

Original contributions

Prognostic value of the time interval between surgery and adjuvant radiotherapy in patients treated for early stage invasive cervical cancer

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Aim. Assessment of the prognostic value of the time interval between surgery and adjuvant postoperative radiotherapy.

Material and methods. A retrospective analysis of 96 early stage cervical cancer patients, initially treated with surgery. All patients received postoperative radiotherapy in case of positive pelvic lymph nodes or inappropriate surgical margins. All patients received external beam radiotherapy, dose range 43.2 Gy and 46 Gy, and additionally, intracavitary brachytherapy – (LDR) with a mean dose 35 Gy, measured at 0.5 cm below the vaginal cylinder. Cox's proportional hazards model was performed to evaluate independent factors affecting survival. The incidence of treatment-related toxicity was also recorded and scored according to the RTOG/EORTC toxicity scale. The minimum follow-up was 60 months.

Results. Among 96 patients in 5-year follow-up, 78 (81%) were still alive without evidence of disease. The 5-year disease free survival for the node negative group was 92%, and for the nodes positive group – 56% ($p < 0.0004$). The analysis of prognostic value of the time interval between surgery and adjuvant radiotherapy for the group of 71 patients has demonstrated that the time interval of 32.5, 44.5, and over 60 days, resulted in a 5-year disease – free survival of 91%, 88% and 83% respectively. The time interval between surgery and radiotherapy over 60 days was also a significant factor negatively affecting survival ($p < 0.035$).

Conclusions. The results of our study confirm the role of the nodal status as the most important prognostic factor affecting the survival of patients treated surgically for stage Ib cervical carcinoma. For patients after non radical surgery the delay between surgery and radiotherapy is a statistically significant prognostic factor affecting survival.

Znaczenie rokownicze czasu rozpoczęcia napromieniania pooperacyjnego w leczeniu chorych na raka szyjki macicy we wczesnym stopniu klinicznego zaawansowania

Wstęp. Ocena znaczenia prognostycznego czasu, jaki upłynął od operacji chorych na inwazyjnego raka szyjki macicy do rozpoczęcia uzupełniającego napromieniania.

Materiał i metoda. Przedmiotem analizy retrospektywnej była grupa 96 chorych, pierwotnie operowanych z powodu raka szyjki macicy w stopniu klinicznego zaawansowania Ib i napromienianych uzupełniająco w przypadku obecności niekorzystnych rokowniczo czynników, takich jak: przerzuty do regionalnych węzłów chłonnych, nieradykalna operacja pierwotna. Uzupełniająca radioterapia polegała na napromienianiu na obszar miednicy w dawce 43,2 do 46 Gy z następową brachyterapią dopochwową – LDR w dawce 35 Gy, specyfikowanej na głębokości 0,5 cm od powierzchni aplikatora. Posługując się wielowariantową analizą według modelu hazardu proporcjonalnego Cox'a, oceniono znaczenie prognostyczne wybranych czynników rokowniczych. Okres obserwacji po leczeniu wynosił minimum 60 miesięcy.

Wyniki. Spośród 96 chorych objętych obserwacją, okres 5 lat bez objawów choroby przeżyło 78 (81%) kobiet. Odsetek przeżyć 5-letnich w grupie chorych, u których nie stwierdzono przerzutów do węzłów chłonnych miednicy, wyniósł 92%, natomiast z przerzutami do węzłów – 56% ($p < 0,0004$). Analiza wpływu odstępu czasu od zabiegu operacyjnego do rozpoczęcia uzupełniającej radioterapii w grupie 71 chorych, napromienianych uzupełniająco po nieoptymalnym zakresie operacji, dostarczyła następujące wyniki: odsetek przeżyć 5-letnich ze średnim czasem opóźnienia w rozpoczęciu napromieniania wynoszącym: 32,5; 44,5 oraz ponad 60 dni wynosił odpowiednio: 91%, 88% i 83%. Rokowanie w grupie chorych napromienianych po okresie od operacji przekraczającym 60 dni było znamienne gorsze w porównaniu z grupą, w której odstęp pomiędzy etapami leczenia wynosił do 30 dni ($p < 0,035$).

