

# Combined proton and carbon ion radiotherapy for uterine cervical squamous cell carcinoma: A retrospective analysis

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## Research Article

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# Abstract

**Background:** To skip brachytherapy from external radiation and brachytherapy for cervical carcinomas, a combined proton and carbon ion radiotherapy (PCRT) was used. This retrospective study reported the toxicity and short-term outcome.

**Methods:** 16 cervical SCC patients were consecutively treated with PCRT in our center from August 2016 to July 2019. The acute and late toxicities, overall survival (OS), local control rate (LC), progression-free survival (PFS) and distant metastasis-free survival (DMFS) were analyzed.

**Results:** For 16 cervical SCC, the prescribed dose for tumor was 76 Gy to 85.6 Gy (relative biologic efficacy (RBE)). With a median follow-up of 34.3 (range, 20.7-56.8) months, all of the acute toxicity were grade 1-2 with 12.5% of hepatic toxicity, 75% of hematological toxicity and 18.8% of gastroenteric toxicity. No acute urinary toxicity occurred. No severe late toxicity was observed during the follow-up period. At the last follow-up visit, 11 patients were alive, 4 patients died and 1 lost for follow-up; 3 patients had local recurrences and 6 patients had distant metastases. OS, LC, PFS, and DMFS at 1-year, 2-year and 3-year were 100%, 100% and 77.9%; 86.7%, 86.7% and 78.0%; 75.0%, 68.8% and 61.9%; and 87.5%, 81.3% and 75.0%, respectively.

**Conclusions:** PCRT was feasible to deliver high dose to cervical SCC, and the outcome was quite good. We thought that brachytherapy had the potential to be skipped when PCRT was used and long term results need to be further investigated.

Trial registration: This was a retrospective analysis and it was retrospectively registered. The registration number was NCT05141825 and the date of registration was November 30<sup>th</sup>, 2021.

## Background

Uterine cervical carcinoma is one of the most common cancers of women in the world [1]. Radiotherapy has been widely used to treat uterine cervical carcinoma. For patients with FIGO IB2-IVA radiotherapy combined with cisplatin-based chemotherapy is the standard of care [2]. In terms of radiation technique, the external irradiation, followed by brachytherapy, intracavitary, or interstitial implantation to cervical lesions is commonly used. However, the local control is not satisfactory enough, especially for the bulky tumors. The associated anemia and hypoxia, which are very often in uterine cervical carcinomas, lead tumors to the radio-resistant. Nevertheless, delivery of high dose is limited due to the intolerance of adjacent intestine and colon. Although, brachytherapy could boost dose to the primary tumor, but might not deliver sufficient dose to bulky tumors [3–4]. To improve local control, new radiation technique, proton and heavy ion, had been tried to treat cervical carcinomas.

Because of proton physical dosimetric advantage, it has been used to irradiate uterine cervical carcinoma, and showed the decreased toxicity [5–8]. The most advanced technique, intensity modulated proton therapy (IMPT) with pencil beam scanning could further decrease the doses to small bowel, colon,

bladder, rectum, head of femur and pelvis [5]. Therefore, it has more potential to spare normal organs, and meanwhile to deliver higher doses to targets compared to photon irradiation [7].

Carbon ion radiotherapy (CIRT) also has the physical dosimetric advantages. Besides, it possess biological advantages due to the nature of high linear energy transfer (LET) in the Bragg peak, which has strong inactivation effect on tumors with relative biological effect (RBE) of 2-3 [9–10], and low oxygen enhancement ratio (OER). National Institute of Radiological Sciences (NIRS), in Japan has completed several phase I/II or phase II clinical trails and showed high dose CIRT could improve the local control of the uterine cervical carcinoma [11]. CIRT with concurrent chemotherapy was safe for bulky tumors and could improve local control and overall survival [12].

Brachytherapy is a necessary part of irradiation for cervical carcinomas. However, we intended to skip it by combined proton and carbon ion radiotherapy (PCRT). Because there are radiation sensitive organs, intestine and colon adjacent to uterine cervical carcinoma, CIRT only would probably injure them more severe and result in more toxicity than proton. Therefore, we used proton for the primary tumor and pelvic nodes and CIRT boost for the clinical cervical tumors and metastatic nodes. In this report, we retrospectively analyzed the cervical carcinoma patients we treated with PCRT to observe its safety, tolerance and local control and survival. This study was approved by Ethical Committee of our center.

