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Prognostic value of the number and laterality of metastatic inguinal lymph nodes in vulvar cancer: Revisiting the FIGO staging system

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Abstract

Objective: Inguinal lymph node (LN) metastasis is an important prognostic factor in vulvar cancer. Our aims were to analyze the prognostic value of LN metastasis with regard to the number of LNs that were involved and their laterality and compare these results with the current FIGO staging system.
Methods: A retrospective analysis was performed in a series of 234 individuals who underwent inguinal lymphadenectomy for vulvar squamous cell carcinoma from January 1980 to February 2010.
Results: The mean age was 68 years. One hundred seven (45.7%) patients had LN metastasis. Despite the FIGO staging, we did not observe any significant difference in the risk of recurrence or death between patients with 1 positive LN and ≥2 positive LNs. Moreover, there was no difference in outcome between the presence of 1 and 2 positive LNs. On categorizing patients into 3 groups—absence of LN involvement, 1–2 positive LNs, and ≥3 positive LNs—we achieved a significantly better prognostic correlation for progression-free survival, disease-specific survival, and overall survival. Extracapsular spread retained a prognostic role for the risk of recurrence in multivariate analysis. Further, for patients with ≥2 positive LNs, the presence of bilateral positive LNs did not negatively impact the risk of recurrence or death compared with those with unilateral positive LNs.
Conclusions: Our data suggest that the prognostic effect of bilateral LNs reflects the worse prognosis of multiple positive LNs. Regarding prognosis, LN involvement should be categorized into 2 groups—1–2 positive LNs and ≥3 positive LNs.

Keywords: Vulvar cancer; Lymph node metastasis; Lymphadenectomy; Prognosis; Tumor staging

Introduction

Vulvar cancer accounts for approximately 3%–5% of all gynecological malignancies.[1] It usually affects women with a median age of 65–70 years,[2] and the majority of cases (~90%) is squamous cell carcinoma (SCC).[1,2]

The prognosis is linked to inguinal lymph node (LN) involvement, and hematogenic metastasis is a rare event, even with the presence of LN metastasis.[1,2] Thus, LN status is the most important prognostic factor—5-year survival ranges from 90% for patients without LN metastasis to 24% when 5 or 6 LNs are involved.[3]

In 1988, the International Federation of Gynecology and Obstetrics (FIGO) staging system for vulvar cancer shifted from a clinical to surgical-pathological classification due to the lack of accuracy in the prediction of the LN status by the physical examination.[4] In 2009, the FIGO staging system was revised,[5,6] and 4 major changes in stage III were introduced, having previously comprised a heterogenous group of patients with negative or positive nodes.

Today, only patients with positive nodes are classified as stage III. Moreover, the number of involved LNs, the size of LN metastasis, and the presence of extracapsular spread are taken into account. In addition, the presence of bilateral positive nodes is not an independent prognostic factor when

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a correction is made for the number of positive lymph nodes.[7]

Our aims were to analyze the prognostic value of LN metastasis regarding the number of LNs involved, the prognostic value of the bilaterality of LN metastasis, and compare the results to the current FIGO staging system in patients with vulvar SCC.

Patients and methods

This retrospective analysis included 234 individuals with vulvar SCC who underwent surgical treatment, including inguinal lymphadenectomy, at the Department of Gynecologic Oncology, AC Camargo Cancer Hospital, from January 1980 to February 2010. The Institutional Review Board approved the study.

The clinical features that were analyzed were age, type of vulvar surgery (wide local excision or radical vulvectomy), and type of inguinal lymphadenectomy (unilateral or bilateral). The pathology data included: tumor size, depth of invasion, the number of LNs that were resected, the presence of LN metastasis, and the presence of bilateral LN metastasis.

