

**Surgical treatment of lymph node metastases in stage IB cervical cancer.
The laterally extended parametrectomy procedure: Experience with a 5
year follow-up.**

Ph.D. thesis

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SUMMARY OF THESIS

1. In this 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 tumour 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.

2. 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, the 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. To better define the significance of prognostic factors of LEP operated lymph node positive patients will need further data collecting.

3. In our opinion adjuvant treatment is indicated following LEP surgery, where: disease spread beyond the anatomy border of the excision (positive surgical margins, tumour spread to the ureter channel) or tumour diffusion direction (tumour breakthrough of the lymph node capsule, tumour spread to the uterine corpus) indicated poor prognosis, unlikely to be influenced by a

more extensive parametrectomy. The poor overall 5 year survival (more fatal outcome compared to the surgery only cohort of patients) of this cohort of patients accentuate the prognostic importance of these factors.

4. There is a foreseeable risk of morbidity associated with radical hysterectomy including bladder dysfunction, urinary tract fistulae and large volume blood loss. There is a predictable correlation between extent of parametrium dissection and morbidity.

5. Strong evidence of an increased prevalence of a second primary cancer after radiotherapy has been proven by several studies. With the use of combined surgery and postoperative radiation therapy, severe morbidity can be expected in about 10-30% of patients. Radiotherapy results in reduction of the length, caliber and lubrication of the vagina, while surgery leaves the vagina in a more functional condition. The use of LEP surgery will avoid the radiotherapy induced morbidity.

6. 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, and quality of life and cost aspects of LEP against LEP and adjuvant chemotherapy and/or chemo-radiotherapy would need further studies.

OBJECTIVES AND FINDINGS OF THE PRESENT STUDY

Objectives of the present study:

1. Improving survival chances in pelvic lymph node metastases early stage cervical cancer patients by an extended connective tissue clearance of the pelvis.
2. Improving the quality of life of the above mentioned cohort of patients by a surgical treatment modality, that do not include radiotherapy or chemo-radiotherapy.
3. Decreasing the treatment induced second cancer risk by a surgical treatment modality, that do not include radiotherapy or chemo-radiotherapy.
4. Study the treatment toxicity of the new extensive surgical procedure.
5. Study the significance of prognostic factors in LEP operated patients.
6. Establishing the adjuvant treatment indication criteria in LEP operation patients.

Findings of present study:

1. 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.

2. The surgery leaves the vagina in a more functional condition while the radiotherapy results in reduction of the length, caliber and lubrication of the vagina. 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.

3. We can state, that radiotherapy related toxicity (ovarian ablation, vaginal stenosis, bowel and bladder dysfunction and late complications that second primary cancer - expected in about 10-30% of all cases) can be avoided by the use of the Wertheim LEP procedure.

4. The treatment toxicity of the new extensive surgical procedure: bladder dysfunction, urinary tract fistulae and large volume blood loss. There is a predictable correlation between extent of parametrium dissection and morbidity.

5. Pathology stage IIA or IIB seem to predict poorer prognosis than pathology stage IB in our material. Similar correlations between pathology disease stage and tumour size have been reported in the literature.

6. The adjuvant treatment indication criteria in LEP operation patients: disease spread beyond the anatomy border of the excision (positive surgical margins, tumour spread to the ureter channel) or tumour diffusion direction (tumour breakthrough of the lymph node capsule, tumour spread to the uterine corpus).

1. INTRODUCTION

1.1. Epidemiology

Cervical cancer is the second most common cancer in women worldwide and the most common female cancer in many developing countries. Annual global estimates for the year 2000 were 470,600 new cases and 233,400 deaths. Both the incidence and mortality rates are likely to be underestimated in underresourced countries because of poor registry reporting. In the United States, 11,270 new cases 4,070 deaths were anticipated in 2009.

The mean age for cervical cancer is 51,4 years, with the number of patients fairly evenly divided between the age groups 30 to 39 and 60 to 69 years. There is a trend toward increasing stage with increasing age, suggesting that older patients are not being screened as often as younger patients.

1.2. History of the treatment

It was Pare in the 16th century who first proposed the amputation of a cervical carcinoma as treatment. However, at this time surgery resulted in a high mortality and even in the 19th century when Freund proposed and performed surgery for the management of cervical cancer mortality rates was still unacceptably high. The birth of the 20th century saw advances being made in surgical specialities with the introduction of safer anaesthetics, better antiseptics and antibiotics. Surgeons such as Clark in America and Wertheim in Austria were pioneering the use of radical surgery with the aim of curing cervical cancer. Furthermore, Schauta was treating cervical cancer with radical vaginal surgery and Okabayashi was developing his radical hysterectomy technique in Japan. At the same time, radiotherapy was being developed following the discovery of radium by the Curies and its therapeutic application by Abbe. Many, even Wertheim himself, thought that radiotherapy would

replace surgery for the treatment of cervical cancer. However, in the mid 20th century the radical hysterectomy and lymphadenectomy was reintroduced mainly through the work of Victor Bonney in England and Joe Meigs in America.

