

Can the histopathology influence the outcome of early-stage cervical cancer?

J. Jonska-Gmyrek¹, A. Zolciak-Siwinska¹, L. Gmyrek²

¹ The Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Department of Radiotherapy, Warsaw

² The Holy Family Hospital, Gynecological Oncology Department, Warsaw (Poland)

Summary

Purpose of investigation: The assessment of the histology influence on survival in early-stage cervical cancer patients treated with surgery. **Materials and Methods:** The retrospective analysis of 71 cervical adenocarcinoma (AC), International Federation of Gynecology and Obstetrics (FIGO) Stage IB, treated initially with surgery, between 1989 and 1999 and 43 squamous cell cancer (SCC) patients, treated with the same method, between 1998 and 1999, was performed. Cox multi-variant analysis and the Kaplan-Meier methods were performed (the level of statistical significance, $p \leq 0.05$). **Results:** The ten-year overall survival (OS) of AC and SCC patients was 67.5% and 90%, $p = 0.015$. The ten-year disease free survival (DFS) was 63% and 85%, $p = 0.022$, respectively. After adjusting the significant prognostic factors, patients with AC had significantly worse treatment outcomes than patients with SCC: DFS (relative risk (RR) 1.85, 95% CI = 1.28-2.69, $p = 0.001$) and OS (RR 1.65, 95% CI = 1.65-2.33, $p = 0.005$). **Conclusion:** Prognosis of early cervical AC patients, treated with surgery, appears to be less favorable as compared to patients with SCC, treated with the same method.

Key words: Cervical cancer; Adenocarcinoma; Squamous cell cancer; Radiotherapy; Surgery; Treatment outcomes.

Introduction

Well-developed screening program declined cervix cancer incidence and mortality. During the last 50 years, incidence of adenocarcinoma (AC) increased from 5% to 15%, while the incidence of squamous cell cancer (SCC), especially in well developed countries, has decreased significantly [1]. According to Surveillance, Epidemiology and End Results program (SEER) data, carcinoma in situ (CIS) rates almost doubled, whereas rates for invasive SCC declined. Adenocarcinoma in situ (AIS) rates have significantly increased among younger women, while incidence and mortality rates of AC have been stable since 1990. The cytology screening has been considered as less effective at reducing the incidence and mortality rates in AC than in SCC [2, 3]. However, Mathew *et al.* pointed out that even in detection of AC, cytology in combination with HPV screening for high-risk HPV types may give the possibilities of early cervical lesions detection [4]. The prognostic significance of histological type, especially in early cervical cancer, is the subject of controversy. According to some authors, the treatment outcome is similar in early AC and SCC of the uterine cervix [5-8]; according to others the prognosis in AC is less favorable [9, 10]. Treatment methods are also the subject of discussion: should they be the same or different? In view of the existing controversy, the present authors conducted a retro-

spective analysis of their own material to assess the influence of pathological diagnosis on treatment outcomes in cervical cancer (CC) patients after surgery.

Materials and Methods

Between January 1989 and December 1999, 142 consecutive AC patients and between January 1998 and December 1999, 242 SCC patients were treated at the Maria Skłodowska - Curie Memorial Cancer Center in Warsaw. Among the total of 384 patients, 71 AC and 43 SCC patients FIGO (International Federation of Gynecology and Obstetrics) Stage IB were treated initially with surgery. Due to the higher incidence of SCC, these patients were treated during the shorter period in order to be a control group. AC constituted 11.8% of all cervical cancer patients. The clinical material of the current study constituted a group of 71 patients with cervical AC and 43 patients with SCC. The characteristics of the patients is detailed in Table 1. Patients were treated with radical hysterectomy (RH) according to Wertheim-Meigs procedure or simple hysterectomy (SH). RH was performed on 36 (50.5%) AC and 27 (63%) SCC patients. SH was performed in 35 (49.5%) AC and 16 (36%) SCC patients.

