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CT-Guided Iodine-125 seed brachytherapy for oligometastatic gynecologic malignancies: long-term survival and predictors of response

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Purpose: This retrospective study aimed to evaluate the efficacy, safety, and prognostic factors of CT-Guided Iodine-125 seed brachytherapy for oligometastatic gynecologic malignancies.

Methods: Sixty-two patients with oligometastatic gynecologic malignancies were treated with Iodine-125 seed brachytherapy. Objective response rate (ORR), local control rate (LCR), overall survival (OS), and adverse events were evaluated. Survival rates were calculated using the Kaplan-Meier method. Univariate and multivariate analyses were performed using logistic regression and Cox proportional hazards models to explore factors affecting efficacy.

Results: The ORR evaluated at 6 and 12 months were 61.0% and 67.0%, respectively. The 6- and 12-month LCR were 100% and 88.7%, respectively. The 1-, 2-, 3-, and 4-year survival rates were 88.7%, 65.7%, 53.2%, and 42.8%, respectively. Postoperative adverse events included grade 1 chronic radiation dermatitis in one pati ent, and postoperative hemorrhage with intratumoral liquefactive necrosis (secondary

infection not ruled out) in another. Multivariate logistic regression analysis revealed that the dose delivered to 90% of the target volume (D90) (odds ratio [OR] = 0.970; 95% confidence interval [CI]: 0.951, 0.990; $P = 0.003$) was a significant predictor of short-term treatment response. Specifically, a D90 ≥ 105.6 Gy was associated with superior treatment response. Furthermore, multivariate Cox analysis showed that all local therapy (all-LT) (Hazard Ratio [HR] = 0.220; 95% CI: 0.097, 0.496; $P < 0.001$) was a protective factor for OS.

Conclusion: Iodine-125 seed brachytherapy appears safe and effective for oligometastatic gynecologic malignancies. A D90 ≥105.6 Gy was associated with better efficacy, and all-LT may prolong survival.

Clinical trial number: not applicable.

Keywords

gynecologic malignancies; oligometastatic disease; Iodine-125 seed; Brachytherapy; overall survival

Malignant tumors of the female reproductive system, primarily cervical, endometrial, and ovarian cancers, pose a substantial threat to women's health, demonstrating an incidence of 30.3 per 100,000 and a mortality rate of 13.2 per 100,000[1]. Recurrent and metastatic gynecologic malignancies are frequently encountered and are typically treated with systemic therapy, with or without local therapy. Of note, current guidelines highlight the importance of local therapy specifically for oligometastatic cervical and endometrial cancers[2][3].

In 1995, Hellman and Weichselbaum first proposed the concept of

oligometastatic disease (OMD). OMD represents an intermediate state between localized disease and widespread metastatic disease, serving as a critical stage for potentially prolonging overall survival (OS) in patients with advanced gynecologic malignancies[4][5][6]. Notably, the SABR-COMET phase II trial indicated a substantial survival benefit with stereotactic ablative radiotherapy (SABR), elevating the 5-year OS rate from 17.7% to 42.3%[7]. the OligoCare cohort study reported 1- and 3-year LCR of 95.0% and 88.6%, respectively[8]. Specifically regarding gynecologic malignancies, Yegya-Raman et al. observed that the median progression-free survival (PFS) ranged from 3.3 to 21.7 months following SABR[9]. Within the spectrum of local therapies, SABR has emerged as the primary non-surgical modality for managing OMD. Nevertheless, its application in the re-irradiation setting is often constrained by the heightened risk of radiation-related adverse events[10][11]. Conversely, Iodine-125 seed brachytherapy can substantially reduce the dose delivered to organs at risk (OARs)[12]. Via continuous low-dose-rate irradiation, The iodine-125 seed exerts potent cytotoxic effects against both hypoxic tumor cells and those traversing various stages of the cell cycle. Currently, exploratory studies of Iodine-125 seed brachytherapy specifically for oligometastatic gynecologic malignancies remain scarce. Therefore, this study retrospectively analyzed patients with oligometastatic gynecologic malignancies treated with Iodine-125 seed brachytherapy, and reports the preliminary clinical outcomes.

