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Computed Tomography-Guided Interstitial High-Dose-Rate Brachytherapy in the Local Treatment of Primary and Secondary Intrathoracic Malignancies

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Introduction: Image-guided interstitial (IRT) brachytherapy (BRT) is an effective treatment option as part of a multimodal approach to the treatment of isolated lung tumors. In this study, we report our results of computed tomography-guided IRT high-dose-rate (HDR) BRT in the local treatment of inoperable primary and secondary intrathoracic malignancies.

Methods: Between 1997 and 2007, 55 patients underwent a total of 68 interventional procedures for a total of 60 lung lesions. The median tumor volume was 160 cm^3 (range, 24–583 cm^3). Thirty-seven patients were men and 18 were women, with a median age of 64 years (range, 31–93 years). The IRT-HDR-BRT delivered a median dose of 25.0 Gy (range, 10.0–32.0 Gy) in twice-daily fractions of 4.0 to 15.0 Gy in 27 patients and 10.0 Gy (range, 7.0–32.0 Gy) in once-daily fractions of 4.0 to 20.0 Gy in 28 patients.

Results: The median follow-up was 14 months (range, 1–49 months). The overall survival rate was 63% at 1 year, 26% at 2 years, and 7% at 3 years. The local control rate for metastatic tumors was 93%, 82%, and 82% and for primary intrathoracic cancers 86%, 79%, and 73% at 1, 2, and 3 years, respectively. Pneumothoraces occurred in 11.7% of interventional procedures, necessitating post-procedural drainage in one (1.8%) patient.

Conclusions: In patients with inoperable intrathoracic malignancies, computed tomography-guided IRT-HDR-BRT is a safe and effective alternative to other locally ablative techniques.

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For patients with localized primary lung cancer or oligometastatic pulmonary disease, surgical resection is widely recognized as the only potentially curative treatment and has shown clear evidence to improve survival.[1–4] Nevertheless, a considerable proportion of patients are not considered candidates for lung surgery for medical and technical reasons. In other cases, patients may refuse surgical intervention. For these patients, minimally invasive therapies have attained increasing utilization, mostly in the form of hyperthermic techniques such as radiofrequency ablation (RFA) and laser-induced thermotherapy (LITT).[5–11]

Computed tomography (CT)-guided interstitial (IRT) high-dose-rate (HDR) brachytherapy (BRT) enables the highly conformal administration of very large radiation doses to a circumscribed volume. This modality has proven efficacious in the treatment of both primary and secondary cancers at various sites.[12–21] CT-guided IRT-BRT seems to be an attractive alternative to other local interventional treatment techniques because it ensures not only accurate image guidance but also precisely predictable energy deposition. Nevertheless, a paucity of outcome data exists regarding the treatment of intrathoracic tumors with image-guided IRT-HDR-BRT.[13,22] The aim of this review is to report our clinical experience with CT-guided IRT-HDR-BRT in the local treatment of inoperable intrathoracic malignancies.

PATIENTS AND METHODS

Patients

Between January 1997 and December 2007, 55 patients were treated with CT-guided IRT-HDR-BRT for primary or secondary intrathoracic tumors. All patients included were not surgical candidates secondary to excessive medical comorbidities, previous lung surgery, or refusal to undergo surgical procedures.

The study population included 37 men and 18 women, with a median age of 64 years (range, 31–93 years). Patients

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with primary intrathoracic cancers (non-small cell lung cancer [NSCLC] and malignant pleural mesothelioma [MPM], $n = 41$, 74.5%) and patients with pulmonary metastases ($n = 14$, 25.5%) were treated. Patients with primary cancers had initial histologic confirmation of malignancy in all cases. Among patients with pulmonary metastases, biopsy confirmation was performed in eight patients and omitted in six cases.

All patients with metastatic disease had progressive metachronous lesions with the underlying primary malignancy treated at the time of BRT. In patients with primary cancers, treatment was performed for progressive or local recurrent disease. Among those, 13 (31.7%) patients had undergone thoracic surgery and 29 (70.7%) had received external beam radiotherapy (EBRT). Thirty-one patients (75.6%) had undergone chemotherapy (ChT) as a part of their primary treatment regimen.

