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Bevacizumab Efficacy and Recurrence Pattern of Persistent and Metastatic Cervical Cancer

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Abstract. *Background/Aim: The aim of this study was to evaluate the efficacy of bevacizumab combined with cisplatin and paclitaxel for persistent, recurrent, or metastatic cervical cancer. Materials and Methods: This is a retrospective review of medical records of patients with persistent, recurrent, or metastatic cervical cancer. Results: Of the 52 patients, 33 (63.5%), 7 (13.5%) and 12 (23.1%) had recurrent, persistent and metastatic disease, respectively. Twenty-seven patients (51.9%) had prior platinum exposure. Possible bevacizumab-related serious adverse events included hypertension (n=3/52, 5.8%), febrile neutropenia (n=4/52, 7.7%) and fistula (n=2/52, 3.8%). Thirty-two recurrences (61.5%) and 20 deaths (38.5%) were noted. Median progression-free and overall survival was 9.8 months and 15.3 months, respectively. Recurrence included loco-regional (17/32, 59.4%), nodal (11/32, 34.4%), distant site (10/32, 31.3%) and peritoneal seeding (6/32, 18.8%). Conclusion: Bevacizumab with cisplatin and paclitaxel for treating persistent, recurrent or metastatic cervical cancer is feasible and well tolerated. Loco-regional recurrence was most frequent. Overall survival was worse with recurrence at >2 sites or distant metastases.*

Cervical cancer is the fourth most frequently diagnosed cancer and the fourth leading cause of cancer-related death in women (1). Although the rate of cervical cancer in developed countries has dramatically decreased because of cytologic screening and HPV vaccination programmes, it is still the most common gynaecological cancer (2, 3). The World Health Organization estimates that 569,847 new cervical cancer cases were diagnosed worldwide in 2018 (1), with 11.3 new cases of cervical cancer per 100,000 people projected to occur in Korea (4).

Surgery, chemo-radiation, or the combination provide an effective cure of early-stage and locally advanced cervical cancers (5, 6). The failure rate in treatment is 15-30% for International Federation of Gynecology and Obstetrics (FIGO) stage I-II disease and 40-60% for stage III disease (7, 8). However, treatment options for patients with recurrence, distant metastasis (FIGO stage IVB) or non-resectable local recurrence are limited, with a poor prognosis and a 5-year survival rate of 5-15% (5, 6, 8-10).

In GOG 169, combined treatment with paclitaxel and the platinum-based agent cisplatin significantly increased progression-free survival (PFS) (5, 9, 11). By comparison, paclitaxel plus carboplatin provides equal efficacy, but lower toxicity than paclitaxel plus cisplatin as a primary treatment for metastatic cervical cancer (5). Despite advances in standard platinum-based combination chemotherapies, however, the median overall survival (OS) remains poor, ranging from 7 to 12 months in most patients (5, 10, 12).

Angiogenesis plays a critical role in tumour growth, progression and metastasis in cervical cancer (5-7). Bevacizumab, an anti-vascular endothelial growth factor (VEGF) humanized monoclonal antibody that disrupts angiogenesis in tumours, is effective for the treatment of advanced cervical cancer (5, 13). The results of the GOG 240 phase III randomized trial of bevacizumab demonstrated that adding bevacizumab to paclitaxel-topotecan or paclitaxel-cisplatin significantly prolonged survival compared with paclitaxel-topotecan or paclitaxel-cisplatin in patients with persistent, recurrent or metastatic disease. The addition of bevacizumab to either of these regimens resulted in an

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increase in median OS of 3.6 months (16.8 months *vs*. 13.3 months) (6, 10). Several other studies reported outcomes and safety for patients with persistent, recurrent or metastatic cervical cancer treated with bevacizumab combined with a platinum-based agent comparable to those of the GOG phase III trial (2, 8). However, there are no reports describing the pattern of cervical cancer recurrence after bevacizumab treatment, although some studies have reported the recurrence patterns of other cervical cancer treatment regimens (14-17).

In the present study, the efficacy and safety of paclitaxel plus cisplatin in combination with bevacizumab in patients with persistent, recurrent or metastatic cervical cancer were evaluated. We also analysed the pattern of recurrence after combination chemotherapy with bevacizumab.

Materials and Methods

This retrospective study was conducted after approval from the Institutional Review Board of Seoul National University Hospital (No. 1803-134-933).

