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Impact of radiation source activity on short- and long-term outcomes of cervical carcinoma patients treated with high-dose-rate brachytherapy: A retrospective cohort study

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HIGHLIGHTS

- 510 patients with median (interquartile) follow-up time of 47.1 (33.9–66.4) months.
- 9-fold activity varieties; 17 source replacements at intervals ranging 93–199 days.
- LRFS and MRFS using LR were significantly non-inferior to that of HR.
- LR was significantly better in partial early stage patients' long-term outcomes.
- Support optimized balance on clinical, financial and environmental considerations.

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ABSTRACT

Objective. High-dose-rate (HDR) afterloading brachytherapy using Iridium-192 source involves large radiation activity varieties due to fast decay. It was unknown but clinically desirable to evaluate its impacts on patient outcomes to support more informed decisions.

Methods. Data of 510 cervical carcinoma (CC) patients were retrospectively included. High-radioactive (HR) and low-radioactive (LR) groups were statistically defined per patient-specific average mean-dose-rate (MDR) of all fractions. The cutoffs were calculated using R-3.6.1 packages based on significance of correlation with binary outcome or survival time. Categorized 1-month and 3-month follow-up results were analyzed as short-term outcomes. Long-term outcomes were evaluated using local recurrence-free survival (LRFS) and metastatic recurrence-free survival (MRFS). Propensity-score-matched (PSM) pairs were generated to reduce bias.

Results. The median follow-up time was 47.1 months (interquartile range: 33.9 months–66.4 months), involving MDR varieties of up to 9 folds ranging from 6059.99 cGy/h to 54013.66 cGy/h due to 17 source replacements at intervals ranging from 93 days–199 days. Both short-term (1-month: $p = 0.22$; 3-month: $p = 0.79$) and long-term (LRFS: $p = 0.10$; MRFS: $p = 0.46$) outcomes showed no significant difference between HR and LR. Subgroup analysis displayed significantly better results in LR for stage I–II (3-month, $p = 0.02$) and stage II (LRFS, $p = 0.04$) patients. Both LRFS and MRFS of LR were significantly non-inferior to HR ($p \le 0.02$).

Conclusions. LR is clinically non-inferior or partially superior to HR for CC treatment using HDR, which dispels concerns of potentially undermined patient outcomes when source replacement is delayed.

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1. Introduction

Cervical carcinoma (CC) is the fourth most common cancer diagnosed in women worldwide, near 85% of which occurred in low- and middle- income countries, causing considerable social and economic burdens [1]. As a critical component of definitive radiation therapy for CC, brachytherapy provides dose boost to the cervix, which improves local control probabilities and overall survival rates significantly [2].

According to the activities of radiation source, brachytherapy is classified into high-dose-rate (HDR) and low-dose-rate (LDR) treatment. Since the commercial manufacture of high-activity source became reliable in 1960s, HDR has been dominantly applied to CC treatment because of many physical advantages over LDR, such as decreased radiation exposure to clinical staff and the general public, shortened hospitalization, and improved stability of the applicators [3,4]. Different biological effects between HDR and LDR have been investigated thoroughly in both prospective and retrospective studies [5,6], suggesting biological benefits from LDR in terms of normal tissue repair [7,8], although the impact on patient survival [9,10] was statistically insignificant.

Iridium-192 (Ir-192) is broadly used for HDR afterloading brachytherapy, which has relatively short half-life of ~74 days. However, delayed source replacement is very common in clinics due to many possible reasons, such as unexpected public events, administrative regulations, supply shortage, or budget limitation especially for hospitals serving few HDR patients, etc., which causes large varieties of dose rate in treatment delivery. Less efficient source activity inevitably increases delivery time, patient uncomfortableness and motion uncertainties. However, it is unknown if there is a potential biological impact of lower source activity on patient short-term and long-term outcomes, i.e., differences in both acute and late effects, within the dose-rate scope of HDR modality (>12 Gy/h) [11], which might be different from that of LDR. These missing evidences are needed to support more informed clinical decisions such as prescription adaptation and optimization, which is the aim of this study.

