The prognostic value of the number of positive lymph nodes and the lymph node ratio in early-stage cervical cancer

Ester P. Olthof¹,² | Constantijne H. Mom² | Malou L. H. Snijders³ | Hans H. B. Wenzel¹ | Jacobus van der Velden² | Maaike A. van der Aa¹

¹Department of Research and Development, Netherlands Comprehensive Cancer Organization, Utrecht, The Netherlands
²Department of Gynecological Oncology, Amsterdam University Medical Center, University of Amsterdam, Amsterdam, The Netherlands
³Department of Pathology, Amsterdam University Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Correspondence
Ester P. Olthof, Department of Research and Development, Netherlands Comprehensive Cancer Organization, Godebaldkwartier 419, 3511 DT Utrecht, The Netherlands.
Email: e.olthof@iknl.nl

Abstract
Introduction: To establish the impact of the number of lymph node metastases (nLNM) and the lymph node ratio (LNR) on survival in patients with early-stage cervical cancer after surgery.

Material and methods: In this nationwide historical cohort study, all women diagnosed between 1995 and 2020 with International Federation of Gynecology and Obstetrics (FIGO) 2009 stage IA2–IIA1 cervical cancer and nodal metastases after radical hysterectomy and pelvic lymphadenectomy from the Netherlands Cancer Registry were selected. Optimal cut-offs for prognostic stratification by nLNM and LNR were calculated to categorize patients into low-risk or high-risk groups. Kaplan–Meier overall survival analysis and flexible parametric relative survival analysis were used to determine the impact of nLNM and LNR on survival. Missing data were imputed.

Results: The optimal cut-off point was ≥4 for nLNM and ≥0.177 for LNR. Of the 593 women included, 500 and 501 (both 84%) were categorized into the low-risk and 93 and 92 (both 16%) into the high-risk groups for nLNM and LNR, respectively. Both high-risk groups had a worse 5-year overall survival (p < 0.001) compared with the low-risk groups. Being classified into the high-risk groups is an independent risk factor for relative survival, with excess hazard ratios of 2.4 (95% confidence interval 1.6–3.5) for nLNM and 2.5 (95% confidence interval 1.7–3.8) for LNR.

Conclusions: Presenting a patient's nodal status postoperatively by the number of positive nodes, or by the nodal ratio, can support further risk stratification regarding survival in the case of node-positive early-stage cervical cancer.

KEYWORDS
lymph node metastasis, lymph node ratio, radical surgery, survival, uterine cervical cancer

Abbreviations: CI, confidence interval; EHR, excess hazard ratios; FIGO, International Federation of Gynecology and Obstetrics; LNR, lymph node ratio; nLNM, number of lymph node metastases; SLN, sentinel lymph node.

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1 | INTRODUCTION

Cervical cancer is the fourth most frequently diagnosed type of cancer and the fourth leading cause of cancer deaths among women worldwide. In high-income countries, about half of all cervical cancers are diagnosed at an early stage. The presence of lymph node metastases is one of the most important prognostic factors. The 5-year overall survival rate for patients diagnosed with early-stage cervical cancer and negative nodes is 87%–95%, compared with 65%–80% in patients with positive lymph nodes. The risk of pelvic lymph node metastases increases per International Federation of Gynecology and Obstetrics (FIGO) (2009) stage with reported incidence rates of 1%, 12%–22%, and 10%–27% for stages IA2, IB, and IIA, respectively. Furthermore, lymph node metastases are now considered as stage IIIC in the FIGO 2018 classification.

The prognostic impact on survival of various characteristics of lymph node metastases has been assessed in several ways, of which the most widely used is the number of lymph node metastases (nLNM). A relatively new prognostic factor is lymph node ratio (LNR), the ratio between the number of positive and retrieved nodes after surgery. The value of this ratio has already been demonstrated in various other malignancies. However, conflicting results about the importance of LNR and the therapeutic effect of lymphadenectomy in cervical cancer make it necessary to critically reassess the prognostic value of LNR and to identify the best cut-offs for risk stratification with regard to survival.

