

GYNAECOLOGY

Adjuvant Hysterectomy Followed Radiotherapy in Cervical Cancer

Surawute Leelahakorn MD,*
Chantawat Sheanakul MD,*
Manit Sripramote MD,*
Sumonmal Manussirivithaya MD,*
Tauwalai Tawaramorn MD,*
Luddawun Nakwong MD,**
Tanatip Tuntiwatana MD,**
Somnuek Jesadapatarakul MD.***

* Department of Obstetrics and Gynecology

** Department of Radiology

*** Department of Pathology Bangkok Metropolitan Administration Medical College and Vajira Hospital

ABSTRACT

Objective To evaluate the benefits of hysterectomy followed radiotherapy in CA cervix in Reduction of pelvic recurrence and improvement of survival.

Design Retrospective descriptive analysis.

Setting Department of Obstetrics and Gynecology, Bangkok Metropolitan Administration Medical College and Vajira Hospital.

Subjects Sixty patients with cervical cancer stage 1B ,2A and 2B treated with radiotherapy followed by hysterectomy during October 1993 - October 1998.

Main outcomes measurement Residual cancer at the cervix, pelvic recurrence, distant recurrence, survival and complications.

Results The records of sixty patients with cervical cancer were reviewed. They had a mean age of 46.8 ± 10.0 years and a mean parity of 3.3 ± 2.4 . Fifty- two patients [86.7 %] were stage 2B ,5 [8.3 %] were stage 2A and 3 [5.0 %] were stage 1 B . Thirty-three patients [55.0 %] were adenocarcinoma (ADCA), 25 [41.7 %] were squamous cell carcinoma (SCC) and 2 [3.3 %] were adenosquamous carcinoma (ADSCC). These patients received XRT in the dose of 4600-5000 cGy and ICRT in the dose of 4000 cGy. Time interval from completion of radiotherapy to hysterectomies were done within a mean time of 49.5 ± 16.6 days after complete radiotherapy. All underwent extrafascial hysterectomies (95%) except 3 had modified radical hysterectomies [5.0 %]. Para-aortic lymph nodes dissections was part of the surgical procedure performed on 55 patients [93.3 %] . 24 out of 60 patients [40.0 %] had residual cancer at the cervix (pathologic incomplete response :PIR), four of them had cancer at surgical margins (positive margins). Thirty-six patients [60.0 %] had no residual cancer at the cervix (pathologic complete response : PCR). Five patients [8.3%] had

para-aortic lymph nodes metastases at the time of surgery: 2 in the PCR group and 3 in the PIR group. Unsatisfactory clinical response to radiotherapy and ADCA or ADSCC histologic types was significantly associated with the PIR. With a mean follow up time of 26.6 + 16.3 months [3-64], 4 patients [6.7 %] had pelvic recurrence: 1 [2.8 %] in the PCR group and 1 [5.0 %] in the PIR with completely resected group and 2 [50.0 %] in the positive margins group. Five patients [8.3 %] had new distant recurrence: 1 [2.8 %] in the PCR group, 3 [15.0 %] in the PIR with completely resected group and 1 [25.0 %] in the positive margins group. The overall distant metastases was 8.3%[5 patients]. Prognosis of the positive margins group was the worst [recurrent rate = 75.0%], of the PIR with completely resected group was the better [recurrent rate = 30 %] and of the PCR group was the best [recurrent rate = 5.6 %]. Intra-operative complications occurred 6.7 %, post-operation occurred 21.7 % but severe complications occurred 8.3 % and all were completely corrected.

Conclusion Hysterectomy followed radiotherapy in cervical cancer stage 1B ,2A and 2B has some benefits in patients with unsatisfactory clinical response to radiotherapy or in ADCA or ADSCC histologic types .

