The extent of aortic lymphadenectomy in locally advanced cervical cancer impacts on survival

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ABSTRACT

Objective: The prognostic impact of surgical paraaortic staging remains unclear in patients with locally advanced cervical cancer (LACC). The objective of our study was to evaluate the results of the surgical technique of preoperative aortic lymphadenectomy in LACC related to tumor burden and disease spread to assess its influence on survival.

Methods: Data of 1,072 patients with cervical cancer were taken from 11 Spanish hospitals (Spain-Gynecologic Oncology Group [GOG] working group). Complete aortic lymphadenectomy surgery (CALS) was considered when the lymph nodes (LNs) were excised up to the left renal vein. The extent of the disease was performed evaluating the LNs by calculating the geometric means and quantifying the log odds between positive LNs and negative LNs. The Kaplan-Meier method was used to estimate the survival distribution. A Cox proportional hazards model was used to account for the influence of multiple variables.

Results: A total of 394 patients were included. Pathological analysis revealed positive aortic LNs in 119 patients (30%). LODDS cut-off value of −2 was established as a prognostic indicator. CALS and LODDS <−2 were associated with better disease free survival and overall survival than suboptimal aortic lymphadenectomy surgery and LODDS ≥−2. In a multivariate model analysis, CALS is revealed as an independent prognostic factor in LACC.

Conclusion: When performing preoperative surgical staging in LACC, it is not advisable to take simple samples from the regional nodes. Radical dissection of the aortic and pelvic regions offers a more reliable staging of the LNs and has a favorable influence on survival.

Keywords: Cervical Cancer; Survival Rate; Disease-Free Survival; Lymph Node Excision; Lymphatic Metastasis

INTRODUCTION

Cervical cancer spreads primarily to regional lymph nodes (LNs) [1]. Recently, the International Federation of Gynecology and Obstetrics (FIGO) of 2018 has modified the
staging of cervical cancer, including the LN status in the classification system that currently assigns patients with positive pelvic LN stage IIIC1 and women with aortic LN disease as stage IIIC2 [2].

Frequently, patients with cervical cancer are diagnosed in a locally advanced stage (FIGO IIA2-IVA and IB3). In these patients, the standard and most effective treatment is concomitant chemotherapy and pelvic radiotherapy. Aortic LN involvement is observed in 17%–24% of patients with locally advanced cervical cancer (LACC) [3].

Determination of aortic LN status is essential for planning the irradiation field in cases of LACC to avoid unnecessary irradiation and decrease associated morbidity [4].

The previous data justify the need to identify patients who present with aortic LN metastases, and are therefore tributary to receive treatment with extended field external radiotherapy in that region. However, a discussion about the best way to assess aortic LN status in patients with LACC remains open. Imaging studies, especially positron emission tomography-computed tomography (PET-CT), are less invasive but have low sensitivity for evaluation of aortic LN [5].

On the other hand, surgical staging is much more aggressive, although it provides more reliable information on the status of the aortic nodes. The prognostic and therapeutic value of paraaortic surgical staging remains unclear in patients with LACC, and there are some discrepancies in the scientific literature regarding this topic [6].

However, the risk of recurrence of other solid tumors according to the LN status suggests that the patient's prognosis or tumor recurrence may be influenced, not only by the nodal status in the paraaortic region, but also by the tumor burden in the LN, the number of positive or the location [7,8].

The number of regional nodes varies from one individual to another; therefore, it can lead to confusion. Underestimating the number of LN metastasis is a significant weakness of the staging system for cervical cancer. In an attempt to reduce this confusion, we have related the affected nodes with the volume of nodal disease through the log odds of positive LNs (LODDS).

The so-called LODDS, that is, the natural logarithm of odds between the number of positive and negative LNs, has also been described as a better discriminant prognostic factor than the simple positive LN count in some gastrointestinal cancers [9].