Materials and Methods

Patients

This retrospective study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee(2026-LW-272), and the need for informed consent was waived owing to the minimal risk posed to participants. From March 2018 to December 2024, based on the following inclusion and exclusion criteria, a total of 62 patients were ultimately included in this study (**Fig. 1**).

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: i) histologically confirmed primary gynecologic malignancies; ii) oligometastatic disease occurring after first-line standard treatment; and iii) ≤5 growing or newly developed metastatic lesions, including regional lymph node metastases. Oligometastasis was defined as a controlled primary tumor with the presence of a limited number (≤5) of growing or newly developed metastatic lesions, including regional lymph node metastases[9]. The diagnosis of oligometastasis was confirmed by a multidisciplinary team based on imaging findings, with pathological verification when clinically indicated.

The exclusion criteria were as follows: i) widespread metastatic gynecologic malignancies; ii) double primary malignancies; iii) uncontrolled primary tumor; and iv) receipt of concurrent Iodine-125 seed brachytherapy and other local ablative therapies (e.g., thermal ablation, external beam radiotherapy, or chemoembolization) targeting the same metastatic lesion.

Iodine-125 seed brachytherapy

One week prior to seed implantation, patients underwent planning CT of the

target region in the designated treatment position (prone, supine, or lateral decubitus). The acquired images were transferred to a treatment planning system (TPS; SSGI Inc., USA). Physicians manually delineated the gross tumor volume (GTV) and organs at risk (OARs). The clinical target volume (CTV) was generated by uniformly expanding the GTV by 5 mm. OAR dose constraints were referenced using equivalent external beam radiotherapy dose conversion[13]. Seed activities ranged from 11.1 to 29.6 MBq, with a prescribed dose of 80–140 Gy. Subsequently, medical physicists optimized needle trajectories, seed positions, and dose distributions within the target and adjacent OARs, generating dose-volume histograms (DVHs).

Prior to the procedure, Iodine-125 seed activity was measured using a radionuclide calibrator (CRC-25R; Capintec Inc., USA). If the deviation in measured activity was within 5%, the seeds were loaded into the sterile applicator device housing for subsequent implantation. Under combined ultrasound and CT guidance, implantation needles (model 1820-C; Mick Radio-Nuclear Instruments, USA) were advanced to the predetermined locations. For large tumors or complex anatomical regions, a 3D-printed template (Unicorn 3DSL450M; Beijing Unicorn Science and Technology Ltd., China) was utilized to facilitate precise needle guidance and seed implantation. Following the preoperative plan, Iodine-125 seeds were implanted intraoperatively using a Mick200-TPV applicator (Mick Radio-Nuclear Instruments, USA), with real-time adjustment of seed positions and numbers as needed. Following needle removal, manual compression was applied to the puncture site for 10–20 minutes. An immediate postoperative CT scan was then performed to evaluate for

bleeding, hematoma, air embolism, and other procedural complications. Upon returning to the ward, patients maintained local compression with a sandbag for an additional 2-4 hours. Within 1 week post-implantation, a follow-up CT scan of the target area was obtained, and the imaging data were imported into the TPS for postoperative dosimetric verification and quality assurance.

Efficacy Evaluation and Influencing Factors

The primary endpoint was OS, defined as the time from commencement of Iodine-125 seed brachytherapy to all-cause mortality. Local tumor response was evaluated per RECIST version 1.1 and dichotomized into objective response (complete response [CR] or partial response [PR]) or non-response (stable disease [SD] or progressive disease [PD]). The objective response rate (ORR) was defined as (CR + PR) / total evaluable patients × 100%, and the local control rate (LCR) was defined as (CR + PR + SD) / total evaluable patients × 100%.