## Methods

### Patient eligibility

The patients selection eligibility criteria were: (1). histologically proven cervical squamous cell carcinoma (cervical SCC); (2). International Federation of Gynecology and Obstetrics (FIGO) stage (2014) IB2-IIIB, without rectum invasion; or FIGO stage IA-IB1, who refused surgery or were contraindication for surgery due to comorbidity diseases; (3). received PCRT with or without chemotherapy for curative intention.

From our center database 16 cervical SCC patients from August 2016 to July 2019 were eligible for the analysis. Their clinical characteristics were shown in Table 1. The median age was 48.5 years (range: 30 to 74). The median size of maximal diameter of tumor was 5.5 cm (range: 2.9–9.5) before treatment. The tumor size decreased after induction chemotherapy in 4 patients. The median size of maximal length of tumor was 7.0 cm (4.7–9.5 cm) in those 4 patients and it decreased to 4.8 cm (3.2-6.0 cm) after induction chemotherapy.

Table 1  
The clinical characteristics in 16 cervical squamous cell carcinomas

Characteristics	Patient number
Age	
Median (range) (year)	48.5 (30–74)
Clinical stage (FIGO)	
IB1-B2	2
IIA-B	7
IIIA-B	7
ECOG	
0	15
1	1
Anemia before radiotherapy	
Yes	7
No	9
Induction chemotherapy	
Yes	7
No	9
Concurrent chemotherapy	
Yes	13
No	3*
*One patient only received 1 cycle of current chemotherapy	

## PCRT

Patients were requested to keep the same cookbook and avoid aerogenous food during irradiation period in order to decrease the gas in intestine and colon. Before CT simulation and each irradiation fraction patients were requested to have similar bladder urine filling around 150-200 ml by keeping the same drinking habit, and rectum should be kept empty by enema. Patients were immobilized in the supine position on the individualized vacuum lock with thermoplastic mask on patients' pelvic. Two sets of 3-mm-thick CT were acquired for treatment planning: plain scan and enhancement scan. Pelvic MRI was acquired when needed.

Gross tumor volume (GTV) was defined as the primary lesion in cervix identified by MRI or PET. Clinical target volume (CTV) consisted of CTV1, CTV2, CTV3 and CTVIn. CTV1 was defined as the pelvic lymph node regions (common iliac, internal iliac, external iliac, obturator and presacral node regions) and suspicious lymph nodes (LN). CTV2 was defined as high-risk clinical region, including CTV3, uterus, cervix not included in GTV, bilateral parametrium, ovaries, subterminal vagina. CTV3 was defined as GTV expanded with a 5-mm margin. CTVIn was defined as enlarged lymph nodes with a 5-mm margin. Planning target volume (PTV) included CTV plus a 5-mm margin for positioning uncertainty, and more margins at the beam directions.

The prescribed doses were listed in Table 2. Proton of 46 Gy (RBE) in 23 fractions was delivered to CTV1. Various proton plus carbon or pure carbon ion boost doses were given to GTV or CTVIn. Biological effect dose (BED) was calculated by Linea-Quadratic model with  $\alpha/\beta$  of 10Gy.

PCRT quality assurance included water phantom dose verification before irradiation; KV X-ray position verification films before each irradiation; and CT review weekly and necessary plan modification when needed.

Table 2  
The list of PIRT doses in 16 cervical SCC.

Does	Total dose (Gy (RBE))	BED10 (Gy)	Patient number
proton 46Gy (RBE)/23fx with carbon ion boost of 30Gy (RBE)/10fx*	76	94.2	4
proton 46Gy (RBE)/23fx with carbon ion boost of 35Gy (RBE)/10fx	81	102.7	2
proton 46Gy (RBE)/23fx plus carbon 35.2Gy (RBE)/8fx	81.2	105.9	1
proton 46Gy (RBE)/23fx with carbon ion boost of 36Gy (RBE)/9fx	82	105.6	7
proton 46Gy (RBE)/23fx with carbon ion boost of 39.6Gy (RBE)/9fx	85.6	112.2	1
proton 62Gy (RBE)/31fx with carbon ion boost of 15Gy (RBE)/5fx	77	93.9	1
* 46GyE (RBE) to CTV1; various carbon ion doses to GTV or CTVIn.			

