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Full Length Article

The value of PFS36 as a primary endpoint for radiotherapy trials in patients with LACC: individual patient data from the Chinese NCC and validation from 26 RCTs

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ABSTRACT

Objective: A conventional endpoint for locally advanced cervical cancer (LACC) clinical trials is overall survival (OS) with five years of follow-up. The primary hypothesis was that progression-free survival (PFS) with three years of follow-up (PFS36) would be an appropriate primary surrogate endpoint.

Materials and methods: The primary hypothesis, which was developed from our data, was further investigated using phase III randomized controlled trials and then externally validated using retrospective studies up to 2023. Correlation analysis at the treatment-arm level was performed between 2-, 3-, 4-, and 5-year PFS rates and 5-year OS.

Results: A total of 613 patients with histologically confirmed cervical cancer who underwent radiotherapy or chemoradiation at our institute between January 2010 and December 2013 were eligible. The recurrence rates for years 1 through 5 were 12.9%, 7.3%, 3%, 2.3%, and 1.8%, respectively. Patients who did not achieve PFS36 had a 5-year OS rate of 30.3%. However, patients who achieved PFS36 had a 5-year OS rate of 98.2%. Further data were extracted from 26 randomized phase III trials on LACC. The trials included 55 arms, with a pooled sample size of 7,281 patients. Trial-level surrogacy results revealed that PFS36 (r^2, 0.732) was associated with 5-year OS. The correlation between PFS36 and OS was externally validated using independent retrospective data.

Conclusion: A significant positive correlation was found between PFS36 and OS at 5 years of follow-up both within patients and across trials. These results suggest that PFS36 is an appropriate endpoint for LACC clinical trials of radiotherapy-based regimens.

1. Introduction

Cervical cancer is the fourth most common cancer in women worldwide, with about 570,000 new cases and approximately 300,000 deaths annually.[1-3] Both the incidence and mortality rates of cervical cancer increased in 2020, with about 109,700 new cases and about 59,100 deaths reported in China.[4-6] Concurrent chemoradiotherapy (CCRT) has been considered the gold standard treatment for decades for patients with locally advanced cervical cancer (LACC). Research has shown that the 5-year overall survival rate (OS) of LACC is 60–80%, with a 30–40% progression or relapse rate under the current standard treatment. However, although studies have confirmed the efficacy of immunotherapy in recurrent and metastatic cervical cancer,[7-8] identifying an effective radiotherapy (RT) combined treatment scheme for patients with LACC is imperative. So far, multiple international multicenter randomized controlled trials (RCTs) have been conducted globally on this issue.

While the OS has generally served as the primary endpoint in RCTs, it necessitates substantial sample sizes and extended follow-up periods to ascertain survival advantages. Such requirements elevate clinical de-

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velopment expenses and prolong the introduction of novel therapies into clinical practice. Several studies of various malignant tumors have demonstrated that utilizing disease-free survival (DFS) and progression-free survival (PFS) as primary endpoints in clinical trials can potentially reduce the required sample size and shorten the evaluation period.[9-10] Traditionally, the main endpoint was the 5-year OS[11-12]; however, long-term follow-up studies with a 10-year OS have also been documented.[13] Recent studies investigating the combination of immunotherapy with CCRT have utilized the 2-year PFS as an early surrogate endpoint. The Keynote-A18 trial reported a significant increase in 2-year PFS when pembrolizumab was incorporated into CCRT.[14] Therefore, the Food and Drug Administration (FDA) approved pembrolizumab with CCRT for patients with the International Federation of Gynecology and Obstetrics (FIGO) 2014 Stage III-IVA cervical cancer on January 12, 2024. Nonetheless, preliminary findings from the CALLA trial did not demonstrate an improvement in 2-year PFS with the addition of durvalumab to CCRT.[15] Hence, whether the 2-year PFS is directly correlated with the 5-year OS remains to be elucidated, pending long-term follow-up results.[16] However, there is still a gap in the understanding of the extent to which early PFS is indicative of the 5-year OS. Besides, the clinical significance of early surrogate endpoint in LACC clinical trials remains unclear. Effective early research endpoints can accelerate the translation of research findings into clinical practice. Therefore, exploring the correlation between early research endpoints and long-term survival benefits is of great significance. The present study endeavored to investigate the correlation between early progression survival time and the 5-year OS in LACC patients.

2. Materials and methods

2.1. Patient selection and study population

The data of patients diagnosed with LACC from a single center were retrospectively reviewed and collected. The inclusion criteria included patients receiving RT or CCRT. Eligible participants were patients with histologically confirmed cervical carcinoma, FIGO 2009 stage IB-IVA undergoing RT treatment in our institute between January 2010 and December 2013. Overall, 613 patients were recruited. Because this study used existing data without enrolling any human subjects, it was exempted from institutional review board (IRB) review.

2.2. Treatment

All patients received radiotherapy. CCRT was the standard treatment for LACC (n = 547, 89.2%), whereas RT alone (n = 66, 10.8%) was acceptable for patients with advanced age or insufficient renal function. Neoadjuvant chemotherapy was performed on a select group of patients (n = 110, 17.9%) with smaller tumor sizes when surgical intervention was deemed feasible. Adjuvant chemotherapy was administered to 93 patients (15.2%) for whom clinicians deemed necessary based on their disease situation. The chemotherapy protocol involved paclitaxel along with cisplatin or an alternative platinum-based agent. For radiotherapy, patients underwent whole pelvic external beam radiation therapy (EBRT) in conjunction with high-dose-rate brachytherapy (HDR-BT). They received a cumulative EBRT dose ranging from 45 to 50 Gy, supplemented by an additional boost of 10–15 Gy directed at any enlarged lymph nodes. HDR-BT was performed weekly, with 5–7 Gy given each time. Dose accumulation at point A ranged from 80 to 85 Gy (Equivalent dose in 2 Gy/f, EQD2), adjusted according to the disease stage. For CCRT, platinum-based chemotherapy was prescribed alongside EBRT. Of the 547 patients who received CCRT, 324 (52.8%) received platinum alone, 200 (32.6%) received platinum and paclitaxel, and 23 (3.8%) received platinum and fluorouracil (5FU).

2.3. Statistical analysis

PFS was defined as the time from initiation of treatment to disease progression, recurrence, or death from any cause. PFS36 was defined as survival with no progression at 36 months after initial treatment. Annual hazards were calculated as the annual number of events divided by the total follow-up time accumulated by the patients at risk in that year. An Epanechnikov kernel was used to smooth hazard rate curves. For sensitivity analysis, PFS was also evaluated at other milestones (12, 24, and 36 months). The Kaplan-Meier method was used to estimate the survival curve. Bilateral $P < 0.05$ was considered statistically significant. Statistical analyses were performed using R (version 3.6.2; http://www.r-project.org/).