Follow-up time spanned from the date of surgery to the last date for which information was available. Progression-free survival (PFS) was defined as the time from surgery to the date of recurrence or last follow-up. Overall survival (OS) was defined as the time from surgery to the date of death or last follow-up. Disease-specific survival (DSS) was defined as the time from surgery to the date of death due to vulvar cancer or last follow-up. The database was generated in SPSS, version 16.0 (SPSS, Inc., Chicago, IL) for Mac. The association between parametric variables was assessed by chi-square or Fischer's exact test. Survival curves were constructed by Kaplan–Meier life table analysis. Clinico-pathological factors that showed statistically significance ($p < 0.05$) in univariate analysis were included in multivariate analysis by Cox regression. In multivariate analysis, only patients with positive LN were included. As only 45 (42%) patients with positive nodes had depth of invasion evaluated, it was excluded from the multivariate analysis. For all tests, an alpha error up to 5% ($p < 0.05$) was considered significant.

Results

Clinical and pathological data

The patients' clinical and pathological data are summarized in Table 1.

The mean age was 68 years (range: 15–91). Median tumor size was 4.5 cm (range: 1–18). One hundred and five (44.8%) patients had depth of invasion analyzed, with a median of 10 mm (range: 2–37 mm). Two hundred nineteen patients (93.6%) had radical vulvectomies, and 15 (6.4%) had wide local excision. One hundred fifty-seven (67.1%) underwent bilateral inguinal lymphadenectomy, and 77 (32.9%) received unilateral inguinal lymphadenectomy.

Table 1
Clinical and pathological characteristics of the 234 patients with vulvar cancer submitted to inguinal lymphadenectomy.

Variable	
Median age (y)	68 (range, 15–91)
Median tumor size (cm)	4.5 (range, 1–18)
Depth of invasion (mm)	10 (range, 2–37)
	No. of patients (%)
Type of vulvar surgery	
Radical vulvectomy	219 (93.6)
Wide local excision	15 (6.4)
Inguinal lymphadenectomy	
Bilateral	157 (67.1)
Unilateral	77 (32.9)
LN metastasis	
No	127 (54.3)
Yes	107 (45.7)
Number of positive LN	
1	31 (29)
2	31 (29)
3 or more	45 (42)

LN: Lymph node.

A median of 17 inguinal LNs (range: 1–57) were resected. One hundred seven (45.7%) patients had LN metastasis, with a median of 2 positive LNs (range: 1–16). Of those with positive LNs, 31 (29%), 31 (29%), and 45 (42%) patients had 1, 2, and 3 or more positive LNs, respectively. Fourteen (13%) of 107 patients with positive LN had extracapsular spread.

Eighty (50.3%) patients who underwent bilateral lymphadenectomy had LN metastasis, versus 27 (36%) of those with unilateral lymphadenectomy ($p = 0.049$). Of those with bilateral lymphadenectomy, 33 (41.2%) had bilateral LN metastasis.

Median follow-up time was 29.6 months (range: 1–301.5). At the end of the follow-up, 95 patients (40.6%) were alive with no evidence of disease, 93 (39.7%) had died due to cancer, 37 (15.8%) died of other causes, and 9 (3.9%) were alive with evidence of disease.

Recurrence and survival

The 5-years PFS, OS, and DSS rates were 55.8%, 50.4%, and 61.1%, respectively.

The presence of LN metastasis negatively impacted the risk of recurrence (72.9% vs 35.8%; $p < 0.001$), death (64.7% vs 34%; $p < 0.001$), and death from cancer (78.2% vs 41.3%; $p < 0.001$) in 5 years.

Only 11 (10.3%) patients with LN metastasis received adjuvant radiotherapy. One patient had 1 positive LN and the others had 2 or more. However, absence of adjuvant radiotherapy did not negatively impact 5-years PFS ($p = 0.35$), DSS (0.90), and OS ($p = 0.75$).

We first stratified patients into categories per the FIGO staging system, considering macrometastasis in 1 LN or $\geq$2 LNs. However, we failed to observe any significant

difference between patients with 1 positive LN and ≥2 positive LNs with regard to 5-years PFS (40.4% vs 33.3%; $p = 0.36$), DSS (45.3% vs 39.3%; $p = 0.19$), or OS (40.7% vs 31.1%; $p = 0.096$) (Fig. 1).

