LÁSZLÓ UNGÁR , LÁSZLÓ TARNAI

Early stage lymph node positive cervical cancer treated with laterally extended parametrectomy (LEP)

Abstract:

Introduction: In 2003, we published our preliminary experience with the use of an operative technique (laterally extended parametrectomy, the LEP procedure) without adjuvant therapy, in the treatment of 29 stage IB, cervical cancer patients with pelvic lymph node metastases. In our present paper, by an extended recruiting period, with a completed 5 years follow up, we studied the outcome of LEP operations, used with the same indications.
Methods: In 70 out of 106 LEP-Wertheim operated patients, no adjuvant treatment was used. In 36 patients, where histology suggested tumor spread beyond the threshold of our surgery, adjuvant chemo-radiotherapy was advised. 5 years follow up was completed (without lost for follow up) for the whole cohort of patients.
Results: In 70 patients treated by LEP procedure alone, the overall 5-years survival was 91.4%. For those 36 patients, who were excluded due to disease spread above study criteria, 5 years survival was 44%. Complications in 10% of cases necessitated a second operation. Apart from transient hyper continence and one case of permanent incontinence, no severe quality of life consequence of the operation was observed.
Conclusions: Our results suggest that in 2/3rd of pelvic lymph node positive, stage IB cervical cancer cases surgery alone could provide equal or better survival (without the toxicity of chemo-radiotherapy), than any kind of multimodality treatment alternatives. LEP procedure should be considered a treatment option for stage IB cervical cancer patients with pelvic lymph node metastases.

Keywords: cervical cancer, lymph node metastasis, laterally extended parametrectomy

Introduction:

Lymph node metastasis in early stage cervical cancer has consistently been identified as the single most important risk factor for recurrence of the disease [1,2,3]. Recurrence in lymph node positive patients is unlikely to be cured by salvage treatment [4]. In patients undergoing radical hysterectomy for stage IB cervical cancer, metastasis to the pelvic lymph nodes is found in approximately 15-20% of the cases [1, 2]. The number of affected nodes [1,3,4] as well as the size of nodal metastases [1,6,7,8] carry added prognostic implications, but the presence of even a single involved node appears to decrease life expectancy significantly [9,10,11]. In a high proportion of patients who relapse after radical hysterectomy, pelvic recurrence can be identified as the initial pattern of failure [12]. This phenomenon has initiated the routine use of adjuvant pelvic radiotherapy in patients with pelvic nodal metastases. However, nonrandomized retrospective studies have not demonstrated a survival advantage for adjuvant radiotherapy in this group of patients [10,11].

Burghardt et al., Benedetti-Panici et al. Girardi et al. have all documented the location of parametrial lymph nodes, and found them to be randomly distributed, with an equal number of metastatic parametrial lymph nodes in the lateral and medial parametria [13,14,15,16]. Based upon these findings, the complete removal of all of the parametrium was recommended by the same authors, alleging that parametrial metastases occur equally in all parts of the parametrium.

In 1993, an extensive surgical technique was introduced in St. Stephen Hospital for the treatment of cervical cancer patients with histology proven pelvic lymph node metastases [17,18]. Traditional Wertheim procedure - with or without adjuvant radiotherapy - failed to cure 15-40% of patients with lymph node positive stage IB cervical cancer [3,12,20]. We presumed, if survival benefit for the new “laterally extended parametrectomy” (LEP) would decrease the disease related death-rate by equal or more than 50%, the

advantage of the procedure might be demonstrated on a relatively small but homogenous cohort of patients matched with historic data. Since 1999, clinical trials have reported a decreased risk for recurrence when using chemo- and radiotherapy in the adjuvant treatment of patients with high-risk early stage cervical cancer following radical surgery [21,22] and specifically in lymph node metastasis early stage cervical cancer cases [23]. Adjuvant chemotherapy without radiotherapy was found equally or more efficient also, than radiotherapy in lymph node metastasis early stage cervical cancer [24]. In a recent survey [25] no uniformity was found in the treatment policy of SGO members in the treatment of lymph node metastasis early stage cervical cancer. Preliminary results of our ongoing clinical trial [17,18] suggested however a better chance for survival and a smaller risk for severe side effects than that of reported with the use of concomitant radical surgery and chemo- irradiation [19]. This reality encouraged us to complete our present series in spite of protocol recommendation about adjuvant chemo-radiation for the treatment of patients with high-risk early stage cervical cancer [26].

