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An analysis of 5-year survival of patients with cervical cancer treated with curable intent in relation to selected prognostic factors. A population-based study

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Aim. The study was aimed at evaluating 5-year survival and the selected prognostic factors in radically treated cervical cancer patients living in the provinces of Kielce, Opole, and Warsaw. These regions are characterised by diversified mortality rates and diversified access to cancer prevention and treatment.
Material. Three cohorts of, altogether, 738 women who had contracted the disease in the years 1990-1996 and were identified using population data collected by the Cancer Registries from the voivodeships of Kielce (K), Opole (O) and Warsaw (W).
Method. Age-standardised 5-year survival rates and the relative excess risk of death (RER) were calculated using the life-table methods and Hakulinen's multi-variant regression models.
Results. The regions were found to differ significantly in the proportion of patients treated in different advancement of the disease, mainly the early stages (I: K – 64.6%, O – 39.4%, W – 44.0%), but not in age group distribution or histopathological diagnosis. The overall 5-year survival rate was 71.1% and by stages amounted to: I – 88.5%, II – 57.7%, III – 43.6%. In the regions under study, survival reached: K – 73.5%, O – 60.7%, W – 75.9%. In Stage I differences were only insignificant, although meaningful, for Stage II (K –51.0%, O – 43.0%, W – 69.7%) and, also in the youngest age groups (for the age below 45 survival rates were: K – 73.2%, O – 50.5%, W – 82.2%).
Also the "waiting time" for treatment was significantly different: K – 63.2; O – 61.5; W – 52.4 days. However, there were no marked differences in the duration of teleradiotherapy. The multi-variant analysis showed that the factors responsible for significant increase in RER include: disease advancement ($p<0.0001$), delay in treatment by more than 60 days ($p=0.04$), and place of residence related to place of treatment ($p<0.03$).
Conclusions. The 5-year survival rates of cervical cancer patients in Poland differ from region to region not only due to the proportion of stages of advancement, but also as a consequence of different standards of treatment, mainly of patients in Stage II and Stage III.

Analiza pięcioletnich przeżyć chorych na raka szyjki macicy leczonych radykalnie w zależności od niektórych czynników rokowniczych. Badanie populacyjne

Cel. Ocena 5-letnich przeżyć oraz niektórych czynników rokowniczych u chorych na raka szyjki macicy leczonych radykalnie, zamieszkałych w województwach kieleckim i opolskim oraz w Warszawie – regionach o zróżnicowanej umieralności, a także dostępności profilaktyki i leczenia onkologicznego.
Materiał. Materiał stanowiły trzy kohorty liczące łącznie 738 kobiet, które zachorowały w latach 1990-96 i zostały zidentyfikowane na podstawie danych populacyjnych Rejestrów Nowotworów w Kielcach (K), Opolu (O) oraz w Warszawie (W).
Metody. Wskaźniki 5-letnich przeżyć, standaryzowane według wieku, oraz względny wzrost ryzyka zgonu (RER) obliczono stosując metodę tabel trwania życia i wielowymiarowej regresji Hakulinena.

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W y n i k i. Badane regiony były znacznie zróżnicowane pod względem proporcji chorych w poszczególnych stopniach zaawansowania choroby, głównie stopni wczesnych (I: K – 64,6%, O – 39,4%, W – 44,0%). Nie było natomiast znaczących różnic w grupach wieku i w rozpoznaniu histopatologicznym. Wskaźnik 5-letnich przeżyć ogółem wynosił 71,1%, zaś według stopni zaawansowania: I – 88,5%, II – 57,7%, III – 43,6%. W badanych regionach przeżycia wynosiły: K – 73,5%, O – 60,7%, W – 75,9%). W stopniu I zróżnicowanie było niewielkie, znaczące zaś w stopniu II (K – 51,0%, O – 43,0%, W – 69,7%), oraz w najmłodszych grupach wieku (u chorych młodszych niż 45 lat przeżycia wynosiły: K – 73,2%, O – 50,5%, W – 82,2%). Również „czas oczekiwania" na leczenie był istotnie zróżnicowany i wynosił: K – 63,2; O – 61,5; W – 52,4 dni. Nie stwierdzono natomiast znacznych różnic w czasie trwania teleradioterapii. Analiza wielowymiarowa wykazała, że czynnikami istotnie zwiększającymi RER są: zaawansowanie choroby (p<0,0001), opóźnienie leczenia ponad 60 dni (p=0,04) oraz miejsce zamieszkania, co wiązało się z miejscem leczenia (p<0,03).
W n i o s k i. Pięcioletnie przeżycia chorych na raka szyjki macicy w Polsce są zróżnicowane regionalnie, nie tylko w wyniku różnej proporcji stopni zaawansowania, ale także wskutek różnych standardów leczenia, głównie chorych w stopniu II i III.

Key words: cervical cancer, population-based survival, prognostic factors
Słowa kluczowe: rak szyjki macicy, przeżycia populacyjne, czynniki rokownicze

Introduction

Cancer of the uterine cervix in Poland continues to pose a massive health problem. It is responsible for about 2,000 deaths each year and the respective mortality rates are: the crude rate $10.0/10^5$ and standardised rate: $6.8/10^5$ [1]. Owing to prevention achievements and tremendous diagnostic and treatment progress in many countries, the number of deaths caused by this cancer has significantly declined with the mortality rates dropping down to about $4/10^5$ [2].