2.4. Literature search and study selection

Inclusion criteria were: RCTs and retrospective studies focusing on the long-term survival outcomes in LACC patients treated with CCRT or

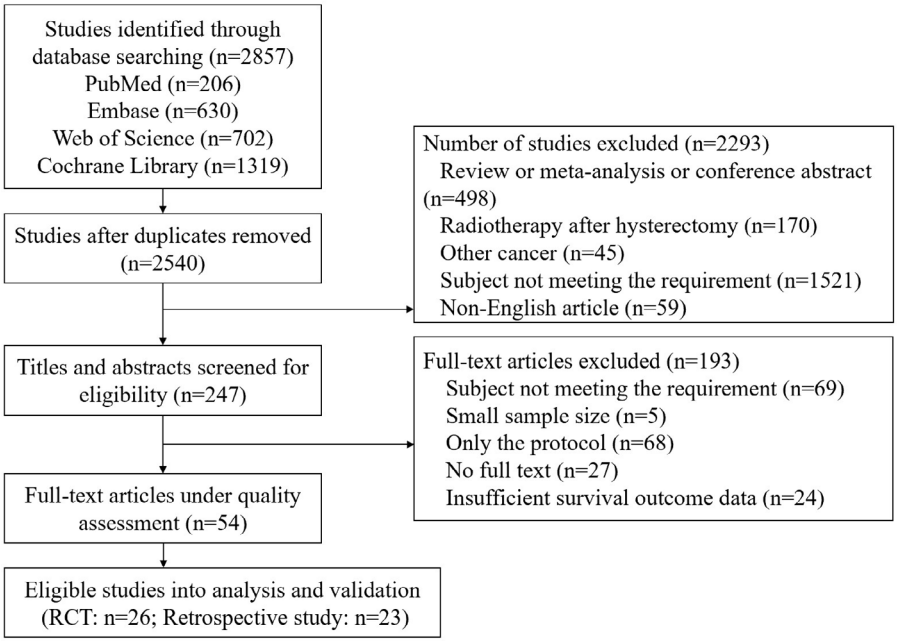

Fig. 1. Flow chart showing the inclusion of studies.

RT alone and RCTs that used radiation therapy as the backbone treatment and provided adequate follow-up data for PFS assessment (refer to endpoint definitions). Exclusion criteria included studies on recurrent or metastatic cervical cancer, phase I trials, and studies with insufficient survival data.

Web of Science, Embase, Cochrane, and PubMed databases were systematically searched for relevant RCTs and retrospective studies published after December 31, 1998, using 'cervical cancer and radiotherapy' as search terms. Only formal publications were selected. Two researchers independently conducted the literature search. Any discrepancies regarding study selection were resolved through a consensus discussion with a third researcher.

2.5. Study inclusion and quality control

Data used in the assessment were obtained from formal publications and conference abstracts. Potential bias in eligible RCTs was evaluated across seven domains using the Cochrane Collaboration tool. Overall, 26 qualified RCTs with 55 treatment arms were included for trial- and treatment arm-level analyses (Fig. 1). The 26 RCTs included 7281 patients (with a median sample size of 132), and the follow-up time of each study ranged from 2.4 to 9.4 years. The majority of RCTs reported 5-year OS (n = 10) and 5-year PFS/DFS (n = 10), followed by 3-year PFS/DFS (n = 8), 2-year PFS/DFS (n = 2), and 4-year PFS/DFS (n = 2). After a thorough review of each article's definitions, it was found that DFS and PFS were quite similar. Given their minimal impact on the results, they were consolidated as PFS in our subsequent analysis.

Retrospective data were utilized to validate RCT findings on the correlation between PFS and OS. For retrospective cohort studies, the Newcastle-Ottawa Scale (NOS) was employed to assess the quality, awarding up to 9 stars based on the criteria of selection, comparability, and outcome assessment. After excluding studies with a high risk of bias, 23 retrospective studies were included in the external validation (Fig. 1). The average NOS score was 6.9 stars. The 23 retrospective studies encompassed 4856 patients, with individual arms ranging from 9 to 406 patients (with a median of 118). The median follow-up duration was 2.83–8.1 years.

2.6. Data extraction

For the RCTs, sample size, patient characteristics, primary endpoint, follow-up duration, standard and treatment arms, 5-year OS, and 2-, 3-, 4-, and 5-year PFS rates were extracted. The hazard ratio (HR) was not extracted as it was unreported in most of the articles (n = 16). When an RCT was reported multiple times, the latest report that provided the longest duration of follow-up was selected. Study sample size, patient characteristics, treatment, median follow-up time, 5-year OS, and 2-, 3-, 4-, and 5-year PFS rates were extracted from retrospective studies. Data on survival rates at designated intervals were obtained from the full text (marked with "*"). For any unreported survival data, values were extracted from the Kaplan-Meier survival curve using the Engauge Digitizer.

2.7. Evaluation of the correlation between PFS and OS in RCTs

The correlation analyses of the RCTs were performed at the arm level, weighted by the trial size. At the arm level, the linear correlation between the 2-, 3-, 4- and 5-year PFS rates and the 5-year OS rate was evaluated by the correlation coefficient r, with a weight depending on the sample size of each treatment arm. An r^2-value approaching 1 indicated a strong correlation. The 95% confidence intervals (CIs) of r^2 were calculated using the bootstrap method with 1000 replications.

Table 1
Baseline clinical characteristics of patients from the NCC.