Patients and methods

Between 1994 and 2005, 106 cases of Stage IB cervical cancer - with intra operative histology proven pelvic lymph node metastases - were treated by the "LEP Wertheim" procedure. Bilateral LEP (for the treatment of lymph node metastasis identified in both sides of the pelvis) was applied in six cases.

All of our patients were explored with the intent of performing a routine Piver type 3 Wertheim procedure with pelvic lymphadenectomy. Intra-operative histology finding of lymph node metastasis on frozen section predicated the use of the more extensive LEP procedure. National population registry and the National Health Care registry (every citizen of the Hungarian Republic is covered by the National Health Scheme, and no oncology treatment is provided outside NHS hospitals of the country) provided dependable survival information and data in regard of chemo and/or radiotherapy following surgery of all cases.

Patients' characteristics were as follows:

Age ranged between 24-61 years with a mean age of 41 years. General condition was acceptable for an extensive surgical procedure (ASA 1-2) in all cases. 15 patients have received neoadjuvant radio or chemo-radiotherapy prior to surgery.

In 70 cases, where histology suggested complete removal of the potentially tumor containing lymph-vessel and lymph node containing fibro-fatty tissue, no adjuvant treatment was used. Histology type of the 70 cases operated without adjuvant treatment, were as follows: tumor was squamous cell in 57 (81%) cases, adenocarcinoma in 7 (10%) cases and glassy-cell carcinoma in 6 (9%) cases. Histology revealed occult tumor spread to the vaginal vault in 12 (17%) cases (pathology stage: pIIA), and to the parametrium in 16 (23%) patients (pathology stage: pIIB). 5 years follow up was completed in all cases.

Out of the 42 cases of pathology stage pIB, there were 5 cases with micro metastasis in one lymph node, 25 cases with one >5mm diameter metastasis containing lymph node, 8 cases with more than one positive lymph nodes in one region, 4 cases with tumor positive lymph nodes in more than one regions in the pelvis (Table I.). In the group of patients with tumor spread to the vaginal vault n=12 (17%) (stage pIIA), there was micro metastasis in 1 case, metastasis with >5mm diameter in one lymph node were found in 8 cases, multiple metastatic lymph nodes in one region was found in 1 case, in 2 cases more than one regions were found to contain tumor positive lymph nodes. In the group of patients with parametrial spread n=16 (23%) (stage pIIB), there were micro metastasis in 1 case, one positive lymph node with metastasis >5mm diameter was found in 6 cases, multiple metastatic lymph nodes were found in one region in 1 case, more than one regions were found with positive lymph nodes in 8 cases. Lymph node metastases in the whole cohort of 70 patients were microscopic (less than 5mm in diameter) in 7 cases (10%). In the other 63 cases, the size of the lymph node metastasis was more than 5 mm, and/or more than one positive lymph nodes were detected.

In 36 out of the total 106 LEP operated patients, final histology revealed the extent of the disease exceeding our criteria for LEP without adjuvant treatment. One of the following parameters or their combination were found: disease involvement of the surgical margins (5 cases), disease at the site of the ureter channel (13 cases), tumor spread to the uterine corpus (11 cases), lymph node metastasis that broke through the capsule of the affected lymph

node/nodes (3 cases), presence of microscopic lymph node metastases at the periaortic area (4 cases). Adjuvant chemo- and/or radiotherapy were advised in these cases.

