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Post-recurrence survival in patients with cervical cancer

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HIGHLIGHTS

- The 5-year post-recurrence disease-specific survival (PR-DSS) rate was 39.1% in patients with early-stage cervical cancer.
- The strongest factors for PR-DSS were primary tumour size and the presence of symptoms at diagnosis of recurrence.
- The presence of symptoms at recurrence remained a significant prognostic factor after correction for lead-time bias.
- PR-DSS was best in patients without LN involvement or LVSI suffering from solitary asymptomatic recurrence.

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ABSTRACT

Background. Up to 26% of patients with early-stage cervical cancer experience relapse after primary surgery. However, little is known about which factors influence prognosis following disease recurrence. Therefore, our aims were to determine post-recurrence disease-specific survival (PR-DSS) and to identify respective prognostic factors for PR-DSS.

Methods. Data from 528 patients with early-stage cervical cancer who relapsed after primary surgery performed between 2007 and 2016 were obtained from the SCANN study (Surveillance in Cervical CANcer). Factors related to the primary disease and recurrence were combined in a multivariable Cox proportional hazards model

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to predict PR-DSS.

Results. The 5-year PR-DSS was 39.1% (95% confidence interval [CI] 22.7%–44.5%), median disease-free interval between primary surgery and recurrence (DFI1) was 1.5 years, and median survival after recurrence was 2.5 years. Six significant variables were identified in the multivariable analysis and were used to construct the prognostic model. Two were related to primary treatment (largest tumour size and lymphovascular space invasion) and four to recurrence (DFI1, age at recurrence, presence of symptoms, and recurrence type). The C-statistic after 10-fold cross-validation of prognostic model reached 0.701 (95% CI 0.675–0.727). Three risk-groups with significantly differing prognoses were identified, with 5-year PR-DSS rates of 81.8%, 44.6%, and 12.7%.

Conclusions. We developed the robust model of PR-DSS to stratify patients with relapsed cervical cancer according to risk profiles using six routinely recorded prognostic markers. The model can be utilised in clinical practice to aid decision-making on the strategy of recurrence management, and to better inform the patients.

1. Introduction

Early-stage cervical cancer generally has a good prognosis with abundant evidence showing improvements in survival in the last few decades [1]. Nevertheless, 5%–26% of early-stage patients experience relapse following primary treatment [2–4].

The 5-year survival rate in patients with disease recurrence varied considerably, from 15.0% to 50.0%, in prior studies [5–9]. This indicates substantial heterogeneity of cohorts. The available literature has mainly focused on survival after primary treatment, and factors such as FIGO stage, tumour size, tumour histology, age, lymph node (LN) status, and parametrial involvement were the most frequently reported prognostic parameters [10–13]. Only a handful of studies have investigated the prognostic factors for post-recurrence disease-specific survival (PR-DSS) in multivariable settings. The available data suggest there is a broad portfolio of potential prognostic parameters, including the disease-free interval from surgery to the diagnosis of recurrence (DFI1) [9], recurrence type and localization [5,7,8,14], presence of symptoms at the diagnosis of recurrence [5], levels of C-reactive protein and albumin [7], HPV16 negativity [6], and lymphatic/lymphovascular space invasion (LVSI) [5]. However, the prior studies were mostly based on single-centre, retrospective cohorts of between 43 and 165 patients with disease relapse, and long study periods of up to 16 years [6,7–9,]. The only multi-institutional study was limited to 70 relapsing patients [5]. Furthermore, no comprehensive model incorporating risk factors for PR-DSS in early-stage cervical cancer has been reported so far.

In our study, we have used a large database of patients with early-stage cervical cancer who were registered in the retrospective international SCCAN study (Surveillance in Cervical CANcer). Our aims were to determine PR-DSS of the patients and to identify potential prognostic factors, by combining factors recorded at primary treatment and at the diagnosis of recurrence.

