Early stage cervical cancer : quality of cancer care and quality of life

Pieterse, Q.D.

Chapter 3

The number of pelvic lymph nodes in the quality control and prognosis of radical hysterectomy for the treatment of cervical cancer.

Q.D. Pieterse [1], G.G. Kenter [1], K.N. Gaarenstroom [1], A.A.W. Peters [1], S.M. Willems [2], G.J. Fleuren [2], J.B.M.Z. Trimbos [1].
[1] Dept. of Gynaecology, Leiden University Medical Centre, Leiden, the Netherlands
[2] Dept. of Pathology, Leiden University Medical Centre, Leiden, the Netherlands
Eur J Surg Oncol 2007; 33:216-221

Abstract

Objective: To determine if the number of removed lymph nodes in radical hysterectomy with lymphadenectomy (RHL) influences survival of patients with early stage cervical cancer and to analyze the relation of different factors like patient age, tumour size and infiltration depth with the number of nodes examined in node-negative early stage cervical cancer patients.

Methods: Of consecutive patients, who underwent RHL between January 1984 and April 2005, 331 had negative nodes (group A) without adjuvant therapy and 136 had positive nodes (group B). The Kaplan-Meier method and Cox regression model were used to detect statistical significance. Factors associated with excision of nodes were confirmed with linear regression models.

Results: The median number of removed nodes was 19 and 18 for group A and group B, respectively. There was no significant relationship between the number of removed nodes and the cancer specific survival (CSS) or disease free survival (DFS) for patients of group A (p=0.625 and p=0.877, respectively). The number of removed nodes in group B was not significantly associated with the CSS (p=0.084) but it was for the DFS (p=0.014). Factors like patient age, tumour size and infiltration depth were not associated with the number of nodes.

Conclusions: No relation was found between the number of negative nodes examined after RHL for the treatment of early stage cervical cancer and CSS or DFS. However, a higher amount of removed lymph nodes leaded to a better DFS for patients with positive nodes. It is suggested that patients with positive nodes benefit from a complete pelvic lymphadenectomy and a sufficient yield of removed nodes.

Introduction

Pelvic lymphadenectomy is widely performed as part of the treatment of patients with cervical cancer stage I-IIa (1-6). Spread of the disease outside the cervix, especially in the pelvic nodes, has the strongest effect on prognosis (5-8). The goal of lymphadenectomy is to remove and diagnose cancer cells that have been transported to the lymphatic tissue draining the uterine cervix and the upper vagina. A systemic lymphadenectomy can reliably establish the presence or absence of lymph node involvement, with the attendant consequences for prognosis and treatment (5).

In other cancers such as breast cancer, it has been suggested that removal of the axillary regional nodes in patients with breast cancer is important for long-term survival, even when such nodes are interpreted as pathologically negative (9-15).

In endometrial carcinoma the role of lymphadenectomy remains a topic of continuing debate. Literature data document the possible therapeutic benefit of selective lymphadenectomy in the management of patients with early stage endometrial cancer. However, it remains an unresolved issue whether a minimum number of nodes should be required to consider the lymphadenectomy as adequate, since data from randomized studies are lacking (16-19). Benedetti-Panici et al. reported in their randomized clinical trial that systematic lymphadenectomy improves the progression-free survival in women with optimally debulked advanced ovarian carcinoma (20). They supported the concept of therapeutic lymphadenectomy.

For the treatment of early stage cervical cancer, the therapeutic value of lymphadenectomy is also still a matter of debate. Other authors emphasized the possible beneficial effect of removing metastatic lymph nodes, especially when they are bulky (21-27). The aim to remove all accessible lymphatic tissue in the pelvis might also include micrometastases which have a high rate by false-negatives on CT and MRI, and the inaccuracy of intraoperative lymph node palpation (34). Furthermore, the number of removed nodes is underlined by some authors as a matter of quality of the surgery (5;21). Yet, it has never been proven that the removal of nodes itself leads to better survival figures (26).

The aim of the present study is to determine if the number of removed pelvic lymph nodes in radical hysterectomy with pelvic lymphadenectomy (RHL) influences survival of patients with early stage cervical cancer. As it is a clinical impression that the number of reported lymph nodes can depend on several factors, including anatomic differences between patients, variations in local inflammatory parameters, variations in surgical techniques, processing of the specimen and its examination by the pathologist, the second purpose of this study is to examine the association of patient, tumour and treatment characteristics with the number of lymph nodes examined in early stage cervical cancer patients.

