

Hypofractionated Image-Guided Radiation Therapy for Patients with Limited Volume Metastatic Non-small Cell Lung Cancer

Michael D. Hasselle, MD,* Daniel J. Haraf, MD,* Kyle E. Rusthoven, MD,§ Daniel W. Golden, MD,* Ravi Salgia, MD, PhD,† Victoria M. Villafior, MD, Niket Shah, BS,* Philip C. Hoffman, Steven J. Chmura, MD, PhD,*‡ Philip P. Connell, MD,* Everett E. Vokes, MD,* Ralph R. Weichselbaum, MD,*‡ and Joseph K. Salama, MD||

Introduction: Outcomes data treating patients with oligometastatic (≤ 5 metastases) non-small cell lung carcinoma (NSCLC) with hypofractionated image-guided radiotherapy (HIGRT) are limited. **Methods:** Consecutive oligometastatic NSCLC patients were reviewed from a prospective database. Patients were included if all active diseases were treated with HIGRT. Lesions that had received prior radiation or had radiographic/metabolic resolution after chemotherapy were not treated with HIGRT. Local control of all treated lesions, distant control, progression-free survival (PFS), overall survival (OS), and control of individual lesions (LeC) were calculated.

Results: Twenty-five patients with median of 2 treated oligometastatic lesions were included. Median follow-up was 14 months. Median age was 66 years. Nineteen patients received systemic therapy before HIGRT and 11 had progressive disease after their most recent systemic therapy before HIGRT. Median OS and PFS were 22.7 and 7.6 months. The 18 months local control, distant control, OS, and PFS were 66.1%, 31.7%, 52.9%, and 28.0%. Greater than two sites treated with HIGRT, nonadenocarcinoma histology, prior systemic therapy, and progression after systemic therapy were associated with worse PFS. Sixty-two individual lesions of median size 2.7 cm were treated. For extracranial lesions, median total and fraction dose were 50 and 5 Gy. Median standard equivalent dose in 2 Gy fractions for extracranial lesions was 64.6 Gy yielding 18 months LeC of 70.7%. Standard equivalent dose ≥ 64.6 Gy increased LeC ($p = 0.04$). Two patients experienced grade 3 toxicity.

Conclusions: HIGRT for oligometastatic NSCLC provides durable LeC and may provide long-term PFS in some patients. Future

HIGRT studies should optimize patient selection and integration with systemic therapy.

Key Words: Non-small cell lung cancer (NSCLC), Oligometastases, Radiation, Outcomes.

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Metastasis is the leading cause of cancer death in patients with lung cancer. Non-small cell lung cancer (NSCLC) represents 85% of lung cancers (187,000 cases) with greater than one-half of patients either presenting with or subsequently developing metastatic disease.^{1,2} Patients with metastatic NSCLC usually receive treatment with either cytotoxic or targeted systemic agents alone or in combination. Third-generation chemotherapy doublets, such as cisplatin and docetaxel, are more effective than prior regimens.^{3–6} However, even with the most effective agents, response rates are generally $<30\%$, and median survival from diagnosis is approximately 1 year.^{5,7} For patients who progress after first-line chemotherapy, additional systemic agents are less effective with response rates to second-line therapy, ranging from 7 to 11% with median survivals of 6.7 to 8.3 months.^{8–11} As most of patients progress, improvements in therapy are clearly needed.

Patients with metastatic NSCLC do not always present with widespread metastatic disease. An analysis of metastatic NSCLC patients demonstrated that 50% of patients presented with one to five metastatic sites in limited organs. Furthermore, analyses of patterns of progression in metastatic NSCLC patients reveal up to 64% progress exclusively in known sites of disease after first-line systemic therapy.^{12,13} Based on the hypothesized clinical state of oligometastases, wherein a cancer's metastatic potential is limited in number,^{14,15} there may exist a window when local therapy to all sites of known metastases can provide durable remission in a subset of patients. Furthermore, improving systemic therapies may reduce the microscopic metastatic burden, rendering patients into a state of induced oligometastases. Although clinical evidence supporting an oligometastatic state in NSCLC is relatively limited, long-term survivorship has been

Section of Hematology/Oncology, *Departments of Radiation and Cellular Oncology, and †Pathology, and ‡Ludwig Center for Metastasis research, University of Chicago, Chicago, Illinois; §Coastal Carolina Radiation Oncology, Conway, South Carolina; and ||Department of Radiation Oncology, Duke University Medical Center, Durham, North Carolina.

