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Research Article

Prognostic Factors for Cervical Cancer in FIGO-Stages IA-IIB in a 10-Year Period in the Region of Uppsala, Sweden: Population Cohort Study

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ABSTRACT

Background: The incidence of cervical cancer in Sweden decreased to 8/100,000 in the year 2011 but has from 2014 increased to 11/100,000. The noted increase was, mainly observed in FIGO-stages IA-IB, where patients usually are asymptomatic and detected in screening.

Materials and Methods: The study population consisted of 253 patients with cervical carcinoma in FIGO-stages IA-IIB. The patients were referred to the Department of Gynecology at the Akademiska University Hospital in Uppsala for decision of treatment from 2008 to 2017.

Results: Clinical and pathological features of cervical carcinoma were compared according to the subtypes: squamous cell carcinoma (n=150), adenocarcinoma (n=74) and adeno-squamous cancer (n=29). Other rare histological types (n = 6) were excluded. Finally, 207 (82%) out of the 253 referred patients, had primary surgical treatment and 29 (14%) patients had additional oncological treatment. The remaining 46 patients (18%) received primary oncological treatment. In the present study 45 (17.8%) developed recurrent disease. Prognostic factors for disease-free survival in Cox-regression analysis were stage (IA versus IIB) (p = 0.000) and histopathologic subtype (p = 0.009). In a survival analysis the disease-free survival differed between the histological subtypes; 62 % for squamous cell cancer in cervix, 48 % for adenocarcinoma, and 32 % for adeno-squamous cancer (Chi-square = 6,221; p = 0,045). Logistic regression analysis including treatment details, showed no other predictive factors for recurrent disease.

Conclusion: The results from this study suggest that prognostic factors for disease-free survival are FIGO-stage (IA –IIB) and histopathology, but not tumor grade, age or choice of treatment.

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Introduction

The cervical cancer incidence in Sweden decreased from 24/100,000 in 1965 to 8/100,000 in 2011, but it has increased to 11/100,000 from 2014 [1, 2]. The increase appears to correlate to screening history were the incidence in Sweden, as in many western countries, decreased markedly after the introduction of cytological screening in the 1960s [2]. However, from 2014 the incidence of cervical cancer in Sweden had an about 20% increase, which is corresponding to approximately 100 extra annual new cases compared to the previous period. A previous report suggests that the overall increase is associated with an increased cancer risk in women aged below 65 in early FIGO stages (IA-IB), adequately screened with normal cytological and especially in some counties (laboratories) in Sweden results [2, 3].

Carcinoma of the uterine cervix is globally the second most common tumor in women. More than 80% of cervical cancer cases occur in developing countries with 483 000 estimated new cases and 274 000 deaths yearly [4]. Furthermore, GLOBOCAN 2018 database has published ASR (age standardized rates per 100,000) and cumulative risks to age 75 by sex (female / male) and cancer site worldwide 2018, that estimated number of new cervix cancer cases were 569.8 with ASR =13.1 and Cumulative Risk = 1.36 [5].

The FIGO classification is still the most commonly used staging system for female genital cancers. However, according to the latest FIGO staging guidelines, examination under anaesthesia including cystoscopy, are no longer mandatory and radiological tumor volume as well as parametrial invasion should be recorded separately [6]. In the Nordic

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countries, the annual incidence of new cervical cancer cases was 1390 in 2011-2015 [7]. Pre-treatment diagnostic imaging has reported to affect the FIGO stage in more than half of the Nordic centers and the pre-treatment planning at multi-disciplinary team meetings incorporate findings from imaging examinations such as ultrasound, magnetic resonance imaging (MRI) in combination with PET-CT [6].