2. Methods

2.1. Study design and participants

The SCCAN (Surveillance in Cervical CANcer) international, multicentre, retrospective cohort study evaluated the recurrence patterns of cervical cancer survivors. The SCCAN study consortium consisted of 20 tertiary centres, which treated large volumes of patients, 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 preoperative assessment according to American Joint Committee on Cancer - Cervix Uteri Cancer Staging; (iii) primary surgical management, including fertility-sparing procedures; (iv) and ≥ 1 year of follow-up data. Patients were eligible irrespective of adjuvant treatment, neoadjuvant chemotherapy, tumour type, LN status, or LN staging. Patients were ineligible 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 <1 year (with the exception of patients who relapsed or died in the first year post-surgery). The database comprised data from 4343 patients with early-stage cervical cancer.

The study 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.

2.2. Data collection

The following data regarding the primary treatment were collected: type of uterine procedure, type of parametrectomy, surgical approach, LN staging and its extent, type of neoadjuvant therapy, and type of adjuvant treatment. The type of parametrectomy was classified using the Querleu–Morrow modified classification system [15]. Disease characteristics included information about the type and largest size of the tumour (pathologically confirmed), pathologic stage, number and size of removed/positive LNs, parametrial involvement, LVSI, and grade. The tumours were classified histologically according to the World Health Organization classification and were consequently clustered into five main groups: adenocarcinoma, adenosquamous cancer, squamous cell carcinoma, neuroendocrine cancer, and others. Information regarding disease recurrence, included the diagnosis, precise location of the recurrence, presence of symptoms, and treatment modality.

After the patients´ data were received, the database was cleaned and patients were excluded if they were missing information on key predictor variables, including tumour type and size, follow up information (date of the last visit, disease status at the last visit, date of recurrence/death).

2.3. 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 the mean with standard deviation or the median with interquartile range. Missing values for grade (24.8% patients) were identified as not suitable for combining with another grade group and estimation of the probable grade value (imputation) for individual patients was necessary. The imputation of unknown grade values was based on multivariable regression approach with age, number of positive pelvic LNs, largest tumour size, LVSI, histotype, pT and adjuvant therapy as predictors of grade value. The imputation resulted in five datasets that were consequently analysed separately and later the individual results were pooled to minimise the imputation bias.

DFI1 was calculated as the time from surgery to the date of recurrence. The median time to death after recurrence was calculated as the time from the date recurrence was diagnosed to disease-related death.

The associations between patient characteristics and the PR-DSS were evaluated using univariable and multivariable Cox proportional hazard models and described by hazard ratios with 95% confidence intervals (CI) together with the statistical significance. A backwards stepwise algorithm and Akaike information criterion were used to choose the optimal multivariable model from the predictors that significantly influenced PR-DSS in univariable analyses ($p < 0.1$). The discriminative ability of the model was assessed using Harrell's C-index. Ten-fold cross-validation was performed to obtain estimates of model performance that were adjusted for in-sample optimism. A risk score was derived from the regression coefficients (β), which were weighted to the maximum sum of 100 points. The results of the model were expressed by Kaplan–Meier curves based on the stratified risk score. All analyses were performed using SPSS 25.0.0.1 (IBM Corp, Armonk, NY, USA) and R-3.6.1 (https://cran.r-project.org/).

3. Results

3.1. Cohort characteristics

We analysed the data from 528 patients (out of 4343 patients submitted to the SCCAN database; see Cibula et al. 2021; [16]) who underwent primary surgical treatment of early-stage cervical cancer and experienced disease recurrence.

