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Radiotherapy for local recurrences of endometrial cancer after surgery and vaginal brachytherapy

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Aim. The aim of the study was to evaluate the effectiveness of radiotherapy for local recurrences of endometrial cancer after primary surgery and vaginal brachytherapy.
Material and methods. Forty one patients with histopathologically proven local recurrences of endometrial cancer were treated in years 1990-1998. The treatment of recurrences consisted of external beam irradiation of the pelvis (mean dose 46 Gy) plus intracavitary brachytherapy LDR/MDR with dose of 40-45 Gy at 0.5 cm below the surface of the mucosa. Follow-up ranged from 6 to 60 months (median 19 months). Survival curve was calculated with Kaplan-Meier method. The log-rank test was used to evaluate the influence of the following prognostic factors on the survival: time from the completion of primary treatment to the diagnosis of recurrence, and localisation of the relapsing tumor.
Results. The probability of survival of 3 and 5 years was 0.33 and 0.21. Both analysed prognostic factors – time to the diagnosis and localisation of the recurrence had a satisfically significant influence on survival. The risk of death from the disease was significantly higher with extravaginal spread of the tumor and with the time gap of less than 1 year after completion of primary treatment. (Relative risk 1.40 and 1.44, 95% C.I.)
Conclusion. The results of treatment, confirmed a very serious prognosis in this particular group of patients, with the use of presently available methods of treatment. Better methods of identification of prognostic factors which might be predictive of developing a recurrence are reguired. Better methods of early detection of relapses and more effective treatment may contribute to the better survival of these high risk patients.

Wyniki napromieniania nawrotów miejscowych raka błony śluzowej macicy po pierwotnym leczeniu operacyjnym i dopochwowej brachyterapii

Cel pracy. Celem pracy była ocena wyników radioterapii nawrotów miejscowych raka błony śluzowej macicy po pierwotnym leczeniu operacyjnym i brachyterapii dopochwowej.
Materiał i metody. Przedmiotem analizy było 41 chorych z nawrotem miejscowym raka błony śluzowej macicy, który rozpoznano i leczono w Klinice Nowotworów Narządów Płciowych Kobiecych Centrum Onkologii w Warszawie w latach 1990-1998. W leczeniu nawrotów stosowano teleradioterapię na obszar miednicy małej w średniej dawce 46 Gy, w części przypadków brachyterapię dopochwową w dawce 40-45 Gy na głębokości 5 mm od powierzchni ściany pochwy. Okres obserwacji po zakończeniu leczenia nawrotów wynosił od 6 do 60 miesięcy (mediana 19 miesięcy). Metodą Kaplana-Meiera wyznaczono krzywą przeżycia analizowanej grupy chorych. Posługując się testem log-rank oceniono wpływ wybranych czynników prognostycznych na przeżycia: czas wystąpienia nawrotu od zakończenia leczenia pierwotnego oraz lokalizacja nawrotu.
Wyniki. Obliczone metodą Kaplana-Meiera prawdopodobieństwo 3 letniego przeżycia wynosiło 0,33, a 5 letniego 0,21. W analizie wpływu czynników prognostycznych na przeżycia, zarówno lokalizacja nawrotu, jak i czas od zakończenia leczenia pierwotnego, były znamienne statystyczne. Ryzyko zgonu było znamiennie wyższe u chorych z spoza pochwowym szerzeniem się nowotworu oraz przy czasie wystąpienia nawrotu krótszym niż jeden rok (współczynnik ryzyka wynosił odpowiednio 1,40 i 1,44, 95% (przedział ufności).
Wnioski. Wyniki analizy obserwacji 41 kobiet z nawrotem miejscowym raka błony śluzowej macicy potwierdziły poważne rokowanie w tej grupie chorych. Wskazuje to na pilną potrzebę identyfikacji istotnych czynników prognostycznych, wpływających na wybór leczenia uzupełniającego po pierwotnym leczeniu operacyjnym, co pozwoliłoby zmniejszyć częstość występo-

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wania nawrotów. Nadal istnieje konieczność poszukiwania skuteczniejszych metod diagnostyki i terapii wznów raka błony śluzowej macicy.

Key words: endometrial cancer, local recurrence, radiotherapy
Słowa kluczowe: rak błony śluzowej macicy, nawrót miejscowy, radioterapia

Carcinoma of endometrium is the second most common malignancy of the female genital tract in Poland [1]. A steady increase of incidence over the last decades is similar to the trend observed in other developed countries. In majority of cases it is diagnosed in clinical stage I -FIGO [2], when radical surgery and vaginal brachytherapy results in 90% 5-year survival [3]. However, in some cases recurrences occur. They are usually localised in the vagina or pelvis. The incidence of recurrences depends on clinical stage of the disease and the method of primary treatment. About 10-15% cases treated with surgery alone have central recurrence confined to the vagina [4]. The reccurence rate may be lowered to 4-5% with the implementation of postoperative vaginal brachytherapy [4]. Radiotherapy plays a major role in the treatment of relapsing endometrial cancer after surgery. About 25-30 % of women can be cured by this modality [5-7]. The authors present their results of radiotherapy for local recurrences of stage I endometrial cancer after primary surgery and adjuvant vaginal brachytherapy.

