# Post-recurrence disease specific survival in cervical cancer patients

David Cibula[1], Lukáš Dostálek[1], Jiri Jarkovsky[2], Stijn C.H. Mom[3], Aldo Lopez[4], Henrik Falconer[5], Giovanni Scambia[6], Ali Ayhan[7], Sarah H. Kim[8], David Isla Ortiz[9], Jaroslav Klat[10], Andreas Obermair[11], Giampaolo Di Martino[12], Rene Pareja[13], Ranjit Manchanda[14], Jan Kosťun[15], Ricardo dos Reis[16], Mehmet Mutlu Meydanli[17], Diego Odetto[18], Laky Rene[19], Ignacio Zapardiel[20], Vit Weinberger[21], Klára Benešová[2], Martina Borčinová[1], Fernando Cardenas[4], Emelie Wallin[5], Luigi Pedone Anchora[6], Huseyin Akilli[7], Nadeem R. Abu-Rustum[8], Salim Abraham Barquet Muñoz[9], Veronika Javůrková[10], Daniela Fischerová[1], Luc R.C.W. van Lonkhuijzen[3]

[1] Gynecologic Oncology Center, Department of Obstetrics and Gynecology, First Faculty of Medicine, Charles University and General University Hospital (Central and Eastern European Gynecologic Oncology Group, CEEGOG), Prague, Czech Republic

[2] Institute of Biostatistics and Analyses, Faculty of Medicine, Masaryk University, Brno, Czech Republic

[3] Amsterdam Medical Center, Amsterdam, The Netherlands

[4] Department of Gynecological Surgery, National Institute of Neoplastic Diseases, Lima, Peru

[5] Department of Pelvic Cancer, Karolinska University Hospital and Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden

[6] Fondazione Policlinico Universitario A. Gemelli, IRCCS, UOC Ginecologia Oncologica, Dipartimento per la salute della Donna e del Bambino e della Salute Pubblica, Rome, Italy

[7] Baskent University School of Medicine Department of Gynecology and Obstetrics Division of Gynecologic Oncology, Ankara, Turkey

[8] Memorial Sloan Kettering Cancer Center, USA

[9] Gynecology Oncology Center, National Institute of Cancerology Mexico, Mexico

[10] Department of Obstetrics and Gynecology, Faculty of Medicine, University Hospital and University of Ostrava, Ostrava, Czech Republic

[11] Queensland Centre for Gynaecological Cancer; The University of Queensland

[12] University of Milano-Bicocca, Department of Obstetrics and Gynecology, Gynaecologic Oncology Surgical Unit, ASST-Monza, San Gerardo Hospital, Monza, Italy

[13] Department of Gynecologic Oncology, Instituto Nacional de Cancerología, in Bogotá, Colombia

[14] Wolfson Institute of Preventive Medicine, Barts Cancer Centre, Queen Mary University of London, & Barts Health NHS Trust, London, UK

[15] Department of Gynaecology and Obstetrics, University Hospital Pilsen, Charles University, Prague, Czech Republic

[16] Department of Gynecologic Oncology and Reproductive Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas 77030, United States

[17] Department of Gynecologic Oncology, Zekai Tahir Burak Women's Health and Research Hospital, University of Health Sciences, Ankara, Turkey
[18] Department of Gynecologic Oncology, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano, Buenos Aires, Argentina
[19] Gynecology, Medical University of Graz, Graz, Austria
[20] Gynecologic Oncology Unit, La Paz University Hospital - IdiPAZ, Madrid, Spain
[21] University Hospital Brno, Medical Faculty of Masaryk University

**Corresponding author:** David Cibula, Gynecologic Oncology Center, Charles University and General University Hospital, Apolinarska 18, 12000 Prague, Czech Republic. Tel.: +420224967451. E-mail: dc@davidcibula.cz

## Abstract

**Background** Up to 26% of early-stage cervical cancer patients relapse after primary surgical treatment. However, little is known about the factors affecting prognosis following disease recurrence. Hence, the aim of this study was to evaluate post-recurrence disease-specific survival (PR-DSS) and to identify respective prognostic factors.

**Methods** Data from 528 early-stage cervical cancer patients who relapsed after primary surgical treatment performed between 2007-2016 were obtained from the SCANN study (Surveillance in Cervical CANcer). Parameters related both to primary disease and recurrence were combined to develop a multivariable Cox proportional hazards model predicting PR-DSS.

**Results** Five-year PR-DSS reached 39.1% (95% CI: 22.7% - 44.5%) with median disease-free interval between primary surgery and recurrence (DFI1) of 1.5 years and median survival after recurrence of 2.5 years. Six variables significant in multivariable analysis were included in prognostic model; two related to primary treatment: largest tumour size and lymphovascular space invasion; and four related to recurrence: DFI1, age at recurrence, presence of symptoms, and recurrence type. C-statistics of the final model after 10-fold internal validation equalled 0.701 (95% CI: 0.675 - 0.727). Three risk groups significantly differing in prognosis were identified, with 5-year PR-DSS of 81.8%, 44.6%, and 12.7% in the highest risk group.

**Conclusions** We developed the first robust model of PR-DSS, stratifying relapsing cervical cancer patients according to their risk profile using six traditional and easily accessible prognostic markers. Developed model can be utilized in clinical practice as one of the parameters in the choice of modality and intensity of recurrence treatment.

**Highlights:**

- In in cervical cancer patients after primary surgical treatment, survival after recurrence (PR-DSS) reached 39.1% at 5-years post-recurrence.
- Strongest factors of PR-DSS were the size of the primary tumour and the presence of symptoms at recurrence diagnosis.
- Presence of symptoms at recurrence remained significant prognostic factor even after correction for lead-time bias.
- The best PR-DSS had LN and LVSI negative stage I patients suffering from solitary asymptomatic recurrence.