Characteristic	Number of patients, n (%)			
	Total n = 613	Non-PFS36 n = 143	PFS36 n = 470	P value
Age, years				0.122
31–40	32 (5.2)	10 (7.0)	22 (4.7)	
41–50	172 (28.1)	42 (29.4)	130 (27.6)	
51–60	243 (39.6)	63 (44.0)	180 (38.3)	
61–70	134 (21.9)	25 (17.5)	109 (23.2)	
≥71	32 (5.2)	3 (2.1)	29 (6.2)	
BMI, kg/m^2				0.748
< 18.5	23 (3.8)	7 (4.9)	16 (3.4)	
18.5–23.9	285 (46.5)	69 (48.2)	216 (46.0)	
24–29.9	274 (44.7)	61 (42.7)	213 (45.3)	
≥ 30	31 (5.1)	6 (4.2)	25 (5.3)	
SCC-Ag				< 0.001
≤1.5	108 (17.6)	23 (16.1)	85 (18.1)	
1.6–5.0	179 (29.2)	31 (21.7)	148 (31.5)	
5.1–10.0	113 (18.4)	19 (13.3)	94 (20)	
10.1–20	93 (15.2)	25 (17.5)	68 (14.5)	
> 20	120 (19.6)	45 (31.4)	75 (15.9)	
HGB, g/L				0.003
< 60	15 (2.4)	7 (4.9)	8 (1.7)	
60–89	135 (22.0)	43 (30.1)	92 (19.6)	
90–109	267 (43.6)	58 (40.6)	209 (44.4)	
≥ 110	196 (32.0)	35 (24.4)	161 (34.3)	
Tumor size, cm				0.001
≤ 4	235 (38.3)	36 (25.2)	199 (42.3)	
4.1–5.9	276 (45.1)	75 (52.4)	201 (42.8)	
≥ 6	102 (16.6)	32 (22.4)	70 (14.9)	
PLNM				<0.001
No	293 (47.8)	46 (32.2)	247 (52.6)	
Yes	320 (52.2)	97 (67.8)	223 (47.4)	
PALNM				< 0.001
No	578 (94.3)	120 (83.9)	458 (97.4)	
Yes	35 (5.7)	23 (16.1)	12 (2.6)	
Pelvic wall involvement				< 0.001
No	373 (60.8)	57 (39.9)	316 (67.2)	
Yes	240 (39.2)	86 (60.1)	154 (32.8)	
FIGO 2009 stage				< 0.001
IB	26 (4.3)	4 (2.8)	22 (4.7)	
IIA	17 (2.7)	2 (1.4)	15 (3.2)	
IIB	324 (52.9)	49 (34.3)	275 (58.5)	
IIIA	6 (1.0)	2 (1.4)	4 (0.8)	
IIIB	232 (37.8)	84 (58.7)	148 (31.5)	
IVA	8 (1.3)	2 (1.4)	6 (1.3)	
FIGO 2018 stage				< 0.001
IB	16 (2.6)	4 (2.8)	12 (2.5)	
IIA	5 (0.8)	1 (0.7)	4 (0.9)	
IIB	193 (31.5)	20 (14.0)	173 (36.8)	
IIIA	3 (0.5)	0 (0)	3 (0.6)	
IIIB	71 (11.6)	21 (14.7)	50 (10.6)	
IIIC1r	282 (46.0)	72 (50.3)	210 (44.7)	
IIIC2r	35 (5.7)	23 (16.1)	12 (2.6)	
IVA	8 (1.3)	2 (1.4)	6 (1.3)	

Abbreviations: BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; HGB, hemoglobin; NCC, National Cancer Center of China; PALNM, para-aortic lymph node metastasis; PLNM, pelvic lymph node metastasis; SCC-Ag, squamous cell carcinoma antigen.

2.8. External validation in retrospective studies

To validate our findings, predictive linear regression models developed using RCT data were applied to retrospective studies with adequate survival data. The predicted 5-year OS rate was calculated by substituting the actual 2-, 3-, 4-, and 5-year PFS rates from the retrospective studies into the linear regression equation derived from the RCTs. For example, the 5-year OS rates based on the reported 2-, 3-, 4-, and 5-year PFS rates from the retrospective studies were predicted using the following equation: 5-year OS = $\alpha \times$ 2-, 3-, 4-, or 5-year PFS + β, where α represents the slope, which describes the rate and direction of the

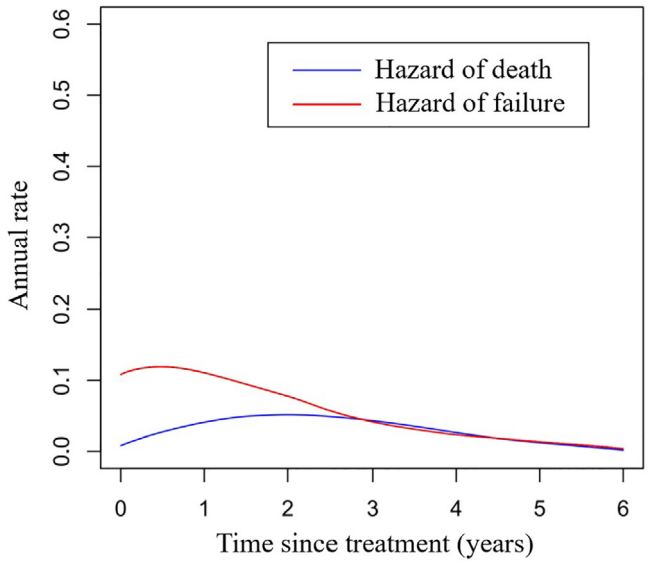

Fig. 2. Smoothed hazard plots of death and progression over time (the dynamics of the annual hazards of death and failure).

change of "5-year OS" with respect to "2-, 3-, 4- or 5-year PFS". It indicates the change in 5-year OS associated with a 1-unit change in the corresponding PFS rate (2-, 3-, 4- or 5-year), while β represents the y-intercept.

By applying the regression equation derived from the RCT data to the PFS rates reported in retrospective studies, we validated the predictive ability of the model and assessed whether PFS could reliably predict the 5-year OS in a real-world setting. This helps establish PFS as a valid surrogate endpoint for OS in this disease context.

Meanwhile, both the predicted and actual 5-year OS rates were visualized using scatter plots, which were generated using the ggplot2 package in R software (version 3.6.2, R Foundation for Statistical Computing). All statistical analyses were conducted by SPSS (version 26.0, IBM Inc.).

3. Results

3.1. Individual patient characteristics and survival based on data from the National Cancer Center (NCC) of China

The median age was 54 years (interquartile range, 48–61 years). The median follow-up time was 61.5 months, with 168 patients (27.4%) with disease progression and 109 patients (17.8%) succumbing within 5 years. The 1-, 2-, 3-, 4-, and 5-year OS rates for all patients were 96.8%, 91.9%, 86.4%, 84.0%, and 82.4%, respectively. Furthermore, the 1-, 2-, 3-, 4-, and 5-year PFS rates for all patients were 86.9%, 79.4%, 76.1%, 73.7%, and 72.7%, respectively. Of the 613 patients, 143 experienced disease progression within 36 months, while 470 did not. Statistically significant differences were observed between the two groups regarding PFS36 attainment, encompassing squamous cell carcinoma antigen, hemoglobin, tumor size, pelvic lymph node metastasis, and pelvic wall involvement. These parameters demonstrate their potential to predict an unfavorable early prognosis. The baseline clinical characteristics of patients are summarized in Table 1. Approximately 73.3% of all deaths occurred within 36 months. A smooth hazard map shows that the maximum annual mortality risk for years 1 through 5 was 17.4%, 26.6%, 29.4%, 12.8%, and 8.3%, respectively (Annual hazard rate over time, Fig. 2). The median time from recurrence to death was 12.2 months (95% CI, 11.59–12.74). The recurrence rates for years 1 through 5 were 12.9%, 7.3%, 3%, 2.3%, and 1.8%, respectively. The annual risk of progression and death from the third year was <3%. About 47.3% of all recurrences occurred during the first year, 71.4% during the first two years, and 85% during the first three years.

