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# Pattern of invasion is of prognostic value in surgically treated cervical cancer patients

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**Abstract**

*Objectives.* Different patterns of invasion (representing different grades of tumor cell dissociation) are associated with prognostic outcome in cancer. We evaluated the prognostic value of different patterns of invasion (PI) in cervical carcinomas (CX).

*Methods.* Six hundred eleven surgically treated CX (FIGO IB to IIB) were re-evaluated histologically regarding the PI, using a three-level scoring system. Closed PI was defined as cohesive growth with well-delineated (pushing) borders. In finger-like PI the tumor grows in solid cords/trabecles. Highly dissociative growth in small groups or single cells was defined as spray-like PI. Types of PI were correlated to tumor stage, histomorphologic factors and prognostic outcome.

*Results.* Sixty percent of the tumors showed a spray-like PI, 30% a finger-like PI and only 7.4% were of the closed type. Spray-like PI showed a significant correlation with advanced stage disease, lymphovascular space involvement, poorly differentiated tumors and pelvic lymph node metastases. Spray-like PI was accompanied by a reduced 5-year overall survival when compared to the finger-like and closed PI (68.7% vs. 80.9% vs. 88.5%; $P = 0.0004$). The prognostic impact of the PI disappeared in node-positive patients ($P = 0.06$) but persisted in patients without pelvic lymph node disease ($P = 0.03$). In multivariate analysis, using COX regression model, the PI represented as independent prognostic factor.

*Conclusions.* Spray-like PI (i.e., highest degree of tumor cell dissociation) is associated with advanced tumor stages, increased rate of recurrency and a reduced overall survival. In separate analysis of patients with and without lymph node metastases, the impact of PI persisted only in node-negative cases as a prognostic factor.


*Keywords:* Cervical cancer; Prognosis; Tumor cell dissociation; Invasive front; Pattern of invasion

## Introduction

Several types of growth patterns have been described in various types of carcinomas, such as in gastric and endometrioid adenocarcinomas or in head and neck, tongue and skin cancers [1–5].

Broders [6] and Matzloff [7] were among the first to describe different types of patterns of invasion (PI) in cervical cancer. Since then, research in this area has been sparse [8–11].

As proposed in different studies, the growth patterns at the front of the tumoral invasion reflects the morphologic feature of tumor cell dissociation [1,5,10,11]. The knowledge of the prognostic impact of different types of infiltrative growth in surgically treated cervical carcinomas CX is limited and the results are contradictory [10–14]. We therefore evaluated the different types of infiltrative growth in surgically treated CX.

## Materials and methods

Data from patients with CX, staged FIGO IB to IIB, were obtained from the files of our so-called Wertheim–Archive [15], and the original histologic slides were re-examined. Patients who received neoadjuvant therapy, those with

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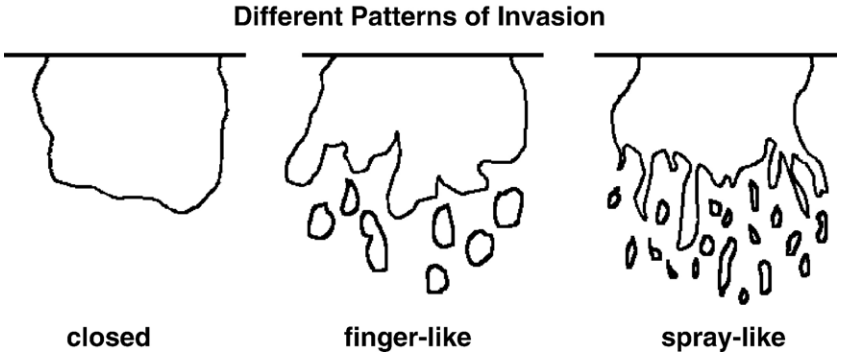


Fig. 1. Schematic description of the modified three-level scoring system for the description of the different types of infiltrative growth [4,8,13,14]. For details, see text.

incomplete local tumor resection (R1 or R2 resection) and tumors of other histologic type such as squamous cell and adenocarcinomas were excluded from the study. All women were treated with radical abdominal hysterectomy Piver type III [16] with systematic pelvic lymphadenectomy. Cases with pelvic lymph node metastases and/or parametrial involvement received adjuvant combined radiation therapy. The surgical specimens were handled in a standardized manner as described earlier [17]. All tumors were staged and classified according to the most recent WHO and TNM classifications [18,19].