Material and Methods

Patient characteristics and study design

Between January 1984 and April 2005, 643 patients with stage I-IIa cervical carcinoma were treated in our centre with RHL. Relevant clinical and pathological parameters of this group were prospectively collected in a database. For the first purpose of this study we used 2 groups: a group with negative nodes (n=503) and a group with positive nodes (n=140).

Patients in our centre received adjuvant radiotherapy if lymph node involvement, parametrial invasion or positive surgical margins were found. Since 1997, patients with at least 2 of the following 3 risk factors also received postoperative radiotherapy: pathological tumour size (≥40mm), depth of invasion (≥ 15 mm) and capillary lymphatic space involvement.

From the group with negative nodes, 143 patients received adjuvant radiotherapy and 5 patients received chemotherapy. These 148 patients were excluded. Twenty patients were excluded because data of the total number of examined lymph nodes were missing, and 4 patients were excluded because an incomplete lymphadenectomy was performed due to various reasons. For the further analysis 331 patients remained (group A).

Para aortic lymph nodes were removed in 4 patients with positive nodes. These patients were excluded from the study, because it has been reported that para aortic node dissection could influence the survival (27;28). For the further analysis 136 patients with positive nodes remained (group B). Hundred thirty one patients received adjuvant radiotherapy and 14 received chemotherapy. In this group 10 patients did not have a complete lymphadenectomy.

To investigate the relationship between patient, tumour and treatment characteristics and the number of removed nodes, we only studied the group of patients with negative lymph nodes (group A), since it has been a former policy to abandon a complete lymphadenectomy when lymph node metastases were found during surgery.

All patients in the study were treated by the same four gynaecologic oncologists (GGK, AAWP, JBT, KNG) during this period. Fifteen percent of the patients in group A and 24% of the patients in group B were referred from Suriname (South America) for their treatment. In all cases a RHL type III was performed (29).

Lymphadenectomy consisted of removal of all the fatty tissue from 6 different stations: along the common iliac vessels until halfway the aortic bifurcation, the external and internal iliac vessels, and the obturator fossa, at both sides. Parametrial nodes were not included in the counting of number of nodes. Para aortic nodes were only removed in case of palpable enlarged nodes or confirmed positive common iliac nodes at frozen section. In the current study there were no para aortic lymph nodes removed in patients of group A and B. The follow-up was closed on April 2005 and ranged from 0 to 223 months for the group with negative nodes and 0 to 220 months for the group with positive nodes. The mean and median duration of follow-up for the group with negative nodes was 57 months and 53

months, respectively; for the group with positive nodes 37 months and 18 months, respectively. The disease free survival (DFS) was defined as the time from RHL to cytologically or histologically proven evidence of recurrent disease or date last seen. Cancer specific survival (CSS) was defined as the time from date of operation to death by tumour or date last seen.

Pathologic examination

Radical hysterectomy specimens were routinely examined. Four µm thick tumour sections of formalin-fixed, paraffin embedded material were stained with haematoxylin and eosin (H&E). The following tumour characteristics were documented: tumour size, histological tumour type, capillary lymphatic space involvement (CLS) and depth of invasion. CLS was considered positive when neoplastic cells were seen within endothelium-lined spaces. The depth of invasion was measured from the most superficial epithelial-stromal interface of the adjacent intra-epithelial process to the lower limits of invasion (30).
At pelvic lymph node dissection the lymph nodes were labeled according to site. After arriving at the department of pathology, the specimens were formalin fixed. The next day, conventional lymph node retrieval technique was performed for each specimen separately, i.e. inspection, palpation, and/or serial sectioning of the resected tissue. Certain (often larger) lymph nodes were measured and sectioned in multiple slides of 2 to 3 mm after which representative samples were embedded. Smaller (possible) lymph nodes were totally embedded. The 4 µm thick sections of formalin-fixed, paraffin embedded material were stained with haematoxylin and eosin (H&E).

Data analysis

The relationship between the number of removed nodes and the survival of patients was examined graphically with the Kaplan-Meier method. The number of nodes was categorized as <10, 10-15, 16-20, 21-25, 26-30 and >30 nodes. We also analyzed the number of lymph nodes examined with a cut-off based on the median number of nodes in the cohort. The Cox regression model was used to determine statistical significance (31;32). Furthermore, the relationship between the following variables; patient age, referral from Surinam, postmenopausal status, conisation before surgery, tumour size, infiltration depth, CLS and the number of removed lymph nodes was investigated by using univariate and multivariate linear regression models. The parameter of Surinam origin of the patients was included because historically patients with cervical cancer from Surinam (SA) are referred to the Leiden University Medical Centre for treatment. These patients have a different ethical origin as compared to the Dutch patients. The number of removed nodes was regarded as a normally distributed continuous variable in the linear regression models, because a histogram showed an almost normal distribution. Statistical significance was assigned at a level of $p<0.05$.