Key words : adjuvant hysterectomy, cervical cancer, combined therapy

The management of bulky cervical cancer stage 1B , 2A, 2B was controversial. Most authors recommended radiotherapy as the primary treatment, since radical hysterectomy was not curative.⁽¹⁻⁸⁾

The major problem of radiotherapy alone in these bulky tumor was pelvic recurrence. Durrance, in 1969 , suggested that extrafascial hysterectomy followed radiotherapy would reduce the frequency of pelvic recurrence in these groups.⁽¹⁾ Many authors such as Nelson , Fletcher , Rutledge , Edinger and Gallion agreed with him.^(1,2,9-12) Gallion , in 1985, claimed that the incidence of pelvic recurrence reduced from 19 % to 2% and extra-pelvic recurrence from 16 % to 7 % without an increase in treatment-related complications.⁽⁹⁾ Some other investigators, however, questioned the validity of this approach, believing that the patients survival would not be improved due to extra-pelvic recurrence but increased morbidity was encountered.^(3,13-16)

The purpose of our study was to evaluate the benefits of hysterectomy followed radiotherapy in cervical cancer stage 1B ,2A,2B in reduction of pelvic recurrence and improvement of survival.

Materials and methods

The records of 60 patients with cervical cancer stage 1B , 2A, 2B treated with radiotherapy followed by hysterectomy at Vajira Hospital during October 1993 and October 1998 were reviewed. These patients were evaluated and staged by the tumor treatment team that composed of gynecologic oncologists , radio-oncologists and pathologists. The patients then received XRT in the dose of 4600- 5000 cGy [23-25 fractions] and ICRT in the dose of 4000 cGy [4 fractions]. Four to six weeks after completion of radiotherapy they were reevaluated and classified as satisfactory response to radiotherapy if the cervix was small, soft, smooth surface and as unsatisfactory response if the cervix was large , firm , irregular , nodular or ulceration. We agreed to do hysterectomy during 6-12 weeks after complete radiotherapy if there were no other conditions that the surgery must be postponed. The surgical specimens were examined by the pathologists and then reviewed by the tumor treatment team . Adjuvant therapy was discussed and given to the patient with risk factors of recurrence such as positive margins or metastases to nodes. The patients were followed-up every 2-3 months in the first two years and every 6 months there after.

The statistics used were : mean with standard deviation for analysis of age , parity of the patients and size of the tumor, : percent for other clinical characteristics , : chi-square test for evaluation of the correlation of clinical factors and outcomes : Kaplan-Meier survival curve for the prognosis of the patients.

Results

The 60 patients included in this study had a mean age of 46.8 ± 10.0 years [29-75] and a mean parity of 3.3 ± 2.4 [0-11]. Most of them [52 patients or 86.7 %] were stage 2 B only 5 patients [8.3 %] were stage 2A and 3 [5.0%] were stage 1B . Thirty-three patients [55.0 %] were adenocarcinoma (ADCA), 25 [41.7 %] were squamous cell carcinoma (SCC) and 2 [3.3 %] were adenosquamous carcinoma (ADSCC) .

The characteristics of tumors were infiltrating type in 38 patients [63.3 %] and exophytic type in 22 patients [36.7 %] The mean diameter of cervical lesions was 4.4 ± 0.9 cm [3-6]. Twenty-seven patients [45.0 %] had cervical lesions larger than 4 cm while 33 [55.0 %] were 4 cm or smaller. ADCA group and ADSCC group were smaller than SCC group [4.1 ± 0.7 cm vs. 4.0 ± 0.0 cm vs. 4.8 ± 0.9 cm]. (table 1)

Four to six weeks after complete radiotherapy the patients were reevaluated. 28 patients [46.7 %] were satisfactory clinical response to radiotherapy and 32 patients [53.3 %] were unsatisfactory clinical response. The mean size of the cervix after radiotherapy was 2.9 ± 0.6 cm [3.0-6.0] , 45 patients [75.0 %] had cervical size of 3 cm or larger and 15 [25.0 %] had cervical size of smaller than 3 cm. (table 2)

The mean time interval between complete radiotherapy and surgery was 49.5 ± 16.6 days [27-81]. Fifty-seven patients [95.0 %] underwent extrafascial hysterectomies and 3 patients [5.0 %] had modified radical hysterectomies. Para-aortic lymph nodes dissections were performed in 56 patients [93.3 %]. The mean operative time was 148 ± 29 minutes [60-240] .The mean blood loss was $424 \pm$

262 ml.[100-1600] and the mean blood transfusion was 0.7 ± 0.8 units [0-4]. Intra-operative complications occurred in 4 patients [6.7 %], 2 had bleeding more than 1000 ml , 1 had injury to the small bowel and another one had injury to the bladder. Post-operative complications occurred in 13 patients [21.7%]. Nine patients had chronic infected and delayed healing of vagina stumps , 2 patients had infected abdominal wounds. More serious complications occurred in 5 patients [8.3 %] ; three were partial gut obstructions, one was leakage of ureter with urenoma and the last one was small vesico-vaginal fistula. All patients with complications were completely corrected. (table 6)