For the description of the different types of infiltrative growth, we used a modified three-level scoring system and the criteria described previously [8,11,13,14].

Briefly, this scoring system differentiates between a closed, a finger- and a spray-like pattern of invasion. The closed or pushing pattern of invasion is characterized by a cohesive tumor growth with well-delineated but infiltrating borders and "pushing" margins (Fig. 1). Regardless of the presence of one small finger-like infiltration edge in a well-delineated tumor, the tumor was classified as closed type. A finger-like PI, on the contrary, shows a trabecular tumor growth in solid cords and cell groups with rounded edges, whereas the spray-like PI is defined by tumor growth in very small groups of infiltrating cells with sharpened tips, sometimes accompanied with the occurrence of single infiltrating cells in the cervical stroma (Fig. 1).

The intensity of the peritumoral inflammatory response was evaluated semi-quantitatively. The scoring system ranged from a negative and weak inflammatory response to a moderate and strong inflammatory reaction. The scores were obtained from a microscopic field using a 10-fold objective.

Follow-up data regarding recurrent disease and death were obtained from the clinical files.

Overall survival and recurrence-free survival were analyzed using Kaplan–Meier curves and log-rank test. Cox regression models, adjusted for clinicopathologic variables were fitted to evaluate the impact of different patterns of invasion on overall survival.

*P* values less than 0.05 were considered as statistically significant. All statistical analyses were performed using the software package SPSS for Windows®, release 11.5.1 (SPSS GmbH Munich, Germany).

Table 1
Patients characteristics

| | *N* | % |
|---|---|---|
| Stage distribution | | |
| FIGO IB1 | 304 | 49.8 |
| FIGO IB2 | 67 | 11.0 |
| FIGO IIA | 74 | 12.1 |
| FIGO IIB | 166 | 27.2 |
| Age distribution | | |
| ≤35 years | 197 | 32.2 |
| >35 years | 414 | 67.8 |
| Pelvic lymph node involvement | | |
| No | 411 | 67.3 |
| Yes | 200 | 32.7 |
| Lymphovascular space involvement | | |
| No | 217 | 35.5 |
| Yes | 394 | 64.5 |
| Tumor grade | | |
| G1 | 279 | 45.7 |
| G2 | 192 | 31.4 |
| G3 | 140 | 22.9 |
| Peritumoral inflammatory response | | |
| None/weak | 299 | 48.9 |
| Moderate | 141 | 23.1 |
| Strong | 171 | 28.0 |
| Pattern of invasion | | |
| Finger-like | 222 | 36.3 |
| Spray-like | 344 | 56.3 |
| Closed | 45 | 7.4 |

## Results

Six hundred eleven patients were included in the study. Their characteristics are given in Table 1. The median follow-up time was 75 months (95% confidence interval 67–83 months).

The majority of the tumors showed a high degree of tumor cell dissociation, represented by spray-like PI (56.3%; Fig. 2a), followed by finger-like PI (36.3%; Fig. 2b). The closed type of PI was seen only in 7.4% (Fig. 2c). Spray-like PI was significantly associated with lymphovascular space involvement, the occurrence of pelvic lymph node metastases and poorly differentiated (G3) tumors. There was no correlation to the grade of the peritumoral inflammatory response and the age of the patients at the time of the diagnosis (Table 2). The spray-like PI was significantly more common in FIGO stage II tumors.

There was also a difference between the different patterns of invasion regarding the 2-year and 5-year recurrence-free and overall survival (Tables 3a and 3b; Fig. 3).

In a separate analysis of node-negative and node-positive cases, the prognostic relevance of the pattern of invasion regarding recurrence-free as well as overall survival disappeared in node-positive patients but persisted in node-negative ones (Tables 3a and 3b).

Because of the fact that the closed type of PI was very rare in our study (7.4% of all cases) and was associated with a very good prognostic outcome, a separate analysis of the cases excluding this pattern of invasion was performed. In that analysis, a spray-like PI was accompanied by a significantly reduced 5-year overall survival ($P = 0.0012$). Also, in that