2. Methods and materials

2.1. Patients and dose-rate

Under appropriate IRB approval (ID: 2019YJZ63), this single institutional retrospective cohort study examined 747 patients with pathologically-confirmed FIGO (International Federation of Gynecology and Obstetrics) stage IA-IVB CC, who were treated with external beam radiotherapy and intracavitary brachytherapy under consistent protocols at our hospital between April 2011 and April 2017. Using intensity modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT) techniques, prescribed dose of 45 Gy in 25 daily fractions was delivered to the planning target volume (PTV), with or without concurrent chemotherapy according to NCCN (National Comprehensive Cancer Network) guidelines. Concurrent chemotherapy was not applied to some patients because: (1) patients were of an early stage; (2) patients refused chemotherapy; (3) patients were too old or too weak to receive chemotherapy; (4) patients' white blood cell counts were too low during brachytherapy, etc. The clinical target volume (CTV) covered the gross disease, corpus, whole uterus, parametria, sufficient vaginal margin from the gross disease (at least 3 cm), presacral nodes, and nodal volumes at risk. For patients with gross lymphadenopathy, a simultaneous integrated boost regimen of 60 Gy in 25 fractions was prescribed to the involved lymph nodes.

Intracavitary brachytherapy boost using Ir-192 HDR technique was applied to patients in 3–4 weeks after the first fraction of external beam radiotherapy. The equivalent dose in 2 Gy (EQD2) (assuming an α/β ratio of 10) to point A (a reference location 2 cm superior and 2 cm lateral to the central cervical os) ranged from 80 Gy to 85 Gy. The doses to point A, rectum, and bladder were calculated according to the International Commission on Radiation Units and Measurements (ICRU-38) recommendations [12]. The external and brachytherapy treatment planning were performed on Varian Eclipse system (Varian Medical System, Palo Alto, CA) and Oncentra Brachy system (Elekta AB, Stockholm, Sweden) respectively. Intracavitary brachytherapy was delivered on microSelectron Digital (HDR-V3) Brachytherapy Afterloader (Elekta Inc., Atlanta, GA, USA) using an Ir-192 source.

In accordance with the recommendation of NCCN Guidelines version 1.2020 for cervical cancer [13], it was attempted to limit the entire radiotherapy course including both external beam radiotherapy and brachytherapy within 56 days, or 8 weeks. The mean overall treatment time of the involved patients was 43.3 days (95% CIs were 42.8 to 43.8 days respectively), and only 10 out of 510 (1.96%) patients' overall treatment time were beyond 56 days.

To be more clinically relevant, the mean-dose-rate (MDR) was used for this study instead of the encapsulated source activity [14]. To simplify the problem, patients experiencing source replacement during their HDR treatment courses were excluded from this study. The dose-rate of each patient was represented by the average MDR value of the consecutive treatment fractions. To differentiate from the naming of HDR vs. LDR, high-radioactive and low-radioactive within the dose-rate range of HDR were abbreviated as HR and LR respectively, which were retrospectively and statistically defined by cut-off values of average MDR determined by receiver operating characteristic (ROC) analysis, according to the method in Okazaki's work [15].

2.2. Patient follow-up

Radiographic imaging was performed 1 month and 3 months after treatment, and clinical examination was performed 3 months after treatment. Follow-up examinations were conducted every 3 months for the first two years; every 6 months from the third to the fifth years; and annually since the sixth year. Examinations comprised physical examination, liver and kidney function, pelvic MRI, abdominal CT, thoracic CT and lymph node ultrasonography, etc. Per our clinical protocols, all radiographic imaging was evaluated and reconfirmed by at least two experienced radiologists. The short-term outcome was evaluated based on patients' response at 1-month and 3-month after brachytherapy according to RECIST 1.1 (Response Evaluation Criteria in Solid Tumors), which is commonly used for solid tumors to reflect the acute effect of treatment [16], including CR (complete response), PR (partial response), SD (stable disease), and PD (progressive disease) respectively. The long-term outcome was evaluated as patients' local recurrence-free survival (LRFS) and metastatic recurrence-free survival (MRFS) respectively in at least 6 months after brachytherapy, unless local recurrence or metastatic recurrence was observed before that, which were the major causes of clinical failure for cervical carcinoma [5]. The LRFS and MRFS were selected because of their strong association with the local control and reflection on the brachytherapy outcome [17]. LRFS was defined from the start of radiotherapy to central recurrence. Considering brachytherapy treats primary tumor mostly and has less effect on lymph nodes, the nodal recurrences were not included in this study. For the patients with suspicious central recurrences, biopsy was carried out to confirm. MRFS was defined from the start of radiotherapy to distant metastasis. Patients with metastasis were not excluded from the LRFS analysis. All the recurrences were scored, not just the first recurrence.

2.3. Propensity score matching and statistical analysis

To balance the patient baseline covariates between HR and LR groups, propensity score matching (PSM) was performed using the MatchIt package [18]. The nearest neighbor matching method was used to create the synthetic populations with matched baseline covariates. Propensity scores were estimated using a logistic regression model based on age, pathology, staging, tumor differentiation, number of treatments, treatment durations between the first and last treatment

days, mean dose, pre-treatment serum indices (squamous cell carcinoma antigen, SCC, carbohydrate antigen 199/CA199, Carcinoembryonic antigen/CEA, etc.), and whether concurrent chemoradiation was used. One-to-one matching without replacement was performed using a 0.1 caliper width, and the resulting score-matched pairs were used in subsequent analyses.

