



Satellite lymphovascular space invasion: An independent risk factor in early stage cervical cancer



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HIGHLIGHTS

- Comparing conjoined LVSI with satellite LVSI, satellite LVSI is correlated with higher risk for both recurrence and death.
- Satellite LVSI is an important independent prognostic factor for both recurrence and survival in early stage cervical cancer.
- Adjuvant treatment may be considered in women with satellite LVSI, even in the absence of Delgado criteria.

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ABSTRACT

Objective. This study was performed to determine whether satellite LVSI in women with early stage cervical carcinoma is an independent prognostic factor for recurrence and survival.

Methods. A total of 210 eligible patients with FIGO stages IA2 and IB1 cervical carcinoma, who underwent radical hysterectomy or radical trachelectomy with pelvic lymphadenectomy between January 2000 and December 2012, were included. Variables studied included age, histology type, differentiation grade, tumor size (TS), depth of invasion (DI), lymph node metastasis (LNM), conjoined lymphovascular space invasion (LVSI) and satellite LVSI. Univariate and multivariate analyses were performed to define variables that best predict recurrence and survival.

Results. Univariate analysis showed that differentiation grade, depth of invasion, tumor size, lymph node metastasis, and both conjoined LVSI and satellite LVSI were significantly associated with recurrence and survival. Using multivariate analysis, differentiation grade (HR 3.63, 95%-CI 1.51–8.72), conjoined LVSI (HR 5.95, 95%-CI 1.57–22.53) and satellite LVSI (HR 7.45, 95%-CI 3.03–18.27) were independent prognostic factors for recurrence; LNM (HR 5.55, 95%-CI 1.52–20.26) and satellite LVSI (HR 8.94, 95%-CI 2.43–32.95) were prognostic factors for overall survival. For patients with low-risk cervical cancer without LNM only satellite LVSI correlated significantly with disease-free and overall survival.

Conclusion. Differentiation grade, DI, TS, LNM, and conjoined LVSI as well as satellite LVSI were prognostic factors for DFS and OS. Satellite LVSI is the most important factor predicting DFS and OS in early stage cervical cancer, especially when lymph nodes are negative.

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1. Introduction

Stage IA2 LVSI positive and stage IB1 cervical cancer is treated with either radical hysterectomy with pelvic lymph node dissection or radical trachelectomy with pelvic lymph node dissection in young patients who wish to preserve their fertility. The chance for recurrence is low (5–11%), but in most cases recurrent cervical cancer is lethal [1].

Known prognostic factors for recurrence in early stage disease are lymph node metastasis (LNM), lymphovascular space invasion (LVSI), tumor size (TS) and depth of tumor invasion (DI); other factors like age, surgical margins, histology, and tumor grade remain controversial [2–10]. Studies have shown that adjuvant pelvic radiotherapy significantly reduces the risk of recurrence and improves disease-free survival, although it has not been shown to improve overall survival for these women [11]. Delgado et al. developed a scoring system regarding the best combination of prognostic factors for disease-free survival and recurrence, used by the Gynecologic Oncology Group (GOG); irrespective of nodal status, radiotherapy is advised in case of early-stage cervical

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cancer in the presence of at least 2 of the following unfavorable prognostic tumor characteristics: lymphovascular space invasion, tumor diameter ≥ 40 mm and depth of invasion $> 1/3$ or > 15 mm [2,12,13]. LVSI is one of the best prognostic factors for disease-free and overall survival [8], and was first described by Friedell and Parsons [14]. Probably not only the presence of LVSI, but also the quantity of LVSI might be important [15]. Roman et al. investigated the influence of quantity of LVSI in women with early stage cervical cancer and found that quantity of LVSI significantly correlated with the risk of lymph node metastasis and subsequently with time to recurrence [16]. Recently, Herr et al. evaluated the prognostic impact of different categories of LVSI (i.e. conjoined LVSI and satellite LVSI) on survival in women with stage IA1–IB cervical cancer. They showed a significant increase in risk of recurrence in women with satellite LVSI, defined as lymphatic and/or vascular space invasion of tumor cells at least 10 mm from the tumor. Moreover, they showed that women with satellite LVSI had a shorter disease-free and overall survival compared to women with conjoined LVSI (LVSI near the tumor) [17]. To our knowledge, the study by Herr et al. is the only study so far evaluating the risk of satellite LVSI.

This study was established to further investigate risk factors for recurrence and survival of women with early stage cervical cancer, i.e. stages IA2 and IB1, with a focus on satellite LVSI, in order to better determine high-risk patients for whom adjuvant therapy may be beneficial.

2. Materials and methods

This retrospective study was performed at the Department of Obstetrics and Gynecology at the Radboud University Medical Center in Nijmegen and included all patients ($n = 222$) diagnosed with stage IA2 or IB1 cervical cancer between January 2000 to December 2012.