# Introduction

Early-stage cervical cancer carries generally good prognosis with multiple evidence for survival improvement during the past few decades.[1] Despite that, 5-26% of early-stage patients still relapse after the primary treatment.[2-4]

A 5-year survival rate in relapsing patients has been reported in the broad range of 15.0-50.0%,[5-9] indicating that they represent a heterogeneous group substantially differing in prognosis. Though, available literature mainly focuses on the survival after the primary treatment, with FIGO stage, tumour size and histology, age, lymph node status, and parametrial involvement as most frequently reported prognostic parameters.[10-13] Only a handful of studies have analysed prognostic factors for post-recurrence disease-specific survival (PR-DSS) in multivariable setting. The available data suggested broad portfolio of potential prognostic parameters, such as length of disease free interval from surgery to recurrence diagnosis (DFI 1),[9] type and localization of recurrence,[5,7,8,14] presence of symptoms at the time of diagnosis,[5] levels of C-reactive protein and albumin,[7] HPV16 negativity,[14] and lymphatic/ lymphovascular space invasion.[5] However, previously published studies were mostly based on single-institutional data with retrospective cohorts including between 43 to 165 relapsing patients from long study periods of up to 16 years.[7-9,14] The only multi-institutional study was limited to only 70 relapsing patients.[5] No comprehensive model incorporating risk factors for PR-DSS in early-stage cervical cancer has been introduced so far.

In our study we have used the large database of early-stage cervical cancer patients from the retrospective international SCCAN study (Surveillance in Cervical CANcer). The aim was to evaluate PR-DSS in relapsing patients and to identify respective prognostic factors, using parameters related both to the time of primary treatment and recurrence diagnosis.

# Methods

**Study design and participants**

The SCCAN (Surveillance in Cervical CANcer) international, multicentre, retrospective cohort study evaluated the recurrence patterns in the cervical cancer survivors. The SCCAN study consortium consisted of 20 tertiary centres of excellence, with large volume of cervical cancer cases, located in Europe, Asia, North America, and Latin America.

Patients were retrospectively included if they met the following inclusion criteria: (i) histologically confirmed cervical cancer treated between 2007 and 2016; (ii) TNM stage T1a-T2b (based on the preoperative assessment; American Joint Committee on Cancer - Cervix Uteri Cancer Staging); (iii) primary surgical management including fertility-sparing procedures; (iv) and at least 1 year of follow-up data availability. Patients were eligible irrespective of adjuvant treatment, neoadjuvant chemotherapy, tumour type, lymph node status, or lymph node staging.

Patients were not eligible if they had precancer disease (including CIN 3 neoplasia), they were treated with definitive radiotherapy/ chemoradiation, primary surgical treatment was abandoned intra-operatively, or follow-up data availability was limited to less than one year. Overall, data of 4343 early-stage cervical cancer patients were included into the database.

The protocol was approved by the institutional review board of the lead institution (General University Hospital in Prague, Czech Republic) in 2016. Institutional review board approval at the participating sites was a prerequisite for participation. Due to the retrospective nature of the study, the need for informed consent was waived by the Institutional Review board. The study was performed in accordance with the Declaration of Helsinki.

**Data collection**

Following data about the primary treatment were collected: type of uterine procedure, type of parametrectomy, surgical approach, lymph node (LN) staging and its extent, type of neoadjuvant therapy, and type of adjuvant treatment. The type of parametrectomy was classified using Querleu–Morrow modified classification system.[15] Regarding disease characteristics, we collected data about the type and largest size of the tumour (pathologically confirmed), pathologic stage, number and size of removed/ positive lymph nodes, parametrial involvement, lymphovascular space invasion, and grade. Histological types of the tumours were classified according to WHO classification and were consequently clustered to the six main groups: Adenocarcinoma, Adenosquamous cancer, Squamous cell carcinoma, Sarcoma, Neuroendocrine cancer, and cluster of others. In relation to the disease recurrence, the data about the recurrence diagnosis, precise location of the recurrence, presence of symptoms, and recurrence treatment modality were collected.

After the patients´ data were received, the database was cleaned and excluded were patients with missing information on key predictor variables, such as tumour and surgery characteristics (tumour type, tumour size), adjuvant therapy, and details about the follow up (date of the last visit, disease status at the last visit, and date of recurrence/ death).

**Data analyses**

Standard descriptive statistics were used to summarize the data: categorical variables were described by absolute and relative frequencies; continuous variables were described by mean with standard deviation and median with interquartile range. Missing values of grade (24.8% patients) were for multivariable analysis imputed on the basis of other predictors (age, number of positive pelvic lymph nodes, largest tumour size, LVSI, histotype, pT, adjuvant therapy); in total, five different data set were created by multiple imputation and therefore the subsequent results had to be pooled. Disease free interval (DFI 1) was measured as period from the surgery to the date of recurrence or death of disease, which ever occurred sooner. Median time to death was calculated as a period from the date of recurrence diagnosis to death.

The relation between patients' characteristics and analysed endpoint (post-recurrence disease-specific survival; PR-DSS) was evaluated by univariable and multivariable Cox proportional hazard models and described by hazard ratios, their 95% confidence intervals and statistical significance. A backward stepwise algorithm and Akaike information criterion (AIC) were used to choose the optimal multivariable model from predictors which were found to have a significant impact on disease-free survival in univariable analyses ($p < 0.1$). Discrimination ability of the model was assessed using the Harrell's C-index. A 10-fold cross-validation was performed to obtain estimates of model performance that are adjusted for in-sample optimism. A risk score was derived from regression coefficients (β) of the model which were weighted to the maximum sum of 100 points. The results of the model were expressed by Kaplan-Meier curves based on stratified risk score. Analysis was computed using SPSS 25.0.0.1 and R-3.6.1.

# Results

**Cohort characteristics**

We analysed the data from 528 patients after primary surgical treatment of early-stage cervical cancer. All patients either experienced recurrence or disease-related death in case that recurrence was not diagnosed prior to death of the patient (17 patients).