Study population and data collection. We retrospectively reviewed medical records of patients with persistent, recurrent or metastatic cervical cancer treated at Seoul National University Hospital between April 2014 and February 2018. Only patients treated with cisplatin plus paclitaxel and bevacizumab were included in the analysis. All patients received bevacizumab 15 mg/kg on day 1, paclitaxel 135 mg/m^2 infusion for 24 h on day 1 after bevacizumab and then cisplatin 50 mg/m^2 on day 2, every 3 weeks until disease progression, unacceptable toxicity or complete response was noted.

Cervical cancer was histologically confirmed in all patients who were included in the study. Patients who had received previous treatment with bevacizumab were excluded. Clinicopathologic data including age, histology, primary treatment, number of chemotherapy cycles, tumour response, dose reductions, recurrence date, pattern of recurrence and side effects were collected.

Complete blood counts and biochemistry panels along with renal function and liver profiles were performed every 21 days, and computed tomography (CT) scans of the abdomen and pelvis were carried out every 3 treatment cycles. In patients with measurable disease, tumour response was assessed according to the Response Evaluation Criteria in Solid Tumor (RECIST ver. 1.1). PFS was defined as the time from the first day of treatment until disease progression was noted or the date of the last follow-up, whereas OS was defined as the time from the first day of treatment until death or the date of the last follow-up.

Toxicity was assessed according to the National Cancer Institute's Common Toxicity Criteria (CTCAE v. 4.0). Febrile neutropenia (grade 3) was defined as an absolute neutropenia count of <1000/mm^3 with a single body temperature measurement of >38.3˚C or a sustained temperature of ≥38˚C for longer than 1 h. Grade 3 hypertension was defined as blood pressure of 160/100 mmHg or more. Fistulas were defined as the presence of signs of local inflammation on clinical examination and as confirmation of pelvis-abdomen CT scans.

Statistical analysis. Categorical variables are presented as frequencies and percentage and continuous variables are expressed as median with range. Survival was calculated according to the Kaplan–Meier method and the differences between survival curves were compared using the log-rank test. A p-value <0.05 was considered indicative of statistical significance. All data were analysed using SPSS software (version 21.0; SPSS Inc., Chicago, IL, USA).

Table I. *Patients' characteristics (n=52).*

	N=52 (%)
Age (years) (range)	54.0 (32-81)
Histology	
Squamous	37 (71.2)
Adenocarcinoma	12 (23.1)
Adenosquamous	1 (1.9)
Others	2 (3.8)
Primary treatment	
Radical hysterectomy/lymphadenectomy	30 (57.7)
Chemoradiation	11 (21.2)
Paclitaxel-cisplatin-bevacizumab	11 (21.2)
Prior regimens*	
Median	1
Range	0-4
Disease presentation	
Recurrent	33 (63.5)
Persistent	7 (13.5)
Metastatic	12 (23.1)
Prior platinum-based chemo-radiotherapy	
No	25 (48.1)
Yes	27 (51.9)
Bevacizumab administered(cycle)	
Median	6
Range	1-14
Recurrence after TPA	
No	20 (38.5)
Yes	32 (61.5)
Death	
No	29 (55.8)
Yes	20 (38.5)

Values are presented as median (range) or number (range or %). *Number of prior regimens included cisplatin as a chemosensitizing agent during radiation. TPA: Paclitaxel – cisplatin – bevacizumab.

Table II. *Tumor response to bevacizumab combined with cisplatin and paclitaxel.*

Response	n=52
Complete response (CR)	8 (15.4)
Partial response (PR)	18 (34.6)
Stable disease (SD)	10 (19.2)
Progression disease (PD)	16 (30.8)

Values are presented as number (%).

Results

Characteristics of the study population. A total of 57 patients received bevacizumab with cisplatin plus paclitaxel (TPA)