Patients were qualified to the adjuvant treatment, based on the risk features. High-risk features were: large lesion > four cm, metastases to lymph nodes, positive surgical margins or parametrial involvement. Intermediate risk factors were: deep stromal invasion (DSI, > 2/3), lymphovascular space invasion (LVSI), tumor size over three cm. Patients with one high or one intermediate risk factor received adjuvant treatment. When lym-

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Table 1. — Characteristics of the study patients.

Variables	ACC (n=71)	SCC (n=43)
Age (min, max)	54.9 (30-85)	54.1 (25-81)
WHO status		
0	50 (70.4%)	33 (76.7%)
1	19 (26.8%)	8 (18.6%)
>1	2 (2.8%)	2 (4.7%)
Hemoglobin level		
(min, max)	(6, 16)	(4.1, 16)
Mean (SD)	12.2 (2.0)	12.1(2.2)
Grade of differentiation		
Well	12 (17%)	4 (9%)
Moderately	32 (45%)	26 (61%)
Poorly	27 (38%)	13 (30%)
Tumor size		
≤ 3 cm	62 (88%)	39 (91%)
> 3 cm	9 (12%)	4 (9%)
Lymph node metastasis		
Yes	8 (11.3%)	6 (14%)
No	21 (29.6%)	21 (48.8%)
No data	42 (59.1%)	16 (37.2%)
LVSI		
Yes	17 (23.9%)	4 (9.3%)
No	33 (46.5%)	30 (69.8%)
No data	21 (29.6%)	9 (20.9%)

AC: adenocarcinoma; SCC: squamous cell carcinoma; WHO: World Health Organization; SD: standard deviation; LVSI: lymphovascular space invasion; EBRT: external beam radiotherapy; BT: brachytherapy.

phadenectomy was not performed, patients were qualified to external beam radiotherapy (EBRT) and brachytherapy (BT).

Adjuvant treatment was started within five weeks after surgical treatment. Adjuvant BT only was performed in patients with stromal invasion < 1/3 with no other risk factors.

Complementary BT only was performed on 15 (21.1%) AC and 24 (55.8%) SCC patients. Complementary EBRT combined with BT was performed on 56 (78.9%) AC and 19 (44.2%) SCC patients. EBRT was performed using gamma radiation with an energy of 1.25 MeV (Mega-electronvolt), and X photons of energy nine MeV, technique two or four field, by two-dimensional (2D) planning. The fractionated dose was 1.8 - 2 Gray (Gy). The total dose was 43 to 50 Gy. High dose rate (HDR) BT, performed using iridium (Ir 192) with a vaginal cylinder, two 7.5 Gy fractions, specifying the dose 0.5 cm from the surface of the applicator. For HDR as a sole treatment method, 22.5 Gy in three fractions was applied. In the case of a broad scar at the top of the vagina, low dose rate (LDR) BT with a caesium (Cs 137) was applied with the use of Fletcher applicator in 45 Gy dose given in two fractions every two weeks.

Patients were followed-up every three months for the first two years and twice per year thereafter. The present authors analyzed the following factors: histology, age, performance status according to the World Health Organization (WHO) scale, the tumor diameter > three cm, hemoglobin level before treatment, and the treatment method.

All time intervals were calculated from the final day of treatment. The events recorded for disease-free survival (DFS) were disease progression or death from any cause. Influence of selected factors on overall survival (OS) and DFS were examined using multivariate Cox model of proportional survival, survival curves were plotted using the Kaplan-Meier model, a comparison of