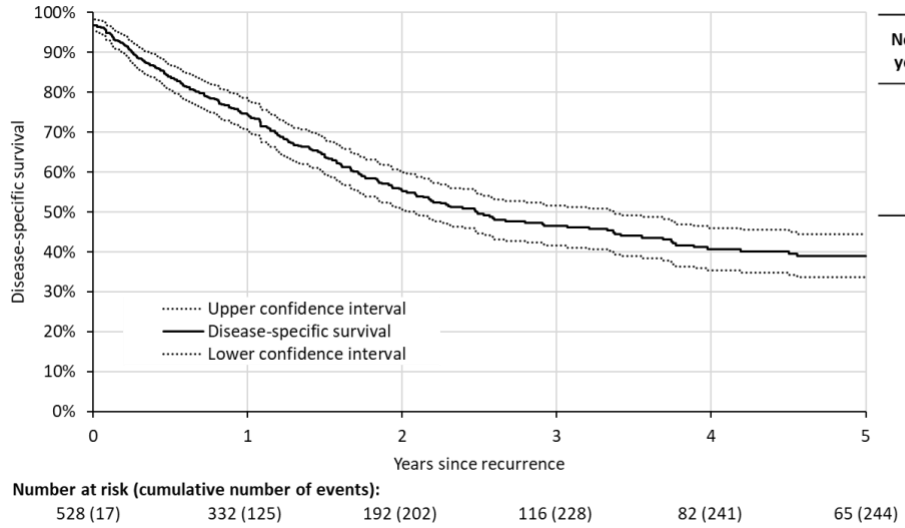
Characteristics of the relapsed patients at the time of primary diagnosis and at relapse are summarized in Table 1. At the time of primary treatment, majority of patients had squamous cell

carcinoma (60.2%) or adenocarcinoma (24.6%), primary tumour size of 2-3.99 cm (42.6%), negative pelvic lymph nodes (63.8%), 58.3% had lymphovascular space invasion, but only 8.3% had positive parametria. Majority of patients underwent radical hysterectomy (90.5%), followed by simple hysterectomy (3.6%) and radical trachelectomy (2.8%). Adjuvant treatment was administered to 62.7% of patients.

The recurrence was solitary in 61.0% of patients, out of which in 72.7% localized in pelvis (234/322) and in 27.3% distantly (88/322). Multifocal recurrence was diagnosed in 37.5% of patients, located in the pelvis and distantly in 65.2% (129/198) or distantly only in 30.8% (61/198). In 51.7% of patients, recurrence was symptomatic, and in 35.8% asymptomatic. Prevailing treatment modality for recurrence was chemotherapy (34.1%), chemoradiotherapy (21.8%), surgery ± chemoradiotherapy (21.6%), while only 4.4% of patients did not receive any further treatment (Table 1).

**Post-recurrence disease-specific survival (PR-DSS)**

PR-DSS in the whole cohort reached 39.1% (95% CI: 33.7; 44.5) at 5 years after recurrence diagnosis (Fig. 1). Median disease-free interval (DFI 1) between the primary surgery and the recurrence diagnosis for the whole cohort was 1.5 years and median time to death after recurrence according to Kaplan-Mayer estimates was 2.5 years.




| No. of years | Disease-specific survival after recurrence (95% confidence interval) |
|---|---|
| 1 | 74.5% (70.6%; 78.4%) |
| 2 | 55.1% (50.4%; 59.9%) |
| 3 | 46.6% (41.6%; 51.6%) |
| 4 | 40.7% (35.4%; 46.0%) |
| 5 | 39.1% (33.7%; 44.5%) |

**Figure 1** Disease-specific survival after recurrence in all relapsed patients (N=528). Time 0 represents the date of recurrence diagnosis.

**Univariable analysis of PR-DSS prognostic factors**

The results of the univariable analysis of the prognostic factors are summarized in Table 2. Certain characteristics of the primary tumour turned to be significant, such as number of positive lymph nodes, largest tumour size, LVSI, grade and parametrial invasion. Additionally, recurrence localization, type of recurrence, DFI 1, and presence of symptoms at the time of recurrence diagnosis were also significantly associated with PR-DSS.

***Localization and type of the recurrence***

Localization of the recurrence was significantly associated with PR-DSS ($p \leq 0.027$), reaching at 5-years 46.9%, 36.2% and 25.0% for pelvic, distant, and combined recurrences, while the median time to death for the respective groups was 47, 30, and 18 months (Fig. 2A).

Type of recurrence was also significant determinant of PR-DSS irrespective of its localization, reaching at 5-years 47.9% and 23.9% for solitary and multifocal recurrence, respectively, with median time to death of 19 and 17 months (Fig. 2B).

***Disease free interval from primary surgery to recurrence (DFI 1)***

PR-DSS was clearly dependent on the DFI 1. At 5-years, PR-DSS of patients was 29.0%, 40.8% and 49.9% for patients with DFI 1 <1 year, 1-2 years, and ≥2 years, respectively, with median time to death of 19, 35, and 48 months (Fig. 2C). The difference between the groups was significant except between 1-2 years and ≥2 years ($p = 0.195$).

***Presence of symptoms at the time of diagnosis***

Significant differences in PR-DSS and median time to death were observed when comparing patients differing in presence of symptoms at the time of recurrence diagnosis (Fig. 2D): 35.8% patients were asymptomatic and 51.7% symptomatic. PR-DSS at 5 years was 55.3% and 28.3% with median DFI 1 of 18 and 19 months, and median time to death of 76 and 20 months in asymptomatic and symptomatic patients, respectively.

In order to exclude the role of a lead-time bias, the survival difference between symptomatic and asymptomatic patients was also calculated from the date of primary surgery (Fig. 2E). The difference in PR-DSS remained significant ($p < 0.001$). Median time from primary surgery to death equalled 156 and 52 months for patients with asymptomatic and symptomatic recurrence.

An additional significant difference was found between symptomatic and asymptomatic patients in recurrence localization ($p = 0.026$). Symptomatic recurrences were more frequently located distantly

while pelvic recurrences were more frequently diagnosed in asymptomatic patients. Frequency of combined recurrences did not differ between the groups.

The presence of symptoms significantly correlated with the type of visit when the recurrence was diagnosed ($p < 0.001$), as the vast majority of asymptomatic recurrences (96.3%) were diagnosed at pre-scheduled visit and 94.5% of recurrences diagnosed at unscheduled visit were symptomatic. Still, 55% (151/273) of all symptomatic recurrences were diagnosed at the scheduled visits.

We did not observe any time-dependent trend in frequency of symptoms presence among relapsing patients in relation to the length of the DFI 1 ($p = 0.108$).