## Chemotherapy

Seven patients received induction chemotherapy for 1 to 4 cycles before PCRT. During PCRT 13 patients received concurrent chemotherapy with cisplatin (40mg/m<sup>2</sup>, once a week) for 6 to 7 cycles, but 1 patient, for 1 cycle.

## Follow-up and statistics

Acute toxicity (occurring within 90 days from the start of radiation) was evaluated by National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, and the late toxicity (continuing or occurring beyond 90 days), by Radiation Therapy Oncology Group (RTOG). Patients were examined weekly during radiation period and followed-up monthly for 3 months, and every 3 months afterwards. Local failure and distant metastasis were diagnosed based on clinical examinations and/or the evidence of CT, MRI, PET, or biopsy. Overall survival (OS), local control rate (LC), progression-free survival (PFS) and distant metastasis-free survival (DMFS) were estimated from the first day of PCRT by Kaplan-Meier method. Cox's proportional hazard model was used for multivariate analysis. All statistical analyses were performed by SPSS Statistics (SPSS Inc., Chicago, IL, USA).

## Results

### Tolerance and toxicity

All of 16 patients tolerated PCRT very well, and completed PCRT as the planned. None of the patients had their PCRT interrupted because of the toxicity. The last follow-up was performed in September 2021 with the median follow-up time of 34.3 months (range, 20.7-56.8).

All of the acute toxicity were grade 1-2 with 12.5% of hepatic toxicity, 75% of hematological toxicity and 18.8% of gastroenteric toxicity. No acute urinary toxicity occurred. No severe late toxicity was observed during the follow-up period.

### Tumor control and survival

At the last follow-up visit, 11 patients were alive; 1 patient died of local failure; 3 patients died of distant metastasis; and 1 patient got lost for follow-up. Overall, 3 patients had local recurrences and 6 patients had distant metastases. OS, LC, PFS, and DMFS at 1-year, 2-year and 3-year were 100%, 100% and 77.9%; 86.7%, 86.7% and 78.0%; 75.0%, 68.8% and 61.9%; and 87.5%, 81.3% and 75.0%, respectively (Figure 1).

### Prognostic factors

From univariate analysis (Table 3-5) stage corrected with OS ( $p=0.025$ ) (3-year OS of 100% in stage IB1-IIIB2 vs. 40.0% in stage IIIA-IIIB). The tumor size before any treatment predicted OS ( $p=0.037$ ) (3-year OS of 100% in the tumors with maximal GTV length of  $\leq 5.5$ cm vs. 57.1% in those  $>5$ cm). Other clinical parameters did not show any prognostic values. Multivariate analysis showed that neither of those factors were independent favorable predictors for OS.

Table 3  
Univariate analysis for overall survival (OS) in 16 cervical SCC patients.

Variable	subgroup	n	3-year OS (%)	p value
Concurrent chemotherapy	No	3	66.7	0.663
	Yes	13	80.8	
Induction chemotherapy	No	9	77.8	0.478
	Yes	7	80.0	
Stage	IB1-IIIB2	9	100.0	<b>0.025</b>
	IIIA-IIIB	7	40.0	
Regional node metastasis	No	7	100.0	0.222
	Yes	9	57.1	
Maximal length of GTV before any treatment (cm)	<= 5.5	8	100	<b>0.037</b>
	>5.5	8	57.1	
Anemia before radiotherapy	No	9	100	0.074
	Yes	7	44.4	

Table 4  
Univariate analysis of local control (LC) in 16 cervical SCC patients.

Factor	subgroup	n	3-year LC rate (%)	P value
Concurrent chemotherapy	No	3	66.7	0.492
	Yes	13	80.2	
Induction chemotherapy	No	9	87.5	0.461
	Yes	7	64.3	
Stage	IB1-IIIB2	9	87.5	0.263
	IIIA-IIIB	7	71.4	
Regional LN metastasis	No	7	83.3	0.615
	Yes	9	77.8	
Maximal length of GTV before any treatment (cm)	<= 5.5	8	83.3	0.947
	>5.5	8	75.0	
Anemia before radiotherapy	No	9	87.5	0.086
	Yes	7	57.1	

Table 5  
Univariate analysis of distant metastasis-free survival (DMFS) in 16 cervical SCC patients.