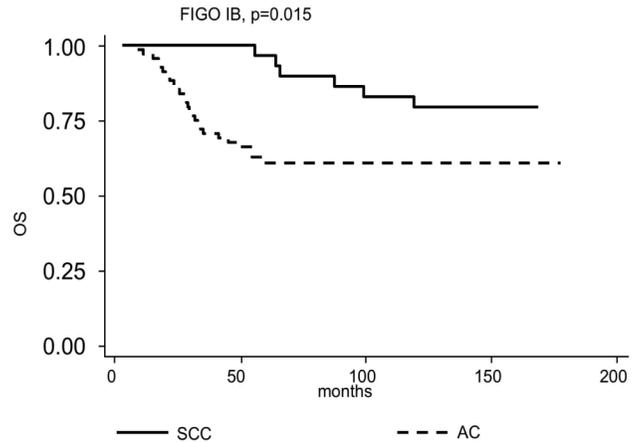


Figure 1. — The OS probability comparison between SCC and AC patients with cervical cancer FIGO Stage IB, treated surgically, depending on the histology, $p = 0.015$. SCC: squamous cell cancer; AC: adenocarcinoma; FIGO: International Federation of Gynecology and Obstetrics; OS: overall survival.

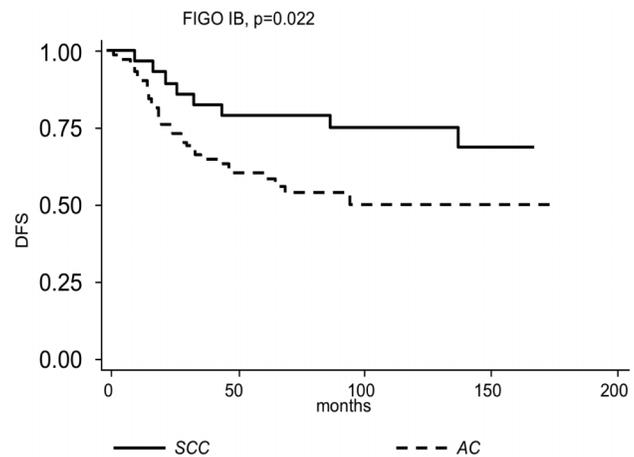


Figure 2. — Comparison of the DFS curves in patients with cervical cancer FIGO Stage IB, treated surgically, depending on the histology, $p = 0.022$. SCC: squamous cell cancer; AC: adenocarcinoma; FIGO: International Federation of Gynecology and Obstetrics; DFS: disease free survival.

curves was performed using the log-rank test. As the level of statistical significance, $p \leq 0.05$ was accepted.

Results

Median follow-ups for patients with AC and SCC were 81 months (40.5 to 174) and 80 months (8.7 to 168). Five-year OS and DFS was 96% and 79% vs. 65% and 60% for SCC and AC, respectively ($p = 0.015$, $p = 0.022$). The ten-year OS and DFS was 84% and 75% for SCC vs. 62% and 51% for AC. The comparison between survival curves is presented in Figures 1 and 2.

Multivariate analysis of DFS and OS revealed independent prognostic factors, as hemoglobin level before treatment: ≥ 13 vs. < 13 , $p = 0.03$ (OS), $p = 0.004$ (DFS) in both types of the tumor, the general condition of patients with AC, $p = 0.002$ (OS), $p = 0.005$ (DFS), and the diameter of SCC tumors, $p = 0.044$ (OS). After adjusting the significant prognostic factors, patients with AC had significantly poorer DFS (RR 1.85, 95% CI = 1.28-2.69, $p = 0.001$) and OS (RR 1.65, 95% CI = 1.65-2.33, $p = 0.005$) than SCC.

Discussion

The standard method of early cervical cancer treatment is surgery and adjuvant radiotherapy (RT) or radiochemotherapy (RT-CHTH) in case of the presence of risk factors. The limitations of the present study include the retrospective material, quantity of analyzed group, and the limited histological data in some patients, as well as the fact that during the analyzed period, RT-CHTH was not a standard care.

Over the years, an upward trend has been observed in the incidence of AC of the cervix which also applies to younger and younger ages [1, 11]. The results of treatment of patients with AC presented in the literature are varied [6-8, 10-14]. The essence of the problem is emphasized particularly in the early stages of the disease, when it would seem that a complete cure can be achieved.