Comparisons between HR and LR groups were performed using the R-3.6.1 packages: OptimalCutpoints, survMisc, and relative survival packages based on significance of correlation with binary outcome or survival time [19]. The short-term results were divided into 2 groups: CR and others (a combination of PR, SD and PD), to comply with the binary data requirement of OptimalCutpoints. The determinations of optimal cut-off values for short-term results were based on the maximum Youden index for ROC curves [20]. Using OptimalCutpoints package with Youden method and 95% confidence level, the ROC curves were created by plotting the sensitivity against specificity at various cut-off settings about patients' short-term results. For long-term survival analyses, the optimal cut-offs were selected using the R-3.6.1 packages, which provides automatized systematic univariate Cox regression-based analysis of all available cut-offs for LRFS or MRFS [21,22]. The "coxph" function from survival package was used to fit Cox proportional hazard model to the binary (outcome) and continuous (survival time) covariates respectively, and cutpoints were then computed with the "cutp" function (survMisc package).

Chi-square test or Fisher's exact test (if the sample number in any category was less than 5) was performed for the categorical data. *t*-test was used for normally distributed continuous data, otherwise Wilcoxon test was performed. Shapiro-Wilk method was used for the normality test. Survival analyses (LRFS and MRFS) were determined using Kaplan-Meier method and were compared using Log-rank test. The ability of individual pathological variables to predict overall survival rates was assessed using Cox regression analysis. A two-sided p-value < 0.05 was considered as statistically significant.

To support clinical decisions such as institutional optimization of source replacement frequency, this work further tested if LR is biologically non-inferior to HR brachytherapy in terms of LRFS and MRFS. The 5-year local-/metastatic-recurrence in the HDR brachytherapy was assumed to be 12.5%(10–15%)/27.5%(25–30%) in accordance with previous results [15,23–26] based on similar patient groups. A maximum efficacy loss of 5% for local-recurrence and 10% for metastatic-recurrence in the LR group was accepted, suggesting non-inferior results if the 5-year local-/metastatic-recurrence did not exceed 17.5%/37.5%, with a margin of 5%/10% respectively. This was equivalent to a hazard ratio less than 1.4 (local recurrence) or 1.36 (metastatic recurrence) respectively. The non-inferiority margins were deliberately chosen by collectively considering historical data from institutional experiences, expert consensus, published data [27–29], and the risk-benefit profile of recurrence. The non-inferiority was evaluated by comparing whether the upper bound of the two-sided 95% confidence interval (CI) for the hazard ratio was equal to or below the pre-specified non-inferiority margin.

3. Results

3.1. Patients and source activities

In the cohort of 747 CC patients, 47 (6.3%) were excluded from this study because of treatment interruption by massive bleeding or uterine perforation; 104 (13.9%) were excluded because of intra-course source replacement; and 86 (11.5%) were excluded because of insufficient medical records. Up to 9 folds of MDR varieties were observed in the treatments of the remaining 510 patients, ranging from 6059.99 cGy/h to 54013.66 cGy/h due to 17 source replacements (Fig. 1). The median source replacement interval was 128 days, ranging from 93 days to 199 days.

The mean age of all 510 patients was 53 years (range 25–83). Squamous cell carcinoma accounted for 95.9%, and most were moderately- (53.9%) or poorly- (26.9%) differentiated. A majority of patients were of FIGO stage II (56.7%) or stage I (21.0%) according to 2009 FIGO staging system. These patients were statistically grouped by different cutoff values according to specific analysis purposes (Supplementary Material: Tables S1-S2). The corresponding MDR distributions (vertical black lines) of each patient during the treatment course were plotted as Fig. 1, where the red dots indicated the mean MDR values.

3.2. Short-term evaluation

The MDR cut-off value of 18878.14 cGy/h for the 1-month follow-up differentiated 364 (71.4%) HR patients from 146 (28.6%) LR patients. The categorical results (CR/PR/SD) based on RECIST 1.1 were 181/178/5 (CR rate = 49.7%) in the HR group and 85/58/3 (CR rate = 58.2%) in the LR group respectively. HR or LR patients were matched one-to-one using PSM, resulting 141 data pairs for Wilcoxon test. As shown in Table 1, no significant difference was observed in the 1-month follow-up between the HR (73-CR, 66-PR, 2-SD, 0-PD; CR rate = 51.8%) and LR (84-CR, 54-PR, 3-SD, 0-PD; CR rate = 59.6%) groups, with $p = 0.22$.