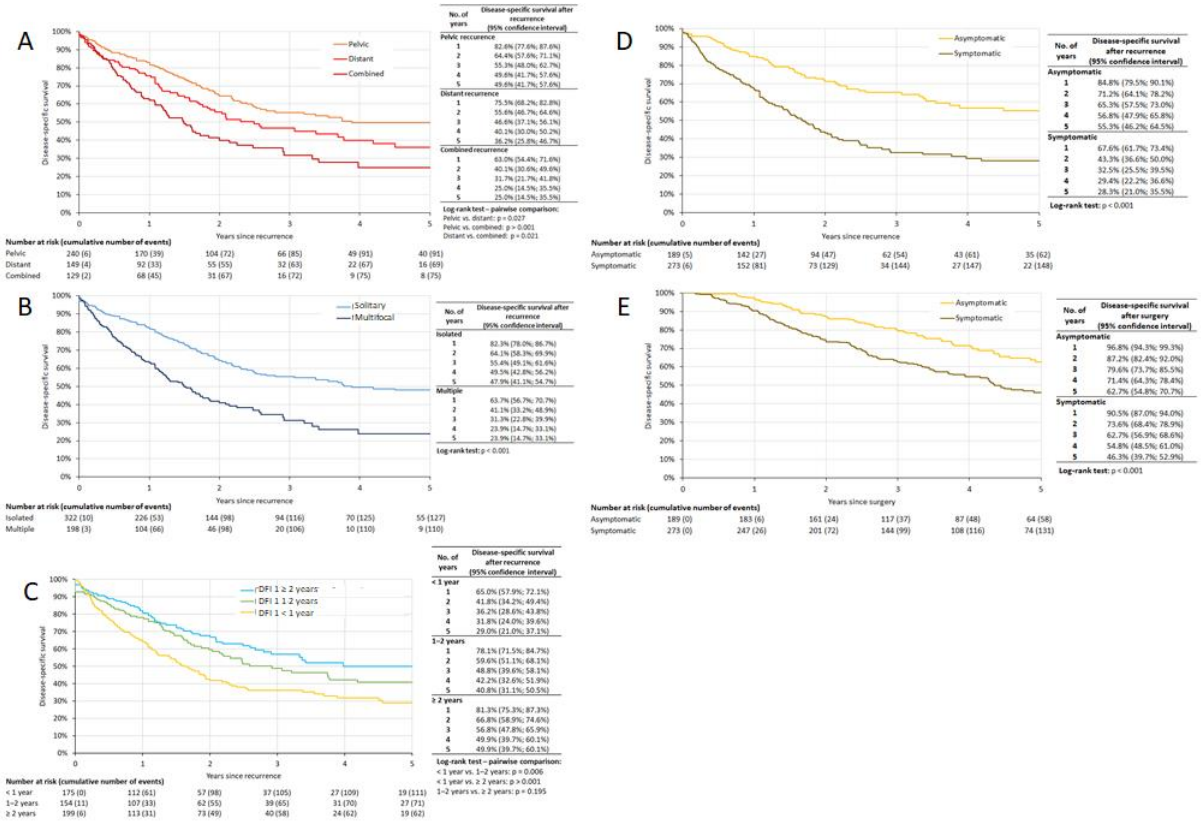


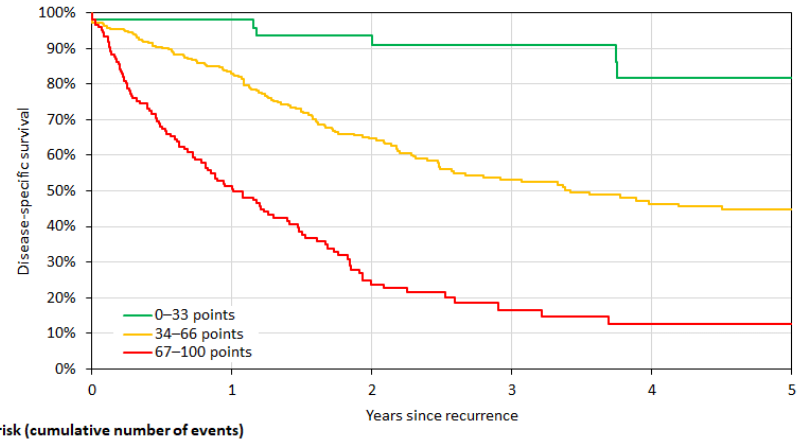

**Figure 2** Disease specific survival of recurring patients according: **A:** Recurrence localization; **B:** Type of recurrence; **C:** disease-free interval (DFI 1) from primary surgery to recurrence diagnosis; **D:** presence of the symptoms at the time of diagnosis: Time 0 represents time of recurrence diagnosis; **E:** presence of the symptoms at the time of diagnosis: Time 0 represents time of primary surgery.

**Prognostic model development**

In the multivariable analysis, significant PR-DSS prognostic factors included two characteristics from the time of primary treatment (largest tumour size and LVSI) and four recurrence-related factors (age at recurrence, DFI 1, presence of symptoms at the time of diagnosis, and solitary/ multifocal type of recurrence) (Table 3). The Harrell's concordance statistic factor (C-statistics) of the resulting model was 0.712 (95% CI: 0.678; 0.746). After performing the 10-fold internal cross-validation, the average AUC reached 0.701 (95% CI: 0.675; 0.727).

The beta coefficients of the multivariable model were consequently converted into the risk points (Table 3). Based on the results, three groups stratifying the patients according to the risk score were created: (i) 0-33 points; (ii) 34-66 points; and (iii) 67-100 points. Pairwise comparison of the groups proved significant in PR-DSS prognosis between the groups ($p < 0.001$).