More recently, a LODDS major of −1.05 was defined as a dangerous independent prognostic indicator for disease free survival (DFS) in high-risk patients who underwent radical surgery followed by adjuvant treatment in cervical cancer. Among the various methods used for assessment of LN status, LODDS was the most powerful predictor associated with both, recurrence and overall survival (OS), as they are more discriminatory than the number of metastatic LNs to predict OS in cervical cancer with positive nodes (LODDS considers the tumor burden or the extent of the lymphadenectomy) [10].

Both pelvic and aortic surgical lymphadenectomies are performed to achieve better staging of the LN stage in cervical cancer. Furthermore, it allows reducing the extent of the therapeutic radiation field [11-13].
There is no evidence about which is the most appropriate technique to perform such lymphadenectomy—LN sampling or radical dissection—or whether finally, it has any influence on survival [14-16].

In this study, we evaluated the surgical technique of preoperative aortic lymphadenectomy in the LCC related to tumor burden and the extent of the disease to assess its influence on survival. In this context, a multicentric retrospective registry was carried out in a cohort of patients with (LACC), uniformly treated in specialized cancer units in tertiary hospitals in Spain (Spain-Gynecologic Oncology Group [GOG] working group).

**MATERIALS AND METHODS**

Data from patients with LACC from 11 Spanish hospitals with a high volume of gynecological cancers (Spain-GOG working group) were analyzed.

From 2000 to 2016 all cases were analyzed retrospectively after receiving Institutional Board approval of the Vall d’Hebron Universitari Campus Hospital (PR AMI 159/2015). For the purpose of this study, the cases in which the data on the surgical technique were completely filled were selected. At admission, we obtained an informed consent allowing the use of clinical data for research purposes from every patient included in the study.

LACC was defined as patients with at least stage IB2, according to the latest 2009 FIGO classification. Exclusion criteria were: patients with stage IVB, patients treated by radiotherapy only, and patients with missing data for surgical staging.

The clinical LN stage was studied by magnetic resonance imaging (MRI) and/or PET-CT. Any nodular image on the MRI with a size greater than 10 mm was considered suspicious for infiltration. In PET-CT studies, focal areas of abnormal uptake of F-18 fluorodeoxyglucose (FDG) were assessed qualitatively, with non-detectable FDG uptake defined as negative, and assessed as positive when there was a moderate uptake with a marked increase in absorption in relation surrounding tissues.

The kind of treatment applied to these patients was decided by each center within a multidisciplinary oncology committee considering the characteristics of the patient and the tumor.

During surgical paraaortic staging, all nodes from the bifurcation of the aorta to the left renal vein were removed. Pelvic lymphadenectomy was only performed when enlarged nodes were found on preoperative imaging tests. Complete aortic lymphadenectomy surgery (CALS) was defined as a complete and radical paraaortic dissection up to the left renal vein, and suboptimal aortic lymphadenectomy surgery (SALS) when only a sampling of the paraaortic or pelvic ganglia was performed. Minimally invasive surgery, laparoscopic, or robotic, was used in all patients at the surgeon’s discretion and according to the availability of resources.

All patients were subsequently treated by chemoradiotherapy and received external pelvic radiotherapy at the total dose of 45 Gy (25 fractions) in 5 weeks with a concomitant weekly basis of 40 mg/m² of Cisplatin. They also received intracavitary brachytherapy (30 Gy) to complete external pelvic radiotherapy.
Follow-up of patients was made under the discretion of each center. Generally, with gynecological explorations every 6 months, and with imaging test at least every 12 months. The surgery date was used to calculate DFS and OS.

LODDS was defined as: $\log \left( \frac{\text{Number of positive LN retrieved} + 0.5}{\text{Number of total LN retrieved} - \text{Number of positive LN retrieved} + 0.5} \right)$. The LODDS, considering both the number of positive LN and the number of negative LN retrieved in the lymphadenectomy, relate the extent of the lymphadenectomy and the burden of LN involvement.

1. Statistical analysis

The Geometric mean, due to their mathematical characteristics, is more representative than the arithmetic means when there are very extreme values in the variables as it happens with the number of dissected LNs, since the influence of the most extreme values of both the highest and the lowest decreases [17].