Adverse Events

Patients were closely monitored postoperatively and during the follow-up period for adverse events, including bleeding, hematoma, seed migration, and intestinal fistula, among others. Radiation-induced toxicities were graded using the Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer (RTOG/EORTC) grading system.

Statistical Analysis

Statistical analyses were performed using SPSS version 25.0. Quantitative data are presented as mean ± standard deviation (SD) or median with interquartile range

(IQR), while categorical data are expressed as frequencies and percentages. Comparisons of continuous variables were conducted using the independent-samples t-test or Wilcoxon rank-sum test, as appropriate. Univariate and multivariate analyses were performed using logistic regression and Cox proportional hazards models to identify prognostic factors. Survival curves were estimated using the Kaplan-Meier method, and differences between groups were assessed using the log-rank test. A P value < 0.05 was considered statistically significant.

Results

Patient Characteristics

62 patients (100 lesions) with oligometastatic gynecologic malignancies were

Table 1 Baseline Patient Characteristics

Characteristics		n	%
Age, years	<50	15	24.2
	≥50	47	75.8
Tumor type	Cervical cancer	37	59.7
	Endometrial cancer	10	16.1
	Ovarian cancer	7	11.3
	Fallopian tube cancer	1	1.6
	Vaginal cancer	1	1.6
	Vulvar cancer	4	6.5
	Uterine leiomyosarcoma	2	3.2
Prior therapies	Surgery + Radiotherapy + Chemotherapy	40	64.5
	Radiotherapy + Chemotherapy	7	11.3
	Surgery + Radiotherapy	1	1.6
	Radiotherapy	1	1.6
	Surgery + Chemotherapy	9	14.5
	Surgery	4	6.5
Number of lesions	1 ~ 2	34	54.8
	3 ~ 5	28	45.2
Postoperative combined systemic therapy	Yes	46	74.2
	No	16	25.8
all-LT	Yes	30	48.4
	No	32	51.6
D90 (Gy)*	114.5±25.6		
D100 (Gy)*	67.6±25.5		
Maximum diameter (mm)*	29.5（IQR, 20.0 - 42.7）		

*mean ± standard deviation or median with interquartile range

treated with CT-guided Iodine-125 seed brachytherapy. Seed activity ranged from 11.1 to 29.6 MBq, and the prescribed dose was 80-140 Gy. The follow-up duration was defined as the interval from the date of the initial seed implantation to the date of death or the last known follow-up. The median follow-up time for the entire cohort was 21.7 months (range, 8.0-92.0 months). Detailed clinical characteristics are shown in **Table 1**.

Local therapy (LT) was categorized into two strategies: all-LT and partial-LT. all-LT was defined as treatment delivered to all identifiable lesions on preoperative imaging, while partial-LT targeted only the dominant or symptomatic lesions.

Efficacy

The median follow-up time was 21.7 months (range, 8.0-92.0 months). The ORR evaluated at 6 and 12 months were 61.0%(61/100) and 67.0%(65/97), respectively. The 6- and 12-month LCR were 100%(100/100) and 88.7%(86/97), respectively. As of June 30, 2026, 31 patients had died. The causes of death included tumor progression (n = 28), pulmonary embolism (n = 1), and myocardial infarction (n = 2).The 1-, 2-, 3-, and 4-year survival rates were 88.7%, 65.7%, 53.2%, and 42.8%, respectively. The survival analysis is shown in **Fig. 2** and a representative case is shown in **Fig. 3**.

The logistic regression analysis evaluated the following covariates: tumor type, concurrent systemic therapy, maximum tumor diameter, D90, and D100. Univariate analysis revealed significant associations of maximum tumor diameter, D90, and D100 with treatment response at 6 months post-implantation. Subsequent multivariate

analysis identified D90 as an independent predictor of 6-month post-implantation treatment response (**Table 2**). Furthermore, receiver operating characteristic (ROC) curve analysis determined an optimal cutoff value of 105.6 Gy for D90, yielding a corresponding area under the curve (AUC) of 0.714(**Fig. 4**).