Some patients, however, have not accepted the adjuvant treatment, and in some cases toxicity made the radiotherapist to use a reduced dose of chemo and/or radiation treatment. Some cases were treated before the adoption of chemo-radiotherapy as standard treatment (before 1999) at our oncology service. In view of poor prognostic factors as well as adjuvant treatment modality and dosage, individuals of this cohort of 36 patients were not comparable to each other, hence did not provide any deductions in view of treatment efficacy.

The LEP Wertheim procedure:

On the side of the lymphatic metastasis, the main branches of the hypogastric artery and vein are clamped and dissected. Common iliac artery and vein are elevated from the pelvic sidewall. At the pelvic edge of the clean surface of the psoas muscle, the pelvic sequence of the lumbo-sacral nerve is exposed. The parietal branches of the hypogastric artery and vein, situated above the lumbal branch of the lumbosacral nerve, are dissected at the site where they enter the pelvic sidewall structures (psoas muscle). The distal extension of the dissection of the lumbo-sacral plexus reveals the suprapiriformis foramen.

Sacral branches of the lumbo-sacral nerve and the piriformis muscle between the nerve branches are cleaned of the overlying connective tissue. Parietal branches of the hypogastric vessels (ilio-lumbal, superior and inferior gluteal, pudendal and obturator artery and vein) are then dissected on the surface of the lumbosacral nerve, or the levator ani muscle or the piriformis muscle. Completion of the dissection should result in the complete removal of the fibro-fatty tissue lateral to the rectum, together with the hypogastric blood vessels of the pelvis.

Inspection of the operative site from medial to lateral reveals the clean surface of the sacrum, sacral and lumbal branches of the lumbo-sacral nerve, the piriformis muscle between the nerve branches, the foramen supra piriformis at the distal pelvic edge of the nerve plexus and the levator, obturator and psoas muscles around the nerve covered area. The common and external iliac arteries and veins, the ureter and the obturator nerve bridge above the pelvic sidewall. Routine periaortic lymphadenectomy is also part of the procedure. A urethral or suprapubic catheter is left in place

for 6 days following the operation. In cases of hypercontinence, self-catheterization is utilized on the 7th postoperative day in cases with a urethral catheter, or use of the suprapubic catheter is prolonged.

Operating time of the LEP Wertheim procedure ranged from 2h 50min to 6h, (mean 4h-5min). Blood transfusion was necessary in 63 out of our 70 cases. Two to seven units of red blood cell concentrate were administered (mean 3.3 units).

Results:

5 years after surgery, 64 out of the 70 patients (91.4%) - treated without adjuvant therapy - were alive (all patients of this study were followed longer than 5 years after surgery). A 75% 5 years overall survival was detected for the whole cohort of 106 patients. In 36 patients, where final histology revealed disease spread beyond the threshold of our LEP criteria, and adjuvant treatment was recommended, the overall 5 years survival was 44%.
No treatment related death occurred in this cohort of patients.
Characteristics of fatal outcome cases: All 3 recurrences that were treated by our group – among the 70 operated only patients **-** were detected within the first two years of follow up. Site of the detected recurrences were the supra-clavicular group of lymph nodes in two cases and pulmonary metastasis in one case. The three remaining patients, who died in the first 5 years of the follow up period and no reliable data were available of, were statistically considered as disease related death cases, although none of them received chemo or radiotherapy. All three patients treated with recurrence in our institution received chemo and/or radiotherapy. In spite of the treatment, all patients died of their disease.

In view of correlation between pathology stage and unfavorable outcome: one patient died from the group of 42 pathology stage IB (pIB) patients, four were among the 12 patients with stage pIIA disease, and one died from the 16 patients with stage pIIB disease. If overall survival chance is evaluated with regard to lymph node status, in five of the six fatal outcome cases more than one group of lymph nodes were involved, in one case a single group of positive