In England, a retrospective population-based observational study using register data of 11,951 women diagnosed with cervical cancer between 2006 and 2010 was undertaken to explore how the different morphological subtypes affected survival [8]. Age-standardized survival rates by morphological subtype were, presented alongside with excess mortality modelling accounting for the impact of demographic, diagnostic and tumor factors. The three main morphological subtypes (squamous cell carcinoma, adenocarcinoma and adeno-squamous carcinoma) in that study had similar one-year net survival rates of approximately 85%, and there were no differences at five years with adjusted survival rates of 55-65%.

However, some earlier studies have reported worse survival for patients with adeno-squamous cervical cancer with advanced stage, but not early

stage (IB-IIB) disease [9]. Furthermore, in a study from China including 8751 patients in FIGO stages I-IV all treated with definitive radiotherapy, both cancer-specific and overall survival was worse for patients with adenocarcinoma and adeno-squamous carcinoma compared with squamous cell carcinoma [10]. In this retrospective study, we will investigate how the three main morphological subtypes (squamous cell carcinoma, adenocarcinoma and adeno-squamous carcinoma) have impact on recurrence and survival.

Materials and Methods

Patients with biopsy verified cervical carcinoma were referred from hospitals within the Uppsala Medical Region to the regional referral center in the Department of Gynecology at the Akademiska University Hospital in Uppsala for decision of treatment during a 10-year period from January 1, 2008 to December 31, 2017 (Table 1). Samples were collected, in compliance with the Helsinki Declaration and used in accordance with the Swedish Biobank Legislation [11]. The Ethical Review Act was approved by the Uppsala Ethical Review Board, decision (Dnr.2018 / 322) [12].

Table 1: Patient's characteristics (n=259) for all patients in FIGO-stages IA-IIB. The study included 253 patients after six patients with other histology were, excluded (clear cell tumors (n = 2), neuroendocrine tumors (n = 2) and spino-cellular tumors (n = 2)) which, are presented in this table, but not included in this work.

Patient's characteristics (n=259)	n	%
Age (median)	45.9 years (range 22-83 years)	
FIGO-stage	259	
IA	45	(17.4)
IB	162	(62.5)
IIA	14	(5.4)
IIB	38	(14.7)
Histopathology		
Squamous cell carcinoma	150	(57.9)
Adenocarcinoma	74	(28.6)
Adeno-squamous	29	(11.2)
Other*	6	(4.6)
Tumor grade		
G1	58	(21.4)
G2	77	(28.4)
G3	89	(32.8)
Ungraded	35	(12.9)
Type of Operative treatment	210	
Trachelectomy	27	(13.1)
Total hysterectomy	30	(14.3)
Radical hysterectomy	153	(72.6)
Primary oncological treatment	49	
Radio-chemotherapy	40	(81.6)
Primary radiotherapy	9	(18.4)
Postoperative oncological treatment	29	
Radio-chemotherapy	27	(93.1)
Radiotherapy	2	(6.9)

Other* tumors of other histology (clear cell tumors (n = 2), neuroendocrine tumors (n = 2) and spino-cellular tumors (n = 2) are presented in this table, but not included in this work.

Totally 253 patients with the histological diagnosis of squamous cell cancer, adenocarcinoma and adeno-squamous cancer in cervix in FIGO

stages IA-IIB were included in this study, but other rare histological types (n = 6) presented in the (Table 1), were excluded from statistical

analysis. The records and histopathologic reports of the 253 patients were retrospectively, reviewed and the variables studied are shown in the (Tables 1, 2, 3 & 4). Clinical examination and FIGO staging by an expert gynaecologist and a gynaecologic oncologist were undertaken. Histology was determined at the time of diagnosis at a central tumor

board conference before final decision of treatment (primary oncologic treatment or operation) with results of CT and MRI presented. However, the final histopathological diagnosis was determined post-operatively at a new central tumor board conference for decision of eventual postoperative treatment.

Table 2: Clinical and pathological features of cervical carcinoma, compared after the subtypes squamous cell carcinoma, adenocarcinoma and adeno-squamous cancer, (n=253).