Material and methods

From January 1990 to December 1998, 41 women were treated with radiotherapy for local recurrences of endometrial carcinoma.

The primary treatment consisted of total abdominal hysterectomy and bilateral salpingooophorectomy in 29 patients, and hysterectomy plus pelvic lymphadenectomy in 12 patients. The microscopic examination confirmed the diagnosis of well and moderately differenciated adenocarcinoma of endometium with superficial myometrial invasion. All patients were treated postoperatively with vaginal brachytherapy. The treatment was conducted with afterloading LDR and HDR technique. The dose of 45 Gy for LDR and 21 Gy for HDR was given at 5 mm below the surface of the vaginal mucosa. After the completion of treatment all patients were followed up every 3--4 months for the first two years. A recurrence was diagnosed 2-30 months after initial treatment and confirmed microscopically in all analysed patients. A specimen for microscopic examination was obtained with punch biopsy, fine needle aspiration or explorative laparotomy. Modern image techniques like CT, NMR were used to exclude the existence of distant metastases.

External beam irradiation was the principal form of treatment for local relapses. A two parallel opposed or four – field box technique was employed for pelvic irradiation. The total dose delivered to the pelvis was 46-50 Gy, with fractions of 1.8 Gy. Patients with the tumour localised in the distal part of the vagina received additional intracavitary irradiation with the dose of 45 Gy at 5mm – Cs137 LDR. Median follow-up was 19 months (range 4-60 months). Survival analysis using Kaplan-Meier method was used to calculate survival curve [8].

The influence of the following prognostic factors on survival was evaluated with the Cox model of proportional hazards: localisation of the recurrence and time gap from primary treatment to the diagnosis of it. Backword method was used to select the variables statistically significant at $p = 0.05$.

Results

The clinical data on 41 patients with locally recurrent endometrial cancer is presented in Table I.

Tab. I. Patients characteristics

		N=41	(100%)
Age	average	64	
	range	44-82	
	median (25%,75%)	68.0 64.7	
Clinical stage	I A	3	(7.3%)
	I B	26	(63.4%)
	I C	12	(29.3%)
Histopathological grading	G-1	16	(39.0%)
	G-2	22	(53.7%)
	G-3	3	(7.3%)
Time (months) to the diagnosis of recurrence	to 12 months	16	(39.0%)
	13-24	17	(41.5%)
	25-36	8	(19.5%

Median age at the time of relapse was 64 years (range 44-81), 75% of women were younger than 70 years. In 39% of patients, a recurrence was diagnosed within the first, and in 80% – within two years after primary treatment.

In none of 41 women a recurrence was diagnosed later than 36 months after initial surgery. Sites of recurrences are presented in Table II.

Tab. II. Site of recurrences

Site	No. of patients	(%)
vaginal apex	9	(22.0)
distal vagina	12	(29.0)
suburethral region	6	(14.7)
vagina + parametria	10	(24.5)
inguinal nodes	2	(4.9)
pelvic nodes	2	(4.9)
Total	41	(100)

Vagina was the most frequent site of tumour a – 21 patients (51%). Vaginal recurrence with parametrial extension was diagnosed in 10 patients (24.5%). Subure-

thral region was the site of recurrence in 6 cases (14.7%). The probability of surviving 3 and 5 years (calculated with Kaplan-Meier method) was 0.33 and 0.21, respectively. Overall survival curve is presented on Figure 1.

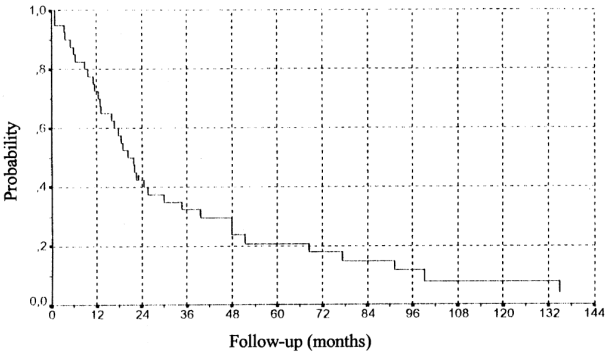

Fig. 1. Overall survival

Both prognostic factors analysed: site of the recurrence and time to the diagnosis had a statistically significant influence on survival ($p \leq 0.05$).