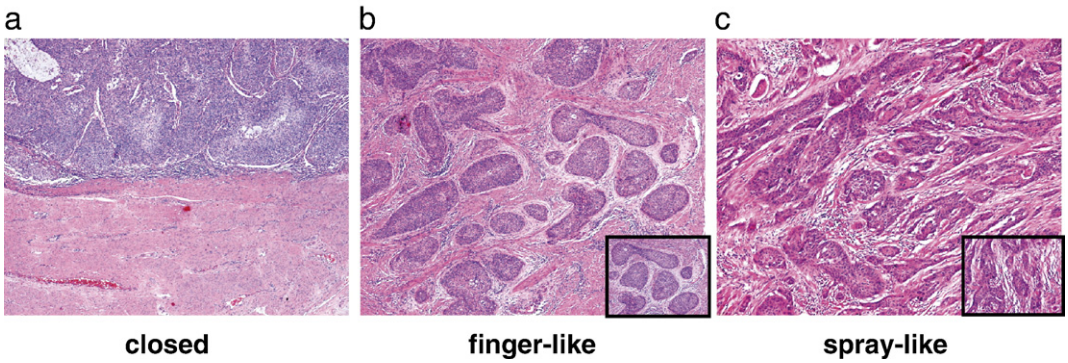


Fig. 2. Histologic pictures of the different types of infiltrative growth: (a) closed pattern of invasion with cohesive tumor growth with well-delineated infiltrating borders and "pushing" margins; (b) finger-like pattern of invasion with trabecular tumor growth in solid cords and tumor cell nests; (c) spray-like pattern of invasion with tumor growth in small groups of infiltrating cells and high tumor cell dissociation.

analysis, the prognostic relevance of the different patterns of invasion persisted in node-negative patients regarding recurrence-free as well as overall survival (Fig. 4). However, the prognostic relevance of the different types of invasion disappeared in patients with metastatic disease in pelvic lymph nodes (Fig. 5).

In the multivariate analysis using the stepwise Cox regression model, the different patterns of invasion represented as an independent prognostic factor (Table 4).

## Discussion

A high grade of tumor cell dissociation, represented by dissociative, non-cohesive tumor growth at the front of the invasion, morphologically characterized by an infiltration of small tumor cell clusters into the surrounding tissue (i.e., spray-like pattern; 4, 5, 11), has been reported to be of prognostic value in different types of carcinomas [1–4]. For gynecologic malignancies, the spray-like pattern of invasion is well established in the minimal deviation type of endocervical and the recently recognized endometrioid type endometrial adenocarcinoma with minimal deviation pattern [20].

In squamous cell carcinoma of the skin and the lower lip, a high grade of tumor cell dissociation, represented by a spray-like pattern of invasion (PI), was significantly associated with a high frequency of metastatic as well as recurrent disease [5,21].

Crissman et al. [10] were unable to see any prognostic value of the PI using a four-level scoring system in advanced CX treated by radiation therapy. Similar results were reported for patients who received radiation therapy prior to radical hysterectomy [22].

However, in cervical cancer patients with primary surgical treatment, high tumor cell dissociation with spray-like infiltration was associated with a reduced 5-year overall survival and an increased risk for metastatic disease [8,13,23,24]. It has been reported that the spray-like PI was significantly associated with an increased frequency of

Table 2
Correlation of the different patterns of invasion to clinicopathologic parameters

| | Pattern of invasion (%) | | | *P* value |
|---|---|---|---|---|
| | Closed | Finger-like | Spray-like | |
| Stage distribution | | | | |
| FIGO IB1 | 10.5 | 37.2 | 52.3 | |
| FIGO IB2 | 10.4 | 46.3 | 43.3 | |
| FIGO IIA | 5.4 | 28.4 | 66.2 | |
| FIGO IIB | 1.2 | 34.3 | 64.5 | 0.001 |
| Age distribution | | | | |
| ≤35 years | 8.1 | 34.0 | 57.9 | |
| >35 years | 7.0 | 37.4 | 55.6 | 0.675 |
| Pelvic lymph node involvement | | | | |
| No | 9.0 | 38.2 | 52.8 | |
| Yes | 4.0 | 32.5 | 63.5 | 0.014 |
| Lymphovascular space involvement | | | | |
| No | 17.1 | 34.1 | 48.8 | |
| Yes | 2.0 | 37.6 | 60.4 | <0.0001 |
| Tumor grade | | | | |
| G1 | 7.5 | 46.6 | 45.9 | |
| G2 | 6.3 | 34.9 | 58.9 | |
| G3 | 8.6 | 17.9 | 73.6 | <0.0001 |
| Peritumoral inflammatory response | | | | |
| None/weak | 7.4 | 35.5 | 57.2 | |
| Moderate | 7.1 | 31.2 | 61.7 | |
| Strong | 7.6 | 42.1 | 50.3 | 0.337 |