Results

Number of lymph nodes

The mean age at the time of the operation among the patients with negative lymph nodes (group A) was 43.3 years (SD 11.5) (Range 21-82 years) in contrast to the patients with positive lymph nodes (group B) who had a mean age of 47.0 years (SD 13.6) (Range 25-80 years). The clinical and histological characteristics of the 2 groups of patients with early stage cervical cancer are listed in Table 1. In group A the median number of lymph nodes examined was 19 (mean, 19.90; SD, 8.16) with a range of

Characteristics	Group A (n=331) n	Group B (n=136) n
Age		
<40	148	51
≥40	183	85
Mean	43.3	47.0
Minimum	21	25
Maximum	82	80
SD	11.5	13.6
Tumour size		
≥40mm	35	63
<40mm	233	61
Unknown	63	12
Maximum	70	110
Minimum	0	0
Mean	19.2	42
Depth of invasion		
≥15mm	44	76
<15mm	27	55
Unknown	13	5
Maximum	25	65
Minimum	0	0
Mean	6.4	16
CLS		
Positive	52	95
Negative	25	31
Unknown	29	10
Referred from Surinam		
Yes	48	32
No	283	104
Postmenopausal		
Yes	65	42
No	266	94
Conisation		
Yes	109	11
No	222	125

Table 1. Clinical and histological characteristics of the patients with early stage cervical cancer, node negative (group A) and node positive (group B).

4-53. The median number of lymph nodes examined in group B was 18 (mean, 17.47; SD, 7.91) with a range of 1-38. The number of examined lymph nodes in both groups followed a normal distribution. Table 2 shows the number of examined nodes in both groups categorized into 6 groups.

Number of removed lymph nodes (analysis groups)	**Group A (n=331) n**	**Group B (n=136) n**
<10	22	23
10-15	85	35
16-20	83	30
21-25	73	26
26-30	33	17
>30	35	5

Table 2. Number of removed nodes in patients with negative lymph nodes (group A) and positive lymph nodes (group B), categorized into 6 analysis groups.

Negative lymph nodes and prognosis

Overall, the CSS and DFS of the patients with negative nodes did not differ between the 6 analysis groups. Also there was no difference in the CSS and the DFS between the group with less than 19 removed lymph nodes and the group with 19 or more removed lymph nodes. The Cox regression model did not show a significant relationship between the number of removed lymph nodes and the CSS or DFS (p=0.625 and p=0.877, respectively).

Positive lymph nodes and prognosis

The number of removed lymph nodes in patients with positive nodes was positively correlated with a better DFS (p=0.014). Figure 1 shows the DFS curves for the 6 analysis groups of patients with positive nodes. The DFS curves of the group less than 18 removed lymph nodes and the group with 18 or more removed lymph nodes are shown in Figure 2. The Cox regression model did not show a significant relationship between the number of examined lymph nodes and CSS (p=0.084). The number of removed positive nodes for these patients is listed in Table 3. The number of positive nodes was positively correlated with a better CSS (p=0.017) and DFS (p=0.048).

Number of removed positive lymph nodes	**Group B n**
1	65
2	30
3	21
4-14	20

Table 3. Number of removed positive nodes in patients with positive lymph nodes (group B).

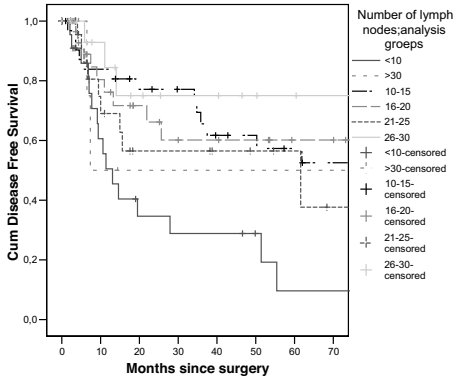

Figure 1. Disease free survival of the categorized 6 analysis groups, of patients with positive lymph nodes (Group B).