To make these reassessments, this study was conducted to establish the impact of nLNM and LNR on the survival of patients with early-stage cervical cancer who were treated with radical hysterectomy and lymphadenectomy, and to determine if these parameters can be useful for further risk stratification with respect to survival.

2 | MATERIAL AND METHODS

2.1 | Study design

A nationwide historical cohort study was performed by analyzing data between 1995 and 2020 from the Netherlands Cancer Registry, containing population-based data of more than 95% of all cancer patients in the Netherlands since 1989. The date of death was obtained by annual linkage with the Personal Records Database. Women with the following inclusion criteria were enrolled in this study: (a) clinical stage IA2–IIA1 cervical cancer (FIGO 2009), (b) treated by completed radical hysterectomy and pelvic lymph node dissection, and (c) one or more pathologically confirmed lymph node metastases (>0.2 mm). Patients who received neoadjuvant therapy were excluded. Data on patient, tumor, and treatment characteristics were included, as well as follow-up from diagnosis and vital status. Information on location of the metastatic node (either pelvic or para-aortic) was not available in the registry. Data on body mass index, tumor diameter (clinical, or pathological when missing), invasion depth, lymphovascular space invasion, and resection margin distance were available from 2010. LNR was defined as the ratio of positive nodes to the total number of retrieved nodes.

2.2 | Statistical analyses

An optimal cut-off point was determined for nLNM and LNR to classify patients into low-risk and high-risk groups for survival analysis by using the Evaluate Cut points application. The program uses “maxstat” function from the survival package in R to calculate maximally selected rank statistics on survival outcome and continuous covariates, after which a cut-off point is computed. Both values were manually confirmed by means of the log rank and Cox proportional hazards test. Discrete variables were compared using Fisher’s exact test and the Kaplan–Meier method was used to construct overall survival curves. The relative survival is the ratio of overall survival in a patient cohort to the expected survival of a comparable group in the general population, using national life tables matched by age, sex, and period. To calculate the relative survival and excess hazard ratios (EHR) with corresponding 95% confidence intervals (CI) and p values, a proportional hazards model was used, according to the flexible parametric approach with the stpm2 command in Stata. This flexible parametric survival model can fit relative survival models by incorporating expected mortality. Complete case analysis was not feasible for 234 women because of missing data of covariates (see Table 1), which were regarded as missing at random. To account for this, multiple imputation changed equations model and Nelson–Aalen estimate of the cumulative hazard were used to impute 30 data sets by using the same variables as the multivariable analysis. To establish the validity of the imputed data, observed values of complete cases with imputed values were compared (see Table S1). Values of p less than 0.05 were considered statistically significant. South Texas Art Therapy Association SE 16 (StataCorp) and R 4.0.2 (Rstudio 1.3.1073.0) software were used for analyses.

2.3 | Ethical approval

This study was approved by the Privacy Review Board of the NCR (#210015) on July 20, 2021.
RESULTS

3.1 Patient characteristics

The optimal cut-off point calculated for nLNM was four and for LNR was 0.177. A total of 593 women were included in the analysis, of whom 500 and 501 (both 84%) were categorized into the low-risk and 93 and 92 (both 16%) into the high-risk groups for nLNM and LNR, respectively. Clinical and pathological data of the total cohort are listed in Table 1. Most patients had stage IB1 disease (77%) and were treated by laparotomy (88%). The surgical approach did not differ between the low-risk and high-risk groups according to nLNM (p = 0.16) or LNR (p = 0.71). A sentinel lymph node (SLN) procedure, followed by a pelvic lymphadenectomy, was performed in 4% of patients. In total, five patients were diagnosed with micro-metastases (>0.2 to ≤2 mm). The median numbers of positive and retrieved nodes were 2 (range 1–34 nodes) and 23 (range 2–60 nodes), respectively. Adjuvant therapy was administered to 95% of the patients and did not differ between the low-risk and high-risk groups. Administration of adjuvant therapy was equally distributed over the risk groups, before and after a guideline adjustment implemented in 2001. The median follow-up time was 88 months (range 3–270 months).