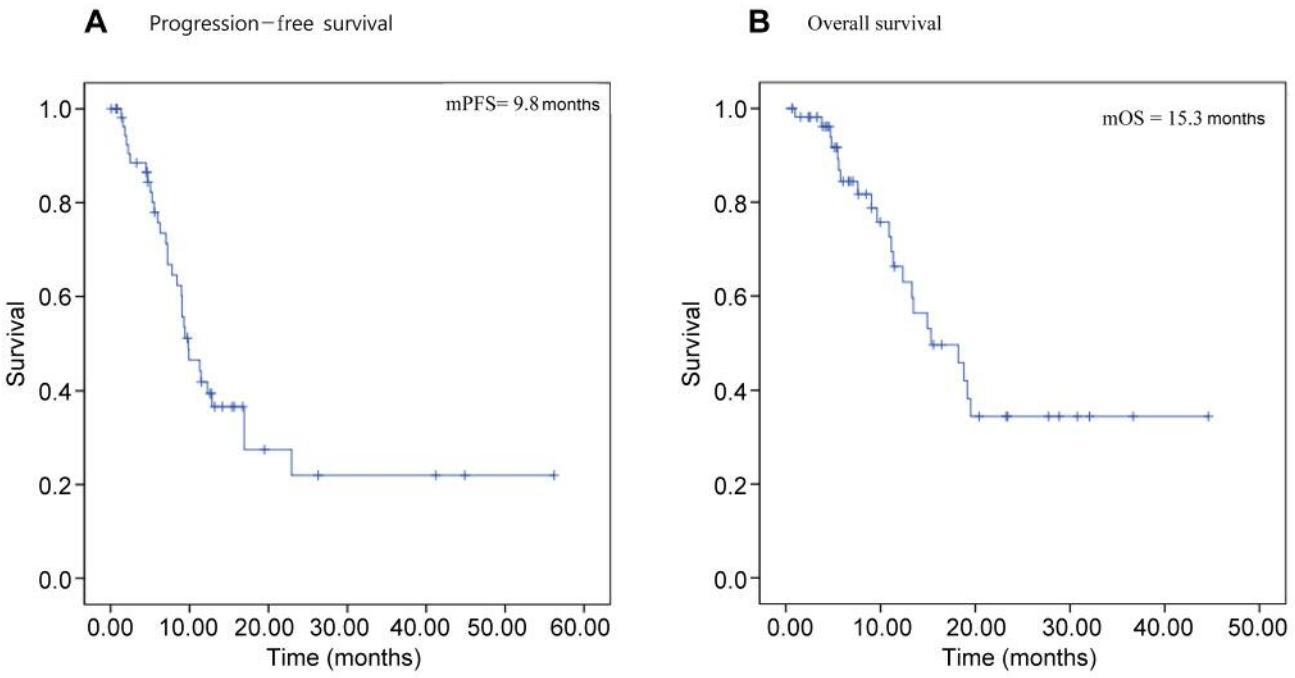

Figure 1. *Kaplan–Meier curves of (A) PFS and (B) OS in patients treated TPA. mPFS: Median progression-free survival; mOS: median overall survival; TPA: paclitaxel-cisplatin-bevacizumab.*

during the study. Five patients underwent fewer than three sessions of chemotherapy and did not undergo CT imaging. A total of 52 patients with recurrent, persistent or metastatic cervical cancer were thus included. The clinicopathologic characteristics of the study participants are summarized in Table I. The median age at initial administration of TPA was 54 years. The majority of patients (71.2%) presented with squamous cell carcinoma histology, whereas 23.1% of patients had adenocarcinoma, 1.9% of patients had adeno-squamous carcinoma and 3.8% of patients had cancers of other histologic types. Approximately three-fourths of patients (77%) had recurrent or persistent disease, and the remainder (23%) had metastatic disease.

Primary radical surgery, primary chemo-radiotherapy, and primary treatment consisting of TPA were performed in 57.7% (n=30), 21.2% (n=11) and 21.2% (n=11) of patients, respectively. In addition, 51.9% (n=27) of patients had received prior treatment with cisplatin combined with chemo-radiotherapy. The median number of TPA treatment regimens delivered was 6 (range=1-14) (Table I).

Tumour response and survival. A complete response was observed in 15.4% of patients (n=8), whereas 34.6% (n=18) had a partial response, 19.2% (n=10) had stable disease and 30.8% (n=16) exhibited disease progression (Table II). Among patients with recurrent disease, 60.2% exhibited more than a partial response after bevacizumab combined with paclitaxel and cisplatin.