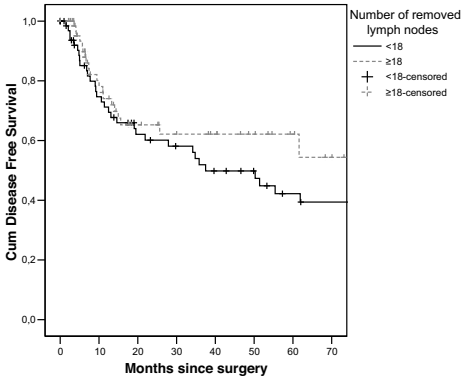

Figure 2. Disease free survival of the 2 groups with a cut-off based on the median number of removed nodes, in patients with positive lymph nodes (Group B).

Relationship between several factors and the number of lymph nodes examined

To evaluate a possible relationship between several patient and tumour characteristics and the number of examined lymph nodes, we used the patients of group A, with negative lymph nodes (n=331). The univariate and multivariate linear regression models using the variables patient age, referral from Surinam, postmenopausal status, conisation before surgery, tumour size, infiltration depth and CLS, did not show that any of these factors were associated with the number of examined lymph nodes.

Discussion

The role of the number of removed pelvic lymph nodes after RHL for the treatment of early stage cervical cancer was evaluated for patients with negative and positive lymph nodes. Furthermore, the association of different factors with the number of lymph nodes was examined.

The strength of the current study is the fact that a prospective database and a consecutive series of patients were used. Furthermore, all patients were treated by the same group of gynaecologic oncologists.

The therapeutic value of removing lymph nodes, especially when they are bulky, has been reported by different authors (21-27;33). However, the number of removed lymph nodes in the quality control of the surgical treatment of early stage cervical cancer has never been evaluated before. The hypothesis that removal of a larger number of regional nodes in patients with breast cancer improves survival is nowadays strongly supported by both prospective randomized trials and multiple retrospective stud-

ies of large groups of women (9-15). This may be explained as being due to understaging caused by examination of too few lymph nodes (more likely for node-negative patients) or as a real association between the extent of the dissection and improved disease control (more likely for node-positive patients) (34).

From the present study of patients with negative as well as positive nodes, it can be concluded that a large variability in the number of lymph nodes exists. Despite this finding, there was no evidence that a higher number of examined lymph nodes lead to better survival figures for patients with negative lymph nodes. Thus the explanation of a possible relation between the number of examined nodes and survival caused by examination of too few lymph nodes (understaging) could not be confirmed for these patients. In contrast, the current study did show an association between the extent of the dissection and a better disease control, as a larger number of removed lymph nodes prolonged the DFS for patients with positive lymph nodes. However, the improvement in DFS was not translated into an improvement in CSS. One possible explanation for this might be that the follow-up has been too short and a longer period might be needed before long-term survival values are definitive.

The large variability in the number of examined lymph nodes is difficult to explain. The stable group of surgeons does not seem to have impact on the extent of the surgery, which might lead to variable numbers of removed nodes. One explanation could be the fact that the number of reported nodes may not reflect the number of removed nodes. Total node count is not only a reflection of completeness of lymphadenectomy, but is also dependent on the pathologist's evaluation of the surgical specimen. Total node count and thorough evaluation of all lymph nodes in the specimen are depending on the pathologist's macroscopic evaluation, and are therefore subject to bias. In our centre, the conventional lymph node retrieval technique was used embedding all large and easily recognized lymph nodes. If a structure was not a lymph node by inspection or palpation, it was embedded completely, reducing the risk to leave any lymph node in the fatty tissue. Hereby the pathologist's bias was reduced to a minimal. Compared with other studies, the median number of removed nodes in the current study is somewhat lower (1;2;28;35;36). The reason for this difference might be that in our study parametrial nodes were not included in the number of nodes and para aortic nodes were not removed in the patients of this study. Furthermore, 10 patients of the group with positive nodes did not undergo a complete lymphadenectomy, as the procedure was aborted in view of subsequent radiation.

Surgery is still the most important treatment variable in most solid cancers and its impact has been emphasized in past decades. A better control of the quality of surgical procedures in oncology is possible and may have a major impact on outcomes of cancer patients (37).

This is the first study that has evaluated the number of removed lymph nodes in the quality control of the surgical treatment of early stage cervical cancer and the possible association of different factors with the number of lymph nodes examined. In a previous analysis we reported on the effect on survival of pelvic lymphadenectomy of 294 patients with early stage cervical cancer treated by RHL (26). Patients with positive nodes and with complete lymphadenectomy (n=23) had significantly less

recurrences compared to patients with positive nodes with incomplete lymphadenectomy (n=40). The complete lymphadenectomy showed an independent beneficial effect on the DFS. The findings of the current study are in line with the results of this previous analysis (26).