Wniośki. W leczeniu skojarzonym raka szyjki macicy w stopniu zaawansowania Ib, stan regionalnych węzłów chłonnych jest najistotniejszym czynnikiem rokowniczym, natomiast czas, jaki upłynął od operacji do rozpoczęcia napromieniania, jest zmiennym statystycznie czynnikiem prognostycznym w grupie chorych po nieoptymalnym zakresie operacji pierwotnej.

Key words: cervical cancer, adjuvant radiotherapy, prognostic factors

Słowa kluczowe: rak szyjki macicy, radioterapia uzupełniająca, czynniki rokownicze

Introduction

Cervical cancer is the most common form of gynaecological malignancy in Poland with approximately 4000 new cases diagnosed every year. In this group, early stage (Ib, IIa) cervical cancer accounts for only 25-30% cases. Radical surgery and/or radiotherapy performed in early stages of cervical cancer allows to obtain a 5-year disease free survival rate of 80% [1].

The benefit of initial surgical treatment lies in the possibility of obtaining a lot of histological material in order to assess risk factors [1, 2]. The prognosis of surgically treated patients with cervical cancer is related to the presence of regional lymph node metastases, histological malignancy, parametrial extension, close or positive surgical margins and extensive lymph vascular space invasion. Patients with any of these risk factors are determined to be at high risk for recurrence and therefore it is sensible to consider loco regional radiotherapy for this group. For patients with adverse prognostic factors, post-operative radiation improves relapse-free survival [2]. A vast majority of papers have assessed the influence of such parameters as dose per fraction, total dose, dose intensity and technical aspects of intracavitary brachytherapy on relapse-free survival for cervical cancer patients treated initially with surgery [2-4]. A review of the literature does not give any information about the prognostic importance of the time interval between initial surgery and adjuvant radiotherapy for patients treated for early stage invasive carcinoma of the cervix. The extensive clinical material of our institution has led us to assess the prognostic value of the time interval between surgical treatment and adjuvant radiotherapy for the group of patients treated at the Maria Skłodowska-Curie Memorial Cancer Centre in Warsaw.

Material and methods

We performed a retrospective analysis of 96 early stage (Ib) invasive cervical cancer patients with histopathologically diagnosed squamous cell carcinoma. In the case of 25 patients, initial surgical treatment – radical hysterectomy modo Wertheim-Meigs, was performed in the Maria Skłodowska-Curie Memorial Cancer Centre in Warsaw. The remaining 71 patients were treated surgically in other Departments, where they underwent simple hysterectomy. All patients underwent adjuvant

radiotherapy. Before radiotherapy, pathologic examination of the material was performed in order to assess the presence of risk factors. The most important risk factors were positive nodal spread, histological malignancy, inadequate surgical margin or absence of evaluation of regional nodal status (simple hysterectomy).

The adjuvant radiotherapy consisted of external beam radiotherapy to the entire pelvis with brachytherapy to the apex of the vagina. Photon energy used for external beam irradiation ranged between 1.25 MeV (Co60) and 18 MeV. The decision to use either two or four fields was individualized, depending on the size of the patient. A daily dose of 1.8, 2.0, 2.1 Gy to a total dose ranging between 43.2 and 46 Gy in 22-24 fractions was delivered.

As the second part of treatment, intravaginal brachytherapy using the afterloading system of Low-Dose-Rate (LDR/MDR) was performed. The total dose, calculated at 0.5 cm from the surface of the applicator, was 35 Gy in two fractions with a 10-14 days interval.

The incidence of treatment related side effects to the small intestine, the rectum and the bladder was recorded and scored weekly both during the treatment and after the completion of therapy, during follow-up examination, according to the RTOG / EORTC toxicity scale.

The minimum follow-up period was 60 months.

The survival probability was calculated with the Kaplan-Meier method. Multidimensional analysis of the prognostic factors (regional lymph node status, time interval between surgery and adjuvant radiotherapy) was carried out with Cox proportional risk model [6].

P value of less than 0.05 was considered statistically significant.

Results

Among the 96 patients 78 (81%) were still alive without evidence of disease after a 5-year follow-up. The 5-year survival rate for patients with negative lymph nodes was 92%, for the node positive group – 56% ($p < 0.0004$).

Patient survival is presented in Figure 1.