Further, we stratified the number of LNs that were involved into 3 categories: 1 positive LN, 2 positive LNs, and ≥3 positive LNs. There was no difference in 5-years OS (40.7% vs 41.6%; $p = 0.42$), DSS (45.3% vs 52.1%; $p = 0.97$), or PFS (40.4% vs 41.8%; $p = 0.92$) between the presence of 1 and 2 positive LNs, respectively. We also found better 5-years OS (41.6% vs 23.6%; $p = 0.32$), DSS (52.1% vs 30.1%; $p = 0.097$), and PFS (41.8% vs 27.1%; $p = 0.20$) for patients with 2 positive LNs when compared to ≥3 positive LNs, however without statistical significance.

Based on this lack of difference in outcomes, we categorized patients by number of involved LNs into 3 groups: absence of LN involvement (0 LNs), 1–2 positive LNs, and ≥3 positive LNs. Consequently, we achieved a better correlation between the number of LNs that were involved and prognosis. Five-year PFS was 72.9% for those with 0 LNs, 41.1% for 1–2 positive LNs ($p < 0.001$), and 27.1% for ≥3 positive LNs ($p = 0.094$). Five-year DSS was 78.2% for 0 LNs, 48.7% for 1–2 positive LNs ($p = 0.004$), and 30.1% for ≥3 positive LNs ($p = 0.025$). Five-year OS was 64.7% for 0 LNs, 41% for 1–2 positive LNs ($p = 0.012$), and 23.6% for ≥3 positive LNs ($p = 0.064$) (Fig. 2).

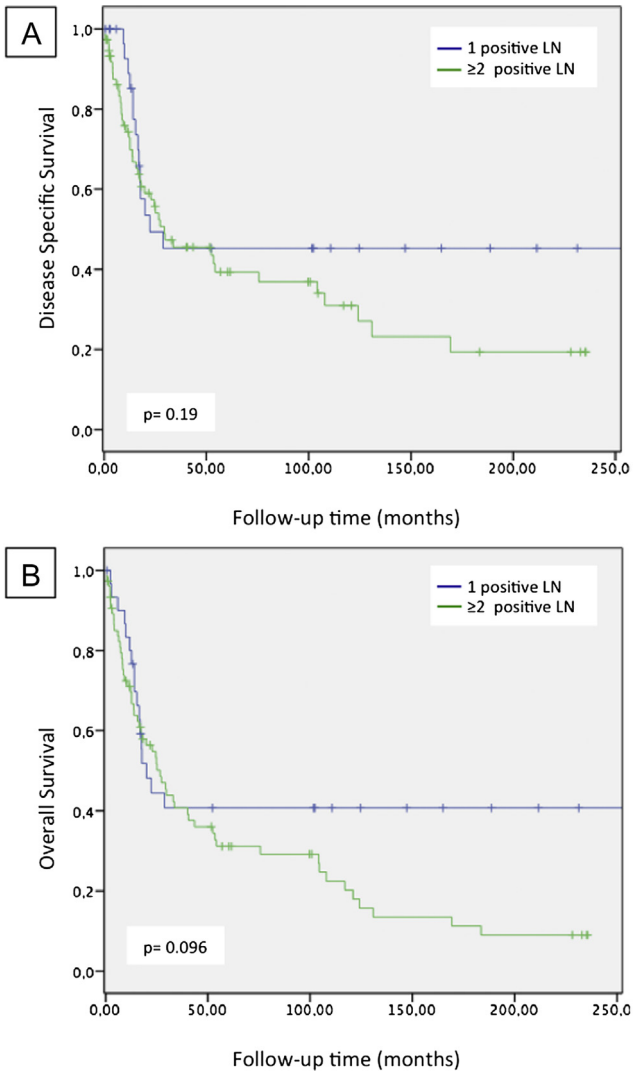

Figure 1. (A) Disease-specific survival curves for patients with 1 positive lymph node (LN) and ≥2 positive LNs; (B) Overall survival curves for patients with 1 positive LN and ≥2 positive LNs.

