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Outcomes of patients with intermediate risk early stage cervical adenocarcinoma – a single institution experience

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Summary

Purpose of investigation: To assess the treatment efficacy in FIGO Stage I AC (adenocarcinoma, AC) patients with a special focus on treatment failure. *Materials and Methods:* Among 93 patients with AC of the uterine cervix, 33 patients with FIGO Stage I were treated with radical hysterectomy (RH) and adjuvant treatment, according to the presence of risk factors in the histopathology protocol. *Results:* The median follow-up after treatment was 61 (range: 7-96) months. Recurrence developed in six (18%) of the 33 patients; two died of cervical cancer. In three cases (9%), recurrence was outside the pelvis and in three (9%) loco-regional recurrence was confirmed. All recurrences occurred in the intermediate and high-risk group. *Conclusion:* Outcomes of patients with intermediate risk factors in early cervical AC treated with surgery and adjuvant radiotherapy (RT) are unsatisfactory. The studies confirming how patients with intermediate risk factors may benefit from adjuvant chemoradiotherapy (CRT) seem to be necessary.

Key words: Adenocarcinoma; Cervical cancer; Radiochemotherapy; Surgery; Treatment outcome.

Introduction

Cervical cancer is the second cancer in women worldwide [1]. Due to the development of a screening program, the incidence has decreased, particularly for squamous cell cancer (SCC) [2]. However, the detection of cervical adenocarcinoma (AC), especially at early stages in young women, has increased [3, 4]. This trend is also due to the lower sensitivity of the PAP smear for precancerous AC lesions and presumably increasing exposure to human papillomavirus (HPV) as a result of changing sexual habits and increased HPV transmission [4, 5]. The International Federation of Gynecology and Obstetrics (FIGO) classification is the standard method for survival probability assessment in cervical cancer. It does not take into account possible prognostic factors. The standard treatment for patients with early stage cervical cancer is a radical hysterectomy (RH) with or without radiotherapy (RT)/chemoradiotherapy (CRT) when risk factors are present. The addition of chemotherapy to radiation after RH includes those with positive lymph nodes, positive parametrium, or positive surgical margins [6]. If two intermediate risk factors are present, according to Sedlis *et al.* [7, 8], the adjuvant therapy is radiation alone, and there has been no study that compares chemoradiation to radiation alone in patients with intermediate risk factors.

Although the efficacy of RH and pelvic lymphadenectomy for early cervical AC has been demonstrated, the presence of risk factors correlates with treatment failure [1, 6-11]. According to some studies, postoperative CRT can offset the negative impact of these factors on survival [6, 12, 13]. Other studies have shown no benefits of CRT [11, 14]. Some authors have reported that non-squamous histology is one of the main adverse risk factors in cervical carcinoma [10, 14-17]. Therefore, the survival of patients with AC after RH and the optimal treatment modality remains the subject of debate. The purpose of this study was the assessment of treatment outcome in FIGO Stage I cervical AC patients, treated initially with surgery with a special focus on treatment failure.

Materials and Methods

During the period from 2009 to 2013, 93 patients with Stage I-IV A cervical AC (based on FIGO classification) were treated at Radiotherapy Department of The Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology in Warsaw. Among this group, 33 consecutive patients with FIGO Stage I AC were treated surgically without any prior treatment. Before the RH, the work-up for all patients included clinical examination, MRI, chest X-ray, blood count, and biochemistry. Only patients with no visible parametrial infiltration (PI) or enlarged nodes were qualified for surgical treatment. Before treatment, a written in-

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formed consent was given by each of the women.

The RH procedure consisted of excision of the uterus with the parametrium and upper one-third of the vagina, removal of the ovaries and fallopian tubes, and bilateral pelvic lymph node dissection. In one case, due to the young patient age and superficial stromal infiltration (SI), pelvic laparoscopic lymphadenectomy and trachelectomy were performed. The depth of SI, lymph node status, presence of lymphovascular space invasion (LVSI), and PI were assessed by an institutional pathologist.

Sedlis *et al.* [7, 8], and Peters *et al.* criteria [6] were used to identify a group of patients requiring adjuvant treatment. Lymph node metastases, large lesion (> 4 cm), positive surgical margins or PI were high risk factors. Intermediate risk factors were LVSI, SI > 1/3, tumor size > 3 cm. and < 4 cm. Patients with one high or two intermediate risk factors received adjuvant CRT. CRT was also performed in patients with one intermediate risk factor when less than six lymph nodes were examined. None of these criteria included histopathologic type. Adjuvant treatment started within 3-5 weeks after surgery. High dose rate (HDR) BT was performed using iridium (Ir 192; nominal activity: 10 Ci) applied as two 7.5 Gy doses using a vaginal cylinder to apply the dose 0.5 cm from the surface of the applicator. The HELAX and ARIA systems were used for treatment planning, according to The International Commission on Radiation Units and Measurements; ICRU 50 and ICRU 62 protocols, using the 3D conformal technique. All patients were treated with high megavoltage photons from a linear accelerator X 15 MeV. External beam radiotherapy (EBRT) was administered up to 45–46 Gy in daily fractions of 1.8–2 Gy at the planning target volume (PTV) region five times per week. The target volume and organs at risk were delineated in the CT scans. A 7-mm margin in all directions around the clinical target volume (CTV) defined the PTV. Concomitant chemotherapy (CCT) consisted of weekly infusions of cisplatin (40 mg/m^2 dose) with appropriate hydration.