Also shown in Table 1, the same method was used to analyze the 3-month follow-up data, where 177 (36.7%) HR patients and 305 (63.3%) LR patients were compared based on the MDR cut-off value of 26392.99 cGy/h. The categorical results were CR/PR/SD/PD = 144/30/0/3 (CR rate = 81.4%) in the HR group and 264/34/3/4 (CR rate = 86.6%) in the LR group respectively. PSM matching generated 163 data pairs for Wilcoxon test, which suggested no significant difference between the HR group (135-CR, 25-PR, 0-SD, 3-PD; CR rate = 82.8%) and LR group (137-CR, 22-PR, 2-SD, 2-PD; CR rate = 84%), with $p = 0.79$.

3.3. Long-term evaluation

The median follow-up was 47.1 months (interquartile range 33.9–66.4) for all 510 patients, among which 31 (6.08%) patients developed local recurrence, and 92 (18.04%) developed metastatic recurrence. Of the 101 (19.8%) died patients, 75 (74.3%) died of cervical cancer, and 5 (5%) died of second malignancy.

3.3.1. Local recurrence-free survival

Regarding LRFS, 180 (36.1%) HR and 318 (63.9%) LR patients were compared using the MDR cut-off value of 26435 cGy/h. The median follow-up was 42.23 months in the HR group and 52.37 months in the LR group respectively. Cervical recurrence was observed in 16 (8.9%) HR patients and 15 (4.7%) LR patients respectively during follow-up. The 1-, 3-, 5-year LRFS were 96.6%, 91.9%, 89.4% in the HR group and 98.1%, 96.4%, 95.6% in the LR group respectively. Table 2 displayed the comparison after HR and LR patients were matched one-to-one using PSM, where Kaplan-Meier method suggested that the 1-, 3-, 5-year LRFS were 96.4%, 92.0%, 89.3% in the HR group and 98.8%, 96.8%, 94.7% in the LR group respectively (Log-rank test: $p = 0.10$, Fig. 2(a)). The baseline characteristics of the 169 matched pairs displayed no significant differences ($p > 0.05$).

3.3.2. Metastatic recurrence-free survival

As for MRFS, 257 (51.4%) HR patients and 243 (48.6%) LR patients were compared using MDR cut-off value of 22215.17 cGy/h. The median follow-up was 43.13 months in the HR group and 51.5 months in the LR group. Metastatic recurrence was observed in 52 (20.2%) HR patients and 40 (16.5%) LR patients respectively during follow-up. The 1-, 3-, 5-year MRFS were 91%, 81.9%, 77.8% in the HR group and 90.1%, 85.7%, 82.1% in the LR group respectively. Table 2 displayed the comparison after HR and LR patients were matched one-to-one using PSM, where Kaplan-Meier method suggested that the 1-, 3-, 5-year LRFS were 91.4%, 82.5%, 78.3% in the HR group and 89.9%, 85.1%, 81.1% in the LR group respectively (Log-rank test: $p = 0.46$, Fig. 2(b)). The baseline

