Heliyon 10 (2024) e24666

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Chemotherapy alone versus chemotherapy plus ^{125}I brachytherapy for the second-line treatment of locally recurrent cervical cancer after/with radical treatment: A propensity score analysis

Zhimei Huang [a,1], Wang Yao [b,1], Zhihui Zhong [a], Guang Yang [a], Jihong Liu [c], Haifeng Gu [c,**], Jinhua Huang [a,*]

[a] Department of Minimal Invasive Intervention, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, 510060, PR China

[b] Department of Interventional Oncology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, 510080, Province Guangdong, PR China

[c] Department of Gynecological Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, 510060, PR China

ARTICLE INFO

Keywords:
Cervical cancer
Local recurrence
Overall survival
Disease-free survival
Complication

ABSTRACT

Rationale and objectives: The primary aim of this study was to conduct a retrospective comparative analysis of the survival outcomes in patients with recurrent cervical cancer (CC). Specifically, we aimed to compare the efficacy of chemotherapy alone versus the combined approach of chemotherapy and ^{125}I brachytherapy subsequent to the failure of initial chemotherapy treatment.

Materials and methods: Patients diagnosed with recurrent CC subsequent to the failure of initial chemotherapy from January 2007 to December 2016 were enrolled from 2 hospitals. These patients were then divided into two groups: Group A, which underwent second-line chemotherapy alone, and Group B, which received both second-line chemotherapy and ^{125}I brachytherapy. The assessment of overall survival (OS) and progression-free survival (PFS) was carried out through propensity score matching (PSM) (1:1), Kaplan-Meier curves, log-rank tests, and Cox proportional hazard regression for survival analysis.

Results: A matched cohort comprising 88 patients each in Group A and Group B was included in the study. In Group A, the 1-, 2-, and 3-year cumulative PFS rates were 40.9 %, 15.9 %, and 5.7 % respectively, while in Group B, these rates were significantly higher at 79.5 %, 48.9 %, and 25.0 % ($P = 0.003$). Similarly, the 1-, 2-, and 3-year cumulative OS rates among Group A were 67.0 %, 27.3 %, and 5.7 % compared to 89.8 %, 63.6 %, and 30.7 % among Group B, suggesting a difference with statistical significance ($P < 0.001$) between the two groups. Moreover, the incidence of complications was similar between groups ($P = 0.698$).

* Corresponding author. Department of Minimal invasive intervention, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, 651, Dongfeng East Road, Guangzhou, 510060, PR China.

** Corresponding author. Department of gynecological oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, 651, Dongfeng East Road, Guangzhou, 510060, PR China.

E-mail addresses: guhf@sysucc.org.cn (H. Gu), huangjh@sysucc.org.cn (J. Huang).

[1] The first two authors contributed equally to this manuscript.

https://doi.org/10.1016/j.heliyon.2024.e24666
Received 29 November 2023; Received in revised form 25 December 2023; Accepted 11 January 2024
Available online 14 January 2024

Conclusions: Our findings suggest that the combined approach of chemotherapy and ^{125}I brachytherapy yields superior therapeutic effects but similar complication rates compared to chemotherapy alone in patients experiencing local recurrence of CC following failed initial chemotherapy.

Abbreviations and acronyms

CC	Cervical cancer
EBRT	External beam radiotherapy
GGO	Ground-glass opacity
ECOG-PS	Eastern Cooperative Oncology Group performance score
PSM	propensity score matching
TPS	treatment planning system
PD	prescribed dose
GTV	gross tumor volume
IV	intravenous
CE	contrast-enhanced
OS	overall survival
PFS	progression-free survival
ORR	objective response rate
DCR	disease control rate
SCCa	squamous cell carcinoma antigen

1. Introduction

Cervical cancer (CC) accounts for 528,000 new cases annually, resulting in over 266,000 deaths globally [1]. Primary treatments for early-stage CC typically involve surgery and external beam radiotherapy (EBRT) [2]. However, failure of first-line treatment affects 30−50 % of patients, leading to loco-regional recurrence [3]. The 2021 NCCN Clinical Practice Guidelines in Oncology (NCCN guidelines) for CC recommend individualized EBRT or combined surgery with intraoperative radiotherapy as treatments for locoregional recurrence [4]. In clinical practice, chemotherapy is commonly used as a palliative therapy to enhance outcomes in CC patients with recurrence [5]. According to the ground-glass opacity (GGO) guidelines, optimal regimens for recurrent/metastatic CC involve chemotherapy utilizing cisplatin, paclitaxel, and bevacizumab [6]. Yet, there exists no consensus on second-line chemotherapy for patients with recurrent CC [7], underscoring the urgent need for novel therapies targeting loco-regional recurrence.

The use of radioactive ^{125}I brachytherapy has emerged as an alternative for various malignant tumors due to minimal surgical trauma and reduced complications. Kittel et al. demonstrated the favorable effectiveness of ^{125}I brachytherapy in enhancing overall survival (OS) and distant metastasis-free survival in low-risk pancreatic tumors [8]. Similarly, Yan et al. established the efficacy of ^{125}I brachytherapy for locally recurrent nasopharyngeal carcinoma, which resulted in a obviously reduced occurrence rate of complications [9]. Recently, studies by Qu et al. and Liu et al. further substantiated the effectiveness of image-guided radioactive ^{125}I brachytherapy for pelvic recurrent CC subsequent to EBRT [10,11]. Nevertheless, large-scale studies on ^{125}I brachytherapy for CC remain limited. Consequently, this study sought to compare the therapeutic impact of chemotherapy alone against the combination of chemotherapy and ^{125}I brachytherapy in patients experiencing locally recurrent CC.

2. Materials and Methods

2.1. Study design and ethics

This retrospective study adhered to the ethical principles outlined in the 1975 Declaration of Helsinki, which were updated in Brazil in 2013. Besides, it was approved by the Ethical Committee of the First Affiliated Hospital of Sun Yat-Sen University (No. 2018-561), as well as Sun Yat-Sen University Cancer Center (No. YB2018-17).

2.2. Study population

The study enrolled all CC patients experiencing local recurrence subsequent to radical treatment and initial chemotherapy failure across 2 hospitals. Inclusion criteria included: (1) patients aged 18–75 years old; (2) patients diagnosed through radiographic imaging (CT/MRI/positron emission tomography/computed tomography [PET-CT]) with local recurrence, and a maximum of three tumors, each <5 cm in diameter; (4) patients who have not had any other malignancies within the last 2 years. Exclusion criteria included: (1)

patients who had extensive metastasis; (2) patients who had severe liver or renal insufficiency, chronic obstructive pulmonary diseases, cardiac diseases, impaired coagulation function, diabetes mellitus, as well as other chronic conditions that could potentially affect their ability to tolerate therapy; (3)patients with an Eastern Cooperative Oncology Group performance score (ECOG-PS) > 2; (4) patients who had previously received systemic therapies such as targeted therapy, immune therapy, or second-line therapy; (5) patients lacking at least 1 month of follow-up.

