

# Dose–Response Relationship in Single-Fraction CT-Guided HDR Brachytherapy for Breast Cancer Liver Metastases: Defining a Clinically Relevant D98 Threshold

**Magdalena Peszyńska-Piorun**

Copernicus Memorial Hospital in Lodz Comprehensive Cancer Center and Traumatology,

**Przemysław Janiak**

Copernicus Memorial Hospital in Lodz Comprehensive Cancer Center and Traumatology,

**Piotr Mężeński**

Copernicus Memorial Hospital in Lodz Comprehensive Cancer Center and Traumatology,

**Łukasz Kuncman**

Medical University of Lodz

**Magdalena Orzechowska**

Medical University of Lodz

**Federico Mastroleo**

European Institute of Oncology IRCCS

**Sylwia Sroka**

Saint John's Cancer Center

**Ewa Wojtyna**

Saint John's Cancer Center

**Konstantinos Ferentinos**

German Oncology Center, University Hospital of the European University Cyprus

**Kathrin Hering**

University Hospital Leipzig

**Hai Minh Ha**

University Hospital Magdeburg

**Daniel Medenwald**

LMU University Hospital

**Matthias P Fabritius**

LMU University Hospital

**Stefanie Corradini**

Friedrich-Alexander-Universität Erlangen-Nürnberg

**Max Seidensticker**

LMU University Hospital

**Jens Ricke**

LMU University Hospital

**Frederik Fuchs**

LMU University Hospital

**Paul Rogowski**

LMU University Hospital

**Dariusz Garmol**

Affidea Nu-med Center of Oncological Diagnostics and Therapy

**Mariusz Masiuk**

Affidea Nu-med Center of Oncological Diagnostics and Therapy

**Tomasz Surowiak**

Affidea Nu-med Center of Oncological Diagnostics and Therapy

**Jacek Fijuth**

Medical University of Lodz

**Mateusz Bilski**

**bilskimat@gmail.com**

Affidea Nu-med Center of Oncological Diagnostics and Therapy

---

## Research Article

**Keywords:** Breast cancer, liver metastases, brachytherapy, D98, dose–response, competing risks

**Posted Date:** May 15th, 2026

**DOI:** <https://doi.org/10.21203/rs.3.rs-9331484/v1>

**License:** © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

**Additional Declarations:** No competing interests reported.

---

# **Dose-Response Relationship in Single-Fraction CT-Guided HDR**

## **Brachytherapy for Breast Cancer Liver Metastases: Defining a Clinically**

### **Relevant D98 Threshold**

Magdalena Peszyńska-Piorun<sup>1</sup>, Przemysław Janiak<sup>1</sup>, Piotr Mężeński<sup>1</sup>, Łukasz Kuncman<sup>2,3</sup>,  
Magdalena Orzechowska<sup>4</sup>, Federico Mastroleo<sup>5,6</sup>, Sylwia Sroka<sup>7</sup>, Ewa Wojtyna<sup>7</sup>,  
Konstantinos Ferentinos<sup>8</sup>, Kathrin Hering<sup>9</sup>, Hai Minh Ha<sup>10</sup>, Daniel Medenwald<sup>11</sup>, Matthias P  
Fabritius<sup>11</sup>, Stefanie Corradini<sup>12</sup>, Max Seidensticker<sup>11</sup>, Jens Ricke<sup>11</sup>, Frederik Fuchs<sup>13</sup>, Paul  
Rogowski<sup>13</sup>, Dariusz Garmol<sup>14</sup>, Mariusz Masiuk<sup>14</sup>, Tomasz Surowiak<sup>14</sup>, Jacek Fijuth<sup>2,3</sup>,  
Mateusz Bilski<sup>14,15</sup>

#### **Affiliations:**

1. Radiotherapy Treatment Planning Department, Copernicus Memorial Hospital in Lodz  
Comprehensive Cancer Center and Traumatology, Lodz, Poland
2. Department of Radiotherapy, Medical University of Lodz, Lodz, Poland
3. Department of External Beam Radiotherapy, Copernicus Memorial Hospital in Lodz  
Comprehensive Cancer Center and Traumatology, Lodz, Poland
4. Department of Molecular Carcinogenesis, Medical University of Lodz, Lodz, Poland
5. Division of Radiation Oncology, European Institute of Oncology IRCCS, 20141 Milan, Italy
6. Department of Radiation Oncology, Mayo Clinic, Rochester, MN, United States
7. Department of Medical Physics, Saint John's Cancer Center, Lublin, Poland
8. Department of Radiation Oncology, German Oncology Center, University Hospital of the  
European University Cyprus, Limassol, Cyprus
9. Department of Radiotherapy and Radiation Oncology, University Hospital Leipzig,  
Stephanstraße 9a, Leipzig, Germany

10. University Clinic for Radiation Therapy, University Hospital Magdeburg A. R, Magdeburg, Germany

11. Department of Radiology, LMU University Hospital, LMU Munich, Marchioninstraße 15, 81377 Munich, Germany

12. Department of Radiation Oncology, University Hospital, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany

13. Department of Radiation Oncology, LMU University Hospital, LMU Munich, Marchioninstraße 15, 81377 Munich, Germany

14. Department of Radiotherapy, Affidea Nu-med Center of Oncological Diagnostics and Therapy, Zamość, Poland

15. Clinics of Radiotherapy, Medical University of Lublin, Lublin, Poland

**Keywords:** Breast cancer; liver metastases; brachytherapy; D98; dose–response; competing risks.

## **Highlights**

- D98 was the most consistent dosimetric parameter associated with response and progression outcomes after single-fraction HDR brachytherapy for breast cancer liver metastases.

- A near-minimum target coverage threshold of approximately 18 Gy was associated with improved objective response rates (ORR) and radiographic progression-free survival (rPFS).

- D90 was associated with response but did not correlate with time-to-event outcomes, suggesting limited utility as a primary planning metric.

- Lesion-level analysis (single metastasis per patient) enabled a direct and unbiased assessment of dose–response relationships.

47 • Near-minimum coverage metrics may represent a clinically actionable target for  
48 standardizing HDR brachytherapy planning.

