Journal of BUON **13:** 363-368, 2008

ORIGINAL ARTICLE

Five-year overall survival and prognostic factors in patients with cervical cancer in Bulgaria

P. Kostova[1], V. Zlatkov[2], S. Danon[3]

[1]Gynecology Clinic, National Oncological Hospital, Sofia; [2]Medical University, Department of Obstetrics and Gynecology, Sofia; [3]Cancer Registry, National Oncological Hospital, Sofia, Bulgaria

Summary

Purpose: *To perform a population-based analysis on the 5-year survival rate and to analyse the significance of various prognostic factors for survival in patients with cervical cancer in Bulgaria for the period 1993-2002.*

Patients and methods: *A total of 9,457 women were analyzed using the data of the National Cancer Registry. Their mean age was 51.41 years. Survival analysis was performed using the life table method. Analysis of factors affecting survival was performed by the Cox proportional hazards regression model. The statistical processing was carried out with the SPSS program/PC+v.11.01 for Windows.*

Results: *The overall cumulative 5-year survival was 47.12%. According to age, higher survival was observed in women younger than 35 years. Women in towns had better survival than those in villages. Significant difference was observed between squamous cell carcinoma and adenocarcinoma and some rare histological types. According to stage, survival was higher for stages I and II and was decreasing with advancing disease stage. Better survival was achieved with surgical treatment. In the Cox regression analysis, the highest relative risk was associated with advanced clinical stage, with symptomatic therapy only, with rare histological types, age over 65 years, and village residents.*

Conclusion: *According to these results, Bulgaria is among the countries with low 5-year cervical cancer survival. Survival at the population level depends on several factors. The most important among them could be attributed to the absence of organized cervical screening.*

Key words: Bulgaria, cervical cancer, 5-year survival, prognostic factors

Introduction

Survival has been accepted as an indicator in monitoring cancer control activities. In this context it must be considered together with incidence and mortality [1]. Survival is usually studied to evaluate the effectiveness of a treatment, but it should be remembered that it is the average result of the whole range of cancer control work, including screening, early diagnosis and organization of treatment services [2]. Survival in different populations may be influenced by a range of prognostic and other factors. Some prognostic factors, such as age, are always available and usually some other tumor-related variables like cervix uteri subsite (exo- or endocervix) and histological type are also available [3].

Survival of cervical cancer patients varies with age, with a clearly decreasing trend with increasing age. This trend may be related to some biological factors or may be the result of the higher prevalence of co-morbid diseases. Relative 5-year survival rates vary among geographic regions, with quite good prognosis in low-risk regions, even in developing countries where many cases present at relatively advanced stage [3].

There are time trends in survival of cervical cancer. The major improvements in the first half of the 20th century were due to improving the stage at diagnosis and to the better results of treatment, particularly as a

Correspondence to: Petya Kostova, PhD. Gynecology Clinic, National Oncological Hospital. 6, Plovdivsko pole Street, 1756 Sofia, Bulgaria. Tel: + 359 888 233 606, Fax: + 359 295 332 25, E-mail: petyakostova@yahoo.com

Received 19-11-2007; Accepted 30-12-2007

result of advances in radiotherapy. The relatively unfavorable trends in survival may be the result of a counterbalance between the effect of screening and improvement of treatment [4].

Cox proportional hazards models are widely used to explain the effect of different variables on survival time. Usually, several independent variables including age, histological type, grade, tumor volume, lymph node status and country are simultaneously included in the model [4].

In Bulgaria cervical cancer is still a medical and social problem. It ranks second among gynecological tumors. The number of new cases ranged from 509 to 1086 cases for the period 1970-2002. The standardized incidence was in the range of 9.9 to 19.4/100,000 and the standardized mortality ranged from 2.6 to 6.2/100,000 (Figure 1). Comparative analysis of the basic epidemiological indices for cervical cancer shows that Bulgaria is included among the highly affected countries in Europe and has a medium position among the countries worldwide.