Group A comprised 963 recurrent CC patients receiving second-line chemotherapy alone, while Group B consisted of 521 recurrent CC patients undergoing combined therapies between January 2007 and December 2016. According to the inclusion and exclusion criteria, 156 patients were included in Group A, and 117 patients were included in Group B. To mitigate potential confounding effects, propensity score matching (PSM) analysis was carried out using the nearest-neighbor matching method for one-to-one matching between groups, employing a calliper of 0.10. Consequently, post PSM analysis, 176 patients with locally recurrent disease were equally allocated to Group A (n = 88) and Group B (n = 88) (Fig. 1). Subsequent OS rates were recalculated.

2.3. ^{125}I brachytherapy

In this study, the ^{125}I seed, resembling a cylindrical titanium package body (Atom High Tech, Beijing, China), was utilized. The treatment plan for each patient was developed using treatment planning system (TPS) software (YuanBo, Beijing, China) in conjunction with CT images imported by TPS approximately 1–2 weeks before implantation. With the help of TPS, the possible puncture path was designed, the necessary number of seeds was calculated, and a dose-volume histogram was generated. The prescribed dose (PD) averaged 120 Gy and was determined following the recommendations of the American Brachytherapy Society for

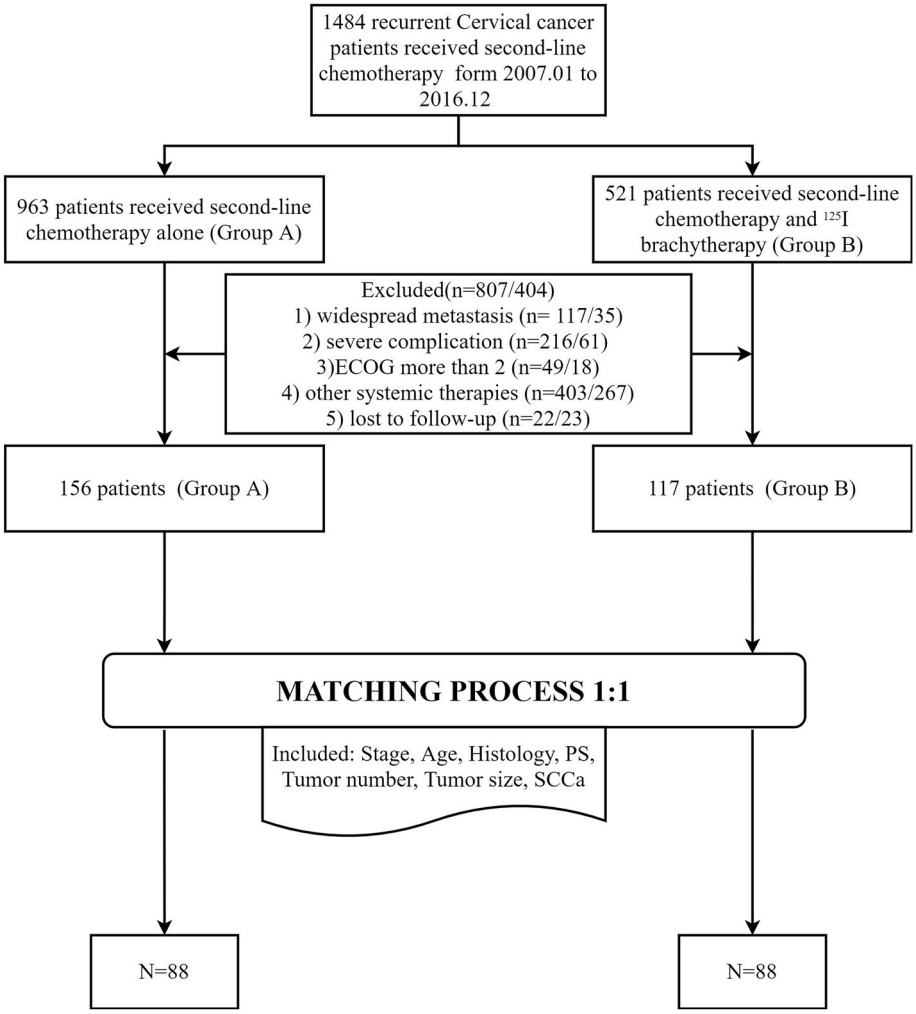

Fig. 1. Flowchart illustrating the selection process for individuals with the local recurrence of cervical cancer following the unsuccessful radiotherapy and initial chemotherapy, comparing Group A to Group B. Group A: second-line chemotherapy alone; Group B: combination of second-line chemotherapy and ^{125}I brachytherapy.

prostate cancer or based on previous studies on ^{125}I brachytherapy [12–14]. Continuous dose optimization ensured that the mean peripheral dose aligned with the planned dose, with 90 % of the gross tumor volume (GTV) receiving 90 % of the PD.

The ^{125}I relevant parameters included: (1) Length of 4.5 mm; (2) Diameter of 0.8 mm with a 3.0 mm × 0.5 mm silver column inside (initial radioactivity of 0.8 mCi; average energy of 27–35 keV; half-life of 59.6 days; half layer of 0.25 mm for lead; antitumor activity of 1.7 cm; and initial dose rate of 7 cGy/h); (3) Wall thickness of 0.05 mm for the titanium in the external shell. Before ^{125}I brachytherapy, CT imaging (section thickness of 5 mm) targeting the areas of interest were collected, delineating the planning target volume (PTV), GTV, and surrounding organs. GTV was typically 1–1.5 cm fewer than PTV's boundary.

^{125}I seed implantations were conducted by two interventional radiologists with the experience in this field for more than 5 years. The location of the applicator for brachytherapy on the patient's body surface was identified in relation to the plan generated by TPS before the operation. Subsequent to the local anesthesia with 1 % lidocaine (5–10 ml), an 18-gauge applicator (Atom High Tech) was placed into the lesions, positioned against their deepest margins using CT. During implantation, voltage was set at 120 kV, with 200 mAs per section, 5 mm in section thickness, 0.75 s for rotation time, and a planned CT dose of 10.0 mGy. Besides, a turntable/clip implant gun was affixed to the applicator for the implantation process, after which a CT scan was performed, aiming to verify whether the distribution of implanted ^{125}I seeds matched with the preoperative plan. If necessary, supplemental implantation was considered.

2.4. Chemotherapy

This study implemented 2 s-line chemotherapy regimens as follows: (1) intravenous (IV) chemotherapy involving Abraxane (260 mg/m^2 for a minimum of 3 h) and bevacizumab (15 mg/kg for at least 1 h); (2) IV chemotherapy comprising topotecan (0.75 mg/m^2 on Days 1–3) and bevacizumab (15 mg/kg on Day 1). Patients received pretreatment with dexamethasone, diphenhydramine, and an H2 receptor antagonist before paclitaxel infusion (e.g., cimetidine or ranitidine). Additionally, all patients received prophylactic antiemetic treatment (ondansetron/granisetron). Treatment cycles continued for 6 cycles (21 days/cycle), unless disease progression or toxicity intolerance occurred. Dosage reduction or treatment interruption was executed upon detection of adverse events (AEs).