From the pathologic reports of surgical specimens , 36 patients [60.0 %] had no residual cancer at the cervix or pathologic complete response [PCR] but two of them [5.6 %] had para-aortic lymph nodes metastases . There were 24 patients [40.0 %] that had residual cancer at cervix or pathologic incomplete response [PIR] and 20 patients[33.3 %] of this group had been completely resected [PIR with completely resected] but 4 [6.7 %] had cancer at surgical margins (positive margins). Three of the PIR group had para-aortic lymph nodes metastases. (table 3)

Multiple factors were evaluated with the finding that only histologic types of ADCA or ADSCC and unsatisfactory clinical response to radiotherapy were significantly associated with PIR.(table 4)

Patients were followed with a mean time of 26.6 ± 16.3 months [3 -62] 4 patients [6.7 %] had pelvic recurrence with a mean time to recurrence of 15.9 ± 9.7 months [6-47] , one [2.8 %] from the PCR group, one [5.0 %] from the PIR with completely resected group , two [50.0 %] from the positive margins group.(table 5)

Three of the five patients with para-aortic lymph nodes metastases[8.3 %] had adjuvant para-aortic radiotherapy and the two from the PCR group had no recurrence for 54 and 64 months of follow-up but the other one from the PIR group had recurrence in 29 months, one patient from the PIR group was

given Megace and recurrence occurred within 21 months, the last one from the PIR group received chemotherapy for 5 course and loss follow up.

Five patients [8.3 %] had distant metastases after surgery, one from the PCR group [1/36 or 2.8 %], three from the PIR with completely resection group [1/20 or 5.0 %] and the last one from PIR with

positive margins group [1/4 or 25.0 %].(table 5)

Fifty- four patients [90.0 %] were alive with a mean follow -up time of 27.1 ± 16.6 months [3-62]. Six patients [10.0 %] were dead with a mean survival time of 21.6 ± 12.8 months [6-29]. Recurrence free survival times and overall survival times are presented in Figures 1 and 2.

Table 1. Clinical characteristics of the patients

	Patient's characteristics	Number (%)
Number of the patients		60
Age of the patients		46.8 ± 10.0 [29-75] yr.
Parity of the patients		3.3 ± 2.4 [0-11]
Stage of the cancer	1B ²	3 [5.0 %]
	2A ²	5 [8.3 %]
	2B	52 [86.7 %]
Histology of the cancer	ADCA	33 [55.0 %]
	ADSCC	2 [3.3 %]
	SCC	25 [41.7 %]
Characteristics of the tumor	Infiltrating type	38 [63.3 %]
	Exophytic type	22 [36.7 %]
Sizes of the primary tumor	Mean	4.4 ± 0.9 [3.0-6.0] cm.
	ADCA group	4.1 ± 0.7 cm
	SCC group	4.8 ± 0.9 cm
	ADSCC group	4.0 ± 0.0 cm
	size > 4 cm	27 [45.0 %]
	size \leq 4 cm	33 [55.5 %]

Table 2. Clinical evaluation after radiotherapy

	Clinical evaluation	Number (%)
Clinical response to radiotherapy		
	Satisfactory	28 [46.7 %]
	Unsatisfactory	32 [53.3 %]
Sizes of the cervix (mean)		2.9 ± 0.6 [2-4] cm
	< 3 cm	15 [25.0 %]
	\geq 3 cm	45 [75.0 %]

Table 3. Pathologic reports of surgical specimens

Pathologic reports		Number (%)
No residual cancer at the cervix [PCR]		36 [60.0 %]
-without para-aortic lymph nodes metastases		34
-with para-aortic lymph nodes metastases		2
Residual cancer at the cervix [PIR]		24 [40.0 %]
a) PIR with completely resected		20 [33.3 %]
-without para-aortic lymph nodes metastases		17
-with para-aortic lymph nodes metastases		3
b) PIR with positive margins		4 [6.7 %]
-without para-aortic lymph nodes metastases		4
-with para-aortic lymph nodes metastases		0
Total		60