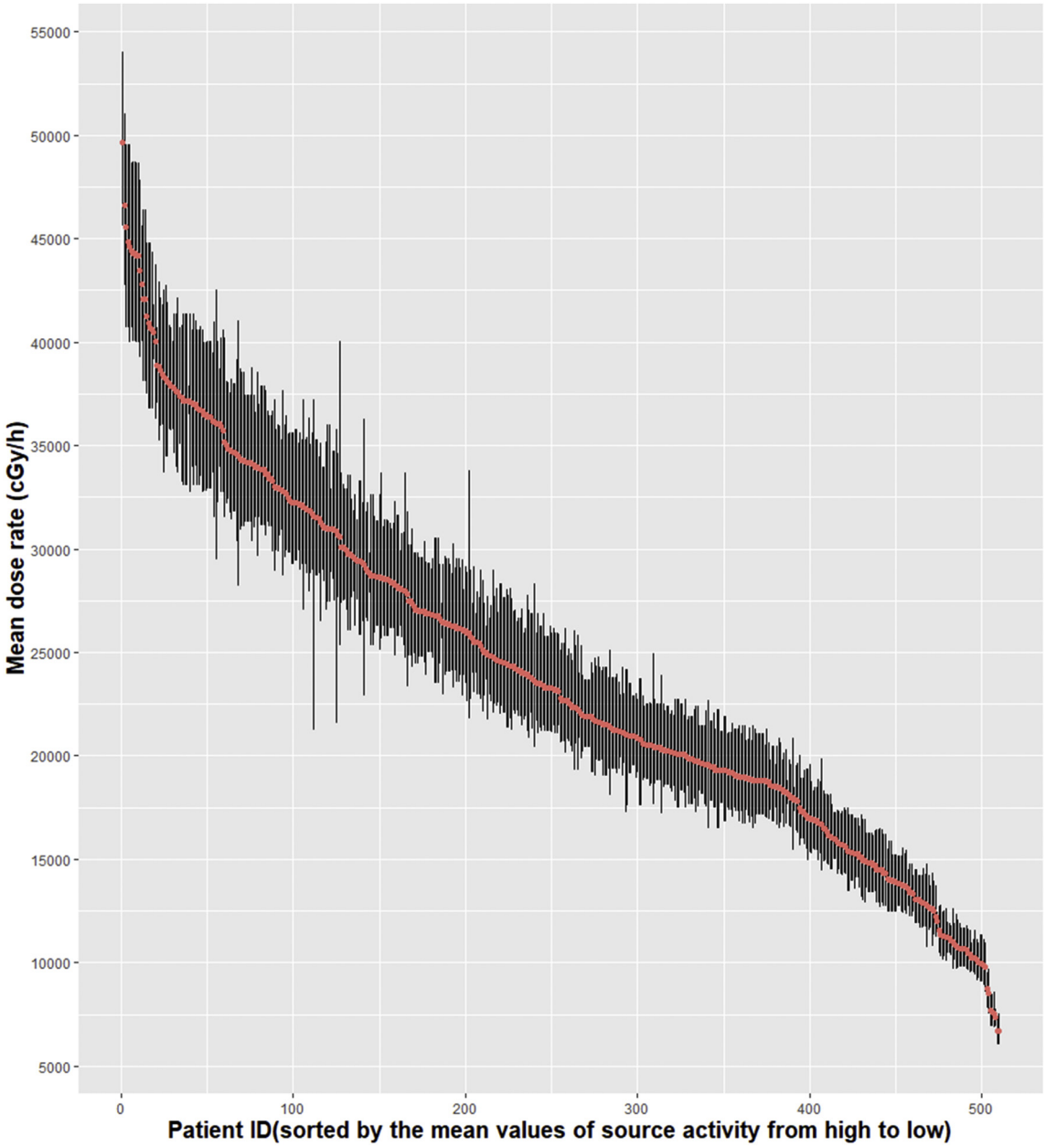

Fig. 1. Distribution (vertical black lines) of mean-dose-rate (MDR) of Ir-192 brachytherapy sources for each patient. The red points represent the patient-specific MDR average values of various fractions of the treatment course.

characteristics of the 199 matched pairs displayed no significant differences ($p > 0.05$).

3.4. Non-inferiority test

The hazard ratio (LR vs. HR) and its two-sided 95% CIs were provided by the Cox model, a regression method for survival data [30]. For local recurrence, the hazard ratio was 0.49 and the 95%CIs were 0.21 to 1.16 respectively. For metastatic recurrence, the hazard ratio was 0.84 and the 95%CIs were 0.53 to 1.33 respectively. The Local- ($p < 0.01$) and Metastatic- ($p < 0.02$) recurrence in the LR group was significantly non-inferior than that in the HR group.

3.5. Subgroup analysis

Subgroup analysis was performed by stratifying the cohort according to the stages. Sub-optimal performance ($0.6 < AUC < 0.7$) was observed in the AUCs of stage II and stage I–II (Fig. 3) ROC curves for patients' local recurrence with coordinates of maximum Youden index. For the stage II patients ($n = 283$, 58.8%), 82 data pairs were generated using a cutoff value of 26435 cGy/h on survMisc package. As shown in Table 2, the 1-, 3-, and 5-year LRFS of stage II patients in HR group were lower than the corresponding rates of LR group (Log-rank test: $p = 0.04$; Fig. 2(c)). For the stage I–II patients ($n = 390$, 78.3%), 124 data pairs were generated after PSM using a cutoff value of 26435 cGy/h. The 1-, 3-, and 5-year LRFS of stage I–II patients in the HR group were lower than the corresponding rates of LR group (Log-rank test: $p = 0.06$; Fig. 2(d)).

Similar subgroup analysis displayed no significant difference of MRFS between the HR and LR in both stage II and stage I–II subgroups. As shown in Tables 2, 77 data pairs of stage II patients were generated after PSM using a cutoff value of 19286.02 cGy/h. No significant difference was observed between the MRFS of HR and LR in stage II patients (Log-rank test: $p = 0.55$). For stage I–II patients, 125 data pairs were generated after PSM using a cutoff value of 26337.87 cGy/h. No significant

Table 1
Short-term comparison of PSM matched data.