169 The Cox proportional hazards model included all-LT, number of lesions,

Table 2 Factors Associated with Short-Term Efficacy of Iodine-125 seed brachytherapy in oligometastatic gynecologic malignancies: A Logistic Regression Analysis

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Tumor type				
Cervical cancer				
Endometrial cancer	3.900 (0.800 ~ 19.009)	0.092		
Ovarian cancer	3.900(0.645 ~ 23.598)	0.138		
Others	5.571(0.880 ~ 35.268)	0.068		
Combined systemic therapy	0.465 (0.188 ~ 1.149)	0.097		
Maximum diameter	1.028 (1.006 ~ 1.050)	**0.012**		
D90	0.970(0.951 ~ 0.990)	**0.003**	0.970(0.951 ~ 0.990)	**0.003**
D100	0.976 (0.957 ~ 0.996)	**0.020**		

OR = Odds Ratio, CI = Confidence Interval.

Table 3 Univariable and Multivariable Cox Proportional Hazards Model for Overall Survival in oligometastatic gynecologic malignancies

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
all-LT* (Yes vs. No)	0.22 (0.10 ~ 0.50)	**<.001**	0.22 (0.10 ~ 0.50)	**<.001**
Number of lesions ≥2(Yes vs. No)	0.53 (0.26 ~ 1.08)	0.080		
Combined systemic therapy (Yes vs. No)	0.68 (0.31 ~ 1.47)	0.324		
Initial stage (I+II vs. III+IV)	1.34 (0.66 ~ 2.73)	0.417		
Tumor type				
Cervical cancer				
Endometrial cancer	0.46 (0.16 ~ 1.27)	0.134		
Ovarian cancer	0.64 (0.19 ~ 2.18)	0.477		
Others	0.72 (0.24 ~ 2.11)	0.546		

HR = Hazard Ratio, CI = Confidence Interval.

*1 patient received microwave ablation for hepatic metastases, 1 patient received microwave ablation for pulmonary metastases, 1 patient received combined proton therapy and microwave ablation for pulmonary metastases, and 1 patient received external beam radiotherapy for retroperitoneal lymph node metasta;

concurrent systemic therapy, initial stage, and tumor type. Univariate analysis demonstrated a significant association between all-LT and OS. Subsequent multivariate analysis of variables with a univariate *P* value < 0.1 confirmed all-LT as an independent predictor of OS (**Table 3 and Fig. 5**).

Adverse Events

Intraoperatively, no massive hemorrhage or localized hematomas were encountered. One patient developed right groin skin pigmentation (4 × 2 cm) at 1 month postoperatively, consistent with grade 1 chronic radiation dermatitis, which resolved completely by 5 months after surgery. In a separate case, a patient with left chest wall metastasis from cervical cancer experienced postoperative hemorrhage following Iodine-125 seed brachytherapy; CT confirmed a left pleural effusion consistent with bleeding. On postoperative day 2, the patient developed a fever (peak ~39.5°C, without chills) that was refractory to empiric antibiotic therapy. By postoperative day 20, CT revealed intratumoral liquefactive necrosis. Aspiration yielded purulent necrotic debris, but cultures remained persistently negative. Although a secondary infection could not be ruled out, the patient received an 8-day course of intravenous meropenem, with temperatures decreasing to ~38°C and the fever resolving completely by 2 months after seed implantation. No other adverse events attributable to the procedure, including radiation pneumonitis, neuropathy, or radiation enteritis, were documented.

Discussion

Over the past four decades, substantial improvements in overall survival have been observed globally among patients with gynecologic malignancies. In particular, the 5-year relative survival rates for cervical cancer have increased by 20 to 40 percentage points in some regions[14]. As reported by Yang et al., patients with cervical cancer who achieved progression-free survival with three years (PFS36) had a 5-year OS rate of 98.2%, compared with only 30.3% in those without PFS36, highlighting the profound detrimental impact of disease progression on overall survival[15]. A distinct transitional state exists between locally advanced and widely metastatic disease, defined by a limited metastatic burden and localized anatomical spread. It is at this stage that aggressive local therapy holds the promise of achieving durable remission and consequently prolonging overall survival[16].

