

# Results on the treatment of uterine cervix cancer: ten years experience

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## Summary

The aim of the study is to present our experience in the treatment of uterine cervix cancer over the last decade.

This is a retrospective study of 90 patients with cervical cancer treated in a University Department of Obstetrics and Gynecology from 1993 to 2002. After the disease was histologically confirmed and staged the patients were treated according to stage with surgery (S) radiotherapy (RT), RT alone or Chemoradiation (C-RT). The course of the disease and follow-up was traced from patient notes and after a structured telephone questionnaire.

Mean age of patients was  $48 \pm 14.3$  years (29-84). Nine of 90 patients (10%) were lost to follow-up. FIGO (1994) staging was I in 50% of patients, II in 33.5%, III in 13.5% and IV in 3%. The size of tumor was  $\leq 4$  cm in 75%. Of the tumors 87% were of squamous histology and 13% adenocarcinomas. Patients were treated with cone biopsy (5.5%), type I hysterectomy pelvic RT (10%), radical (type II-III) hysterectomy and pelvic lymphadenectomy  $\pm$  radiotherapy (41%), RT alone in 38% and C-RT in 5.5%. Incidence of complications after surgery was 19.5% and after RT 12.5%. Mean follow-up was  $41 \pm 19$  months (6-110). Five-year survival in Stage I was 84%, Stage II 64% and Stage III 40%. A single patient with Stage IV disease is alive with disease after two years.

In conclusion uterine cervical cancer has improved survival because of early diagnosis. Treatment should be individualized according to the status of disease. Surgery and RT had similar rates of complications.

**Key words:** Uterine cervical cancer; Treatment; Radical hysterectomy; Radiotherapy.

## Introduction

Uterine cervix cancer is the third worldwide cause of cancer (incidence of 9.8%) after breast cancer (21%) and colonic cancer (10.1%) [1]. In 1998 uterine cervix cancer was the cause of death in of 230,000 women in the world in developing (220,000) and developed countries (17,000) comprising 0.9% of total mortality in women [2]. In Greece, although cervical screening by Pap smears is widely available, less than 30% of women are screened. The incidence of cervical cancer is 7.25:100,000 and the mortality is 2.04:100,000 [3]. Screening by cervical smears however has contributed to early diagnosis (70% are diagnosed in Stage I and 10% as microinvasive) allowing for improved prognosis or conservative treatment [4].

Clinical staging is crucial and, combined with radiographic studies, results in treatment planning by a multidisciplinary team [5, 6]. Prognostic factors affecting the course of the disease are stage, size of tumor, depth of invasion, histological type and the presence of nodal metastases [7, 9, 10].

The aim of this study is to report our experience of a decade of treatment of cervical cancer in our department.

## Materials and Methods

This is a retrospective study of 90 women with cervical cancer treated from 1993-2002 in a University Department of Obstetrics and Gynecology with the assistance of Departments of Radiotherapy and Oncology. Patient characteristics (age, stage, histology, grade and size of tumor, and lymph node status where applicable) along with treatment and outcome were retrospectively collected through patients' notes and follow-up examination of the patients. When examination was not possible a structured telephone questionnaire was applied to gather the relevant information. Patients were initially staged and appropriate biopsies were taken. Further evaluation consisted of radiological workup by CT scan or MRI, chest X-rays and blood tests. Treatment was applied according to stage, age, preservation of fertility wishes and general medical condition of the patient and included surgery (cone biopsy (CB), total hysterectomy or radical hysterectomy with pelvic lymphadenectomy) and/or radiotherapy or chemoradiation. Our intention was to avoid combined treatment where possible so a number of larger tumors although resectable were irradiated. Paraortic lymphadenectomy was done in case of positive pelvic nodes, but no procedure was abandoned. Indications for postoperative radiotherapy included positive lymph node status, involved margins and invasion of the outer third of the cervical stroma. Advanced stages were treated with radical pelvic radiotherapy with or without concomitant platinum chemotherapy.

Statistical evaluation was done with the SPSS software using the t-test, chi-square and Fisher's exact test. Values  $< 0.05$  were considered statistically significant.