The lesions treated by BRT had a median volume of 160 cm^3 (range, 24–583 cm^3) with a mean value of 211 cm^3. Pretreatment evaluation was based on contrast-enhanced chest CT in all patients. In four (7.2%) patients treated since 2006, fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT was also performed. Invasive procedures were not part of staging modalities. Lesion-specific treatment before BRT consisted of thoracic EBRT with median 36.0 Gy (range, 20–90 Gy) in 36 (65.4%) patients and multiple cycles of different ChT regimes in 49 (89.0%) patients. No patient received ChT or additive EBRT in conjunction with BRT, and no patient received further EBRT to the implant sites following BRT. The median Karnofsky Performance Score (KPS) at the time of BRT was 80 (range, 60–100). Details of the treated lesions are presented in Table 1.

Brachytherapy

Our technique of CT-guided IRT-BRT has been described in detail elsewhere.[12] In short, catheter placement was performed using CT-guidance (Somatom Plus 4, Siemens, Erlangen, Germany). Round-tip plastic catheters of 6F diameter and 200 mm length (OncoSmart ProGuide Round Needle-Nucletron, Veenendaal, The Netherlands) were implanted using a rigid tungsten alloy obturator of the same length and diameter (OncoSmart ProGuide Obturator-Nucletron, Veenendaal, The Netherlands). This allowed for maintenance of catheter integrity and stability during insertion. After removal of the obturator, positional control was obtained by generating CT images with the catheter in situ. Thus, maximum insertion depth, direction, and position of the implanted catheters were estimated by interactive CT scanning. Number, geometrical alignment, and distance between the catheters were dependent on the size, shape, and location of the tumor. For spherical lesions up to 3 cm in diameter, one central catheter was usually utilized. In larger or nonspherical tumors, multiple catheters were used. For lesions adherent to the chest wall, this allowed, in principle, the insertion of more applicators than those located centrally. Although a parallel catheter alignment without course intersections inside the implanted volume is ideal, anatomy-oriented treatment planning allowed for individual catheter configurations. The goal was to have the largest distance between catheters to be not more than 3 cm.

After catheter placement, a contrast-enhanced (iodide contrast media: Imeron 300, Bracco Imaging, Konstanz, Germany) spiral CT (slice thickness, 3.0 mm; table movement, 3.0 mm) of the treatment area was acquired for three-dimensional (3D) treatment planning.[23] Tumor demarcation with corresponding target volume (PTV) delineation was performed using ProSoma virtual simulation software (Medcom GmbH, Darmstadt, Germany). For 3D-dose optimization,[23] performed using Plato BPS (Nucletron, Veenendaal, The Netherlands), active source dwell positions were selected along the catheters to ensure placement inside the PTV and to assure a location at 5.0 to 10.0 mm below the PTV surface. The dose distribution was normalized relative to the calculated mean dose value on the PTV surface with the reference dose specified as the 100% value (Figures 1*A, B*).

Treatment schemes and dose restrictions were individually determined depending on the tumor location to spare adjacent risk structures. Although treatment plan optimization was carried out with respect to conformity, maximum single spinal cord doses $\leq$8 Gy with maximum total spinal cord doses $\leq$20 Gy were our institutional constraints in radiation-naive patients. For preirradiated sites, treatment schemes and restrictions were determined after careful inspection of the dose-volume histogram (DVH) to ensure cumulative spinal cord dose $\leq$60 Gy. For preservation of lung function, $\leq$5 Gy to $\geq$70% of the ipsilateral lung served as the specified dose limit. Treatments were performed over consecutive days with an interfractional interval of at least 6

TABLE 1. Details of the Lesions Treated With Interstitial Brachytherapy

	No. of Patients (%)	No. of Lesions (%)	No. of Interventions (%)
Tumor entity			
Colorectal carcinoma	2/55 (3.6%)	2/60 (3.3%)	2/68 (2.9%)
Soft-tissue sarcoma	7/55 (12.7%)	7/60 (11.6%)	8/68 (11.7%)
Hypernephroid renal carcinoma	2/55 (3.6%)	2/60 (3.3%)	2/68 (2.9%)
Metastases of NSCLC	2/55 (3.6%)	6/60 (10.0%)	7/68 (10.2%)
Primary NSCLC	36/55 (65.4%)	36/60 (60.0%)	40/68 (58.8%)
Primary malignant pleural mesothelioma	5/55 (9.0%)	6/60 (10.0%)	8/68 (11.7%)
Unknown primary	1/55 (1.8%)	1/60 (1.6%)	1/68 (1.4%)

NSCLC, non-small cell lung cancer.