The mean observation period was 15.3 months (range=0.76-56.21 months), during which 32 cases of recurrence (61.5%) and 20 deaths (38.5%) were noted (Table I). The median length of PFS was 9.8 months [95% confidence interval (CI)=7.72-11.92 months], whereas the median length of OS was 15.3 months (95%CI=9.13-21.50 months) (Figure 1). The median PFS and OS of patients who received TPA as primary treatment were longer than those of the group who had received previous radical hysterectomy or cisplatin with concurrent chemo-radiotherapy (CCRT) (PFS; 11.5 months *vs*. 9.0 months (p=0.93), OS; 18.2 months *vs*. 14.9 months (p=0.74). The median PFS and OS of the patients who had never received prior cisplatin combined chemo-radiation were longer than those who received cisplatin with CCRT (PFS, 11.5 months *vs*. 9.3 months, p=0.97; OS, 18.2 months *vs*. 13.5 months, p=0.59).

The PFS and OS of patients who experienced recurrence at more than two sites were shorter than those of patients who experienced no recurrence or recurrence at only one site after bevacizumab with cisplatin plus paclitaxel (PFS, 6.3 months *vs*. 9.0 months, p=0.63; OS, 11.3 months *vs*. 18.8 months, p=0.01). The OS of patients who experienced recurrence at two sites *versus* those with recurrence at more than three sites was significantly different (15.3 months *vs*. 3.8 months, p=0.015).

The PFS of patients who experienced recurrence with distant metastasis *versus* those who did not was similar (7.2 months *vs*. 7.2 months, p=0.32). However, the OS of patients

Table III. *Adverse events and dose modification of treatment.*

	N=52 (%)
Dose reduction	
No	36 (69.2)
Yes	16 (30.8)
Only paclitaxel reduction	2 (3.8)
Only cisplatin reduction	0 (0)
Paclitaxel plus cisplatin reduction	1 (1.9)
All reduction	10 (19.2)
Bevacizumab skip	3 (5.8)
Adverse event (grade≥3)	
Febrile neutropenia	4 (7.7)
Hypertension	3 (5.8)
Fistula	2 (3.8)

Values are presented as number (%).

Table IV. *Recurrence pattern after bevacizumab combined chemotherapy.*

Recurrence or progression disease pattern	N=32 (case 46) (%)
Loco-regional	19 (59.4)
Nodal	11 (34.4)
Peritoneal seeding	6 (18.8)
Distant	10 (31.3)

Values are presented as number (%).

who experienced recurrence with distant metastasis *versus* those who did not was significantly different (11.3 months *vs*. 19.2 months, p=0.003).

The median number of bevacizumab cycles administered was 6 (range=1-14 cycles). Among patients who received fewer than 6 cycles and more than 7 cycles of TPA, the PFS was 11.3 months (95%CI=6.26-16.4 months) and 9.3 months (95%CI=8.58-10.0 months), respectively (p=0.7). The median OS for these same groups of patients was 18.2 months (95%CI=10.68-25.73 months) and 15.3 months (95%CI=10.88-19.74 months), respectively (p=0.63).

Safety. Febrile neutropenia was noted in 7.7% of patients (n=4), and all patients who had febrile neutropenia were hospitalized for antibiotics and granulocyte-colony stimulating factor (G-CSF) treatment. After febrile neutropenia treatment, all patients received a reduction in chemotherapy dose and prophylactic G-CSF in the next cycle. A total of 5.8% (n=3) of patients were diagnosed with hypertension of grade 3 or higher and placed on medication. Only 3.8% of patients (n=2) had fistula, one of which was a rectovaginal fistula, and the other a genitourinary fistula. One of these patients was previously treated with cisplatin with CCRT. A total of 30.8% (n=16) of patients received chemotherapy with a dose reduction. 80% (13/16) of them have reduced chemotherapy including bevacizumab (Table III).

Pattern of recurrence. Recurrence was documented in 61.5% of patients (n=32). A total of 46 recurrence sites were found among these 32 patients, involving loco-regional (59.4%, n=19), nodal (34.4%, n=11), peritoneal seeding (18.8%, n=6) and distant metastasis (31.3%, n=10) (Table IV). Approximately half of the recurrences were loco-regional. The most common site of distant metastasis was the lung (7/10, 70%). Recurrence at one site was observed in 59.4% (19/32) of patients, and the remaining patients who experienced recurrence had it at more than two sites.

Discussion

Clinical and pathological data indicate that treatments involving molecular targeting of angiogenesis are among the most promising therapeutic options for patients with advanced, persistent or recurrent cervical cancer (10, 13). The 'real-world' data of the present study revealed that treatment regimens involving bevacizumab are well tolerated and have a low incidence of serious adverse events. The efficacy and safety profiles of bevacizumab in the present study were generally consistent with the results of the GOG 240 randomized phase III trial (10).

