IMR Press

Original Research

Is primary chemoradiation a better treatment? A retrospective study of early-stage node-positive cervical cancer

Nan Zhang[1], Hong Zheng[1,*]

[1] *Department of Gynecology, Peking University Cancer Hospital and Institute, Key Laboratory of Carcinogenesis and Translational Research, Ministry of Education of People's Republic of China, 100142 Beijing, China*

*Correspondence: zhhong306@hotmail.com (Hong Zheng)

DOI:10.31083/j.ceog4806216

Submitted: 21 December 2020 Revised: 15 February 2021 Accepted: 5 March 2021 Published: 15 December 2021

Background: Cervical cancer is the second most frequently diagnosed cancer and the third leading cause of cancer death for women in developing countries. Radical hysterectomy with bilateral pelvic lymph node dissection is usually preferred for patients with stage IB1-IIA2 disease. Currently, imaging has certain limitations in the diagnosis of lymph node metastasis, and the accuracy of detection remains unsatisfactory. Indeed, only pathological examination after removal of the suspected metastatic lymph nodes during surgery can conclusively identify the presence of metastasis. Furthermore, if a lymphatic metastasis is detected, there are no clear guidelines regarding whether to complete radical surgery or to conduct a systematic lymphadenectomy followed by adjuvant concurrent chemoradiotherapy. This retrospective study aimed to compare the efficacy and safety of the two treatment modalities in this patient population. *Methods*: Forty-nine stage IB1-IIA2 cervical cancer patients with lymphatic metastasis confirmed by systematic pelvic and paraaortic lymph node dissection from 2007 to 2018 were reviewed. The patients were treated with either primary chemoradiation or radical hysterectomy followed by adjuvant chemoradiation after lymphadenectomy. Survival states and adverse events of the two treatments were compared. *Results*: The median follow-up time was 45 (range 11–119 months) months. In the non-radical surgery group, one patient (1/15, 6.7%) relapsed and died, while in the radical surgery group, seven patients (7/27, 25.9%) relapsed and five (5/27, 18.5%) died. A significant difference was found in the mean progression-free survival (PFS) between the two groups, which was 69 (95% confidence interval 49.118–88.882) months in the non-radical surgery group and 44 (95% confidence interval 35.857–52.143) months in the radical surgery group ($p < 0.01$). There was a significant difference in three-year PFS (86% vs. 71%, $p < 0.01$) between the groups. Grade 3–4 toxicity was comparable between the two groups (26.7% vs. 25.9%, $p = 0.958$). *Conclusion*: For stage IB1-IIA2 cervical cancer patients with positive lymph nodes, primary chemoradiation after pelvic and paraaortic lymphadenectomy seems to have better survival outcomes compared with radical hysterectomy by laparoscopy plus chemoradiation. Since this is a retrospective study with limited cases, evidence from a randomized controlled study is needed to confirm the optimal treatment for early-stage node-positive cervical cancer.

Keywords

Cervical cancer; Lymphatic metastasis; Radical hysterectomy

1. Background

Cervical cancer is the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death in women, with an estimated 570,000 diagnosed cases and 311,000 deaths in 2018 globally [1]. In China, it is the sixth most common malignancy, the eighth most common cause of cancer death in women and the first most common cause of gynecologic cancer death [2]. Lymphatic metastasis is one of the most important prognostic factors in cervical cancer patients [3]. Surgical treatment is usually preferred for patients with stage IB1-IIA2 cervical cancer, especially in women of childbearing age [4]. Concurrent chemoradiotherapy with platinum is indicated in patients with surgically confirmed lymphatic metastasis [4]. Currently, radiologic examinations such as computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) can be performed before treatment, if available. However, the accuracy of the evaluation of lymph node metastasis through imaging is not satisfactory. It was reported that lymph node metastasis was detected with a sensitivity of 57% for CT, 75% for MRI, and 68% for PET, respectively, and with a specificity of 91% for CT, 75% for MRI, and 72–84% for PET, respectively [5–7]. Only pathological examination after removal of the suspected metastatic lymph nodes during surgery can clearly identify the presence of metastasis. If lymphatic metastases are identified, there is no evidence indicating whether the best course is to complete the radical surgery or, alternatively, to perform systematic lymphadenectomy followed by adjuvant concurrent chemoradiotherapy. This retrospective study aimed to compare the efficacy and safety of these two treatment modalities.

