

Reirradiation of late local recurrences of carcinoma of the cervix after primary radiotherapy

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Purpose. To assess long term results of reirradiation of late local recurrences of carcinoma of the cervix.

Material and methods. Between 1980 and 1995, 55 patients received reirradiation for local recurrence of carcinoma of the cervix. The time gap between primary radiotherapy and the diagnosis of local recurrence was at least 10 years (range 10-32 years). Secondary radiotherapy consisted of brachytherapy, external beam irradiation or combination of both methods, depending on the tumor site and volume. Low dose rate Ra226 and Cs137 sources were used for brachytherapy with the dose of 18-62 Gy at 0,5 cm below the tumor base. Two field technique was used for external beam irradiation with the dose 20-50 Gy. The follow-up ranged from 10 to 142 months. Survival curves were calculated using the Kaplan-Meier method for patients with respect to the site of the tumor. The tolerance of reirradiation was also evaluated.

Results. The 5- and 3-year survival in the analyzed group was 9.1% and 27.3% respectively. The 5-year survival for 24 patients with the tumor limited to the cervix and vagina was 20.8%. The risk of serious complications of reirradiation was high at 18% with one lethal complication (6.7%).

Conclusions. The results of the study confirm the effectiveness of reirradiation of small volume central recurrences limited to the vaginal apex. A long term cure can be achieved in this subset of patients. Only palliative result can be expected in the locally advanced cases with parametrial extension of the tumor. Because of high incidence of severe complications, reirradiation should be considered primarily in patients medically unfit for radical exenterative surgery.

Wyniki powtórnego napromieniania późnych nawrotów miejscowych raka szyjki macicy po pierwotnej radioterapii

Celem pracy była ocena wyników odległych powtórnego napromieniania nawrotów miejscowych inwazyjnego raka szyjki macicy po pierwotnej radioterapii.

Materiał i metody. W okresie 1980-1995 55 chorych przebyło powtórne napromienianie z powodu późnych nawrotów miejscowych raka szyjki macicy po pierwotnej radioterapii. Do powtórnego napromieniania kwalifikowano chore z rozpoznaną wznową obejmującą pochwę lub przymacicza rozpoznane w okresie minimum 10 lat po zakończeniu leczenia pierwotnego. Leczenie wznów polegało na zastosowaniu teleradioterapii w dawce 20-50Gy, brachyterapii dojamowej z wykorzystaniem izotopu Ra-226 lub Cs-137 w dawce 18-62 Gy. Okres obserwacji po leczeniu wynosił od 10 do 142 miesięcy. Metodą Kaplana-Meiera obliczono krzywe przeżycia dla chorych z uwzględnieniem lokalizacji nawrotu. W ocenie wyników dokonano oceny tolerancji leczenia - częstości i typów wczesnych odczynów popromiennych.

Wyniki. Odsetek przeżyć 5-letnich wyniósł 9,1%, a 3-letnich 27,3%. Spośród 24 chorych ze wznową centralną ograniczoną do pochwy okres 5 lat przeżyło 20,8% leczonych. Ocena tolerancji leczenia potwierdziła wysokie ryzyko średnich i ciężkich odczynów popromiennych wynoszące 18%. Zaobserwowano jedno powikłanie śmiertelne - 6,7% ogółu leczonych.

Wnioski. Doświadczenia z powtórnym napromienianiem późnych nawrotów raka szyjki macicy potwierdzają skuteczność tej metody w przypadku wznów centralnych ograniczonych do pochwy. Uzyskany odsetek przeżyć 5-letnich 20,8% zbliżony jest do wyników uzyskiwanych po operacjach wytrzewiających.

Efektywność powtórnego napromieniania w przypadku nawrotów w przymaciczach jest ograniczona i ma charakter wyłącznie paliatywny. Powtórne napromienianie jest interesującą opcją terapeutyczną dla chorych, które nie kwalifikują się do radykalnych operacji egzenteracyjnych lub nie akceptują tej metody leczenia.