For all these reasons, we considered that the geometric mean of the number of dissected nodes (total, aortic, and pelvic) is an excellent approximation to the advisable number of nodes to dissect in the lymphadenectomy of each area, in cases where optimal surgery has been performed.

A cumulative sum (CUSUM) control chart of expected minus observed deaths was used between the value of the LODDS on a continuous scale and the vital status—alive or dead—to determine the optimal cut-off point for the LODDS variable [18].

Inferential statistical analysis was based on the Mann-Whitney test for continuous variables and the $\chi^2$ test or Fisher’s exact test for categorical variables. The Kaplan-Meier method was used to estimate the OS distribution. Comparisons of survival were made using the log-rank test. A Cox regression was performed, including possible confounding factors for OS and the type of lymphadenectomy performed. Values of $p<0.05$ were considered to denote significant differences. Statistical analysis was performed using Stata Statistical Software Release 16 (StataCorp LLC, College Station, TX, USA).

RESULTS

From 2000 to 2016, 1,072 patients were treated for LACC in our institutions. Among them, 634 had undergone surgical staging, but only 394 had complete surgical records and met the inclusion criteria. The patients’ main clinicopathological characteristics can be seen in Table 1.

CUSUM chart obtained for LODDS was monotonic, indicating that the higher the LODDS, the more deaths in the follow-up, with the prognostic cut at −2 (best prognosis below −2). Thus, a cut-off value of −2 was established as a prognostic indicator (Fig. 1).

The median age of patients at diagnosis was 50 years (range, 24 to 79 years). Most FIGO patients were IIb (53%), and the most common histology was squamous cell carcinoma (82.8%) and adenocarcinoma (15.8%). There were no FIGO IVB patients.

The characteristics of the surgical LN retrieved are shown in Table 2. The total number of LN recovered was 7,238, and 766 (11%) were N1. The 171 (43%) of patients were N1; 119 (30%) of
patients have positive aortic LN; 92 (56%) of patients undergoing pelvic lymphadenectomy had positive pelvic LN. The median of positive LN in the aortic region was 2 (range, 0–31). Regarding the distribution of the aortic region, the aortic supramesenteric region, although a smaller number of LN was retrieved, a high number of positive LN were found (10%). In these series, the negative predictive value of imaging tests for aortic supramesenteric LN was 89%, 93% for aortic inframesenteric LN, and 50% for pelvic LN. These outcomes indicate that a negative image of LN involvement is only reliable for the aortic supramesenteric and inframesenteric region, but no for the pelvic region. The low positive predictive values of the imaging tests for aortic supramesenteric, aortic inframesenteric, and pelvic LN, were 25%; 16%; 56%, respectively. These values indicate that a positive image is not trustworthy for any region due to the high number of false positives.
Moreover, in 18% of LN retrieved, skip metastasis to the aortic supramesenteric region was found without the involvement of the aortic inframesenteric LNs. Similarly, 6.7% of positive aortic LNs and 3% in the supramesenteric region were found without pelvic LN in those cases where a pelvic lymphadenectomy was performed.

The geometric mean values of the total number of LNs retrieved are shown in Supplementary Table 1 as an indicator of the advisable extent of lymphadenectomy in patients that received complete lymphadenectomy in LACC.

![CUSUM chart](image)

Fig. 1. CUSUM chart obtained for LODDS.

CUSUM, cumulative sum; LODDS, log odds of positive lymph nodes.