Kaplan-Meier analysis revealed that patients who did not achieve PFS36 exhibited a 5-year OS rate of 30.3%, whereas those who successfully attained PFS36 had a 5-year OS rate of 98.2% (Fig. 3). This suggests that patients who achieve PFS36 have significantly favorable outcomes, whereas those experiencing earlier progression tend to have poorer survival rates. Therefore, PFS36 can be a logistics deadline for further evaluation.

3.2. Treatment arm-level correlation between PFS and OS in RCTs

A total of 55 chemoradiotherapy/RT arms from 26 RCTs were included,[11,13,17-41] of which 21 reported a 5-year OS, 4 arms reported 2-year PFS, 16 arms reported 3-year PFS, and 21 arms reported 5-year

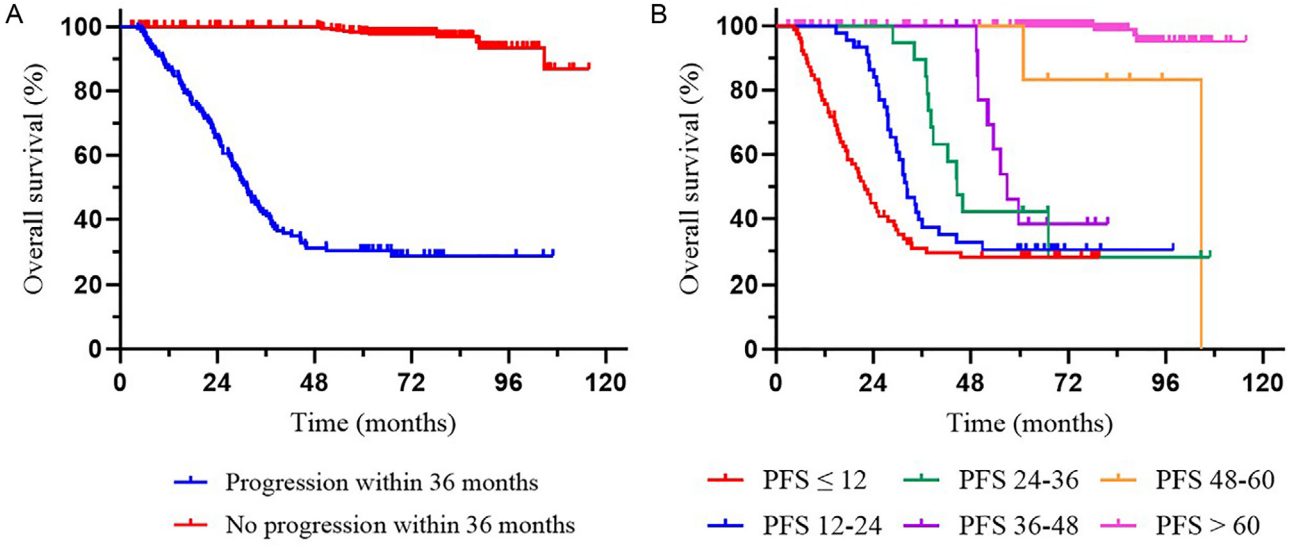

Fig. 3. Kaplan-Meier survival analysis on patients from the NCC. (A) The OS of patients who achieved PFS36 after initial treatment. (B) The OS at different time points of patients who progressed. NCC, National Cancer Center of China; PFS, progression-free survival; OS, overall survival.

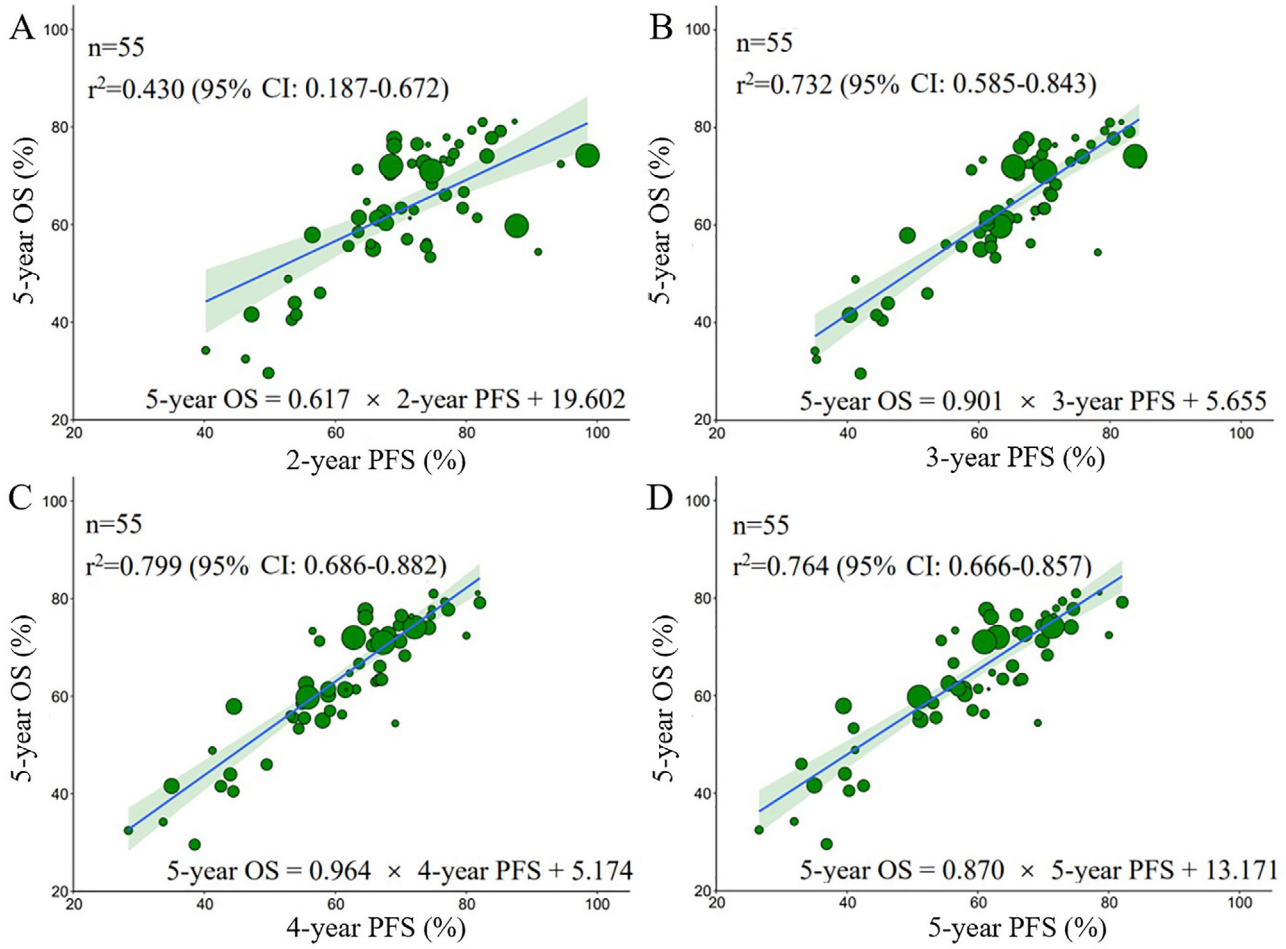

Fig. 4. Arm level correlation between PFS and OS in randomized controlled trials. (A) 2-year PFS and 5-year OS, (B) 3-year PFS and 5-year OS, (C) 4-year PFS and 5-year OS, and (D) 5-year PFS and 5-year OS. Circle size is proportional to the number of patients in each treatment arm. The solid blue line represents the fitted weighted linear regression line; the light green zone represents its 95% confidence interval; r indicates the correlation coefficient. PFS, progression-free survival; OS, overall survival.