Key words: cervix cancer, late recurrence, reirradiation

Słowa kluczowe: rak szyjki macicy, wznowa miejscowa, powtórne napromienianie

Introduction

Local recurrences are the major cause of treatment failure in patients with invasive carcinoma of the cervix. They occur in about 15-20% of women with stage I disease treated either with surgery or radiotherapy. Their incidence increases to 40-60% in patients with stage II and III [1]. The risk of developing a recurrence is the highest within the first two years after primary treatment. Only 2% of women who survived a period of 5 years subsequently develop a local failure [2]. The diagnosis of local recurrence forms a very challenging clinical problem to the gynecologist oncologist. It is generally agreed that recurrent disease after radical radiotherapy should be treated with surgery. The 5-year survival rate of 30-40% can be achieved with exenterative surgery for the treatment of central recurrences [3, 4]. The application of radical surgery in patients with late recurrences is often limited by a compromised general condition and poor acceptance of exenteration. For them reirradiation is the only reasonable treatment option. The results of secondary radiotherapy of pelvic relapses of cervical cancer show, that 25-35% of patients can be cured by a combination of external beam irradiation and brachytherapy [5-9].

The purpose of this retrospective study is to present a 15-year experience in reirradiation of local recurrences of carcinoma of the cervix.

Materials and methods

From January 1980 to December 1995, 55 cases of late recurrent carcinoma of the cervix were treated at the Department of Gynecologic Oncology of Cancer Center and Institute of Oncology. All patients were primarily treated with radiotherapy consisting of external beam irradiation and brachytherapy. For teletherapy cobalt-60 machines and 4-18MeV linear accelerators were used. The pelvic dose ranged from 42 to 46Gy given in 21-24 fractions. The fraction dose was 1.8-2.0Gy. The intracavitary treatment consisted of two low dose rate insertions of Radium 226, or Cesium 137. The dose delivered to point A was 45-55Gy. To define a late local recurrence of cervical cancer the following criteria had to be met: the presence of the lesion with microscopic features similar to the primary tumor of the cervix, minimal disease free survival of 10 years after completion of primary radiotherapy. The sites of recurrent tumor were vaginal apex - 24 cases and vagina with parametrial extension of the disease - 31 cases. Secondary irradiation was planned according to the site of the recurrence, the presence of parametrial involvement, radiation dose and tolerance of primary irradiation. Both intracavitary and interstitial brachytherapy was used for the treatment of central recurrences limited to the vagina. The dose measured at 5mm below the surface of the mucosa was 20-45Gy. External be-

am irradiation was added to boost the dose of radiation to the pelvic side wall. The two field technique was used with the dose to the pelvis of 20-45Gy.

A detailed clinical characteristic of the analyzed group are presented in Table I.

The follow up ranged from 10 to 96 months. Relapse free survival was calculated with Kaplan-Meier method for subpopulation of patients with two different localizations of recurrences. Differences in proportions were evaluated by the Fisher Exact test. Statistical significance was considered as $p < 0.05$.

Table I. Local recurrences of carcinoma of the cervix – clinical characteristic

Type of recurrence No of patients	Time gap between primary treatment and diagnosis of recurrence	Clinical symptoms of recurrence	
vagina, cervix 24	10-29 yrs (median 15.8 yrs)	asymptomatic	5
		bleeding	15
		discharge	8
vagina, parametria 31	10-32 yrs (median 17.9 yrs)	pelvic pain	20
		discharge	11
		bleeding	9
		leg edema	6

Results

The 3- and 5-year survival rates for the whole analyzed group were 27.3% (15/55) and 9.7% (5/55), respectively. In women with the central recurrence limited to the vagina the 5-year survival was 20.8% (5/24) and 3 patients survived more than 10 years. No long term survivors were observed in patients with parametrial extension of the recurrence. The survival ranged from 4 to 36 months (median 17 months) Table II.

The survival curves for two subpopulations of patients with vaginal only and parametrial recurrence are presented on Figure 1.