Table 1: Clinicopathological characteristics of all patients

| Patient characteristics (n = 593) | n | % |
|----------------------------------|---|---|
| Age (years), median [range]      | 43 [21–86] |
| BMI (kg/m²), median [range]      | 24 [16–47] |
| FIGO 2009 stage                  |     |   |
| IA2                              | 8  | 1 |
| IB1                              | 455| 77|
| IB2                              | 76 | 13|
| IIA1                             | 54 | 9 |
| Tumor diameter (cm)              |     |   |
| ≤2                               | 78 | 13|
| >2-4                             | 177| 30|
| >4                               | 112| 19|
| Unknown                          | 226| 38|
| Histological subtype             |     |   |
| Squamous                         | 414| 70|
| Non-squamous                     | 179| 30|
| Differentiation grade            |     |   |
| 1                                | 21 | 4 |
| 2                                | 196| 33|
| 3                                | 262| 44|
| Unknown                          | 114| 19|
| Invasion depth (mm)              |     |   |
| <3                               | 12 | 2 |
| 3-5                              | 36 | 6 |
| >5                               | 228| 38|
| Unknown                          | 317| 54|
| Parametrial invasion             |     |   |
| Absent                           | 486| 82|
| Present                          | 103| 17|
| Unknown                          | 4  | 1 |
| LVSI                             |     |   |
| Absent                           | 58 | 10|
| Present                          | 258| 43|
| Unknown                          | 277| 47|
| Close resection margins          |     |   |
| Absent                           | 275| 46|
| Present                          | 26 | 5 |
| Unknown                          | 292| 49|
| Surgical approach                |     |   |
| Laparotomic                      | 524| 88|
| Laparoscopic                     | 46 | 8 |
| Unknown                          | 23 | 4 |
| Sentinel node procedure          |     |   |
| Absent                           | 24 | 4 |
| nLNM, median [range]             | 2  [1-34] |
| Retrieved lymph nodes, median [range] | 23 [2–60] |

Abbreviations: BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; LNR, lymph node ratio; LVSI, lymphovascular space invasion; nLNM, number of lymph node metastases.

3.2 Prognostic impact of nLNM

In univariable survival analysis for nLNM, the EHR for patients in the high-risk group was 2.7 (95% CI 1.8–3.8; p < 0.001) compared with patients in the low-risk group (Table 2). After correcting for
In univariable survival analysis for LNR, an EHR of 2.6 (95% CI 1.8–3.8; p < 0.001) was found in case of a high ratio (Table 2). After correction for confounders, the high-risk group remained associated with poor relative survival (EHR 2.5; 95% CI 1.7–3.8; p < 0.001), similar to non-squamous histological subtypes (EHR 1.7; 95% CI 1.2–2.5; p = 0.007). Patients in the high-risk group had a worse 5-year survival than those in the low-risk group.
(p < 0.001), with 5-year overall survival rates of 58% (48%–68%) vs. 79% (75%–83%) (Figure 2). As the potential benefit of LNR over nLNM results from the incorporation of retrieved nodes, we also conducted analysis of the number of retrieved nodes as a surrogate for the extent of the lymphadenectomy. However, it was not associated with survival in univariable analysis (EHR 1.0; 95% CI 0.98–1.02; p = 0.83).

### 3.4 nLNM vs. LNR

Classification according to nLNM or LNR seems to have a similar prognostic performance (EHR of 2.4 and 2.5, respectively). Even though the number of patients in the low-risk and high-risk groups was almost the same for the classification based on nLNM and LNR, 51 patients were categorized differently (Table 3). Patients categorized as low-risk according to nLNM, but as high-risk according to LNR (n = 26; 4%) and vice versa (n = 27; 5%), had a poor relative survival (EHR of 1.7 and 1.8, respectively) compared with patients who were categorized in both low-risk groups (n = 474; 80%). Categorization in both high-risk groups (n = 66; 11%) indicated the worst relative survival (EHR 3.2; 95% CI 2.1–4.8).

| TABLE 3 Univariable subgroup analysis for the low- and high-risk groups on 5-year relative survival |
|---------------------------------|-----|-----|------|---------|--------|
| nLNM | LNR | n   | EHR | 95% CI  | p value   |
|------|-----|-----|-----|---------|-----------|
| <4    | <0.177 | 474 | 1.00 | Reference | —          |
| ≥4    | <0.177 | 27  | 1.78 | 0.87–3.63 | 0.12       |
| <4    | ≥0.177 | 26  | 1.71 | 0.83–3.53 | 0.15       |
| ≥4    | ≥0.177 | 66  | 3.21 | 2.14–4.83 | <0.001*    |

Abbreviations: CI, confidence interval; EHR, excess hazard ratio; LNR, lymph node ratio; nLNM, number of lymph node metastases.