The analysis of the time interval between surgical treatment and postoperative radiotherapy for the group of 71 patients treated with radiotherapy after non-radical surgery has led to the following conclusions: the 5 – year disease-free survivals for the intervals of 32.5, 44.5 and over 60 days were 91%, 88% and 84%, respectively (Figure 2). The prognosis for patients, for which the interval exceeded 60 days, was statistically worse, as compared to the group, in which this interval lasted 30 days or less ($p < 0.035$) (Figure 1).

Table I. Parameters of the assumed risk model (Cox model)

Variable	Standard error	Coefficient beta	Relative risk	Critical level p	Test value
Time interval between surgery and RTH	0.010816	1.022962	4.40566	0.035828	2.09897
Positive pelvic lymph nodes	0.556213	0.141514	12.35858	0.000440	- 3.51548

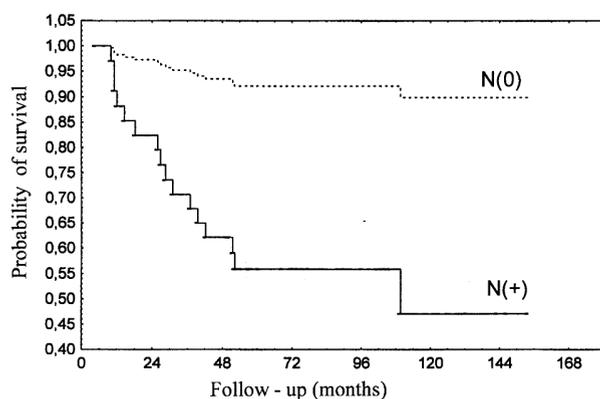


Figure 1. Survival probability for patients with confirmed regional lymph node metastases and for patients without the lymph nodes assessment
N 0 – negative lymph nodes; N(+) – lymph nodes positive or not assessed

The acute treatment-related side-effects were observed in 37.5% patients, mainly involving the large and small intestine and urinary tract. Late sequelae of grade III and IV were observed in 6.2% and 3.1% of cases, respectively. The most frequent grade I and II side-effect was diarrhea, while grade III and IV – cystitis with infrequent hematuria, proctitis and chronic leukopenia.

During the follow-up time, there were three treatment-related complications, requiring medical intervention – two cases of recto-vaginal fistula formations treated by colostomy and one case of ileus at the level of the small intestine – treated surgically. No fatal treatment-related toxicities were noted.

The basic data concerning the early and late side-effects of radiation are presented in Table II.

Table II. Tolerance of treatment – treatment related side effects

	Frequency	The most frequent type of postirradiation reaction	N (Number of incidents)
Acute	37.5% 36/96	Cystitis	16
		Diarrhea	7
		Leucopenia	7
		Nausea, vomits	6
Late sequelae (grade I, II)	6.7% 6/96	Chronic leucopenia	2
		Cystitis	2
		Proctitis	2
Late sequelae (grade III, IV)	3.1% 3/96	Rectum stenosis	1
		Fistula recto-vaginalis	2

Discussion

Adjuvant radiotherapy is an integral part of early stage cervical cancer treatment initiated with surgery [2]. The value of postoperative radiotherapy as a long-term survival aspect is a controversial matter. The view that adjuvant radiotherapy does reduce local recurrences, but does not influence the 5-year survival, is rather prevalent [2-4, 7, 8]. Patients who have undergone radical hysterectomy

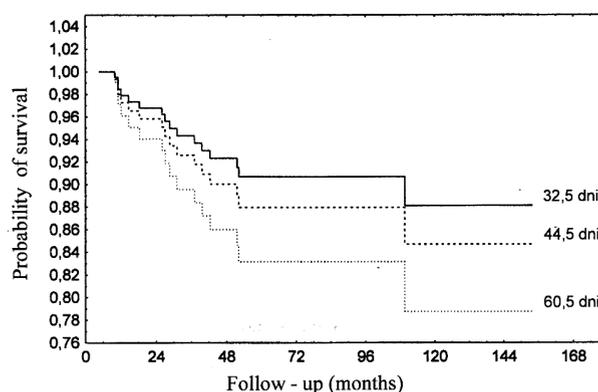


Figure 2. Survival probability in aspect of the time interval between surgery and adjuvant radiotherapy