Until the results of other trials are known, the outcome of the present study suggests that there is no relation between the number of tumour negative nodes examined after a RHL for the treatment of early stage cervical cancer and CSS or DFS. However, the number of examined lymph nodes leads to better DFS figures for patients with positive lymph nodes. This suggests that patients with early stage cervical cancer with positive lymph nodes benefit from a sufficient number of removed lymph nodes. And because on forehand, one does not know whether the removed pelvic lymph nodes will be positive or negative, the most important clinical consequence of the present study is that one should complete the lymphadenectomy when frozen section reveals lymph node involvement during RHL.

References

(1) Girardi F, Pickel H, Winter R. Pelvic and parametrial lymph nodes in the quality control of the surgical treatment of cervical cancer. Gynecol Oncol 1993; 50:330-333.

(2) Girardi F, Haas J. The importance of the histologic processing of pelvic lymph nodes in the treatment of cervical cancer. Int J Gynecol Cancer 1993; 3:12-17.

(3) Baltzer J, Kopcke W, Lohe KJ, Kaufmann C, Ober KG, Zander J. [Surgical treatment of cervix cancer. Treatment results and data on the postoperative course over a minimum of 5 years following uniform surgery and standardized histological examination of the histological material of 1092 patients at 4 university gynecology clinics]. Geburtshilfe Frauenheilkd 1984; 44:279-285.

(4) Ketcham AS, Hoye RC, Taylor PT, Deckers PJ, Thomas LB, Chretien PB. Radical hysterectomy and pelvic lymphadenectomy for carcinoma of the uterine cervix. Cancer 1971; 28:1272-1277.

(5) Kjorstad KE, Kolbenstvedt A, Strickert T. The value of complete lymphadenectomy in radical treatment of cancer of the cervix, Stage IB. Cancer 1984; 54:2215-2219.

(6) 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; 156:988-996.

(7) Delgado G, Bundy BN, Fowler WC, Jr., Stehman FB, Sevin B, Creasman WT et al. A prospective surgical pathological study of stage I squamous carcinoma of the cervix: a Gynecologic Oncology Group Study. Gynecol Oncol 1989; 35:314-320.

(8) Kenter GG, Ansink AC, Heintz AP, Delemarre J, Aartsen EJ, Hart AA. Low stage invasive carcinoma of the uterine cervix stage I-IIA morphological prognostic factors. Eur J Surg Oncol 1988; 14:187-192.

(9) Krag DN, Single RM. Breast cancer survival according to number of nodes removed. Ann Surg Oncol 2003; 10:1152-1159.

(10) Tepper JE, O'Connell MJ, Niedzwiecki D, Hollis D, Compton C, Benson AB, III et al. Impact of number of nodes retrieved on outcome in patients with rectal cancer. J Clin Oncol 2001; 19:157-163.

(11) Chan AD, Essner R, Wanek LA, Morton DL. Judging the therapeutic value of lymph node dissections for melanoma. J Am Coll Surg 2000; 191:16-22.

(12) Fisher B, Redmond C, Fisher ER, Bauer M, Wolmark N, Wickerham DL et al. Ten-year results of a randomized clinical trial comparing radical mastectomy and total mastectomy with or without radiation. N Engl J Med 1985; 312:674-681.

(13) Harris JR, Osteen RT. Patients with early breast cancer benefit from effective axillary treatment. Breast Cancer Res Treat 1985; 5:17-21.

(14) Johansen H, Kaae S, Schiodt T. Simple mastectomy with postoperative irradiation versus extended radical mastectomy in breast cancer. A twenty-five-year follow-up of a randomized trial. Acta Oncol 1990; 29:709-715.

(15) Cabanes PA, Salmon RJ, Vilcoq JR, Durand JC, Fourquet A, Gautier C et al. Value of axillary dissection in addition to lumpectomy and radiotherapy in early breast cancer. The Breast Carcinoma Collaborative Group of the Institut Curie. Lancet 1992; 339:1245-1248.

(16) Creutzberg CL. Lymphadenectomy in apparent early-stage endometrial carcinoma: do numbers count? J Clin Oncol 2005; 23:3653-3655.