49 E-mails:

50 me.peszynska@kopernik.lodz.pl

51 pt.janiak@kopernik.lodz.pl

52 mezenski.piotr@gmail.com

53 bilskimat@gmail.com

54 lukasz.kuncman@umed.lodz.pl

55 orzechowska.mag@wp.pl

56 Federico.Mastroleo@ieo.it

57 ssroka@cozl.pl

58 ewojtyna@cozl.pl

59 Konstantinos.Ferentinos@goc.com.cy

60 haiminh.ha@med.ovgu.de

61 daniel.medenwald@uk-halle.de

62 kathrin.Hering@medizin.uni-leipzig.de

63 Matthias.Fabritius@med.uni-muenchen.de

64 jacek.fijuth@umed.lodz.pl

65 Stefanie.Corradini@uk-erlangen.de

66 max.Seidensticker@med.uni-muenchen.de

67 jens.Ricke@med.uni-muenchen.de

68 frederik.fuchs@med.uni-muenchen.de

69 paul.rogowski@med.uni-muenchen.de

70 darek.garmol@gmail.com

tomasz.surowiak@affidea.com

mariusz.masiuk@affidea.com

## **Abstract**

### **Background**

The optimal dosimetric parameter predicting clinical outcomes after single-fraction CT-guided high-dose-rate brachytherapy (HDR-BT) for breast cancer liver metastases (BCLM) remains undefined, limiting standardization of treatment planning.

### **Methods**

This multicenter retrospective study included 65 patients with BCLM treated with single-fraction CT-guided HDR-BT. To enable a direct evaluation of dose–response relationships, only patients with a single treated liver metastasis were included. This approach minimizes inter-lesion dosimetric heterogeneity and allows a clearer attribution of clinical outcomes to specific dose–volume parameters. Dose–volume histogram parameters (D100, D98, D95, D90, Dmean) were analyzed in relation to 12-month objective response (ORR), radiographic progression-free survival (rPFS), and liver-restricted progression-free survival (rLRPFS). Thresholds were explored using ROC analysis and Youden’s index.

### **Results**

Among evaluated parameters, D98 emerged as the most consistent predictor of outcome. A threshold of approximately 18.3–18.4 Gy was associated with improved ORR ( $p=0.04$ ) and rPFS ( $p=0.03$ ). While D90 was associated with ORR at higher thresholds, it did not translate

into time-to-event benefit. For rLRPFS, D100 showed a borderline association. No grade  $\geq 2$  hepatic toxicity or radiation-induced liver disease (RILD) was observed.

## **Conclusions**

D98 appears to be a clinically relevant and reproducible dosimetric parameter associated with treatment outcomes after single-fraction HDR-BT for BCLM. A threshold around 18 Gy may represent a clinically actionable planning benchmark for target coverage in single-fraction HDR-BT, supporting the standardization of treatment delivery and warranting prospective validation.

## **Introduction**

Breast cancer liver metastases (BCLM) constitute a clinically relevant subset of metastatic breast cancer and are being encountered with increasing frequency in the era of effective systemic therapy. Prolonged survival and improved control of extrahepatic disease have generated a growing cohort of patients with liver-dominant or oligometastatic progression, in whom metastasis-directed therapy (MDT) has become an integral component of contemporary management. MDT aims to prolong progression-free survival, defer systemic treatment escalation, and, in selected patients, improve long-term outcomes (1-3). For liver metastases, established local treatment approaches include surgical resection, thermal ablation, and stereotactic body radiotherapy (SBRT) (1-3). However, a substantial proportion of patients are ineligible for these modalities because of lesion size, multifocal involvement, proximity to major vascular or biliary structures, or unfavorable anatomical conditions (1). In this setting, computed tomography (CT)-guided interstitial high-dose-rate brachytherapy

(HDR-BT) has emerged as a minimally invasive, highly conformal alternative, capable of delivering ablative doses with steep dose gradients while sparing uninvolved liver parenchyma (4-6). Clinical series have reported high local control rates and acceptable toxicity profiles, supporting CT-guided HDR-BT as an effective option for selected patients with liver metastases, including BCLM (4-6). The multicentre BRALIBREST study represents the largest real-world cohort of patients with breast cancer liver oligometastases treated with CT-guided HDR-BT and provides important clinical benchmarks in this setting (7). In that analysis, survival outcomes were favorable and dosimetric parameters emerged as key determinants of prognosis: a gross tumor volume (GTV) D90  $\geq 25$  Gy was associated with improved survival, whereas higher tumor burden – including multiple metastases and larger lesion volumes ( $>10$  cm<sup>3</sup>) – adversely influenced outcome (7). These findings underscored the importance of adequate target coverage and established a dose–outcome association for HDR-BT in BCLM at the patient level. However, because these observations were derived from patient-level analyses, they do not clarify which dosimetric descriptor best reflects lesion-level dose adequacy. From a dosimetric standpoint, HDR-BT differs fundamentally from external-beam radiotherapy. In SBRT, dose is typically prescribed to a defined isodose surface, and coverage metrics such as D95 or V100 are widely used surrogates of adequate target irradiation (8). By contrast, interstitial HDR-BT is characterized by steep intra-lesional dose gradients and pronounced intratumoural heterogeneity, with high central doses and relatively lower peripheral coverage (4-6). Under these conditions, small regions of underdosage – particularly at the tumor margin – may be clinically relevant, as even limited “cold spots” can permit tumor persistence (9). In SBRT for liver metastases, near-minimum dose metrics have been associated with local control, and parameters such as D98 are increasingly used to characterize target coverage. (9,10). In brachytherapy, however, absolute minimum dose metrics such as D100 are highly sensitive to geometric uncertainties and

sampling effects, whereas near-minimum volumetric parameters such as D98 may provide a more robust and clinically meaningful representation of peripheral target coverage (11). Despite this rationale, near-minimum coverage metrics have not been systematically evaluated in a homogeneous BCLM cohort treated with single-fraction HDR-BT. Accordingly, a critical knowledge gap remains: although D90 has demonstrated prognostic value at the patient level (7), it is unclear which dosimetric parameter most consistently reflects lesion-level dose adequacy and correlates with radiographic response and liver-focused progression outcomes.

Against this background, we conducted a multicentre retrospective analysis of patients with BCLM treated with single-fraction CT-guided HDR-BT, restricting the cohort to single-lesion treatments to allow a direct and unbiased assessment of dose–response relationships. The aim of this study was to identify a clinically relevant and reproducible target coverage metric associated with radiographic outcomes and to explore a threshold that might support standardization of HDR-BT treatment planning for BCLM.