The characteristics of the patients at the times of primary diagnosis and disease recurrence are summarized in Table 1. The median follow-up period from primary surgery in the cohort was 3.3 years (25th–75th percentile, 2.2–5.4). At the time of primary treatment, the majority of patients had squamous cell carcinoma (60.2%) or adenocarcinoma (24.6%), primary tumour size of 2–3.99 cm (42.6%), and negative pelvic LNs (63.8%). LVSI was positive in 58.3%, but only 8.3% had positive parametria. Radical hysterectomy (90.5%) was the most frequent procedure, 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% (322) of patients, located in the pelvis in 72.7% of these patients (234/322) or at a distant site in 27.3% (88/322). The recurrence was multifocal in 37.5% of patients, with pelvic and distant recurrence in 65.2% of these (129/198) or in multiple distant sites in 30.8% (61/198). The prevailing treatment modalities for disease recurrence were chemotherapy (34.1%), chemoradiotherapy (21.8%), and surgery combined with radiotherapy or chemotherapy (14.6%). Only 4.4% of patients did not receive any treatment for disease recurrence (Table 1).

3.2. Post-recurrence disease-specific survival (PR-DSS)

The PR-DSS reached 39.1% (95% CI 33.7–44.5) at 5 years after the diagnosis of recurrence (Fig. 1). The median DFI1, calculated as the interval between primary surgery and diagnosis of recurrence, was 1.5 years and the median time to death after recurrence was 2.5 years, as estimated using the Kaplan–Meier method.

3.3. Univariable analysis of prognostic factors for PR-DSS

The results of the univariable analysis of the prognostic factors for PR-DSS are summarized in Table 2. Some primary tumour characteristics were statistically significant in univariable analyses, including the number of positive LNs, largest tumour size, LVSI, grade, and parametrial invasion. Furthermore, the location and type of recurrence, DFI1, and the presence of symptoms at diagnosis of recurrence were significantly associated with PR-DSS.

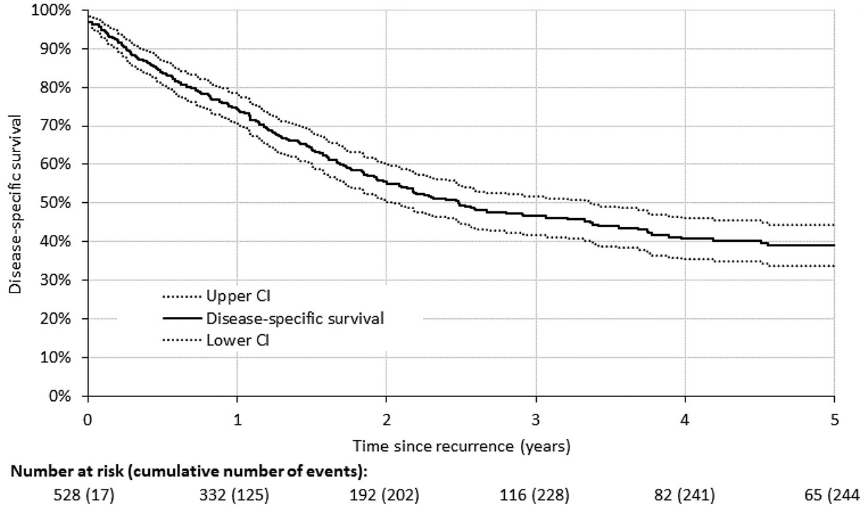
Table 1
Baseline characteristics of patients with cervical cancer recurrence after surgery.

Characteristics		Value*
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 LNs	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	Adenocarcinoma	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%)
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 location	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%)
	Surgery	37 (7.0%)
	Surgery + radiotherapy or chemotherapy	77 (14.6%)
	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 causes	4 (0.8%)
	Died of disease	251 (47.5%)
	No evidence of disease	129 (24.4%)

FU: follow-up; LVSI: lymphovascular space invasion; NA: not available.
* Categorical variables are described with absolute and relative frequencies. Continuous variables are described as the mean ± standard deviation and median (interquartile range).

3.3.1. Location and type of recurrence

The location of the recurrence was significantly associated with PR-DSS ($p \leq 0.027$), with 5-year rates of 49.6%, 36.2%, and 25.0% for pelvic, distant, and combined (pelvic + distant) recurrence,



No. of years	Disease-specific survival after recurrence (95% CI)
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%)

Fig. 1. Post-recurrence disease-specific survival (PR-DSS) after recurrence in all relapsed patients (N = 528). Time 0 represents the date of diagnosis of recurrence. CI: confidence interval.

respectively. The median time to death after recurrence in these three groups was 47, 30, and 18 months (Fig. 2A).

