Impact of histological subtype on the response to chemoradiation in locally advanced cervical cancer and the possible role of surgery

SILVIU VOINEA[1], CĂTĂLIN GABRIEL HERGHELEGIU[2,3], ANGELA SANDRU[1], RALUCA GABRIELA IOAN[2,3], ROXANA ELENA BOHILȚEA[2,4], NICOLAE BACALBAȘA[2,5], LAURA IOANA CHIVU[6], FLORENTINA FURTUNESCU[7], DIANA CATALINA STANICA[8] and ADRIAN NEACȘU[8]

[1]Department of Surgery, Oncology Institute 'Prof. Dr. Alexandru Trestioreanu', 'Carol Davila' University of Medicine and Pharmacy, 050474 Bucharest; [2]Department of Obstetrics and Gynecology, 'Carol Davila' University of Medicine and Pharmacy, 020021 Bucharest; [3]'Polizu' Clinical Hospital, 'Alessandrescu-Rusescu' National Institute for Healthcare of Mother and Child, 050474 Bucharest; [4]Department of Obstetrics and Gynecology, University Emergency Hospital Bucharest, 050098 Bucharest; [5]Department of Obstetrics and Gynecology, 'I. Cantacuzino' Clinical Hospital, 030167 Bucharest; [6]Department of Pathophysiology, 'Carol Davila' University of Medicine and Pharmacy, 020021 Bucharest; [7]Department of Public Health and Management, Faculty of Medicine, 'Carol Davila' University of Medicine and Pharmacy, 050463 Bucharest; [8]Department of Obstetrics and Gynecology, 'Sfantul Ioan' Emergency Clinical Hospital, 042122 Bucharest, Romania

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Abstract. Cervical cancer is one of the most common cancers in women in developing countries, second only to breast cancer, with more than 450.000 new cases every year. Romania has the highest incidence of cervical cancer in Europe; more than four times the incidence found in Western Europe. Radiotherapy with or without chemotherapy is considered in most countries the gold standard for locally advanced cervical cancer. In Romania, if downstaging occurs after radiotherapy, adjuvant surgery is routinely performed. Thus, in the present study, we investigated the rate of residual cancer in patients with locally advanced cervical cancer who underwent surgery after concurrent chemoradiotherapy and to determine the impact of tumor histological subtype on the chemoradiotherapy response. Of a total of 461 patients with locally advanced cervical cancer that underwent chemoradiotherapy and adjuvant surgery, 254 had a partial response defined as the presence of residual tumor at pathology examination. Depending on the histological subtype of the cervical cancer, partial response was obtained in 50.6% of squamous cell carcinoma cases and in 77.6% of adenocarcinoma or adenosquamous carcinoma cases. The present study demonstrated that cervical cancer patients with adenocarcinomas and adenosquamous carcinomas had a significantly poorer treatment response to chemoradiotherapy than those with squamous cell carcinomas. We consider that in such cases where residual tumor is present, adjuvant surgery is mandatory for improving the survival rates.

Correspondence to: Dr Cătălin Gabriel Herghelegiu, Department of Obstetrics and Gynecology, 'Carol Davila' University of Medicine and Pharmacy, 8 Eroii Sanitari Boulevard, 020021 Bucharest, Romania
E-mail: cnr_cata@yahoo.com

Professor Roxana Elena Bohilțea, Department of Obstetrics and Gynecology, University Emergency Hospital Bucharest, 169 Splaiul Independenței, 050098 Bucharest, Romania
E-mail: r.bohiltea@yahoo.com

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Introduction

Cervical cancer is one of the most common cancers in developing countries, second only to breast cancer, with more than 450,000 new cases every year (1). Romania has the highest incidence of cervical cancer in Europe with 28.6 cases/100,000, more than four times the incidence found in Western Europe (1,2). This is in part explained by the lack of an effective nationwide screening program that would allow the detection and treatment of premalignant cervical/precancerous lesions. In addition, due to the ineffective screening program, many cases are diagnosed at a later stage than in developed countries (3-11). As a consequence, treatment response is generally poorer, with a death rate of 0.38 per new case in Romania, compared to just for 0.21 per new case in developed countries such as Germany (2,12).

Given these particularities found in developing countries, where the number of patients diagnosed at a later stage is considerable, we aimed to ascertain the role of surgery in the multimodal treatment of locally advanced cervical cancer. Most studies and guidelines recommend radiotherapy with or without chemotherapy as the gold standard for locally advanced cervical cancer (13). Furthermore, some studies

suggest that performing surgery after radiotherapy does not improve therapeutic outcome and moreover it increases patient morbidity (14). However, the great majority of locally advanced cases diagnosed in Romania are treated with radiotherapy and if there is a good response and downstaging occurs, usually adjuvant surgery is performed. The most important argument for this therapeutic plan is that in many cases, radiotherapy in association or not with chemotherapy is not able to completely destroy the malignant cells and up to 40-50% of patients have histopathological evidence of residual tumor (15). Additionally, by performing surgery, better local control of the disease is achieved (16). Thus, we consider surgery as having an essential role in treating locally advanced cervical cancer.