There were no differences in the clinicopathological characteristics of our patients and those of previous studies (2, 8, 10). Our patients were slightly older, however, and had less prior platinum exposure than patients in previous studies (51.9% *vs*. 70-75%).

The GOG240 study demonstrated an improvement in median OS from 13.3 months with chemotherapy alone to 16.8 months with chemotherapy combined with bevacizumab. When compared with chemotherapy involving cisplatin plus paclitaxel, the addition of bevacizumab resulted in an improvement in OS from 15.0 to 17.5 months. In this study, the OS was shorter than that reported in the GOG 240 study. Godoy-Ortiz *et al*. reported a median OS of 21.5 months (2), whereas Tinker *et al*. reported a median OS of 12.1 months (8). The results in 'real-world' patients differed from those in the GOG240 randomized controlled trial. However, the outcomes for first-line treatment in previous clinical studies were consistent with the GOG 240 study. Compared with a median OS of 17.5 months reported by Tinker *et al*. (8), we found a median OS of 18.2 months in primary treatment.

The pattern of recurrence after bevacizumab combined chemotherapy in the present study suggested that the number of relapse sites and recurrence pattern are both related to OS. Almost 60% of patients had loco-regional recurrence, with the lungs being the most common site of metastasis. These

results did not differ significantly from those reported for other chemotherapy regimens.

Toxicity associated with bevacizumab, particularly leading to gastrointestinal perforation, has been of concern. In the GOG 240 trial, the total rate of fistula formation was 15%. Godoy-Ortiz *et al*. reported a 22% fistula formation rate. In our review of 52 patients, there were only two fistula cases reported (3.8%), one involving a genitourinary fistula and one involving a rectovaginal fistula. By comparison, Tinker *et al*. reported a fistula rate of 3.7% (n=1) (8). This finding occurred in a front-line, real-world practice setting, and adverse events rarely led to treatment discontinuation. The low rate of fistula formation may be due to the small patient population and development of radiation treatment technologies with lower toxicity.

The present study had several limitations. First, this was a retrospective study of actual experience with bevacizumab treatment according to national insurance records in Korea. Second, the study's sample size was small. Finally, we were not able to collect patient performance status for this review because these data were not recorded in the medical record.

In conclusion, bevacizumab in combination with cisplatin and paclitaxel for the treatment of persistent, recurrent or metastatic cervical cancer is feasible and well tolerated in a real-world clinical practice. Local recurrence is often observed at the time of relapse.

Conflicts of Interest

The Authors have no conflicts of interest in regard to this study.

Authors' Contributions

Nara Lee: participated in the design, planning, clinical data collection, analysed and interpreted data and drafted the manuscript; Seik Kim: interpreted data, reviewed the manuscript ; Maria Lee: participated in the design, planning, analysed and interpreted data and drafted the manuscript; Heeseung Kim: participated in the design, planning and reviewed the manuscript; Jaeweon Kim: participated in the design, planning, critically reviewed the manuscript; Nohhyun Park: participated in the design, planning, critically reviewed the manuscript; Yongsang Song: participated in the design, planning, critically reviewed the manuscript.

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References

1 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA and Jemal A: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin *68(6)*: 394-424, 2018. PMID: 30207593. DOI: 10.3322/caac.21492

2 Godoy-Ortiz A, Plata Y, Alcaide J, Galeote A, Pajares B and Saez E: Bevacizumab for recurrent, persistent or advanced cervical cancer: Reproducibility of GOG 240 study results in "real world" patients. Clin Transl Oncol *20(7)*: 922-927, 2018. PMID: 29222647. DOI: 10.1007/s12094-017-1808-x

3 Monk BJ, Sill MW, Burger RA, Gray HJ, Buekers TE and Roman LD: Phase II trial of bevacizumab in the treatment of persistent or recurrent squamous cell carcinoma of the cervix: a gynecologic oncology group study. J Clin Oncol *27(7)*: 1069-1074, 2009. PMID: 19139430. DOI: 10.1200/JCO.2008.18.9043

4 Jung KW, Won YJ, Kong HJ and Lee ES: Prediction of cancer incidence and mortality in Korea, 2018. Cancer Res Treat *50(2)*: 317-323, 2018. PMID: 29566480. DOI: 10.4143/crt.2018.142