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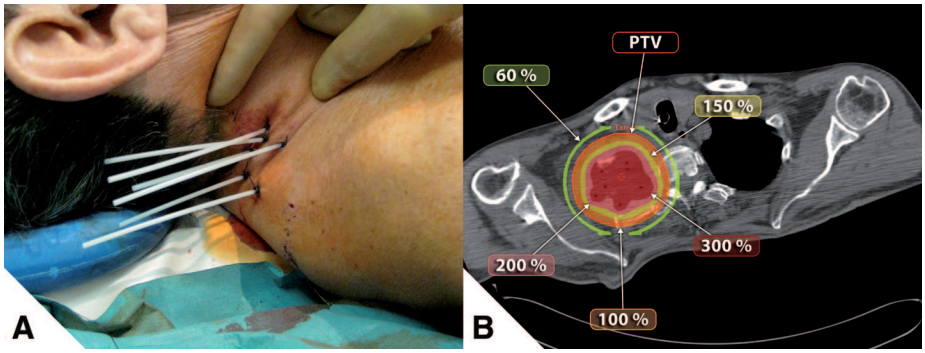

FIGURE 1. A 74-year-old man with adenocarcinoma of the right-sided superior sulcus. The radiation-naive patient rejected surgery and radiochemotherapy and was treated by sole interstitial high-dose-rate brachytherapy receiving four fractions of 8.0 Gy over 2 consecutive days to a total physical dose of 32.0 Gy. *A,* Image of the interstitial implant after completion of the computed tomography (CT)-guided catheter insertion procedure. The six flexible catheters are fixed at the entrance points on the skin surface by surgical suture. *B,* Axial CT image with superimposed two-dimensional (2D)-isodose distribution after CT-based three-dimensional (3D)-treatment planning for a plane lying centrally to the target extension. The color gradation represents red = 300% isodose = 24.0 Gy, pink = 200% isodose = 16.0 Gy, yellow = 150% isodose = 12.0 Gy, orange = 100% isodose = 8.0 Gy, and light green = 60% isodose = 4.8 Gy. The tumor volume is red delineated (PTV) with the six implanted catheters identifiable as dark dots inside it. The central tumor volume is covered at least by the 300% isodose and receives total doses of at least 96.0 Gy within 48 hours. The spinal cord is only marginally covered by the 60% isodose and receives a fractionated total dose far below 20.0 Gy.

hours. Catheters were removed immediately after the last fraction. All irradiations were performed using an Iridium-192 (^{192}Ir) HDR-afterloading system (microSelectron-HDR, Nucletron, Veenendaal, The Netherlands) with an apparent initial source activity of approximately 370 GBq.

Assessment and Statistical Analysis

Treatment assessment was based on tumor volume response. This method was deemed to be more accurate than a two-dimensional (2D) diameter description[24] and defined according to modified World Health Organization response criteria for solid tumors[25] at 8 to 12 weeks after BRT. Any decrease of more than 30% in tumor volume was interpreted as partial response (PR), any increase of more than 20% as progressive disease (PD), and no measurable lesions (except CT findings of residual scar tissue with no contrast enhancement) were considered as complete response (CR). Stable disease (SD) met neither PR nor PD criteria. Tumor volume was measured using the IPS module of PLATO BPS (Nucletron, Veenendaal, The Netherlands) and the virtual simulation software ProSoma (MedCom GmbH, Darmstadt, Germany) based on contrast-enhanced CT scans. After the initial treatment evaluation, further follow-up was complemented by contrast-enhanced CT at 8- to 12-week intervals thereafter. Not all patients returned for every scheduled examination; however, data collection allowed external CT reading or information acquisition from referring physicians.

Statistical analyses were performed using the Kaplan-Meier method[26] and comparisons made using the log-rank test.[27] The time point of treatment initiation was the date of the first BRT procedure. The end point of interest for overall survival (OS) was death from any cause. The end point of interest for local control (LC) was local failure after SD, PR, or CR. In the absence of pathologic confirmation of malignancy, local failure was defined as tumor growth or regrowth per CT scan compared with the previous CT scan. As some patients had more than one BRT procedure, survival analysis was performed among all patients with respect to each patient's first BRT procedure, whereas complications were analyzed with respect to all performed interventions. For matching purposes of the different treatment schemes included in our study, the EQD_2 was calculated. EQD_2 is the equivalent dose as if the treatment was given with a 2.0 Gy conventional fractionation based on the following formula:

$$EQD_2 = nd\frac{\left(1+\frac{d}{(\alpha/\beta)}\right)}{\left(1+\frac{2}{(\alpha/\beta)}\right)}$$

where α/β = the ratio of the tissue, n = the number of BRT fractions, and d = the dose per BRT fraction. For our calculations, the α/β ratio was taken to be 10 Gy.[28]

RESULTS

Radiotherapy Details

A total of 68 interventional procedures were performed on 55 patients for the treatment of 60 tumors (Table 1). Eleven (20.0%) patients received multiple implants. Of those, seven patients received a second or third implant for local disease progression, four patients a second implant for new intrapulmonal metastases, and one patient a second implant for a new contralateral MPM. All patients received treatment for only one single lesion per interventional session with no patient having multiple simultaneous sites implanted. All implants were performed under local anesthesia with mepi-

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vacaine hydrochloride and conscious sedation with midazolam plus pethidine intravenously.