Table 1
Baseline characteristics between Group A and Group B.

Characteristic n(%)	Before match			After match		
	Group A (n = 156)	Group B (n = 117)	*P*-value	Group A (n = 88)	Group B (n = 88)	*P*-value
Age						
Mean ± SD (y)	48.1 ± 9.1	50.9 ± 11.8	0.025	48.5 ± 9.2	49.8 ± 10.9	0.387
≤60 y	86(55.1)	55(47.0)	0.221	50(56.8)	44(50.0)	0.450
>60 y	70(44.9)	62(53.0)		38(43.2)	44(50.0)	
ECOG PS						
0	139(89.1)	108(92.3)	0.412	80(90.9)	85(96.6)	0.212
1	17(10.9)	9(7.7)		8(9.1)	3(3.4)	
FIGO staging						
I-IIB	132(84.6)	64(54.7)	0.000	64(72.7)	64(72.7)	1.000
IIB+	24(15.4)	53(45.3)		24(27.3)	24(27.3)	
Histology						
Squamous	114(73.1)	88(75.2)	0.760	66(75.0)	62(70.5)	0.209
Adenocarcinoma	34(21.8)	25(21.4)		18(20.5)	23(26.1)	
Adenosquamous	2(1.3)	2(1.7)		0(0.0)	2(2.3)	
Others	6(3.8)	2(1.7)		4(4.5)	1(1.1)	
Differentiation						
High	11(7.1)	6(5.1)	0.787	9(10.2)	4(4.5)	0.345
Moderate	71(45.5)	56(47.9)		40(45.5)	44(50.0)	
Low	74(47.4)	55(47.0)		39(44.3)	40(45.5)	
Recurrence position						
Pelvic	73(46.8)	80(68.4)	0.000	51(57.9)	57(64.7)	0.086
Extra-pelvic	59(37.8)	11(9.4)		21(23.9)	10(11.4)	
Both	24(15.4)	26(22.2)		16(18.2)	21(23.9)	
Lesion number						
≤2	71(45.5)	72(61.5)	0.010	46(52.3)	46(52.3)	1.000
3	85(54.5)	45(38.5)		42(47.7)	42(47.7)	
Tumor diameter						
Mean ± SD (cm)	3.3 ± 1.9	3.2 ± 1.6	0.716	3.2 ± 1.7	3.1 ± 1.7	0.844
≤3 cm	104(66.7)	62(53.0)	0.025	61(69.3)	48(54.5)	0.062
>3 cm	52(33.3)	55(47.0)		27(30.7)	40(45.5)	
SCCa						
At recurrence	8.6 ± 1.3	6.2 ± 1.2	0.201	7.9 ± 1.9	6.1 ± 1.4	0.447
After treatment	11.4 ± 1.8	6.7 ± 1.4	0.043	9.7 ± 2.0	7.1 ± 1.9	0.332

Data in bracket was percent of patients. The data in two groups were compared by using the Chi square test. Non-normally distributed data is represented by median and quartile.
Abbreviation: Group A: second-line chemotherapy alone; Group B: second-line chemotherapy and ^{125}I brachytherapy.

2.5. Follow-up

All patients were censored on December 31, 2021. Unenhanced and contrast-enhanced (CE) CT images were obtained using a CT scanner with 1–5 mm collimation. Three-dimensional (3D) PET scans (Allegro; Philips Medical Systems, Andover) were conducted for instances of suspected tumor recurrence or residual tumors. For Group B, CE-CT pelvic, abdominal, and chest images were collected at 1 and 3 months, followed by assessments every 3 months. In comparison, for Group A, CE-CT images were collected every 3 months. The retrospective image comparison was carried out by two senior radiologists (>15 years of experience) to reach a consensus; otherwise, a third senior radiologist assisted in determining the results.

2.6. Definition of clinical outcomes

The primary endpoint was recognized as death. Additionally, the main observational outcomes included OS and local control (LC) rate. OS was calculated from initial treatments to either death or the end of follow-up. Progression-free survival (PFS) was measured from second-line treatments to tumor progression. Local recurrence referred to lesions at the surgical margin, while distant metastasis denoted newly discovered lesions distinct from those identified within local recurrences. Objective response rate (ORR) was defined as complete response (CR) plus partial response (PR), while disease control rate (DCR) encompassed CR, PR, and stable disease (SD). Furthermore, a major complication was characterized by an incidence greater than 5 %, while severe complications referred to life-threatening conditions necessitating immediate intervention.