The type of recurrence was also a significant determinant of PR-DSS, independently of location, with 5-year rates of 47.9% and 23.9% for solitary and multifocal recurrence, respectively, and median time to death after recurrence of 47 and 18 months (Fig. 2B).

3.3.2. Disease free interval from primary surgery to recurrence (DFI1)

PR-DSS was clearly dependent on the DFI1. The 5-year PR-DSS was 29.0%, 40.8% and 49.9% among patients with a DFI1 of <1 year, 1–2 years, and ≥ 2 years, respectively. The median time to death after recurrence was 19, 35, and 48 months, respectively (Fig. 2C). The difference in PR-DSS was significantly different among the groups,

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

Characteristic		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**
DFI1	>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 diagnosis of recurrence	No	189	Reference	
	Yes + NA[†]	339	2.229 (1.669–2.977)	**<0.001**
Recurrence location (NA in 10 patients)	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 (NA in 8 patients)	Solitary	322	Reference	
	Multifocal	198	2.036 (1.572–2.638)	**<0.001**
Recurrence type (NA in 10 patients)	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**

CI: confidence interval; HR: hazard ratio; LN: lymph node; LVSI: lymphovascular space invasion; NA: not available; DF1: disease-free interval from primary surgery to the diagnosis of recurrence.

* Characteristics at the time of primary surgery.

[1] Univariable analysis of LVSI showed that records with missing LVSI variable were not significantly differing from LVSI negative patients (HR 1.14 (95% CI, 0.70, 1.85); $p = 0.596$) and were therefore pooled together.

[†] Univariable analysis of presence of symptoms showed that records with missing information were not significantly ($p = 0.243$) differing from symptomatic patients ([HR 2.336 (95% CI: 1.734; 3.148)] vs [HR 1.87 (95% CI, 1.23; 2.84 1]) and were therefore pooled together. *p*-values in bold font are significant at $p < 0.05$.