Histology	Squamous cell carcinoma No (%)	Adeno-carcinoma No (%)	Adeno- squamous carcinoma No (%)	P value
	150 (%)	74 (%)	29(%)	
Age (t-test)	46.8 years	44.3 years	44.2 years	0.369
FIGO-stage				
IA	33 (22)	9 (12)	3 (10)	
IB	86 (57)	50 (68)	22 (76)	
IIA	7 (5)	5 (7)	2 (7)	
IIB (chi-2 test)	24 (16)	10 (13)	2 (7)	0.282
Tumor grade				
G1	17 (30)	38 (67)	2 (3)	
G2	47 (63)	20 (26)	9 (12)	
G3	59 (69)	10 (12)	16 (19)	
Ungraded (chi-2 test)	27 (77)	6 (17)	2 (6)	0.000
Recurrent disease				
Without	120 (80)	66 (89)	22 (76)	
With (chi-2 test)	30 (20)	8 (11)	7 (24)	0.152

Table 3: Treatment modality compared after the subtypes squamous cell carcinoma, adenocarcinoma and adeno-squamous cancer, (n=253).

Histopathology	Squamous cell carcinoma No (%)	Adeno-carcinoma No (%)	Adeno- squam. Ca No (%)	P value
	150 (%)	74 (%)	29(%)	
Operative treatment				
Total (n = 207)				
Radical hysterectomy (n = 150)	73 (48.7 %)	54 (36.0 %)	23 (15.3 %)	
Total hysterectomy (n = 30)	25 (83 %)	5 (17 %)	0	
Trachelectomy (n = 27)	21 (77.8 %)	5 (18.5 %)	1 (0.37%)	
(chi-2 test)	119	64	24	0.003
Post-operative oncological treatment (n = 29)				
Radio-chemotherapy (n=27)	14 (52 %)	5 (18 %)	8 (30 %)	
Radiotherapy (only) (n=2)	1 (50 %)		1 (50 %)	
(chi-2 test)				0.775
Primary oncological treatment (n = 46)				
Radio-chemotherapy	23 (62 %)	10 (30 %)	4 (8 %)	
Primary radiotherapy (chi-2 test)	8 (89 %)	0	1 (11%)	0.170

Table 4A: Cox-regression. Prognostic factors for disease-free survival for the whole series of patients (n=253).

Variable	Unadjusted			Adjusted results			p-value
	HR	-95% C.I.	+95% C.I.	HR	-95% C.I.	+95% C.I.	
Age	1,022	1,002	1,042	1,008	0,985	1,032	0,488
FIGO-stage							0,000
IA	0,104	0,031	0,352	0,186	0,043	0,809	0,025
IB	0,193	0,101	0,367	0,181	0,086	0,383	0,000
IIA	0,230	0,068	0,780	0,235	0,066	0,837	0,025
IIB	Reference			Reference			
Histopathology							0,009
Adeno-carcinom	0,307	0,114	0,826	0,190	0,060	0,601	0,005
Squamous cell	0,422	0,188	0,950	0,310	0,130	0,739	0,008
Adeno-squam.	Reference			Reference			
Tumor grade							0,305
G1	6,072	0,757	48,682	6,471	0,642	65,235	0,113
G2	8,366	1,103	63,455	5,156	0,540	49,233	0,154
G3	8,553	1,147	63,808	3,618	0,365	35,893	0,272
Ungraded	Reference			Reference			

Table 4B: Logistic regression. Predictive factors for recurrent disease for the whole series of patients (n=253).