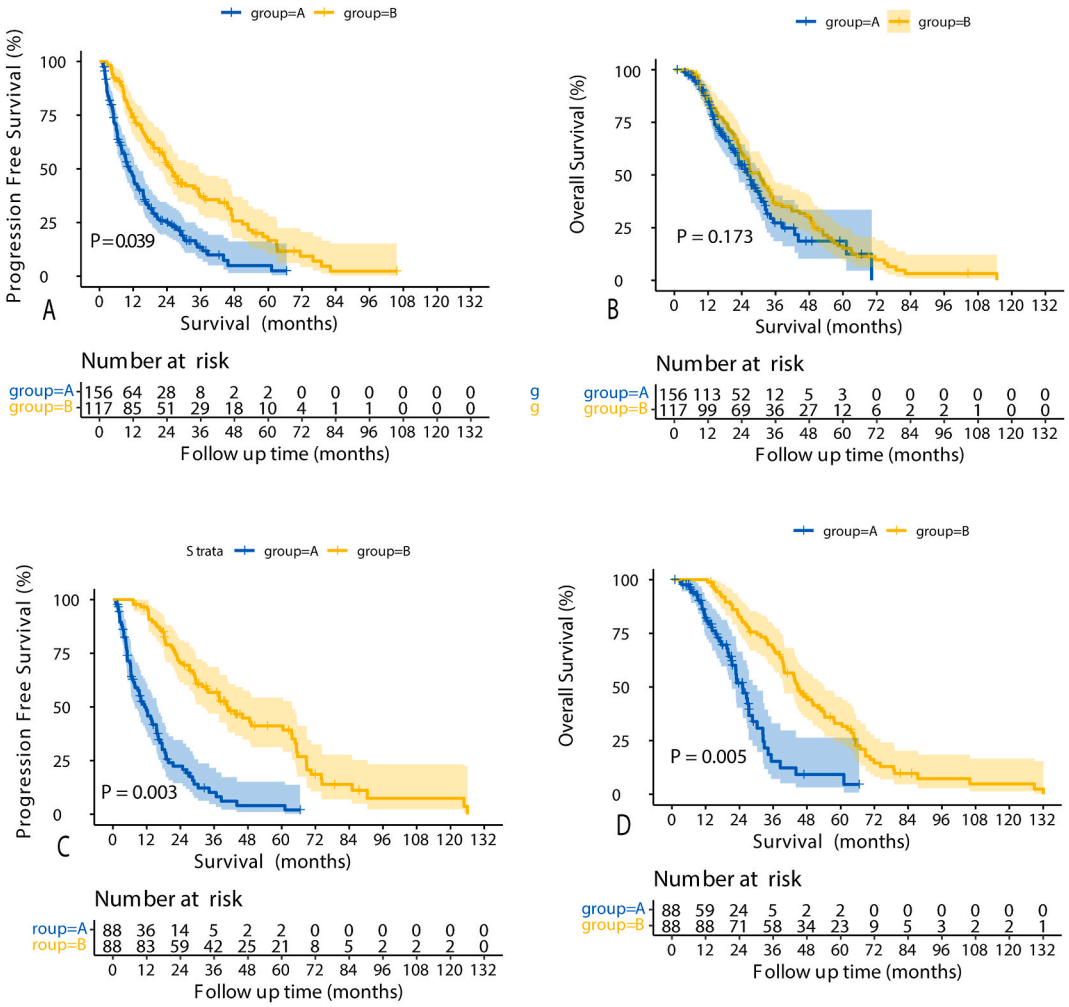

Fig. 2. Kaplan-Meier curves depicting OS and PFS between Group A and Group B. PFS (A) and OS (B) curves before matching, followed by PFS (C) and OS (D) cures after matching. OS: overall survival; PFS: progression-free survival; Group A: second-line chemotherapy alone; Group B: combination of second-line chemotherapy and ^{125}I brachytherapy.

2.7. Statistical analysis

Data analysis utilized SPSS 20.0 (Chicago, III). PSM analysis was performed using R software (TIBCO, Silicon Valley, CA). Continuous data with normal distributions were compared using Student's t-test, while skewed distributions were assessed using Wilcoxon's rank sum test. Categorical variables were analyzed using the chi-square test. Survival analysis involved Kaplan-Meier curves accompanied by the Mantel-Cox log-rank test. Moreover, Cox proportional hazards regression analysis identified independent prognostic factors for OS. A P value < 0.05 indicated to be statistically different.

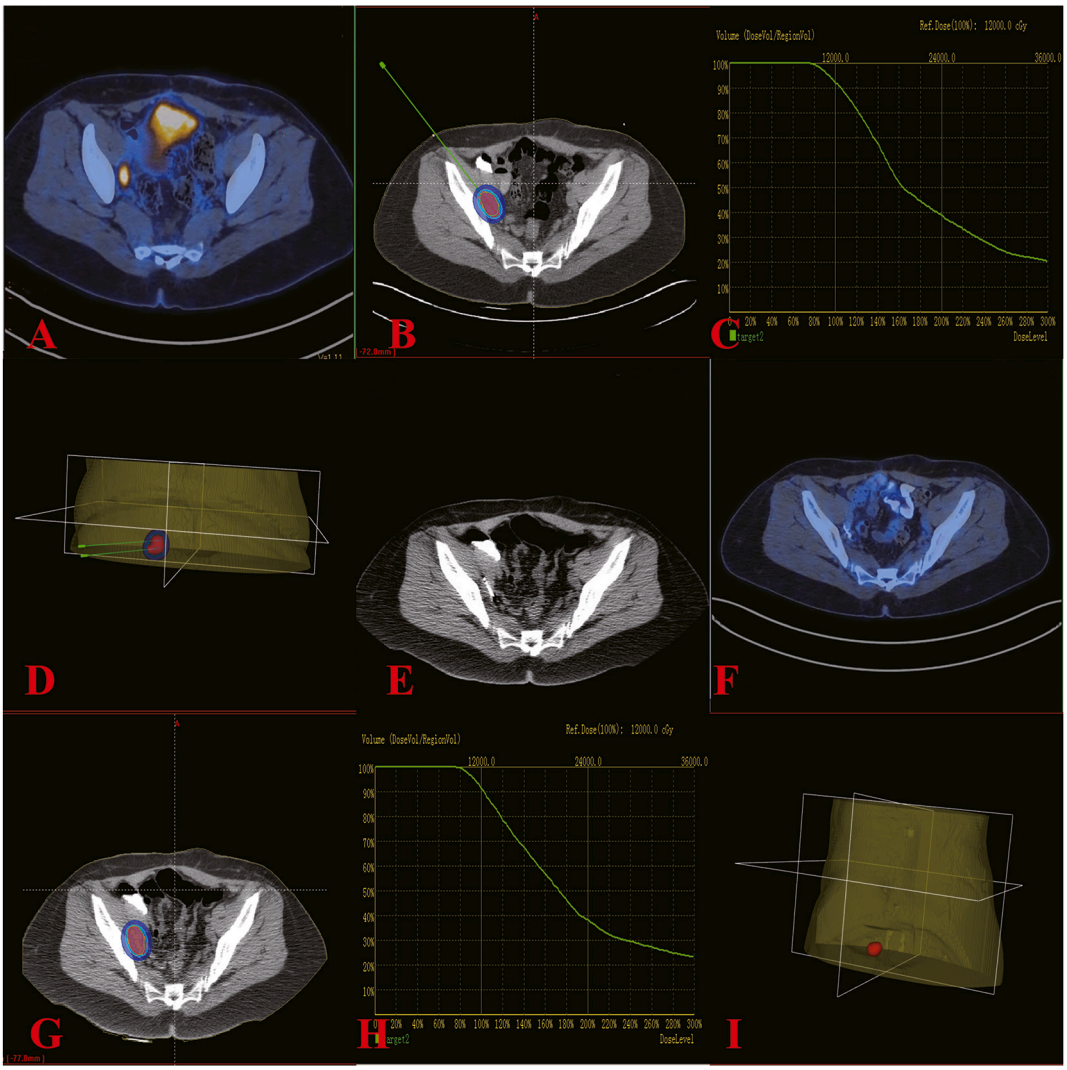

Fig. 3. Example of follow-up medical records of a 47 years old cervical cancer patient with recurrence involving pelvic lymph nodes after radical treatment and combined treatments of second-line chemotherapy and 125I brachytherapy. After 6 months, PET-CT revealed the disappearance of metabolic activity in the lesion, with the patient achieving CR. (A): Preoperative PET-CT indicating metabolically active right iliac paravascular lymph node metastasis with a size of approximately 1.5 × 2.0 cm; (B): Preoperative TPS planning diagram. The red line: 90 % prescription dose (108Gy isodose line); The red area: the dose range of 108Gy or greater; The light blue line: 60 % prescription dose (72Gy isodose line); The light blue area: the dose range of 72Gy or greater; The dark blue line: 30 % prescription dose (36Gy isodose line); The dark blue area: the dose range of 36Gy or greater; (C): DVHfigure; (D): Preoperative 3D image of particle irradiation; (E): Postoperative particle distribution map; (F): Postoperative PET-CT demonstrating complete inactivation of the lesion; (G): Postoperative TPS planning diagram. The red line: 90 % prescription dose (108Gy isodose line); The red area: the dose range of 108Gy or greater; The light blue line: 60 % prescription dose (72Gy isodose line); The light blue area: the dose range of 72Gy or greater; The dark blue line: 30 % prescription dose (36Gy isodose line); The dark blue area: the dose range of 36Gy or greater; (H): Postoperative DVH figure; (I): Postoperative 3D image of particle irradiation.