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Address for correspondence: Joseph K. Salama, MD, Department of Radiation Oncology, Box 3058, Duke University Medical Center, Durham, NC 27710. E-mail: joseph.salama@duke.edu

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reported after resection of brain¹⁶ and adrenal metastases.¹⁷ These data suggest at minimum a progression-free survival (PFS) benefit may be obtained from metastasis-directed treatment for a subset of oligometastatic NSCLC patients.

Based on these data, and studies reporting that more than half of such patients would meet inclusion criteria for hypofractionated radiotherapy at some point during their systemic treatment,¹² we began offering hypofractionated image-guided radiation therapy (HIGRT) for nonsurgical metastatic NSCLC patients with extracranial oligometastatic lesions in 2004. Herein, we report our experience.

PATIENTS AND METHODS

Eligibility

Patients were identified retrospectively from a prospectively maintained database of patients with limited metastatic disease from a variety of primary tumors treated on or off protocol using HIGRT. Patients were included in this analysis if they had histologically or cytologically proven stage IV (American Joint Committee on Cancer 6th edition) or recurrent NSCLC with one to five sites of metastatic and primary disease. All patients were evaluated by an attending radiation oncologist to determine eligibility for HIGRT and were required to receive treatment to all known sites of active disease. Lesions receiving prior radiation (if radiographically stable) or with radiographic/metabolic resolution after chemotherapy were declared inactive and did not receive HIGRT. This analysis was approved by the University of Chicago's institutional review board.

Treatment

Systemic Therapy

Patients received a variety of chemotherapeutic and targeted agents at the discretion of the treating medical oncologist usually before HIGRT. The typical interval between systemic therapy and HIGRT was a minimum of 2 weeks. Chemotherapy was not given concurrently with HIGRT.

Radiation Therapy

Before HIGRT, all patients were simulated in custom-made immobilization devices. For nonosseous metastases of the thorax and upper abdomen, patients underwent contrast-enhanced computed tomography (CT)-based radiation planning including four-dimensional (4D) CT scans to allow visualization and assessment of respiratory-induced tumor motion. For pulmonary lesions with limited respiratory motion, an internal target volume (ITV) was generated based on maximal intensity projection images from the entire respiratory cycle of the gross tumor volume. The patient was subsequently treated free breathing/continuously throughout the respiratory cycle. For lesions with marked respiratory motion, end-expiratory respiratory gating was employed. Maximum intensity projection images were created representing only the respiratory gating window on which a gating ITV was contoured representing tumor motion within the gating window. Diagnostic images (magnetic resonance imaging, FDG-PET, triple phase CT, etc.) were anatomically

registered to the planning CT scans routinely to assist with target delineation. Subsequently for both techniques, the ITV was expanded 5 to 12 mm to account for setup reproducibility and lesion location at the treating physician's discretion to create the planning target volume (PTV).

A variety of nonoverlapping axial fields and noncoplanar fields were combined to achieve the optimal radiation distribution to tumors while minimizing radiation to surrounding tumor-free organs. Normal tissue tolerances were compounded from the available literature.^{18,19} Prescription doses varied based on inclusion on an in-house single institution protocol. For patients treated on protocol, each metastatic lesion was assigned to one of five anatomic regions based on potential normal tissue complication, which determined the dose escalation schedule (lung, liver, abdominal, head and neck, and extremity). The starting dose for all sites was 24 Gy delivered in three 8 Gy fractions and escalated in 2 Gy per fraction increments using a standard 3 × 3 schema. Protocol patients received three fractions of radiotherapy separated by a minimum of 48 hours and a maximum of 192 hours. For patients treated off protocol, radiation planning techniques were identical to those treated on protocol. We used a previously established 10-fraction schedule^{20–22} delivering a cumulative dose of 50 Gy in 5 Gy daily radiation fractions for most patients. Intracranial radiosurgery for brain metastases was performed in the usual fashion with doses per standard guidelines.²³

Each treatment was personally supervised by an attending physician. Before each treatment, daily image guidance with gated kilovoltage (kV) images and/or nongated kV cone beam CT scans was acquired after the patient was placed in the treatment position. Appropriate adjustments were made to ensure that nearby bony anatomy correlated to the planning CT scan. Most target lesions could also be visualized on kV cone beam CT scan to confirm that they were encompassed by the planning target volume.