Compared to the achievements in the countries implementing a successful screening program these data prove the inefficiency of the model practiced in this country so far. The successful results reported at the beginning referred to the stabilization of the basic epidemiologic indices, but they have been followed by gradual deterioration in all screening activities [5].

A comparative analysis on overall survival of cervical cancer cases in Bulgaria and in the USA was reported by Danon in 1999 [6]. The survival in Bulgaria was significantly lower (47.91 vs. 91.90% in the USA) and this difference was due to the delayed diagnosis of cases in Bulgaria.

The purpose of this study was to perform a population-based analysis on the 5-year cumulative survival rate and to analyse the significance of various prognostic factors for survival in patients with cervical cancer in Bulgaria.

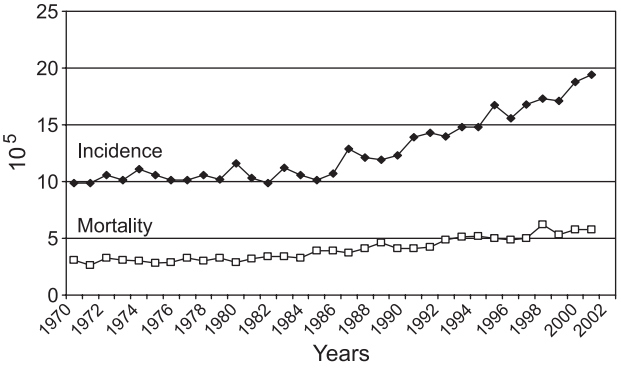

Figure 1. Standardized incidence and mortality of cervical cancer in Bulgaria, 1970-2002.

Patients and methods

A total of 9,457 women with invasive cervical cancer during the period 1993-2002 were retrospectively analysed, using the data of the Bulgarian National Cancer Registry. The mean age of the patients was 51.41 years (range 19-93). Survival analysis was performed using the life table method.

Analysis of factors affecting survival was performed by the Cox proportional hazards regression model, including the following variables: age, residence, histological type, clinical stage and treatment modality.

The statistical processing was carried out by the SPSS program/PC + v.11.01 for Windows. The selected level for statistical significance was at $p< 0.05$.

Results

The observed overall cumulative 5-year survival was 47.12%.

The results for survival according to the different examined factors (age, residence, histology, stage and kind of treatment) are presented in Figures 2-6. The results of the Cox regression model are shown in Table 1.

According to age, higher survival was observed in women younger than 35 years, followed by those aged between 36 and 45. There was a tendency for decreasing survival with the increase of age which was statistically significant (p=0.0000) (Figure 2). Women over 65 had the highest relative risk for death (RR=2.352).

Women living in towns had better survival (50.14%) than those living in villages (38.03%; p= 0.0000) (Figure 3). Women in villages had higher relative risk for death (RR=1.411; p=0.0000).

Concerning 5-year overall survival significant difference according to the histological type was observed between squamous cell carcinoma and adenocarcinoma and some rare histological types (Figure 4). The relative risk for death for adenocarcinoma was lower (RR=0.960) than the one for squamous cell carcinoma (RR=1.000). Women with some rare histological types (mucoepidermoid, adenosquamous, and carcinosarcoma) had the highest relative risk for death (RR=2.601).

In relation to stage, survival was higher for the early stages (I and II; 74.30% and 49.22%; p=0.000, respectively) and decreased with advancing disease

Table 1. Summary of Cox regression analysis

Variables	*RR of death*	*95% CI*	*p-value*
Age (years)			
0-35	1	Reference	
36-45	1.098	0.968-1.246	0.147
46-55	1.336	1.182-1.510	0.000
56-65	1.483	1.305-1.686	0.000
> 65	2.352	2.080-2.659	0.000
Residence			
Town	1	Reference	
Village	1.411	1.317-1.511	0.000
Histological type			
Squamous cell	1	Reference	
Adenocarcinoma	0.960	0.863-1.068	0.451
Other	2.601	1.741-3.886	0.000
Clinical stage			
I	1	Reference	
II	2.473	2.238-2.732	0.000
III	5.061	4.584-5.588	0.000
IV	12.030	10.494-13.790	0.000
Unknown	2.048	1.688-2.486	0.000
Type of treatment			
Surgery	1	Reference	
Radiotherapy	2.216	1.967-2.496	0.000
Surgery + Radiotherapy	1.085	0.965-1.220	0.171
Chemotherapy	4.551	3.223-6.425	0.000
Radio + Chemotherapy	3.578	2.975-4.303	0.000
Surgery + Radio + Chemotherapy	1.991	1.631-2.429	0.000
Symptomatic	7.195	6.228-8.314	0.000