The assessment of tolerance of reirradiation has shown that in 18% (10/55) of cases the treatment had to be discontinued because of the presence of acute reaction from the critical organs. Persistent leucopenia and small bowel irritation were the most frequent causes of hospitalization, treatment delays and in some cases discontinuation of radiotherapy (Table III).

The overall incidence of late complications was 9% (6/55) and 22% (6/15) in those who survived at least 3 years. Three patients required a surgical intervention to manage late bowel stricture and occlusion. One patient

Table II. Methods and results of treatment of the late recurrences of cervical cancer

Type of recurrence No of patients	Method of treatment	No of patients	>5	Survival - years 3-5	<3
cervix, vagina 24	brachytherapy	9	4	1	5
	brachyth + teletherapy	10	1	7	2
	teletherapy	5	-	1	4
vagina, parametria 31	brachytherapy	6	-	1	5
	brachyth + teletherapy	6	-	-	6
	teletherapy	19	-	-	19

Table III. Early acute complications of reirradiation

Type of reaction	No	%
diarrhoea with dehydration	9/55	16.3
acute cystitis	7/55	12.7
acute skin reaction	6/55	10.9
leucopenia	9/55	16.4
discontinuation of treatment	10/55	18.2

(1,8%) died of acute hemorrhagic cystitis 3 years after secondary irradiation. No sign of persistent disease was found on autopsy. The summary of clinical data about the late complications is presented in Table IV.

Table IV. Late complications of reirradiation

Type of complications	No	%	% of patients with survival > 3 yrs	
proctitis	3/55	5.4	3/15	20.0
skin necrosis	1/55	1.8	1/15	6.7
sigmoid colon stricture	1/55	1.8	1/15	6.7
haemorrhagic cystitis (lethal)	1/55	1.8	1/55	6.7

No correlation has been found between the number of late complications and combined dose of radiation from primary and secondary radiotherapy.

Discussion

Local recurrences of invasive carcinoma of the cervix are the most frequent cause of treatment failure. The majority of them appear within the first 2 years after radiotherapy or radical surgery. Late recurrences, diagnosed later than 5 years after primary treatment are a unique clinical entity. Their incidence is low- 1-2% of all treated patients

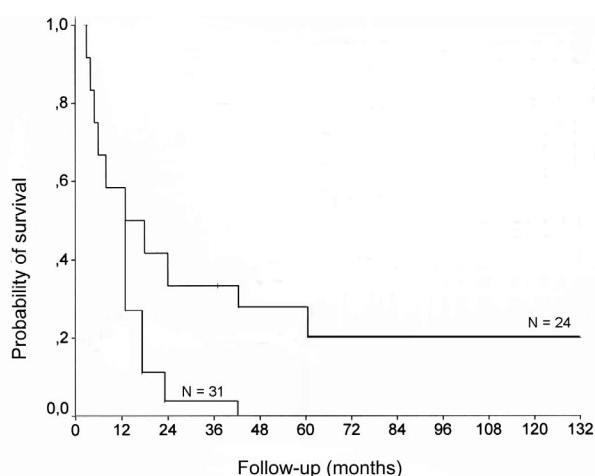


Figure 1. Probability of survival of patients with central recurrence (N= 24) and with parametrial involvement (N= 31)

and 4-5% cured of the disease and is independent of clinical stage and pathology of the primary tumor [2]. The etiology of late recurrences is not clear. Some investigators advocate the existence of the dormant cells which have a potential to proliferate and to form a recurrent tumor. These tumors are also considered to be second primary tumors developed in the previously irradiated area. There are some doubts about the role of past history of radiotherapy as the incidence of late local recurrences is similar in patients treated primarily with radiotherapy and surgery.

The diagnosis of the late treatment failure bears a serious prognosis to the patient and poses a difficult challenge to the gynecologist oncologist.