Results of a study [3] done on data covering all the cervical cancer cases in the voivodships of Kielce and Opole, and in the City of Warsaw are consistent with reports saying that the 5-year survival rates in Poland are rather low [4-6], and the disease advancement and diagnosis of adenocarcinoma are the most important prognostic factors in this disease [7-9].

Clinical studies emphasize significance of prognostic factors dependent on cancer disease, and among them, those most important are: the stage of disease, tumour size, histological diagnosis, and presence of metastases in lymphatic nodules and then, the depth and extent of infiltration [10]. Factors, dependent on the patient condition include: his performance status, inclusive of the level of haemoglobin. Factors, depending on the treatment are: dose and duration of radiotherapy, application of brachytherapy and cisplatin. In clinical studies, the role of adenocarcinoma diagnosis and patient's age are controversial as independent prognostic factors.

The unfavourable proportion of early cancer stages in Poland can, to some extent, explain the low 5-year survival rate values. However, the regional differentiation of the survival rates evaluated for the same advancement stages (especially Stage I and II) suggests some diversity in treatment standards [3]. This part of the analysis attempts to evaluate the effect of some factors related to the treatment.

The aim of the study was to compare the survival of patients with cervical cancer receiving curative treatment; living in the voivodships of Kielce, Opole, and in Warsaw, as well as to evaluate the effect of time between diagnosis and beginning of treatment, and also the number of days of teleradiotherapy on the prognosis for these patients, taking into consideration the stage of disease, histological diagnosis, and the patient's age at diagnosis.

Material and method

Three cohorts were created – altogether 738 women with invasive cervical cancer – 206 from the Kielce and 193 from the Opole voivodships and 339 from Warsaw City – diagnosed between the years 1990 and1996 as the primary malignancy. The patients were referred for radical treatment, which was completed in line with the plan, that is, they received the full prescribed teleradiotherapy and brachytherapy doses of 85-90 Gy (of this, at least 46 Gy in teleradiotherapy) administered to point A in fractioned doses and/or were subject to radical surgery.

The patients were identified using the Cancer Registry data in Kielce, Opole and Warsaw. The demographical data and clinical information about the patients were collected by persons with medical background, in a uniform way, following a common, earlier provided protocol. The data was checked for correctness by the regional study co-ordinator. The investigators used Cancer Registry data, medical records, and other relevant medical documentation obtained from all the hospitals and other places where these documents could be found. The documentation was available for 88% of the patients reported to Cancer Registries whose files carried comment on curative treatment being planned. In the Kielce voivodship, in the files of 80 patients with a diagnosis of cervical cancer Stage I the dates for the beginning of treatment were missing hence, these patients were excluded from the delay treatment analysis and from the duration of radiotherapy analysis.

The clinical data included: the clinical advancement stage acc. to the FIGO classification, histological diagnosis, date of treatment onset, and the methods of treatment. In case of patients receiving radiotherapy it was checked whether they had received the planned radiotherapy doses. The time from diagnosis to the beginning of treatment was calculated using the earliest date of reporting to the Cancer Registry and the date of treatment beginning, which were extracted from the patients' medical records (if the diagnosis date in the medical records was earlier than that in the Cancer Registries, it was corrected with the appropriate methods).

The patients were treated with surgical methods, irradiation from external fields and brachytherapy as standalone

or in combination, according to the various protocols (different sequences of methods applied, different radiation sources, intervals pre-scheduled in therapy), which rendered the treatment methods incomparable. Hence, in the analysis of treatment time as a prognostic factor the study was limited to the number of days of teleradiotherapy. Based on data from literature, the teleradiotherapy time was considered as extended if it was longer than 35 working days (7 weeks) [11, 12].

The effects of the following prognostic factors were evaluated: FIGO clinical advancement Stages I, II, and III, age groups: 15-44, 45-64, 65-74, and 75 and over, diagnosis of squamous cell carcinoma and adenocarcinoma, the number of days from diagnosis to beginning of treatment: up to 30, 30-60, and over 60, as well as the place of inhabitation: voivodships of Kielce and Opole, and the city of Warsaw.

The patients were followed up for 5 years. Missing data concerning their date of death or the last observation were completed with data obtained from the Census Office.

According to the methods applied for multi-centre studies and in order to allow for comparisons, statistical analysis was performed by one team using uniform methodology recommended by WHO-IARC for population studies on cancer [13]. The collected data was checked and processed separately for each Cancer Registry. SAS (the SAS software was used under the Licence Agreement No. 89601 which allows the Maria Skłodowska-Curie Cancer Center and Institute of Oncology to use this software free of charge) software was used in the statistical analysis. For the evaluation of prognostic factors distribution we applied the Chi square test, variance analysis, and Tykey's multiple comparison test. The statistical significance level was adopted as $p \leq 0.05$.

Software SURV2, recommended for computing population survival was used for the calculation of relative 5-year survival rates and the 95% confidence interval [14, 15]. For the computation of relative survival rates we used life expectancy tables specific for Warsaw, while calculations for the voivodships of Kielce and Opole, relied on average values for Poland.

The relative excessive risk of death (RER) was calculated with the method of multi-variant regression analysis, modified by Hakulinen and Tenkanen, and recommended for studies based on data from population-based cancer registries where the death cause is usually unknown [16]. This method allows to evaluate the difference between risk of death in the study group and in the reference group, this risk being taken into consideration for the general population in the region under study.