3. Results

3.1. Comparative analysis of patient baseline features

The comparative analysis of baseline features between pre-match and post-match cohorts were performed (Table 1). The median of the follow-up duration reached up to 30.5 months (range: 1.0 month −132.1 months). Among the pre-match cohort, significant differences were observed between groups in terms of FIGO staging, recurrence position, and the number of lesions ($P < 0.05$); however, all variables in the two groups displayed similarity in the post-match cohort.

In the 117 patients of Group B, 316 lesions underwent ^{125}I brachytherapy, out of which 292 (92.4 %) achieved TPS dose verification after the operation. Besides, 5 patients underwent ^{125}I seed implantation and received the planned dose. The median counts of ^{125}I seeds and implanted needles were 48.8 (range: 6−158) and 6 (range: 3−12), respectively. The median duration of the implantation process was 68 min (range: 42−100 min) with a median radiation dose of D90 at 129 Gy (range: 100–169 Gy). The median percentage of GTV receiving 100 % of the PD (V100) and the dose encompassing 95 % of the GTV (D95) were 94.6 % (range: 85.3−100 %) and 133.1 Gy (range: 105.5–171.9 Gy), respectively. Notably, all patients in both groups completed chemotherapy without experiencing any serious complications.

3.2. Survival analysis

Prior to PSM, the 1-, 2-, and 3-year cumulative PFS rates exhibited significant differences across groups, as depicted in Fig. 2A ($P = 0.039$); meanwhile, the one-, two-, and three-year cumulative rates of OS were similar in both groups, as shown in Fig. 2B ($P = 0.173$). Subsequent to PSM, the one-, two-, and three-year cumulative rates of PFS reached up to 40.9 %, 15.9 %, and 5.7 % in Group A and 79.5 %, 48.9 %, and 25.0 % in Group B, respectively, showing a significant difference between the groups, as shown in Fig. 2C ($P = 0.003$). Additionally, the one-, two-, and three-year cumulative rates of OS reached up to 67.0 %, 27.3 %, and 5.7 % in Group A and 89.8 %, 63.6 %, and 30.7 % in Group B, further demonstrating a significant difference between the groups, as shown in Fig. 2D ($P = 0.005$).

3.3. Comparative analysis of local response (LR) as well as overall response

Comparison of LR and overall response across groups was conducted prior to and post PSM (Table 2). Prior to PSM, the ORR and DCR for LR were 36.5 % and 56.4 % for Group A, and 47.9 % and 86.3 % for Group B, respectively. For overall responses, the ORR and DCR for Group A were 35.9 % and 55.8 %, respectively; for Group B, they were 35.0 % and 69.2 %, respectively. The groups exhibited significantly different DCRs for the LR ($P < 0.001$) and overall response ($P = 0.024$) between the groups, whereas the ORRs showed comparable results across the groups ($P = 0.061$; $P = 0.884$). Following PSM, the ORR and DCR for LR were 36.4 % and 54.5 % in Group A, and 46.6 % and 86.4 % in Group B, respectively. In Group A, the ORR and DCR for overall responses were 36.4 % and 54.5 %, respectively; however, in Group B, they were 34.1 % and 70.5 %, respectively. The DCRs for the local and overall responses were significantly different between the groups ($P < 0.001$; $P = 0.003$), while the ORRs were similar between groups ($P = 0.170$; $P = 0.753$). Fig. 3A–I illustrates that following second-line chemotherapy and ^{125}I brachytherapy treatment based on the TPS plan, CT images depicted nearly complete remission of tumors in the right iliac lymph node metastasis.

Table 2
Treatment responds between Group A and Group B.

Assessment using RECIST	Before PSM			After PSM		
	Group A (N = 156)	Group B (N = 117)	P value	Group A (N = 88)	Group B (N = 88)	P value
Local responds						
CR	22(14.1)	19(16.2)	0.625	12(13.6)	14(15.9)	0.672
PR	35(22.4)	37(31.6)	0.089	20(22.7)	27(30.7)	0.234
SD	31(19.9)	45(38.5)	0.001	16(18.2)	35(39.8)	0.002
PD	68(43.6)	16(13.7)	<0.001	40(45.5)	12(13.6)	<0.001
OR	57(36.5)	56 (47.9)	0.061	32(36.4)	41(46.6)	0.170
DCR	88(56.4)	101(86.3)	<0.001	48(54.5)	76 (86.4)	<0.001
Overall responds						
CR	22(14.1)	17(14.5)	0.921	12(13.6)	13(14.8)	0.830
PR	34(21.8)	24(20.5)	0.798	20(22.7)	17(19.3)	0.580
SD	31(19.9)	40(34.2)	0.008	16 (18.2)	32(36.4)	0.007
PD	69 (44.2)	36(30.8)	0.024	40(45.5)	26(29.5)	0.030
OR	56(35.9)	41(35.0)	0.884	32(36.4)	30(34.1)	0.753
DCR	87(55.8)	81(69.2)	0.024	48(54.5)	62(70.5)	0.003

Data in bracket was percent of patients. The data in two groups were compared by using the Chi square test.
Abbreviation: PSM: propensity score match; RECIST: Response Evaluation Criteria in Solid Tumor; CR: complete response; PR: partial response; SD: stable disease; PD: progression disease; ORR: objective response rate; DCR: disease control rate, Group A: second-line chemotherapy alone; Group B: second-line chemotherapy and ^{125}I brachytherapy.

3.4. Cox proportional hazards regression

In the univariable analysis, it was determined that ECOG-PS (HR: 2.204. 95 % CI: 1.142–4.255, $P = 0.019$), position of recurrence (HR: 1.300, 95 % CI: 1.026–1.647, $P = 0.030$), tumor diameter (HR: 5.546, 95 % CI: 3.508–8.769, $P < 0.001$), and fluctuations in squamous cell carcinoma antigen (SCCa) levels (HR: 1.935, 95 % CI: 1.352–2.823, $P < 0.001$) impacted OS with statistical significance ($P < 0.10$). Furthermore, multivariable analysis revealed that ECOG-PS (HR: 2.580, 95 % CI: 1.297–5.135, $P = 0.007$), the position of recurrence (HR: 1.699, 95 % CI: 1.337–2.158, $P < 0.001$), the diameter of tumors (HR: 2.497, 95 % CI: 2.103–2.964, $P < 0.001$), and the alternations in the levels of SCCa (HR: 1.740, 95 % CI: 1.182–2.561, $P = 0.005$) could independently predict the OS of patients (Table 3).