The authors followed patients every three months for the first two years and twice per year after that. Biopsies were obtained to confirm recurrence or the diagnosis was based on clinical examination with a CT or MRI and detection of elevated tumor markers. Complications affecting the bladder and rectum were scored using the Radiation Oncology Group Early and Late Radiation Morbidity; scoring system. DFS and OS were defined as the time interval between surgery and the first evidence of recurrence or death from any cause, respectively. We calculated the DFS and OS rates using the Kaplan-Meier method and compared using the log-rank test. The outcomes from the group of patients treated with RH and patients treated with RH-BT-CRT were assessed.

Results

Patient characteristics are presented in Table 1. The median age was 50 (23-75) years. The median follow-up after treatment was 61 (range: 7-96) months.

During post-surgical histopathology procedures, four (12%) patients were found to have lymph node metastases, 19 (58%) SI (>1/3), six (18%) PI, and seven (21%) LVSI, and microinvasion of the uterine corpus was confirmed in two cases.

The median number of lymph nodes obtained was 16 (range: 7-23). Fourteen patients with FIGO Stage IA2, IB1 or superficial invasion with SI < 1/3 without any risk factors were observed after RH. Four patients with SI > 1/3 without any other risk factors, had EBRT and BT. Combined BT and CRT were performed in 12 patients.

The median number of CCT cycles was four (range: 1-5).

Table 1. — *Patient characteristics (n= 33).*

Feature	N (%)
Median age (range)	50 (min 23, max 75)
FIGO Stage	
IA2	3 (9.1)
IB1	30 (90.9)
Pathologic type	
Pure Adenocarcinoma	17 (51.5)
Adenosquamous	3 (9.1)
Endometrioid	1 (3.0)
Mucinous	6 (18.2)
Clear cell	1 (3.0)
Endocrine	1 (3.0)
Glassy cell	1 (3.0)
Papillary	3 (12)
Grade	
Well differentiated G1	11 (33.3)
Moderately differentiated G2	17 (51.5)
Poorly differentiated G3	2 (6.1)
Unknown	3 (9.1)
LVSI	
Yes	7 (21.2)
No	26 (78.8)
N+	
Yes	4 (12.1)
No	29 (87.9)
PI	
Yes	6 (18.1)
No	27 (81.9)
Tumor size (cm)	
< 3	27 (82)
3-4	6 (18)
> 4 cm	0
SI	
Up to 1/3	14 (42)
>1/3	19 (58)
Treatment	
RH	17 (51.5)
RH+BT+EBRT	4 (12.0)
RH + BT+CCR	12 (36.3)
CHT: 4 or more courses	10 (83.3)
CHT: less than 4 courses	2 (16,7)
Recurrence	
Yes	6 (18.2)
No	27 (81.8)

N: number of patients, LVSI: lymphovascular space invasion, N+ : lymph node metastasis, PI: parametrial infiltration, SI: stromal invasion, RH: radical hysterectomy, BT: brachytherapy, EBRT: external beam radiotherapy, CCR: radiochemotherapy, CHT: chemotherapy.

Ten patients received four or more courses, and two patients received one to three courses of CCT. CCT was stopped after the first course in one patient who developed renal failure. One patient developed hematological toxicity after three courses of CCT. Relapse was confirmed in six patients (18%). Despite the completion of the full adjuvant treatment regimen, three patients in the high-risk group developed loco-regional recurrences. Two of the six patients with PI had a local failure. One patient with lymph

Table 2. — *Clinical and pathological features in recurrent patients.*

Patient number	Histopathologic features	Treatment	Type of failure
1	TD >3 cm, SI >1/3, PI	46Gy+2x7.5Gy+5xDDP	Apex of the vagina
2	SI >1/3, PI	46Gy+2x7.5Gy+5xDDP	Infiltration of the rectum and bladder
3	N+	46Gy+2x7.5Gy+5xDDP	Pelvic lymph nodes
4	SI >1/3	46Gy+2x7.5Gy	Pulmonary metastases
5	LVSI +, N+, SI >1/3	46Gy+3x7.5Gy+1xDDP-increasing renal failure	PALN
6	SI >1/3	46Gy+2x7.5Gy	Presacral region and bones

TD: tumor diameter; SI: stromal invasion; PI: parametrial involvement; N+: lymph node metastasis; LVSI: lymphovascular space invasion; PALN: para-aortic lymph nodes; DDP: weekly cisplatin 40 mg/m².

node metastases detected by pathological methods developed recurrence in the pelvic lymph nodes. Among patients with distant metastases, one had suboptimal treatment because of the only one course of cisplatin, due to increasing renal failure. Two patients younger than 40 years and with an entire thickness of the stromal infiltration were treated with RH and RT. Two patients died due to disease recurrence. The pathological tumor features of the patients with recurrences are presented in Table 2.