However, the results of the present study did not confirm this. It turned out that the prognosis of AC at an early-stage, treated with primary surgery, compared with SCC, was less favorable. The difference in survival was statistically significant. The five-year OS and DFS for AC in the present study was 65% and 60%, respectively.

The five-year OS of early AC patients presented in the literature varies between 63.2% and 88.8%, the five-year DFS between 47.4% and 72.7% [12, 14, 15].

Similarly to the present results, some authors reported a significant value of histopathology even at an early stage of the disease when treated surgically [11, 12, 14, 16-18].

As the result of population-based retrospective study of 24,562 CC patients presented by Galic *et al.*, the authors found that the survival of patients with early-stage AC was inferior to that of stage-matched patients with SCC. When compared with women with SCC, the multivariable RR for death from AC was 1.39 (95% CI, 1.23 - 1.56) [16].

As the result of multivariate analysis, reported by Lai *et al.*, the histological type was confirmed as an independent prognostic factor for DFS [(RR): 1.279, 95%/CI, $p = 0.0092$] and OS (RR: 1.259, 95% CI), $p = 0.0146$ [12].

Park *et al.* presented the results of the study of 1,218 cervical cancer patients. The difference between AC and SCC in OS and DFS was statistically significant. Patients with

AC had significantly poorer DFS (RR 2.07, 95 CI = 1.37-3.12 $p = 0.001$) and OS (RR 2.56, 95% CI = 1.65-3.96, $p < 0.001$) than those with SCC [14]. The aforementioned data support the present results. The value of histopathology in early CC in this study was statistically significant. AC did significantly worse.

Some authors showed no difference between survival of patients in early stage of both histological types [7-9, 15, 19]. No difference in survival between the two histological types was demonstrated in the study conducted by Ayhan *et al.* The OS and DFS of 521 patients in Stage I AC and SCC was respectively: 86.4%, 83.1% vs. 87.7%, 84.0% [6].

Due to the fact that the methods of treatment in both types of cancer are the same, it is worth paying attention to other clinic-pathological factors that may affect survival. Prognostic factors presented in individual studies are varied. One of the frequently mentioned, in addition to the clinical stage, is the tumor differentiation [7, 13, 15, 17]. However, in the present authors' material, this factor did not reach the statistical significance.

There was also no demonstrated prognostic value of age, while the general condition of the WHO, 1-3 vs. 0, was statistically significant. The lymph nodes metastases were not analyzed due to the lack of data. In the literature, this is one of the most frequently administered prognostic factors [4, 10, 14, 15, 20].

Tumor size is a factor that has a statistically significant effect on prognosis in patients with SCC, whereas in patients with AC it remains irrelevant. Perhaps it has to do with the fact that patients eligible for treatment were characterized by a slight infiltration of the cervix, the size of which did not exceed three cm, and often endophytic infiltration in the AC. This factor is mentioned in the literature, but more often as a result of the analysis of patients with advanced stages [10, 15]. Hemoglobin levels showed prognostic value in both types of pathology. This factor is acknowledged in the literature [16].

It is difficult to compare the above results because the study cohorts were heterogeneous in terms of different factors, such as histopathology, lymph nodes status, hemoglobin level, tumor size, treatment methods, and others.

As is apparent from the data in the literature and analysis of the present authors' material, surgical outcome of AC at an early stage seems to be less favorable than the SCC in the same stage when using the same therapeutic methods.

Conducting research on the level of molecular diagnostics, allowing to select group of patients with AC of the cervix with the least favorable prognosis, thus requiring the use of targeted therapy, seems to be necessary.

Conclusion

Prognosis of early cervical AC treated with surgery, appears to be less favorable as compared to patients with SCC, treated with the same methods.

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Address reprint requests to:
 J. JONSKA - GMYREK
 The Maria Skłodowska-Curie Memorial
 Cancer Center and Institute of Oncology
 Roentgen Street, 5
 02-781 Warsaw (Poland)
 e-mail: jonska@wp.pl