PFS (Table 2). The 2-year ($r^2 = 0.430$; 95% CI, 0.187–0.672; Fig. 4A), 3-year ($r^2 = 0.732$; 95% CI, 0.585–0.843; Fig. 4B), 4-year ($r^2 = 0.799$; 95% CI, 0.686–0.882; Fig. 4C), or 5-year ($r^2 = 0.764$; 95% CI, 0.666–0.857; Fig. 4D) PFS correlated linearly with 5-year OS.

3.3. Association between PFS and OS in retrospective studies

Subsequently, the PFS predictive models from the RCTs (Fig. 4) were validated using 41 treatment arms from retrospective studies.[42-64] The predicted 5-year OS rate of each treatment arm was calculated using the actual 2-, 3-, 4-, or 5-year PFS rate (Table 3). The correlation between the actual and predicted 5-year OS rates closely approached the diagonal line, demonstrating a close approximation between predicted and actual OS outcomes (Fig. 5A-D). Furthermore, the predicted 5-year OS rate was significantly positively correlated with the actual 5-year OS rate, with correlation coefficient (r) of 0.811. This affirms that PFS36 could serve as a reliable predictor of OS.

4. Discussion

Cervical cancer is the fourth leading cause of cancer mortality globally, posing a significant health problem, especially in developing countries. At present, CCRT is the primary treatment method for LACC. Notably, immunotherapy has made significant strides in the treatment of recurrent and metastatic cervical cancer. Several clinical trials of RT combined with immunotherapy for patients diagnosed with LACC have reported preliminary results.[14,15,65] While there is an urgent need to expedite patient access to breakthrough therapies, measurement of the 5-year OS requires a longer time. However, early surrogate endpoints can be used to shorten the time of clinical trial protocol evaluation, allowing the best treatment strategy to be applied to clinical practice. Thus, establishing an efficient, accurate, and predictive early surrogate endpoint in clinical trials is imperative. Although the FDA has approved pembrolizumab with CCRT for patients with FIGO Stage III-IVA cervical cancer based on the result of a 2-year PFS benefit, the correlation between early PFS and 5-year OS has not been elucidated. To the best of our knowledge, this is the first study to evaluate the early surrogacy endpoint in patients with LACC treated with radiotherapy.

Currently, CCRT is the standard treatment for LACC. In theory, studies should include patients who receive standard treatment. However, in clinical practice, some patients with LACC may not tolerate CCRT due to advanced age or abnormal renal function but may instead receive RT alone. Other patients may receive adjuvant chemotherapy due to tumor persistence after CCRT. Additionally, numerous RCTs have compared CCRT with other RT-combined treatment modalities, all of which used RT as the backbone. Therefore, the present study included clinical trials that focused on RT alone, CCRT, neoadjuvant chemotherapy, followed by CCRT/RT, adjuvant chemotherapy after CCRT/RT, and other combined treatment modalities, all of which utilized RT as the core treatment. However, there is currently no report on the long-term data of CCRT combined with immunotherapy, thus it is impossible to include

Table 2
Summary of randomized controlled trials included in the trial- and treatment arm-level analyses.