2. Methods

Forty-nine stage IB1-IIA2 cervical cancer patients who received surgical treatment at Peking University Cancer Hospital from October 2007 to September 2018 were reviewed. The preoperative staging was performed according to the Federation International of Gynecology and Obstetrics (FIGO) 2009 standards. All enrolled patients had

suspected lymph node metastasis as determined by MRI before surgery and confirmed to have lymph node metastasis by rapid pathological examination of frozen tissue. The surgeon told the patient before operation that the radical surgery could be abandoned or finished after the confirmation of lymph node metastasis by rapid pathological examination and the treatment was mainly determined according to the patient's wishes. The patients were divided into two groups according to their different treatment regimens: a radical surgery group and a non-radical surgery group.

For patients receiving radical surgery, radical hysterectomy after systematic pelvic and para-aortic lymph node excision by laparoscopy was performed, and the pathological results showed negative vaginal resection margin and parametrial invasion. For patients receiving non-radical surgery, the decision to forego radical surgeries were abandoned after systematic pelvic lymph node excision and para-aortic lymph node dissection through laparoscopy or an extraperitoneal approach. Patients in both groups received adjuvant concurrent chemoradiotherapy after the surgery.

The synchronous chemotherapy regimen was cisplatin, 40 mg/m^2, with a maximum dose of 60 mg per week for a total of 6 weeks. The pelvic radiotherapy dose was 45–50 Gy, with comprehensive coverage of tumor beds and pelvic lymph nodes. The intracavity radiotherapy doses were 10–12 Gy at point A in the group receiving radical surgery and 30–35 Gy at point A in the group receiving non-radical surgery.

Following each surgery, follow-up was conducted with the patients by reviewing their clinical records or calling them on the phone. The latest follow-up was in July of 2019.

The endpoint was PFS, which was defined as the first observation of local recurrence or distant metastasis. PFS was estimated by the Kaplan-Meier method and the difference between the two groups was compared by the log-rank test in univariate analysis. Statistical significance was tested by χ^2 test. Statistical analysis was performed using SPSS 21.0 (SPSS Inc., Chicago, IL, USA) with a significance level of $p = 0.05$.

3. Results

Seven of the 49 patients were lost to follow-up, and the clinical characteristics of the remaining 42 patients and the pathological characteristics of their cancers are summarized in Table 1. No significant difference in the clinical characteristics of the patients or the pathological characteristics of their disease was noted between the two groups. The median follow-up time was 45 months (range from 11 to 110 months). The follow-up times of the non-radical surgery and radical surgery groups were 69 and 38 months, respectively, with a significant difference between the two groups. At the time of the analysis, eight patients had a recurrence (seven in the radical surgery group and one in the non-radical surgery group). All recurrences occurred with distant organ involvement and three of them had both local and distant recurrences. One patient in the non-radical surgery group and five patients in the radical surgery group died of relapsed disease. The incidence rates of recurrence and metastasis in both groups are shown in Table 2.

The median PFS times in the non-radical surgery group and radical surgery group were 69 months (95% confidence interval 49.12–88.88) and 44 months (95% confidence interval 35.86–52.14), respectively, with a significant difference ($p = 0.019$). The survival curve is shown in Fig. 1.

A significant difference in the three-year PFS between the two groups was observed, with an 86% PFS in the non-radical surgery group and a 71% PFS in the radical surgery group ($p < 0.01$).

No deaths related to adverse events of the treatments were found. There was no significant difference in the rate of grade 3–4 toxicities ($p = 0.958$). In the non-radical surgery group, two cases of grade 3–4 hematological adverse events, one case of grade 3 gastrointestinal adverse events and one case of vesicovaginal fistula were observed. Four cases of grade 3–4 hematological adverse events, one case of grade 3 gastrointestinal adverse events, one case of vesicovaginal fistula and one case of ureteral fistula were observed in the radical surgery group (Table 3).

4. Discussion

Lymph node metastasis is a crucial high-risk prognostic factor in early-stage cervical cancer, as the five-year survival rate decreases from 82–90% to 38–61% with lymphatic metastasis [8]. The incidence rates of lymph node metastasis in stage IB and IIA cervical cancer are 12–22% and 10–27%, respectively [9–12]. As positive lymph nodes may indicate adjuvant therapy, the FIGO 2018 staging standard uses lymph node metastasis as one of the staging factors. According to this standard, patients with only pelvic lymph nodes are staged as IIIC1 and patients with para-aorta lymph node involvement are staged as IIIC2 [13].