Kaplan-Meier PR-DSS curve for the three respective risk-score groups is shown in Fig. 5. 5-year disease specific survival equalled 81.8%, 44.6%, and 12.7% in groups with increasing risk score.




| No. of years | Disease-specific survival (95% confidence interval) |
|---|---|
| **0–33 points** | |
| 1 | 98.1% (94.5%; 100.0%) |
| 2 | 90.9% (82.3%; 99.5%) |
| 3 | 90.9% (82.3%; 99.5%) |
| 4 | 81.8% (67.5%; 96.0%) |
| 5 | 81.8% (67.5%; 96.0%) |
| **34–66 points** | |
| 1 | 83.0% (78.7%; 87.4%) |
| 2 | 64.6% (58.7%; 70.5%) |
| 3 | 53.1% (46.4%; 59.7%) |
| 4 | 46.4% (39.3%; 53.5%) |
| 5 | 44.6% (37.4%; 51.9%) |
| **67–100 points** | |
| 1 | 51.2% (43.0%; 59.5%) |
| 2 | 23.7% (15.8%; 31.6%) |
| 3 | 16.6% (8.9%; 24.3%) |
| 4 | 12.7% (5.1%; 20.3%) |
| 5 | 12.7% (5.1%; 20.3%) |

**Log-rank test – pairwise comparison:**
p < 0.001 for all pairs

**Number at risk (cumulative number of events)**

| | | | | | | |
|---|---|---|---|---|---|---|
| 0–33 points | 53 (1) | 46 (1) | 34 (4) | 26 (4) | 18 (6) | 16 (6) |
| 34–66 points | 318 (9) | 218 (49) | 134 (93) | 79 (114) | 57 (123) | 44 (125) |
| 67–100 points | 149 (3) | 66 (69) | 22 (99) | 9 (104) | 5 (106) | 4 (106) |

**Figure 5** Disease specific survival after recurrence of all patients stratified by risk score (N=528). Time zero was set at date of recurrence diagnosis.

**Long-time survivors with no evidence of disease at 3-years post-recurrence**

Sixty-four patients with no evidence (NED) of disease at 3-years post recurrence treatment were identified (Supplementary table 1). The best long-term survival prognosis had, as expected, stage I patients without neither positive LN nor LVSI at the time of primary treatment, who suffered from asymptomatic solitary recurrence. Surprisingly, DFI 1 did not reach significance between those who remained free of disease and patients who recurred or died within 3 years after the first recurrence ($p = 0.058$).

Interestingly, among long-term survivals, there were also cases of belonging to higher risk groups. Overall, 10 patients had positive LN at the time of primary treatment, nine of them received adjuvant radiotherapy or chemoradiation after primary surgery. All those patients had isolated recurrence localized in the pelvis (6), in the abdominal cavity (2) or in lungs (2). Chemoradiation was the prevailing therapy of the recurrence (7 cases).

Moreover, six of the long-term survivors had multifocal recurrence, always combining pelvic localization with either abdominal cavity (4) or lungs (2).

Third interesting group of higher-risk long-term survivors were 20 patients diagnosed with extrapelvic (distant) recurrence, majority of whom had primary tumour size <2 cm (14 cases). Recurrence was predominantly localized in abdominal cavity (abdominal 9x, ovary 1x) or in the lungs (7x). Majority, 13 patients, were treated for recurrence by surgery, eventually in combination with adjuvant chemoradiation.

## Discussion

The aim of this retrospective international multicentre study was to evaluate a post-recurrence disease-specific survival (PR-DSS) and to identify respective prognostic factors in relapsing cervical cancer patients who previously underwent primary surgical treatment for early-stage disease. 528 patients experiencing recurrence were identified in the cohort of 4343 cases included in the SCCAN study database. The PR-DSS reached 39.1% at five years post-recurrence with the median survival after recurrence of 2.5 years and DFI 1 of 1.5 years. The key predictive factors related to PR-DSS in the multivariate setting were two factors from the time of primary treatment (largest pathological tumour size and LVSI), as well as four recurrence-related characteristics (age at recurrence, DFI 1, recurrence type, and presence of symptoms at the time of diagnosis). Based on the multivariable model, we stratified the cohort into 3 risk-groups significantly differing in prognosis with PR-DSS at 5-years of 81.8%, 44.6%, and 12.7%.

As the majority of early-stage cervical cancer patients are cured, the literature is rather scarce concerning the post-recurrence prognosis and related risk factors. Moreover, all previously published studies were based on limited cohorts of 43-165 relapsing patients, covering mostly heterogeneous populations treated for all disease stages by different modalities, which, with one exception,[5] were all based on single institutional data.

In the study of 121 stage I/II recurrent cervical cancer patients after primary surgical treatment in single Taiwanese hospital, PR-DSS was directly related to extravaginal relapse (HR 2.56; 95% CI: 1.28-

5.12; $p$ = 0.008) and inversely to HPV16 positivity (HR 0.6; 95= CI: 0.38-0.96; $p$ = 0.033).[6] In a more heterogeneous group of 116 relapsed patients treated between 1998 and 2014 in Austria, a history of previous radiotherapy (HR 2.7; 95% CI: 1.1-6.9; $p$ = 0.03), peritoneal carcinomatosis/ multiple recurrent sites (HR 4.2; 95% CI: 1.9-9.3; $P$ < 0.001), and Glasgow index composed of serum C reactive protein and albumin levels (HR 1.6; 95% CI: 1.1-2.5; $p$ = 0.01) were identified as negative prognostic factors in multivariable analysis.[7] In a similar cohort from Japan, including 165 cases with recurrence primarily treated for all stages of disease, only localization of recurrence remained significant in the multivariable analysis of PR-DSS.[8] Though, only limited number of prognostic variables were tested in this study, neither analysing recurrence localization-unrelated characteristics nor DFI 1.[8] Finally, data from 70 relapsing patients with FIGO stage 1A1-1B1 drawn from the Danish National Cohort Study identified multiple sites of recurrence (HR 2.72; 95% CI: 1.32-5.61; $p$ = 0.0066), LVSI (HR 2.23; 95% CI: 1.04-4.8; $p$ = 0.04), and presence of symptoms at recurrence (HR 2.52; 95% CI: 1.08-5.9; $p$ = 0.033) as simple risk factors for PR-DSS.[5]

None of the previously published studies aimed to create a comprehensive model for PR-DSS risk-groups stratification according to their prognosis. Such prognostic models were, however, developed for relapsing patients with ovarian or endometrial cancers. The PR-DSS nomogram based on the results of 4,739 GOG-trials patients with advanced-stage high-grade ovarian carcinoma was composed of DFI 1, tumour histology, performance status, FIGO stage, and age of the patient; while DFI 1 alone accounted for 85% of the prognostic information.[16] In recurrent endometroid endometrial cancer, PR-DSS stratification of risk groups was done according to the type of recurrence, level of cancer antigen 125 at the time of the recurrence diagnosis, and on DFI 1.[21] In our study, six easily accessible prognostic variables were included in the prognostic model for PR-DSS. The strongest risk factor related to PR-DSS was the size of the primary tumour, followed by the presence of symptoms at the time of diagnosis.