nodes was detected, but the lymph node metastases was more than 5 mm in diameter and this patient had stage pIIB disease.
Short term complications (within the first 3 post operative weeks): 45 patients out of 70 (64%) healed without any complications. In two cases, bleeding required reoperation. In three patients, embolectomy was needed due to intra-operative thrombosis of the femoral artery. In two patients, temporary urinary diversion was needed either due to partial necrosis of the urinary bladder or the injury of the ureter. Both patients – following reconstructive surgery - recovered without residual symptoms. Transient hypercontinence was noted in 29 patients (41%). Use of self-catheterization and/or the prolonged use of the suprapubic catheter solved the hypercontinence within one to six weeks in all cases. In seven patients, fever above 38°C lasting longer than three days necessitated targeted antibiotic treatment.
Long term complications: 59 out of 70 patients (84%) recovered without any long term complaints. In one patient, laparotomy was needed to treat an adhesions related strangulated ileus 4 months after the LEP Wertheim procedure. In five cases, late ureter strictures were detected. Ureter stent was used in three cases, and resection and reimplantation of the ureter in two cases. All six patients were symptom free at the time of follow up. In four patients, mild leg edema on the side of the LEP procedure was noted. In one patient, grade II treatment refractory incontinence occurred. This patient has had to use a pad ever since her operation.

Discussion

In the present study, we report the results of the laterally extended parametrectomy (LEP Wertheim procedure) without adjuvant treatment in 70 patients with Stage IB cervical cancer, with pelvic lymph node metastasis, where histology indicated complete removal of the potentially tumor containing lymph-vessel and lymph node containing fibro-fatty tissue. A 91, 4% overall survival was achieved with a completed follow up of more than 60 months for each patient. Survival results of our series suggest, that LEP Wertheim procedure

in stage IB pelvic lymph node positive cervical cancer cases - selected by our criteria - provides at least the same or better survival than any reported results of less extensive surgery with adjuvant chemo-radiotherapy [18, 21,26]. Identical results of extensive surgery without adjuvant radiotherapy was recently published by Hoeckel [27] in the same condition.

Disease free 5 year's survival was not addressed in this study. However, since recurrences in lymph node positive patients are unlikely to be cured [4], difference between overall 5 years survival and disease free 5 year's survival in this cohort of patients must not be significant.

The limited number of cases did not allow a statistical analysis between pathology stages, number and size of lymph node metastasis and outcome of the disease. However, all six patients who died had either macroscopic and/or multiple lymph node metastases. Pathology stage IIA or IIB seem to predict poorer prognosis than pathology stage IB in our material. Similar correlations between pathology disease stage and tumor size have been reported in the literature [28]. To better define the significance of prognostic factors of LEP operated lymph node positive patients will need further data collecting.

We stipulated conditions indicative for adjuvant treatment following LEP surgery, where 1: disease spread beyond the anatomy border of the excision (positive surgical margins, tumor spread to the ureter channel) or tumor diffusion direction (tumor breakthrough of the lymph node capsule, tumor spread to the uterine corpus) indicated poor prognosis, unlikely to be influenced by a more extensive parametrectomy. The 44% overall 5 years survival (6x more fatal outcome compared to the surgery only cohort of patients) of this cohort of patients accentuate the prognostic importance of these factors. In view of these prognostic factors as well as adjuvant treatment modality and dosage, our patients were multifarious, not comparable to each other, hence did not provide dependable deductions. Indications and type of adjuvant treatment following LEP surgery needs further research.

There is a foreseeable risk of morbidity associated with radical hysterectomy including bladder dysfunction, urinary tract fistulae and large volume blood loss [13,29,30,31]. There is a predictable correlation between extent or parametrium dissection and morbidity [32].

Blood loss necessitated blood transfusion in the majority of our operations, more frequent than it has been reported in relation with traditional radical hysterectomy [15]. The resection of the intra-pelvic hypogastric blood vessel system seems to carry an added risk of extensive blood-loss.

In three patients femoral artery embolus necessitated embolectomy. Femoral artery embolus has not been listed as a usual radical hysterectomy complication in the related literature [13]. The experience with these cases prompted us to get prepared for an embolectomy, when we start a LEP procedure.