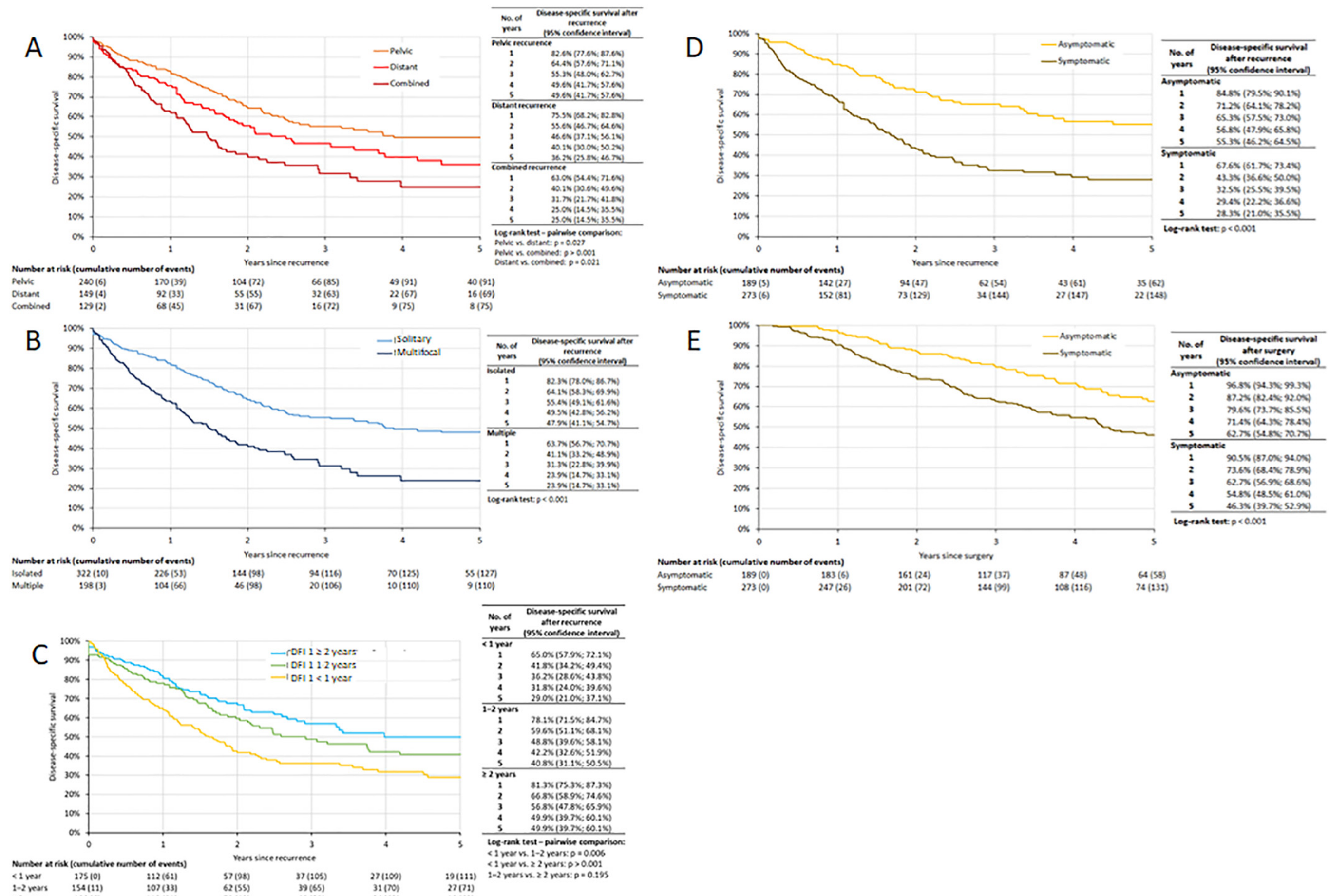


Fig. 2. Disease-specific survival of recurring patients divided according to the following prognostic factors: (A) location of recurrence; (B) type of recurrence; (C) disease-free interval (DFI1) calculated as the time from primary surgery to the time when recurrence was diagnosed; (D) presence of symptoms at the time of recurrence diagnosis, where time 0 represents the time when recurrence was diagnosed; and (E) presence of symptoms at the time of recurrence, where time 0 represents the time of primary surgery.

except for the comparison between the 1–2 years and ≥ 2 years groups ($p = 0.195$).

3.3.3. Presence of symptoms at the diagnosis of disease recurrence

There were significant differences in PR-DSS and the median time to death between the symptomatic and asymptomatic patients at the diagnosis of recurrence (Fig. 2D); 35.8% (189/528) patients were asymptomatic and 51.7% (273/528) were symptomatic. The PR-DSS at 5 years was 55.3% and 28.3%, the median DFI1 was 18 and 19 months, and the median time to death after recurrence was 76 and 20 months in asymptomatic and symptomatic patients, respectively.

In order to exclude the possibility of a lead-time bias, we also compared survival from the date of primary surgery between the symptomatic and asymptomatic patients (Fig. 2E). The difference in PR-DSS remained significant in this analysis ($p < 0.001$). The median time from primary surgery to death was 156 and 52 months in asymptomatic and symptomatic patients, respectively.

The location of recurrence was also significantly different between symptomatic and asymptomatic patients ($p = 0.026$). Symptomatic recurrence was more frequently located in distant sites whereas pelvic recurrence was more frequently diagnosed in asymptomatic patients. The frequency of combined pelvic + distant recurrence did not differ between the two groups.

The presence of symptoms was significantly correlated with the type of visit when the recurrence was diagnosed ($p < 0.001$). Recurrence was diagnosed at pre-scheduled visits in the vast majority of asymptomatic patients (96.3%; 182/189). By contrast, only 55% of patients with symptomatic recurrence were diagnosed at the scheduled visits (150/273). Overall, 94.5% of the recurrences diagnosed at unscheduled visit were symptomatic.