Patients returned for follow-up every 2 weeks for the first month, monthly for 3 months, and then every 3 months thereafter. Appropriate imaging studies (whole-body CT and/or FDG-PET) were performed 1 month after the completion of treatment and then every 3 months thereafter. Magnetic resonance imaging was routinely used to assess intracranial response. Each metastatic lesion was considered independently and assessed for response using axial unidimensional measurements per RECIST criteria. Patterns of first and cumulative progression were determined by following all target and nontarget lesions (primary tumors and all metastatic sites) on all follow-up imaging studies. Toxicity was scored using the Common Toxicity Criteria version 3.0.

Statistics

Patient- and lesion-based analyses were performed. For the patient-based analysis, the following end points were evaluated: PFS defined as the time to progression or death, overall survival (OS), local control (LC) defined as no progression of all HIGRT-treated metastases within a patient, and distant control (DC) defined as progression outside of treated lesions. Progression in a lesion not treated with HIGRT but with another modality before the first HIGRT

course (i.e., standard fractionation radiotherapy) was not scored as distant progression. However, these were included in the PFS calculation. The time to reach each end point was defined from the start of HIGRT to the time of progression/death. Six patients underwent a second course of HIGRT for limited distant progression. The patient-based analysis focused only on the first course. For lesion-based analysis, the only end point evaluated was lesion control (LeC), which was defined as no increase in lesion size $\geq 20\%$ on single dimensional axial measurement. All lesions were included in LeC regardless of whether they were treated during the first or a subsequent course of HIGRT. All end points were estimated using the Kaplan-Meier method.

Univariate analysis (UVA) was performed using the log-rank test. A p value < 0.05 was considered statistically significant for UVA. However, given the small patient numbers and the heterogeneity of the patient population, subset analyses are considered exploratory. Multivariate analysis was not performed because of the limited number of events.

RESULTS

Twenty-five patients with oligometastatic NSCLC met the inclusion criteria. Eleven patients were treated on protocol from December 20, 2004, to July 9, 2008. Fourteen patients were treated off protocol, 12 of whom were treated after July 9, 2008. Patient and tumor characteristics are given in Table 1. The median age was 66 years. Eleven patients had adenocarcinoma and 14 had other NSCLC histologies. Fifteen patients received HIGRT after presenting with metastatic disease (stage IV) as their initial diagnosis, while 10 initially had stage III or lower disease and subsequently developed metastases that prompted HIGRT.

Treatment details can be found in Table 2. Nineteen (76%) patients received systemic therapy before HIGRT, usually one regimen comprising two systemic agents. Sixteen patients (84%) received a platinum-based doublet as part of their prior systemic therapy, most commonly carboplatin and paclitaxel (10 patients). Eighteen patients received HIGRT to all sites of disease and seven received treatment only to active (growing and/or PET-positive) disease sites. A median of 2 (range, 1–5) oligometastatic lesions were treated per patient during their first course of HIGRT. The treatment sites are listed in Table 1.

HIGRT was well tolerated with acceptable toxicity. Five patients experienced grade 2 toxicity including two patients with chest wall pain (one from rib fracture and one without radiographic evidence of fracture), two patients with acute dysphagia, and one patient with fatigue. Two patients experienced grade 3 toxicity: one patient had fatigue interfering with activities of daily living, which was significantly improved within 2 months, and another patient had radiation pneumonitis requiring steroids and a hospital admission.