Presence of LN extracapsular spread negatively impacted PFS (2 years PFS: 12.6% vs. 46.4%; $p = 0.015$) and OS (5 years OS: 9.7% vs. 37,4%; $p = 0.046$) (Fig. 3). Although presence of extracapsular spread also correlated to worst DSS, it did not achieved statistical difference (5 years DSS: 15.6% vs. 44.6%; $p = 0.07$).

For patients with positive LN, presence of extracapsular spread was the only variable that retained a prognostic role for the risk of recurrence in multivariate analysis. (HR 2.13, CI 95% 1.04–4.33; $p = 0.037$). No variable retained a prognostic role for the risk of death and death from cancer in multivariate analyzis (Table 2).

When we considered all patients who underwent bilateral inguinal lymphadenectomy, bilateral lymph node involvement was correlated with worse OS (44.6% vs 25.9%; $p = 0.012$) and DSS (49.1% vs 36.9%; $p = 0.088$). However, this initial analysis included patients with unilateral involvement and only 1 positive LN—patients who should be considered to have unilateral metastasis, per the definition.

Thus, we evaluated the 61 patients with bilateral lymphadenectomy who had at least 2 involved LNs. Of these subjects, 23 (37.7%) had 2 positive LNs and 38 (62.3%) had ≥3 LNs. Twenty-eight (45.9%) had unilateral involvement, and 33 (54.1%) had bilateral LN involvement. Notably, for patients with ≥2 positive LNs, the presence of bilateral positive LNs did not negatively impact PFS (31.1% vs 44.5%; $p = 0.23$), DSS (36.9% vs 47.4%; $p = 0.15$), or OS (25.9% vs 40.1%; $p = 0.06$) compared with those with unilateral positive LNs.

Discussion

LN involvement is the most important prognostic factor in vulvar cancer.[1,2] The 2009 FIGO staging system guidelines for vulvar cancer[6] contained a major change to the definition of stage III cancer. Now, stage III is divided into 3 categories with regard to the number and size of positive LNs and the presence of extracapsular invasion. Patients with 1 positive LN (metastasis >5 mm) are considered to have stage IIIa, and patients with 2 or more positive LNs (metastasis >5 mm) have stage IIIb. The presence of extracapsular invasion is now considered stage IIIC, remaining a significant and well-established prognostic factor. Bilateral positive node is no longer considered a prognostic factor.