*Statistically significant.
4 | DISCUSSION

This study establishes the impact of nLNM and LNR on survival in patients with node-positive early-stage cervical cancer after radical hysterectomy and pelvic lymphadenectomy. We demonstrate that both parameters are independently associated with impaired survival, using ≥4 nodal metastases and a ratio of ≥0.177 as optimal cut-offs. Despite the potential benefit of LNR, by taking into account not only the number of positive nodes, but also the extent of lymphadenectomy, both parameters had similar prognostic performances. Translated into clinical practice, this means that patients with ≥4 positive nodes and/or a ratio of ≥0.177 are expected to have worse prognosis. Therefore, both parameters may contribute to further risk stratification regarding survival, which could be useful in decision-making for adjuvant therapy.

One of the largest studies on this topic compared multiple prognostic classification systems for nodal metastases in cervical cancer of the squamous subtype (n = 928). LNR (≥0.16), nLNM (≥5), FIGO 2018 stage (IIIC1/IIIC2), and the log odds of positive nodes (≥0.61), were reported as prognostic factors for survival. nLNM was the most predictive parameter of survival. The negative association between nLNM and prognosis was also demonstrated in studies including both squamous and non-squamous cervical cancer. One of these studies was an analysis of 2222 node-positive cervical cancer patients, demonstrating 5-year overall survival rates of 77% vs. 63%, for patients with ≤2 vs. >2 nodal metastases, respectively (p < 0.001).

Regarding LNR, multiple studies were published on prognostic performance with respect to survival in node-positive early-stage cervical cancer. Li et al evaluated the association of nLNM and LNR with survival in 273 patients with 2018 stage IIIC1 cervical cancer, after radical hysterectomy. Similar to our study, the number of retrieved nodes was not associated with survival, but the number of positive nodes (<2 vs. ≥2) and the ratio (<0.08 vs. ≥0.08) were. In multivariable analysis, LNR (but not nLNM) was identified as an independent prognostic factor for overall survival (p = 0.001). In a study by Aslan et al, a high LNR (≥0.05) was an independent adverse prognostic factor for overall survival as well. Furthermore, in a study by Joo et al, 397 patients with nodal metastases were categorized into three groups according to LNR: <0.1, 0.1–0.4, and >0.4. This study showed that survival decreases when LNR increases, with 5-year overall survival rates of 83%, 66%, and 17%, respectively. In summary, the prognostic values of nLNM and LNR have been demonstrated before. Some studies (including the largest) are in favor of nLNM, whereas others are in favor of LNR. Our study contributes to the current literature, as this is the largest study, to our knowledge, on all histological subtypes of cervical cancer, while differentiating between a nodal debulking or a dissection in the case of few retrieved nodes. Nevertheless, the numbers of retrieved nodes (range 2–60) matches earlier studies on lymphadenectomy (range 4–85). Moreover, it has been common policy in the Netherlands not to perform a radical hysterectomy if only bulky nodes are removed. To bypass this problem, some studies use a lower limit of 10 or more retrieved nodes. In our study, we chose not to, because this would exclude patients with few nodes present. Besides, we were unable to demonstrate better survival after more retrieved nodes. This was in contrast to non-squamous histological subtype, which was independently associated with poor prognosis, which has also been demonstrated in previous studies.