Variable	OR	-95% C.I.	+95% C.I.	OR	-95% C.I.	+95% C.I.	p-value
Age	1,029	1,007	1,052	1,002	0,976	1,030	0,865
FIGO-stage							0,150
IA	0,061	0,016	0,231	0,093	0,010	0,862	0,037
IB	0,130	0,059	0,288	0,143	0,023	0,898	0,038
IIA	0,232	0,055	0,970	0,210	0,037	1,183	0,077
IIB							
Histopathology							0,114
adenocarcinom	0,318	0,106	0,952	0,242	0,061	0,958	0,043
Squamous cell	0,656	0,265	1,626	0,626	0,228	1,715	0,362
Adenosquamous							
FIGO-grade							0,630
G1	2,612	0,521	13,098	3,048	0,467	19,872	0,244
G2	4,459	0,969	20,517	2,439	0,410	14,505	0,327
G3	4,923	1,083	22,373	1,888	0,311	11,479	0,490
Ungraded							
Treatment							0,170
Operation only	0,115	0,054	0,247	0,677	0,119	3,861	0,661
Op. + postop.	0,416	0,153	1,128	1,806	0,299	10,897	0,519
Prim. onk. treatment.							

Statistical Methods

The Pearson's Chi-square test was, used for testing proportional differences in univariate analyses. The survival curves were, generated by using the Kaplan-Meier technique and differences between curves were, tested by the Chi-square test. Cox regression analysis was, used to estimate the impact of prognostic factors for disease-free survival. Predictive factors for recurrent disease were, analysed with logistic regression models. All tests were two-sided and the level of statistical significance was $p \leq 0.05$. The STATISTICA 13.4 (Stat Soft TM) statistical package was used for the analyses.

Results

Totally, 207 (82%) out of 253 patients included in the study, had primary surgical treatment and the remaining 46 patients (18%) received primary

oncological treatment (radio-chemotherapy or radiotherapy). Clinical and pathological features of cervical carcinoma, compared according to the subtypes squamous cell carcinoma (n=150), adenocarcinoma (n=74) and adeno-squamous cancer (n=29) are shown in the (Tables 2 & 3). No association between the three histological subtypes and age ($p=0.369$), FIGO stage ($p=0.282$) or recurrent disease ($p=0.152$) respectively, could be detected.

However, the difference in distribution of tumor grade between the three different histological subtypes was highly significant ($p=0.000$), where adenocarcinoma usually (67 %) were G1 tumors (well differentiated) compared with squamous cell carcinoma (G1:30 %) and adeno-squamous carcinoma (3 %), respectively. On the contrary, tumors of squamous cell carcinoma most often (69 %) were G3 tumor (low differentiated) compared with adenocarcinoma (12 %) and adeno-squamous carcinoma (19 %). Furthermore, in this study, the ungraded

tumors usually were of squamous cell carcinoma histology. Thus, 27/35 ungraded tumors (77 %) were of squamous cell carcinoma histology compared with six (17 %) of adenocarcinoma histology and two (6 %) of adeno-squamous histology, respectively (Table 2).

Totally, 207 out of the 253 patients in the study had primary surgical treatment and the type of surgery chosen for the three histological types differed ($p=0.003$) (Table 3). Thus, 73/119 patients (61.3 %) with squamous cell carcinoma were treated with radical hysterectomy, compared with 54/64 patients (84.0 %) with adenocarcinoma tumors and 23/24 patients (96 %) with tumors of adeno-squamous histology. For the ungraded tumors 32/35 patients were diagnosed in stage IA and only 11/32 (34 %) were operated with radical hysterectomy, 15 (47%) with total hysterectomy and six (18%) patients were treated with trachelectomy. The three remaining patients (two patients in FIGO-stage IIB and one patient in FIGO-stage IIA) all had treatment with primary radio-chemotherapy.

In total, 29/207 (14 %) operated patients had postoperative oncological treatment (Table 3) and the remaining patients had surgical treatment only. There was no difference between the three histological groups according to post-operative treatment with 27/29 (93 %) patients treated with radio-chemotherapy and two (7 %) patients had only radiotherapy.