The most common histologic variant of cervical cancer is squamous cell carcinoma (SCC) with an incidence of up to 80-95% (17,18), but due to the wide implementation of screening programs in developed countries and detection of premalignant disease, its incidence showed a marked decline over the past 40 years (18,19). Unfortunately, the same is not true for other histologic variants. There has been a constant rise in the incidence of endocervical adenocarcinomas over the last 40, especially in young women. The incidence of endocervical adenocarcinomas has doubled in the last decades, representing ~20-25% of cases of cervical cancer (18,20,21). Studies suggest that hematoxylin and eosin staining is sufficient for establishing the histology of primary endocervical adenocarcinoma and its variants, and that more expensive immunohistochemistry is not always mandatory (21). From the wide spectrum of cervical adenocarcinoma subtypes we will focus on two of most common variants: Adenocarcinoma usual endocervical subtype (AC) and adenosquamous carcinoma (ASC) (16,20). The most common variant is the AC subtype, that account for 75-80% of all cases of invasive cervical adenocarcinomas (21,22). A high density of medium sized round or oval glands and loss of lobular arrangement characterize these tumors. A wide variety of architectural patterns can be encountered ranging from papillary growth, tubular glands, and cribriform glands to solid areas of undifferentiated cells, depending on how well the tumor is differentiated. Cells typically show intracytoplasmic mucin that is usually abundant and mitotic activity; also apoptotic bodies are quite common (21,23). ASC of the cervix is less common than AC, but still accounts for up to 5-10% of cervical carcinomas and is composed of a malignant glandular component and a malignant squamous component (24,25). Both components are clearly visible on hematoxylin and eosin staining, without the need for histochemical stains. The glandular component is usually of endocervical subtype but it may also be mucinous or mixed endocervical and mucinous, endometrioid or clear cell. The squamous component may be glycogenated (21,26).

Although not mandatory, immunohistochemistry (IHC) can offer greater information regarding the exact diagnosis and tumor characteristics and it should be performed when possible. For example, to distinguish between endocervical AC and endometrioid AC, IHC is usually warranted. The presence of carcinoembryonic antigen (CEA) and p16 expression combined with the absence of progesterone receptors (PRs) and estrogen receptors (ERs) favor a cervical origin (27).

Studies have shown that patients with AC/ASC histology have worse survival outcome than those with SCC (19,28). However, the tumor response to chemoradiotherapy of AC/ASC compared to SCC has been rarely studied. The present study was designed to investigate the rate of residual cancer in patients with locally advanced cervical cancer who underwent surgery after concurrent chemoradiotherapy and to find out the impact of tumor histological subtype on the chemoradiotherapy response.

Patients and methods

Patients. Data were obtained retrospectively for all patients with locally advanced cervical cancer, treated between January 2005 and December 2014 at the Oncology Institute of Bucharest, Romania. The patients were staged according to the International Federation of Gynecology and Obstetrics (FIGO) staging criteria (29) and only patients with FIGO stages IIB-IVA were selected. Depending on the histological classification of the tumor, patients were divided into an SCC histology group or an AC/ASC histology group. All patients were treated by the same multidisciplinary team according to the same protocol.

The data collected retrospectively did not contain personal information and only the agreement of the Ethics Committee of the Oncology Institute 'Prof. Dr. Alexandru Trestioreanu' Bucharest was required and obtained without the need of informed consent or the consent of the patient/legal representative in the case of minors.

A comprehensive/rigorous staging protocol was used, consisting of clinical examination, including vaginal and rectal exam. The protocol also included computed tomography and/or magnetic resonance imaging (chest-abdomen-pelvis). For cases in which bladder or rectum involvement was suspected, the staging protocol also included cystoscopy and colonoscopy. Patients with evidence of distant metastasis were excluded from the study.

Treatment. The treatment plan first included chemoradiotherapy. For radiotherapy the protocol was whole pelvic external beam radiation with a total dose of 50.4 Gy and two high dose rate brachytherapy with a total dose of 15 Gy to A point. Concurrent chemotherapy was administered, consisting of cisplatin 40 mg/m^2 weekly for a total of 5 weeks.

In all cases, adjuvant surgery was performed after 6-8 weeks from the completion of chemoradiotherapy. The type and extent of the surgical intervention was determined according to pre-treatment data, post-radiation observations and operative findings. In the majority of cases, type II or III radical hysterectomy (radical abdominal hysterectomy with bilateral pelvic lymphadenectomy or Wertheim-Meigs procedure) was performed. In 10 cases where bladder or rectum involvement was confirmed, pelvic exenteration (partial or complete) was performed.