Iodine-125 seed brachytherapy delivers continuous low-energy gamma rays, exerting persistent cytotoxic effects against tumor cells within the target volume while minimizing collateral damage to adjacent OARs.In this study, the LCR at 6 and 12 months post-implantation were 100% and 88.7%, respectively, and the 1-, 2-, 3-, and 4-year survival rates were 88.7%, 65.7%, 53.2%, and 42.8%, respectively. Regarding treatment-related toxicities, One patient developed grade 1 chronic radiation dermatitis, and another patient experienced postoperative hemorrhage with intratumoral liquefactive necrosis. Reshko et al. reported 1- and 3-year survival rates of 70% and 39%, respectively, for SBRT in recurrent, persistent, or oligometastatic extracranial gynecologic malignancies, with 4.3% of patients experiencing ≥ grade 2 toxicities[17]. Huck et al. documented a 2-year survival rate of 78% following

SBRT for recurrent oligometastatic ovarian cancer[18]. Li et al. reported a 3-year survival rate of 44.4% for VMAT in recurrent cervical cancer, with 28% of patients experiencing ≥ grade 3 acute toxicities, and 18% experiencing ≥ grade 3 late toxicities[19]. In summary, postoperative survival after Iodine-125 seed brachytherapy appears broadly comparable to that reported for external beam radiotherapy, while the rate of severe adverse events appears lower. Possible explanations are as follows: (1) Owing to the low-energy photon spectrum (27–35 keV) and tissue half-value layer of 2 cm, I-125 seeds exhibit a steep peritumoral dose fall-off. This physical characteristic facilitates achieving the prescribed D90 to the GTV while ensuring sharp sparing of adjacent OARs; (2) protracted low-dose-rate irradiation exerts cytotoxic effects regardless of cell-cycle phase while facilitating the repair of sublethal injury in normal tissues; and (3) auxiliary intraoperative maneuvers, including contrast visualization of hollow organs, fluid-assisted displacement, and gel-spacing, effectively displace critical structures (eg, bowel, major vessels, and nerves), thereby further enhancing the safety margin.

This study identified all-LT as an independent prognostic factor for improved OS in patients with gynecologic malignancies treated with Iodine-125 seed brachytherapy. Xu et al. reported median OS values of 40.9, 34.1, and 30.8 months in patients with synchronous oligometastatic Non-small Cell Lung Cancer (NSCLC) receiving all-LT, partial-LT, and non-LT, respectively. The difference between the all-LT group and the partial-LT or non-LT group was statistically significant ($p < 0.001$), whereas the

difference between the partial-LT and non-LT groups was not[20]. Wiesweg et al. similarly reported a median OS of 27.8 months among patients with oligometastatic NSCLC overall, compared with 34.4 months in those who received all-LT[21]. So et al. reported in a phase II clinical trial of SBRT plus pembrolizumab for PD-1-resistant recurrent and metastatic head and neck squamous cell carcinoma that all-LT prolonged median OS compared with SBRT to only a single metastasis while leaving other lesions untreated (10.1 vs. 7.6 months). They also found that patients with PFS > 3 months had a higher frequency of central memory CD8+ T cells and significantly up-regulated CXCR5 expression in memory B cells[22]. all-LT may maximally reduce tumor burden, mitigate tumor heterogeneity and clonal evolution, suppress the proliferation of drug-resistant clones, and enhance sensitivity to systemic therapy. In addition, as a form of radiotherapy, radioactive seed implantation may release tumor-associated antigens and elicit a specific immune response; combining this approach with immunotherapy may further improve clinical outcomes[23][24]. Therefore, radioactive seed implantation targeting all oligometastatic lesions may help prolong survival.