| Characteristics                  | Total (n=394) | SALS (n=11) | CALS (n=383) | p-value |
|----------------------------------|--------------|-------------|--------------|---------|
| LODDS total LN retrieved        | −2.0±1.5     | −1.0±2.3    | −2.0±1.5     | 0.002   |
| LODDS total LN cut-off ≤−2      |              |             |              | 0.049   |
|                                 | 283 (71.8)   | 5 (45.5)    | 278 (72.6)   |         |
|                                 | 111 (28.2)   | 6 (54.5)    | 105 (27.4)   |         |
| Total No. of LN retrieved       | 17 (1–83)    | 15 (3–30)   | 17 (1–83)    | 0.310   |
| Total No. of positive LN retrieved | 1 (0–1) | 0 (0–1) | 1 (0–1) | 0.280   |
| Total LN status (pN)            |              |             |              | 0.047   |
| Negative                        | 223 (56.6)   | 3 (27.3)    | 220 (57.4)   | <0.001  |
| Positive                        | 171 (43.4)   | 8 (72.7)    | 163 (42.6)   |         |
| LODDS aortic LN                 | −2.0±1.5     | −1.0±2.3    | −3.0±1.5     | 0.030   |
| LODDS aortic LN cut-off ≤−2     |              |             |              |         |
|                                 | 291 (73.9)   | 5 (45.5)    | 286 (74.7)   |         |
|                                 | 103 (26.1)   | 6 (54.5)    | 97 (25.3)    |         |
| Total No. of aortic LN retrieved | 13 (1–53) | 10 (3–28) | 13 (1–53) | 0.110   |
| Total No. of aortic positive LN retrieved | 0 (0–31) | 2 (0–8) | 0 (0–31) | 0.200   |
| Aortic LN status (pN)           |              |             |              | 0.075   |
| No                              | 275 (69.8)   | 5 (45.5)    | 270 (70.5)   |         |
| Yes                             | 119 (30.2)   | 6 (54.5)    | 113 (29.5)   |         |
| LODDS pelvic LN                 | −2.0±1.4     | −1.0±1.9    | −2.0±1.4     | 0.510   |
| Total No. of pelvic LN retrieved | 9 (1–31)    | 14 (2–20)   | 9 (1–31)     | 0.410   |
| Total No. of pelvic positive LN retrieved | 1 (0–18) | 2 (1–3) | 1 (0–18) | 0.840   |
| Pelvic LN status (pN)           |              |             |              | 0.075   |
| Negative                        | 71 (43.6)    | 0           | 71 (44.7)    |         |
| Positive                        | 92 (56.4)    | 4 (100)     | 88 (55.3)    |         |

Values are presented as mean±standard deviation, number (%) or median (minimum–maximum).

CALS, complete aortic lymphadenectomy surgery; LN, lymph node; LODDS, log odds of positive lymph nodes; SALS, suboptimal aortic lymphadenectomy surgery.
There were 16 (4.2%) and 39 (10.2%) patients with intra and postoperative complications, respectively. The most frequent intraoperative complications were hemorrhagic accidents mainly at the ports of entry in the abdominal wall and occasionally accidental injuries of major vessels. The majority of cases of postoperative complications consisted in the appearance of lymphocysts in first place and ureteral lesions in second place. No postoperative mortality was observed.

1. Analysis of survival

Medians OS for CALS and SALS were 18 and 139 months, respectively (Fig. 2). Medians OS for aortic LODDS minor of −2, and equal or major of −2, were 161 and 36 months, respectively.

Mean follow-up was 57.3 months (95% CI=52.5–62.2). During follow-up 157 patients (39.8%) died. One hundred and twenty-six patients experience recurrence during follow-up. CALS and LODDS <−2 were associated with better DFS and OS than SALS and LODDS ≥−2 (Table 3).

Table 4 describes the multivariate Cox regression, where the extension of preoperative aortic lymphadenectomy is shown as an independent prognostic factor in LACC.

![Fig. 2. Medians OS for CALS and SALS (p log-rank=0.003).](https://ejgo.org)

CALS, complete aortic lymphadenectomy surgery; OS, overall survival; SALS, suboptimal aortic lymphadenectomy surgery.

| Characteristics         | 12 mo | 24 mo | 36 mo | 48 mo | 60 mo |
|-------------------------|-------|-------|-------|-------|-------|
| % OS complete surgery*  | 94    | 81    | 70    | 66    | 60    |
| % OS no-optimal         | 55    | 45    | 45    | 36    | 36    |
| % DFS complete surgery† | 88    | 75    | 70    | 68    | 65    |
| % DFS no-optimal        | 88    | 74    | 59    | 59    | 59    |
| % OS LODDS <−2‡         | 94    | 85    | 76    | 73    | 68    |
| % OS LODDS ≥−2          | 87    | 68    | 51    | 44    | 39    |
| % DFS LODDS <−2§        | 88    | 80    | 75    | 72    | 70    |
| % DFS LODDS ≥−2         | 88    | 59    | 55    | 53    | 50    |

DFS, disease free survival; LODDS, log odds of positive lymph nodes; OS, overall survival.