Trial	Inclusion criteria	Primary endpoint	Median FU, years	No. of patients	Treatment	PFS, %					OS, %	
						HR	2-y	3-y	4-y	5-y	HR	5-y
Grisby, 1999[11]	Age 18–75 years, IIIb-IVa, squamous cell carcinoma, KPS≥50	5-y OS	9.4	61	RT		33.3	29.2	23.6	22*		32
			8	59	CCRT (Misonidazole)		35.5	32.8	30.6	29*		34
Morris, 1999[17]	IIb-IVa, squamous/adeno/adenosquamous carcinoma	5-y OS	3.6	193	RT		56	49	44	40*		58*
				193	CCRT (FU+DDP)		73	68	68	67*		73*
Wong, 1999[18]	I-II, age ≤65 years, no heart disease, ECOG 0–1	5-y OS	6.4	110	RT		75	71	70	70		68
				110	CCRT+ACT		85	83	82	82		79
Symonds, 2000[19]	IIb-IVa, squamous or adenosquamous carcinoma, ECOG 0–1, age ≤70 years	3-y OS	5.4	100	RT	0.89*	47.4	40*	36.7	35	0.79*	30
				104	NACT+RT		53	45*	44	40		40
Waggoner, 2006[20]	IIb-IVa, squamous/adeno/adenosquamous carcinoma, GOG 0–3, PALN-	5-y OS	NA	182	CCRT (non-smoker)	1.31*	65.7	60.3	58	51.2	1.51*	55
				133	CCRT (smoker)		53.8	46.1	44	40		44
Kim, 2008[21]	IIb-IVa, ECOG 0–2, PALN-	4-y OS	3.3	77	CCRT (FU+DDP)		72.9	69.6	67*	67		63
				77	CCRT (DDP)		85.3	68.8	66*	62.8		63
Duenas, 2012[22]	IIb	5-y OS	NA	156	CCRT	0.77*	75.1	69.8	69.8	69.8	0.81*	71
				160	CCRT+ACT		83.2	75.8	74.2	74.2		74
	III-IVa	5-y OS	NA	100	CCRT	0.59*	62	57.4	53.6	53.6	0.56*	56
				99	CCRT+ACT		78.1	69.7	69.7	69.7		75
DiSilvestro, 2014[23]	IB2, IIA, IIB, IIIB, and IVA, GOG 0–2, PALN-	3-y OS	2.4	194	CCRT		66.4	64.4*	61.5	57.8		61
				185	CCRT+ACT		67.4	63*	55.5	55.5		63
Li, 2014[24]	Age 20–65 years, IIb-IIIb, squamous cell carcinoma, KPS≥70	5-y OS	NA	96	RT		74.5	62.5	54.4	41		53*
				96	CCRT		79.6	70.7	63.6	56.3		67*
Li, 2018[25]	Age 18–70 years, Ib2-IVa, KPS≥70, excluded small-cell carcinoma and carcinosarcoma	2-y OS	3.3	80	CCRT (Single channel applicator)		82.5*	80	75	75		81
				71	CCRT (Fletcher applicator)		77.5*	74	66	66		73
da Costa, 2019[26]	Age 18–70 years, IIb-IVa, ECOG 0–2	3-y PFS	2.64	52	CCRT	1.84*	76.5	60.4*	56.5	56.5	2.79*	73
				55	NACT+CCRT		52.8	40.9*	40.9	40.9		49
Tsai, 2010[27]	Ib-IVa, PLN+, PALN-, KPS≥70	4-y OS	4.4	63	CCRT		81	79	77*	73		79
				66	CCRT (PET)		79	77	75*	70		76
Al, 2014[29]	IIb-IVa, squamous/adeno/adenosquamous carcinoma, PALN-	5-y OS	5	50	CCRT (WP)		91	78.1	69.1	69.1*		60.4*
				52	CCRT (EF)		94.4	84.5	80.3	80.3*		72.4*
Zuliani, 2014[30]	IIIb, squamous cell carcinoma, KPS≥70	5-y OS	3.6	75	RT		65	55*	53	51*		54*
				72	CCRT		74	66*	61	61*		56*
Basu, 2016[31]	III, KPS≥60	3-y OS	2.4	105	CCRT (DDP)		71*	62*	59	59		57
				104	CCRT (RA+IFN)		58*	52*	49	33		46
Harima, 2016[32]	Ib-IVa, ECOG 0–2, PALN-	5-y OS	3.9	50	CCRT	0.517	63.2	63.2	60.6	60.6*	0.49*	64.8*
			5.3	51	CCRT+HT		75.8	73.5	73.5	70.8*		77.8*
Lertsanguansinchai, 2004[33]	KPS>60	3-y OS	3.35	109	RT (LDR BT)		79.4	69.9*	66.8	66.8		63.4
			3.1	112	RT (HDR BT)		69.9	69.9*	67.1	63.8		63.4
Noda, 2006[34]	IIIb, age 20–80 years, squamous cell carcinoma	5-y OS	NA	109	CCRT (low dose Z-100)	0.67*	63.5	60.2	54.9	53.1	0.67*	58.2*
				108	CCRT (high dose Z-100)		54.1	44.4	42.5	42.5		41.5*
Tang, 2012[35]	IIb-IVa, age 18–70 years, adeno/adenosquamous carcinoma, ECOG 0–1	5-y OS	5	440	CCRT		87.7	63.3	55.8	51.0		59.7
				440	CCRT+ACT		98.5	83.8	72.1	71.4		74.1
Rose, 2007[13]	IIb-IVb, squamous/adeno/adenosquamous carcinoma, PALN-, KPS≥30	10-y OS	8.8	176	CCRT (DDP)		67.7	61.2	58	58*		60*
				173	CCRT (DDP+5FU+hydro)		63.6	61.2	58	57*		61*
				177	NACT (hydro) +RT		47.2	40.3	34.9	35*		40*
Tovanabutra, 2021[37]	IIb-IVa, age 18–70 years, squamous/adeno/adenosquamous carcinoma, ECOG 0–2	5-y OS	3.4	129	CCRT	1.22*	72.5	70.1	70.1	65.9*	1.27*	76.5*
				130	CCRT+ACT		68.4	66	65.7	61.6*		70.4*
Marnitz, 2020[38]	IIb-IVa, squamous/adeno/adenosquamous carcinoma	5-y OS	7.5	121	CCRT (lymphadenectomy)		76.8	71.1	66.8	65.3		66.1
				119	CCRT (no surgery)		73.9	61.9	55.3	53.6		55.5
Tiwari, 2021[39]	IB2-IVa	3-y OS	3	71	CCRT (LN boost)		71.7	67.6*	63.4	63.4		72.5
				90	CCRT (no LN boost)		63.4	58.9*	57.6	54.4		71.3
Kim, 2016[36]	IB1 with PLN+, IB2-IIIA or IIIB with unilateral pelvic side wall extension and IVA, PALN-, squamous/adenocarcinoma	5- DFS	7.02	38	CCRT (PRT)		72.9	72.1	71.3	71.3*		76.2*
				38	CCRT (EFI)		82.5	78.4	78.4	78.6*		77.2*
Mileshkin, 2023[40]	Ib1-IVa, PLN+, PALN-, squamous/adeno/adenosquamous carcinoma, ECOG 0–2	5-y OS	5	456	CCRT	0.87*	68.5	66*	62.8	63*	0.90*	72*
				463	CCRT+ACT		74.7	70*	67.3	61*		71*
Fujiwara, 2022[41]	Ib2-IVa, squamous/adeno/adenosquamous carcinoma, age 25–75 years, ECOG 0–2	PFS	NA	178	CCRT	0.92*	69.0	67.3	64.6	61.3*	1.04*	77.6*
				173	CCRT+ACT		69.0	66.4	64.6	62*		76.1*

* Represents data directly reported in the full text.
Abbreviations: ACT, adjuvant chemotherapy; BT, brachytherapy; CCRT, concurrent chemoradiotherapy; DDP, cisplatin; ECOG, Eastern Cooperative Oncology Group; EF, extended field; EFI, extended field irradiation; FU, fluorouracil; GOG, Gynecologic Oncology Group; HDR, high dose rate; HT, hyperthermia; hydro, hydroxyurea; IFN, Interferon; KPS, Karnofsky performance status; LDR, low dose rate; LN, lymph node; NACT, neoadjuvant chemotherapy; PALN, para-aortic lymph node; PET, positron emission tomography; PLN, pelvic lymph node; PRT, pelvic radiotherapy; RA, 13-cis-retinoic; RT, radiotherapy; WP, whole pelvic; Z-100, ZERIA Pharmaceutical Corporation.

Table 3
Summary of retrospective studies included in the prediction model validation.