With respect to each patient's first BRT procedure, 27 (49.0%) patients received twice-daily fractions of median 6.0 Gy (range, 4.0–15.0 Gy) and 28 (50.9%) patients once-daily fractions of median 8.0 Gy (range, 4.0–20.0 Gy) to a median total HDR dose of 20.0 Gy (range, 7.0–32.0 Gy). When expressed as EQD_2, the median dose to the implanted sites was 29.8 Gy.

In addition to the prescribed reference dose, the D_{90}, as determined by the DVH of the PTV, is reported. Similarly, dose heterogeneity was specified by V_{100}, V_{150}, and V_{200}. Median values for our series were V_{100} = 88.5% (range, 63.0–98.0%), V_{150} = 58.0% (range, 42.0–80.0%), and V_{200} = 40.0% (range, 27.0–63.0%). The median achieved D_{90} value was equivalent to 95.0% (range, 44.0–127.0%) of the prescribed reference dose.

Response, Survival, and Disease Control

The overall response (defined as the sum of CR and PR) at median 11 weeks after BRT was 67.2% (37 patients) with 10 (18.1%) patients exhibiting CR and 27 (49.0%) PR. Of the remaining 18 patients, 15 (27.2%) had SD, and three (5.4%) had PD. Metabolic responses by FDG-PET/CT were available in all four patients with pretreatment PET-based evaluation but were not considered in the scoring of responses. In all cases, there was complete resolution of metabolic activity with the patients exhibiting partial radiological response.

The median OS was 15.5 months with an OS rate of 63% at 1 year, 26% at 2 years, and 7% at 3 years (Figure 2). The estimated overall LC was 88% at 1 year, 81% at 2 years, and 75% at 3 years. The LC rate for metastatic tumors was 93%, 82%, and 82% and for primary intrathoracic cancers 86%, 79%, and 73% at 1, 2 and 3 years, respectively (Figure 3).

Twenty-three of 41 (56.0%) patients with primary intrathoracic tumors experienced extrapulmonary disease progression after a median of 5.4 months (range, 1–35 months), and 13 (31.7%) died as a consequence. Of the 14 patients treated for secondary pulmonary malignancies, eight (57.1%) patients developed extrapulmonary disease progression after a median of 11.5 months (range, 7–21 months). Six patients (42.8%) died as a consequence. Intrapulmonary disease progression was the cause of death in four (7.2%) patients. In addition, there were 31 (56.3%) deaths of intercurrent causes (myocardial infarction, pulmonary embolism, cerebrovascular bleeding, hemorrhage of the digestive tract, septic shock, alcohol-induced hepatic failure, general deterioration, and suicide). Overall follow-up ranged from 5 weeks to 49 months (median, 14 months), and 35 patients reached the 1-year, 12 patients the 2-year, and three patients the 3-year follow-up. One (1.8%) patient was alive at the time of reporting (i.e., March 2010).

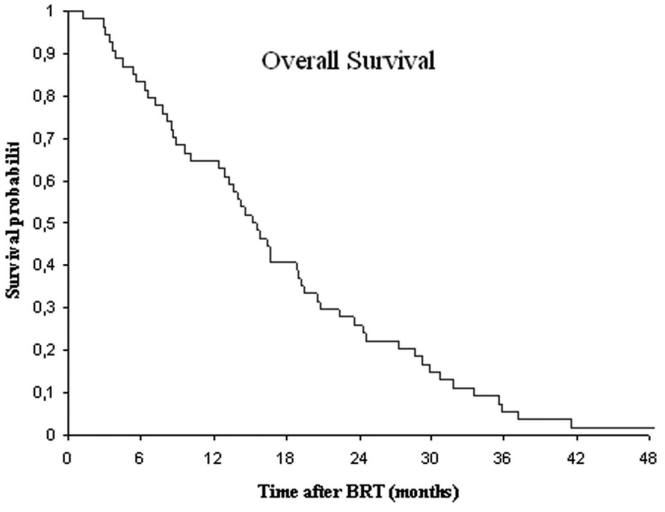

FIGURE 2. Kaplan-Meier curve for overall survival after interstitial brachytherapy.