Results

Patients characteristics

The description of patients who had completed treatment in tune with the protocol assigned to the study regions is presented in Table I. The largest group of the radically treated patients was diagnosed as Stage I of the disease advancement (358 or 48.5%), the second largest – as Stage II (284 or 38.5%). Ninety-six patients (13.0%) were treated at Stage III of the disease. The largest age group was that between 45 and 64 years (48.6%) and younger, under 44 (31.8%). Squamous cell carcinoma represented 89.5% and adenocarcinoma – 7.5% of cases.

The study regions differed significantly as to the proportion of patients in various stages of disease advancement ($p<0.001$). Patients with Stage I cervical cancer from the voivodship of Kielce made up the largest group – 64.6%, from Warsaw – 44.0% and from the Opole voivodship – 39.4%. There were no significant differences in the distribution of age groups ($p=0.11$) and between the proportions of the squamous cell and adenocarcinoma ($p=0.71$).

Table I. Patient characteristics

	Kielce voivodship	Opole voivodship	Warsaw	All	p
	Number of patients **%**				
Stage of disease					
I	133 **64.6**	76 **39.4**	149 **44.0**	358 **48.5**	
II	62 **30.1**	83 **43.0**	139 **41.0**	284 **38.5**	
III	11 **5.3**	34 **17.6**	51 **15.0**	96 **13.0**	
					<0.001
Age group (years)					
15-44	62 **30.1**	60 **31.1**	113 **33.3**	235 **31.8**	
45-64	97 **47.1**	104 **53.9**	158 **46.6**	359 **48.6**	
65-74	35 **17.0**	28 **14.5**	53 **15.6**	116 **15.7**	
75+	12 **5.8**	1 **0.5**	15 **4.5**	28 **3.9**	
					0.11
Histopathological diagnosis					
squamous cell carcinoma	185 **89.8**	176 **91.2**	300 **88.5**	661 **89.5**	
adenocarcinoma	14 **6.8**	14 **7.3**	27 **8.0**	55 **7.5**	
others and NS	7 **3.4**	3 **1.5**	12 **3.5**	22 **3.0**	
					0.71

Table II. Stages of disease by age group and place of living

	I	II	III	p
	Number of patients **%**			
15-44				
Kielce voivodship	22 **56.4**	14 **35.9**	3 **7.7**	
Opole voivodship	25 **45.5**	23 **41.8**	7 **12.7**	
Warsaw	61 **54.0**	38 **33.6**	14 **12.4**	
				0.52
45-64				
Kielce voivodship	26 **44.8**	27 **46.6**	5 **8.6**	
Opole voivodship	44 **41.5**	44 **41.5**	18 **17.0**	
Warsaw	66 **41.8**	71 **44.9**	21 **13.3**	
				0.96
> 65				
Kielce voivodship	5 **17.2**	21 **72.4**	3 **10.3**	
Opole voivodship	7 **21.9**	16 **50.0**	9 **28.1**	
Warsaw	22 **32.4**	30 **44.1**	16 **23.5**	
				0.12

Table II shows the proportions of patients by disease advancement stages and age groups. The share of Stage I cancer declined with patient age, while the number of more advanced stages increased. It should be noted that the proportions of advancement stages were found to be particularly unfavourable in the youngest women living in the voivodship of Opole. When compared with the other regions, the proportion of Stage I patients was around 10 percent points, whereas Stage II patients made about 7 percent points, although this difference was not statistically significant (p=0.52). Similarly, within the same area we found an unfavourable proportion of advancement stages in the groups aged 45-64 years.

The 5-year survivals

The 5-year survival rate for all the patients was 71.1% and it varied from the most favourable in Warsaw -75% to the lowest values in the voivodship of Opole – 60.7%. The survival rate in the voivodship of Kielce was 73.5%.

As can be seen from Table III, the relative 5-year survival rates were dropping with disease advancement stage and amounted to: I – 88.5%, II -57.7%, and III – 43.6%, and in patients with the diagnosis of adenocarcinoma (59.9%), as compared to squamous cell

Table III. Five-year relative survival rates by stage of disease, age group and morphology

	Kielce voivodship	Opole voivodship	Warsaw	All
	Number of patients **5-year relative survival rate %** (95% PU)			
Stage of disease (FIGO)				
I	133 **86.5** (78.7-92.4)	76 **88.7** (78.8-95.2)	149 **90.2** (83.5-94.9)	358 **88.5** (84.2-92.0)
II	62 **51.0** (38.1-64.4)	83 **43.0** (32.6-54.3)	139 **69.7** (60.9-77.8)	284 **57.7** (51.5-63.9)
III	11 **38.9** (16.2-69.2)	34 **40.5** (25.3-58.3)	51 **46.8** (33.1-61.5)	96 **43.6** (33.7-54.4)
Age group (years)				
15-44	62 **73.2** (60.9-82.8)	60 **50.5** (38.1-62.9)	113 **82.2** (73.9-88.3)	235 **71.7** (65.6-77.2)
45-64	97 **71.7** (61.6-80.4)	104 **64.9** (55.0-74.0)	158 **70.8** (63.0-77.8)	359 **69.4** (64.2-74.2)
65-74	35 **72.5** (53.4-88.6)	28 **66.3** (45.3-85.2)	53 **77.6** (61.8-90.8)	116 **73.3** (62.7-82.9)
75+	12 **100.0** (59.2-130.7)	1 **-** -	15 **62.6** (31.0-100.5)	28 **82.2** (54.9-108.1)
Histopathological diagnosis				
squamous cell carcinoma	185 **73.7** (66.3-80.3)	176 **61.2** (53.5-68.6)	300 **76.9** (71.2-81.9)	661 **71.8** (67.9-75.4)
adenocarcinoma	14 **62.3** (35.5-85.7)	14 **60.6** (34.6-83.4)	27 **58.4** (39.2-76.1)	55 **59.9** (46.0-73.0)
others and NS	7 **-** -	3 **-** -	12 **-** -	22 **77.2** (55.0-92.2)