Local control serves as a key determinant of OS, underscoring the critical importance of optimizing local disease management[20][21]. This study identified D90 as an independent predictor of 6-month post-implantation treatment response, with D90 ≥105.6 Gy significantly associated with superior treatment response. Owing to the lack of a universally standardized protocol for radioactive seed implantation, inter-operator variability can directly compromise the final dose distribution and

clinical outcomes. Based on our findings, we recommend that the prescription dose to the clinical target volume exceed 105.6 Gy in patients with oligometastatic gynecologic malignancies. This should be achieved through CT-guided implantation with 3D-printed template assistance, intraoperative real-time treatment planning, and postoperative dynamic dosimetric verification to optimize the dose distribution. For large tumors, a fractionated implantation strategy may be considered. In cases with liquefactive necrosis, intraoperative injection of contrast agent into the cystic cavity—followed by prompt drainage and sclerotherapy—helps prevent seed displacement or sedimentation, thereby minimizing the risk of local underdosing and enhancing treatment efficacy.

Functioning as a minimally invasive brachytherapy technique, Iodine-125 seed brachytherapy achieves favorable tumor control with minimal treatment-related morbidity, representing a promising therapeutic avenue for oligometastatic gynecologic malignancies. Nevertheless, critical knowledge gaps persist regarding the optimal therapeutic window, dose-prescription parameters, and rational integration with systemic therapies. These results should be interpreted with caution, given the inherent limitations of this retrospective analysis, including the modest cohort size, restricted follow-up, and pote ntial for residual confounding. Future multicenter, prospective trials with larger sample sizes and longer observation periods are essential to corroborate the clinical utility of comprehensive Iodine-125 seed brachytherapy in this setting.

Declarations

Ethics approval and consent to participate

This retrospective study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by Hebei General Hospital Ethics Committee(2026-LW-272). and the need for informed consent was waived owing to the minimal risk posed to participants.

Consent for publication

Not Applicable.

Availability of data and materials

The datasets used and analyzed during the present study are available from the corresponding author at the reasonable request.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authors' contributions

HZ and XD are the study sponsors. HZ and SR designed research process; HZ, SR, XD, SN, JZ, and SZ screened and reviewed all literature that conforms to the inclusion criteria and complete statistical analysis of the data; HZ, SR, ZG, HY, KX and ZL interpreted the outcomes; HZ made the decision to submit the article for publication. All authors read and approved the finally manuscript.

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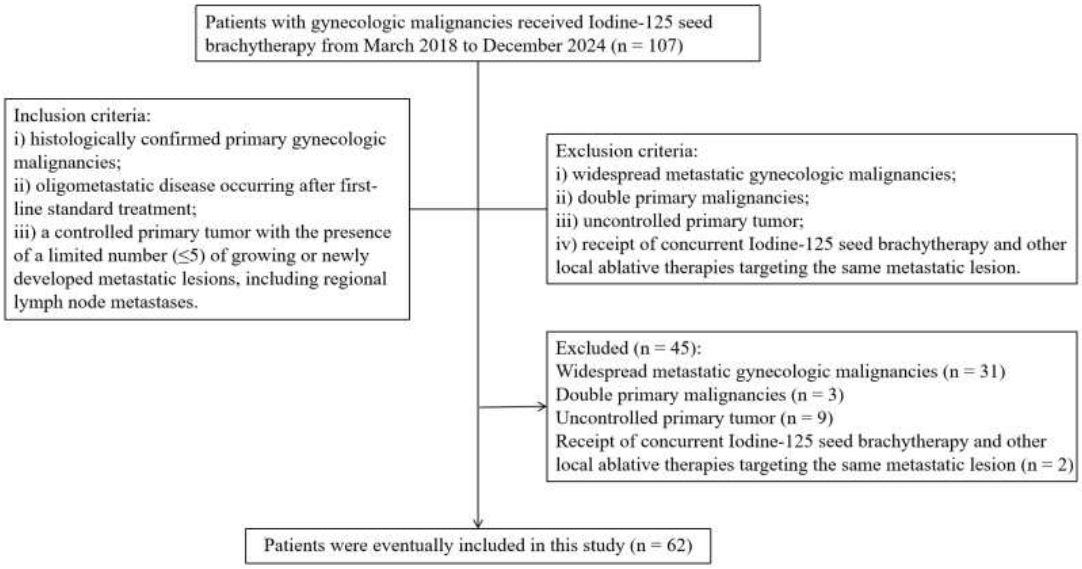
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395
396 **Fig. 1** Patient flow diagram
397