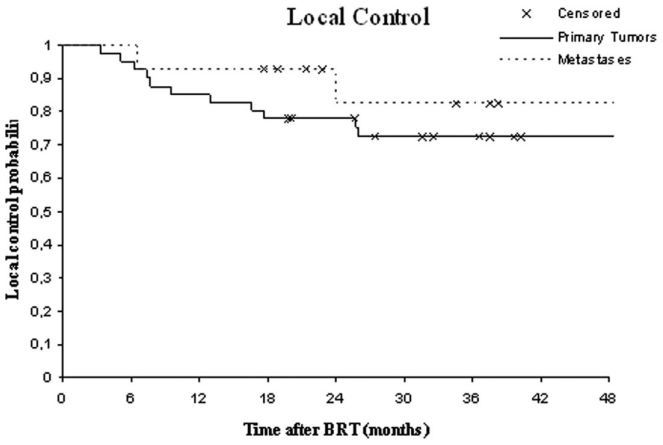

FIGURE 3. Kaplan-Meier curves for local control after interstitial brachytherapy.

Prognostic Factors

The variables considered for analysis were median EQD_2 (<29.8 Gy versus ≥29.8 Gy), median pretreatment tumor volume (<160 cm^3 versus ≥160 cm^3), and relative tumor volume reduction ($[V_{\text{before BRT}} - V_{\text{after BRT}}]/V_{\text{before BRT}}$, <85% versus ≥85%). In univariate analysis, we failed to show a statistically significant correlation between survival and tumor volume reduction, pretreatment tumor volume, or applied treatment dose.

With respect to LC failure, we could confirm tumor volume reduction to have an impact on local tumor control with a rate of 84% at 12 months after volume reduction less than 85% versus 100% for volume reduction ≥85% (p = 0.048). In contrast, we failed to show a statistically significant correlation between pretreatment tumor volume or applied treatment dose and achieved LC rate.

In our series, complete tumor remissions were accomplished only in tumors ≤110 cm^3 (Figure 4). Taking the limit volume of 110 cm^3 as a threshold, we found that LC at 12 months was 84% for lesions less than 110 cm^3 versus 88% for lesions ≥110 cm^3 (p = 0.397). This difference was not statistically significant. Additionally, there was no statistically significant correlation between response rates and applied treatment dose.

Complications

Sixteen (23.5%) acute adverse events occurred in 68 interventional procedures with no procedure-related lethal

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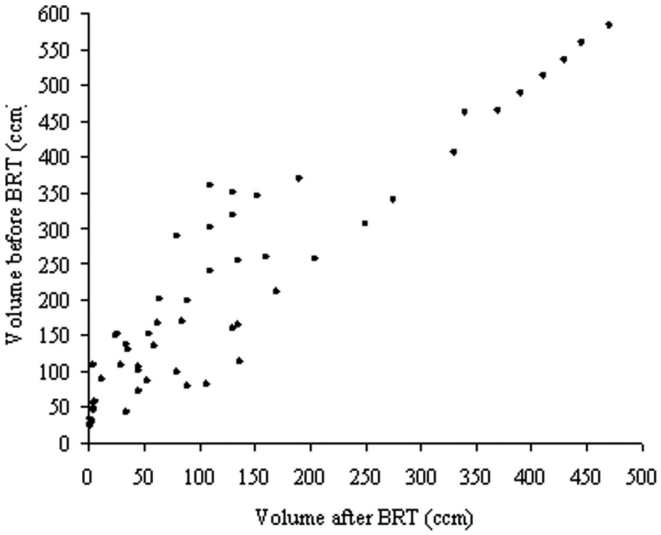

FIGURE 4. Relationship of tumor volumes before and after interstitial brachytherapy for 55 patients with respect to each patient's first brachytherapy (BRT) procedure.

TABLE 2. Complications of Interstitial Brachytherapy

Complication (Type)	No. of Interventions (%)	Extent
Pneumothorax (acute)	7/68 (10.2%)	Minor (self-resolving)
	1/68 (1.4%)	Major (requiring chest tube)
Cough (acute)	5/68 (7.3%)	Minor (conservatively treated)
Pneumonia (acute)	1/68 (1.4%)	Major (requiring IV antibiotics)
Upper extremity edema (acute)	1/68 (1.4%)	Minor (conservatively treated)
Upper extremity dysesthesia (acute)	1/68 (1.4%)	Minor (conservatively treated)

IV, intravenous.

events and no late toxicities (Table 2). Eight (11.7%) of the complications were pneumothoraces, all of which developed after catheter removal. Seven were self-limiting and associated with the treatment of peripheral tumors. One required chest-tube drainage and developed after treatment of a centrally located tumor. One case of acute upper extremity edema and one case of acute upper extremity dysesthesia were associated with procedures in the ipsilateral superior sulcus. Both events had minor sequelae and resolved completely with conservative care. One case of major pneumothorax and one case of acute-onset pneumonia required hospitalization for 15 and 21 days, respectively. There was no discernible statistical correlation between complication rates and pretreatment tumor volume or applied treatment dose. The median length of hospital stay was 5 days (range, 3–21 days).