## **Materials and Methods**

### ***Study Design and Patient Cohort***

This retrospective multicentre analysis included 65 consecutive female patients with BCLM treated with HDR-BT. To ensure a robust assessment of the relationship between dosimetric parameters and clinical outcomes, the present analysis was restricted to patients with a single treated liver metastasis. This approach was intentionally adopted to minimize confounding related to inter-lesion dosimetric heterogeneity. In patients with multiple metastases, each lesion exhibits distinct dose–volume parameters, making it difficult to attribute clinical outcomes to a specific dosimetric profile. By limiting the cohort to single-lesion treatments, we aimed to establish a direct and interpretable association between target coverage and

oncologic endpoints. This approach also reduces potential bias related to competing lesion behavior and avoids dilution of dose–response signals inherent to patient-level analyses in multi-lesion cohorts. Prescription doses ranged from 15 to 25 Gy (median, 20 Gy) in a single fraction and were individualized based on lesion characteristics, prior therapies, and organ-at-risk constraints. The study adhered to STROBE principles and was approved by the relevant institutional review boards. Procedural details and treatment workflow have been reported previously [7].

### ***Clinical endpoints***

The primary endpoint was the objective radiographic response rate (ORR) of the GTV1 lesion at 12 months, assessed on contrast-enhanced computed tomography or magnetic resonance imaging according to RECIST 1.1 criteria [12]. ORR comprised complete and partial responses. Secondary endpoints included radiographic progression-free survival (rPFS) and liver-restricted radiographic progression-free survival (rLRPFS). rPFS was defined as the interval from HDR-BT to first liver progression (local GTV1 failure or new liver metastases) or death, as applicable. Isolated extrahepatic progression was censored to preserve the liver-focused nature of this endpoint. rLRPFS was analyzed within a competing-risk framework. The event of interest was any radiographic liver progression. Competing events included isolated extrahepatic progression, death without liver progression, and initiation of new systemic therapy for non-hepatic reasons. All endpoints were defined at the lesion level (GTV1) to ensure consistency with the dosimetric analysis framework. Hepatic safety was assessed using cumulative liver biochemistry toxicity for alanine aminotransferase, aspartate aminotransferase, and bilirubin, graded according to CTCAE. Acute ( $\leq 3$  months) and late ( $> 3$  months) toxicities were recorded.

## ***Dosimetric analysis and plan-quality indices***

Cumulative dose-volume histograms for each GTV were exported for quantitative analysis. We prioritized absolute physical dose metrics representing minimum and near-minimum coverage (D100, D98, D95, and D90), as well as mean dose (Dmean). In addition, volumetric coverage parameters- V100 was recorded descriptively. To characterize the steep dose gradients inherent to single-fraction interstitial HDR-BT, a homogeneity index (HI) was calculated for each GTV1 according to the formula

$$HI = 1 - \frac{D_{min}}{D_{max}}$$

The applied HI therefore corresponds to a transformed variant of the radical dose homogeneity index described in the radiotherapy plan-evaluation literature [13]. In the present analysis, Dmin was represented by GTV1 D100 as a practical surrogate for the minimum dose within the target. Higher HI values indicated greater dose heterogeneity. V100 was retained as a descriptive surrogate of target coverage. For the radiobiological context, selected metrics were converted to biologically effective dose and equivalent dose in 2 Gy fractions using the linear-quadratic model. Given the debate regarding the validity of the linear-quadratic formalism at high single-fraction doses, these values were treated as comparative indices rather than exact measures of biological effect [14,15].

## ***Statistical analysis***

Analyses focused on the GTV1 subset (n = 65). A two-step procedure was used to evaluate associations between dose-volume histogram metrics and clinical endpoints. First, receiver operating characteristic analyses using Youden's index were performed to determine optimal dose thresholds for each metric (D100, D98, D95, D90, and Dmean) in relation to binary 12-month outcomes. Area under the receiver operating characteristic curve values were calculated with 95% confidence intervals [16]. Second, patients were dichotomized according

to the identified receiver operating characteristic thresholds, and associations with binary 12-month outcomes were assessed using Fisher's exact test. Time-to-event outcomes were analyzed from the date of HDR-BT. rPFS was estimated using the Kaplan-Meier method and compared using the log-rank test. rLRPFS was estimated using the Aalen-Johansen estimator and compared using Gray's test within a competing-risk framework to account for competing non-hepatic progression and death events [17]. Competing events included isolated extrahepatic progression, death without liver progression, and initiation of new systemic therapy for non-hepatic reasons. All statistical tests were two-sided, and nominal p values < 0.05 were considered noteworthy in this exploratory analysis. Statistical analyses were performed in R (version 4.5.0). Given the exploratory nature of the analysis and multiple comparisons across correlated dosimetric parameters, p-values were interpreted descriptively without formal adjustment for multiplicity. Artificial intelligence language tools (DeepL Write and Grammarly) were used solely to improve the grammar and readability of the manuscript. The authors reviewed and approved all edits, and these tools were not used for data analysis, interpretation, or generation of scientific conclusions.

## **Results**

### ***Patient characteristics and dosimetric overview***

A total of 65 patients with 65 liver metastases were included in the analysis. Baseline lesion and dosimetric characteristics are summarised in Table 1. Among all evaluated dose-volume histogram parameters, near-minimum target coverage metrics demonstrated the most consistent association with clinical outcomes. In this single-lesion-per-patient subset, the median baseline GTV1 volume was 18.8 cm<sup>3</sup> (interquartile range [IQR] 8.8–67.8 cm<sup>3</sup>; range 0.84–226.2 cm<sup>3</sup>) and, by definition, was identical to the total liver metastatic burden before brachytherapy. The prescription dose was 20 Gy in most cases (range 15–25 Gy), delivered as

a single HDR fraction. The dosimetric characteristics of GTV1 coverage, including the distributions of D100, D98, D95, D90, and Dmean, are reported in Table 1.

**Table 1.** Dosimetric characteristics of GTV1 for the selected cohort.

| Parameter                 | Value                                             |
|---------------------------|---------------------------------------------------|
| Volume (cm <sup>3</sup> ) | Median 18.8 (IQR 8.8–67.8; range 0.84–226.19)     |
| Prescription dose (Gy)    | Median 20.0 (range 15.0–25.0)                     |
| GTV1 D100 (Gy)            | Median 12.91 (IQR 10.84–16.76; range 6.39–25.94)  |
| GTV1 D98 (Gy)             | Median 17.52 (IQR 15.70–20.42; range 9.29–30.24)  |
| GTV1 D95 (Gy)             | Median 20.03 (IQR 17.73–22.47; range 10.69–33.78) |
| GTV1 D90 (Gy)             | Median 22.58 (IQR 20.16–25.10; range 12.74–39.03) |
| GTV1 Dmean (Gy)           | Median 51.49 (IQR 44.93–60.40; range 28.70–84.03) |

### ***Plan-quality indices***

Plan-quality indices reflected the expected high-gradient, heterogeneous dose distributions typical of interstitial single-fraction HDR brachytherapy, while maintaining high target coverage. In the GTV1 subset, the mean V100 was 94.7% (standard deviation [SD] 4.2%), indicating consistently high coverage of the target by the prescription isodose. The mean homogeneity index (HI) was 0.94 (SD 0.04), confirming steep intra-target dose gradients and pronounced hotspots, as expected for interstitial HDR-BT. The standard deviation suggests a relatively consistent distribution of HI values within the study cohort, indicating limited inter-patient variability in dose homogeneity. Taken together, these indices provided the dosimetric context for the coverage-oriented dose–response analyses.