Groups	CR/PR/SD/PD			
	1-month		3-month	
	HR	LR	HR	LR
All patients	73/66/2/0 141 pairs, $p = 0.22$	84/54/3/0	135/25/0/3 163 pairs, $p = 0.79$	137/22/2/2
Stage II	46/31/0/0 77 pairs, $p = 0.79$	48/28/1/0	58/14/0/2 74 pairs, $p = 0.42$	62/10/0/2
Stage I–II	62/47/1/0 110 pairs, $p = 0.22$	71/38/1/0	97/20/0/2 119 pairs, $p = 0.02$	109/10/0/0

The *p*-values were given by Wilcoxon test for the rank categorical results.
1-month and 3-month mean the patients' response at 1-month and 3-month respectively after brachytherapy according to RECIST 1.1.
Abbreviations: *HR* High radioactive; *LR* Low radioactive; *CR* Complete response; *PR* Partial response; *SD* Stable disease; *PD* Progressive disease.

difference was observed between the MRFS of HR and LR in stage I–II patients (Log-rank test: $p = 0.39$).

For the short-term evaluations in stage II group after PSM matching, as shown in Table 1, differences between HR (46-CR, 31-PR, 0-SD, 0-PD; CR rate = 59.7%) and LR (48-CR, 28-PR, 1-SD, 0-PD; CR rate = 62.3%) of 1-month were not significant ($p = 0.79$). The differences between HR (58-CR, 14-PR, 0-SD, 2-PD; CR rate = 78.4%) and LR (62-CR, 10-PR, 0-SD, 2-PD; CR rate = 83.8%) at 3-month were also not significant ($p = 0.42$). For PSM matched stage I–II patients, the differences between the HR (62-CR, 47-PR, 1-SD, 0-PD; CR rate = 56.4%) and LR (71-CR, 38-PR, 1-SD, 0-PD; CR rate = 64.5%) of 1-month were not significant ($p = 0.22$). However, the results of LR (109-CR, 10-PR, 0-SD, 0-PD; CR rate = 91.6%) were significantly better than that of HR (97-CR, 20-PR, 0-SD, 2-PD; CR rate = 81.5%) at 3-month ($p = 0.02$).

4. Discussion

Although other isotope with longer half-life such as Cobalt-60 can reduce the frequency of source replacement, it is technically more feasible to produce Ir-192 sources with smaller sizes, which is critical for dose optimization and delivery. Therefore, Ir-192 sources are dominantly used for HDR brachytherapy worldwide [31]. However, the relatively short half-life of ~74 days makes it both financially and environmentally costly to replace Ir-192 source frequently [14], especially for hospitals serving few HDR patients. It is practically inevitable to have unexpected or intended delayed source replacement due to many reasons, which induces tremendous dose-rate varieties at the moment of treatment delivery (up to 9 folds in this study for example). The confident application of HDR can be supported by a lot of pervious physical and biological comparisons with LDR treatments [4,9,32]. As a result of source decay and replacements, the dose-rate varieties within the scope of HDR modality do not undermine the physical advantages of HDR over LDR in terms of better dose optimization, safer public shielding and shorter treatment time. However, the biological impact of different HDR dose rates was unknown but clinically desirable to assist more informed decisions.

Based on 510 CC patients with median follow-up of 47.1 months, this retrospective cohort study investigated the biological impact of source activity varieties of HDR treatment on both short-term and long-term outcomes, covering MDR range of 6059.99 cGy/h to 54013.66 cGy/h within the dose-rate scope of HDR modality. Low risk of local recurrence (6.08%) and metastatic recurrence (18.04%) were observed in the whole cohort, where the outcomes in the HR and LR groups displayed no significant difference ($p > 0.05$). Significant non-inferiority of LR over HR has been biologically proved based on predefined margins of 5% and 10% for local- ($p < 0.01$) and metastatic-recurrence ($p < 0.02$) respectively. Although it takes longer time to deliver the same prescribed dose using LR source and may increase patient discomfort, most short-term and long-term outcomes were in favor of LR than HR (as shown in Tables 1-2 and Figs. 2(a–b)). Sub-group analysis suggested better LRFS ($p = 0.06$) and 3-month follow-up results ($p < 0.05$) of LR group than that of HR group for stage I–II patients. Among the stage II patients, LR group also showed significantly better LRFS ($p < 0.05$). These results demonstrated that LR is significantly non-inferior or even partially superior to HR in terms of local control for patients with early-stage CC.

The aforementioned data provided different and complementary evidences in the dose-rate range of HDR, in addition to the existing LDR knowledge which suggested better normal tissue repair of LDR [7,8] without significant difference in terms of patient survival [9,10]. It was

Table 2
Long-term comparison (LRFS and MRFS) of PSM matched data.