*p=0.003; †p=0.33; ‡p<0.001; §p=0.001.
Our study describes the extent of lymphadenectomy as an independent prognostic factor in patients with LACC. Patients with CALS have a reduction in the risk of disease progression or death of 63%.

As mentioned in the introduction, the debate about LN assessment is still open. Our results demonstrate kind of confusion in the preoperative imaging, mostly CT scan and PET-CT, in the initial assessment of tumor spread to the aortic region, due to the high rates of false-positive LN retrieved. This fact coincides with other authors who reported similar results [19].

False-negative rates for PET CT in the aortic LN in patients with LACC have been reported as high as 13% with low sensitivity [20]. This coincides with our results, where a rate of 10% was obtained.

Contrarily, surgical aortic LN staging reveals a more realistic status of the aortic LN, as reveals the little concordance that generally exists between imaging tests and the most real LN stage obtained thanks to surgery.

One of the questions to be answered is the worth of performing a radical lymphadenectomy or a simply sampling, which we call suboptimal lymphadenectomy. Some authors reported a survival benefit in salvage and radical aortic lymphadenectomy either in recurrence or in surgical staging with negative imaging preoperative test [21,22]. In that line, our data demonstrate that a radical lymphadenectomy up to the renal vein improves both DFS and OS.

In rare cases, paraaortic LNs may be directly involved. A posterior cervical lymphatic trunk may drain lymph directly from the cervix into the paraaortic nodes, or rare cases of fusion between the cervical and uterine lymphatics may result in nodal metastases skipping to the L4 region via the gonadal vessels. Tumor emboli from the cervix can also reach the subaortic nodes directly via a posterior route [23-25].

| Characteristics                  | HR   | 95% CI      | p-value |
|----------------------------------|------|-------------|---------|
| Lymphadenectomy                  |      |             |         |
| Complete                         | 0.37 | 0.17–0.81   | 0.01    |
| No-optimal (reference)           | 1.00 |             |         |
| Grouped FIGO stage               |      |             |         |
| II                               | 1.43 | 0.88–2.33   | 0.15    |
| III                              | 1.72 | 0.94–3.15   | 0.08    |
| IV                               | 2.30 | 0.52–10.08  | 0.27    |
| I (reference)                    | 1.00 |             |         |
| Histology                        |      |             |         |
| Adenocarcinoma                   | 1.61 | 1.01–2.55   | 0.04    |
| Others                           | 0.62 | 0.35–2.54   | 0.51    |
| Squamous (reference)             | 1.00 |             |         |
| Histologic grade                 |      |             |         |
| G2                               | 1.52 | 0.53–4.40   | 0.44    |
| G3                               | 2.31 | 0.81–6.60   | 0.12    |
| Unknown                          | 1.65 | 0.57–4.79   | 0.35    |
| G1 (reference)                   | 1.00 |             |         |
| Size long axis (mm)              | 1.00 | 0.99–1.01   | 0.65    |
| Age                              | 1.01 | 1.00–1.02   | 0.33    |
| Body mass index (kg/m²)          | 1.01 | 0.98–1.04   | 0.54    |

CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio.
In our data, we found nodal jumps from the inframesenteric zone or pelvis to the supramesenteric zone, 18% and 6.7%, respectively. In these cases, surgical aortic staging would also have a beneficial effect by acting as cytoreduction surgery in these cases, although these rates are not line with previous literature where the possibility of skipping metastasis to the supramesenteric region is rare [26].

However, the minimum number of LN that should be harvested to qualify a lymphadenectomy as “adequate” is still a matter of debate. The harvest of the LN retrieved from the aortic region is not well defined in the literature range from 3 to 20 LN in the aortic area [27,28]. In our opinion, the geometric mean of LN retrieved is the best approximation to the ideal number of LN to be retrieved in a CALS when there is absence of more evidence.