## **Radiographic response**

At 6 months after HDR-BT, 47 of 65 lesions (72%) achieved an ORR, whereas 18 lesions (28%) showed stable disease (SD) or progressive disease (PD). At 12 months, radiographic response assessment was available for 57 of 65 lesions (88%); among these, 47 lesions (82%) maintained an ORR, and 10 lesions (18%) had SD/PD. Eight patients were not evaluable at 12 months because of missing or non-contrast imaging, early progression at other sites precluding adequate liver assessment, or loss to follow-up. These response rates are summarised in Table 2.

**Table 2.** Radiographic response at 6 and 12 months after CT-guided HDR brachytherapy for the selected cohort.

| Time point | ORR (CR/PR) | SD/PD    | Evaluable lesions<br>(n) |
|------------|-------------|----------|--------------------------|
| 6 months   | 47 (72%)    | 18 (28%) | 65                       |
| 12 months  | 47 (82%)    | 10 (18%) | 57                       |

## **Liver-restricted progression**

For liver-restricted outcomes, the Fisher-based threshold screening suggested the strongest signal for D100. In Supplementary Table S1, the ROC-derived threshold for D100 was 16.3 Gy (95% CI 10.7–20.2 Gy;  $p = 0.05$ ), whereas D98 at 19.4 Gy (95% CI 15.3–23.3 Gy) was not significant ( $p = 0.11$ ). Thresholds for D95, D90, and Dmean were also non-significant. In the prespecified competing-risk framework using Aalen-Johansen estimates and Gray's test, the strongest signal remained with D100, although this association was borderline rather

than statistically significant. For GTV1 D100, the threshold of 16.3 Gy was associated with a borderline difference in the cumulative incidence of rLRPFS (Gray's  $p = 0.10$ ). For D98, the corresponding threshold of 19.4 Gy did not show a significant association (Gray's  $p = 0.30$ ). ROC-derived thresholds for D95, D90, and Dmean likewise did not show relevant associations in the competing-risk analysis (Supplementary Table S2, Figure 3).

### ***Dose–response analyses (ROC-based thresholds)***

#### ***Objective response at 12 months***

ROC analysis using Youden's index identified near-minimum coverage metrics as the most informative predictors of 12-month ORR. For D98, the optimal ROC-derived threshold was 18.4 Gy (95% CI 17.2–24.3 Gy). Patients with GTV1 D98  $\geq 18.4$  Gy were significantly more likely to achieve a 12-month ORR than those below this threshold ( $p = 0.04$ , Fisher's exact test). For D90, the ROC-derived threshold was 30.8 Gy (95% CI 21.0–35.8 Gy), and values above this threshold were also significantly associated with 12-month response ( $p = 0.03$ ). In contrast, ROC-derived thresholds for D100 (14.9 Gy), D95 (21.1 Gy), and Dmean (52.3 Gy) did not reach statistical significance for 12-month ORR ( $p = 0.14$ ,  $0.15$ , and  $0.49$ , respectively). These associations are shown in Figure 1 and detailed in Supplementary Table S1.

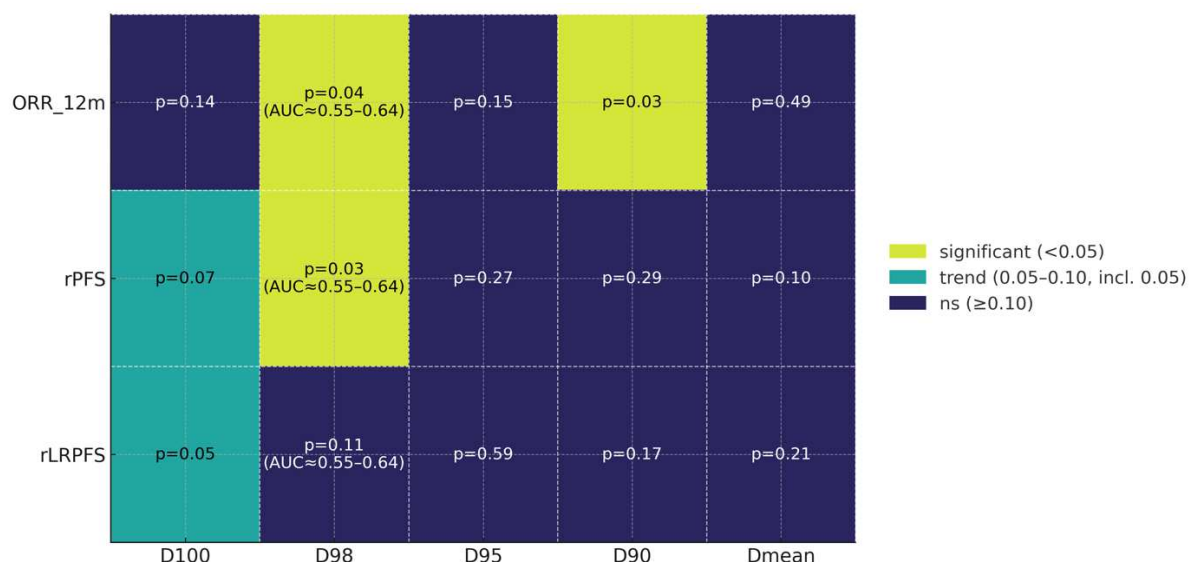


**Figure 1.** Heatmap summarising exploratory associations between GTV1 dose-volume histogram metrics and radiographic outcomes. Receiver operating characteristic-derived thresholds were identified for each metric in relation to 12-month outcomes, and corresponding p-values from Fisher's exact test are shown for objective radiographic response (ORR), radiographic progression-free survival (rPFS), and liver-restricted progression. AUC values are provided for each metric-endpoint combination.