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## Results

Nine (10%) of the 90 patients were lost to follow up. Patient characteristics are presented in Table 1. Mean age of the patients was  $48 \pm 14.3$  years (range 29-84). Squamous cell cancers were the most common in 79 (87%) patients and adenocarcinoma in 11 (13%). According to FIGO (1994) staging of cervical cancer 45 (50%) patients were in Stage I, 30 patients (33.5%) in Stage II, 12 patients (13.5%) in Stage III and three (3%) in Stage IV. The size of the tumor was  $\leq 4$  cm in 68 (75%) of the patients and  $> 4$  cm in 22 (25%). Grade of tumor was G1 in 18 (20%) patients, G2 in 46 (51%) and G3 in 26 (29%). Treatment applied is presented in Table 2. Cases with Stage IA1 were treated by knife cone biopsy or simple total abdominal hysterectomy (Piver type I) while cases with Stages IA2-IIA underwent radical hysterectomy (Piver type III) and pelvic lymphadenectomy and/or radiotherapy as previously stated. Five patients (5.5%), two with leiomyomas and three with histological diagnoses of CIN 3 after punch biopsy, had undiagnosed cervical cancer and were treated by hysterectomy type I. Hysterectomy specimens showed Stage IA2 invasive disease in two patients and IB1 in three. The latter underwent postoperative pelvic radiotherapy and are alive and well. Pelvic node dissection was carried out in 37 (41%) patients and paraortic node dissection in seven (8%). Mean number of dissected nodes was  $16 \pm 7$  (2-33) and lymph node invasion was found in 9/37 (24%).

Table 1. — Patient characteristics.

	No.	%
Age (yrs)		
< 40	32	35.5%
$\geq 40$	58	64.5%
Histology		
Squamous	79	88%
Adenocarcinoma	11	12%
Stage (FIGO)		
IA	13	14.5%
IB	32	35.5%
II	30	33.5%
III	12	13.5%
IV	3	3%
Tumor size		
$\leq 4$ cm	68	75%
$> 4$ cm	22	25%
Grade		
G1	18	20%
G2	46	51%
G3	26	29%

Table 2. — Treatment in relation to stage.

Treatment	IA1	IA2-IB2	IIA	IIB-IV	Total
Cone biopsy	5 (5.5%)	$\emptyset$	$\emptyset$	$\emptyset$	5 (5.5%)
Hysterectomy					
Type I $\pm$ RT	4 (4.5%)	5 (5.5%)	$\emptyset$	$\emptyset$	9 (10%)
Radical hysterectomy and pelvic lymphadenectomy $\pm$ RT	$\emptyset$	31 (34.5%)	6 (6.5%)	$\emptyset$	37 (41%)
RT alone	$\emptyset$	$\emptyset$	8 (9%)	26 (29%)	34 (38%)
Chemoradiation	$\emptyset$	$\emptyset$	$\emptyset$	5 (5.5%)	5 (5.5%)

Table 3. — Complications of treatment.

Complications	Intra/postoperative (no. = 51)	RT $\pm$ Chemo (no. = 39)	p
Hemorrhage/transfusion	4 (7.5%)	0	p = 0.1
Injury of obturator nerve	1 (2%)	0	p = 1
Arterial injury	1 (2%)	0	p = 1
Fistulas			
vesicovaginal	1 (2%)	1 (2.5%)	p = 0.8
ureterovaginal	2 (4%)	0	p = 0.3
rectovaginal	0	2 (5%)	p = 0.4
Ileus	1 (2%)	0	p = 1
Radiation enteritis	0	2 (5%)	p = 0.1
Total	10 (19.5%)	5 (12.5%)	p = 0.4

Table 4. — Five-year survival according to clinical-pathologic prognostic factors.

	N	5-year survival (%)	p
Age (yrs)			
< 40	12	9 (75%)	p = 0.6
$\geq 40$	28	19 (68%)	
Stage			
I	18	15 (84%)	p = 0.04
II	15	10 (64%)	
III	5	2 (40%)	
IV	2	0 (0%)	
Histology			
squamous	35	24 (68.5%)	p = 0.7
adenocarcinoma	5	3 (60%)	
Tumor size (cm)			
$\geq 4$	27	18 (67%)	p = 0.07
$> 4$	13	8 (61.5%)	
Lymph node status			
POS	9	7 (78%)	p = 0.3
NEG	6	3 (50%)	

Complications of surgical therapy as measured by the Franco-Italian system [8] were mainly grade 1-3 and were slightly higher than radiotherapy (19.5% vs 12.5%,  $p = 0.4$ ). Intraoperative complications consisted of hemorrhage (transfusion of  $6 \pm 4$  units, range 2-16), nerve injury and arterial injury. Postoperative complications were from the urinary tract (6% - fistulas) and ileus, which resolved spontaneously (2%), and post radiotherapy complications were mainly from the bowel in 10% of the patients (fistulas and radiation enteritis) and a vesicovaginal fistula (2.5%).