Factor	subgroup	n	3-year DMFS rate (%)	P value
Concurrent chemotherapy	No	3	100.0	0.234
	Yes	13	69.2	
Induction chemotherapy	No	9	88.9	0.728
	Yes	7	57.1	
Stage	IB1-IIIB2	9	88.9	0.313
	IIIA-IIIB	7	57.1	
Regional LN metastasis	No	7	85.7	0.959
	Yes	9	66.7	
Maximal length of GTV before any treatment (cm)	<= 5.5	8	100.0	0.069
	>5.5	8	50.0	
Anemia before radiotherapy	No	9	77.8	0.622
	Yes	7	71.4	

## Discussion

Cervical carcinoma in late stages were believed the radio-resistant due to the tumor hypoxia, which resulted from the associated anemia. Therefore, to achieve good outcome, high dose of radiotherapy is necessary. The external irradiation followed by brachytherapy irradiation, intracavitary or interstitial implantation, has been the standard irradiation technique. Typically, patients were irradiated with external beam radiotherapy of 45 to 50 Gy, and followed by intracavitary brachytherapy with 3 to 5 fractions of 5 to 7 Gy per fraction (BED10 of 72.6Gy- 119.5 Gy). However, intracavitary brachytherapy might not deliver a sufficient dose to extensive and bulky tumors in stage III or IVA disease [13–14]. In that case, interstitial brachytherapy could be used [15–16]. However, it was invasive and had limited indications. In an effort to exclude brachytherapy, the dosimetric comparison studies had been done between external irradiation plus brachytherapy and external irradiation alone with stereotactic radiotherapy or IMRT [17–18]. However, the high dose to central tumors by brachytherapy could not be reproduced by stereotactic radiotherapy or IMRT. Moreover, a retrospective analysis showed that curative external irradiation and brachytherapy achieved a higher 5-year cancer specific survival than external irradiation alone in cervical carcinoma, which implied the important role of brachytherapy [19]. However, intracavitary or interstitial implantation brachytherapy brought patients inconvenience, or procedures was invasive. Therefore, most advanced irradiation techniques were tried to deliver intensive doses in a hope to skip the brachytherapy.

Although our analysis was a retrospective study, we had some basic considerations to implement PCRT for cervical SCC. Our intention was to exclude brachytherapy from the combination of external beam and brachytherapy, and meanwhile to keep a similar outcome as that in the external and brachytherapy. From dosimetric comparative study of cervical carcinoma, intensity-modulated proton radiotherapy (IMPT) had a significant reduction for the mean dose of small bowel and functional bone marrow than photon techniques such as IMRT, helical tomotherapy and RapidArc [5–6]. Furthermore, mean dose to the bladder and rectum was decreased by 7-9 Gy with IMPT in patients with pelvic radiation [5]. Volume of pelvic bone marrow receiving 10 Gy-20 Gy or 40Gy was associated with hematologic toxicity [20–24]. Thus, protons offered the best sparing of small bowel, rectum and pelvic bone marrow, and could contribute to a significant reduction of acute and late gastrointestinal and hematologic toxicity in cervical carcinoma radiotherapy, especially when combined with concurrent chemotherapy. However, on the other hand, cervical carcinoma often contained a large percentage of radio-resistant hypoxic cells due to the associated anemia. The proton, as low LET beam, would probably not be effective enough to sterilize hypoxic cells. Carbon ion beam is a high LET beam and possesses both physical and biological advantages. From experimental and clinical studies, it had shown strong capabilities to inactivate malignancies with RBE of 2 to 3. Moreover, it could overcome tumor hypoxia with decreased OER of around 2. Actually, CIRT had been used to treat cervical carcinomas and yielded good outcome for locally advanced bulky cervical SCC [11]. Therefore, we irradiated the cervical tumor and pelvic nodes by proton of 46Gy (RBE), and followed by CIRT boost doses to cervical gross tumor and the metastatic nodes.

From 16 consecutively treated patients in our center by PCRT with 76 Gy (RBE) -85.6 Gy (RBE) (BED10 of 93.9Gy-112.2Gy), LC and OS rates at 1-year, 2-year and 3-year were 86.7%, 86.7% and 78.0%; 100%, 100% and 77.9% respectively. This result was as good as that reported by modern external irradiation and brachytherapy (Table 6) [3–4, 25–30]. Also it was comparable to NIRS reports [29, 30]. All acute toxicity in our patients were Grade 1-2, and no severe late toxicity occurred during the follow-up period. Compared with that in external beam radiotherapy plus brachytherapy, or CIRT, the toxicity of PCRT seemed to be less [3, 25–28, 30–31].