### ***Radiobiological interpretation of near-minimum thresholds***

Using the linear–quadratic model with an assumed tumor  $\alpha/\beta$  ratio of 10 Gy, the near-minimum GTV coverage thresholds for D98 and D100 corresponded to approximate radiobiological dose equivalents. The ROC-derived GTV1 D98 threshold of 18.3 Gy corresponded to an estimated biologically effective dose (BED10) of approximately 51.8 Gy and an estimated equivalent dose in 2 Gy fractions (EQD2\_10) of approximately 43.2 Gy. The corresponding D100 threshold of 16.3 Gy yielded an estimated BED10 of approximately 42.9 Gy and an estimated EQD2\_10 of approximately 35.8 Gy. Given the uncertainty surrounding the validity of linear–quadratic-based BED/EQD2 conversions at high single-

fraction doses, these values should be regarded as model-based comparative estimates with known limitations rather than exact measures of biological effect. As such, they are presented primarily to facilitate cautious contextual comparison with published SBRT dose ranges.

### ***Time-to-event analyses: rPFS and rLRPFS***

#### ***Radiographic progression-free survival (rPFS)***

For rPFS, D98 again showed the most robust association among the evaluated coverage metrics. The ROC-derived threshold for D98 was 18.3 Gy (95% CI 14.8–23.2 Gy). Dichotomization at this threshold identified a significant association with the 12-month rPFS status ( $p = 0.03$ , Fisher's exact test). D100 at 12.7 Gy (95% CI 10.7–15.5 Gy) showed a borderline association ( $p = 0.07$ ). In contrast, D95 (21.1 Gy) and D90 (22.6 Gy) were not significantly associated with 12-month rPFS ( $p = 0.27$  and  $0.29$ , respectively), and Dmean at 44.0 Gy (95% CI 33.8–72.8 Gy) showed at most a borderline signal ( $p = 0.10$ ) (Supplementary Table S1).

Kaplan–Meier analyses stratified by the D98 threshold of 18.3 Gy demonstrated separation of the rPFS curves, with patients achieving  $D98 \geq 18.3$  Gy showing a higher probability of remaining free of liver progression over time than those below the threshold. In the time-to-event analysis, the D98 threshold remained the only statistically significant discriminator (log-rank  $p = 0.03$ ), whereas D100, D95, D90, and Dmean were not significant (Supplementary Table S2, Figure 2).

Kaplan–Meier estimates of rPFS stratified by D98 threshold

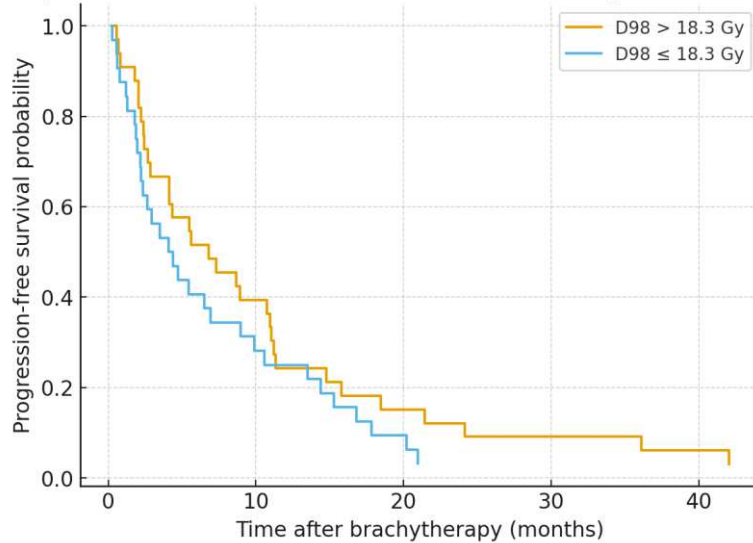


**Figure 2.** Kaplan–Meier analysis of radiographic progression-free survival (rPFS) in the GTV1 subset (n = 65), stratified by the ROC-derived threshold for D98 (18.3 Gy). Curves show rPFS for patients above and below the threshold. The log-rank p-value is shown.

#### ***Liver-restricted radiographic progression-free survival (rLRPFS)***

For liver-restricted outcomes, the Fisher-based threshold screening suggested the strongest signal for D100. In Supplementary Table S1, the ROC-derived threshold for D100 was 16.3 Gy (95% CI 10.7–20.2 Gy;  $p = 0.05$ ), whereas D98 at 19.4 Gy (95% CI 15.3–23.3 Gy) was not significant ( $p = 0.11$ ). Thresholds for D95, D90, and Dmean were also non-significant. In the prespecified competing-risk framework using Aalen–Johansen estimates and Gray’s test, the strongest signal remained with D100, although this association was borderline rather than statistically significant. For GTV1 D100, the threshold of 16.3 Gy was associated with a borderline difference in the cumulative incidence of rLRPFS (Gray’s  $p = 0.10$ ). For D98, the corresponding threshold of 19.4 Gy did not show a significant association (Gray’s  $p = 0.30$ ). ROC-derived thresholds for D95, D90, and Dmean likewise did not show relevant

associations in the competing-risk analysis (Supplementary Table S2, Figure 3). Figure 3 presents 12-month estimates derived from the competing-risk analysis.

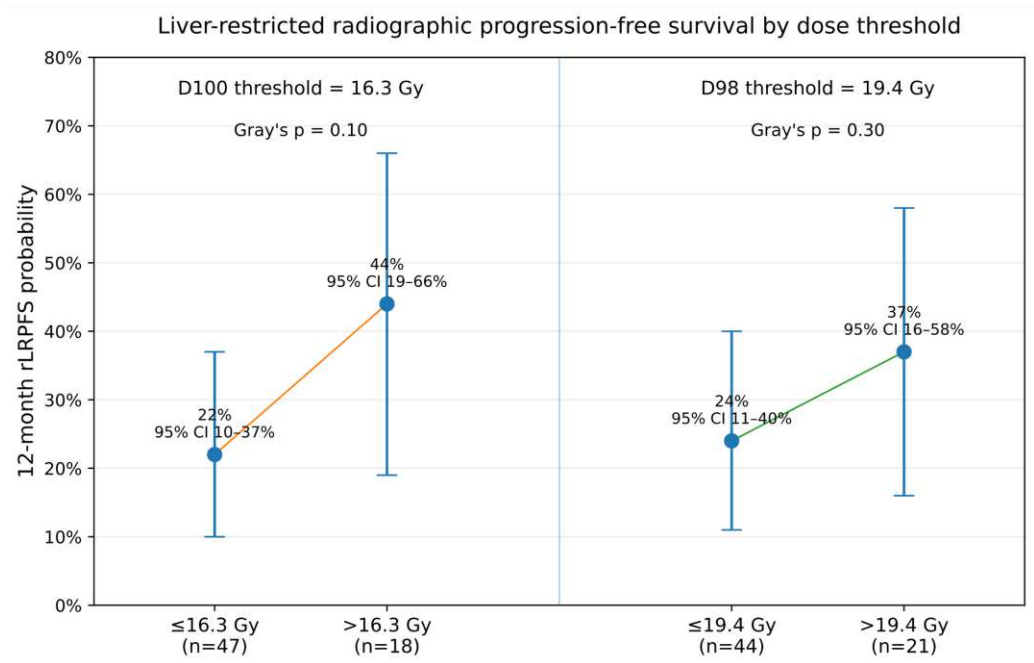


**Figure 3.** Twelve-month estimates derived from the competing-risk analysis of liver-restricted progression in the GTV1 subset (n = 65). Panel A shows results for D100 stratified at 16.3 Gy and panel B for D98 stratified at 19.4 Gy. Points represent 12-month estimates and error bars indicate 95% confidence intervals. Gray's test p-values are shown for each threshold comparison.