(17) Kilgore LC, Partridge EE, Alvarez RD, Austin JM, Shingleton HM, Noojin F, III et al. Adenocarcinoma of the endometrium: survival comparisons of patients with and without pelvic node sampling. Gynecol Oncol 1995; 56:29-33.

(18) Vizza E, Galati GM, Corrado G, Sbiroli C. Role of pelvic lymphadenectomy in the management of stage I endometrial cancer: our experience. Eur J Gynaecol Oncol 2003; 24:126-128.

(19) Cragun JM, Havrilesky LJ, Calingaert B, Synan I, Secord AA, Soper JT et al. Retrospective analysis of selective lymphadenectomy in apparent early-stage endometrial cancer. J Clin Oncol 2005; 23:3668-3675.

(20) Panici PB, Maggioni A, Hacker N, Landoni F, Ackermann S, Campagnutta E et al. Systematic aortic and pelvic lymphadenectomy versus resection of bulky nodes only in optimally debulked advanced ovarian cancer: a randomized clinical trial. J Natl Cancer Inst 2005; 97:560-566.

(21) Hacker NF, Wain GV, Nicklin JL. Resection of bulky positive lymph nodes in patients with cervical carcinoma. Int J Gynecol Cancer 1995; 5:250-256.

(22) Morice P, Castaigne D, Pautier P, Rey A, Haie-Meder C, Leblanc M et al. Interest of pelvic and paraaortic lymphadenectomy in patients with stage IB and II cervical carcinoma. Gynecol Oncol 1999; 73:106-110.

(23) Downey GO, Potish RA, Adcock LL, Prem KA, Twiggs LB. Pretreatment surgical staging in cervical carcinoma: therapeutic efficacy of pelvic lymph node resection. Am J Obstet Gynecol 1989; 160:1055-1061.

(24) Hirabayashi K. Individualization of postoperative irradiation in the treatment of stage I and II cervical cancer. Baillieres Clin Obstet Gynaecol 1988; 2:1013-1022.

(25) Potish RA, Downey GO, Adcock LL, Prem KA, Twiggs LB. The role of surgical debulking in cancer of the uterine cervix. Int J Radiat Oncol Biol Phys 1989; 17:979-984.

(26) Kenter GG, Hellebrekers BW, Zwinderman KH, van d, V, Peters LA, Trimbos JB. The case for completing the lymphadenectomy when positive lymph nodes are found during radical hysterectomy for cervical carcinoma. Acta Obstet Gynecol Scand 2000; 79:72-76.

(27) Cosin JA, Fowler JM, Chen MD, Paley PJ, Carson LF, Twiggs LB. Pretreatment surgical staging of patients with cervical carcinoma: the case for lymph node debulking. Cancer 1998; 82:2241-2248.

(28) Benedetti-Panici P, Maneschi F, Cutillo G. Pelvic and aortic lymphadenectomy. Surg Clin North Am 2001; 81:841-858.

(29) Piver MS, Rutledge F, Smith JP. Five classes of extended hysterectomy for women with cervical cancer. Obstet Gynecol 1974; 44:265-272.

(30) Crum CP, Lee KR. Diagnostic Gynecologic and Obstetric Pathology. 1 ed. Amsterdam: Elsevier, 2006.

(31) Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 1966; 50:163-170.

(32) Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53:457-481.

(33) Hockel M, Horn LC, Fritsch H. Association between the mesenchymal compartment of uterovaginal organogenesis and local tumour spread in stage IB-IIB cervical carcinoma: a prospective study. Lancet Oncol 2005; 6:751-756.

(34) Petrik DW, McCready DR, Sawka CA, Goel V. Association between extent of axillary lymph node dissection and patient, tumor, surgeon, and hospital factors in patients with early breast cancer. J Surg Oncol 2003; 82:84-90.

(35) Benedetti-Panici P, Maneschi F, Scambia G, Greggi S, Cutillo D, D'Andrea G. et al. Lymphatic spread of cervical cancer:An anatomical and pathological study based on 225 radical hysterectomies with systemic pelvic and aortic lymphadenectomy. Gynecol Oncol 1996; 62:19-24.

(36) Trimbos JB, Franchi M, Zanaboni F, Velden J, Vergote I. 'State of the art' of radical hysterectomy; current practice in European oncology centres. Eur J Cancer 2004; 40:375-378.

(37) Landheer ML, Therasse P, van de Velde CJ. The importance of quality assurance in surgical oncology. Eur J Surg Oncol 2002; 28:571-602.