As proton and CIRT are new radiation techniques for cervical carcinomas, some technical problems we have to deal with, including uterine motion [32], and position variations of bladder and rectum [33]. The above problems would result in dose delivery uncertainty. We applied some measurements to decrease the gas in intestine and colon, to keep the same bladder urine volume and rectum empty. Recently we took CT by in-room CT just before the dose delivery and confirmed the effectiveness of those measurements on keeping anatomy position consistent.

Concurrent platinum-based chemotherapy is a part of the current standard treatment for patients with FIGO stage IB2-IVA. NIRS carried out a dose-escalation study on locally advanced cervical SCC by CIRT alone in 2014, and showed 2-year OS and LC were 64% and 68.2%, respectively [11]. In 2019, NIRS did another phase 1/2 study on CIRT, but with concurrent chemotherapy, and the 2-year OS and LC were 82% and 67%, respectively [31]. The 2-year OS was improved from 64–82% in concurrent chemo-radiation study, which demonstrated again the importance of concurrent chemotherapy in CIRT as the same as in

photon irradiation. However, concurrent chemotherapy did not improve the outcome in our study probably due to the small example size.

Univariate analysis in our study showed that only stage and tumor size were related to OS as that reported in literature [31]. If we could make the disease down staged before irradiation, it would be of help. Induction chemotherapy might be a strategy to reduce tumor burden in locally advanced cervical carcinomas. A British phase II trial included 46 patients with FIGO stage Ib2-IVa cervical carcinoma showed a good response rate to induction chemotherapy before CCRT, and the 5-year OS was 67% [34], which was better than the outcome after CCRT alone [35]. An international randomized multicenter phase III trial, INTERLACE (NCT01566240) is going on to compare the induction chemotherapy followed by CCRT and CCRT alone. In our center, we are planning to initiate a prospective clinical trial of induction chemotherapy, and concurrent chemotherapy and PCRT for locally advanced cervical carcinomas to further confirm PCRT feasibility and its efficacy.

## Conclusions

In summary, our preliminary result demonstrated that PCRT was feasible to deliver high dose to cervical SCC, and the outcome was quite good. We thought that brachytherapy had the potential to be skipped when PCRT was used. However, as it was a retrospective analysis with small sample size and short follow-up period, the conclusion was very preliminary and long term results need to be further investigated.

Table 6. Comparison of clinical outcomes for cervical carcinomas

## Abbreviations

PCRT: Proton and carbon ion radiotherapy; OS: Overall survival; LC: Local control rate; PFS: Progression-free survival; DMFS: Distant metastasis-free survival; OAR: Organ at risk; NIRS: National Institute of Radiological Sciences of Japan; CIRT: Carbon ion radiotherapy; SPHIC: Shanghai Proton and Heavy Ion Center; SOP: Standard operating procedure; FIGO: International Federation of Gynecology and Obstetrics; CT: Computed tomography; MRI: Magnetic resonance imaging; PET: Positron emission tomography; ECOG: Eastern Cooperative Oncology Group; GTV: Gross tumor volume; CTV: Clinical target volume; PTV: Planning target volume; LN: Lymph nodes; SIB: Simultaneously integrated boost; BED: Biologically effective dose; CTCAE: Common Terminology Criteria for Adverse Events; RTOG: Radiation Therapy Oncology Group; RT= radiotherapy; EBRT= external beam radiotherapy; IGBT = image-guided brachytherapy;

## Declarations

Ethics approval and consent to participate

The study was approved by Ethics Committee of Shanghai Proton and Heavy Ion Center.

Consent for publication

Not applicable

Availability of data and materials

The data and materials of this study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

QZ is responsible for editorial correspondence and have contributed to all of the following: (1) the conception and design of the study, and acquisition, analysis and interpretation of data, (2) contributing reagents/materials/analysis tools, (3) revising the article, (4) final approval of the version to be submitted. ZY, ZSH, PL, ZW, XC, and GLJ have contributed to as the following: (1) acquisition, analysis and interpretation of data, (2) drafting and revising the article. ZY and ZSH were major contributors in writing the manuscript. All authors read and approved the final manuscript.