Majority of patients with cervical cancer are symptomatic at the time of recurrence, with pain, bleeding, cough and ileus as the most prevalent symptoms.[3,17-19] It was previously shown that recurrences in asymptomatic patients are more likely to be small, limited to one location, and tend to be found in patients with good functional status, thus with overall better prognosis and expected longer survival after recurrence.[20,21] Also in our study, asymptomatic recurrences were frequently localized in pelvis and were associated with significant PR-DSS benefit.

However, we are aware that better prognosis after asymptomatic recurrence can result from the lead-time bias: earlier detection makes an impression of longer survival, when in reality, a patient lives with a known recurrence for longer time but dies at the same time as patient diagnosed later, while symptomatic. To eliminate this bias at least partially, survival was also evaluated since the

primary diagnosis. The difference in PR-DSS remained significant between groups with symptomatic and asymptomatic recurrence. Even though this outcome seemingly supports the prognostic importance of active surveillance, retrospective data does not allow for making definitive conclusions. It cannot be ruled out that the survival benefit of asymptomatic recurrences is related to tumour biology, and slow growing, not aggressive tumours, with better prognosis, are more likely diagnosed when they are asymptomatic. Obtaining evidence of the significance of active surveillance is only possible in a prospective study.

It is, however, important to emphasize that 55% of symptomatic recurrences in our study were diagnosed during the scheduled follow-up visits, suggesting that many symptomatic patients waited for the scheduled appointment and did not consult specialist when symptoms arose.

Our study represents, to our knowledge, the largest analysis of PR-DSS pattern in early-stage cervical cancer patients. We utilised a large dataset composed of validated data from carefully selected tertiary centres of excellence with high volumes of cervical cancer patients geographically distributed on four continents. The cohort size was sufficient to analyse prognostic significance of large number of prognostic markers, both related to the primary treatment and to the recurrence diagnosis, all of which are routinely assessed and easily accessible. Furthermore, the discrimination ability of the resulting multivariable model was internally validated using cross-validation and performance was assessed by C-statistics (=0.701), indicating good prognostic accuracy of our model.

The major limitation of this study is its retrospective design, which may cause biases, especially related to patient selection, since only these with complete data availability were registered to the study.

In conclusion, we analysed PR-DSS in early-stage cervical cancer patients who experienced disease recurrence. The PR-DSS reached 39.1% at five years with the median survival after recurrence of 2.5 years and median DFI 1 of 1.5 years. We also developed the first robust model for PR-DSS stratifying relapsing cervical cancer patients according to their risk profile using six traditional prognostic markers. The strongest factor for the length of post-recurrence survival was the maximal size of the primary tumour, followed by the presence of symptoms at the time of recurrence diagnosis, which remained significant even after the correction for lead-time bias. The model allowed for cohort stratification into three risk groups significantly differing in prognosis with PR-DSS at 5-years of 81.8%, 44.6%, and 12.7% in the increasing risk groups.

The best long-term survival prognosis had stage I patients who had neither positive LN nor LVSI at the time of primary diagnosis, suffering from asymptomatic pelvic solitary recurrence. Significantly better prognosis of patients who were asymptomatic at the time of recurrence can serve as a

supporting argument for active surveillance, but its significance can only be verified in a prospective trial.

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# Tables

**Table 1.** Baseline characteristics of patients with cervical cancer recurrence after surgery

| Parameters | | Description* |
|---|---|---|
| **Characteristics at the time of primary treatment** | | |
| Age at surgery | | 47.6 (± 12.6); 46 (38–57) |
| Surgical approach | Open | 325 (61.6%) |
| | Laparoscopic | 126 (23.9%) |
| | Robotic | 62 (11.7%) |
| | Vaginal | 3 (0.6%) |
| | Combined | 12 (2.3%) |
| Positive pelvic lymph nodes | Yes | 174 (33.0%) |
| | LN staging not performed | 17 (3.2%) |
| Largest pathologic tumour size | < 0.5 cm | 24 (4.5%) |
| | 0.5–1.99 cm | 128 (24.2%) |
| | 2–3.99 cm | 225 (42.6%) |
| | ≥ 4 cm | 151 (28.6%) |
| LVSI | Yes | 308 (58.3%) |
| Tumour histotype | Adenocancer | 130 (24.6%) |
| | Adenosquamous | 45 (8.5%) |
| | Neuroendocrine | 19 (3.6%) |
| | Squamous cell | 318 (60.2%) |
| | Other | 16 (3.0%) |
| Grade | 1 | 32 (6.1%) |
| | 2 | 196 (37.1%) |
| | 3 | 169 (32.0%) |
| | NA | 131 (24.8%) |
| Pathologic T stage (pT) | 1a1 | 13 (2.5%) |
| | 1a2 | 27 (5.1%) |
| | 1b1 | 310 (58.7%) |
| | 1b2 | 76 (14.4%) |
| | 2a1 | 42 (8.0%) |
| | 2a2 | 16 (3.0%) |
| | 2b | 44 (8.3%) |
| Positive parametrium | Yes | 44 (8.3%) |
| Adjuvant therapy | Yes | 331 (62.7%) |
| **Characteristics at the time of recurrence** | | |
| Time from surgery to recurrence | *(months)* | 24.3 (± 21.1); 18 (10–32) |
| Age at recurrence | *(years)* | 49.1 (± 12.9); 48 (39–58) |
| Recurrence type and localization | Solitary | 322 (61.0%) |
| | Distant | 88 |
| | Pelvic | 234 |
| | Multifocal | 198 (37.5%) |
| | Combined (pelvic + distant) | 129 |
| | Distant only | 61 |
| | Pelvic | 8 |
| | NA | 8 (1.5%) |
| Type of visit when recurrence was diagnosed | Scheduled | 338 (64.0%) |
| | Unscheduled | 127 (24.1%) |
| | NA | 63 (11.9%) |
| Symptoms at recurrence | Asymptomatic | 189 (35.8%) |
| | Symptomatic | 273 (51.7%) |
| | NA | 66 (12.5%) |
| Recurrence treatment modality | Chemoradiotherapy | 115 (21.8%) |
| | Chemotherapy | 180 (34.1%) |
| | Radiotherapy | 43 (8.1%) |