### *Hepatic laboratory toxicity*

There were no acute CLBT events of grade  $\geq 2$  for ALT/AST or total bilirubin. In the late period, CLBT grade  $\geq 2$  for transaminases occurred in 8 patients (12.3%), including 4 with grade 2 and 4 with grade 3 events, whereas late CLBT grade  $\geq 2$  for bilirubin was observed in 4 patients (6.2%), all grade 3. No cases of classic radiation-induced liver disease were observed.

## Discussion

In this retrospective multicentre analysis of single-fraction CT-guided HDR-BT for breast cancer liver metastases, GTV D98 showed the most consistent exploratory association with 12-month ORR and radiographic progression-free survival among the evaluated target coverage metrics. By contrast, associations with liver-restricted outcomes were less consistent, and the strongest signal for rLRPFS was observed for D100 rather than D98. Taken together, these findings suggest that near-minimum target coverage may be clinically relevant in this setting, while also indicating that different dose metrics may capture partially distinct aspects of tumor control after HDR-BT. From a clinical perspective, these findings suggest that ensuring adequate near-minimum target coverage ( $D98 \geq 18$  Gy) may be more relevant than achieving higher central doses, thereby challenging the traditional emphasis on D90-based metrics in HDR brachytherapy. The observed pattern is clinically plausible. In interstitial HDR-BT, dose deposition within the target is intrinsically heterogeneous, with steep gradients around the applicators and pronounced central dose escalation. Under such conditions, metrics reflecting the adequacy of dose coverage in the peripheral or near-minimum region of the target may be more informative than central dose parameters alone. The identified D98 threshold is also broadly consistent with empirical dose concepts used in CT-guided HDR-BT, where tumor-margin or CTV doses of approximately 18–25 Gy have often been considered adequate for single-fraction ablative treatment [3,4,18,19]. The present exploratory threshold around 18.3–18.4 Gy therefore aligns reasonably well with established clinical practice and with previously reported near-minimum dose values in oligometastatic liver treatment [3,4]. However, this agreement with prior practice should not be interpreted as formal validation. In the present dataset, the threshold was derived and tested within the same cohort and should therefore be regarded as data-derived and hypothesis-generating rather than

definitive. The relative predominance of D98 over more central dose parameters such as Dmean is also of interest from a cross-modality perspective. HDR-BT differs from SBRT not only in delivery technique but also in spatial dose distribution, with substantially greater intratumoural heterogeneity and sharper local dose escalation. Comparative planning studies have similarly shown important differences between CT-guided interstitial HDR-BT and SBRT with respect to target dose coverage and normal liver exposure [5,20,21]. In this context, our findings may suggest that, in HDR-BT, tumor control depends not merely on the magnitude of the central hotspot, but also on the adequacy of coverage of the near-minimum dose region. This interpretation is biologically plausible because insufficient peripheral coverage may permit persistence of viable tumor clonogens despite very high dose deposition in central tumor regions. Nevertheless, this remains an inference rather than a directly proven mechanism in the present study. From a practical planning perspective, these findings may have direct implications for catheter placement strategy and dwell time optimization in CT-guided HDR-BT. Specifically, prioritizing adequate peripheral target coverage rather than central dose escalation alone may represent a more effective approach to maximize treatment efficacy while maintaining organ-at-risk (OARs) constraints. This may be particularly relevant in larger or irregularly shaped lesions, where achieving homogeneous peripheral coverage can be technically challenging. At the same time, the rLRPFS analyses suggest that the true minimum dose region may also remain relevant. In the supplementary analyses, D100 showed the strongest—albeit borderline—signal for rLRPFS, whereas D98 was not statistically significant for this endpoint. This pattern may indicate that lesion-confined control and broader radiographic progression endpoints are not captured by exactly the same dosimetric descriptor. It may also reflect limited statistical power, endpoint definition, or residual instability related to threshold-based analyses. Accordingly, D100 should not be dismissed, but may be better viewed as a complementary exploratory parameter rather than a

primary planning metric, based on the present data. This observation may indicate that the absolute minimum dose remains relevant for preventing intrahepatic relapse, although this hypothesis requires validation. The finding that D90 was associated with 12-month ORR but not with time-to-event endpoints is also noteworthy. D90 has previously been linked to survival in the BRALIBREST setting [7], and it remains an established descriptive metric in brachytherapy reporting. In the present analysis, however, its signal appeared less consistent than that of D98 across endpoints. This may indicate that D90 remains useful for descriptive reporting and comparison with previous series, but may be less suitable than D98 for capturing the near-minimum coverage effect that appears most closely linked to radiographic response in this cohort. Radiobiological interpretation of the observed thresholds requires caution. Using the linear-quadratic model and an assumed tumor  $\alpha/\beta$  ratio of 10 Gy, a D98 threshold of 18.3 Gy corresponds to an approximate EQD2 of 43 Gy, whereas the D100 threshold of 16.3 Gy corresponds to an approximate EQD2 of about 36 Gy. However, the validity of linear-quadratic-based BED/EQD2 conversion at high single-fraction doses remains uncertain [14,15]. These values should therefore be interpreted only as comparative, model-based approximations rather than exact measures of biological equivalence. Likewise, comparisons with SBRT dose prescriptions or guideline-based BED thresholds should be considered exploratory only. In addition, the biological effect of HDR-BT is likely determined not only by the marginal dose but also by the highly heterogeneous spatial dose distribution within and around the target. From a practical planning perspective, the present findings suggest that GTV D98 may be a useful candidate metric for further evaluation, particularly in relation to ORR and rPFS. If confirmed, this would support a planning approach that pays close attention to catheter geometry and dwell-time optimization to improve peripheral target coverage while maintaining compliance with OAR constraints. However, given the retrospective design, the limited sample size, and the threshold-based