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Footnotes

Zhan Yu and Zhengshan Hong contributed equally to this work.

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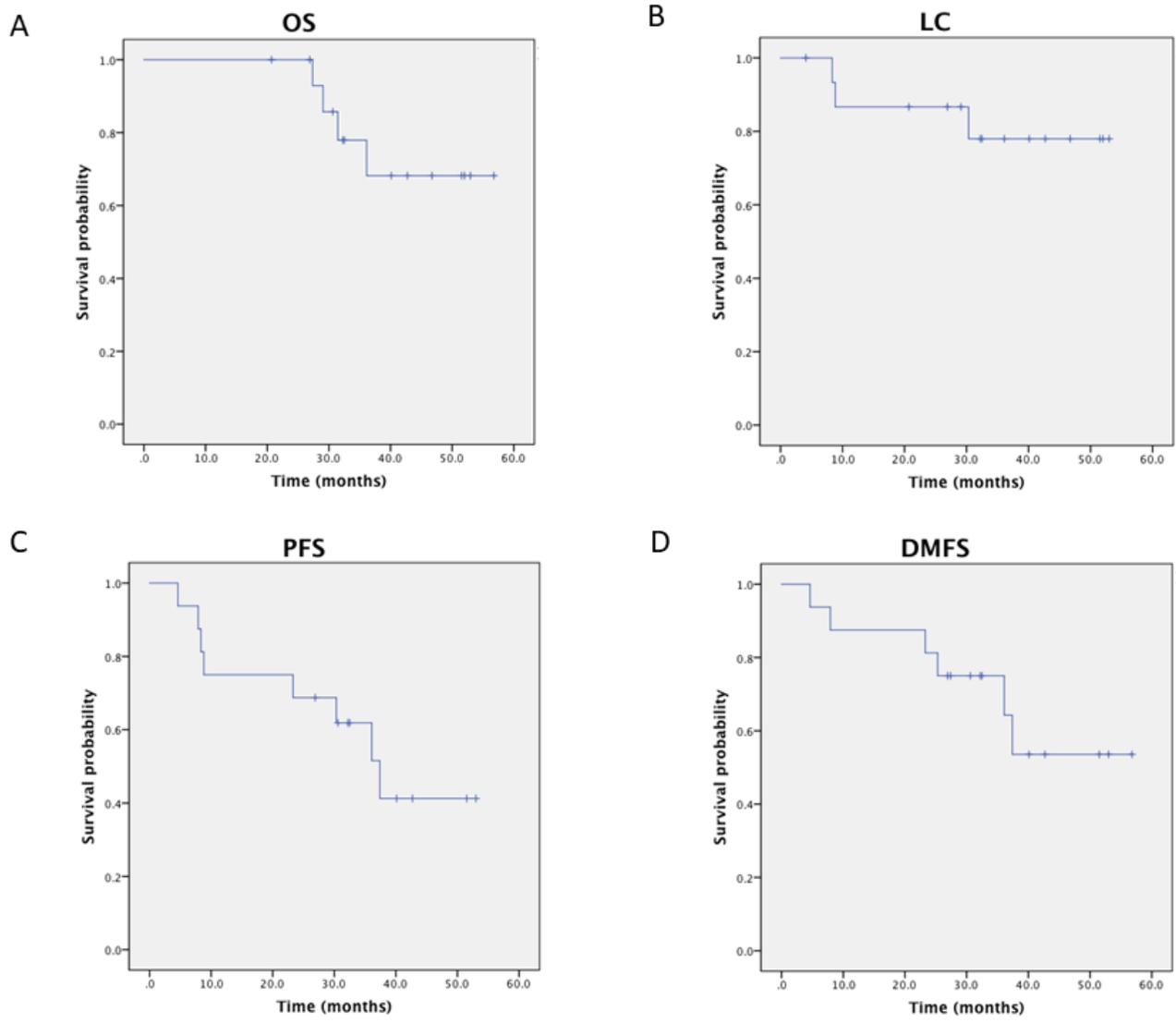
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## Figures



**Figure 1**

(A) Overall survival (OS), (B) local control (LC), (C) progression-free survival (PFS) and (D) distant metastasis-free survival (DMFS) in 16 cervical SCC.