Table 3a
Recurrence-free survival for the different patterns of invasion with separate analysis of node-negative and node-positive patients (in square brackets 95% confidence intervals are given)

| | Pattern of invasion | | | *P* value |
|---|---|---|---|---|
| | Closed | Finger-like | Spray-like | |
| All cases ($n$ = 593) | | | | |
| 2-year recurrence-free survival | 90.8% [82.2–99.4] | 84.1% [79.1–89.0] | 73.9% [69.1–78.7] | |
| 5-year recurrence-free survival | 90.8% [82.2–99.4] | 79.3% [73.7–84.8] | 66.9% [61.5–72.2] | 0.0010 |
| Node-negative patients ($n$ = 401) | | | | |
| 2-year recurrence-free survival | 91.7% [82.8–100.0] | 91.5% [87.1–95.9] | 81.9% [76.6–87.1] | |
| 5-year recurrence-free survival | 91.7% [82.8–100.0] | 87.9% [82.6–93.1] | 77.4% [71.5–83.4] | 0.0409 |
| Node-positive patients ($n$ = 192) | | | | |
| 2-year recurrence-free survival | 85.7% [59.8–100.0] | 65.2% [53.1–77.2] | 60.3% [51.4–69.1] | |
| 5-year recurrence-free survival | 85.7% [59.8–100.0] | 57.1% [44.2–70.0] | 48.0% [38.3–57.8] | 0.1679 |

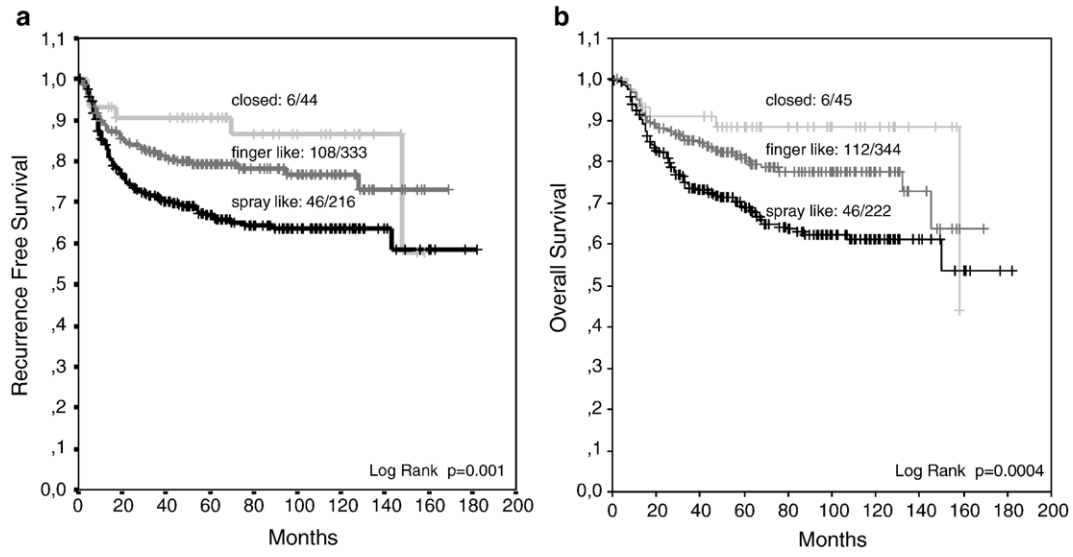


Fig. 3. Kaplan–Meier curve for all patients regarding recurrence-free (a) and overall survival (b) for the different patterns of invasion.

lymphovascular space involvement and large tumor size in FIGO IB tumors [14,25]. Contrary to our results (see Table 2), the rate of metastatic disease in pelvic lymph nodes and the increased rate of recurrent disease was not observed by some authors [26–28]. However, the comparison of these studies to our results is sometimes difficult because of the use of different scoring systems including two and four different types of PI, respectively, as well as the limited number of patients evaluated. Irrespective of the different scoring systems, the common finding of all these studies was that a high grade of tumor cell dissociation was associated with a poor prognostic outcome and a reduced 5-year survival in surgically treated CX patients [11,12,24,25]. The same has been reported by Spiro et al. [4] for patients with oral tongue cancer. In our analysis of surgically treated carcinomas of the cervix uteri, high tumor cell dissociation, represented by a spray-like pattern of invasion, was significantly associated with an advanced tumor stage (FIGO stage II tumors), the occurrence of metastatic disease in pelvic lymph nodes and a reduced recurrence-free as well as overall survival. In a separate analysis of patients with and without metastatic disease in pelvic lymph nodes, the prognostic value of the different patterns of invasion disappeared in node-positive patients, indicating that this parameter is only of impact in women without metastatic disease in pelvic lymph nodes.