In most solid tumors, LN stages are classified according to the number of pathologic nodes found in the different regions and are generally well correlated with the prognosis. In this way, many groups have tried to assess the LN involvement of cervical cancer and its implication in the prognosis. Some authors noted the negative impact of 2 or more LN on survival after adjuvant radiotherapy, noting the importance of the location of positive LN, and showed that metastasis in higher LN was associated with a higher incidence of distant metastases (50% vs. 16%) [29,30].

The efficacy of LODDS in gastric and colorectal cancer has already been reported in large-scale studies, and Calero et al. [9] demonstrated the prognostic superiority of LODDS to classical LN staging. LODDS is a parameter that requires complex calculations and is less intuitive than the FIGO classification for cervical cancer. However, the strength of LODDS lies in their ability to discriminate patients with an equal LN stage by relating tumor burden to the number of LNs retrieved and thus distinguishes the different prognosis between patients with the same stage N, especially when there are no positive nodes.

Our data shows that a LODDS value major of −2 has a significantly higher risk of disease recurrence, specifically DFS, as well as worse OS. In the same line, Kwon et al. [10] found LODDS to be the strongest predictor for both recurrence and survival among the various methods used to assess LN status.

The indication for preoperative LN surgical staging in LACC is still controversial. The only prospective randomized study was conducted by Lai et al. [31] and concluded that there was no difference in DFS and OS between clinical and surgical staging. However, this study received much criticism for its design in which the compared groups were not homogeneous, and the study ended abruptly without reaching the primary endpoint. In the same line, our group (Spain-GOG working group), in a recent publication [13], has not been able to demonstrate an impact on survival for surgical staging compared to clinical ones. However, some other retrospective studies have found it [1]. On the other hand, the ongoing prospective study Lymphadenectomy in Locally Advanced Cervical Cancer Study (LiLACS) by Frumovitz et al. [32] should provide us with answers to all these questions. Meanwhile, our data demonstrate that in case of deciding to perform a preoperative aortic lymphadenectomy, it should be entirely up to renal vein since the extension of the lymphadenectomy has a favorable effect on the survival of patients with LACC.

This study has several limitations, such as the retrospective nature of the study or the absence of pre-established uniform protocol to manage these patients. Also, the small group sample
size in which LN sampling was performed. However, despite this, the comparison with the
group subjected to radical dissection offers sufficient statistical power. On the other hand,
the strengths of this study should be its multicenter nature and its ability to show a way of
managing the LACC of tertiary hospitals in Spain over a long period.

It can be concluded that when the surgical staging of the LN status in LACC is undertaken,
simple sampling of the regional nodes is not advisable. Radical dissection of the aortic and
pelvic regions offers more reliable LN staging and has a favorable influence on survival.
Overall, there is a moderate concordance between imaging tests and actual LN status.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1
Geometric mean values of total number of lymph nodes retrieved in patients with optimal
aortic lymphadenectomy surgery

Click here to view

REFERENCES

1. Leblanc E, Katdare N, Narducci F, Bresson L, Gouy S, Morice P, et al. Should systematic infrarenal para-
aortic dissection be the rule in the pre-therapeutic staging of primary or recurrent locally advanced cervix
cancer patients with a negative preoperative para-aortic PET imaging? Int J Gynecol Cancer 2016;26:169-75.
PUBMED | CROSSREF

2. Bhatla N, Aoki D, Sharma DN, Sankaranarayanan R. Cancer of the cervix uteri. Int J Gynaecol Obstet
2018;143 Suppl 2:22-36.
PUBMED | CROSSREF

3. Benito V, Carbollo S, Silva P, Esparza M, Arenobia O, Federico M, et al. Should the presence of metastatic
para-aortic lymph nodes in locally advanced cervical cancer lead to more aggressive treatment strategies?
J Minim Invasive Gynecol 2017;24:609-16.
PUBMED | CROSSREF