Table 4. Factors that might predict residual cancer at the cervix

FACTORS	SUBSET (residual)	PIR (%)	PCR (%)	TOTAL (%)	P
A) Stages	-1B +2A	2 [25.0 %]	6 [75.0 %]	8 [13.3 %]	0.35 NS
	-2B ²	22 [42.3 %]	30 [57.7 %]	52 [86.7 %]	
B) Histology	-SCC	6 [24.0 %]	19 [76.0 %]	25 [41.7 %]	0.03 Sig***
	-ADCA+ADSCC	18 [51.7 %]	17 [58.6 %]	35 [58.3 %]	
C) Characteristics of the tumors	-Exophytic	8 [36.4 %]	14 [63.6 %]	22 [36.7 %]	0.66 NS
	-Infiltrating	16 [42.1 %]	22 [57.9 %]	38 [63.3 %]	
D) Sizes of the primary tumor	- ≤ 4 cm	16 [50.0 %]	16 [50.0 %]	32 [53.3 %]	0.09 NS
	- > 4 cm	8 [28.6 %]	20 [71.4 %]	28 [46.7 %]	
E) Sizes of the primary tumor	(mean)	4.25 cm	4.51 cm	4.40	0.24 NS
F) Sizes of the cervix after radiation	- < 3 cm	4 [26.7 %]	11 [73.3 %]	15 [25.0 %]	0.22 NS
	- > 3 cm	20 [44.4 %]	25 [55.6 %]	45 [75.0 %]	
G) Sizes of the cervix after radiation	(mean)	3.1 cm	2.8 cm	2.9	0.09 NS
H) Clinical response to radiation	-Satisfactory	5 [17.9 %]	23 [82.1 %]	28 [46.7 %]	0.001 Sig.***
	-Unsatisfactory	19 [59.4 %]	13 [40.6 %]	32 [53.3 %]	

Table 5. Prognosis of the patients

		pelvic recurrence	distant recurrence	para-aortic LN metastases
No residual cancer at cervix	[n=36]	1 [2.8 %] *	1 [2.8 %] **	2 [5.6 %]
Residual cancer at cervix	[n=24]	3 [12.5 %] *	4 [16.7 %] **	3 [12.5 %]
-completely resected	(n=20)	1 (5.0 %)	3 (15.0 %)	3 (15.0 %)
-positive margins***	(n=4)	2 (50.0 %)	1 (25.0 %)	0 (0.0 %)
All patients	[n=60]	4 [6.7 %]	5 [8.3 %]	5 [8.3 %]

* P=0.17 NS ** P=0.07 NS *** one patient loss follow up

Table 6. Operative problems and post-operative complications

	Mean (S.D.)		Range
Time from radiotherapy to surgery	49.5 ± 16.6	days	[27-81]
Operative time	148 ± 29	minutes	[90-240]
Blood loss	424 ± 262	ml.	[100-1600]
Blood transfusion	0.7 ± 0.8	units	[0-4]
		Numbers (%)	
Intra-operative complications	4 [6.7 %]		
-bleeding >1000 ml.	2		
-bowel injury	1		
-bladder injury	1		
Post-operative complications	13 [21.7 %]		
Minor complications	11 [18.3 %]		
-chronic infection of vagina	9		
-wound infection of stumps	2		
Major complications	5 [8.3 %]		
-partial gut obstruction	3		
-leakage of ureter with urethral fistula	1		
-small vesico-vagina fistula	1		

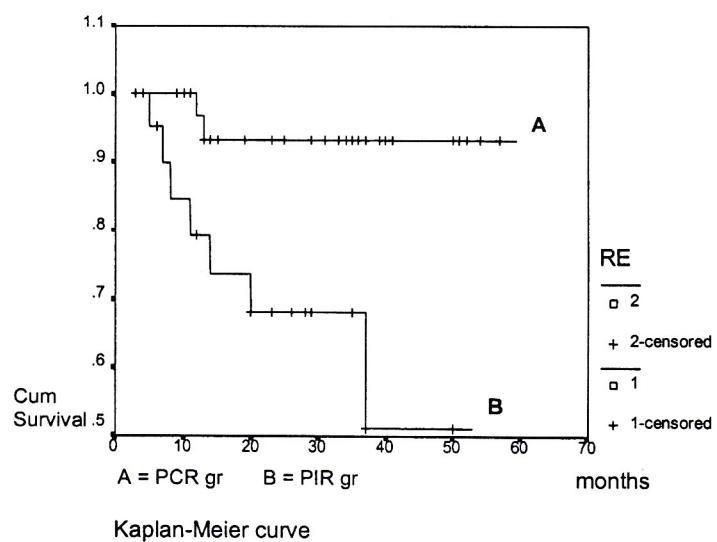


Fig. 1. Disease free survival (From complete radiotherapy).