exploratory methodology, the proposed D98 cut-off around 18.3–18.4 Gy should be viewed as a candidate benchmark for further study rather than an immediately transferable routine planning standard. D100 may provide complementary descriptive information, particularly in exploratory analyses of rLRPFS, and D90 remains useful for continuity with prior brachytherapy reporting [7]. With regard to safety, hepatic tolerance in this cohort appeared favorable. No acute grade  $\geq 2$  laboratory toxicity and no cases of classic radiation-induced liver disease were observed. Late grade  $\geq 2$  elevations in transaminases and bilirubin occurred in a minority of patients. These findings are in line with prior reports supporting the generally acceptable hepatic tolerability of CT-guided liver brachytherapy in appropriately selected patients [3,4,6,7,18,19]. Several strengths of the study should be acknowledged. These include the multicentre design, the focus on a clinically specific BCLM cohort, and the attempt to compare multiple dose-coverage metrics within a single analytical framework. At the same time, the limitations are substantial and should be stated clearly. First, the study is retrospective and non-randomized. Second, the sample size is limited, particularly for threshold-based subgroup comparisons. Third, the cut-offs were derived and tested in the same dataset, which introduces a risk of overfitting and optimism bias. Fourth, several correlated dosimetric parameters and endpoints were examined, so the possibility of false-positive findings due to multiple testing cannot be excluded. Fifth, the 12-month ORR analysis was restricted to evaluable lesions, and selection bias related to imaging availability and 12-month evaluability cannot be excluded. Moreover, ORR at 12 months is not equivalent to LC after focal ablative therapy, as the absence of RECIST-defined response does not necessarily indicate local treatment failure. Finally, the competing-risk analyses for rLRPFS should be regarded as descriptive and exploratory, particularly given the limited sample size and event counts. In addition, the restricted PFS definition used here may be

affected by informative censoring of isolated extrahepatic progression. For these reasons, the present findings should be interpreted cautiously and viewed as hypothesis-generating.

Further research should therefore focus on external and, ideally, prospective validation of near-minimum target coverage metrics in HDR-BT for liver metastases. Additional work may also include voxel-wise dosimetric analyses [22], as well as integration with contemporary systemic treatment strategies and imaging-based response assessment, including immunotherapy [23] and AI-driven radiomics [24]. Such efforts may help determine whether the observed role of D98 reflects a true biological feature of ablative dose delivery or a cohort-specific finding related to the present treatment context.

## **Conclusion**

In this exploratory analysis, D98 was the dose-coverage parameter most consistently associated with 12-month radiographic response and liver-focused progression outcomes after single-fraction CT-guided HDR brachytherapy for breast cancer liver metastases. These results suggest a potential role for near-minimum target coverage metrics in dosimetric evaluation, but they do not establish a definitive surrogate for local control or a validated dose-response threshold. Given the retrospective design, limited cohort size, and methodological constraints of the applied endpoints, the findings should be interpreted cautiously and regarded as hypothesis-generating. External validation in larger prospective cohorts is warranted.

## **Declarations**

## ***Abbreviations***

AUC – area under the curve; BCLM – breast cancer liver metastases; BED – biologically effective dose; CLBT – cumulative liver biochemistry toxicity; CR – complete response; CT

491 – computed tomography; CTCAE – Common Terminology Criteria for Adverse Events;  
492 Dmean – mean dose; EQD2 – equivalent dose in 2 Gy fractions; GTV – gross tumor volume;  
493 HDR-BT – high-dose-rate brachytherapy; HI – homogeneity index; IQR – interquartile range;  
494 LC – local control; MDT – metastasis-directed therapy; MRI – magnetic resonance imaging;  
495 OARs – organs at risk; ORR – objective response rate; PD – progressive disease; PR – partial  
496 response; RECIST – Response Evaluation Criteria in Solid Tumors; RILD – radiation-  
497 induced liver disease; ROC – receiver operating characteristic; rLRPFS – liver-restricted  
498 radiographic progression-free survival; rPFS – radiographic progression-free survival; SBRT  
499 – stereotactic body radiotherapy; SD – stable disease; STROBE – Strengthening the  
500 Reporting of Observational Studies in Epidemiology; V100 – percentage of the target volume  
501 receiving 100% of the prescribed dose; Dmin – minimum dose; D90 – dose delivered to 90%  
502 of the target volume; D95 – dose delivered to 95% of the target volume; D98 – dose delivered  
503 to 98% of the target volume; D100 – dose delivered to 100% of the target volume.

#### 504 ***Ethics approval and consent to participate***

505 The study complied with the Declaration of Helsinki and was approved by the Ethics  
506 Committee of the Lublin Medical Chamber (Lublin, Poland) (approval no. LIL-KB-20/2014).  
507 Owing to the retrospective nature of the study, informed consent to participate was waived.

#### 508 ***Consent for publication***

509 Not applicable.

#### 510 ***Availability of data and materials***

511 The datasets generated and/or analysed during the current study are not publicly available due  
512 to patient privacy and institutional restrictions but are available from the corresponding author  
513 on reasonable request.

#### 514 ***Competing Interests***

515 The authors declare that they have no competing interests.

516 ***Funding***

517 The authors received no specific funding for this work.

518 ***Authors' contributions***

519 Conceptualization: MPP, MB; Methodology and statistics: MPP, PJ, PM, MO, MB;

520 Investigation and data curation: MPP, MB, PJ, PM, EW, SS; Visualization: MPP, PJ, PM;

521 Writing—original draft: MPP, MB, LK, JF; Writing—review and editing: all authors;

522 Supervision: MB, LK. All authors read and approved the final manuscript.

523 ***Acknowledgements***

524 The authors acknowledge the use of artificial intelligence language tools (DeepL Write and  
525 Grammarly) to improve the grammar and readability of the manuscript.

526

527

528 **References**

529 1. Torielli P, McGale J, Liao MJ, et al. Hepatic metastases management: a comparative  
530 review of surgical resection, thermal ablation, and stereotactic body radiation  
531 therapy. *Eur J Cancer*. 2025;228:115691. doi:10.1016/j.ejca.2025.115691.

532 2. Lee SL, Dawson LA, Hosni A. The role of stereotactic body radiation therapy in the  
533 management of liver metastases. *Semin Radiat Oncol*. 2023;33(2):181-192.  
534 doi:10.1016/j.semradonc.2022.11.008.

535 3. Cisek P, Bilski M, Ponikowska J, Wojtyna E, Fijuth J, Kuncman Ł. EORTC/ESTRO  
536 defined induced oligopersistence of liver metastases from colorectal cancer - outcomes  
537 and toxicity profile of computer tomography guided high-dose-rate brachytherapy.  
538 *Clin Exp Metastasis*. 2025 May 12;42(3):29. doi: 10.1007/s10585-025-10348-z.  
539 PMID: 40353987; PMCID: PMC12069121.

