17]. To improve the local control rate and OS, SBRT was attempted in early-stage lung cancer and demonstrated high local control (above 90%) in multi-center, prospective trials [3–5]. However, since tumors that are central, large, and adjacent to ribs demonstrated high toxicity rates when SBRT was performed, risk-adapted fractionation schemes such as HFRT have been attempted to reduce the toxicity while trying to maintain the local control rate. However, a consensus regarding the schemes remains lacking. Table 5 summarizes the clinical outcomes of HFRT in various institutions [18–23]. Tekatli et al. [18,19] reported that 60 Gy in 8 fractions in the treatment of central tumors, but not ultracentral tumors, had comparable OS with SBRT (2-year OS = 62%); however, 60 Gy in 12 fractions in the treatment of ultracentral tumors resulted in 38% grade 3–5 toxicity, although local failure was not observed during the follow-up. NRG Oncology/RTOG 0813 tried a dose-escalating schedule in 5 fractions; 60 Gy in the 5-fraction schedule revealed 7.2% grade 3–5 toxicity with 87.9% of 2-year local control rates [20]. In contrast, the Nordic HILUS trial, a prospective multi-center phase II trial, reported as an abstract, tried 56 Gy in 8 fractions for central tumors and reported 28% grade 3–5 toxicities with 9.5% grade 5 toxicity and more frequently toxicities in tumors close to the main bronchus than those close to a lobar bronchus [21]. RTOG 0813 included a relatively small proportion of ultracentral tumors (17%) compared with our study (45.6%) and defined a central tumor as a lesion within 2 cm from the proximal bronchial tree (PBT), while the HILUS trial defined it as a tumor within 1 cm from PBT; therefore, that could have resulted in the low toxicity rates in RTOG 0813 trial. Additionally, Li et al. [22] demonstrated 96.2% 2-year LC with 3.6% toxicity using 70 Gy in 10 fractions. In this study, approximately half the patients had central tumors and included patients with tumors ad-

### Table 5. Clinical outcomes of hypofractionated radiation therapy in non-small cell lung cancer

| Study, year | n | Dose (BED) | Median follow-up (mo) | Local control | OS | Toxicity ≥ Gr3 |
|-------------|---|------------|----------------------|---------------|----|----------------|
| Bejjak et al. [20], 2019 | 120 | 50–60 Gy/5 fx (100–132 Gy) | 37.1 | 1-yr: 97%; 2-yr: 87.9%; 2-yr: 72.7% | 1-yr: 93.9%; 2-yr: 72.7% | DLT: 7.2% |
| Lindberg et al. [21], 2017 | 74 | 56 Gy/8 fx (95.2 Gy) | NA | NA | NA | 28% |
| Tekatli et al. [19], 2015 | 80 | 60 Gy/8 fx (105 Gy) | 47 | NA | 1-yr: 81%; 2-yr: 62% | 13.9% (Gr5: 7.5%) |
| Tekatli et al. [18], 2016 | 47 | 60 Gy/12 fx (90 Gy) | 29.3 | No LR | 1-yr: 61.5%; 2-yr: 28.7% | 38% |
| Stephans et al. [23], 2017 | 33 | 60 Gy/8 fx (105 Gy) | 22.1 | 2-yr: 87% | 2-yr: 52% | 15.1% |
| Li et al. [22], 2014 | 82 | 70 Gy/10 fx (119 Gy) | 21.1 | 2-yr: 96.2%; 2-yr: 66.9% | 2-yr: 66.9% | 3.6% |
| Current study | 68 | 50–70 Gy/10 fx (75–119 Gy) | 25.5 | 1-yr: 79.8%; 2-yr: 67.8% | 1-yr: 82.8%; 2-yr: 64.1% | 6.3% |

BED, biologic equivalent dose; OS, overall survival; Gr, grade; DLT, dose-limiting toxicity; NA, not available.

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adjacent to the chest wall, large tumors, or multiple lesions. More than half the tumors were < 3 cm, which could have resulted in a high control rate with comparative low toxicity.

In this study, univariate analysis demonstrated that escalation of the total dose did not have a significant association with local control, DFS, and OS. It has been demonstrated in several studies that SBRT regimens with BED $\geq 100$ Gy have better local control and survival rates than with BED $< 100$ Gy; if BED $\geq 100$ Gy was used, the local control rates were > 85% [24–26]. In this study, at the beginning of the treatment of the 10-fraction HFRT regimen due to central location or normal tissue constraints, we were reluctant to use a BED of $> 100$ Gy because of a lack of experience. However, following increase in experience and several reports regarding the safety of HFRT, dose escalation to 65–70 Gy has been attempted. However, since the sample size was not large, high-dose HFRT was performed relatively recently and treated patients had heterogeneous characteristics; therefore, these factors might have resulted in no significant difference in the local control with escalating total dose. Further studies with longer follow-up and large sample size are needed. Also, considering the low rates of toxicity in 10-fraction HFRT, there is room for improving local control by escalating the total dose or fraction size. In contrast, this study demonstrated no difference in toxicity above grade 3 betwen ultracentral and non-ultracentral lesions; however, this may be due to factors such as low toxicity rate and small sample size. Since it has been demonstrated in several studies that SBRT or HFRT for ultracentral lesions is likely to be highly toxic, it is necessary to carefully determine the fraction size and total dose, especially, for ultracentral lesions. Furthermore, in univariate analysis, the PTV volume, but not the tumor size, was statistically associated with local progression; however, it was not associated with DFS and OS. Similarly, Allibhai et al. [9] reported that the tumor size was not associated with local progression but was associated with DFS and OS and that the effects of tumor volume on DFS and OS were more significant than those of tumor size.

Besides, considering low DFS and OS after HFRT and that the most common failure pattern was distant metastasis, adjuvant treatment such as chemotherapy or immunotherapy could be helpful in disease control. The PACIFIC trial demonstrated that treatment with the immune checkpoint inhibitor durvalumab after CRT demonstrated benefits in OS and DFS in patients with stage III unresectable NSCLC [27,28]. Therefore, immunotherapy or chemotherapy after HFRT could be beneficial in DFS and OS, and further studies regarding the adjuvant treatments are warranted.

Our study has a few limitations. It was a retrospective study at a single institution, which could have resulted in potential selection bias. Additionally, the heterogeneity of patients, tumor locations, and various organs at risk could have affected the planning and delivery of RT and, consequently, the clinical outcomes. Despite these limitations, this study included a relatively long follow-up compared with other studies on HFRT. Additionally, as there are few studies on the clinical outcomes of 10-fraction HFRT, this study could help predict the prognosis of the patients treated with this HFRT regimen.

In conclusion, HFRT with 50–70 Gy in 10 fractions demonstrated acceptable toxicity, although the local control rate appears to have a room for improvement via escalation of the total dose or fraction size and, especially, ultracentral tumors require more attention due to concerns of toxicity. For patients who are unfit for SBRT, more studies are required to investigate the optimal fractionation scheme.

Conflict of Interest

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

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