The indication for post-operative radio-chemotherapy was in four patients limited to pelvic lymph node metastases. For the other 23 patients the reason for postoperative treatment included negative prognostic factors such as size of the tumor, tumor invasion of the parametrium or lymph-vascular space invasion and for 5/23 patients it was a combination with pelvic lymph node metastases.

Furthermore, in patients treated with post-operative radio-chemotherapy or radiotherapy 24/29 (83 %), were in pre-operative stage IB ($p=0.000$) and three patients were in pre-operative stage IIA. The two resting

patients both were in stage IA with tumor of squamous cell carcinoma and adeno-squamous histology, respectively, both had treatment with radiotherapy only (Table 3). Thus, it could be concluded, that post-operative oncological treatment was given to 29 (14.0 %) out of 207 patients after preoperative FIGO-staging with clinical examination in combination with preoperative MRT and CT.

In this study 46 (18.2 %) out of the 253 patients had primary oncological treatment with no difference between the three histological subtypes, squamous cell carcinoma, adenocarcinoma and adeno-squamous cancer ($p = 0.172$) (Table 3). Thirty-seven (80.4 %) out of the 46 patients were treated with radio-chemotherapy and nine (19.6 %) were treatment with primary radiotherapy. It also was, noted, that 28 (82.3%) patients out of the 37 patients treated with primary radio-chemotherapy were in FIGO-stage II B. However, comparing pre-operative FIGO-stage (IA-IIB) between the group of patients treated with primary radiotherapy ($n=9$) and the group of 37 patients treated with primary radio-chemotherapy, no differences could be detected.

In the present study 45 patients (17.8%), developed recurrent disease. In this study age was not a prognostic factor for survival or predictive factor for recurrent disease. However, in a Cox-regression analysis histopathology (squamous cell cancer, adenocarcinoma or adeno-squamous cancer) was a significant prognostic factor for disease-free survival ($p = 0.009$) as presented in (Table 4A). Furthermore, in the survival analysis (Figure 1), the 5-year disease-free survival differed between the 3 histopathological sub-groups, (62 % for squamous cell cancer, 48 % for adenocarcinoma and 32 % for adeno-squamous cancer) (Chi-square = 6,221; $p = 0,045$). No association was found between the FIGO stages (IA-IIB) and the histological subgroups in a univariate analysis (Table 2), but in a Cox-regression analysis (Table 4A), FIGO-stage (IA-IIB) was a highly significant ($p = 0.000$) prognostic factor for disease-free survival. The tumor grade was not significant prognostic factor for disease-free survival in a Cox-regression analysis ($p = 0.305$).

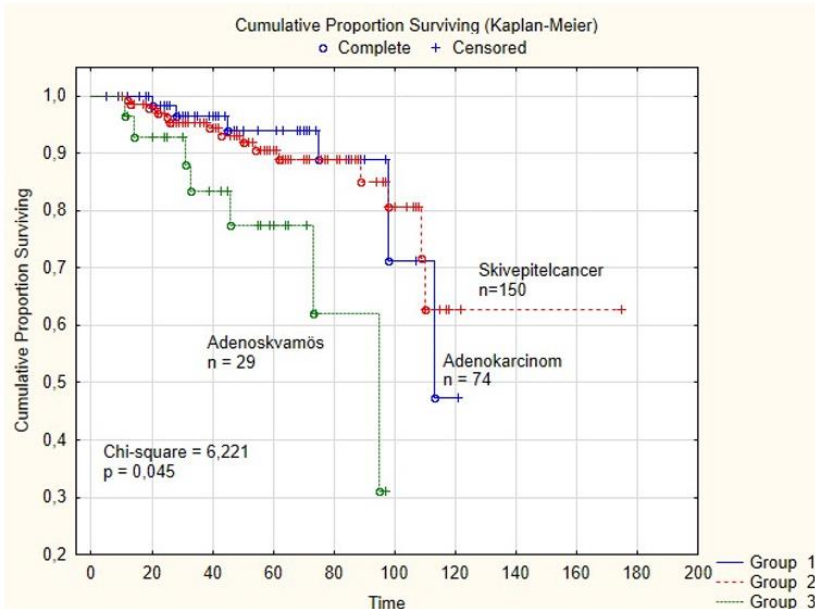


Figure 1: The 5-year disease-free survival was different between the 3 histopathological sub-groups, (62 % for squamous cell cancer, 48 % for adenocarcinoma and 32 % for adeno-squamous cancer (Chi-square = 6,221; $p = 0,045$).