Currently, imaging has certain limitations in the diagnosis of lymph node metastasis. Systematic lymph node dissection for pathological examination is necessary to acquire an accurate diagnosis. Pelvic lymphadenectomy consists of the following bilateral regions: along the common iliac vessels, the external and internal iliac vessels until the crossing of the circumflex vein caudally, and the obturator fossa including the ventral and dorsal of the obturator nerve. In this study, para-aortic lymph node dissection was performed in both groups, and no metastasis was found.

According to the National Comprehensive Cancer Network (NCCN) guidelines, cervical cancer patients with lymph node metastasis should be treated with concurrent chemoradiotherapy following surgery [4]. Cervical cancer patients with local disease may consider concurrent chemoradiotherapy as an initial treatment regardless of the status of lymphatic metastasis since its therapeutic effect is equivalent to surgery. There is controversy over whether to perform radical surgery for cervical cancer patients with localized disease and with intraoperative lymph node metastasis. Several retrospective studies have evaluated the two treat-

Table 1. Patient characteristics.

Characteristics	ALL (n = 42)	Non-radical surgery (n = 15)	Radical surgery (n = 27)	*p*
Age, years				0.967
Median (std)	41.4 (6.28)	42.5 (4.76)	40.6 (7.13)	
Histology				0.655
SCC	34 (81.0%)	13 (86.6%)	21 (77.8)	
AC	5 (11.8%)	1 (6.7%)	4 (14.8%)	
ASC	2 (4.8%)	1 (6.7%)	1 (3.7%)	
Other	1 (2.4%)	0 (0%)	1 (3.7%)	
Pathological grade				0.817
I	1 (2.4%)	1 (6.7%)	0 (0%)	
II	19 (45.2%)	3 (20%)	16 (59.3%)	
III	22 (52.4%)	11 (73.3%)	11 (40.7%)	
Tumor size (cm)				0.439
>4	7 (16.7%)	2 (13.3%)	5 (18.5%)	
≤4	35 (83.3%)	13 (86.7%)	22 (81.5%)	
FIGO stage				0.381
IB1	27 (64.3%)	10 (66.7%)	17 (63.0%)	
IB2	8 (19.0%)	3 (20%)	5 (18.5%)	
IIA1	5 (11.9%)	2 (13.3%)	3 (11.1%)	
IIA2	2 (4.8%)	0 (0%)	2 (7.4%)	
Number of lymph node metastasis				0.439
1	13 (30.9%)	5 (33.3%)	8 (29.6%)	
≥2	29 (69.1%)	10 (66.7%)	19 (70.4%)	

Table 2. Patterns of recurrence and disease status.

	No. of patients (n = 42)	Non-radical surgery (n = 15)	Radical surgery (n = 27)
Recurrence	8 (19.0%)	1 (6.7%)	7 (25.9%)
Local	-	-	-
Distant	5 (11.9%)	-	5 (18.5%)
Both	3 (7.1%)	1 (6.7%)	2 (7.4%)