5 Pfaendler KS and Tewari KS: Changing paradigms in the systemic treatment of advanced cervical cancer. Am J Obstet Gynecol *214(1)*: 22-30, 2016. PMID: 26212178. DOI: 10.1016/j.ajog.2015.07.022

6 Tewari KS, Sill MW, Long HJ 3rd, Penson RT, Huang H, Ramondetta LM, Landrum LM, Oaknin A, Reid TJ, Leitao MM, Michael HE and Monk BJ: Improved survival with bevacizumab in advanced cervical cancer. N Engl J Med *377(8)*: 734-743, 2014. PMID: 28745937. DOI: 10.1056/NEJMx170002

7 Wright JD, Viviano D, Powell MA, Gibb RK, Mutch DG and Grigsby PW: Bevacizumab combination therapy in heavily pretreated, recurrent cervical cancer. Gynecol Oncol *103(2)*: 489-493, 2006. PMID: 16647106. DOI: 10.1016/j.ygyno. 2006.03.023

8 Tinker AV, Fiorino L, O'Dwyer H and Kumar A: Bevacizumab in metastatic, recurrent, or persistent cervical cancer: The BC cancer experience. Int J Gynecol Cancer *28(8)*: 1592-1599, 2018. PMID: 30247250. DOI: 10.1097/IGC.0000000000001351

9 Moore DH, Blessing JA, McQuellon RP, Thaler HT, Cella D and Benda J: Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a gynecologic oncology group study. J Clin Oncol *22(15)*: 3113-3119, 2004. PMID: 15284262. DOI: 10.1200/JCO.2004.04.170

10 Tewari KS, Sill MW, Penson RT, Huang H, Ramondetta LM and Landrum LM: Bevacizumab for advanced cervical cancer: final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240). Lancet *390(10103)*: 1654-1663, 2017. PMID: 28756902.

11 Monk BJ, Sill MW, McMeekin DS, Cohn DE, Ramondetta LM and Boardman CH: Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistent cervical carcinoma: A Gynecologic Oncology Group study. J Clin Oncol *27(28)*: 4649-4655, 2009. PMID:19720909. DOI: 10.1200/JCO.2009.21.8909

12 Choi HJ, Paik ES, Choi CH, Kim TJ, Lee YY and Lee JW: Response to combination chemotherapy with paclitaxel/ifosfamide/platinum *versus* paclitaxel/platinum for patients with metastatic, recurrent, or persistent carcinoma of the uterine cervix: A retrospective analysis. Int J Gynecol Cancer *28(7)*: 1333-1341, 2018. PMID: 30045137. DOI: 10.1097/IGC.0000000000001316

13 Chellappan DK, Leng KH, Jia LJ, Aziz N, Hoong WC and Qian YC: The role of bevacizumab on tumour angiogenesis and in the management of gynaecological cancers: A review. Biomed Pharmacother *102*: 1127-1144, 2018. PMID: 29710531. DOI: 10.1016/j.biopha.2018.03.061

14 Bandyopadhyay A, Mukherjee U, Ghosh S, Ghosh S and Sarkar SK: Pattern of failure with locally advanced cervical cancer - a

retrospective audit and analysis of contributory factors. Asian Pac J Cancer Prev *19(1)*: 73-79, 2018. PMID: 29373895. DOI: 10.22034/APJCP.2018.19.1.73

15 Kong TW, Chang SJ, Piao X, Paek J, Lee Y and Lee EJ: Patterns of recurrence and survival after abdominal *versus* laparoscopic/robotic radical hysterectomy in patients with early cervical cancer. J Obstet Gynaecol Res *42(1)*: 77-86, 2016. PMID: 26554751. DOI: 10.1111/jog.12840.

16 de Foucher T, Bendifallah S, Ouldamer L, Bricou A, Lavoue V and Varinot J: Patterns of recurrence and prognosis in locally advanced FIGO stage IB2 to IIB cervical cancer: Retrospective multicentre study from the FRANCOGYN group. Eur J Surg Oncol *45(4)*: 659-665, 2019. PMID: 30685326. DOI: 10.1016/j.ejso.2018.11.014

17 Sittidilokratna K, Cheewakriangkrai C, Khunamornpong S and Siriaunkgul S: Recurrence patterns after radical hysterectomy in stage IB1-IIA cervical. Asian Pac J Cancer Prev *11(2)*: 499-502, 2010. PMID: 20843140.

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