and in whose case adverse prognostic factors such as metastatic pelvic lymph nodes, lymphatic space invasion, high histological malignancy, and inadequate surgical margins have been assessed present a high risk of recurrence. There also exists another group of patients – those who had undergone surgery for other reasons and in whom the cancer was incidentally found during histopathological evaluation. In the case of these patients histopathological analysis of the margins may not give enough evidence to decide whether surgical treatment alone will provide optimal cure rate. This group consists of patients with negative surgical margins, but without the assessment of pelvic lymph nodes, and also of patients who lack proper diagnostic examination, in whom the diagnosis of cancer was incidental, and parametrial or surgical margins were either microscopically positive, or there were macroscopic pelvic infiltrations left. Most authors list regional lymph node spread as the most important prognostic factor for surgically treated early stage (Ib, IIa) cervical cancer patients [1, 2, 7]. The five-year disease-free survival in early stage cervical cancer patients without any evidence of regional lymph nodes metastases is as high as 80%, while for patients with positive lymph nodes it falls to 50% [1]. Not only the presence of lymph node metastases, but also the number of positive lymph nodes, is prognostically important. Analysis has shown that the five-year survival for patients with 2 positive nodes was 60%, but in case of 4 or more it fell to 20–30% [1, 3]. Our analysis has fully confirmed the power of this factor. The five-year overall survival was significantly higher in the node negative group, as compared to the node positive group – 92% and 56%, respectively ($p < 0.05$). The small number of patients with microscopically confirmed positive lymph nodes did not allow for a more precise analysis its impact on overall survival.

Among a majority of our patients initial surgical treatment was not optimal. The basic indication for postoperative radiotherapy was simple hysterectomy without concomitant assessment of the pelvic lymph nodes. Clinical observations have confirmed the benefit of this treatment in patients initially treated with surgery for conditions other than cancer in whom the diagnosis was incidental [9].

Our observations have confirmed the benefit of adjuvant radiation therapy for early stage cervical cancer patients treated initially with simple hysterectomy. The five year survival rate reached approximately 88% and was similar to that demonstrated by the other investigators [4, 9]. The authors stress that such good results are possible only in case of radical surgery [9]. Apart from all of the biological and pathological risk factors, one of the most important factors is the time interval between surgery and adjuvant radiotherapy. The clinical observation of patients with different localizations of malignancies have confirmed the value of this factor [10-14].

Peters et al. [11] have demonstrated the prognostic importance of the time interval between surgery and adjuvant radiotherapy for head and neck cancer patients. The prognosis for patients who had started radiation during a time interval of 6 weeks or less after surgery was better than the prognosis of patients who started adjuvant radiotherapy after more than 6 weeks.

Buchholz et al. [16] have reported that for patients with breast cancer a lapse of more than 16 weeks between surgery and adjuvant radiotherapy significantly worsens the overall survival and local control probability. Lindner et al. [15] have pointed out, that the time interval between surgery and radiotherapy for endometrial cancer patients is important, and the prognosis for patients starting radiation in 56 or more days after surgery is significantly worse. Similar results were reported by other authors [10, 16, 17]. The results of this study have confirmed the significant influence of this particular factor on the survival time. Five-year survivals differed significantly between the subgroups divided as to the time-lapse between surgery and radiation. The survival probability was as follows: time lapse of less than 32 days – 91%; time lapse of less than 44 days – 88%; time lapse over 60 days – 83%. For patients with pelvic lymph node involvement a delay in radiation onset of over 4 weeks significantly worsened the cure rate.

Other authors who have analysed this factor in view of increasing treatment efficacy have pointed out the necessity of beginning adjuvant radiotherapy as soon as possible after surgical treatment, especially for patients after non radical surgery [10, 12, 16, 17].

In order to begin adjuvant radiotherapy as soon as possible one has to keep in mind the risk of adverse sequelae. There is evidence that starting radiation sooner than after 4 weeks of surgery will increase the risk of acute post-irradiation reactions, especially within the urinary tract.

Both our experiences and literature reports indicate that a 4-to-6-weeks interval between surgery and radiotherapy is a good compromise between efficiency and security of treatment, with a total incidence of grade III and IV late adverse sequelae remaining at 5% or less [18, 19].

Our results allow to conclude that the status of the regional lymph nodes is the most significant prognostic factor affecting survival for early stage cervical cancer patients, treated with surgery and radiotherapy. The effi-

cacy of adjuvant radiotherapy also, to a significant degree, depends on the time interval between initial surgery and radiation. This element is especially statistically significant value among patients after inappropriate surgical treatment.

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