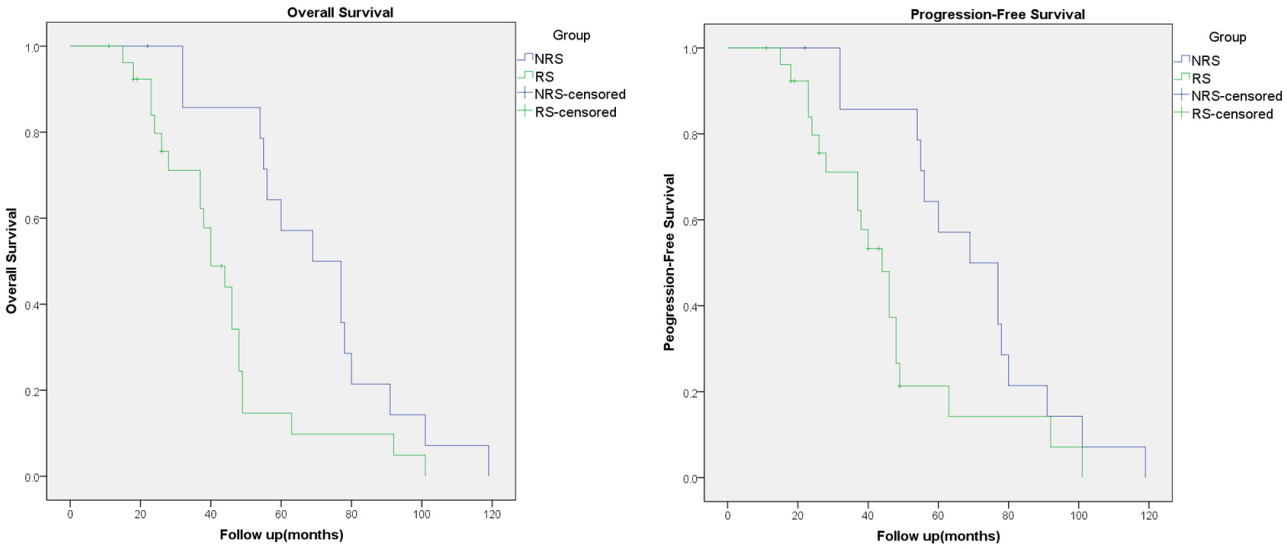

Fig. 1. Kaplan-Meier analysis of progression-free survival and overall survival.

ment modalities. A retrospective multicenter cohort study analyzed 121 patients, 89 of whom received radical surgery with pelvic lymphadenectomy (radical surgery group), while the remaining 32 patients received chemoradiotherapy after

Table 3. Treatment-related toxicity.

CTCAE grade ≥3 toxicity	All	Non-radical surgery	Radical surgery	*p*
				0.958
Blood	6 (14.3%)	2 (13.3%)	4 (14.9%)	
Gastrointestinal	2 (4.8%)	1 (6.7%)	1 (3.7%)	
Genitourinary	3 (7.1%)	1 (6.7%)	2 (7.4%)	

pelvic lymphadenectomy (non-radical surgery group) [14]. There was no difference in overall survival (OS) between the two groups, while the five-year PFS was in favor of the radical surgery group (81% vs. 67%). Grade 3–4 toxicity rates were higher in the non-radical surgery group (59% vs. 30%), mainly because of the difference in chemotherapy-related hematologic toxicity. Another retrospective study consisted of 163 cases in the radical surgery group and 55 cases in the non-radical surgery group [15], with no significant differences in OS or PFS. Furthermore, the ABRAX multicentric, retrospective, cohort study revealed that completion of radical hysterectomy in patients with intraoperative detection of positive lymph node does not improve survival [16]. However, the prognosis of the group receiving non-radical surgery seemed to be superior than that of the group receiving radical surgery in this study, with a longer PFS. The difference might be due to the surgical approach. Owing to the absence of the surgical approach in the multicenter cohort study, radical surgery could be performed by laparotomy or a laparoscopic approach. In this study, all 27 patients in the radical surgery group and 11 patients in the non-radical surgery group underwent laparoscopic surgery, and the other four patients in the non-radical surgery group received extraperitoneal surgery. Both the NCCN and ESGO (European Society of Gynecological Oncology) guidelines previously recommended the laparoscopic approach as an option for radical hysterectomy due to the minimal trauma and rapid recovery. However, at the 2018 International Gynecologic Cancer Society meeting, the LACC study led by the M.D. Anderson Cancer Center in the United States reported that for early-stage cervical cancer patients, patients who underwent minimally invasive surgery had lower disease-free survival and OS and a higher recurrence rate in comparison to those who underwent open abdominal surgery [17]. Nevertheless, previous studies have shown that for early cervical cancer, laparoscopic lymph node dissection does not affect the prognosis compared to open abdominal surgery [18]. In this study, all patients in the radical surgery group underwent laparoscopic surgery, which might lead to poor outcomes. Previous studies have demonstrated that the routine use of uterine manipulators and circulating CO_2 during laparoscopic surgery may result in tumor spillage into the peritoneal cavity [17, 19]. Thus, the precise open abdominal operation of patients in the radical surgery group should be included in future studies to analyze the impact of each surgical approach. Of note, no isolated recurrences were observed, however this may be due to the small sample size.