Women with a parametrial spread of the disease, and in whom a recurrence was diagnosed within a year after primary therapy, had a significantly higher risk of death (risk factor of 1.40 and 1.44 respectively, 95% C.I. = 0.99 and 1.97).

Discussion

Local recurrences are the major causes of treatment failure in endometrial cancer. About 10-15% of women recur even in early clinical stages and with good prognostic factors [6, 9-11]. The vagina is the principal site of recurrence, however parametria and pelvic nodes are also frequently involved. A mechanism of recurrence formation is not entirely clear. A subclinical extrauterine spread of the disease might be responsible for their development [12]. Observation of clinical relapses diagnosed shortly after radical surgery support this hypothesis. A routine implementation of surgical – pathological staging for a precise recognition of all important prognostic factors seems to be a reasonable approach to find the optimal adjuvant treatment and limit the risk of treatment failure.

Both surgery and radiotherapy play a major role in the treatment of local recurrences of endometrial cancer [6]. The final selection of treatment method depends on the site of the tumour (technical feasibility of radical surgical excision) or a history of previous irradiation. None of the treatment methods presently available give a satisfactory results.

In a majority of reports only 20-30% of women treated for recurrence survive a 5-year period [5, 6]. Our study shows a 3-year and 5-year survival of 33% and 21%, respectively, and supports the thesis of poor prognosis in those patients. Only a few reports demonstrate the data indicating a better prognosis in patients with tumours limited to the distal part of the vagina, suitable for radical surgery [6,13]. In this selected group of patients, a 5-year survival of about 40% can be achieved [6]. Several authors suggest, that the site of the recurrence is one of the most important prognostic factors [5, 6, 14]. In our study, the site of the tumour had a significat influence on the survival. Patients with parametrial spread of the disease or positive pelvic nodes had significantly higher risk of death than those with the tumour limited to the vaginal wall. None of the patients in the high risk group survived a period of more than 30 months. Other authors suggest, that the localisation of the recurrence in the distal part of the vagina offers a better chances for radical surgical excision or successful interstitial or intracavitary brachytherapy [6,12].

Many authors investigated the influence of histological grade on the survival. Hart et al. indicated a significantly worse prognosis in patients with Grade 3 tumours than with Grade 1 and 2. Grading has not been included in this analysis because majority of patients had Grade 1 and 2 tumours. It is worth stressing that none of women with Grade 3 lesion survived a period of 30 months.

Time relapsing from the end of primary treatment to the diagnosis of recurrence is not only an important prognostic factor but also plays a considerable role in the selection of secondary treatment [3]. Most authors demonstrated a survival advantage if the time gap to the diagnosis exceeded two years [5, 6]. In the current report, a statistically significant survival advantage has been noted when the time gap was longer than one year. Sears et al. also found a significant survival benefit (70 vs. 40% alive at 5 years) if the relapse-free survival was longer than one year.

Clinical experience with the currently available methods of treatment of recurrent endometrial cancer (surgery, irradiation, chemo- and hormonotherapy) show a limited effectiveness in curing the disease. Every effort should be made to recognise subclinical extrauterine spread of cancer to lower the risk of failure of primary treatment. This goal might be accomplished with wider application of surgical-pathological staging [12]. An important clinical information obtained from a precise staging procedure may indicate the need for adjuvant treatment. Postoperative radiotherapy – both external beam irradiation to the pelvis and intracavitary irradiation is routinely used in high risk patients. Its effectiveness is demonstrated by a higher rate of local control and longer disease-free survival [15]. However some controversies about the role of postoperative pelvic irradiation still exist because of the lack of clinical data based on prospective randomised studies. Therefore some advocate the use of postoperative radiotherapy at the time of recurrence [15]. In the recent study by Jereczek-Fossa, the results of radiotherapy in 73 patients with locally relapsing endometrial cancer confirmed a very disappointing results of treatment initiated at the time of relapse[7]. A 3-year and 5-year survival was 33% and 25%, respectively, leading the authors to the conclusion that pelvic irradiation given

postoperatively could have prevented developing of at least some recurrences. Ackerman et al. in a retrospective study assessed the results of adjuvant pelvic radiotherapy vs. salvage irradiation at the time of recurrence. The authors concluded, that in low risk patients (Grade 1 and 2 tumour with myometrial invasion of less than 50%) there is a marginal survival benefit in favour of irradiated group – 93% vs. 97%. In the high risk group (Grade 3 or any Grade with deep myometrial invasion) the survival advantage for pelvic adjuvant irradiation is more prominent – 90% vs. 80%, respectively, confirming the value of adjuvant treatment.

Local recurrences of endometrial cancer after primary surgery and adjuvant brachytherapy form a rare but very serious clinical problem. Radiotherapy seems to be the most effective method of treatment. About 30% of patients can be cured. This results are far from satisfactory and indicate the need for an intensive search for new methods of treatment.

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