carcinoma (71.8%). In older age groups, a total for all the three regions under study, no lower survival rates were found. However, the Opole voivodship shows the lowest values for all age groups. This is particularly noticeable in younger patients, where the difference between the rates was higher than 20 percent points.

The patients in Warsaw had the highest survival rates in the disease advancement stages under analysis, in all the age groups below 75 years (comparisons are more difficult on elderly patients because of their relatively small number) and in case of patients with the diagnosis of squamous cell carcinoma. When compared to other regions, these differences were especially noticeable in patients with Stage II and in the age group under 45 yrs.

Differentiation of therapeutic methods in use

Most often, in 356 patients (54%) radiotherapy was applied (teleradiotherapy and brachytherapy), while 262 patients (nearly 40%) were treated by combined methods (surgery and radiotherapy in different sequences) and only 40 patients (6%) received surgery alone. Table IV presents the radical treatment methods administered, depending on the disease advancement stage and the patient's place of living. In Stage I, nearly 80% of patients received surgery with adjuvant radiotherapy. In a majority of patients with Stage II (88.4%) and in all the Stage III patients, radiotherapy alone was administered as the treatment method. Radiotherapy alone and radiotherapy combined with surgery were employed more often in the Opole voivodship than in other areas ($p<0.001$). Surgery as a single method was rarely used, while in the Opole voivodship it was used exceptionally. Surgery combined with brachytherapy was prescribed more frequently in Warsaw than in other regions.

The frequency of the treatment methods correlated with the patient age. Surgery and surgery combined with radiotherapy was applied more often to younger women, while radiotherapy alone ($p<0.005$) – to older ones. Most cases of squamous cell carcinoma were treated with methods involving radiotherapy (55.9% of the patients) while adenocarcinoma was usually treated with methods involving surgery (53.1%) ($p<0.002$).

Treatment delay

The number of days between cancer diagnosis and the beginning of treatment was 56.4. The average waiting time for treatment was dependant on the place of living. It is summarised in Table V. In the voivodship of Kielce, it reached, by average, 11 days more, and in Opole – 9 days more than in Warsaw. Only about 20% of the patients in the voivodships of Kielce and Opole began their treatment within 30 days from diagnosis; in Warsaw, the percentage was 44. A large proportion of patients in the voivodships of Kielce and Opole (around 40%) waited for more than 60 days for their treatment to begin. This figure was lower than 30% in case of Warsaw.

Table IV. Methods of treatment of cervical cancer patients by place of living and stage of disease, age group and morphology

	Surgery alone	TRT* + BT**	Surgery +TRT + BT	Surgery + BT
	Number of patients			
	%			
Place of living				
Kielce voivodship	10	68	40	8
	7.9	**54.0**	**31.7**	**6.3**
Opole voivodship	1	113	74	5
	0.5	**58.5**	**38.3**	**2.6**
Warsaw	29	175	80	55
	8.6	**51.6**	**23.6**	**16.2**
Stage of disease (FIGO)				
I	37	19	157	65
	13.3	**6.8**	**56.5**	**23.4**
II	3	251	27	3
	1.1	**88.4**	**9.5**	**1.1**
III	0	96	0	0
	0.0	**100.0**	**0.0**	**0.0**
Age group (years)				
15-44	21	86	71	29
	10.1	**41.5**	**34.3**	**14.0**
45-64	16	174	107	25
	5.0	**54.0**	**33.2**	**7.8**
65-74	3	75	15	14
	2.8	**70.1**	**14.0**	**13.1**
75+	0	21	1	0
	0.0	**95.5**	**4.5**	**0.0**
Histopathological diagnosis				
squamous cell carcinoma	32	332[3]	166	64
	5.4	**55.9**	**27.9**	**10.8**
adenocarcinoma	3	17	26	3
	6.1	**34.7**	**53.1**	**6.1**
others and NS	5	7	2	1
	33.3	**46.7**	**13.3**	**6.7**

* teleradiotherapy
** brachytherapy

Patients in the voivodships of Kielce and Opole waited for radiotherapy alone, as opposed to other methods of treatment (Kielce – 77.7 days, $p=0.005$; Opole – 74.1 days, $p=0.002$). This waiting time in Warsaw was 48.4 days and its duration was not much different from the waiting time for other treatment methods ($p=0.67$). The waiting time for radiotherapy in the voivodships of Kielce and Opole was about 30 days longer than in Warsaw ($p<0.001$).

Patients with Stage I cervical cancer in the Kielce and Opole voivodships, as well as in Warsaw waited for treatment for about the same time. However, those with Stage II in the Kielce voivodship usually waited 33 days longer and in the Opole voivodships – 22 days longer than those in Warsaw. This difference was statistically significant ($p=0.002$).