The five-year DFS rates for patients treated with RH and RH-BT-CRT were 91% (SE 8.8; 95%, CI: 50–99) and 72%, (SE 9.8; 95% CI: 48–86), respectively. The five-year OS rates for patients treated with RH only and RH-BT-CRT were 91% (SE 88; 95% CI: 50–99) and 91% (SE 91; 95% CI: 63–67), respectively.

Early radiation-associated side effects were acceptable. Late radiation-associated side effects affecting the rectum were observed in two patients, including one case of grade 2 bleeding and one case of grade 1 diarrhea. No bladder complications were observed.

Discussion

The primary treatment method for cervical cancer is largely based on the FIGO stage classification. The standard treatment for early cervical cancer is RH with or without adjuvant treatment, depending on presence of high-risk factors, such as lymph node metastases, large lesion (> 4 cm), PI or positive surgical margins, and intermediate-risk factors, such as SI > 1/3, LVSI, and tumor size between 3 and 4 cm. The presence of risk factors is associated with increased recurrence rate [16]. Adjuvant CRT improves OS and DFS [17, 18]. Adjuvant EBRT with or without CCT may be especially beneficial for patients with AC or adenosquamous carcinoma [1, 6, 10, 19]. In a study by Baalbergen *et al.* reporting 305 cervical AC patients, there was no survival benefit when EBRT was performed after RH. This finding suggests that adenocarcinoma may have lower radiosensitivity, although a comparison with CRT was not possible during the study period [20]. Some additional studies have not shown any survival benefit of cisplatin-based CRT, either in early AC or SCC treated primarily with RH [11, 14].

Peters *et al.* recently reported results from the Gynecologic Oncology Group 109/Southwest Oncology 8797/Radiation Therapy Oncology Group 91-12 Trial, which was conducted in a cohort of 243 patients with risk factors. The study showed significant improvement in DFS and OS for high-risk early-stage patients after RH and pelvic lymphadenectomy when concurrent cisplatin-based CCT was added to adjuvant EBRT [6]. In this study, the difference in four-year DFS was nearly the same between AC and SCC patients when CCT was added to EBRT. In one of the largest studies, 368 cervical cancer patients were treated with CRT or RT alone following surgery, and a significant increase in survival rate was observed after combined treatment [21].

In the present study, 68% of patients received four to five courses of CCT. This rate is consistent with data from the literature [22, 23]. According to most reports, the addition of chemotherapy to RT in patients with operable cervical cancer with risk factors should confer improvements in survival, but the data often come from studies with inconsistent methodology, few groups, and a short follow-up period [12, 16, 17].

Six patients (18%) developed relapses in this study. Parametrial invasion, tumor diameter > 3 cm, and deep SI were associated with local recurrence, while deep SI, LVSI, and lymph node metastases were associated with distant relapse. This finding is in accordance with a previously reported study by Van de Putte *et al.* [24].

The five-year DFS rate of 72% in the high-risk early AC patients appears unsatisfactory. The analysis of treatment failure has demonstrated recurrence rates of 33.3% in patients with PI and 50% in those with lymph node involvement detected in post-surgical pathology procedures. It is important to add cisplatin at per-protocol full doses to the EBRT and to search for more effective chemotherapy alternatives. In fact, studies are ongoing to assess the effectiveness of different adjuvant chemotherapy regimens and the RT sequence (concurrent or sequential) regarding the quality of life and life expectancy [9].

Due to the small proportion of patients with AC, it is very difficult to perform a trial involving patients with solely AC histology in early cervical carcinoma. Distant failures are more frequent in AC patients. Further, multicenter studies to assess the effectiveness of molecularly targeted drugs, such as VEGF inhibitors or kinase inhibitors, which may

improve survival, are necessary [10, 25].

In the present authors' earlier study [26] the early cervical adenocarcinoma treated with primary surgery did worse when compared to early squamous cell cancer.

In the study of Lai *et al.* [27], adenocarcinoma cell type confirmed to be an independent prognostic factor.

The limitations of the present study are the small number of patients. The authors report a single institution experience and the incidence of AC is relatively low. However, they believe that this study provides useful information for further investigations.

Conclusion

Outcomes of patients with intermediate risk factors in early cervical AC treated with surgery and adjuvant RT are unsatisfactory. The studies confirming how patients with intermediate risk factors may benefit from adjuvant CCT seem to be necessary.

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