Median follow-up of our patients was  $41 \pm 19$  months (6-110). Complete follow-up data are available for 81 patients (90%). The rate of disease recurrence was 14.5% (12/81), (6/81 Stages IB-IIA, and 6/81 Stages IIB-IV). All cases that recurred in the pelvis (local) and one patient staged IIB and treated with pelvic RT recurred in the paraortic nodes. Recurrence according to stage was 13% (6/46) for Stages IB-IIA and 23% (6/27) for IIB-IV. Local recurrence for operable disease (Stages IB-IIA) treated with surgery only was 13% (3/23) and for combined treatment 7% (1/15) but five-year survival was similar (72% vs 75%). Disease-free interval was  $12 \pm 3.8$  months (range 8-

22). Five-year survival was higher in women aged < 40 years old, squamous histology, tumors < 4 cm and negative lymph nodes but these trends were not statistically significant ( $p > 0.05$ ) (Table 4). Stage I compared to other stages had significantly longer survival ( $p = 0.04$ ).

## Discussion

It has been established that uterine cervical cancer and its precursors are caused by human papilloma virus infection especially of oncoviral serotypes (HPV 16, 18, 31, 33, etc.) [9]. Host factors, smoking, contraceptive pills, immune deficiency and other sexually transmitted diseases are important co-factors in cervical carcinogenesis [10, 12].

The choice of the appropriate mode of treatment in early cervical cancer is crucial for the best survival results with the least toxicity since surgical therapy and radiotherapy for Stages IB-IIA have similar results (both 85%) [11]. Combined therapy is avoided since toxicity is increased from 3% to 12% [12]. Radical hysterectomy initially designed to minimize local relapse according to Halstedian principles [13, 14], was challenged by evidence showing that pelvic nodes are involved by embolic rather than continuous spread from the parametrium [15]. Studies on smaller tumors (IB1) showed that more conservative excision of the parametrium (Piver type II hysterectomy) had similar oncologic results with fewer complications [16, 17]. In our study a type III hysterectomy was performed for Stages IA2-IIA in 41% (37/90) of our patients, excluding five patients with a wrong preoperative diagnosis where simple hysterectomy was supplemented by radiotherapy when invasion was diagnosed who are all alive and well. In the rest of our patients treated with radical hysterectomy alone or with postoperative radiotherapy four patients died in 6-62 months and 11 patients (11/15, 74%) are alive beyond five years.

Regarding prognostic factors it is well accepted that metastasis to the pelvic nodes is a strong factor affecting survival [18, 19]. In our study patients with pelvic node metastases had a 5-year survival of 50% compared to 78% of those without. Tumor size is a significant prognostic factor [20, 21], and the size of 4 cm has been incorporated in the FIGO staging system. In our study survival was 67% for smaller tumors and 61.5% for tumors above 4 cm. Histology of adenocarcinoma has been reported as an adverse factor in many studies [22, 23], and we found less survival (60%) compared to 68.5% in cases with squamous histology.

Previously reported recurrence rates in Stages IB-IIA are 10%-20%, and in Stages IIB-IV 20%-40% [24]. Our study had similar results with 6/46 (13%) of patients recurring in Stages IB-IIA and 6/27 (23%) recurring in Stages IIB-IV [25]. Recurrence rate after radiotherapy alone for Stage IB disease is about 15%. Radical hysterectomy alone in early stages (IB-IIA) carries a 10-25% risk of recurrence [26, 27], and in our patients it was 13% (3/23). It is widely believed that postoperative radiotherapy reduces local recurrences without affecting overall

survival [28]. In our study adjuvant radiotherapy decreased local recurrences to 7% (1/15) but survival was not different (72% vs 75%,  $p > 0.05$ ) between these groups.

Complications of radical surgery were higher than radiotherapy (19.5% vs 12.5%) but are comparable with the 5% of urologic and 3.5% of gastrointestinal complications quoted in the literature [29, 30]. Urological and gastrointestinal complications occur in 2-5% and 4-8% of patients, respectively.

The retrospective collection of data and the small number of patients in different treatment arms is a weakness of this study and conclusions about the effect of various treatment modalities on survival cannot be made.

In conclusion, 50% of our cases were diagnosed in Stage I and their 5-year survival was 84%, significantly better than in more advanced stages. The management of cervical carcinoma is based on individualization of treatment, and complications are not significantly different between surgery and radiotherapy.

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