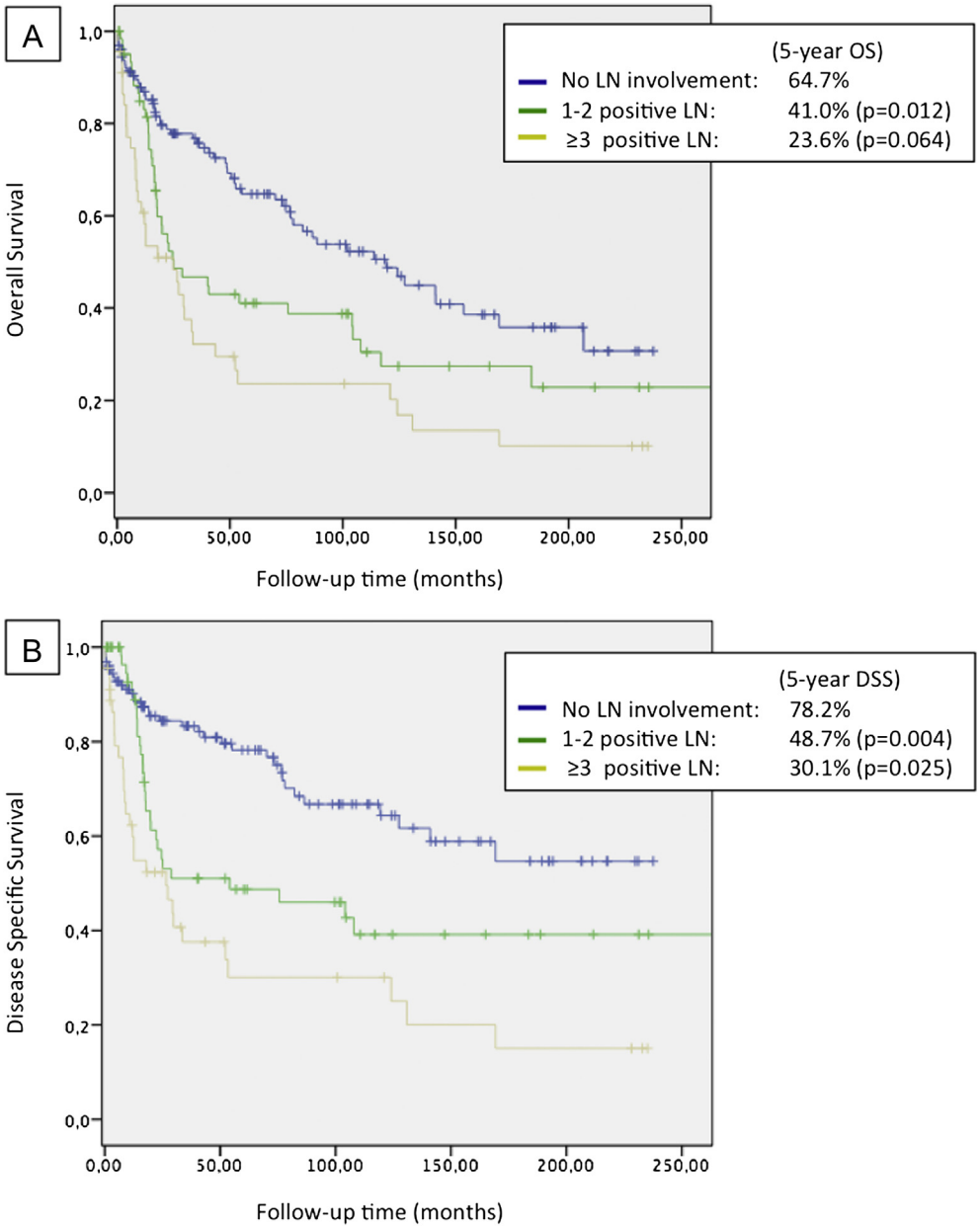

Figure 2. (A) Overall survival (OS) curves for patients with no lymph node (LN) involvement, 1–2 positive LNs, and ≥3 positive LNs. (B) Disease-specific survival (DSS) curves for patients with no lymph node (LN) involvement, 1–2 positive LNs, and ≥3 positive LNs.

Regarding LN-related parameters, in 1983, Hacker et al.[8] published a seminal series of 113 patients with vulvar cancer (104 SCCs) who underwent inguinal LN dissection. On analyzing the number of positive LNs, they noted a 5-year OS of 94% for patients with 1 positive LN, 80% for those with 2 positive LNs, and 12% for those with 3 or more positive LNs.

In 1991, Homesley et al. (GOG trial)[3] published the then-largest series, evaluating 588 patients and suggesting that the most powerful prognostic factor was the number of positive nodes, observing a 5-year survival of 90.9% for those who were negative for LNs versus 75.2% for patients with 1–2 positive LNs ($n = 125$), 36.1% for those with 3–4 positive LNs ($n = 40$), 24% in those with 5–6 positive LNs ($n = 19$), and 0% for subjects with 7 or more positive LNs ($n = 16$). This group defined the risk of death with regard to not only the number of positive nodes but also the presence of unilateral or bilateral metastasis, reporting 70.7% survival for patients with unilateral positive LNs versus 25.4% for those with bilateral positive LNs.