4. Walter F, Rottler M, Nierer L, et al. Interstitial high-dose-rate brachytherapy of liver metastases in oligometastatic patients. *Cancers (Basel)*. 2021;13(24):6250. doi:10.3390/cancers13246250.
5. Bilski M, Korab K, Stapór-Fudzińska M, Ponikowska J, Brzozowska A, Sroka Ł, Wojtyna E, Sroka S, Szlag M, Cisek P, Napieralska A. HDR brachytherapy versus robotic-based and linac-based stereotactic ablative body radiotherapy in the treatment of liver metastases - A dosimetric comparison study of three radioablative techniques. *Clin Transl Radiat Oncol*. 2024 Jul 3;48:100815. doi: 10.1016/j.ctro.2024.100815. PMID: 39070028; PMCID: PMC11279445.
6. Colletini F, Schnapauff D, Poellinger A, et al. Percutaneous computed tomography-guided high-dose-rate brachytherapy ablation of breast cancer liver metastases: initial experience with 80 lesions. *J Vasc Interv Radiol*. 2012;23(5):618-626. doi:10.1016/j.jvir.2012.01.079.
7. Bilski M, Kuncman Ł, Orzechowska M, et al. Survival outcomes and toxicity profile after CT-guided HDR brachytherapy (interventional radiotherapy) for liver oligometastases in breast cancer patients: the BRALIBREST real world multicenter study. *Radiother Oncol*. 2026;214:111280. doi:10.1016/j.radonc.2025.111280.
8. Klement RJ, Sweeney RA, Alheit HM, et al. Dose-volume effects in stereotactic body radiotherapy for liver tumors: a systematic review. *Radiother Oncol*. 2018;126(3):382-390. doi:10.1016/j.radonc.2018.03.002.
9. Ohri N, Tomé WA, Méndez Romero A, et al. Local control after stereotactic body radiation therapy for liver tumors. *Int J Radiat Oncol Biol Phys*. 2021;110(1):188-195. doi:10.1016/j.ijrobp.2017.12.288.

10. Kok END, Jansen EPM, Heeres BC, et al. High versus low dose stereotactic body radiation therapy for hepatic metastases. *Clin Transl Radiat Oncol*. 2019;20:45-50. doi:10.1016/j.ctro.2019.11.004.
11. Kirisits C, Rivard MJ, Baltas D, et al. Review of clinical brachytherapy uncertainties: analysis guidelines of GEC-ESTRO and the AAPM. *Radiother Oncol*. 2014;110(1):199-212. doi:10.1016/j.radonc.2013.11.002.
12. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228–247. doi:10.1016/j.ejca.2008.10.026.
13. Kataria T, Sharma K, Subramani V, Karrthick KP, Bisht SS. Homogeneity Index: An objective tool for assessment of conformal radiation treatments. *J Med Phys*. 2012;37(4):207–213. doi: 10.4103/0971-6203.103606.
14. Guerrero M, Li XA. Extending the linear–quadratic model for large fraction doses pertinent to stereotactic radiotherapy. *Phys Med Biol*. 2004;49(20):4825–4835. doi: 10.1088/0031-9155/49/20/012.
15. Shuryak I, Carlson DJ, Brown JM, Brenner DJ. High-dose and fractionation effects in stereotactic radiation therapy: analysis of tumour control data from 1,308 lesions. *Radiother Oncol*. 2015;115(3):327–334. doi: 10.1016/j.radonc.2015.05.013.
16. Robin X, Turck N, Hainard A, et al. pROC: an open-source package for R and S+ to analyse and compare ROC curves. *BMC Bioinformatics*. 2011;12:77. doi: 10.1186/1471-2105-12-77.
17. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat*. 1988;16(3):1141-1154. doi:10.1214/aos/1176350951.

18. Bilski M, Korab K, Orzechowska M, Ponikowska J, Cisek P, Jereczek-Fossa BA, et al. Comprehensive cohort study: computer tomography-guided high-dose rate brachytherapy as metastasis-directed therapy for liver metastases from colorectal cancer in repeat oligoprogression. *Radiol Med*. 2025 May;130(5):694-705. doi:10.1007/s11547-025-01988-y.
19. Cisek P, Kuncman Ł, Jereczek-Fossa BA, Wojtyna E, Orzechowska M, Sroka S, et al. Computed tomography guided high dose rate brachytherapy for induced oligoprogression of colorectal cancer liver metastases. *Sci Rep*. 2025;15(1):22735. doi:10.1038/s41598-025-09227-0.
20. Dejonckheere CS, Bilski M, Nour Y, Scafa D, Cisek P, Korab K, et al. A dosimetric comparison of different radiotherapy modalities for non-resected oligometastatic liver disease. *Clin Transl Radiat Oncol*. 2025;52:100947. doi:10.1016/j.ctro.2025.100947.
21. Bilski M, Peszynska-Piorun M, Konat-Baska K, Brzozowska A, Korab K, Wojtyna E, Janiak P, Ponikowska J, Sroka S, Cisek P, Fijuth J, Kuncman Ł. Radiotherapy as a metastasis-directed therapy for liver oligometastases: comparative analysis between CT-guided interstitial HDR brachytherapy and two SBRT modalities performed on double-layer and single-layer LINACs. *Front Oncol*. 2024;14:1478872. doi:10.3389/fonc.2024.1478872.
22. Sosa-Marrero C, Acosta O, Pasquier D, Thariat J, Delpon G, Fiorino C, et al. Voxel-wise analysis: a powerful tool to predict radio-induced toxicity and potentially perform personalised planning in radiotherapy. *Cancer Radiother*. 2023;27(5):638-642. doi:10.1016/j.canrad.2023.06.024.
23. Zlotnik O, Krzywoń J, Patel N, Kunovsky L, Kopelovich M, Kakiashvili E, et al. Targeting liver metastases to potentiate immunotherapy in MS-stable colorectal

610 cancer: a review of the literature. *Cancers (Basel)*. 2023;15(21):5210.  
611 doi:10.3390/cancers15215210.

612 24. Khorrami M, Viswanathan VS, Reddy P, Braman N, Kunte S, Gupta A, et al.  
613 Radiomic predicts early response to CDK4/6 inhibitors in hormone receptor positive  
614 metastatic breast cancer. *NPJ Breast Cancer*. 2023;9(1):67. doi:10.1038/s41523-023-  
615 00574-7.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [supplementaryDoseResponse.docx](#)