All surgical specimens were sent for pathology assessment. The tumor response rate to chemotherapy was assessed by preoperative data and histopathological examination of the cervical specimen. A complete response (CR) was defined as the absence of residual tumor at pathology examination. A partial response (PR) was defined as the presence of residual tumor at the pathology examination.

Table I. Characteristics of the patients included in the study.

	All patients	SCC group	AC/ASC group
No. of patients (%)	461 (100)	385 (83)	76 (17)
Age (years)			
Range	28-82	28-82	29-71
Mean	61.7	62.9	59.1
FIGO stage, n (%)			
IIB	393	329 (85.5)	64 (84.2)
IIIA, IIIB	58	47 (12.2)	11 (14.5)
IVA	10	9 (2.3)	1 (1.3)

SCC, squamous cell carcinoma; ASC, adenosquamous carcinoma; AC, adenocarcinoma usual endocervical subtype; FIGO, International Federation of Gynecology and Obstetrics.

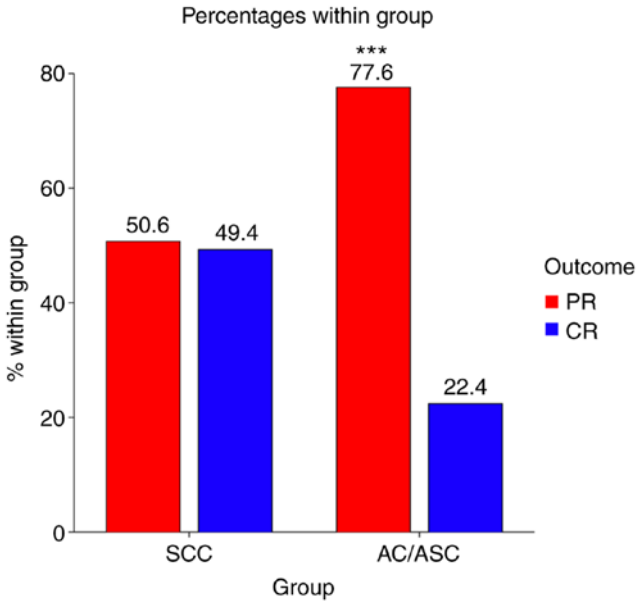

Figure 1. The percentage of cases with partial response after chemoradiotherapy, depending on histological subtype. AC, adenocarcinoma usual endocervical subtype; ASC, adenosquamous carcinoma; SCC, squamous cell carcinoma; PR, partial response; CR, complete response. ***P<0.001, compared with the SCC group.

Statistical analysis. For statistical analysis we used NCSS 2019 Statistical Software (2019) [NCSS, LLC. (ncss.com/software/ncss)] (two proportions comparison test). The results were analyzed and interpreted according to the obtained P-value; P<0.05 was considered to be statistically significant.

Results

Between January 2005 and December 2014, a total of 461 women with locally advanced cervical cancer (stages IIB-IVA), were treated at the Oncology Institute of Bucharest and were included in this study. Of these, 385 patients had SCC histology, being assigned to the SCC group, 49 patients had AC and 27 patients had ASC, being assigned to the AC/ASC group.

The characteristics of the patients are summarized in Table I. Tumor FIGO stage was IIB in 393 cases, IIIA-IIIB in 58 cases and IVA in 10 cases. There were no statistically significant differences between FIGO staging in the SCC group and the AC/ASC group (P>0.05). The mean age for the SCC group was 61.7 years, while for the AC/ASC it was 59.1 years.

From the pathological reports of surgical specimens, PR with residual tumor in the cervix was found in 254 patients (55.1%). Histopathological distribution of the cases is presented in Table II, with residual tumor present in 195 (50.6%) of the 385 SCC cases, and in 59 (77.6) of the 76 AC/ASC cases.

The PR rate for the SCC group was 50.6%, while for the AC/ASC group the PR rate was 77.6%; significantly higher (P<0.001) (Fig. 1). In the AC/ASC group the PR rate was 73.5% for the AC histology and 85.1% for the ASC histology. This finding comes to confirm the poorer response of AC and ASC to chemoradiotherapy.

Discussion

Our results come to confirm that the histologic subtype of the tumor in any malignancy must be taken into account when deciding the therapeutic plan, since depending on the tumor characteristics, the response to therapy can vary widely (30,31). In addition, before establishing the therapeutic options, a rigorous evaluation of the patient for distant metastasis must be performed, since there have been reports of rare metastatic sites such as the spleen from primary cervical cancers (32).