DISCUSSION

Surgical resection is widely considered the preferred treatment for localized primary lung cancer and oligometastatic pulmonary disease.[1–4] However, in practice, there is a subgroup of patients who are not candidates for this approach.[22] Treatment options for these patients include ChT[29,30] with or without EBRT.[31–34] Recently, improvements in survival have been achieved with the implementation of targeted therapies[35,36] using a multimodal approach. Nevertheless, outcomes associated with noninvasive modalities themselves remain dismal.[35–37] In this challenging clinical setting, minimally invasive approaches have drawn increasing attention, especially hyperthermal techniques such as RFA and LITT.[5–8,10,11] Unfortunately, high-complication rates have been reported with these techniques.[5–8,10,38]

CT-guided IRT-HDR-BRT has proven efficacious in the treatment of various primary and secondary malignancies.[12–21] Compared with hyperthermal techniques such as RFA and LITT, factors such as tissue inhomogeneity, thermal conductivity, and tumor perfusion do not prohibit complete ablation.[5–7,10] Moreover, the maximum lesion size for successful radioablation has not been determined. There is a paucity of data on the use of image-guided IRT-HDR-BRT in the treatment of intrathoracic tumors not amenable to surgery. Imamura et al.[13] treated 12 patients with inoperable primary lung cancer by CT-guided ^{192}Ir-HDR-BRT of 20 to 25 Gy. The mean irradiated tumor volume was 37.0 ml, and the achieved response rate was 58.3% with 25% of patients showing CR, 33% PR, and 42% SD. No patient experienced severe complications. Peters et al.[22] treated 30 patients with 83 primary or secondary pulmonary malignancies by single-fraction CT-guided ^{192}Ir-HDR-BRT in 50 therapy sessions. The prescribed dose of 20 Gy was referred to a mean tumor diameter of 25.0 mm, and the overall response rate was 36% with 0% of evaluated lesions exhibiting CR, 36% showing PR, and 42% SD. The LC rate was 91% at 12 months and 86% at 20 months. Six patients (12% of interventions) developed marginal pneumothoraces and one patient (1% of interventions) a major pneumothorax. Our series of 55 patients refers to a median tumor volume of 160 cm^3 with a complete and overall response rate to BRT of 18% and 67%, respectively. The overall local tumor control was 88% at 1 year, 81% at 2 years, and 75% at 3 years with corresponding rates for the subgroup of metastatic tumors of 93%, 82%, and 82%, respectively. These data are similar to those of other HDR-BRT series[13,22] and compare favorably with recently published results of RFA[9] and LITT.[11]

The rate of complications in our series was independent of tumor volume and lower than that reported for hyperthermal techniques.[5–8,10,11] Yasui et al.[6] reported minor pneumothoraces in 35% of sessions, pneumothoraces necessitating a chest tube in 7% of sessions, and an overall complication rate of 76% among 35 patients receiving 54 RFA treatments for 99 thoracic tumors with a median diameter of 19.5 mm. Vogl et al.[10] treated 30 patients with primary lung cancers or pulmonary metastases using LITT. None of the evaluated lesions had a diameter more than 30.0 mm, and the rate of pneumothoraces was 9.8%. Rosenberg et al.[11] reported on 64 patients treated by LITT for pulmonary metastases with a median size of 20.0 mm. Pneumothoraces necessitating drainage developed in 5% of treatments. In our series, we had a 1.4% rate of major pneumothoraces and 10.2% rate of minor pneumothoraces, rates that parallel the results of Peters et al.[22]

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Compared with hyperthermal ablation data, the LC achieved in our series was independent of tumor size. Taking our median tumor volume of 160 cm^3 as a threshold, we found that LC at 12 months was 93% for lesions less than 160 cm^3 versus 96% for lesions $\geq$160 cm^3 ($p = 0.236$). Rosenberg et al.[11] reported a tumor progression rate of 33% for tumors larger than 40.0 mm and a tumor progression rate of 19% for tumors smaller than 15.0 mm. The median progression-free intervals were 1.9 months and 5.0 months, respectively. As a matter of principle, no limitations exist regarding the target volume for IRT-HDR-BRT. The successful application of thermal techniques, on the other hand, correlates with the size of the lesion undergoing treatment. Jin et al.[8] evaluated 21 patients with primary and secondary lung cancers treated by RFA, showing that the mean diameter of completely ablated lesions was 28.0 mm, whereas for partially ablated tumors, it amounted 49.0 mm.