Seven out of 70 patients (10%) had complications requiring a second operation. Less severe complications (hypercontinence, transient leg-oedema, fever) could be solved by conservative treatment. Apart from one case of grade II treatment refractory incontinence, none of our LEP patients complained of severe impairment of quality of life. LEP seems to be an acceptable risk procedure.

Strong evidence of an increased prevalence of a second primary cancer after radiotherapy has been proven by several studies [33,34]. With the use of combined surgery and postoperative radiation therapy, severe morbidity can be expected in about 10-30% of patients [35,36,37,38,39]. Radiotherapy results in reduction of the length, caliber and lubrication of the vagina, while surgery leaves the vagina in a more functional condition [35].

Although in our present series we did not provide a randomized control arm with chemo-radiotherapy, we can state, that radiotherapy related toxicity can be avoided by the use of the LEP procedure in the majority of cases. Since more than 70% of our patients were less than 45 years of age, the preservation of the vaginal function was an important quality of life consideration. However, a long term comparison of oncology outcome, complications, quality of life and cost aspects of LEP against LEP and adjuvant chemotherapy and/or chemo-radiotherapy would need further studies.

In conclusion: our experience suggest, that the LEP procedure provides a good chance for survival with an acceptable risk of complications for the majority of pelvic lymph node positive stage IB cervical cancer patients. We suggest that extensive surgical approaches without adjuvant radiotherapy (with or without adjuvant chemotherapy) should be listed in future cervical cancer treatment

protocols as treatment options for a selected group of early stage cervical cancer patients with pelvic lymph node metastases

References

[1] van Bommel PF, van Lindert AC, Kock HC, Leers WH, Neijt JP. A review of prognostic factors in early-stage carcinoma of the cervix (FIGO I B and II A) and implications for treatment strategy. Eur J Obstet Gynecol Reprod Biol 1987;26(1):69-84.
[2] Kodama J, Seki N, Masahiro S, Kusumoto T, Nakamura K, Hongo A, Hiramatsu Y Prognostic factors in stage IB-IIB cervical adenocarcinoma patients treated with radical hysterectomy and pelvic lymphadenectomy. J Surg Oncol. 2010;101(5):413-7.
[3] Ware RA, van Nagell JR Radical hysterectomy with pelvic lymphadenectomy: indications, technique, and complications. Obstet Gynecol Int. 2010;2010. pii: 587610
[4] Fuller AF Jr, Elliott N, Kosloff C, Lewis JL Jr. Lymph node metastases from carcinoma of the cervix, stages IB and IIA: implications for prognosis and treatment. Gynecol Oncol 1982;13(2):165-74.
[5] Inoue T, Morita K. The prognostic significance of number of positive nodes in cervical carcinoma stages IB, IIA, and IIB. Cancer 1990;65(9):1923-7.
[6] Macdonald OK, Chen J, Dodson M, Lee CM, Gaffney DK Prognostic significance of histology and positive lymph node involvement following radical hysterectomy in carcinoma of the cervix. Am J Clin Oncol. 2009;32(4):411-6.
[7] Alvarez RD, Soong SJ, Kinney WK, Reid GC, Schray MF, Podratz KC, Morley GW, Shingleton HM.: Identification of prognostic factors and risk groups in patients found to have nodal metastasis at the time of radical hysterectomy for early-stage squamous carcinoma of the cervix. Gynecol Oncol 1989;35(2):130-5.
[8] Martimbeau PW, Kjorstad KE, Iversen T. Stage IB carcinoma of the cervix, the Norwegian Radium hospital. II. Results when pelvic nodes are involved. Obstet Gynecol 1982;60(2):215-218.
[9] Delgado G, Bundy B, Zaino R, Sevin BU, Creasman WT, Major F. Prospective surgical-pathological study of disease-free interval in patients with stage IB squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. Gynecol Oncol 1990;38(3):352-7.
[10] Morrow CP. Panel report. Is pelvic radiation beneficial in the postoperative management of stage IB squamous cell carcinoma of the cervix with pelvic node metastasis treated by radical hysterectomy? Gynecol Oncol 1980;10:105-110.
[11] Kinney WK, Alvarez RD, Reid GC, Schray MF, Soong SJ, Morley GW, Podratz KC, Shingleton HM.: Value of adjuvant whole-pelvis irradiation after Wertheim hysterectomy for early-stage squamous carcinoma of the cervix with