Figure 1 shows the 5-year survival rates in relation to the waiting time for treatment. Patients who waited longer than 60 days showed survival rates lower than those who waited a shorter time. This difference was especially noticeable in patients from the Opole voivodship.

Table V. The number of days from diagnosis to beginning of treatment by place of inhabitation and treatment method

	Treatment method	Number of patients	Average number of days between diagnosis and beginning of treatment	Standard deviation
Kielce voivodship				
	surgery alone	4	33.8	9.9
	TRT + BT	29	77.7	57.4
	surgery + TRT + BT	16	46.1	29.9
	surgery + BT	1	31.0	–
	all treatment methods	50	63.2	49.7
Opole voivodship				
	surgery alone	1	41.0	–
	TRT + BT	109	74.1	48.4
	surgery + TRT + BT	68	41.3	35.1
	surgery + BT	5	65.9	37.2
	all treatment methods	183	61.5	46.1
Warsaw				
	surgery alone	27	55.3	63.7
	TRT + BT	155	48.4	54.9
	surgery + TRT + BT	54	58.1	66.9
	surgery + BT	49	56.0	61.5
	all treatment methods	295	52.4	59.4

Differences between the regions:
All treatment methods $p=0.14$
RT only $p<0.001$

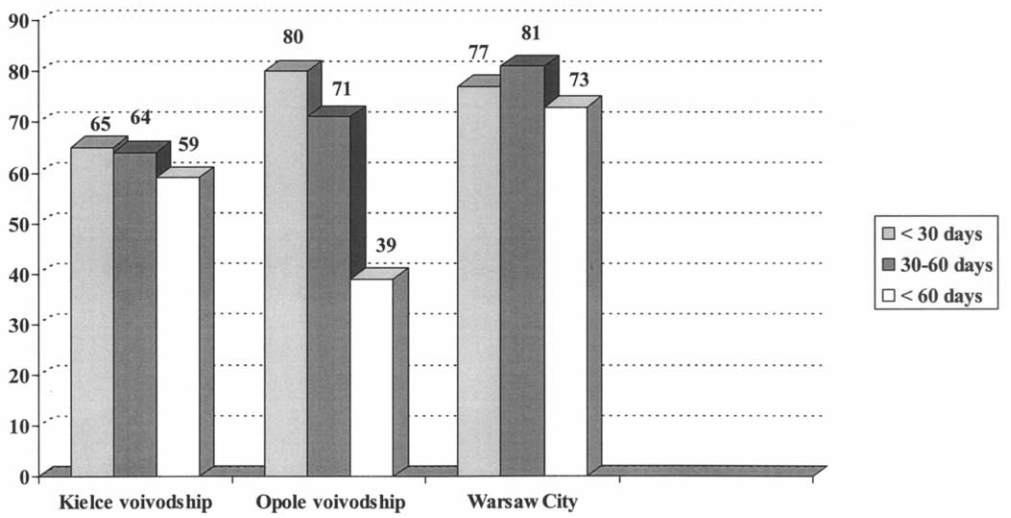

Figure 1. The 5-year relative survival rates of cervical cancer patients by time from diagnosis to begining of treatment, by place of living

Treatment time

Table VI presents the number of teleradiotherapy days calculated for patients treated with irradiation as a standalone method and in combination with surgery. The average number of teleradiotherapy days given to patients receiving irradiation alone and irradiation combined with surgery was 38.4. This time was differentiated chiefly because of different treatment protocols used in the regions involved. The radiotherapy time was between 25.3 days in the voivodship of Kielce to 44.9 days in Opole, and 38.3 in Warsaw.

Only 3 patients in the voivodship of Kielce were treated with teleradiotherapy for longer than 35 days, while it was applied to 67% of patients from the Opole voivodship, and to 74% of patients in Warsaw.

A comparison of survival rates is presented in Figure 2. The small number of patients in the voivodship of Kielce who had an extended treatment time did not allow for a survival rate calculation. The survival rates in the group of patients in the voivodship of Opole who had been irradiated longer than 35 days were 15% lower than those treated with the 7-week regime. This difference was smaller in Warsaw, reaching only 6%.

Extended teleradiotherapy time in the Opole voivodship was observed mainly in patients with higher disease advancement stages. In patients with Stage II (and not much fewer with Stage III), the time was

Table VI. Number of irradiation days in patients treated only with irradiation, and by combined method (radiotherapy + surgery)

	Treatment methods	Number of patients	Average number of days of TRT	Standard deviation
Kielce voivodship				
	RT alone	65	24.6	5.8
	surgery + RT	26	27.1	5.4
	all	91	25.3	5.8
Opole voivodship				
	RT alone	112	47.3	12.9
	surgery + RT	73	41.3	13.6
	all	185	44.9	13.5
Warsaw				
	RT alone	173	38.3	10.1
	surgery + RT	77	38.4	6.5
	all	250	38.3	9.1