| Parameters | | Description* |
|---|---|---|
| | Surgery ± Chemoradiotherapy | 114 (21.6%) |
| | No treatment | 23 (4.4%) |
| | NA | 53 (10.1%) |
| Disease status at the last FU visit | Alive with disease | 144 (27.3%) |
| | Died of other cause | 4 (0.8%) |
| | Died of disease | 251 (47.5%) |
| | No evidence of disease | 129 (24.4%) |

441 FU: follow-up; LVSI: lymphovascular space invasion; NA: not available.

442 * Categorical variables are described by absolute and relative frequencies; mean (± SD) and median
443 (interquartile range) are shown for continuous variables.

444

445

446 **Table 2.** Univariable Cox regression models for prediction of post-recurrence disease-specific survival

| | | N | HR (95% CI) | *p*-value |
|---|---|---|---|---|
| No. of positive pelvic LN* | 0 | 354 | Reference | |
| | ≥1 | 174 | 2.264 (1.757; 2.917) | **< 0.001** |
| Largest pathologic tumour size* | < 0.5 cm | 24 | Reference | |
| | 0.5–1.9 cm | 128 | 3.392 (1.052; 10.939) | **0.041** |
| | 2.0–3.9 cm | 225 | 5.144 (1.633; 16.203) | **0.005** |
| | ≥ 4.0 cm | 151 | 7.320 (2.314; 23.158) | **< 0.001** |
| LVSI* | No + NA[1] | 220 | Reference | |
| | Yes | 308 | 2.307 (1.747; 3.048) | **< 0.001** |
| Tumour histotype* | Squamous cell | 318 | Reference | |
| | Adenocarcinoma | 130 | 0.878 (0.646; 1.194) | 0.408 |
| | Adenosquamous | 45 | 0.767 (0.464; 1.267) | 0.300 |
| | Neuroendocrine | 19 | 1.917 (1.126; 3.264) | **0.017** |
| | Other | 16 | 1.272 (0.689; 2.349) | 0.442 |
| Grade (imputed, pooled)* | 1 | 52 | Reference | |
| | 2 | 256 | 1.297 (0.797; 2.112) | 0.335 |
| | 3 | 220 | 1.846 (1.139; 2.995) | **0.020** |
| Positive parametrium* | No | 484 | Reference | |
| | Yes | 44 | 2.209 (1.497; 3.259) | **< 0.001** |
| Disease free interval from primary surgery to recurrence diagnosis (DFI 1) | > 1 year | 352 | Reference | |
| | < 1 year | 176 | 1.698 (1.320; 2.185) | **< 0.001** |
| Age at recurrence | < 65 years | 457 | Reference | |
| | 65+ years | 71 | 1.417 (0.994; 2.020) | 0.054 |
| Symptoms at the recurrence diagnosis | No | 189 | Reference | |
| | Yes + NA[1] | 339 | 2.229 (1.669; 2.977) | **< 0.001** |
| Recurrence localization (10 NA) | Pelvic | 240 | Reference | |
| | Distant | 149 | 1.427 (1.043; 1.951) | **0.026** |
| | Combined | 129 | 2.072 (1.524; 2.818) | **< 0.001** |
| Recurrence type 1 (8 NA) | Solitary | 322 | Reference | |
| | Multifocal | 198 | 2.036 (1.572; 2.638) | **< 0.001** |
| Recurrence type 2 (10 NA) | Solitary – pelvic | 232 | Reference | |
| | Solitary – distant | 88 | 1.193 (0.817; 1.742) | 0.361 |
| | Multifocal | 198 | 2.179 (1.639; 2.898) | **< 0.001** |

447 LN: lymph node; LVSI: lymphovascular space invasion; NA: not available.

448 *Characteristics at the time of primary surgery.

449 [1]Patients with NA information about the parameter were analysed separately and consequently pooled with
450 the group with the matching analysis result.

451

**Table 3.** Multivariable Cox regression model for prediction of disease-specific death after recurrence

| Predictor | | β | SE (β) | HR | 95% CI | *p*-value | Points (max. 100) |
|---|---|---|---|---|---|---|---|
| Largest pathologic tumour size* | < 0.5 cm | | | Reference | | | 0 |
| | 0.5–1.9 cm | 0.947 | 0.602 | 2.577 | 0.792–8.380 | 0.116 | 20 |
| | 2.0–3.9 cm | 1.269 | 0.593 | 3.557 | 1.113–11.374 | **0.032** | 27 |
| | ≥ 4.0 cm | 1.481 | 0.598 | 4.397 | 1.363–14.184 | **0.013** | 31 |
| LVSI* | No / NA[1] | | | Reference | | | 0 |
| | Yes | 0.672 | 0.148 | 1.957 | 1.463–2.619 | **< 0.001** | 14 |
| Years from surgery to recurrence | > 1 year | | | Reference | | | 0 |
| | < 1 year | 0.516 | 0.132 | 1.676 | 1.294–2.169 | **< 0.001** | 11 |
| Age at recurrence | < 65 years | | | Reference | | | 0 |
| | 65+ years | 0.543 | 0.187 | 1.720 | 1.192–2.482 | **0.004** | 12 |
| Symptoms at the recurrence diagnosis | No | | | Reference | | | 0 |
| | Yes / NA[1] | 0.788 | 0.151 | 2.199 | 1.634–2.958 | **< 0.001** | 17 |
| Recurrence type | Isolated | | | Reference | | | 0 |
| | Multifocal | 0.687 | 0.135 | 1.987 | 1.526–2.587 | **< 0.001** | 15 |

HR: hazard ratio; LVSI: lymphovascular space invasion; NA: not available; SE: standard error.