With respect to the applied treatment dose, Willner et al.[39] were able to show a significant correlation between radiation dose and local tumor control. The authors found a clearly improved effect with EBRT doses $\geq$70 Gy in the primary treatment of NSCLC. Furthermore, Martel et al.[40] estimated that normally fractionated doses of more than 84 Gy are needed to achieve a 50% probability of local tumor control in the treatment of NSCLC. Our data suggest that the delivered treatment dose has no significant impact on LC, neither for the subgroup of metastatic lesions nor in the treatment of primary cancers.

Similar to Peters et al.,[22] we experienced lesions which exhibited a PR to treatment with no further changes over a long follow-up period. Nevertheless, biopsies were not routinely performed in association with follow-up imaging. As almost half of our patients ($n = 27$, 49.0%) received further ChT for systemic disease progression, it is difficult to ascertain which findings were attributable to the BRT per se. On the other hand, 89.0% of our patients were heavily pretreated with ChT, and several had received prior thoracic EBRT. It is questionable whether additional ChT would have had an impact in a microenvironment of previous systemic treatment failure and after repeat irradiation with HDR-BRT. Meanwhile, we had complete tumor volume remissions (Figures 5*A–C*) in 18.1% of patients with lesions $\leq$110 cm^3. Nevertheless, there was no statistically significant difference in local tumor control for lesions less than 110 cm^3 versus $\geq$110 cm^3 ($p = 0.397$). This finding could support the assumption by Peters et al.[22] that in IRT-HDR-BRT of the lung, generally accepted response criteria may not always adequately describe the actual clinical response.

Despite encouraging LC data, long-term survival was poor in our series with an OS rate of only 7% at 3 years. Nevertheless, more than half of our patients (56.3%) did not die of lung cancer but of intercurrent causes. It should be taken into consideration that treatment selection bias may play a role in survival. Greater than 90% of our patients were judged medically inoperable with multiple medical comorbidities. Given that most of patients were also extensively pretreated for local disease progression before BRT, the