However, in logistic regression analysis (Table 4B) the new variable “treatment” was added to the analysis for predictive factors for recurrent disease (Age, FIGO-stage, Histopathology and FIGO grade), but not any significant predictive factor for recurrent disease could be noted in that analysis. Perhaps, those findings could, be explained by the thesis that every patient received her optimal treatment (operation only, post-operative treatment after her operation or primary oncological treatment).

Discussion

The present study included 253 patients with cervical carcinoma in FIGO-stages IA-IIB, referred to the Department of Gynecology at the Akademiska University Hospital for decision of treatment during the 10-year period, 2008 to 2017.

In the univariate analysis, including clinical and pathological features of cervical carcinoma, no differences for age, FIGO-stage or recurrent disease could, be detected between the three main subtypes, squamous cell carcinoma, adenocarcinoma and adeno-squamous cancer. However, the differences in tumor grade was highly significant between the three different histological groups in a univariate analysis, but in the regression analysis, the tumor grade was not prognostic factor for disease-free survival or predictive factor for recurrent disease. On the contrary, the FIGO-stage (IA-IIB) was a highly significant prognostic factor for disease-free survival, but not a predictive factor for recurrent disease.

Finally, histopathology (adenocarcinoma, squamous cell cancer and adeno-squamous cancer) was a highly significant prognostic factor for disease-free survival, but not a predictive factor for recurrent disease. As mentioned above, the tumor grade differed between the three different histological groups in a univariate analysis, but in a Cox-regression analysis, the tumor grade was not prognostic factor for disease-free survival. Thus, tumors of adenocarcinoma usually were, well differentiated (67 %) compared with squamous cell carcinoma (30 %) and tumors of adeno-squamous carcinoma (3 %), respectively. On the contrary, tumors of squamous cell carcinoma usually were low differentiated (69 %) compared with tumors of adenocarcinoma (12 %) and adeno-squamous carcinoma (19 %), respectively.

However, the tumor grade usually is not a prognostic factor in squamous cervical cancer and not taken into account for patient treatment and guidelines for the management of patients with cervical cancer according to the European Society of Gynecological Oncology (ESGO) [13]. Thus, according to ESGO the major tumor-related prognostic factors are FIGO or TNM stage, including a maximum tumor size, extra-cervical tumor extension and nodal involvement. Furthermore, information about the tumor type and depth of cervical stromal invasion is important and finally, presence or absence of lympho-vascular space involvement and the presence or absence of distant metastases [13].

A retrospective observational study from USA including 31.536 women between 1983 and 2013 was, undertaken to examine the association between tumor grade and survival for women with squamous cervical cancer [14]. Among 4045 women in FIGO stage I disease, who underwent surgical treatment without radiotherapy, both grade 2 tumors

(HR=2.54) and the grade 3 tumors (HR=4.48) were independently associated with decreased cancer specific survival compared to grade 1 tumors. Thus, this study suggested that tumor differentiation grade might be a prognostic factor in women with squamous cervical cancer, particularly in early-stage disease. Furthermore, tumor grade is regularly included in histopathology of cervical squamous and adenocarcinoma. However, at present no grading system has achieved universal acceptance and grading of these tumors remains of uncertain value [15].