We did not observe any time-dependent trend in the frequency of symptoms among recurrent patients in relation to the length of the DFI1 ($p = 0.108$).

3.4. Development of the prognostic model for PR-DSS

In the multivariable analysis, the significant prognostic factors for PR-DSS included two characteristics recorded at the time of primary treatment (largest tumour size and LVSI) and four recurrence-related factors (age at recurrence, DFI1, presence of symptoms at the time of diagnosis, and solitary/multifocal type of recurrence) (Table 3). Harrell's concordance statistic factor (C-statistic) of the resulting model was 0.712 (95% CI 0.678–0.746). After performing 10-fold internal cross-validation, the average area under the curve was 0.701 (95% CI 0.675–0.727).

The β coefficients of the multivariable model were consequently converted into risk scores (Table 3). Based on the results, the patients were stratified into three groups according to the risk score: (i) 0–33 points; (ii) 34–66 points; and (iii) 67–100 points. The pairwise comparisons yielded significant differences in the prognosis of PR-DSS between the three risk-score groups ($p < 0.001$).

The Kaplan–Meier curves for PR-DSS in these three risk-score groups are shown in Fig. 3. The 5-year PR-DSS was 81.8%, 44.6%, and 12.7% for the risk scores of 0–33, 34–66, and 67–100, respectively.

Table 3
Multivariable Cox regression model for prediction of post-recurrence disease-specific survival.

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†			Reference			0
	Yes	0.672	0.148	1.957	1.463–2.619	**<0.001**	14
Time 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 diagnosis of recurrence	No			Reference			0
	Yes/NA†	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

CI: confidence interval; HR: hazard ratio; LVSI: lymphovascular space invasion; NA: not available; SE: standard error.
* Characteristics at the time of primary surgery.
† Patients with missing data were analysed separately and consequently pooled with the group with the matching analysis result *p*-values in bold font are significant at $p < 0.05$.

3.5. Long-term survivors with no evidence of disease at 3-years post-recurrence

There were 64 patients with no evidence of disease at 3 years post-recurrence treatment (Supplementary table 1). The best long-term survival prognosis was seen in stage I patients without LN involvement or LVSI at the time of primary treatment who were diagnosed with asymptomatic solitary recurrence.

Interestingly, some long-term survivors belonged to higher-risk groups. Ten patients had LN involvement at the time of primary treatment, of which nine received adjuvant radiotherapy or chemoradiation after primary surgery. These 10 patients were diagnosed with isolated recurrence that was located in the pelvis (six patients), abdominal cavity (two patients), or lungs (two patients). Chemoradiation was the prevailing treatment modality for the recurrence in this subgroup. Six of the long-term survivors had multifocal recurrence localized in the pelvis, abdominal cavity (four patients), or lungs (two patients).

A third interesting group of higher-risk long-term survivors comprised 20 patients diagnosed with extrapelvic (distant) recurrence. Fourteen of these had a primary tumour size of <2 cm. Recurrence was predominantly located in the abdominal cavity (abdominal in nine patient, ovary in one patient) or in the lungs (seven patients). The recurrence was treated by surgery in 13 patients, eventually (in 9 cases) followed by radiotherapy or chemotherapy.

4. Discussion

The aim of this retrospective international multicentre study was to determine the PR-DSS and to identify respective prognostic factors in patients with relapsed cervical cancer who previously underwent primary surgical treatment for early-stage disease. Overall, 528 patients were identified within the cohort of 4343 patients registered in the SCCAN study database. The 5-year PR-DSS rate was 39.1%, with a median survival of 2.5 years after recurrence. The key prognostic factors for PR-DSS identified in the multivariable analysis were two factors related to the time of primary treatment (largest pathological tumour size and LVSI) and four factors related to recurrence (age at recurrence, DFI1, recurrence type, and the presence of symptoms at the time of diagnosis). Based on the multivariable model, we stratified the cohort into three risk-groups with significant differences in prognosis, with 5-year PR-DSS of 81.8%, 44.6%, and 12.7%.