In a multivariate analysis, the pattern of invasion appeared as an independent prognostic factor in the analysis of all patients and of those without pelvic lymph node metastases. To the best of our knowledge, there are no studies in the literature with a separate analysis of the different patterns of invasion in patients with cervical cancer and a separate analysis of cases with and without pelvic lymph node involvement using a uni- and multivariate approach.

For more concise handling of the parameter of the pattern of invasion and for a more exact description of the different patterns of invasion in CX, very complex scoring systems, including numerous levels as discussed by Beecham et al. [22] and others [10,26], should be avoided. Only well-defined scoring systems using a maximum of three levels [2,4,5,13,23] are capable of being used in routine pathology with a good interobserver agreement [11,26] and without being time consuming [11].

On the molecular level, a high grade of tumor cell dissociation was associated with a more frequent p53 expression in endometrial adenocarcinomas [2].

Finally, our data suggest that the spray-like pattern of invasion, representing a high grade of tumor cell dissociation, is positively correlated with a poor prognostic outcome in surgically treated cervical cancer patients. In order to reveal a correlation between the different morphologic types of infiltrative growth and molecular parameters, we are now

Table 3b
Overall survival for the different patterns of invasion with separate analysis of node-negative and node-positive patients (in square brackets 95% confidence intervals are given)

| | Pattern of invasion | | | *P* value |
|---|---|---|---|---|
| | Closed | Finger-like | Spray-like | |
| All cases ($n$ = 611) | | | | |
| 2-year overall survival | 91.0% [82.6–99.4] | 87.8% [83.4–92.1] | 82.2% [78.2–86.3] | |
| 5-year overall survival | 88.5% [78.9–98.0] | 80.9% [75.5–86.2] | 68.7% [63.5–73.9] | 0.0004 |
| Node-negative patients ($n$ = 411) | | | | |
| 2-year overall survival | 91.7% [82.8–100.0] | 95.5% [92.2–98.8] | 89.7% [85.6–93.8] | |
| 5-year overall survival | 88.7% [78.2–99.2] | 89.5% [84.4–94.6] | 80.1% [74.4–85.7] | 0.0352 |
| Node-positive patients ($n$ = 200) | | | | |
| 2-year overall survival | 87.5% [64.6–100.0] | 69.2% [58.0–80.4] | 69.4% [61.3–77.5] | |
| 5-year overall survival | 87.5% [64.6–100.0] | 60.3% [48.0–72.6] | 48.8% [39.2–58.3] | 0.0610 |

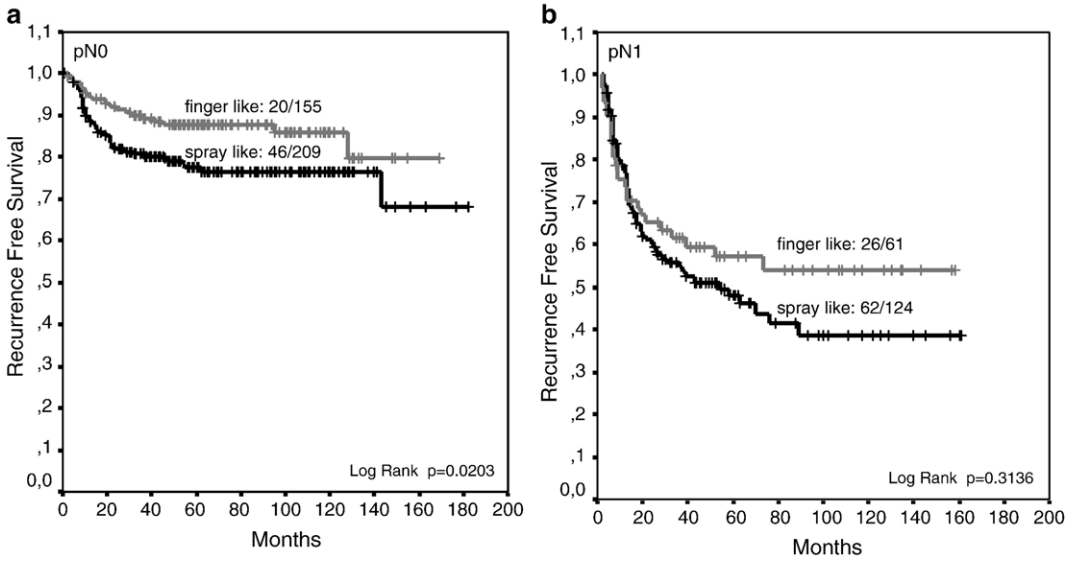


Fig. 4. Kaplan–Meier curve in node-negative patients regarding recurrence-free (a) and overall survival (b) for the spray-like and finger-like pattern of invasion (see text).

proceeding to immunohistochemical studies using the tissue microarray technology for high technical throughput for HGF/SF and its receptor c-met.