RR: relative risk, CI: confidence interval

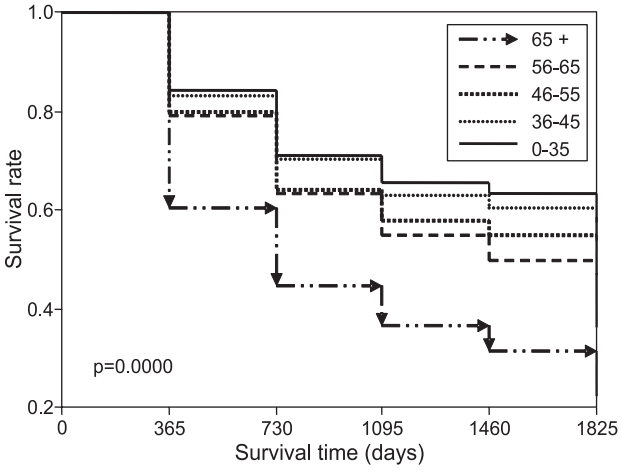

Figure 2. Five-year survival of cervical cancer patients in Bulgaria according to age (1993-2002).

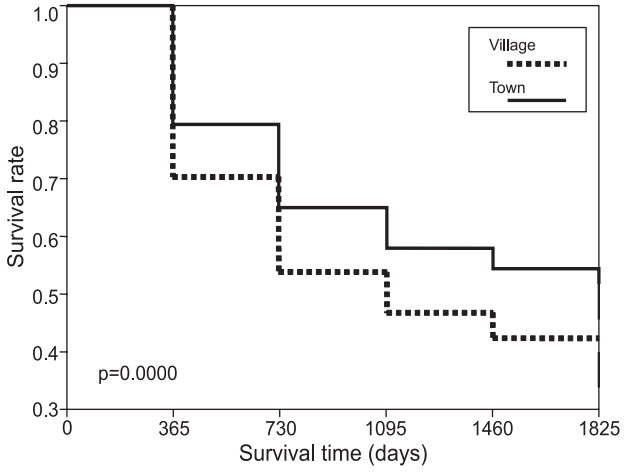

Figure 3. Five-year survival of cervical cancer patients in Bulgaria according to residence (1993-2002).

stage (Figure 5). The results of Cox regression model showed highest relative risk for death for the group of women with clinical stage IV (RR=12.030). The better survival of cases with unknown stage compared with those with IV stage, and the lower risk of women with unknown stage compared to the risk of stages II-IV most probably means that the group with unknown stage consisted of cases with low disease stage, not precisely diagnosed.

Better survival was achieved with surgical treat-

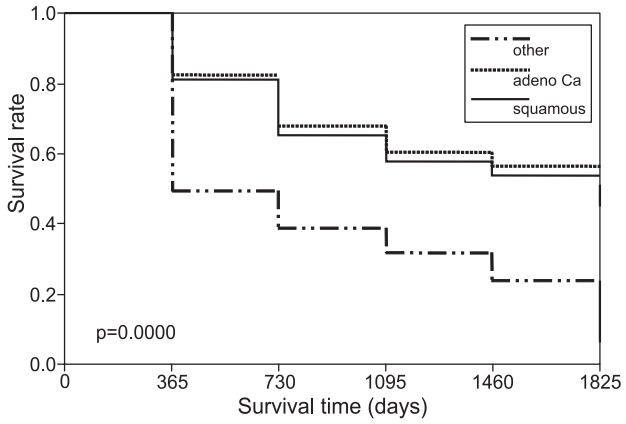

Figure 4. Five-year survival of cervical cancer patients in Bulgaria according to histological type (1993-2002).