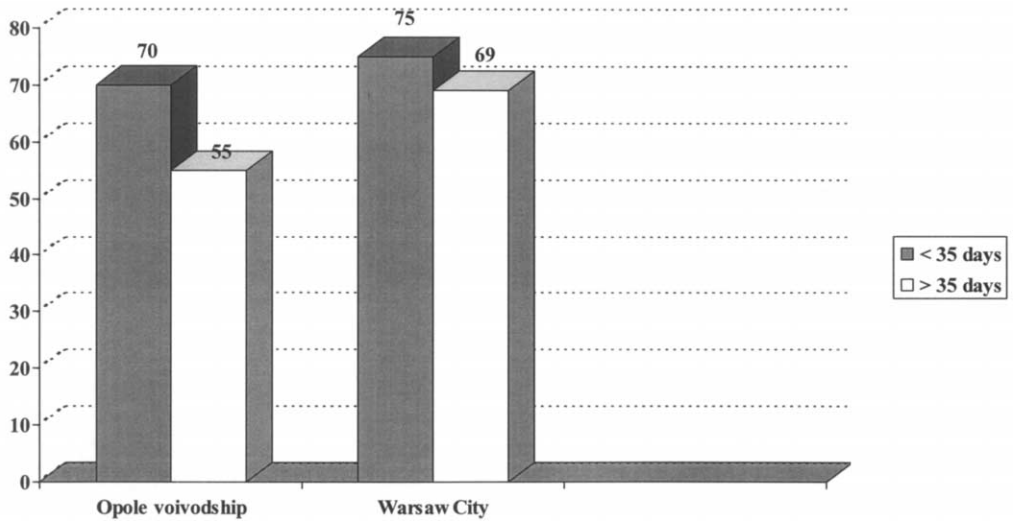

Figure 2. The 5-year relative survival rates of cervical cancer patients treated with radiation upto 35 days vs. treated longer, by place of living

significantly longer than the radiotherapy time of patients with Stage I (p=0.03). No extended radiotherapy time depending on the advancement stage was observed in the voivodship of Kielce and in Warsaw.

Multi-variant analysis

The results of the multi-variant regression analysis are shown in Table VII. Risk factors associated with an increase of the RER include the cancer advancement stage (p<0.0001), the time between diagnosis and beginning of treatment exceeding 60 days (p=0.04), and the place of inhabitation in the voivodships of Opole and Kielce (p<0.03). Histological diagnosis and patient age had no significant impact on the prognosis.

A model, testing the effect of teleradiotherapy time longer than 35 days, shows that RER of death was 1.17, while the difference in RER was not statistically significant (p=0.35). On the other hand, the risk resulting from the disease advancement stage, just like the place of inhabitation, continued to be significantly high. Also, models testing the Opole voivodship and Warsaw, separately, did not reveal the significant role of prolonged teleradiotherapy time (respectively, p=0.54 and p=0.23).

Discussion

As a result of the Government Programme PR-6 and CPBR (Central Research and Development Programme) 11,5 "Cancer Control" in the years 1976-1990, a three-level oncological network was established. It included 12 comprehensive cancer centres for which uniform treatment criteria were developed [17, 18].

Cervical cancer treatment, except for the less advanced stages, requires complex methods employing highly specialised surgery and radiotherapy with vast experience of the doctors and all the medical personnel. Radiotherapy is used as a standalone treatment method and in combination with surgery. It combines irradiation from external fields and brachytherapy. The principal idea of radiotherapy is the appropriate application of available methods in order to administer a proper dose to the tumour and to the metastatic lymph nodes, and to reduce the risk of post-treatment complications. It is

Table VII. Relative excessive risk of death (RER) by stage of disease, age group, morphology, place of living, time from diagnosis to beginning of treatment and number of irradiation days

	RER	95% CI	p
Stage of disease (FIGO)			
I	1.00		
II	**4.83**	**(3.18-7.35)**	**<0.0001**
III	**7.52**	**(4.66-12.14)**	**<0.0001**
Histopathological diagnosis			
squamous cell carcinoma	1.00		
adenocarcinoma	1.42	(0.82-2.43)	0.21
Age group (years)			
15-44	1.00		
45-64	0.82	(0.58-1.15)	0.26
>64	0.76	(0.50-1.16)	0.21
Place of living			
Warsaw	1.00		
Kielce voivodship	**1.87**	**(1.13-3.08)**	**0.02**
Opole voivodship	**1.73**	**(1.25-2.39)**	**0.001**
Days between cancer diagnosis and beginning of treatment			
<30	1.00		
30-60	0.96	(0.64-1.44)	0.84
>60	**1.49**	**(1.03-2.16)**	**0.04**
Days of radiotherapy			
<35	1.00		
>35	1.17	(0.84-1.63)	0.35

important to apply the planned dose at the optimum time because any breaks in irradiation, whatever their reason, reduce the chance for successful treatment. The combined treatment may be modified in various ways. Usually, it begins with surgery, the extent of which is determined according to individual indications and, then, treatment is continued in the form of teleradiotherapy and brachytherapy. Some cases require brachytherapy as the first treatment phase preceding surgery, which removes the reproductive organs together with pelvic lymph nodes and, whenever indications are present (persisting cancer focus within the uterine cervix or lymph nodes) followed by additional teleradiotherapy [19].

Apart from the generally accepted principles, the choice of the treatment procedure depends on the patient's clinical condition and, more often nowadays, her preference if equally effective methods could be offered. The study has shown that the applied treatment methods depended on a high proportion of advanced disease stages. Radiotherapy predominated as a standalone method or in combination with surgery. Surgery was rarely performed alone. It was more frequent among young women, while older patients would rather receive radiotherapy as less traumatic. Most patients suffering from adenocarcinoma received radiotherapy combined with surgery as a method of choice, while radiotherapy predominated in treating the squamous cell carcinomas.