Traditionally surgery is regarded as the optimal modality of treatment of recurrent carcinoma of the cervix after primary radiotherapy. The progress in surgical technique and postoperative care has resulted in a significant improvement in the long term results of exenterative surgery. The 5-year survival of about 40% can be expected for patients with central recurrences treated with perioperative mortality of less than 5% [3]. The practical application of radical surgery for late recurrences of carcinoma of the cervix developed many years after primary radiotherapy is very limited by an advanced age, compromised general condition and poor acceptance of radical surgery by those patients. These limitations make reirradiation the only reasonable therapy available for the women with late recurrences. The clinical experience with retreatment of local recurrences with secondary radiotherapy is limited. Only a few reports on this subject have been published in the recent years [7-9]. The overall 5-year survival of only 9.1% recorded in this series indicates a very serious prognosis in women with locally relapsing carcinoma of the cervix. Better results were achieved in women with central recurrence limited to the vagina. The 5-year survival rate of 20.8% was significantly higher than in cases with parametrial extension of the tumor. The only long term survivors were the women with the tumor limited to the vaginal apex. Other authors also confirmed the prognostic importance of tumor volume and localization [8, 9]. Wang et al. found a significantly higher local control and survival in patients with recurrences in the upper vagina than in the lower vagina. The difference of local control rate and survival was also significant for tumor diameter <4cm and >4cm.

Brachytherapy is the principal method of reirradiation of small volume local recurrences of cervical cancer [9, 11, 12]. The effectiveness of brachytherapy is supported by the results of the present study. All long term survivors were treated with intracavitary treatment. Therapeutic potential of brachytherapy can be further improved by the application of interstitial implants. The local control rate of about 50% with the incidence of moderate-severe complications of less than 15% can be achieved with interstitial brachytherapy [11, 12]. A novel approach to the treatment of local recurrences is the application of permanent Iodine -125 implants. Sharma et al. [13] applied this technique to the treatment of locally relapsing cervical and endometrial cancer. The local control rate

was 75% with the median survival of 26 months. Previous experience with reirradiation of recurrences tumors of different histological types and localization showed a very high incidence of severe complications. In the case of recurrences of cervical cancer the limiting factor was the tolerance of critical organs like bladder and rectum [14]. Because the mechanisms of tissue repair act more effectively in the longer time span, the time gap between the termination of primary radiotherapy and reirradiation in the most important prognostic factor in predicting tolerance of the treatment. More recent clinical observations confirm the effectiveness of the repair mechanisms even in the slowly regenerating tissues like the spinal cord allowing a relatively safe reirradiation of the breast, lung, CNS and pelvic tumors [15, 16].

In the present study time gap from the termination of primary treatment was an important factor predicting good tolerance of reirradiation. The incidence of acute reactions was 22% and the intensity of side effects finally led to discontinuation of the treatment in 18% of patients. Similar rates of early acute reactions and discontinuation of the treatment were presented by other authors [8, 9, 14]. The overall incidence of late moderate and severe complications was 9% and 22% for those who survived a minimum of 3 years and overall mortality was 6.7%. Other investigators reported similar results stressing the importance of a meticulous analysis of the important clinical factors before the treatment is initiated [7, 9, 14]. In order to lower the risk of developing severe complications modern imaging techniques should be used to define the tumor extent more precisely and to limit the dose to the critical organs. The use of conformal external beam irradiation and interstitial brachytherapy may contribute to the better tolerance of reirradiation [14, 17].

Our experience confirms the complexity of the problem of reirradiation of recurrent carcinoma of the cervix after primary radiotherapy. Many clinical parameters like tumor localization, volume, relation to the critical organs, radiation dose at primary treatment and time gap from primary treatment have to be carefully analyzed before the decision to reirradiate is made. The results of this study confirm the value of retreatment of late local recurrences of carcinoma of the cervix. The long term survival after reirradiation similar to the results of radical surgery can be expected for small volume, central recurrences limited to the vaginal apex. The results of treatment of local recurrences with parametrial involvement were less satisfactory and only palliative effect was obtained.

These results indicate the need for further studies on earlier detection and better methods of treatment of late recurrences of carcinoma of the cervix.

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Paper received: 39 September 2001

Accepted: 24 October 2001