pelvic nodal metastasis: a matched-control study. Gynecol Oncol 1989;34(3):258-62.
[12] M. Höckel - Pelvic recurrences of cervical cancer. J Pelv Surg 1999;5: 255-266.
[13] Covens A, Rosen B, Murphy J, Laframboise S, DePetrillo AD, Lickrish G, Colgan T, Chapman W, Shaw P. How important is removal of the parametrium at surgery for carcinoma of the cervix? Gynecol Oncol 2002;84(1):145-9.
[14] Benedetti-Panici P, Maneschi F, D'Andrea G, Cutillo G, Rabitti C, Congiu M, Coronetta F, Capelli A.Early cervical carcinoma: the natural history of lymph node involvement redefined on the basis of thorough parametrectomy and giant section study. Cancer 2000;88(10):2267-74.
[15] Burghardt E, Pickel H, Haas J, Lahousen M. Prognostic factors and operative treatment of stages IB to IIB cervical cancer. Am J Obstet Gynecol 1987;156(4):988-96.
[16] Girardi F, Lichtenegger W, Tamussino K, Haas J. The importance of parametrial lymph nodes in the treatment of cervical cancer. Gynecol Oncol 1989;34(2):206-11.
[17] Ungar L, Palfalvi L. Surgical treatment of lymph node metastases in stage IB cervical cancer: the laterally extended parametrectomy (LEP) procedure. Int J Gynecol Cancer 2003;13(5):647-5
[18] Palfalvi L, Ungar L. Laterally extended parametrectomy (LEP), the technique for radical pelvic side wall dissection: Feasibility, technique and results. Int J Gynecol Cancer 2003;13(6):914-7.
[19] Mabuchi S, Okazawa M, Isohashi F, Ohta Y, Maruoka S, Yoshioka Y, Enomoto T, Morishige K, Kamiura S, Kimura T. Postoperative whole pelvic radiotherapy plus concurrent chemotherapy versus extended-field irradiation for early-stage cervical cancer patients with multiple pelvic lymph node metastases. Gynecol Oncol 2011;120(1):94-100.
[20] Terada KY, Morley GW, Roberts JA Stage IB carcinoma of the cervix with lymph node metastases. Gynecol Oncol 1988;31(3):389-95.
[21] Uno T, Ito H,Itami J, Sato T, Minoura S, Yasuda S, Aruga T, Isobe K, Shigematsu N, Kubo A. Adjuvant pelvic irradiation in patients with pathologic T2b carcinoma of the uterine cervix. Int J Gynecol Cancer 2002;12(2):187-91.
[22] Peters WA,Liu PY, Barrett RJ, Stock RJ, Monk BJ, Berek JS, Souhami L, Grigsby P, Gordon W, Alberts DS. Concurrant chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgary in high-risk early-stage cancer of the cervix. J Clin Oncol 2000;18(8):1606-13.
[23] Mabuchi S, Okazawa M, Isohashi F, Ohta Y, Maruoka S, Yoshioka Y, Enomoto T, Morishige K, Kamiura S, Kimura T. Postoperative whole pelvic radiotherapy plus concurrent chemotherapy versus extended-field irradiation for early-stage cervical cancer patients with multiple pelvic lymph node metastases. Gynecol Oncol 2011;120(1):94-100.
[24] Mossa B, Mossa S, Marziani R. Adjuvant chemotherapy versus radiation therapy after radical surgery in high-risk positive node stage IB/IIA cervical cancer. Eur J Gynaecol Oncol 2010;31(5):545-50.