Despite improving diagnostic methods, surgical techniques, and irradiation technology all over the world, no significant improvement has been seen in the results of treatment of the cervical cancer patients, especially those with more advanced stages. The European cervical cancer average 5-year survival rate in the years 1990-1994 was 62.1% and it grew by as little as 3% in the last decade [5]. Many authors believe that the rate improvement in some countries has resulted from a better access and efficiency of prevention programmes [20].

There are, alas, opposite trends as well. The causes for lower survivals are diverse. Countries which have had long-time screening programmes are witnessing a growth of adenocarcinoma with worse prognosing [21]. Waiting time for treatment in Britain and Canada has become longer [22, 23]. Transition and economic crisis in post-communist countries changed their health service systems and survivals declined as a result of the shrinking proportion of early detected cancers and less effective treatment [20]. The 5-year survival rate estimated for Poland in the 1990s was 48.2%, that is, one of the lowest in Europe [5].

The results of this study, which deals with patients who had received radical treatment and are supposed to be cured. However, even before the treatment was applied, unequal chances to be cured were noticeable in the regions under study, since the proportion of early stages diagnosed were significantly different. The multivariant analysis shows that when the disease advances from Stage I to Stage II, the risk of death grows 5 times. A higher proportion of patients with cancer in Stage II and higher can largely explain the low 5-year survival rates for all the patients and also those belonging to the youngest age groups in the Opole voivodship. However, differences in survivals calculated for stages require special attention.

The 5-years survivals of patients with Stage I cervical cancer living in the analysed regions are similar and are not much different from those published in the FIGO Report, which used data on 11,620 patients and an analogous period of time [24]. We also need to note that

survivals of Warsaw patients with Stages II and III were not significantly different from those included in the Report (there are certain methodological differences in calculating survivals for the FIGO Report, hence the comparisons are not precise). Therefore, the low survival rates in Stage II in the Opole voivodship (27 percent points lower than in Warsaw) and in the Kielce voivodship (19 percent points lower) are even more concern.

The reason for this seems to lie in un-uniform diagnostic and treatment procedures. The patients were treated according to various protocols in many oncological departments. Patients from the Kielce voivodship were usually referred for radiotherapy to the Maria Skłodowska-Curie Cancer Centre and Institute of Oncology in Cracow, and, sometimes, also to Gliwice, Łódź, Rzeszów and Warsaw. Those from the Opole voivodship, were usually sent to a specialist oncological department at the Wojewódzki Szpital Zespolony, Opole (Currently: Opolskie Centrum Onkologii), and those from Warsaw were usually treated at the Maria Skłodowska-Curie Cancer Centre and Institute of Oncology in Warsaw. A small number of patients living in Warsaw received brachytherapy procedures at the Grochowski Hospital in Warsaw. And also the Central Clinical Hospital of the Department of National Defence offered teleradiotherapy treatment.

The presented results show, that the standard of treatment was not equal everywhere, resulting in a longer waiting time and a longer time of teleradiotherapy. Treatments were modified and intervals caused by the patients' health condition, post-surgery healing, irradiation complications, co-morbidity (such as various infectious diseases, diabetes, circulatory failures, glaucoma, injuries in road accidents and by reasons of organisational nature, among them, waiting lists, long week-ends, other technical reasons like equipment breakdowns, service, and travel fatigue.

As was shown by the study, the proportion of patients waiting for treatment for more than 30 days was large – 80% in the Opole and Kielce voivodships, and 55% in Warsaw. These patients waited for teleradiotherapy as the first treatment. Also, patients with higher disease advancement stages waited longer for radiotherapy. The multi-variant analysis shows that waiting for treatment for over 60 days increases the RER of death by nearly 50%.

The study has also shown a small, statistically insignificant, risk increase associated with the number of teleradiotherapy days being higher than 35. Adjusting for the stage of disease, the waiting time for treatment, patient's age, and histological diagnosis, the place of living was still an important risk factor increasing RER by about 80% in the patients from the Kielce and Opole voivodships as compared to those from Warsaw. According to UICC classification, it should be considered as an environmentally related risk factor, i.e. related to the treatment standards, mainly with the radiotherapy duration, the use of brachytherapy, and the frequency of treatment complications [10].

The adverse effect of delayed cancer treatment is known and was often studied in Poland. Following WHO estimations, M. Pawlicki in 1995 assessed that Poland might expect a minimum 15% growth of cure rate by 2004 as a result of early detection and better health service organisation, combined with better diagnostic equipment. In his estimations, Pawlicki relied, beside other sources, on his own studies, which assessed the delay in providing specialised cancer treatment. General Practitioners were responsible for 9 month delays, prolonged diagnostic procedure at a local hospital – average 6 weeks, and waiting for treatment at a cancer clinic in some voivodships – another 3-6 weeks. Delays resulting from wrong diagnosis were even longer [25, 26].

The time between diagnosis and beginning of treatment, the so called "time lost", is one of the most important prognostic factors, especially for patients with fast proliferating cancers, cervical cancer being one of them [22, 27]. The role of this factor is especially significant in advanced stages of the disease [28, 29].

The importance of the "time lost" was also demonstrated by O'Rourke *et al.*, in a prospective study investigating the impact of the "waiting list" for radical radiotherapy in lung cancer patients. The investigators established that 21% of patients "lost" eligibility for radical treatment after waiting the average 94 days [30].