Because the majority of patients with early-stage cervical cancer are cured, the literature is rather scarce concerning the post-recurrence prognosis and related risk factors. All previously published studies

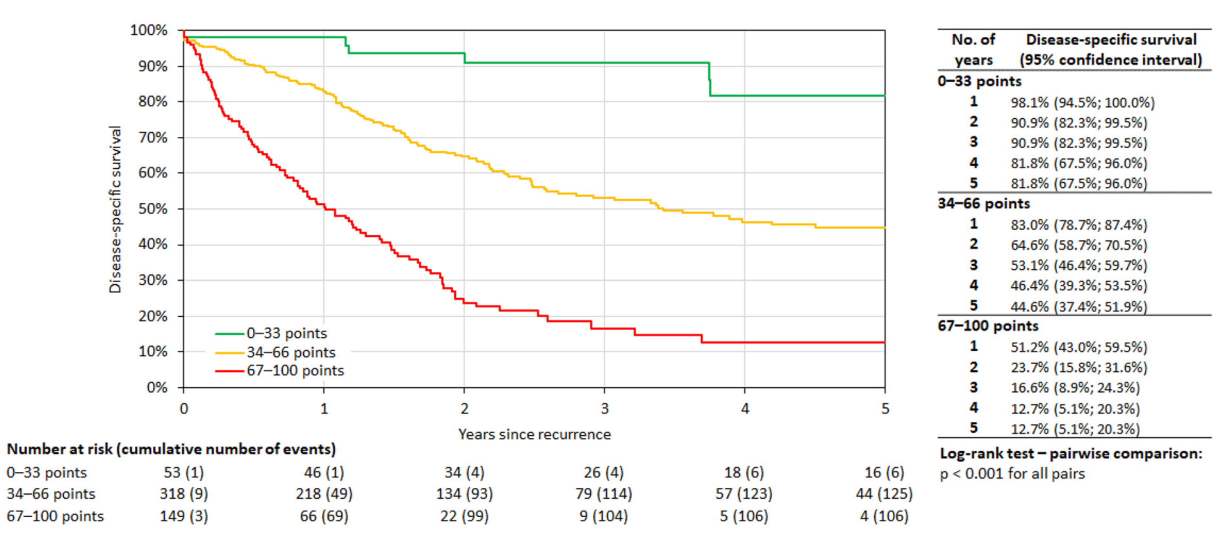


Fig. 3. Post-recurrence disease-specific survival in patients stratified by the risk score ($N = 528$). Time 0 represents the time when recurrence was diagnosed.

involved limited cohorts of 43–165 relapsing patients with heterogeneous characteristics, including various treatment modalities across all disease stages [5–8]. Furthermore, they were all single-centre studies, albeit with one exception [5].

In the study of 121 patients with stage I/II recurrent cervical cancer who underwent primary surgical treatment at a 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 related 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 the multivariable analysis [7]. In a similar cohort from Japan, comprising 165 relapsed patients with primary treatment across all stages of disease, only the recurrence location remained significant in the multivariable analysis of PR-DSS [8]. However, that study considered a limited number of prognostic variables, as the authors did not analyse characteristics unrelated to the recurrence location or DFI1 [8]. Finally, in a study of 70 relapsing patients with FIGO stage 1A1-1B1 drawn from the Danish National Cohort Study, 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 the presence of symptoms at recurrence (HR 2.52; 95% CI 1.08–5.9; $p = 0.033$) were identified as independent risk factors for PR-DSS [5].