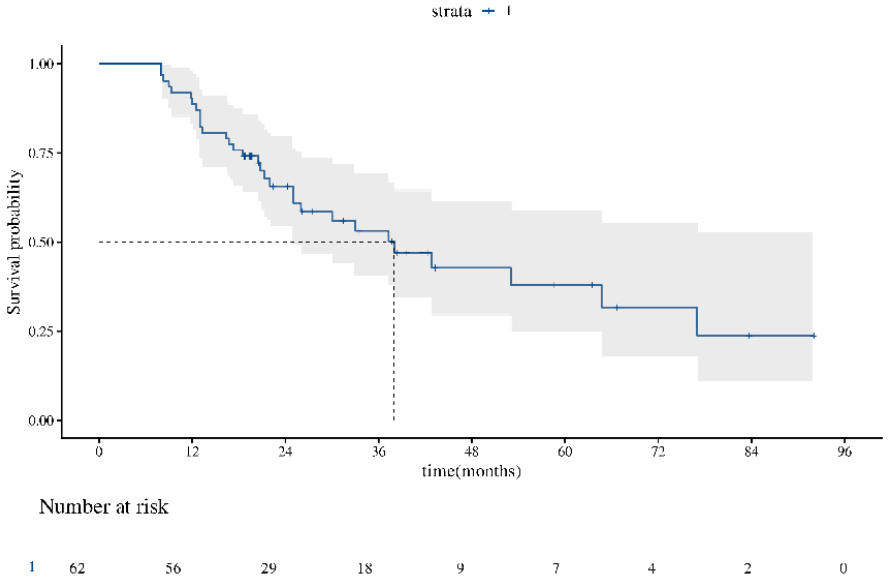


Fig.2 Kaplan-Meier curve of overall survival for all 62 patients.