With a median follow of 14 months, 7 of 25 patients (28%) had no evidence of progression. Five of these seven patients had more than 15 months of follow-up without evidence of progression (range, 15.8–25.7 months). Six patients experienced in-field local progression. One patient of these six had isolated local progression in a HIGRT-treated

TABLE 1. Patient and Tumor Characteristics

Characteristic	
No. of patients	25
Age, yr (range)	66.2 (43.5–79.2)
Histology	
Adenocarcinoma	11
Squamous cell	6
Carcinoma	
Large cell	2
Other or NSCLC NOS	6
Initial stage	
I	3
II	1
III	6
IV	15
Lesion size (cm)	
Mean	3.2
Median (range)	2.65 (0.6–9.6)
Interquartile range	1.8–4.2
Lesions treated per patient	
Median (range)	2 (1–5)
Lesion location ($n = 62$)	
Lung	28
Adrenal gland	8
Lymph node	10
Liver	5
Brain	5
Bone	4
Spleen	1
Muscle	1

NSCLC, non-small cell lung cancer; NOS, not otherwise specified.

lesion, and the remaining five patients had combined distant and local progression (in all cases, local progression was documented at the same time or after distant progression). The 12 and 18 months LC of all treated lesions for a patient undergoing their first course of HIGRT were 74.4% (95% confidence interval [CI] 51.1–88.9%) and 66.1% (95% CI 41.1–84.4%), respectively. The 12 and 18 months DC rates were 45.3 (95% CI 26.7–65.2%) and 31.7% (95% CI 16.1–53.0%), respectively (Table 3). Seventeen patients experienced distant progression, including 12 patients without evidence of local progression. Six of these patients had limited distant progression and were treated with a second course of HIGRT. Seventeen patients received systemic therapy during the follow-up period after HIGRT. In 15 of these patients, systemic therapy was initiated after documented post-HIGRT disease progression.

Median OS and PFS were 22.7 and 7.6 months, respectively. The 12 and 18 months OS were 81.1% (95% CI 58.7–92.9%) and 52.9% (95% CI 28.6–75.8%), respectively. Corresponding PFS values were 42.0 (95% CI 24.1–62.2%) and 28.0% (95% CI 13.5–49.4%), respectively (Table 3, Figures 1A, B). On UVA, more than two sites treated with HIGRT ($p = 0.0020$), prior systemic therapy ($p = 0.025$), progressive disease after prior systemic therapy (versus con-

TABLE 2. Treatment Details

Radiation therapy	
Fractionation schemes (total dose/number of fractions)	
Extracranial	No. of lesions
50 Gy/10	28
24 Gy/3	9
30 Gy/3	8
42 Gy/3	6
70 Gy/20	4
36 Gy/3	2
Intracranial	
18 Gy/1 + WBRT	5
Median SED in 2 Gy fractions for extracranial lesions (range)	64.6 Gy (37.6–73.9 Gy)
Systemic therapy	
Prior systemic therapy	
Yes	No. of patients
No	19
Median prior systemic lines ^a (range)	6
Median prior systemic agents ^a (range)	1 (1–3)
	2 (1–4)

SED is the standard equivalent dose which converts hypofractionated radiation into an equivalent dose using standard 2 Gy fractions.
^a In subset of patients receiving prior systemic therapy.
 WBRT, whole brain radiation therapy.

TABLE 3. Patient Outcomes

	12 mo (95% CI)	18 mo (95% CI)
Outcome		
Overall survival	81.1% (58.7–92.9%)	52.9% (28.6–75.8%)
Progression-free survival	42.0% (24.1–62.2%)	28.0% (13.5–49.4%)
Distant control	45.3% (26.7–65.2%)	31.7% (16.1–53.0%)
Local control ^a (patient based)	74.4% (51.1–88.9%)	66.1% (41.1–84.4%)
Lesion control ^b (lesion based)	85.0% (70.0–93.3%)	65.3% (49.4–81.7%)

^a Local control requires all treated lesions within an individual patient to be controlled.
^b Lesion control requires an individual lesion to be controlled.
 CI, confidence interval.

solidative HIGRT for partial response or stable disease) ($p = 0.04$), and nonadenocarcinoma histology ($p = 0.014$) were associated with worse PFS. Treatment of active disease only (i.e., HIGRT omitted for sites of radiographically evident disease that was not growing or PET-positive) ($p = 0.77$), treatment off protocol ($p = 0.94$), history of prior radiotherapy ($p = 0.58$), HIGRT for metachronous metastases (presented with initial stage I–III) ($p = 0.18$), intracranial disease at HIGRT ($p = 0.07$), and sum of the maximum axial diameter of each treated lesions $>$ median ($p = 0.095$) were not significant. For patients who experienced LC of all treated lesions, the 12 and 18 months OS were 88.2 (95% CI 62.8–97.2) and 68.0% (95% CI 37.2–88.3) compared with 66.7 (95% CI 26.7–91.2) and 22.2% (95% CI 3.3–71.7) for those with local failure ($p = 0.28$, log-rank). Importantly, this

suggests that ability to attain LC may improve survival in patients with metastatic NSCLC.