In this study, the ungraded tumors usually were of squamous cell carcinoma histology (77 %). In a retrospective population-based observational study of 11.951 women with cervical cancer, the excess mortality rates (1-3 years) increased from six months after diagnosis for ungraded tumors and were similar to low-grade tumors [8]. Therefore, it could, be suggested that ungraded tumors were likely to be low-grade tumors. Furthermore, should early invasive cervical carcinoma, which may include the tumors that are too small to grade, not routinely be, graded by pathologists [16].

The strength of this study is that it consists of the complete population of cervical cancer cases in FIGO-stages IA-IIB admitted to one single institution for decision of treatment, with detailed data on tumor characteristics, treatment and follow-up. Totally, 253 out of 259 patients were included in this study when rare histological types have, been excluded. In total, 82% of the study population had primary surgical treatment and 14.0 % had indication for further post-operative oncological treatment. Thus, it could, be speculated that the pre-operative work-up including clinical examination in combination with MRT and CT, had some limitations for correct staging. Since presence of lymph node metastases was the major cause of postoperative oncologic treatment, verification of lymph nodes by PET-CT in selected cases could help minimizing the number of women in need for both surgery and postoperative radiotherapy [6]. The newly introduced technique of sentinel node mapping will probably further decrease the negative consequences of combined therapy. In this study 45 patients (17.8 %) developed recurrent disease and Histopathology (adenocarcinoma, squamous cell cancer and adeno-squamous cancer) was a highly significant ($p = 0.009$) prognostic factor for disease-free survival in the Cox-regression analysis, but not a predictive factor for recurrent disease in the logistic regression analysis.

Furthermore, in a survival analysis (Figure 1), the disease-free survival differed between the three histological subgroups (62 % for squamous cell cancer, 48 % for adenocarcinoma, and 32 % for adeno-squamous cancer). A retrospective population-based observational study from England using cancer registration data of 11.951 women diagnosed with cervical cancer between 2006 and 2010 was, undertaken to explore how the different morphological subtypes affect survival rates [8]. Age-standardized net survival rates by morphological subtype were, presented alongside with excess mortality modelling accounting for the impact of demographic, diagnostic and tumor factors. The three main morphological subtypes (squamous cell carcinoma, adenocarcinoma and adeno-squamous carcinoma) in that study had similar one-year net survival rates of approximately 85%, but there were no differences at five years amongst the three morphological subtypes with adjusted survival rates of 55-65%.

However, some earlier studies have reported worse survival for patients with adeno-squamous cervix cancer in early stage (IB-IIB) whereas other studies were limited to advanced stage [9, 10]. In a study from China, patients in stage IA2-IIA2 underwent radical surgery 2006- 2014 [17]. Of the 5181 patients, 4510 patients had squamous cancer, 488 adenocarcinoma and 183 adeno-squamous cancer and five-year recurrence-free survival was 85.1%, 83.1% and 72.3% respectively ($p < 0.001$).

Furthermore, these earlier studies have reported different survival between all the three morphological subtypes (squamous cell carcinoma, adenocarcinoma and adeno-squamous carcinoma), but some other studies have compared prognosis and survival only between two morphological subtypes [9, 10]. In a study from Lei *et al.* it was, reported, that adeno-squamous carcinoma is a histological type of invasive cervical carcinoma that is composed of a mixture of both malignant glandular and squamous components [18].

However, in some studies, prognosis is compared between two histological types only, adeno-squamous carcinoma and adenocarcinoma of cervix or on the contrary, in a study from USA, the subgroup of squamous cell carcinoma was compared with a subgroup of both adenocarcinoma and adeno-squamous carcinoma together [19-21]. Therefore, it is not optimal to compare prognosis for the three histological subtypes in this work with other studies.

Conclusion

In the present study, FIGO-stage and histopathology (adenocarcinoma, squamous cell cancer and adeno-squamous cancer) were highly significant prognostic factors for disease-free survival. Furthermore, survival analysis, comparing the three histological types, reported worse survival for patients with adeno-squamous cervix cancer compared with adenocarcinoma and squamous cell cancer.

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