Trial	Inclusion criteria	Median follow-up, years	No. of patients	Group	PFS, %				OS, %
					2-y	3-y	4-y	5-y	5-y
Lee, 2018[42]	Ib2-IVa, squamous/adeno/adenosquamous carcinoma, PALN-, ECOG 0–1	5.25	118	CCRT (PRT)	74.2	71.1	65.6	65.6*	75.5*
			80	CCRT (EFI)	91.5	89.0	89.0	86.7*	92.7*
Gerszten, 2006[43]	IIIa & IV excluded, squamous/adenocarcinoma	NA	107	RT (HDR)	72	63	58	54*	53*
			106	RT (LDR)	70	63	58	54*	61*
Pino, 2013[44]	Ib2-IIIb, PALN-	3.6	65	LN-	72.9	72.9	72.9	72.9	84.6
			9	IIIC1	64.8	64.8	51.9	51.9	53.3
			19	IIIC2	55.8	55.8	44.6	44.6	40.2
Koh, 2013[45]	I-IVa, squamous/adenocarcinoma, ECOG 0–1	8.1	32	CCRT	78.1	71.9	68.5	68.5*	75*
Sakaguchi, 2015[46]	Ib-IV, squamous/adeno/adenosquamous carcinoma, ECOG 0–2	4.3	147	Control	68.6	66.7	66.7	64.0	60.8*
			162	UTF	78.6	76.5	76.5	74.2	73.8*
Chargari,2016[47]	Locally advanced cervical cancer, available for CCRT	3.7	186	CCRT	76.0	69.8	65.8	64.9	78
Harsh, 2016[48]	Squamous cell carcinoma	5	142	Ib-IIIa	87.64	79.35	78.05	74.63	78.88
			190	IIIb-IVa	95.45	52.68	33.17	31.06	31.06
Marita, 2018[49]	IIb-IIIb	4.86	67	IIb	91	88	88	88*	84*
			87	IIIa	84	82	81	76*	84*
			53	IIIb	73	69	69	69*	61*
Kroesen, 2019[50]	IIb-IVa, available for thermoradiotherapy	4.3	66	IGBT	75.8	71.2	66.8	66.8*	82.7*
			227	NO-IGBT	62.2	56.6	56.6	56.6*	64.5*
Lee, 2016[51]	Ib-IIb, squamous/adeno/adenosquamous carcinoma	5.16	85	NACT+S	86	81.5	77.1	75.6*	92.1*
			358	CCRT	80.1	77.7	75.6	74*	84.9*
Sonoda, 2015[52]	Ib1-IVa, age ≤ 75 years, squamous/adeno/adenosquamous carcinoma, ECOG 0–2	NA	48	PF	67.3	62.7	58.1	55.2	71.1
			43	P	67.3	62.7	62.7	62.7	86.3
Sol, 2009[64]	Ib-IVa, squamous/adeno/adenosquamous carcinoma, PALN-	3.94	45	CF	75.4	73.2	70.5	67.4*	79.6*
			48	CP	86.8	83.7	83.7	79.1*	80.9*
Watkins, 2011[53]	Ib-IVa	2.83	71	CCRT	60	60*	60	56.7	63
Refaat, 2016[54]	Ib1-IVa, ECOG 0–2, age >18 years	3.08	129	CCRT	73.9	71.6*	70.5	68.7*	70.7*
Tinkle, 2015[55]	Pathologically confirmed cervical cancer, received HDRB of 28 Gy in 4 fraction	3.5	111	CCRT	76.7	67	61*	57	64.1
Hirata, 2014[56]	Squamous cell carcinoma	4.5	121	CCRT	73.1	69.2	65.7	63.4*	80*
Ferrandina, 2021[57]	Age >18 years, Ib2-IVa	3.58	231	O-RS	82.3	76.5	74.7	73.7*	80.4*
		6.33	231	MI-RS	81.5	75.7	74.1	73.0*	85.3*
Wang, 2021[58]	Ib2-IVa, KPS>70	5.17	125	CCRT	82.1	79.4	78.4	75.1*	83.6*
Feijoo, 2022[59]	Age ≤ 80 years, ECOG 0–1, squamous/adeno/adenosquamous carcinoma, undifferentiated cervical cancer	3.7	93	Group 1A	77.2	67.2	61.9	57.4	69.06*
			71	Group 1B	57.9	48.9	47.1	45.2	55.41*
			111	Group 2	66.4	60.6	54.8	50.8	63.27*
			106	Group 3	63.2	59.3	56.9	52.6	67.69*
Tomic, 2021[60]	Ib2-IVa, ECOG 0–1	3.79	48	CCRT	81.7	76.3	76.3	72.8*	76.6*
Wu, 2021[61]	Age <70 years, KPS≥60	4.7	406	CCRT	82.6	79.6*	75.7	74.1*	80.0*
			203	CCRT-ACT	84.9	79.8*	76.4	73.4	80.8*
Moussilmani, 2021[62]	Ib2-IIb	3.27	114	CR	70.6	66.3	64.7	61.9*	84.6*
			102	No CR	66.3	63.3	58.4	58.4*	78.4*
Burchardt, 2021[63]	IIIC1, squamous cell carcinoma	3.17	93	CCRT	78.2	71.7	70	71*	70*

* Represents data directly reported in the full text.
Abbreviations: ACT, adjuvant chemotherapy; CCRT, concurrent chemoradiotherapy; CF, cisplatin plus fluorouracil; CP, cisplatin plus paclitaxel; CR, complete response; ECOG, Eastern Cooperative Oncology Group; EFI, extended-field irradiation; HDR, high dose rate; IGBT, image guided brachytherapy; KPS, Karnofsky performance status; LDR, low dose rate; MI-RS, minimally invasive radical surgery; NACT, neoadjuvant chemotherapy; O-RS, open radical surgery; P, cisplatin; PALN, para-aortic lymph node; PF, cisplatin plus fluorouracil; PRT, pelvic radiotherapy; S, surgery; UTF, tegafur-uracil.

such data. It is noteworthy that combined treatment strategies based on RT may not affect the analysis of the current study.

The present study evaluated PFS36 as a prognostic indicator for subsequent survival under current treatment strategies based on data from our center. It was found that patients who successfully attained PFS36 had excellent long-term outcomes, with a 5-year OS rate of 98.2%. However, patients who did not achieve PFS36 had a poor prognosis, with a 5-year OS rate of 30.3%. Compared with other time points, PFS36 can more effectively stratify patients into two distinct groups, stage notwithstanding. This suggests that PFS36 is a dichotomous variable that provides a clear benchmark for evaluating initial treatment success rate and designing clinical trials. Individual patient data indicated that PFS36 can be used in clinical evaluations.

Based on the above real-world data from a single center, we hypothesize that PFS36 may act as a novel endpoint for clinical trials of the new combined RT modality. We further investigated the level of evidence for hypothesis enhancement using previously published data. RCTs and retrospective studies were searched and screened to assess the predictive value of PFS as an early surrogate endpoint in clinical trials of LACC patients. At present, clinical trials or real-world retrospective data on standard RT for LACC primarily use the 5-year OS as the primary endpoint. Recent studies have reported PFS as the early efficacy endpoint. Therefore, inclusion criteria and quality control were strictly applied