Twelve patients were excluded: four patients did not receive a radical hysterectomy or radical trachelectomy due to positive lymph nodes during surgery, five patients had tumor extension into the vagina or parametrium involvement with positive surgical margins, two were lost to follow-up, and one patient died in an accident shortly after surgery. Clinical and pathological characteristics including stage, grade, histology type, tumor size, depth of invasion, surgical margins, lymph node metastasis and LVSI, conjoined and satellite, were collected. Histopathological diagnoses, i.e. the slides, were re-reviewed on histological type, tumor size, depth of invasion, differentiation grade, type of LVSI and lymph node metastasis by one gynecological pathologist attending the Radboud University Medical Center, Nijmegen. Pathological examination of the cervix was done by a standard protocol. Quadrants of the cervix were sampled and evaluated microscopically, including their relation to the vaginal, pericervical, and parametrial surgical margins. Tissue, which was macroscopically suspect for cancer, was additionally embedded and evaluated. Also, all pelvic and paraaortic lymph nodes that were received, were embedded and carefully studied. Staging was based on the International Federation of Gynecology and Obstetrics (FIGO) staging system. Tumor size, depth of invasion and surgical margins were dichotomized as follows: < 20 mm and ≥ 20 mm, < 15 mm and ≥ 15 mm, < 8 mm and ≥ 8 mm, respectively. Lymphovascular space invasion was defined as the presence of tumor cells inside lymphatic/vascular spaces, i.e. in the luminal space lined by endothelial cells. Conjoined LVSI was defined as lymphatic and/or vascular space invasion of tumor cells in the tumor or at the tumor front, whereas satellite LVSI was defined as lymphatic and/or vascular space invasion of tumor cells at least 10 mm from the tumor (Fig. 1). We also performed separate analyses where we considered LNM as satellite LVSI positive, arguing that all patients with positive lymph nodes also all have satellite LVSI.

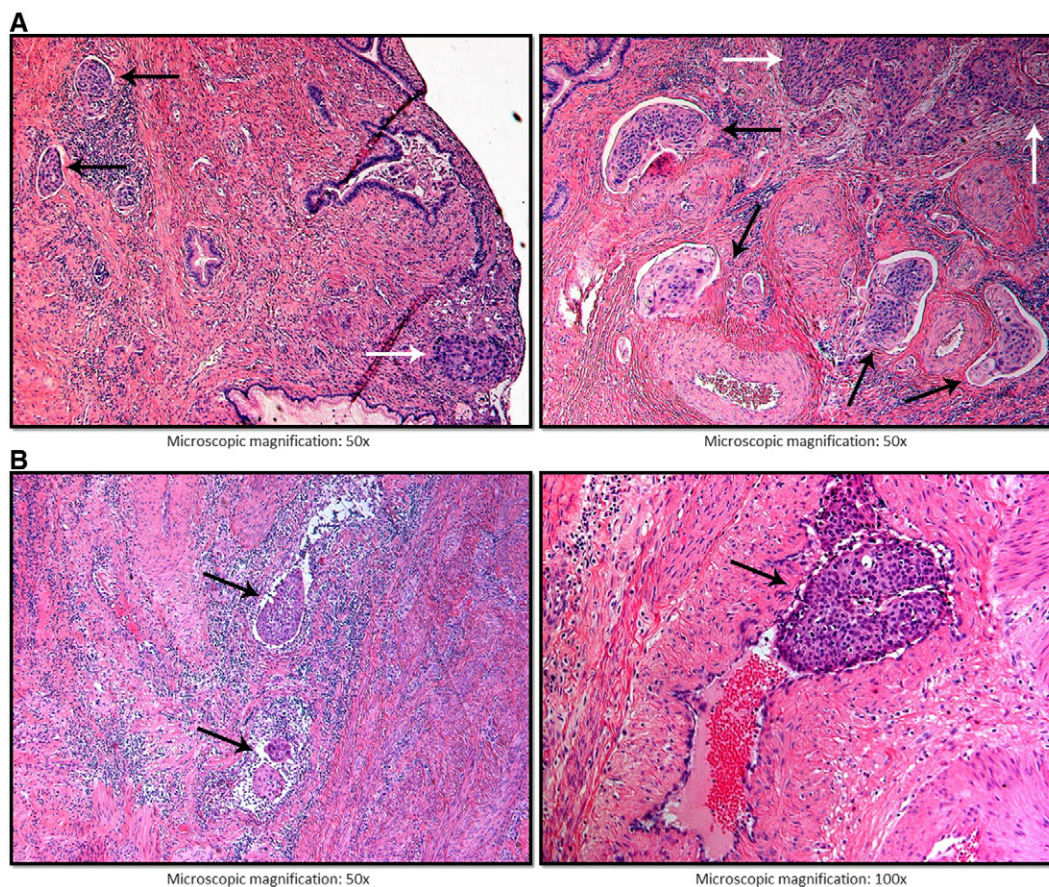


Fig. 1. Hematoxylin–eosin (HE) staining of LVSI in cervical cancer. A. Conjoined LVSI (black arrow), defined as lymphatic and/or vascular space invasion of tumor cells in the tumor or at the tumor front (white arrow). B. Satellite LVSI (black arrow), defined as lymphatic and/or vascular space invasion of tumor cells at least 10 mm from the tumor.

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