	LRFS			MRFS		
Groups	HR	LR	log-rank test	HR	LR	log-rank test
All patients	169 pairs		$p = 0.10$	199 pairs		$p = 0.46$
1 year	96.4%	98.8%		91.4%	89.9%	
3 year	92.0%	96.8%		82.5%	85.1%	
5 year	89.3%	94.7%		78.3%	81.1%	
Stage II	82 pairs		$p = 0.04$	77 pairs		$p = 0.55$
1 year	95.1%	98.8%		93.5%	89.5%	
3 year	90.0%	96.2%		85.6%	86.9%	
5 year	84.6%	96.2%		81.6%	85.2%	
Stage I–II	124 pairs		$p = 0.06$	125 pairs		$p = 0.39$
1 year	96.8%	97.6%		93.6%	89.6%	
3 year	92.5%	96.7%		85.0%	87.1%	
5 year	89.0%	96.7%		80.6%	85.9%	

The *p*-values were given by comparing survival curves of two groups using the Log-rank test.
Abbreviations: *HR* High radioactive; *LR* Low radioactive; *LRFS* Local recurrence-free survival; *MRFS* Metastatic recurrence-free survival.

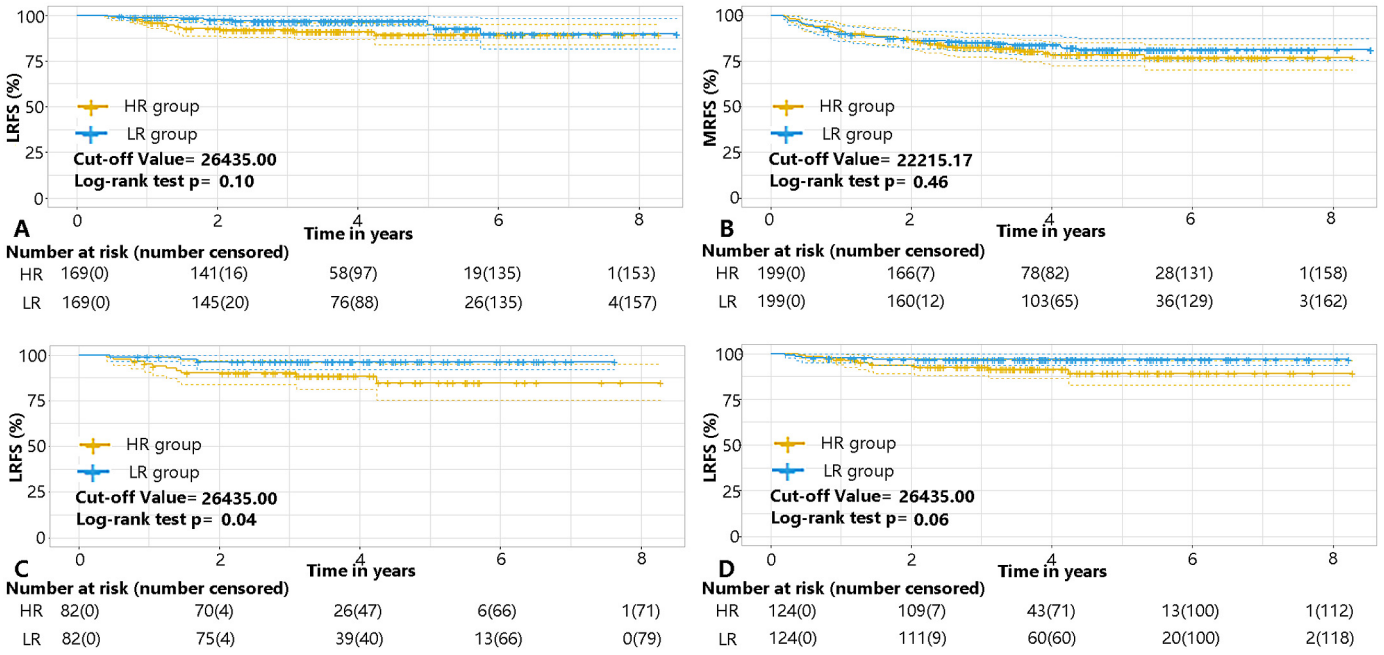

Fig. 2. Kaplan-Meier plots of: (a) local recurrence-free survival for all patients; (b) metastatic recurrence-free survival for all patients; (c) local recurrence-free survival for stage II patients; and (d) local recurrence-free survival for stage I–II patients. The dashed lines indicate the 95% confidence intervals for the survival curves. The vertical tick marks on the curves indicate censored patients. Abbreviations: *HR* High radioactive; *LR* Low radioactive; *LRFS* local recurrence-free survival; *MRFS* metastatic recurrence-free survival. The unit of cut-off values: cGy/h (Mean dose rate).

reported that higher dose-rate might be selectively more damaging to cells with lower alpha/beta ratio, such as late responding normal tissues [32]. Therefore, lower dose-rate was associated with better late tissue effects [33].