4. Marnitz S, Köhler C, Roth C, Füller J, Hinkelbein W, Schneider A. Is there a benefit of pretreatment
laparoscopic transperitoneal surgical staging in patients with advanced cervical cancer? Gynecol Oncol
2005;99:536-44.
PUBMED | CROSSREF
5. Choi HJ, Roh JW, Seo SS, Lee S, Kim IV, Kim SK, et al. Comparison of the accuracy of magnetic resonance imaging and positron emission tomography/computed tomography in the presurgical detection of lymph node metastases in patients with uterine cervical carcinoma: a prospective study. Cancer 2006;106:914-22. PubMed | Crossref

6. Uzan C, Gouy S, Pautier P, Haie-Meder C, Duvillard P, Narducci F, et al. Para-aortic lymphadenectomy in advanced-stage cervical cancer: standard procedure in 2010? Gynecol Obstet Fertil 2010;38:668-71. PubMed | Crossref

7. Monk BJ, Wang J, Im S, Stock RJ, Peters WA 3rd, Liu PV, et al. Rethinking the use of radiation and chemotherapy after radical hysterectomy: a clinical-pathologic analysis of a Gynecologic Oncology Group/Southwest Oncology Group/Radiation Therapy Oncology Group trial. Gynecol Oncol 2005;96:721-8. PubMed | Crossref

8. Kidd EA, Siegel BA, Dehdashti F, Rader JS, Mutch DG, Powell MA, et al. Lymph node staging by positron emission tomography in cervical cancer: relationship to prognosis. J Clin Oncol 2010;28:2108-13. PubMed | Crossref

9. Calero A, Escrig-Sos J, Mingol F, Arroyo A, Martinez-Ramos D, de Juan M, et al. Usefulness of the log odds of positive lymph nodes to predict and discriminate prognosis in gastric carcinomas. J Gastrointest Surg 2015;19:813-20. PubMed | Crossref

10. Kwon J, Eom KY, Kim IA, Kim JS, Kim YE, No JH, et al. Prognostic value of log odds of positive lymph nodes after radical surgery followed by adjuvant treatment in high-risk cervical cancer. Cancer Res Treat 2016;48:632-40. PubMed | Crossref

11. Gil-Moreno A, Franco-Camps S, Cabrera S, Pérez-Benavente A, Martínez-Gómez X, García A, et al. Pretherapeutic extraperitoneal laparoscopic staging of bulky or locally advanced cervical cancer. Ann Surg Oncol 2011;18:482-9. PubMed | Crossref

12. Hasenburg A, Salama JK, Van TJ, Amosson C, Chiu JK, Kieback DG. Evaluation of patients after extraperitoneal lymph node dissection and subsequent radiotherapy for cervical cancer. Gynecol Oncol 2002;84:321-6. PubMed | Crossref

13. Díaz-Fejoo B, Torné A, Tejerizo Á, Benito V, Hernández A, Ruiz R, et al. Prognostic value and therapeutic implication of laparoscopic extraperitoneal paraaortic staging in locally advanced cervical cancer: a Spanish multicenter study. Ann Surg Oncol 2020;27:2829-39. PubMed | Crossref

14. Sakuragi N, Satoh C, Takeda N, Hareyama H, Takeda M, Yamamoto R, et al. Incidence and distribution pattern of pelvic and paraaortic lymph node metastasis in patients with stages IB, IIA, and IIB cervical carcinoma treated with radical hysterectomy. Cancer 1999;85:1547-54. PubMed | Crossref

15. Benedetti-Panici P, Maneschi F, Scambia G, Greggi S, Cutillo G, D’Andrea G, et al. Lymphatic spread of cervical cancer: an anatomical and pathological study based on 225 radical hysterectomies with systematic pelvic and aortic lymphadenectomy. Gynecol Oncol 1996;62:19-24. PubMed | Crossref

16. Bats AS, Mathevet P, Buenerd A, Orliaguet I, Mery E, Zerdoud S, et al. The sentinel node technique detects unexpected drainage pathways and allows nodal ultrastaging in early cervical cancer: insights from the multicenter prospective SENTICOL study. Ann Surg Oncol 2013;20:413-22. PubMed | Crossref