[25] Garg G, Shah JP, Toy EP, Field JB, Bryant CS, Liu JR, Morris RT. Intra-operative detection of nodal metastasis in early stage cervical cancer: A survey of the practice patterns of SGO members. Gynecol Oncol 2011;121(1):143-7.
[26] ACOG Practice Bulletin, Clinical management guidelines for obstetrician-gynecologists. No35, May 2002: Diagnosis and treatment of cervical carcinomas. Obstet Gynecol 2002;99(5):855-866.
[27] Höckel M, Horn LC, Manthey N, Braumann UD, Wolf U, Teichmann G, Frauenschläger K, Dornhöfer N, Einenkel J. Resection of the embryologically defined uterovaginal (Müllerian) compartment and pelvic control in patients with cervical cancer: a prospective analysis. Lancet Oncol 2009;10(7):683-92.
[28] Park JY, Kim DY, Kim JH, Kim YM, Kim YT, Nam JH. Further stratification of risk groups in patients with lymph node metastasis after radical hysterectomy for early-stage cervical cancer. Gynecol Oncol 2010;117(1):53-8.
[29] Averette HE, Method MW, Sevin B-U, Penalver MA. Radical abdominal hysterectomy in the primary management of invasive cervical cancer. In: Rubin SC, Hoskins WJ, editors. Cervical cancer and preinvasive neoplasia. Philadelphia: Lippincott-Raven Publishers;1996.p.189-206.
[30] Frankman EA, Wang L, Bunker CH, Lowder JL. Lower urinary tract injury in women in the United States, 1979-2006. Am J Obstet Gynecol 2010;202(5):495-505.
[31] Ralph G, Winter R, Michelitsch L, Tamussino K. Radicality of parametrial resection and dysfunction of the lower urinary tract after radical hysterectomy. Eur J Gynaecol Oncol 1991;12(1):27-30.
[32] Naik R, Jackson KS, Lopes A, Cross P, Henry JA. Laparoscopic assisted radical vaginal hysterectomy versus radical abdominal hysterectomy--a randomised phase II trial: perioperative outcomes and surgicopathological measurements. BJOG 2010;117(6):746-51.
[33] Pettersson F, Fotiou S, Einhorn N, Silfverswärd C. Cohort study of the long-term effect of irradiation for carcinoma of the uterine cervix. Second primary malignancies in the pelvic organs in women irradiated for cervical carcinoma at Radiumhemmet 1914-1965. Acta Radiol Oncol 1985;24(2):145-51.
[34] Pettersson F, Ryberg M, Malker B. Second primary cancer after treatment of invasive carcinoma of the uterine cervix, compared with those arising after treatment for in situ carcinomas. An effect of irradiation? A cancer registry study. Acta Obstet Gynecol Scand 1990;69(2):161-74.
[35] Landoni F, Maneo A, Colombo A, Placa F, Milani R, Perego P, et al. Randomised study of radical surgery versus radiotherapy for stage I/b-II/a cervical cancer. Lancet 1997;350:535-540.
[36] Kashima K, Yahata T, Fujita K, Tanaka K. Analysis of the complications after radical hysterectomy for stage IB, IIA and IIB uterine cervical cancer patients. J Obstet Gynaecol Res 2010;36(3):555-9.
[37] Hazewinkel MH, Sprangers MA, van der Velden J, van der Vaart CH, Stalpers LJ, Burger MP, Roovers JP. Long-term cervical cancer survivors suffer from pelvic floor symptoms: a cross-sectional matched cohort study. Gynecol Oncol 2010;117(2):281-6.

[38] Güth U, Ella WA, Olaitan A, Hadwin RJ, Arora R, McCormack M. Total vaginal necrosis: a representative example of underreporting severe late toxic reaction after concomitant chemoradiation for cervical cancer. Int J Gynecol Cancer 2010;20(1):54-60.
[39] Undurraga M, Loubeyre P, Dubuisson JB, Schneider D, Petignat P. Early-stage cervical cancer: is surgery better than radiotherapy? Expert Rev Anticancer Ther 2010;10(3):451-60.