3.5. Subgroup analysis

In the subgroup analysis, the OS in Group B was better than that in Group A, particularly within subgroups displaying ECOG PS = 0 ($P = 0.013$), extra-pelvic recurrence ($P = 0.003$), both pelvic and extra-pelvic recurrence ($P = 0.012$), the tumor diameter <3.0 cm ($P < 0.001$), the tumor diameter >3.0 cm ($P = 0.014$), a reduced level of SCCa ($P = 0.001$), as well as an increased level of SCCa ($P = 0.001$). Nevertheless, when analyzing the subgroups with ECOG PS = 1 ($P = 0.393$) or pelvic recurrence ($P = 0.141$), comparative trends were identified across the groups, as shown in Fig. 4A–I..

3.6. AEs

No deaths linked with the treatments were reported within either group. Notably, three significant puncture-related complications (3.4 %) occurred in Group B, comprising one instance of bleeding and two occurrences of implantation metastasis. Within Group A, the total incidence rate of AEs was 75.0 %. Among these, grade 1–2 AEs were documented in 43 out of 88 patients (48.9 %). Major grade 3–4 AEs included leukopenia (13.7 %), pelvic pain (13.6 %), and weight loss (6.8 %). In Group B, the overall incidence rate of AEs was 73.9 %, with grade 1–2 AEs recorded in 45.5 % of patients (40/88). The principal grade 3–4 AEs comprised agranulocytosis (11.4 %), pelvic pain (11.4 %), weight loss (5.7 %), hair loss (5.7 %), and stomatitis (5.7 %). There was no significant disparity in the overall incidence of AEs between the groups (p = 0.698) (Table 4). All patients experiencing AEs received timely treatment and fully recovered within one month.

4. Discussion

Locoregional recurrence or LC failure affects a substantial proportion of patients with CC subsequent to radical surgery or EBRT with chemotherapy, with reported rates ranging from 15 % to 61 % [15,16]. While local recurrence of CC holds potential for curative intervention, only approximately one-third of patients respond to initial chemotherapy, often yielding partial and short-lived responses [5]. Recent advancements in treatment approaches, encompassing targeted therapy and immunotherapy, have been explored as secondary treatments for patients experiencing recurrent CC, yet outcomes have proven unsatisfactory [7,17]. This study has underscored the prolonged OS observed with combined therapy compared to chemotherapy alone in cases of locally recurrent CC. The findings imply that integrating systemic therapy with localized treatment may represent a novel strategy for addressing local CC recurrences.

An estimated 30 %–50 % of patients with advanced CC encounter loco-regional recurrence during treatment [3]. While local relapses present a potential opportunity for cure, systemic treatment yields a low response rate. A few investigations have demonstrated that chemotherapeutic regimens involving multiple drugs may have a potential in enhancing response rates; however, they do not substantially extend patient survival. Notably, the PFS for those undergoing second-line chemotherapy was only 1.5–5 months [18,19]. Consequently, there is an imperative need to combine localized and systemic treatments. Furthermore, this study suggests that local ^{125}I implantation in combination with systemic treatment not only enhances the LR but also improves OS. It is postulated that

Table 3
Results of the univariable and multivariable Cox regression model with regard to OS.

Variable	Univariable analysis		Multivariable analysis	
	HR (95 % CI)	P value	HR (95 % CI)	P value
Age	0.928 (0.567, 1.518)	0.765	NA	NA
ECOG PS	2.204 (1.142, 4.255)	0.019	2.580 (1.297, 5.135)	0.007
FIGO staging	0.997 (0.677, 1.468)	0.987	NA	NA
Histology	0.843 (0.621, 1.143)	0.272	NA	NA
Differentiation	1.081 (0.817, 1.429)	0.587	NA	NA
Recurrence position	1.300 (1.026, 1.647)	0.030	1.699 (1.337, 2.158)	<0.001
Lesion number	1.140 (0.796, 1.633)	0.474	NA	NA
Tumor diameter	5.546 (3.508, 8.769)	<0.001	2.497 (2.103, 2.964)	<0.001
SCCa Change	1.953 (1.352, 2.823)	<0.001	1.740 (1.182, 2.561)	0.005

Abbreviation: OS: overall survival; HR: hazard ratio; PS, performance status; CI: confidence interval; FIGO: Federation of International of Gynecologists and Obstetricians; SCCa: squamous cell carcinoma antigen.