17. Armitage P, Berry G, Matthews IN. Statistical methods in medical research. 4th ed. Oxford: Blackwell; 2002.

18. Royston P. The use of cuscums and other techniques in modelling continuous covariates in logistic regression. Stat Med 1992;11:1115-29. PubMed | Crossref

19. Grigsby PW. The prognostic value of PET and PET/CT in cervical cancer. Cancer Imaging 2008;8:146-55. PubMed | Crossref

20. Gouy S, Morice P, Narducci F, Uzan C, Martinez A, Rey A, et al. Prospective multicenter study evaluating the survival of patients with locally advanced cervical cancer undergoing laparoscopic para-aortic lymphadenectomy before chemoradiotherapy in the era of positron emission tomography imaging. J Clin Oncol 2013;31:3026-33. PubMed | Crossref

21. Gallotta V, Giudice MT, Conte C, Sarandeses AV, D’Indinosante M, Federico A, et al. Minimally invasive salvage lymphadenectomy in gynecological cancer patients: a single institution series. Eur J Surg Oncol 2018;44:1568-72. PubMed | Crossref
22. Dabi Y, Simon V, Carcopino X, Bendifallah S, Ouldamer L, Lavoue V, et al. Therapeutic value of surgical paraaortic staging in locally advanced cervical cancer: a multicenter cohort analysis from the FRANCOCYN study group. J Transl Med 2018;16:326. 
   PUBMED | CROSSREF

23. Pujol H, Prade M. Anatomical extension of invasive carcinoma of the uterine cervix (author's transl). Bull Cancer 1979;66:503-44. 
   PUBMED

24. Buchsbaum HJ. Extrapelvic lymph node metastases in cervical carcinoma. Am J Obstet Gynecol 1979;133:814-24. 
   PUBMED | CROSSREF

25. Rouvier H. Anatomie des lymphatiques de l'homme. Paris: Masson; 1932.

26. Ouldamer L, Fichet-Djavadian S, Marret H, Barillot I, Body G. Upper margin of para-aortic lymphadenectomy in cervical cancer. Acta Obstet Gynecol Scand 2012;91:893-900. 
   PUBMED | CROSSREF

27. Mezquita G, Muruzabal JC, Perez B, Aguirre S, Villafranca E, Jurado M. Para-aortic plus pelvic lymphadenectomy in locally advanced cervical cancer: a single institutional experience. Eur J Obstet Gynecol Reprod Biol 2019;236:79-83. 
   PUBMED | CROSSREF

28. Huang BX, Fang F. Progress in the study of lymph node metastasis in early-stage cervical cancer. Curr Med Sci 2018;38:567-74. 
   PUBMED | CROSSREF

29. Tsai CS, Lai CH, Wang CC, Chang JT, Chang TC, Tseng CJ, et al. The prognostic factors for patients with early cervical cancer treated by radical hysterectomy and postoperative radiotherapy. Gynecol Oncol 1999;75:328-33. 
   PUBMED | CROSSREF

30. Aslan K, Meydani MM, Oz M, Tohma YA, Haberal A, Ayhan A, et al. The prognostic value of lymph node ratio in stage IIIC cervical cancer patients triaged to primary treatment by radical hysterectomy with systematic pelvic and para-aortic lymphadenectomy. J Gynecol Oncol 2020;31:e1. 
   PUBMED | CROSSREF

31. Lai CH, Huang KG, Hong IH, Lee CL, Chou HH, Chang TC, et al. Randomized trial of surgical staging (extraperitoneal or laparoscopic) versus clinical staging in locally advanced cervical cancer. Gynecol Oncol 2003;89:160-7. 
   PUBMED | CROSSREF

32. Frumovitz M, Querleu D, Gil-Moreno A, Morice P, Jhingran A, Munsell MF, et al. Lymphadenectomy in locally advanced cervical cancer study (LiLACS): phase III clinical trial comparing surgical with radiologic staging in patients with stages IB2-IVA cervical cancer. J Minim Invasive Gynecol 2014;21:3-8. 
   PUBMED | CROSSREF