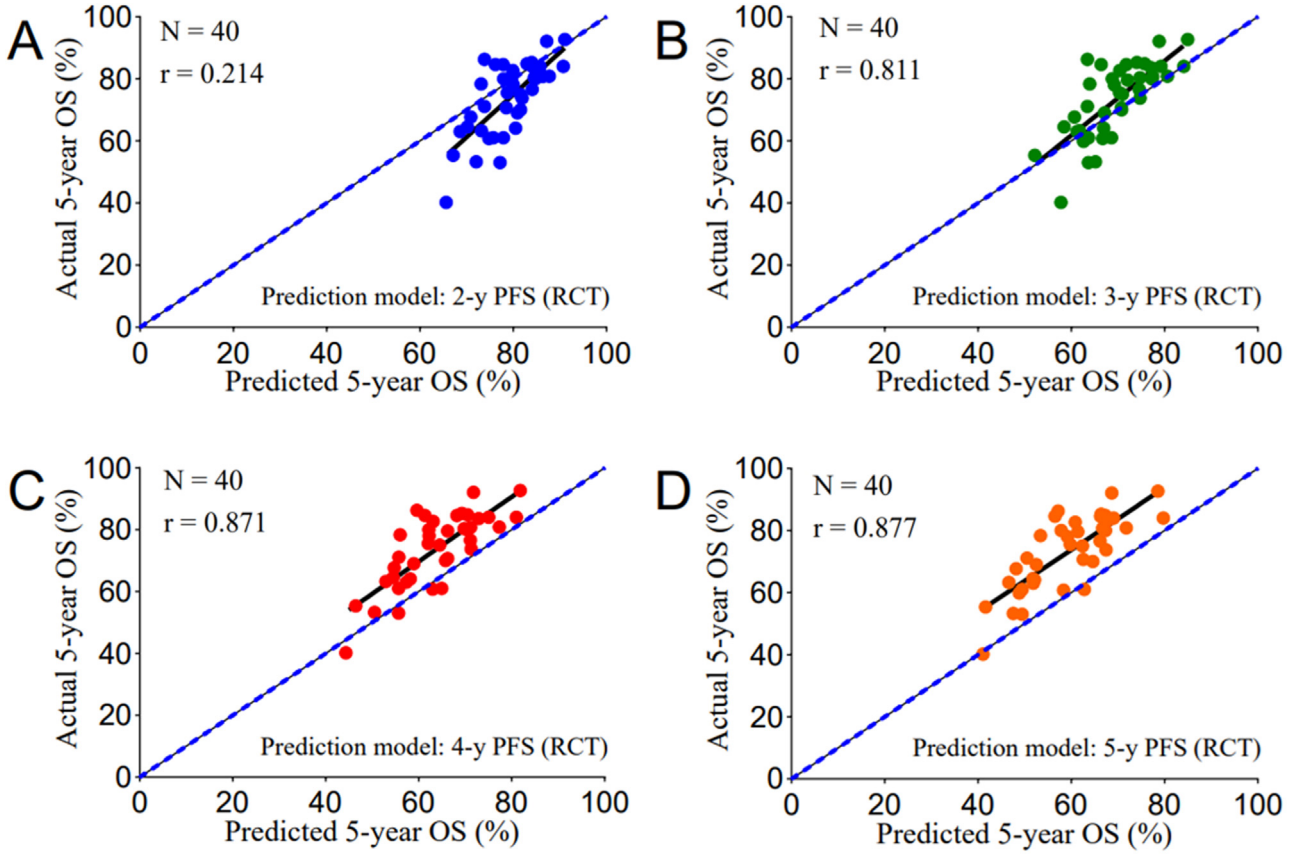

Fig. 5. External validation of the association of PFS with OS. Using PFS linear regression models (as shown in Fig. 4), the predicted 5-year OS, as calculated according to the actual 2-, 3-, 4- and 5-year PFS from the retrospective data (Table 2), is plotted against the actual 5-year OS. The predicted OS estimates relation to the actual OS, as indicated by approaching the diagonal line, i.e., the line of identity; r indicates the correlation coefficient. PFS, progression-free survival; OS, overall survival, y, year.

to identify high-quality RCTs for arm-level analysis and retrospective studies for external validation. In line with single-center individual data results, an analysis of 26 RCTs revealed a linear correlation between PFS36 and the 5-year OS rate at the arm level. Linear analysis of RCT data showed that the predictive power of PFS36 for the 5-year OS (r^2 = 0.732) was significantly higher than that of PFS24 (r^2 = 0.430). These findings suggest that PFS36 has a more predictive value for long-term prognosis. External validation using 3-year PFS rates from retrospective studies showed good calibration between the predicted 5-year and the actual OS rates.

Furthermore, our study showed that PFS36 was directly associated with the 5-year OS in LACC, and PFS36 can be used as an early endpoint to stratify the risk of long-term OS. Clinical trials of new treatment strategies for high-risk LACC patients, including CCRT combined with immunotherapy, are being extensively conducted worldwide and may significantly affect survival. CALLA and Keynote-A18 previously presented conflicting 2-year PFS outcomes. Our findings demonstrated that relying solely on the 2-year PFS may not be an insufficient early endpoint for radiotherapy-based treatment of LACC. Overall, the present study provides evidence supporting the adoption of PFS36 as an early surrogate endpoint in clinical assessments. This approach can help in assessing treatment efficacy promptly and expediting the approval of superior treatment strategies.

This study has several strengths. Firstly, the real-world individual data from our center were comprehensively analyzed and described in detail to strengthen the conclusion. Secondly, the relationship between PFS and OS was confirmed using survival data extracted from high-quality RCTs, further supporting our center's data and bolstering the clinical utility of PFS36 as an early surrogate endpoint. Finally, the linear correlation between PFS36 and 5-year OS rates was externally validated using data from retrospective studies. Dual validation improves the reliability of the outcomes.

Nevertheless, this study also has some limitations. First, individual data came from a single center. Second, a portion of the research data was reported as DFS. Following a careful review of the original article, the definitions of DFS and PFS were similar and therefore uniformly defined as PFS in the present study. Third, the predictive model is built upon research outcomes from patients who underwent RT and/or CCRT. Moreover, it comprises patients who received neoadjuvant/adjuvant chemotherapy and other combined treatment modalities. Any extrapolation of RT combined with immunotherapy to potential clinical application should be considered speculative. Lastly, this study focused on the association between PFS36 and the 5-year OS, and data on long-term survival and long-term recurrence rates is insufficient, limiting the full understanding of patient long-term outcomes.

5. Conclusion

In summary, PFS36 was identified as a dichotomous variable capable of predicting the prognosis of patients with LACC and providing information for patient consultation and prospective clinical trial design. These findings support the use of PFS36 as an efficacious surrogate endpoint in future clinical trials evaluating novel therapies and risk stratification markers.

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.

Data availability

The data that support the findings of this study are available from the corresponding authors, MNH and JSA, upon reasonable request.

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Author contributions

X.Y. conducted the conceptualization. Y.Y. and J.Z. performed the data curation, methodology and formal analysis. X.Y. wrote the original draft. Y.Z. and S.J., W.L., L.W. conducted writing, review and editing. X.Y. acquired funding. L.W., J.A. and M.H. provided resource and conducted the project administration and supervision.

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