Numerous studies conducted over the last two decades have found that the treatment response and overall survival of patients with adenocarcinoma usual endocervical subtype (AC) or adenosquamous carcinoma (ASC) is generally poorer compared with that of patient with squamous cell carcinoma (SCC) (27,28,33,34). Our study comes to confirm once more that tumor response to chemoradiotherapy is worse for AC/ASC histology. The rate of residual tumor was almost 50% higher for AC/ASC group (77.6%) in comparison with the SSC group (50.6%). However, despite these findings, the therapeutic recommendations of these patients did not change over time; the treatment strategy being similar to that used for SCC histology (35).

The results clearly show that there is a need for a more effective treatment protocol for patients with locally advanced cervical cancer who exhibit AC/ASC histology. Some studies suggest that adjuvant surgery may play a crucial role in these cases where residual tumor is still present after chemoradiotherapy (36). The guidelines usually do not recommend surgery for these advanced stages, but depending on the geographic region and local protocols, surgery is often taken into consideration, one such example being Romania (37).

According to the latest recommendations for women with early-stage cervical cancer from IA2 up to IB2, modified radical hysterectomy is preferred over primary radiation therapy (38). Nonradical surgery is recommended for women with microscopic disease with stromal invasion <3 mm in depth in whom there is no evidence of intermediate or

Table II. Histopathological distribution of the cases with residual tumor.

Histology subtype	SCC	AC/ASC	AC	ASC	Total
Total no. of patients	385	76	49	27	461
Patients with residual tumor after chemoradiotherapy, n (%)	195 (50.6)	59 (77.6)	36 (73.5)	23 (85.1)	254 (55.1)

SCC, squamous cell carcinoma, AC, adenocarcinoma usual endocervical subtype; ASC, adenosquamous carcinoma.

high risk features (39). The preservation of fertility may be targeted in carefully selected cases of patients who meet all of the five criteria: Desire to preserve fertility; reproductive age <40 years, at most stage IB1, lack of risk factors for recurrence, only low-risk histology adenocarcinoma or squamous cell carcinoma and mandatory the lack of lymph node metastasis (40).

Primary radiotherapy is reserved for women with several important medical comorbidities and altered general status (41). The cases with early cervical cancer treated primary by surgical approach should continue with adjuvant therapy in the presence of findings that suggests an increased risk of recurrence. The benefit of surgery compared with radiotherapy is the possibility of ovarian conservation through surgery avoiding premature menopause and offering possibilities for reproduction technologies (42).

Regarding the advanced stages of cervical cancer, primary chemoradiation which has demonstrated superior positive results compared to radiotherapy alone is recommended by the latest studies. Radiotherapy in conjunction with chemotherapy, especially brachytherapy results in significant higher rates of survival (43-47). Most centers do not perform hysterectomy after chemoradiation and the results of research performed in this field until now show that after a 3-year follow-up women who underwent hysterectomy exhibit no difference in survival rate (48).

One limitation of our study is that it was conducted at a single institution and that it included a relatively small number of patients with AC/ASC subtypes/histology due to their low incidence. Another limitation is that being a retrospective study, we cannot exclude potential sources of biases, although the FIGO staging was similar for both the SSC and AC/ASC group.

The prognostic significance and treatment response of AC or ASC histologic subtypes in comparison with SCC should be evaluated in further prospective large scale multi-center studies, for a clear conclusion to be drawn and in order to develop a treatment protocol for these subtypes of cervical cancer.

In conclusion, the present study demonstrated that cervical cancer patients with AC/ASC histology have significant poorer treatment response to chemoradiotherapy than those with SCC. Current guidelines for cervical cancer do not take into account the different histologyic subtypes and may not be adequate for all patients, since studies show that response to chemoradiotherapy varies significantly depending on the histologic subtype. We found that in 55.1% of the cases included in the study, despite chemoradiation, there was a partial response, with residual tumor still present. The percentage was significantly higher for the AC/ASC group (77.6%), compared to the SCC group (50.6%). We consider that in such cases where a residual tumor is present, adjuvant surgery is mandatory for improving the survival rates. In literature, the differences regarding the therapeutic response to chemoradiotherapy between AC/ASC and SCC have been rarely studied, thus further research is warrant to draw a definite conclusion.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

SV, REB and CGH collected, analyzed and interpreted the patient data regarding the treatment strategies corresponding to the patients with early stage cervical cancer. AS, RGI, LIC and NB collected the data and made substantial contribution to the conception of the research and statistical analysis. SV, FF, DCS and AN substantially contributed to the conception of the study, the interpretation of the data and the writing of the manuscript. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The data collected retrospectively did not contain personal information and only the agreement of the Ethics Committee of the Oncology Institute 'Prof. Dr. Alexandru Trestioreanu' Bucharest was required and obtained without the need of informed consent or the consent of the patient/legal representative in the case of minors.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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