[1]Patients with NA information about the parameter were analysed separately and consequently pooled with the group with the matching analysis result.

*Characteristics at the time of primary surgery

**Supplementary Table 1.** Comparison of baseline characteristics of patients according to disease status at three years since the recurrence diagnosis.

| Parameters* | | NED | DOD/AWD | *p*-value |
|---|---|---|---|---|
| **Characteristics at the time of surgery** | | | | |
| Age at surgery | | 45.7 (± 12.0); | 47.5 (± 13.0); | 0.368 |
| Surgical approach | Open | 36 (56.3%) | 181 (65.8%) | 0.416 |
| | Laparoscopic | 19 (29.7%) | 55 (20.0%) | |
| | Robotic | 9 (14.1%) | 37 (13.5%) | |
| | Vaginal | 0 (0.0%) | 1 (0.4%) | |
| | NA | 0 (0.0%) | 1 (0.4%) | |
| Positive pelvic lymph | No | 50 (78.1%) | 153 (55.6%) | **< 0.001** |
| | Yes | 10 (15.6%) | 117 (42.5%) | |
| | No LN staging performed | 4 (6.3%) | 5 (1.8%) | |
| Largest pathologic tumour size | < 0.5 cm | 8 (12.5%) | 7 (2.5%) | **0.006** |
| | 0.5–1.99 cm | 15 (23.4%) | 52 (18.9%) | |
| | 2–3.99 cm | 27 (42.2%) | 125 (45.5%) | |
| | ≥ 4 cm | 14 (21.9%) | 91 (33.1%) | |
| LVSI | No / NA | 34 (53.1%) | 91 (33.1%) | **0.004** |
| | Yes | 30 (46.9%) | 184 (66.9%) | |
| Tumour histotype | Adeno | 14 (21.9%) | 69 (25.1%) | 0.158 |
| | Adenosquamous | 6 (9.4%) | 19 (6.9%) | |
| | Neuro | 0 (0.0%) | 15 (5.5%) | |
| | Squamous | 43 (67.2%) | 158 (57.5%) | |
| | Other | 1 (1.6%) | 14 (5.1%) | |
| Grade | 1 | 6 (9.4%) | 12 (4.4%) | **0.012** |
| | 2 | 28 (43.8%) | 83 (30.2%) | |

| Parameters* | | NED | DOD/AWD | *p*-value |
|---|---|---|---|---|
| | 3 | 13 (20.3%) | 95 (34.5%) | |
| | NA | 17 (26.6%) | 85 (30.9%) | |
| Pathologic T stage (pT) | 1a1 | 3 (4.7%) | 3 (1.1%) | 0.124 |
| | 1a2 | 6 (9.4%) | 11 (4.0%) | |
| | 1b1 | 38 (59.4%) | 149 (54.2%) | |
| | 1b2 | 9 (14.1%) | 50 (18.2%) | |
| | 2a1 | 4 (6.3%) | 22 (8.0%) | |
| | 2a2 | 1 (1.6%) | 11 (4.0%) | |
| | 2b | 3 (4.7%) | 29 (10.5%) | |
| Positive parametrium | No | 61 (95.3%) | 246 (89.5%) | 0.233 |
| | Yes | 3 (4.7%) | 29 (10.5%) | |
| Adjuvant therapy | No | 41 (64.1%) | 78 (28.4%) | **< 0.001** |
| | Yes | 23 (35.9%) | 197 (71.6%) | |
| **Characteristics at the time of recurrence** | | | | |
| Age at recurrence | | 47.0 (± 12.0); | 48.6 (± 13.3); | 0.452 |
| Recurrence type | Solitary | 58 (90.6%) | 149 (54.2%) | **< 0.001** |
| | Multifocal | 6 (9.4%) | 118 (42.9%) | |
| | Unknown | 0 (0.0%) | 8 (2.9%) | |
| Recurrence localization | Pelvic | 44 (68.8%) | 104 (37.8%) | **< 0.001** |
| | Distant | 16 (25.0%) | 79 (28.7%) | |
| | Combined | 4 (6.3%) | 82 (29.8%) | |
| | NA | 0 (0.0%) | 10 (3.6%) | |
| DFI 1 | | 21.5 (± 14.9); | 19.2 (± 17.8); | 0.058 |
| Recurrence diagnosis | Scheduled visit | 52 (81.3%) | 156 (56.7%) | **0.007** |
| | Unscheduled | 9 (14.1%) | 74 (26.9%) | |
| | NA | 3 (4.7%) | 45 (16.4%) | |
| Symptoms at recurrence | Asymptomatic | 39 (60.9%) | 73 (26.5%) | **< 0.001** |
| | Symptomatic | 22 (34.4%) | 155 (56.4%) | |
| | NA | 3 (4.7%) | 47 (17.1%) | |
| Recurrence treatment modality | Chemoradiotherapy | 18 (28.1%) | 61 (22.2%) | **< 0.001** |
| | Chemotherapy | 5 (7.8%) | 119 (43.3%) | |
| | Radiotherapy | 10 (15.6%) | 14 (5.1%) | |
| | Surgery ± Chemoradiotherapy | 28 (43.7%) | 45 (16.4%) | |
| | No treatment | 0 (0.0%) | 12 (4.4%) | |
| | Other | 3 (4.7%) | 24 (8.7%) | |
| Disease status at the last FU visit | Alive with disease | 0 (0.0%) | 24 (8.7%) | - |
| | Died of other cause | 0 (0.0%) | 0 (0.0%) | |
| | Died of disease | 0 (0.0%) | 251 (91.3%) | |
| | No evidence of disease | 64 (100.0%) | 0 (0.0%) | |

DFI 1: length of the disease-free interval between primary treatment and recurrence diagnosis; FU: follow-up; LVSI: lymphovascular space invasion; NA: not available.

* Categorical variables are described by absolute and relative frequencies; mean (± SD) and median (interquartile range) are shown for continuous variables. *p*- value of Fisher Exact test (categorical variables) or Mann-Whitney U test (continuous variables) is reported; for all parameters, the category "NA" was not considered when calculating *P* value.