1.3. The most important factors affecting the survival

Lymph node metastasis in early stage cervical cancer has consistently been identified as the single most important risk factor for recurrence of the disease. Recurrence in lymph node positive patients is unlikely to be cured by salvage treatment. 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. The number of affected nodes as well as the size of nodal metastases carry added prognostic implications, but the presence of even a single involved node appears to decrease life expectancy significantly. In a high proportion of patients who relapse after radical hysterectomy, pelvic recurrence can be identified as the initial pattern of failure. 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. 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. 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. Traditional Wertheim procedure - with

or without adjuvant radiotherapy – failed to cure 15-40% of patients with lymph node positive stage IB cervical cancer.

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 and specifically in lymph node metastasis early stage cervical cancer cases. Adjuvant chemotherapy without radiotherapy was found equally or more efficient also, than radiotherapy in lymph node metastasis early stage cervical cancer. In a recent survey 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 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. 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.

2. 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 (NHS), 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.

2.1. Patients’ characteristics

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 tumour 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: tumour was squamous cell in 57 (81%) cases, adenocarcinoma in 7 (10%) cases and glassy-cell carcinoma in 6 (9%) cases. Histology revealed occult tumour spread to the vaginal vault in 12

(17%) cases (pathology stage: pIIA), and to the parametrium in 16 (23%) patients (pathology stage: pIIB). 5 year follow-up was completed in all cases

Out of the 42 cases of pathology stage pIB, there were 5 cases with micrometastasis 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 tumour positive lymph nodes in more than one regions in the pelvis. In the group of patients with tumour spread to the vaginal vault n=12 (17%) (stage pIIA), there was micrometastasis 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 tumour positive lymph nodes. In the group of patients with parametrial spread n=16 (23%) (stage pIIB), there were micrometastasis 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 node was 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), tumour 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 this 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.

2.2. 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 lumbar branch of the lumbosacral nerve are dissected at the site where they enter the pelvic sidewall structures (psoas muscles). The distal end of the dissection of the lumbo-sacral plexus revealed 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-lumbar, medial 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 blood vessels of the pelvis.

Inspection of the operative site from medial to lateral revealed the clean surface of the sacrum, sacral and lumbar branches of the lumbo-sacral nerve, the piriformis muscle between the nerve branches, the foramen suprapiriformis 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 dissected pelvic sidewall. Routine periaortic lymphadenectomy was part of the procedure.

Bilateral LEP was applied in six cases. A urethral or suprapubic catheter was left in place for 6 days following the operation. In cases of hypercontinence, self-catheterization was utilized on the 7th postoperative day in cases with a urethral catheter, or use of the suprapubic catheter was 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).

3. RESULTS

3.1. Survival

5 years after surgery, 64 out of 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 metastases in one case. The 3 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 and/or radiotherapy. All 3 patients 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: 1 patients died from group of 42 pathology stage IB (pIB) patients, 4 were among the 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 diameter and this patient had stage pIIB disease.

3.2. Short term complications (within the first 3 postoperative weeks)

45 patients out of 70 (64%) healed without any complications. In two cases, bleeding required reoperation. In 3 patients, embolectomy was needed due to intra-operative thrombosis of the femoral artery. In 2 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 (41%) patients. 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 7 patients, fever above 38 °C lasting longer than three days necessitated targeted antibiotic treatment.

3.3. Long term complications

59 out of 70 (84%) patients recovered without any long term complaints. In 1 patient, laparotomy was needed to treat an adhesion related strangulated ileus four months after the LEP Wertheim procedure. In five cases late ureteric strictures were detected. Ureteric stent was used in three cases and resection and reimplantation of the ureter in two cases. All 6 patients were symptom free at the time of follow-up. In 4 patients, mild leg-oedema on the side of the LEP procedure was noted. In 1 patient grade II treatment refractory incontinence occurred. This patient has had to use a pad ever since her operation.

4. 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 tumour 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. Identical results of extensive surgery without adjuvant radiotherapy were recently published by Höckel 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, 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 6 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 tumour size have been reported in the literature. 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 disease spread beyond the anatomy border of the excision (positive surgical margins, tumour spread to the ureter channel) or tumour diffusion direction (tumour breakthrough of the lymph node capsule, tumour 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. There is a predictable correlation between extent of parametrium dissection and morbidity.

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

In 3 patients femoral artery embolus necessitated embolectomy. Femoral artery embolus has not been listed as a usual radical hysterectomy complication in the related literature. The experience with these cases prompted us to get prepared for an embolectomy, when we start a LEP procedure.

7 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 1 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. With the use of combined surgery and postoperative radiation therapy, severe morbidity can be expected in about 10-30% of patients. Radiotherapy results in reduction of the length, caliber and lubrication of the vagina, while surgery leaves the vagina in a more functional condition.

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.

5. CONCLUSION

In conclusion, the LEP procedure seems to be an equal or better alternative of presently used treatment policies of patients with pelvic lymph node positive early stage cervical cancer. Our results seem to contradict the traditional therapy concept that surgery alone cannot cure lymph node metastasis from the cervical cancer. In contrast, we found that extensive surgical approaches without adjuvant radiotherapy should be listed in future cervical cancer treatment protocols as treatment options for a selected group of cervical cancer patients with pelvic lymph node metastases.

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