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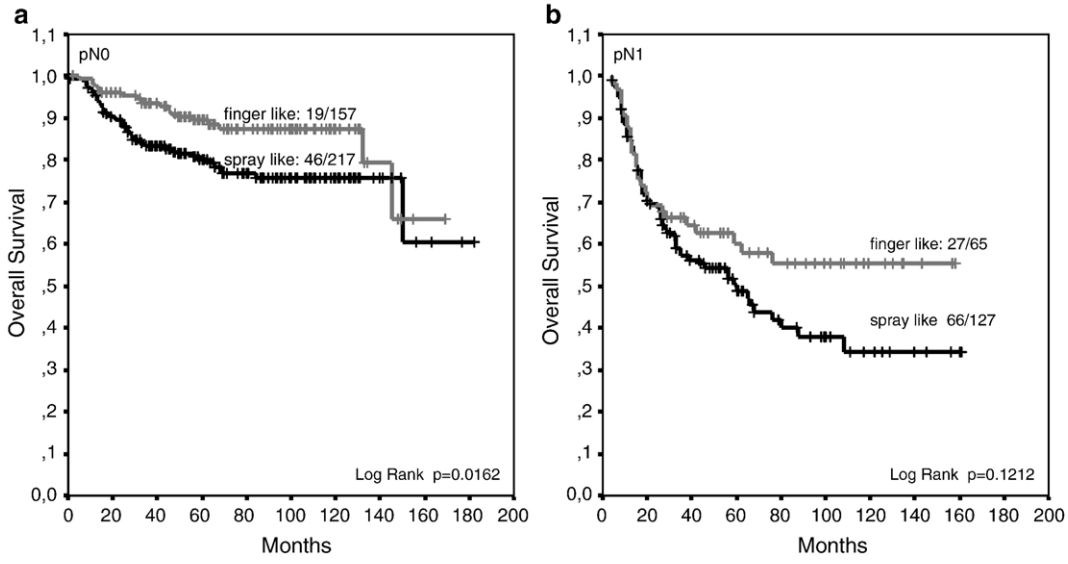


Fig. 5. Kaplan–Meier curve in node-negative patients regarding recurrence-free (a) and overall survival (b) for the spray-like and finger-like pattern of invasion (see text).

Table 4
Results of multivariate analysis of clinicopathologic variables regarding overall survival using COX regression for all patients included in the study (see text)

| | Relative risk | 95% confidence interval | *P* value |
|---|---|---|---|
| Staging | | | |
| FIGO IB1 | Reference | | |
| FIGO IB2 | 1.8 | 1.0–3.0 | 0.042 |
| FIGO IIA | 1.2 | 0.7–2.1 | 0.551 |
| FIGO IIB | 2.2 | 1.4–3.2 | <0.001 |
| Patients age [a] | 1.4 | 1.0–2.0 | 0.037 |
| Lymph node status | 2.4 | 1.7–3.4 | <0.001 |
| LVSI [b] | 1.5 | 0.9–2.3 | 0.086 |
| Tumor grade | | | |
| G1 | Reference | | |
| G2 | 1.2 | 0.8–1.8 | 0.358 |
| G3 | 1.7 | 1.2–2.6 | 0.007 |
| Peritumoral inflammatory response | | | |
| Strong | Reference | | |
| Moderate | 1.0 | 0.6–1.7 | 0.971 |
| None/weak | 1.5 | 1.0–2.4 | 0.042 |
| Pattern of invasion [c] | 1.4 | 1.0–2.1 | 0.047 |

[a] Age ≤35 vs. age >35 years (patients >35 years of age counted as reference).
[b] Lymphovascular space involvement vs. no lymphovascular space involvement (tumors without lymphovascular space involvement counted as reference).
[c] Spray like vs. finger like (tumors with finger-like pattern of invasion counted as reference).

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