None of the prior studies sought to create a comprehensive model for stratification of PR-DSS risk according to the prognosis. However, prognostic models have been developed for relapsing patients with ovarian or endometrial cancers. The PR-DSS nomogram derived from the GOG trials using the data from 4739 patients with advanced-stage, high-grade ovarian carcinoma included DFI1, tumour histology, performance status, FIGO stage, and age of the patient; while DFI1 alone accounted for 85% of the prognostic information [17]. In patients with recurrent endometroid endometrial cancer, stratification by PR-DSS was done according to the type of recurrence, level of cancer antigen 125 at the time recurrence, and DFI 1 [18]. Our prognostic model for PR-DSS included six commonly recorded variables. The strongest risk factor for PR-DSS was the size of the primary tumour, followed by the presence of symptoms at the time of diagnosis.

The majority of patients with cervical cancer are symptomatic at the time of recurrence, with pain, bleeding, cough and ileus being the most prevalent symptoms [3,19–21]. It was previously reported 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. Accordingly, patients are likely to have better prognosis and longer post-recurrence survival [22,23]. Similarly, in our study, the asymptomatic recurrences were frequently localized in pelvis and were associated with significantly better PR-DSS.

However, we are aware that better prognosis after asymptomatic recurrence can result from a lead-time bias. Earlier detection gives the impression of longer survival but, in reality, a patient lives with a known recurrence for longer time but dies at the same interval from initial diagnosis as a patient diagnosed later while symptomatic. In order to reduce this potential bias, we also determined survival time from primary diagnosis. The difference remained highly significant between the symptomatic and asymptomatic patients. Even though this outcome seemingly supports the prognostic importance of active surveillance, retrospective data do not allow to draw definitive conclusions. It cannot be ruled out that the survival benefit of asymptomatic recurrence is related to tumour biology, and slow growing, non-aggressive tumours with better prognosis are more likely to be detected while they are asymptomatic. Evidence supporting the significance of active surveillance can only be obtained in prospective studies.

It is, however, important to emphasize that 55% of patients with symptomatic recurrence in our study were diagnosed at pre-scheduled follow-up visits, suggesting that many symptomatic patients waited for their scheduled appointment and did not consult a specialist when the symptoms first appeared.

To our knowledge, our study represents the largest analysis of PR-DSS among patients with early-stage cervical cancer. We utilised a large dataset composed of validated data from carefully selected tertiary centres that were geographically distributed across four continents and treated high volumes of patients with cervical cancer. The cohort size was sufficient to analyse the prognostic significance of a large number of prognostic markers, assessed at the primary treatment and at the time of recurrence, all of which are routinely assessed and easily accessible. Furthermore, the discriminative ability of the resulting multivariable model was internally validated by 10-fold cross-validation and the performance was assessed using the C-statistic with a value of 0.701, which indicates good prognostic accuracy of our model.

The major limitation of this study is its retrospective design, which may introduce some bias, especially related to patient selection.

In conclusion, we analysed PR-DSS in patients with early-stage cervical cancer in a large cohort of patients who relapsed after primary surgical treatment. The 5-year PR-DSS was 39.1%, the median post-recurrence survival 2.5 years, and the median DFI1 1.5 years. We also developed the robust model for PR-DSS by stratifying the patients according to their risk profile using six routinely recorded prognostic markers. The strongest prognostic factor for PR-DSS was the larger size of the primary tumour, followed by the presence of symptoms at the time of recurrence which remained significant even after the correction for a lead-time bias. The model allowed us to stratify the cohort into three risk groups with significant differences in prognosis and 5-year PR-DSS rates of 81.8%, 44.6%, and 12.7% in the sub-groups.

These results and the associated risk model can be used to better inform patients about their prognosis and to facilitate decision-making process on the recurrence management.

The best long-term survival prognosis was seen in patients with stage I cervical cancer without LN involvement or LVSI at the time of primary diagnosis who suffered from an asymptomatic solitary recurrence located in the pelvis. But interestingly, there were also some patients with multifocal or extrapelvic recurrences who remained free of disease for more than three years after recurrence treatment. The significantly better prognosis of asymptomatic patients and the finding that many patients wait for a scheduled visit, despite symptoms, may support active surveillance, but the significance of this approach can only be verified in prospective trials.

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Declaration of Competing Interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2021.12.018.

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