Lesion-based analysis revealed that 62 individual oligometastatic lesions were treated. Three lesions were excluded from analysis, two because of lack of follow-up imaging and one because it represented reirradiation of the primary tumor site. The median lesion size was 2.65 cm (range, 0.6–9.6 cm). The 12 and 18 months LeC for all treated lesions were 85.0% (95% CI 70.0–93.3) and 65.3% (95% CI 49.4–81.7), respectively.

For extracranial sites, the median total dose was 50 Gy (range, 24–70 Gy) and the median dose per fraction was 5 Gy (range, 3.5–14 Gy). The 12 and 18 months LeC were 86.4% (95% CI 70.6–94.4%) and 70.7% (95% CI 51.7–84.4%), respectively, for extracranial oligometastatic sites. The standard equivalent dose (SED) in 2 Gy fractions was calculated for all extracranial lesions.²⁴ The median SED for extracranial lesions was 64.6 Gy (range, 37.6–73.9 Gy). The 50 Gy in 5 Gy fraction regimen represents an SED in 2 Gy fractions of 64.6 Gy. For three-fraction treatment regimens, fraction sizes ≥ 14 Gy yield an SED above 64.6 Gy, while fraction sizes ≤ 12 Gy yield SED below 64.6 Gy. There was improved ($p = 0.04$) LeC with SED ≥ 64.6 Gy (Figure 2). The 12 and 18 months LeC were 91.6% (95% CI 70.0–98.3%) and 83.3% (95% CI 56.1–95.0%) for SED ≥ 64.6 Gy versus 78.6 (95% CI 50.6–92.8%) and 52.4% (95% CI 26.1–77.2%) for SED < 64.6 Gy. There was no relationship between maximum axial lesion diameter greater than the median of 2.65 cm and LeC ($p = 0.76$). For the five intracranial lesions, all patients received whole brain radiation therapy followed by stereotactic radiosurgery to 18 Gy in one fraction. The 12 months LeC was 80% (95% CI 31.1–97.2%).

DISCUSSION

To the best of our knowledge, this is the first report of patients with limited volume metastatic NSCLC treated to all sites of active cancer with HIGRT. Our data show that HIGRT for selected patients can be delivered safely and is associated with promising clinical outcomes. Our results are consistent with prior surgical studies, which have demonstrated some long-term survivors among patients with metastatic NSCLC undergoing resection of metastatic disease. For example, Wronski et al.¹⁶ reported 5-year survival rates of 13% in a series of 231 patients undergoing resection of NSCLC brain metastases. Tanvetyanon et al.¹⁷ recently performed a pooled analysis of 10 publications including 112 patients undergoing adrenalectomy for metastatic NSCLC and reported 5-year OS of 25 to 26%. These promising outcomes with metastasectomy influenced our decision to offer nonsurgical local therapy to patients with limited volume metastatic disease.

We began to offer HIGRT for patients with limited volume NSCLC metastases after analyses demonstrated that NSCLC patients commonly present with only a few sites of metastases and that the majority of these patients progress first in these known metastatic sites.^{12,13} These data suggest that at least a subset of stage IV NSCLC exhibit characteristics of the oligometastatic state. A tenet of the oligometastatic

FIGURE 1. A, Overall survival for all patients with 95% confidence intervals (CI). B, Progression-free survival for all patients with 95% CI.