Further, 3 groups evaluated other node-related factors, such as percentage of nodal replacement and size of LN metastasis. In 1994, Paladini et al.[9] published a series of 75 patients with vulvar SCC and positive LNs. For patients with 1 positive LN, the most significant prognostic factor

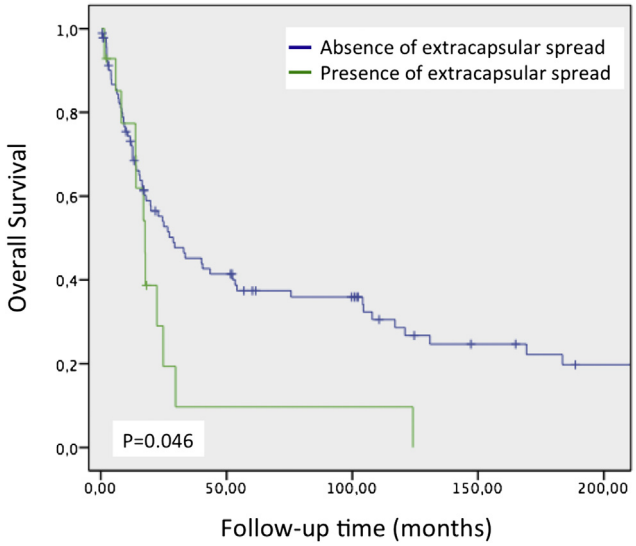

Figure 3. Overall survival (OS) curves for patients with presence and absence of extracapsular invasion.

was the greatest dimension of metastasis in the LN (5-year OS of 86% when the LN metastasis was smaller than 5 mm versus 40% for larger LN metastases). When the number of involved LNs was considered, the 5-year OS was 46% for patients with 1 LN that was involved, 20% for patients with 2 or 3 LNs, and 23% for patients with more than 3 LNs. In 1995, van der Velden et al.[10] corroborated these data and concluded that the number of positive LNs (2 or more) and the rate of LN replacement (above or below 50%) were important prognostic factors by multivariate analysis.

In 2006, Raspagliesi et al.[11] reported their analysis of 110 patients with positive LNs. Among LN parameters, percentage of nodal replacement (above or below 50%) correlated with survival by multivariate analysis. However, in contrast to other studies, the number of involved LNs was not associated with prognosis. For patients with LN metastases, they found that 23% of cases with 1 or 2 positive nodes also had extracapsular invasion or nodal replacement of more than 50%. The group suggested that the prognostic value of the number of positive LNs was dependent on other LN variables. van der Steen et al.[12] examined the new FIGO staging system in their retrospective cohort of 269 patients with vulvar SCC. They evaluated 96 patients with positive LNs and demonstrated that the number of positive LNs had a significant impact on OS ($p = 0.022$) and DSS ($p = 0.004$). Five-year OS was 67% for patients with 1 positive LN, 55% for those with 2 positive LNs, 48% for subjects with 3 positive LNs, and 25% for patients with 4 or more positive LNs. They noted a 5-year DSS rate of 77% for patients with 1 positive LN, similar rates for patients with 2 or 3 positive LNs (approximately 62%), and a worse 5-year DSS for those with 4 or more positive LNs (28%). However, they did not report the comparison between curves by log-rank test.

Recently, Tabbaa et al.[13] also evaluated the prognostic impact of the new FIGO staging system. The large series of 468 patients included 89 with positive LN. The authors did not find statistically difference in DSS between the subgroups of stage III ($p = 0.18$). However, they recognized that the number of patients with 2 ($n = 11$) and ≥ 3 ($n = 16$) positive nodes was small, and therefore impacted the statistical power. When intracapsular LN metastasis was compared to extracapsular spread, differences in DSS only approached statistical significance ($p = 0.07$).

In another recent study, Woelber[14] et al. analyzed the impact of LN metastasis in PFS. Twenty-one (31%) of 157 patients had LN metastasis. Although patients with 1, 2 and >2 positive nodes had respectively PFS of 60%, 43%, and 29%, respectively, they could not find statistical differences among the node-positive groups. Interestingly, in multivariate analysis, the negative effect of additional positive LN was reduced for patients that received adjuvant radiotherapy.

Overall, LN involvement and the number of involved LNs appear to be important prognostic factors for survival. In our series, we initially grouped patients per the new FIGO staging system, but we failed to note any significant difference in outcome (DSS, PFS, and OS) between patients with 1 and ≥ 2 positive LNs.