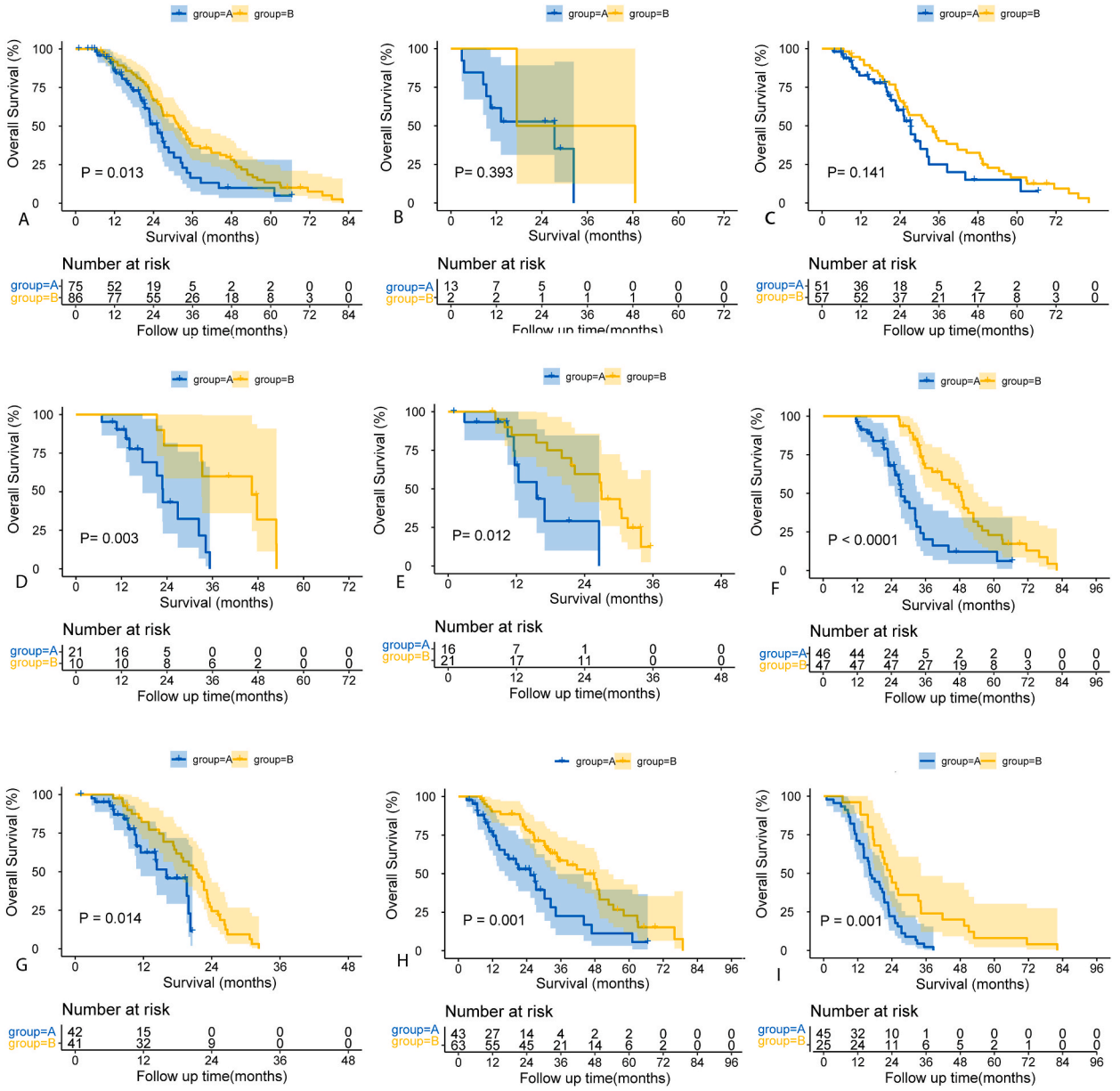

Fig. 4. Subgroup analysis of overall survival. ECOG PS = 0 (A), PS = 1 (B), pelvic recurrence (C), extra-pelvic recurrence (D), both pelvic and out-pelvic recurrence (E), tumor diameter <3.0 cm (F), tumor diameter >3.0 cm (G), SCCa decline (H) and SCCa rise (I).

systemic treatment effectively eradicates residual tumor cells within the bloodstream, while local treatment via ^{125}I implantation facilitates the penetration of chemotherapeutic agents into the locally recurring tumor [20].

The physical condition of patients plays a pivotal role in treatment efficacy, as evidenced by this study, which demonstrated that combined therapy proved more effective for patients with a performance status (PS) score of 0 compared to those with a PS score of 1. This finding aligned with previous reports pertaining to palliative care for advanced cancer patients [21]. A PS score of 1 is frequently linked with poor nutritional status. Research indicates that optimal nutritional status can mitigate muscle depletion, thereby averting drug toxicity and enhancing chemotherapy effectiveness [22,23].Therefore, it is very important to provide nutritional support for patients during treatment.

The prognosis and survival outcomes vary significantly among patients with recurrent CC [19]. Studies have indicated that disease-free survival, tumor volume, surgical margins, and lymph nodes serve as prognostic factors for CC [24–27]. Consistent with prior research, the present study identified the location of tumor recurrence and tumor diameter as independent risk factors for OS. Specifically, pelvic recurrence and tumor diameters less than 3 cm were deemed protective factors. Moreover, the study revealed that systemic chemotherapy in conjunction with ^{125}I implantation conferred superior benefits compared to chemotherapy alone for

Table 4
Adverse events between Group A and Group B.

AEs in total	Group A (N = 88) n (%)		Group B (N = 88) n (%)		*P* value
	Grade 1–2	**Grade 3–4**	**Grade 1–2**	**Grade 3–4**	0.698
	43 (48.9)	23 (26.1)	40 (45.5)	25 (28.4)	
Blood/bone marrow suppression					0.278
Leukopenia	7(8.0)	12(13.7)	6 (6.8)	10(11.4)	NA
Anemia	3 (3.4)	NA	1 (1.1)	NA	NA
Thrombocytopenia	2 (2.3)	1(1.1)	1 (1.1)	1(1.1)	NA
Constitutional symptom					0.905
Weight loss	13 (14.7)	6 (6.8)	11 (12.5)	5 (5.7)	NA
Hair loss	16 (18.2)	3 (3.4)	18 (20.5)	5 (5.7)	NA
Fatigue	9 (10.3)	2 (2.3)	7 (8.0)	3 (3.4)	NA
Stomatitis	7 (8.0)	3 (3.4)	9 (10.2)	5 (5.7)	NA
Cough	8 (9.1)	2 (2.3)	7 (8.0)	3 (3.4)	NA
GI disorder					0.466
Diarrhea	1 (1.1)	NA	2 (2.3)	NA	NA
Vomiting	6 (6.8)	2 (2.3)	3 (3.4)	2 (2.3)	NA
Intestinal fistula	NA	2 (2.3)	NA	1 (1.1)	
Pain					0.880
Abdominal pain	7 (8.0)	4 (4.5)	6 (6.8)	3 (3.4)	NA
Pelvic pain	16 (18.2)	12 (13.6)	18 (20.5)	10 (11.4)	NA
Puncture-related side effects					NA
Bleeding	NA	NA	NA	1 (1.1)	NA
Implantation metastasis	NA	NA	NA	2 (2.3)	NA

Data in bracket was percent of patients. The data in two groups were compared by using the Chi square test.*Data were compared by using Fisher's exact test.
Abbreviation: Group A: second-line chemotherapy alone; Group B: second-line chemotherapy and ^{125}I brachytherapy; NA, not applied.

patients with a limited tumor burden, irrespective of recurrent tumor location and size. These findings suggest that combined therapy holds the potential to substantially prolong survival, offering a new therapeutic approach for addressing locally recurring CC.

In the present study, the rate of seed implantation-related complications stood at 3.4 %, consistent with previous reports [10,11]. Furthermore, although complications did not occur with greater frequency, they were generally mild, with all implantation-related AEs falling below grade III. Notably, the three patients experiencing severe AEs underwent alleviation through surgical intervention. Additionally, most patients in both groups encountered at least one complication related to systemic therapy, with a quarter of patients experiencing complications less than grade III. Consequently, preventive measures before chemotherapy, such as antiemetic and analgesic treatments, hold particular importance.

This study had several limitations. Firstly, it was a retrospective study with a small sample size and short follow-up duration. Thus, multi-center prospective studies with longer follow-up periods are essential for a more comprehensive analysis of patient survival. Secondly, the technique for precise positioning of the implant was constrained by obstacles posed by bone or vital organs, necessitating accurate 3D information regarding tumor location. Thirdly, while immunological and targeted therapies play an increasingly critical role in recurrent CC treatment, follow-up data following first-line and second-line chemotherapy were excluded from this investigation. Therefore, future endeavors should focus on combining localized approaches with post-treatment follow-up strategies for tumors.

5. Conclusion

Combining chemotherapy and ^{125}I brachytherapy exhibited the potential to prolong overall survival of patients with safety profiles akin to the sole chemotherapy, particularly for individuals experiencing the local recurrence of CC subsequent to unsuccessful radiotherapy and initial chemotherapy.

Ethical statement

This is a retrospective study. The study was in accordance with the ethical guidelines of the 1975 Declaration of Helsinki (as revised in Brazil in 2013) and approved by the Ethical Committee of Fist Affiliated Hospital, Sun Yat-Sen University and Sun Yat-Sen University Cancer Center. The approval number are 2018-561 and YB2018-17.

Consent for publication

All authors agreed to publish this article in the journal of radiologia medica.