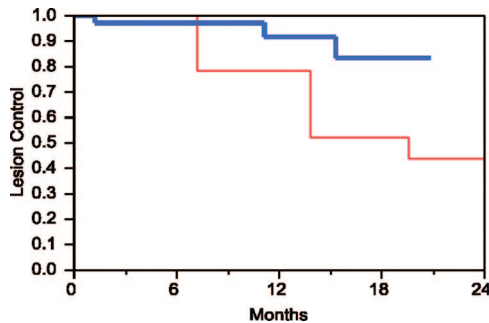
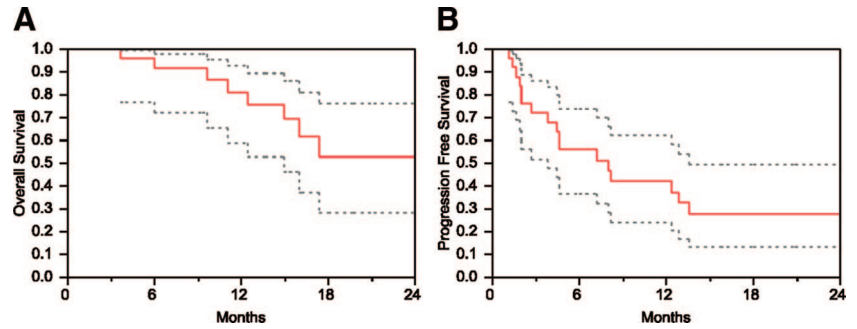


FIGURE 2. Extracranial lesion control for patients with standard equivalent dose ≥ 64.6 Gy in 2 Gy fractions (bold line) and < 64.6 Gy (thin line).

static state is that local therapy may improve PFS and potentially render patients with long-term disease-free survival. In the current study, a trend toward improved survival was observed in patients who attained LC of all HIGRT-treated lesions compared with those with local progression.

Outcomes for patients included in this series are encouraging, especially in light of the fact that 19 patients (76%) previously received first-line systemic therapy and 13 (52%) had documented progression on their most recent systemic regimen before HIGRT. In addition, the median age of our patients was older than patients included on most randomized trials of first-line systemic therapy.^{4,5,8} Despite these unfavorable characteristics, the OS and PFS seem improved compared with outcomes with first- or second-line systemic therapy alone. Because 15 of 17 patients received post-HIGRT systemic therapy after developing disease progression, the PFS results are not skewed by effects of additional systemic therapy. While these patients represent a select subset based on their eligibility for HIGRT, other investigators have reported that more than 50% of patients presenting to a university hospital with advanced NSCLC meet such criteria at some point during their disease course.¹²

One of our primary goals of offering HIGRT for limited volume metastatic NSCLC was to prolong PFS by offering metastasis-directed therapy with limited toxicity—in effect offering another “line” of therapy. Further follow-up is needed to determine the duration of long-term control as their median follow-up is 14 months (range, 3.6–31.7 months). However, the fact that 28% of patients are without evidence of disease is promising and suggests that properly selected patients can benefit from nonsurgical metastasis-directed

therapy. In addition, toxicity was fairly mild and infrequent in patients treated with HIGRT on our study, which is an important consideration that should be weighed against the toxicity of additional lines of chemotherapy.

Our study is limited by the relatively small sample size hindering the power to accurately evaluate the influence of patient- and treatment-related factors on outcome. In addition, metastatic NSCLC is a heterogeneous population, and the efficacy of HIGRT is likely influenced by disease burden, sites of metastases, age, performance status, and number of prior systemic therapy regimens/response to prior systemic therapy. Furthermore, our study population was heterogeneous as it included patients with both synchronous and metachronous metastatic disease who received a variety of systemic and local therapies before HIGRT treatment. Although synchronous metastatic presentation, receipt of prior radiotherapy, and treatment of active disease only were insignificant on UVA, these results must be interpreted with caution due to the small sample size. Finally, different dose/fractionation schemes were used, although we attempted to compensate for this using the SED in 2 Gy fractions. In the context of these limitations, larger prospective studies in this patient population are warranted to determine which subsets of patients with oligometastatic NSCLC are most likely to benefit from HIGRT.

Currently, the North Central Cancer Treatment Group is investigating the role of consolidation radiation therapy by randomizing patients with limited volume NSCLC to observation versus radiation to known metastatic sites after four to six cycles of chemotherapy. This study will assess the role of the addition of HIGRT to systemic therapy in the upfront treatment setting.

CONCLUSIONS

This study demonstrates that HIGRT for oligometastatic NSCLC is associated with minimal toxicity and a high rate of LC for treated lesions. Short-term survival rates are favorable compared with studies using systemic therapy alone. Further follow-up is needed to determine whether long-term PFS and OS can be achieved in this patient population. Prospective studies are required to more accurately determine the safety and efficacy of HIGRT in oligometastatic NSCLC and to better identify subpopulations of patients who are most likely to benefit from local therapy.

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