Also, the risk of recurrence and death did not differ between patients with 1 and 2 positive LNs, similar to Fons et al.,[7] in which DSS was considered. Thus, we opted to group patients with 1 and 2 positive LNs in the same category. Ultimately, we categorized LN involvement into 3 groups—0 LNs, 1–2 positive LNs, and ≥ 3 positive LNs—after which they correlated better with prognosis in

Table 2
Multivariate analysis for the risk, death from cancer, death, and recurrence for patients with positive lymph nodes.

Variable	Category	Risk of death from cancer				Risk of death			Risk of recurrence		
		n	HR	IC 95%	*p*	HR	IC 95%	*p*	HR	IC 95%	*p*
Extracapsular spread	Absent	87	1.00	Reference	0.16	1.0	Reference	0.13	1.0	Reference	0.037
	Present	13	1.65	0.81–3.35		1.64	0.86–3.14		2.13	1.04–4.33	
Number of positive LN	1–2	59	1.00	Reference	0.073	1.0	Reference	0.18	1.0	Reference	0.21
	≥3	41	1.62	0.95–2.77		1.38	0.86–2.22		1.39	0.82–2.35	
Tumor size	≤4 cm	42	1.00	Reference	0.50	1.0	Reference	0.18	1.0	Reference	0.49
	>4 cm	58	1.20	0.70–2.06		1.38	0.85–2.25		1.19	0.71–2.01	

HR: Hazard ratio; IC 95%: Confidence interval, 95%.

terms of DFS, OS, and DSS. The staging system should better stratify patients according to their prognosis, and to this end, our data suggest that patients with 1 and 2 positive LNs should be considered together, with those with ≥3 positive LNs in a separate category. Notably, the number of LN metastasis also negatively impacted the risk of death from cancer in multivariate analyzes.

Another major change in the 2009 FIGO staging system was that bilateral positive LNs were no longer considered a prognostic factor. Our data are consistent with FIGO staging but nevertheless contradicts earlier studies in which bilateral lymph node metastases were found to be an independent prognostic factor[15–17]—results with which we take issue.

In 2009, Fons et al.[7] published in an elegant study, the strengths of which was its uniformity and sample size of 134 patients with positive LNs. They demonstrated that bilateral LN metastasis has prognostic value when patients with 1 positive LN are included in the analysis. On analyzing only patients with 2 or more LN metastases, the group concluded that laterality no longer had an impact on survival, as corroborated by van der Steen et al.[12] and Tabbaa et al.[13]

We also analyzed only patients with 2 or more positive LNs who underwent bilateral lymphadenectomy, and did not observe a significant negative impact of this factor on recurrence or death in patients with bilateral positive LNs compared with those with unilateral positive LNs.

In our series, adjuvant radiotherapy was performed in only 11 (10.3%) of patients with positive nodes. It is important to mention that most of patients that received radiotherapy were treated in last decade after an institutional paradigm shift, where we begun to indicate adjuvant radiotherapy for patients with 2 metastasis lower than 5 mm, LN metastasis larger than 5 mm and presence of extracapsular spread. In our series, adjuvant radiotherapy had no impact in outcome for patients with positive LN, and we believe that this finding may be due to the small number of patients that received adjuvant radiotherapy. However, it is important to emphasize that the lack of adjuvant radiotherapy for most LN positive patients might have a negative impact in our results, and may impaired the comparison with other studies.

Overall, our series was comparable in size to the most significant studies on this topic and contributes valuable data. Moreover, our data can help stratify patients with positive LNs and a higher risk of recurrence or death better. The strength of our study was that it established a significant correlation between groups of patients with positive LNs and included OS, DSS, and PFS in the analysis. Unfortunately, it suffered from institutional bias, spanning nearly 3 decades, and in a retrospective setting, we were unable to evaluate the prognostic role of the size of LN metastasis, and consequently definitive comparison to current FIGO staging system.

In conclusion, our data corroborate current evidence that suggests that the prognostic effect of bilateral LN reflects the worse prognosis of having multiple positive LNs. Our data also suggest that regarding outcomes, positive LN patients are better categorized into 2 groups: those with 1–2 positive LNs and ≥3 positive LNs.

Conflict of interest statement

The authors declare no financial disclosures and no conflict of interest.

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