The strengths of this study were its large sample size and nationwide data coverage. Additionally, we were able to compare nLNM and LNR, by multivariable analysis. Our study has several limitations, all related to its retrospective design. First, historical cohort studies may be inherently biased toward heterogeneous patient populations. Second, details regarding adjuvant therapy, like dosage and type of chemotherapy or radiotherapy, and on the extent of the radical hysterectomy and lymphadenectomy, were missing. These details could impact survival and therefore affect our results. Fourth, invasion depth, lymphovascular space invasion, differentiation grade, and parametrial invasion contained missing data. To deal with these missing data and reduce the risk of bias, we performed multiple imputation: a statistical technique for dealing with missing data. Finally, a guideline adjustment regarding the role of postoperative chemoradiation was implemented during our study period in 2001. Although this potentially could have affected survival outcomes, we expect no bias because the administration of various adjuvant therapies did not differ between the low-risk and high-risk groups before and after 2001.

Monk et al suggested that a subgroup of patients with more than one positive lymph node would benefit more from the addition outcomes as our study. For nLNM, various cut-offs (range ≥2 to ≥4) are reported in literature as well. The diversity in cut-offs is probably due to a variety of inclusion criteria, divergent sample sizes, and/or treatment strategies, leading to dissimilar survival rates. Use of cut-offs for risk stratification should be interpreted with caution, as illustrated in Table 3. Patients who were categorized as low risk by one parameter, but as high-risk by the other, still tend to be at higher risk for death; therefore, it might be valuable to use both parameters when possible. Furthermore, nLNM and LNR are useful prognostic parameters after lymphadenectomy but not after only an SLN procedure, as this latter procedure will not provide full insight of the nodal status and might lead to mispresenting the number of positive and removed nodes. Although the SLN procedure is not yet standard of care globally, it might become so for selected subgroups of patients in the near future. As a consequence, the benefit of powerful prognostic parameters by performing a complete pelvic lymphadenectomy must be weighed against the benefits of less invasive surgery in terms of morbidity. In our study, we expect low-risk of bias because the SLN was always followed by a lymphadenectomy.

Due to the retrospective design of this study, it was impossible to differentiate between a nodal debulking or a dissection in the case of few retrieved nodes. Nevertheless, the numbers of retrieved nodes (range 2–60) matches earlier studies on lymphadenectomy (range 4–85). Moreover, it has been common policy in the Netherlands not to perform a radical hysterectomy if only bulky nodes are removed. To bypass this problem, some studies use a lower limit of 10 or more retrieved nodes. In our study, we chose not to, because this would exclude patients with few nodes present. Besides, we were unable to demonstrate better survival after more retrieved nodes. This was in contrast to non-squamous histological subtype, which was independently associated with poor prognosis, which has also been demonstrated in previous studies.

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In literature, cut-off values for LNR range from 0.05 to 0.40 and there are several studies with comparable cut-offs to our cut-off of 0.177. The two most recent papers showed similar survival
of chemotherapy to adjuvant radiotherapy after radical hysterectomy. This study illustrates that not all node-positive patients benefit equally from adjuvant therapy, and that it is crucial to identify those who might benefit. In line with these findings, we would suggest more research on the addition of chemotherapy, either concomitantly or consequentially, for high-risk patients. Identification of a high-risk group of lymph-node-positive patients may aid in selection of patients that benefit most from additional chemotherapy. Both LNR and nLNM may potentially play a role in this selection. Furthermore, external validation of nLNM and LNR in multiple, disparate data sets should be obtained first, before implementation in clinical practice is possible, especially regarding both cut-off values for low-risk and high-risk groups.

5 | CONCLUSION

Both nLNM and LNR are independently associated with relative and overall survival in node-positive early-stage cervical cancer patients after radical hysterectomy. Representation of a patient’s nodal status by both parameters might therefore be of additional value compared with only indicating the presence or absence of lymph node metastases.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

EO: conceptualization, methodology, formal analysis, data curation, visualization and writing. CH: conceptualization, methodology, writing—reviewing and editing. HW: formal analysis, data curation, writing—reviewing and editing. MS: writing—review and editing. JV: conceptualization, methodology, supervision, writing—reviewing and editing.

ORCID

Ester P. Olthof https://orcid.org/0000-0003-1941-7693

Hans H. B. Wenzel https://orcid.org/0000-0003-4502-2724

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SUPPORTING INFORMATION
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