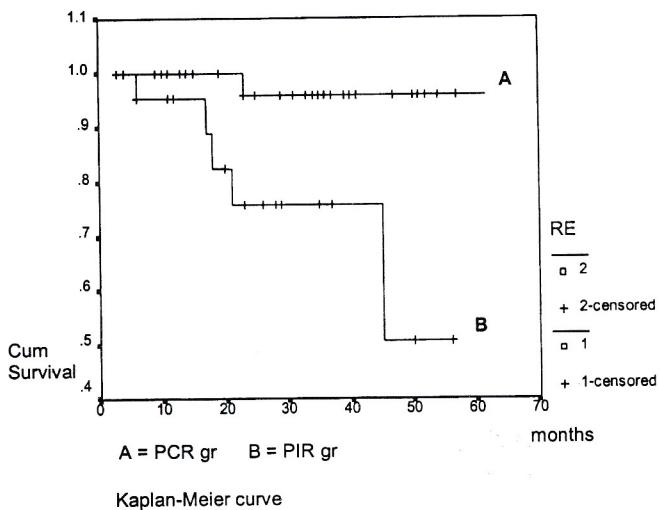


Fig. 2. Overall survival (From complete radiotherapy).

Discussion

The main purpose of hysterectomy followed radiotherapy in the treatment for early-staged bulky cervical cancer is the reduction of pelvic recurrence or persistence of cancer after 6 months.^(1,2,9,10,12) Six to twelve weeks after complete radiotherapy is the best time for hysterectomy because the tissue inflammation is subsided and the fibrosis is not so dense, thus minimising complications.^(5,17)

Residual cancer at cervix (PIR) is associated with pelvic recurrence while if the cervix has no residual cancer (PCR), pelvic recurrence is unlikely to occur.^(2,8,9,12,15) Additional hysterectomy in cases with PCR may be unnecessary and should be omitted. Our suggestion is that the hysterectomy should be reserved only for the patients who still had residual cancer after radiation. However, there was no such tool to accurately detect this entity.

In this study we found that 40.0 % of the patients still had residual cancer while 60% had PCR which was comparable to Murayama's⁽¹²⁾ and Gallion's report⁽⁹⁾ of 37 and 32.5% respectively. Unsatisfactory clinical response to radiotherapy and ADCA or ADSCC histologic types were the two factors

that had significant correlation with PIR.

Pelvic recurrence occurred 16-43 % in the patients treated with radiotherapy alone.^(9,10,14,16) In this study we used combined therapy and pelvic recurrence occurred 6.7 %[4 pt] nearly the same as 7.0 % of Prempree's report⁽¹⁰⁾ but slightly more than 2 % of Gallion's report.⁽⁹⁾ There were only 2.8 % in the PCR group which was less than 12.5 % in the PIR group. In the positive margins group pelvic recurrence occurred for 50.0 % but in the PIR with completely resected group pelvic recurrence occurred only 5.0 %. This may be the support reason of adjuvant hysterectomy after radiotherapy but the surgery should remove all residual cancer.

Distant metastasis is the main reason that many authors object hysterectomy after radiotherapy.^(4,13,14,16) In this study we performed para-aortic lymph node dissection in 56 patients and found that 5 patients [8.3 %] had already para-aortic lymph nodes metastases slightly more than 5 % of Maruyama's report.⁽¹²⁾ This finding means hysterectomy cannot cure these 5 patients. During follow-up, we found new distant recurrence in 5 patients [8.3 %]. This implied that hysterectomy

alone cannot prevent distant recurrence in 10 patients [16.7 %].

Additional para-aortic lymph nodes dissection in this study was not increasing complications and had a benefit of knowing the extent of cancer but was questionable about the therapeutic benefit because the effective adjuvant treatment of para-aortic nodes metastases was not found. We gave para-aortic radiation (LINAC) to three patients and found that two had no recurrence with follow-up times of 54 and 64 months and the other one had recurrence within 29 months of follow-up. The other two patients refused radiotherapy. One was given Megace (also refused chemotherapy) and recurrence occurred within 21 months. The last one was given chemotherapy (cisplatin+5 FU) and had no progression during chemotherapy but she loss follow-up after the fifth course.