Funding

The authors state that this work has not received any funding.

Data availability statement

These data have been uploaded database of Sun Yat-Sen university, which is not accessible to outsiders due to confidentiality. Therefore, the data that support the findings of this study are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Zhimei Huang: Writing - original draft, Validation, Data curation, Conceptualization. **Wang Yao:** Writing - original draft, Validation, Conceptualization. **Zhihui Zhong:** Data curation. **Guang Yang:** Resources, Project administration, Investigation. **Jihong Liu:** Resources, Project administration, Investigation. **Haifeng Gu:** Methodology, Formal analysis. **Jinhua Huang:** Writing - review & editing.

Declaration of competing interest

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.

Acknowledgements

We sincerely express our gratitude to Hui Zhu for her providing language help.

References

[1] J. Ferlay, I. Soerjomataram, R. Dikshit, et al., Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012, Int. J. Cancer 136 (5) (2021) E359–E386.
[2] W.J. Koh, B.E. Greer, N.R. Abu-Rustum, et al., Cervical cancer, version 2.2015, J. Natl. Compr. Cancer Netw. 13 (4) (2015) 395–404, quiz 404.
[3] L. Kumar, S. Gupta, Integrating chemotherapy in the management of cervical cancer: a critical appraisal, Oncology 91 (Suppl 1) (2016) 8–17.
[4] National Comprehensive Cancer Network: NCCN clinical practice guidelines in oncology: Cervical cancer 1 (2021). Available online: https://www.nccn.org/professionals/physician_gls/pdf/nsclc.pdf.
[5] M. Liontos, A. Kyriazoglou, I. Dimitriadis, et al., Systemic therapy in cervical cancer: 30 years in review, Crit. Rev. Oncol. Hematol. 137 (2019) 9–17.
[6] K.S. Tewari, J.J. Java, T.A. Gatcliffe, et al., Chemotherapy-induced neutropenia as a biomarker of survival in advanced ovarian carcinoma: an exploratory study of the gynecologic oncology group, Gynecol. Oncol. 133 (3) (2014) 439–445.
[7] R. Wendel Naumann, C.A. Leath 3rd, Advances in immunotherapy for cervical cancer, Curr. Opin. Oncol. 32 (5) (2020) 481–487.
[8] J.A. Kittel, C.A. Reddy, K.L. Smith, et al., Long-Term efficacy and toxicity of low-dose-rate ^{12s}I prostate brachytherapy as monotherapy in low-, intermediate-, and high-risk prostate cancer, Int. J. Radiat. Oncol. Biol. Phys. 92 (4) (2015) 884–893.
[9] H. Yan, Z. Mo, Z. Xiang, et al., CT-guided ^{125}I brachytherapy for locally recurrent nasopharyngeal carcinoma, J. Cancer 8 (11) (2017) 2104–2113.
[10] A. Qu, P. Jiang, H. Sun, et al., Efficacy and dosimetry analysis of image-guided radioactive ^{125}I seed implantation as salvage treatment for pelvic recurrent cervical cancer after external beam radiotherapy, J Gynecol Oncol 30 (1) (2019) e9.
[11] Y. Liu, P. Jiang, H. Zhang, et al., Safety and efficacy of 3D-printed templates assisted CT-guided radioactive iodine-125 seed implantation for the treatment of recurrent cervical carcinoma after external beam radiotherapy, J Gynecol Oncol 32 (2) (2021) e15.
[12] S. Nag, Brachytherapy for prostate cancer: summary of American Brachytherapy Society recommendations, Semin. Urol. Oncol. 18 (2) (2000) 133–136.
[13] G. Wang, F. Zhang, B. Yang, et al., Feasibility and clinical value of CT-guided ^{125}I brachytherapy for bilateral lung recurrences from colorectal carcinoma, Radiology 278 (3) (2016) 897–905.
[14] F. Gao, C. Li, Y. Gu, et al., CT-guided 125I brachytherapy for mediastinal metastatic lymph nodes recurrence from esophageal carcinoma: effectiveness and safety in 16 patients, Eur. J. Radiol. 82 (2) (2013) e70–e75.
[15] K.S. Pfaendler, K.S. Tewari, Changing paradigms in the systemic treatment of advanced cervical cancer, Am. J. Obstet. Gynecol. 214 (1) (2016) 22–30.
[16] M. Peiretti, I. Zapardiel, V. Zanagnolo, et al., Management of recurrent cervical cancer: a review of the literature, Surg Oncol 21 (2) (2012) e59–e66.
[17] L. Kumar, P. Harish, P.S. Malik, et al., Chemotherapy and targeted therapy in the management of cervical cancer, Curr. Probl. Cancer 42 (2) (2018) 120–128.
[18] L. Kumar, Y.H. Pokharel, S. Kumar, et al., Single agent versus combination chemotherapy in recurrent cervical cancer, J. Obstet. Gynaecol. Res. 24 (6) (1998) 401–409.
[19] S. Boussios, E. Seraj, G. Zarkavelis, et al., Management of patients with recurrent/advanced cervical cancer beyond first line platinum regimens: where do we stand? A literature review, Crit. Rev. Oncol. Hematol. 108 (2016) 164–174.
[20] R. Kitagawa, N. Katsumata, T. Shibata, et al., Paclitaxel plus carboplatin versus paclitaxel plus cisplatin in metastatic or recurrent cervical cancer: the open-label randomized phase III trial JCOG0505, J. Clin. Oncol. 33 (19) (2015) 2129–2135.
[21] P. Cotogni, S. Stragliotto, M. Ossola, et al., The role of nutritional support for cancer patients in palliative care, Nutrients 13 (2) (2021) 306.
[22] F. Bozzetti, Forcing the vicious circle: sarcopenia increases toxicity, decreases response to chemotherapy and worsens with chemotherapy, Ann. Oncol. 28 (9) (2017) 2107–2118.
[23] F. Bozzetti, Chemotherapy-Induced sarcopenia, Curr. Treat. Options Oncol. 21 (1) (2020) 7.
[24] S. Marnitz, C. Kohler, M. Muller, et al., Indications for primary and secondary exenterations in patients with cervical cancer, Gynecol. Oncol. 103 (3) (2006) 1023–1030.
[25] J.S. Berek, C. Howe, L.D. Lagasse, et al., Pelvic exenteration for recurrent gynecologic malignancy: survival and morbidity analysis of the 45-year experience at UCLA, Gynecol. Oncol. 99 (1) (2005) 153–159.
[26] M.C. Fleisch, P. Pantke, M.W. Beckmann, et al., Predictors for long-term survival after interdisciplinary salvage surgery for advanced or recurrent gynecologic cancers, J. Surg. Oncol. 95 (6) (2007) 476–484.
[27] H.M. Shingleton, S.J. Soong, M.S. Gelder, et al., Clinical and histopathologic factors predicting recurrence and survival after pelvic exenteration for cancer of the cervix, Obstet. Gynecol. 73 (6) (1989) 1027–1034.