Most of the recurrences in this study occurred within two years after surgery, suggesting that more intensified surveillance is needed across the first two years following intervention. Differences in the total dose of intracavity exposure may also contribute to the differences in PFS between the two groups. To protect the intestine, bladder and other adjacent pelvic organs, the total dose of intracavity radiation in the radical surgery group was 10–12 Gy, which was lower than that in the non-radical surgery group, the patients of which had retention of the cervix lesion with the total dose of intracavity exposure reaching 30–35 Gy.

Furthermore, patients in the non-radical surgery group began to receive concurrent chemoradiotherapy earlier after surgery (an average interval period of 27.6 days) than those in the radical surgery group (an average interval period of 42.5 days) due to faster recovery following non-radical surgery compared to radical surgery. Thus, the patients in the non-radical surgery group received concurrent chemoradiotherapy in a more timely manner, which may have led to an improved prognosis.

Two patients in the non-radical surgery group and four patients in the radical surgery group reported chemoradiotherapy-related grade 3–4 hematologic toxicity. Grade 3 gastrointestinal toxicity occurred in one patient in each group, which was possibly associated with chemoradiotherapy. One case of vesicovaginal fistula was observed in one patient in each group one month after chemoradiotherapy in the non-radical surgery group and at the end of concurrent chemoradiotherapy in the radical surgery group, both of which was believed to be caused by radiotherapy. One patient in the radical surgery group had a ureter fistula immediately after surgery. A randomized study of radical surgery versus radiotherapy for early stage cervical cancer revealed that the combination of surgery and radiotherapy has the worst morbidity, and in particular urological complications [20]. Due to the small number of cases among the two groups, further studies are needed to fully evaluate any potential adverse events.

This retrospective study has limitations. There were about 200 operations of early cervical cancer to be performed in our institution per year in the past ten years. Since the incidence rates of lymph node metastasis in stage IB and IIA cervical cancer are 12–22% and 10–27%, respectively, about 20–40 node-positive patients were treated in our institution per year. However most patients of early-stage node-positive cervical cancer were usually suggested to take concurrent chemoradiotherapy instead of surgery especially for

postmenopausal women. These reasons led to the small sample size of the study and might also limit the dependability of this study. In addition, the patients with radical hysterectomies may have undetected bias possible giving them a worse prognosis. Such as the patients with larger or more aggressive tumors were more inclined to choose radical surgery. They have received both radical surgery and chemoradiation as opposed to chemo radiation alone. Lastly, the follow-up time of this study was not sufficiently long to evaluate long-term survival rate, especially in respect to the radical surgery group.

5. Conclusions

For local early cervical cancer patients with lymph node metastasis detected during surgery, concurrent chemoradiotherapy without radical hysterectomy appears more effective than laparoscopy, leading to superior prognosis and survival. However, a well-designed prospective study with a large sample size will be needed to confirm these results.

Author contributions

NZ—search, study selection, data collection, interpretation of results, manuscript writing. HZ—search, study selection, manuscript writing. Both authors have read and approved the manuscript.

Ethics approval and consent to participate

Written informed consents were obtained from the patients for publication of this retrospective study of cases. The research was approved by the Ethics Committee of Peking University Cancer Hospital (approval number: 2019YJZ49).

Acknowledgment

We gratefully thank Yunong Gao for supporting this study and helping us during the writing of this manuscript.

Funding

This research received no external funding.

Conflict of interest

The authors declare no conflict of interest.

References

[1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2018; 68: 394–424.

[2] Sun K, Zheng R, Zhang S, Zou XN, Chen R, Gu XY. Report of cancer incidence and mortality in different areas of China, 2015. China Cancer. 2019; 28: 1–11.

[3] Hosaka M, Watari H, Mitamura T, Konno Y, Odagiri T, Kato T, *et al.* Survival and prognosticators of node-positive cervical cancer patients treated with radical hysterectomy and systematic lymphadenectomy. International Journal of Clinical Oncology. 2011; 16: 33–38.

[4] National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: cervical cancer, V.5.2019. Available at: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1426 (Accessed: 10 December 2019).

[5] Liu B, Gao S, Li S. A comprehensive comparison of CT, MRI, positron emission tomography or positron emission tomography/CT, and diffusion weighted imaging-MRI for detecting the lymph nodes metastases in patients with cervical cancer: a meta-analysis based on 67 studies. Gynecologic and Obstetric Investigation. 2017; 82: 209–222.