It was unable to confirm from this study if there was an influence from the much larger intra-patient dose-rate varieties between different fractions for HR patients than that of LR patients. For instance, as shown in Fig. 1, the inter-fractional MDR difference of patient #1 (8380.55 cGy/h) was 5.8 times of patient #510 (1456.85 cGy/h), i.e., LR fractions were delivered with more consistent dose-rate. The involvement of source replacement within the treatment course may further complicate this problem which was also not discussed in this work. Therefore, more radio-biological studies should be conducted focusing on the dose-rate ranges of HDR modality to reveal more mechanism [34] and evidences in the future.

It should be noticed that the retrospective definitions of HR vs. LR in this study were dependent on specific research purposes and patient population statistics. Two methods were used to determine the cut-off values of continuous variables: ROC curves with maximum Youden index was used for short-term evaluation, and automatized systematic univariate Cox regression-based analysis of all available cut-offs was used for long-term outcome evaluation respectively. Both approaches

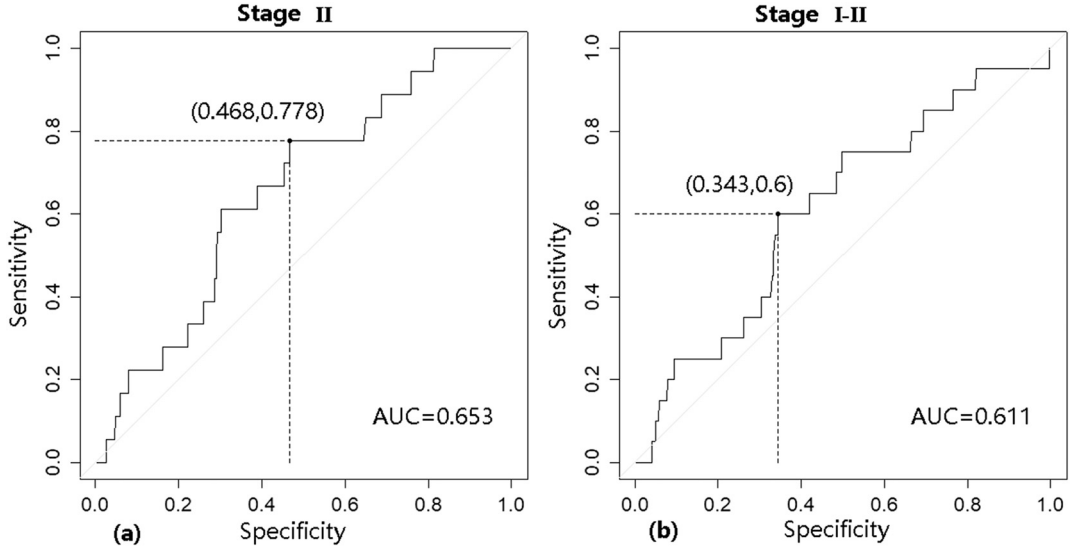

Fig. 3. Local recurrence ROC curves with coordinates for maximum Youden Index of stage II (a) and stage I–II (b) patients respectively, including the optimal cut-off value selections, generated from the OptimalCutpoints package with Youden method and 95% confidence level.

have been widely adopted by other researchers [21,22,35], which avoided arbitrary and subjective cut-off selections.

This work was limited by its retrospective design, where biases cannot be fully excluded even propensity score matching was deliberately conducted. In addition, cervical cancer is very sensitive to radiotherapy [36], hence the low rates of cervical recurrence (6.22%) and metastatic recurrence (18.07%) may require larger population to get significant results in some studies. Therefore, prospective and randomized trials based on more patients are needed to further confirm the findings in the future.

5. Conclusions

This work proved the significant non-inferiority of LR relative to that of HR within the dose-rate scope of HDR, in terms of both short-term and long-term clinical outcomes of cervical cancer patients. Although LR may decrease delivery efficiency and patient comfort, the preliminary evidences can partially justify the application of less efficient source without concerns of negative biological impact on patient outcomes. To the contrary, early stage CC patients may even benefit from the HDR treatment using relatively low-active sources. These findings can be used to guide the clinical decisions such as institutional optimization of the source replacement schedules to balance the financial burden, reduce nuclear waste, and handle unexpected events that prevent regular source replacement.

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Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2020.08.037.

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