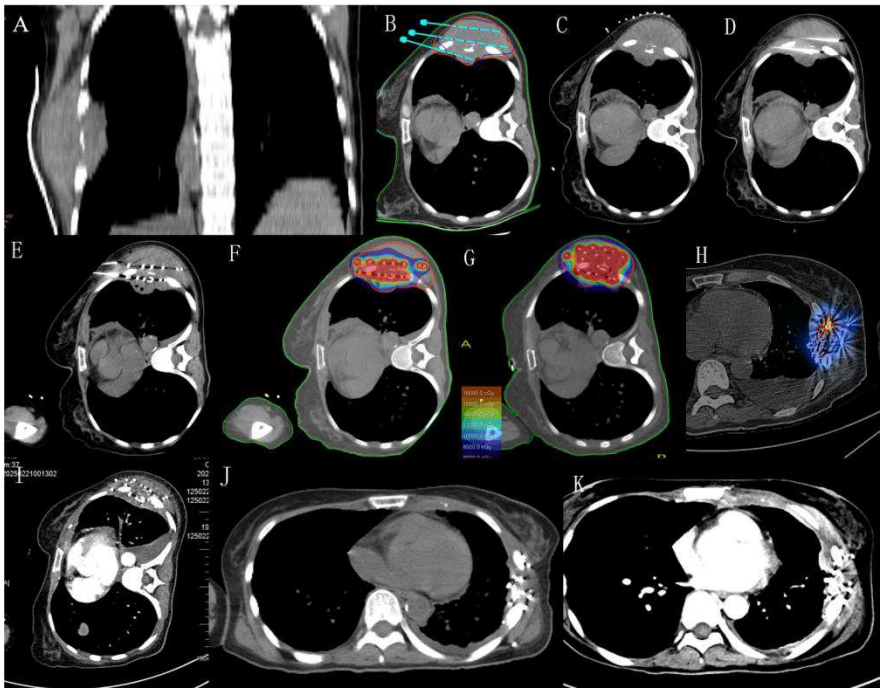
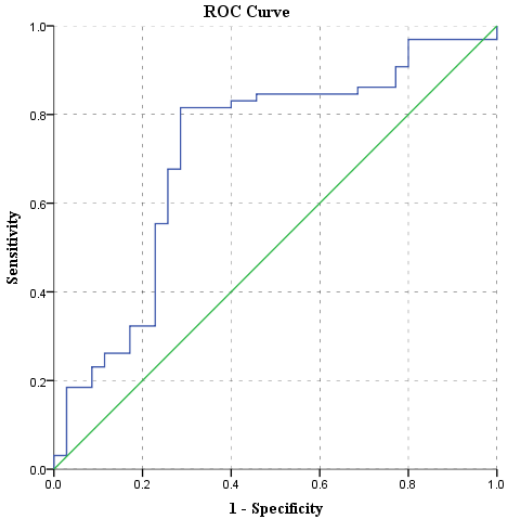
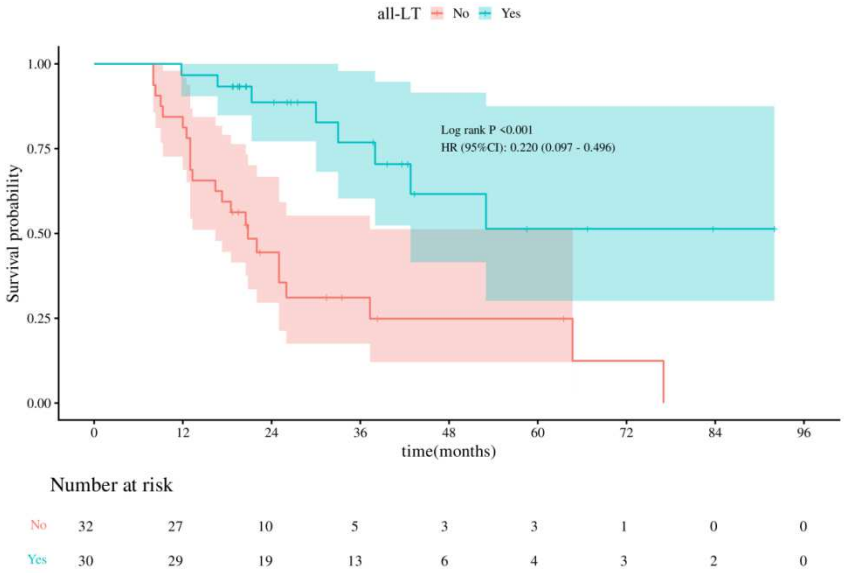


Fig. 3 A patient with stage IB3 cervical squamous cell carcinoma developed a left chest wall metastasis (measuring approximately 79 × 63 × 84 mm) after prior surgery and chemoradiotherapy. (A) Preoperative axial CT image. (B) Preoperative treatment plan formulated by the medical physicist. (C-E) Stepwise seed implantation. (F) Intraoperative treatment planning. (G) Postoperative dosimetric verification. (H) post-implantation SPECT/CT-detected γ-rays. (I) Two months postoperatively. (J) Six months postoperatively. (K) Seven months postoperatively.



409

410 **Fig. 4** Receiver operating characteristic (ROC) curve for D90 in predicting short-term
411 treatment response.



412

413 **Fig. 5** Subgroup analysis of OS based on all-LT (yes vs. no).

414

Supplementary Files

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- TABLE.doc