[6] Kan Y, Dong D, Zhang Y, Jiang W, Zhao N, Han L, *et al.* Radiomic signature as a predictive factor for lymph node metastasis in early-stage cervical cancer. Journal of Magnetic Resonance Imaging. 2019; 49: 304–310.

[7] Papadia A, Gasparri ML, Genoud S, Bernd K, Mueller MD. The combination of preoperative PET/CT and sentinel lymph node biopsy in the surgical management of early-stage cervical cancer. Journal of Cancer Research and Clinical Oncology. 2017; 143: 2275–2281.

[8] Delgado G. Stage IB squamous cancer of the cervix: the choice of treatment. Obstetrical & Gynecological Survey. 1978; 33: 174–183.

[9] Kamura T, Tsukamoto N, Tsuruchi N, Saito T, Matsuyama T, Akazawa K, *et al.* Multivariate analysis of the histopathologic prognostic factors of cervical cancer in patients undergoing radical hysterectomy. Cancer. 1992; 69: 181–186.

[10] Lai C, Chang H, Chang T, Hsueh S, Tang SG. Prognostic factors and impacts of adjuvant therapy in early-stage cervical carcinoma with pelvic node metastases. Gynecologic Oncology. 1993; 51: 390–396.

[11] Benedetti-Panici P, Maneschi F, Scambia G, Greggi S, Cutillo G, D'Andrea G, *et al.* Lymphatic spread of cervical cancer: an anatomical and pathological study based on 225 radical hysterectomies with systematic pelvic and aortic lymphadenectomy. Gynecologic Oncology. 1996; 62: 19–24.

[12] Sakuragi N, Satoh C, Takeda N, Hareyama H, Takeda M, Yamamoto R, *et al.* Incidence and distribution pattern of pelvic and paraaortic lymph node metastasis in stage IB, IIA and IIB cervical carcinoma treated with radical hysterectomy. Cancer. 1999; 85: 1547–1554.

[13] Bhatla N, Aoki D, Sharma DN, Sankaranarayanan R. Cancer of the cervix uteri. International Journal of Gynecology & Obstetrics. 2018; 143: 22–36.

[14] Derks M, Groenman FA, van Lonkhuijzen LRCW, Schut PC, Westerveld H, van der Velden J, *et al.* Completing or abandoning radical hysterectomy in early-stage lymph node-positive cervical cancer. International Journal of Gynecological Cancer. 2017; 27: 1015–1020.

[15] Garg G, Shah JP, Liu JR. Should radical hysterectomy be aborted on intraoperative detection of nodal tumor metastasis in early stage cervical cancer? Journal of Lower Genital Tract Disease. 2010; 14: 374–381.

[16] Cibula D, Dostalek L, Hillemanns P, Scambia G, Persson J, Raspagliesi F, *et al.* Radical hysterectomy in cervical cancer patients with intraoperatively detected positive lymph node: ABRAX multicentric retrospective cohort study (ENGOT-Cx3/CEEGOG CX2). 2020. Available at: https://doi.org/10.1016/j.annonc.2020.08.945 (Accessed: 15 December 2020).

[17] Ramirez PT, Frumovitz M, Pareja R, Lopez A, Vieira M, Ribeiro R, *et al.* Minimally invasive versus abdominal radical hysterectomy for cervical cancer. The New England Journal of Medicine. 2018; 379: 1895–1904.

[18] van de Lande J, von Mensdorff-Pouilly S, Lettinga RG, Piek JM, Verheijen RHM. Open versus laparoscopic pelvic lymph node dissection in early stage cervical cancer: no difference in surgical or disease outcome. International Journal of Gynecologic Cancer. 2012; 22: 107–114.

[19] Kong T, Chang S, Piao X, Paek J, Lee Y, Lee EJ, *et al.* Patterns of recurrence and survival after abdominal versus laparoscopic/robotic radical hysterectomy in patients with early cervical cancer. Journal of Obstetrics and Gynaecology Research. 2016; 42: 77–86.

[20] Landoni F, Maneo A, Colombo A, Placa F, Milani R, Perego P, *et al.* Randomised study of radical surgery versus radiotherapy for stage IB-IIA cervical cancer. The Lancet. 1997; 350: 535–540.