Also, Wyatt R.M. et al., confirmed the unfavourable effect of delay in providing treatment by using mathematical models. Considering the therapeutic effect in slowing down the tumour growth and doubling the treatment time, they demonstrated that a 1-2 month delay in treatment has a significant impact on the probability of disease local recurrence in cervical cancer patients [29].

Shortage of qualified personnel, shortage of treatment equipment, growing cost of treatment and financial scarcity, suffered by the health sector are not only a Polish problem. Despite a declining number of cervical cancer patients in many countries, the waiting lists of patients are becoming longer, though the treatment standards are improving at the same time.

Realizing the adverse effect of treatment delays and the scale of this phenomenon in many countries, researchers and health service system decision makers began giving more attention to the problem. They ventured to propose optimum solutions, which were a compromise between the "time lost" and the cost of treatment. As the result of such analyses, the Joint Council of Clinical Oncology, and the Committee on Standards of the Canadian Association of Radiation Oncologists were among those authorities which recommended commencing radical treatment within 14 days after diagnosis and by no means later than after 28 days [23, 31].

These recommendations provided a basis for further studies on the size and role of this problem. It was estimated that the waiting time for treatment of most cancers in the United States was much shorter than in Canada [32]. The authors also report that the recommendations were hardly ever obeyed in the UK. The

waiting time for radiotherapy in 2001 was almost three times longer than in 1996 and it grew to 35 days. Only 12% of patients received radiotherapy before 4 weeks from being diagnosed for cancer. These facts are caused by the shortage of treatment equipment and personnel [22, 23].

The recent decade has provided ample evidence that extension of irradiation time by more than 7 weeks has a negative effect on radically treated cancer patients' survival. Fyles and Lanciano estimate that every day of treatment extension increases the probability of local recurrence by 1%, especially in higher disease advancement stages [33, 34]. Similar results were obtained by Karolewski in his study of a group of patients treated at the Maria Skłodowska-Curie Cancer Centre and Institute of Oncology in Kraków [35]. At the same time, many reports say that excessive reduction of irradiation time not only fails to improve the treatment results but also reduces its efficiency and encourages complications, many of them quite serious [11, 36].

Low survival rates of cervical cancer patients in the UK, various treatment procedures, and prolonged treatment motivated the Royal College of Radiologists (RCR) in 1996 to recommend procedures intended to strengthen compliance with planned radiotherapy time. RCR recommended to compensate for breaks in treatment by twice-daily irradiation, or on days off work, or increasing the total or fractionated doses [37]. The recommendations generated a measurable improvement in treatment standards. In 2001, the rate of patients treated with continuous teleradiotherapy was 94% and it grew almost five times in relation to 1996, and the total irradiation time was cut down to 39 days [22].

However, the waiting time for radiotherapy became longer at the same time. Coles at al., used a mathematical model to find out that the consequences of prolonged waiting time are not compensated by shorter radiotherapy. The effect of waiting for treatment is very important in cervical cancer patients, especially those with higher advancement stages [22]. Authors stress that recommendations given to-date are arbitrary and temporary because they do not allow for the individual time of cancer growth and its sensitiveness to radiation at different phases of disease. They emphasise an urgent need to develop national treatment standards based on multi-centre clinical studies and a systematic exchange of experience, also, in the area of long-term treatment results and radiotherapy complications in each hospital working on the problem [12]. However, until a measurable improvement is reached in the treatment standard, careful monitoring of the patients on the "waiting list" is indispensable and treatment must be delivered sooner, depending on the individual indications [22].

Owing to financial resources provided by the State Committee for Scientific Research, Kielce, Opole, and Warsaw have set up modern, population-based data bases of cervical cancer patients which store data on selected prognostic factors and treatment procedures. The data resource gathered by them allowed comparative studies and conclusions pointing to the most important shortcomings in treating cervical cancer patients living in the regions under study. A study of population data obtained from Cancer Registries avoided the selection bias, which contaminates other studies which use data from hospitals. Here, the methodology ensured comparativeness of the results obtained and, therefore, the identified regional differences in the cervical cancer patients' chance for cure were real.

Conclusions

1. Regional studies have shown considerable diversity in the 5-year survival rates of cervical cancer patients. This refers to patients with Stage II and the youngest age groups. The unfavourable proportion of the disease advancement stages, which is the most important prognostic factor, only in part explains the poor treatment results found in the area of former Opole voivodship.
2. The long waiting time for treatment (longer than 60 days on the average), particularly for radiotherapy, affecting most of patients from the Kielce and Opole voivodships suffering from advanced cancers, is a factor significantly deteriorating the prognosis and, to some extent, explains the regional differentiation of survival rates.
3. The number of teleradiotherapy days being higher than 35 had no significant effect on the death risk. Lower 5-year survival rates in the group of patients with prolonged teleradiotherapy in the Opole voivodship and Warsaw depended on the disease advancement stage and the time of waiting for the treatment.
4. The place of inhabitation and, therefore, also the place of treatment in the Kielce and Opole voivodships, continued to be independent prognostic factors (RER higher than in Warsaw by about 80%) and it seems to be related to non-uniform treatment standards. This requires further studies leading to the development of national standards for cervical cancer treatment.
5. The study confirms that effective prevention, which improves the proportion of early cancer stages, is the most successful method of cervical cancer control in the population. Advanced cancers are much more difficult to treat, especially in a situation of equipment shortage and long waiting time for treatment.

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