Hysterectomy may be useful in prediction of prognosis because the present of residual cancer at cervix associated with bad outcomes.^(9,12) In this study the prognosis of the PCR group is better than that of the PIR group.

Complications of treatment in this study occurred 21.7 % and seem to be higher than other reports^(3,9,14) but most of them were minor. The more serious complications occurred only 8.3 % and all were completely corrected.

Conclusively, adjuvant hysterectomy after radiotherapy had some benefits in reduction of pelvic recurrence but it should be used in selective conditions such as unsatisfactory clinical response to radiotherapy and in the patients with ADCA or ADSCC.

References

1. Durrance F Y, Fletcher G H, Rutledge F N. Analysis of central recurrent disease in stage 1 and 2 squamous cell carcinomas of the cervix on intact uterus. *Am J Roentgenol Radial Ther nucl Med* 1969;106:831-8.
2. Nelson A J, Fletcher G H, Wharton J T. Indications for adjunctive conservative extrafascial hysterectomy in selected cases of carcinoma of the uterine cervix. *Am J Radial* 1975;123:91-9.
3. Thoms W W, Eifel P J, Smith T L, et al. Bulky endocervical carcinoma : A 23 - year experience . *Int J Radiation Oncology Biol Phys* 1992;23:491-9.
4. Singleton H M, Fowler W C, Jordan J A . *Gynecologic Oncology : Current Diagnostic and Treatment* . London: W.B. Sounders Company Ltd 1996:60-91.
5. Coppleson M . *Gynecologic Oncology*. New York: Cherchill Livingstone 1992:663-709.
6. DiSaia P J, Creasman W T. *Clinical Gynecologic Oncology*. Fifth ed. St. Louis: Mosby-Year Book 1995:51-106.
7. Berec J S, Hacker N F. *Practical Gynecologic Oncology*. Second ed. Baltimore: Williams and Wilkins 1994: 243-84.
8. Hoskins W J, Perez C A , Young R C. *Principle and Practice of Gynecologic Oncology*. Second ed. Philadelphia: Lippincott-Ruven Publishers 1997: 785-857.
9. Gallion H H, van Nagell J , Donalson E S , et al. Combined radiation and extrafascial hysterectomy in the treatment of stage 1 B barrel-shaped cervical carcinoma. *Cancer* 1985;56:265-72.
10. Prempree T , Amornmarn R, Wizenberg M J. A therapeutic approach to primary adenocarcinoma of the cervix. *Cancer* 1985;56:1264-8.
11. Kosiyatrakul T, Benjachai W, Buribhat S. Treatment of uterine cervical cancer. *Thai J of Obstet Gynecol* 1997;9:139-45.
12. Murayama Y, van Nagell, Yoneda J, et al. Dose response and failure pattern for bulky or barrel-shaped stage 1 B cervical cancer treatment by combined photon irradiation and extrafascial hysterectomy . *Cancer* 1989;63:70-6.
13. Mendenhall W M, McCarty P J, Morgan L S, et al. Stage 1B or 2A-B carcinoma of intact uterine cervix \geq 6 cm in diameter : is adjuvant extrafascial hysterectomy beneficial ? . *Int J Radiation Oncology Biol Phys* 1991;21:899-904.
14. Weems D H, Mendenhall W M, Bova F J, et al. Carcinoma of intact uterine cervix , stage 1B, 2A-B \geq 6 cm in diameter : radiation alone vs. preoperative irradiation and surgery. *Int J Radiation Oncology Biol Phys* 1985;11:1911-4.
15. Perez C A, Koa M S. Radiation therapy alone or combined with surgery in the treatment of barrel-shaped carcinoma of the uterine cervix (stage 1B,2A,2B). *Int J Radiation Oncology Biol Phys* 1985;11:1903-9.
16. Eifel P J, Morris M, Oswald M J, et al. Adenocarcinoma of the uterine cervix. *Cancer* 1990;65:2507-14.
17. Q'Quinn A G, Fletcher G H, Wharton J T. Guidelines for conservative hysterectomy after irradiation. *Gynecol Oncol* 1980;9:68-79.