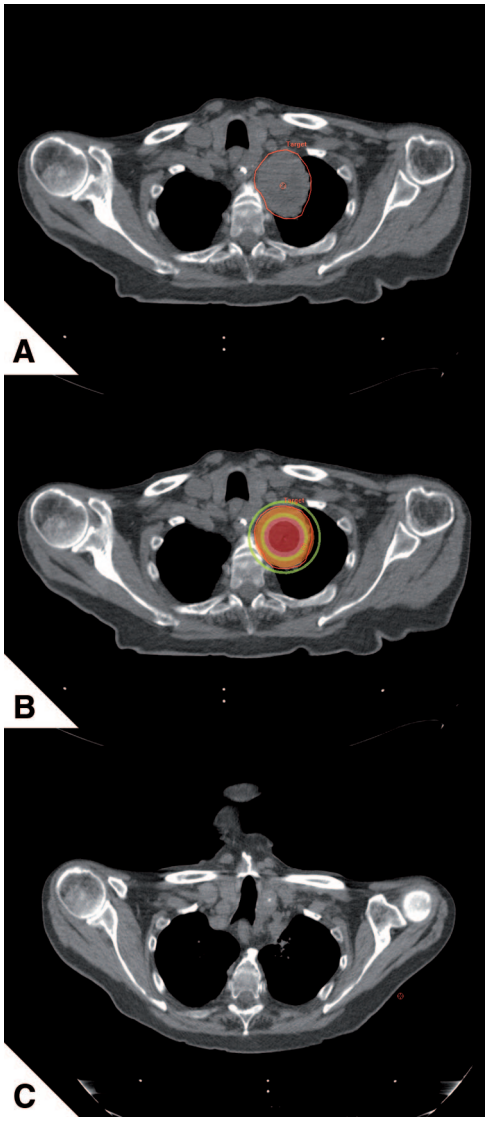

FIGURE 5. A 77-year-old man with squamous cell carcinoma of the left-sided superior sulcus. The patient suffered from chronic obstructive pulmonary disease, chronic renal insufficiency, and chronic cardiac insufficiency as coexisting morbidities and was medically not amenable to lung surgery. He rejected radiochemotherapy and was treated by sole interstitial high-dose-rate brachytherapy receiving four fractions of 8.0 Gy over 2 consecutive days to a total physical dose of 32.0 Gy. *A*, Axial computed tomography (CT)-image obtained before the onset of treatment showing a massive lesion in the apical part of the left lung lobe. The single implanted catheter is marked with a red circle in the central part of the red delineated tumor volume (Target). *B*, Two-dimensional (2D)-isodose distribution after three-dimensional (3D)-treatment planning for a plane lying centrally to the target extension. The color gradation represents the same isodose values as in Figure 1*B*. *C*, Axial CT image obtained at 13 months after brachytherapy showing no tumor regrowth.

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high-rate intercurrent deaths in our current series cannot be considered unanticipated.

As the tolerance of pulmonary parenchymal tissue decreases with increased irradiated lung volumes,[41] conventional radiation techniques rarely achieve durable control without excessive morbidity. Stereotactic body radiation therapy (SBRT) is a sophisticated percutaneous technique that has the potential to improve the therapeutic ratio by reducing treatment volumes, while escalating treatment doses.[42–44] Both robotic delivery devices (CyberKnife, Accuray, Sunnyvale, CA) and gantry-operated linear accelerators have been evaluated in the stereotactic treatment of primary and metastatic lung cancers, either for severe hypofractionated radiotherapy (HSRT) or as single-fraction radioablation (SFRA). For HSRT, dose fractionations from 33 Gy/6 up to 60 Gy/3 fractions have been reported with LC rates ranging from 73.0% crude to 97.7% at 2 years.[45–54] Similarly, a considerable variation in dose schemes has been described for SFRA with doses from 15 to 30 Gy yielding 2-year control rates from 48 to 91%.[55–60] However, the predominantly favorable results reported for SBRT suggest a beneficial prognostic impact of smaller tumor size (<5 cm) on local tumor control. In the reported HSRT studies, the median tumor size for LC more than 85% at 2 years ranged from 4.2 to 43.9 ml and for SFRA from 6.0 to 40.0 ml. In our series, the median tumor volume was 160 cm^3 with an overall LC rate of 81% at 2 years. Another factor which potentially limits SBRT is respiratory tumor motion.[61] Although different methods have been exploited to decrease the volume irradiated (motion-encompassing methods, respiratory-gated techniques, breath-hold techniques, forced shallow-breathing methods, and respiration-synchronized techniques), some of them are difficult to tolerate, and not all patients are suitable for every technique. As such, breathing mobility remains a factor for inaccuracy, and the displacement of tumors due to respiratory motion can be considerable with significant individual variability.[62] Nevertheless, SBRT is a noninvasive technique with proven efficacy in the treatment of small- to medium-sized tumors and is becoming more widely utilized on various treatment platforms. In this context, CT-guided IRT-HDR-BRT is a meaningful additional modality that can be implemented for the treatment of larger lesions or when stereotactic radiation delivery systems are not available. In this study, the inherently nonhomogeneous dose distribution in BRT parallels the intrinsic capability of SBRT to perform simultaneous intratumoral dose boosting.[63] Compared with SBRT, however, BRT provides a higher degree of intratumoral dose heterogeneity with no upper dose limits and a sharper dose fall-off gradient outside the target volume. The latter is of particular importance as it facilitates the application of very high doses to central tumor areas which might experience increased radioresistance due to hypoxic tumor microenviroment.[63]

The treatment schemes in our series were risk adapted based on individual clinical features. Different histologies and symptomatologies, and tumor locations with proximity to critical structures were determining factors for the heterogeneous total doses and the nonuniform number and size of treatment fractions. Although the appropriate HDR scheme for local disease control has not been yet defined, our experience shows that a fractionated approach over consecutive days is safe and feasible. The current procedure in our department encompasses the application of 8.0 Gy twice-daily fractions up to 32.0 Gy independent of tumor volume or location. However, lesion size and position are decisive for the number and alignment of the catheters, associated patient discomfort, and treatment-related risks. All these factors can, in consideration of dose constraints, necessitate the administration of differing treatment schemes.

The limitations of our study are the retrospective design and results from a relatively small population with metastases and primary cancers. Despite these shortcomings, our data show promising control rates and support the implementation of CT-guided IRT-HDR-BRT in the local treatment of primary and secondary intrathoracic malignancies in nonsurgical candidates.

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