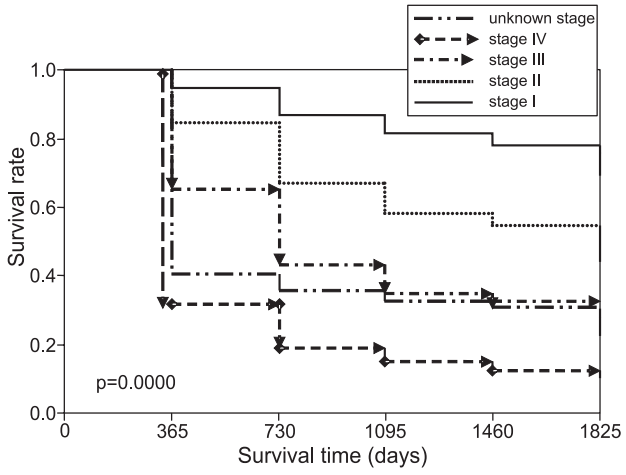

Figure 5. Five-year survival of cervical cancer patients in Bulgaria according to clinical stage (1993-2002).

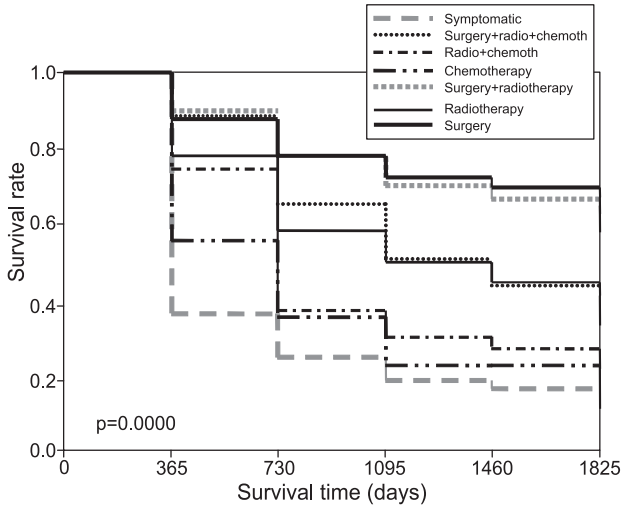

Figure 6. Five-year survival of cervical cancer patients in Bulgaria according to type of treatment (1993-2002).

ment (66.23%) and with surgery combined with radiotherapy - 61.95% (p=0.0000; Figure 6). The highest relative risk for death was seen in women with symptomatic treatment (RR=7.195), followed by those receiving chemotherapy only (RR=4.551; p=0.0000).

Cox regression analysis showed that the most significant prognostic factors for poor survival were delayed diagnosis and advanced disease stage, women aged over 65, those living in villages, patients with rare histological types and those receiving symptomatic therapy only (Table 1).

Discussion

Our results for 5-year survival are low and similar to those reported in the relevant literature. Yeole et al. [7] found 47.7% 5-year survival rate in their study in India for the period 1992-1994. In 2004 Bielska-Lasota et al. [8] reported 52.2% 5-year survival in selected regions of Poland and described it as one of the lowest in Europe. In 2001 the summarized data of 24th FIGO report [4] showed 72.2% 5-year overall survival from 28 countries around the world. In 2005 Zheng et al. [9] in China found 81% 5-year survival while Chung et al. [10] found 79.2% overall 5-year survival in Korea for the period 1993-2002. In Singapore Wang et al. [11] reported in 2003 an improvement on the 5-year cumulative survival rate for the last 25 years from 45 to 65%.

Coker et al. [12] reported in 2000 that older women have the lowest survival and worst prognosis. In 2000 Kim et al. [13] suggested that women over 50 need more intensive therapy and follow-up because of the lower survival in this group. Ioka et al. [14] discussed in 2005 that low survival among older women is due to the more advanced disease at the time of diagnosis.

The data of 24th FIGO report [4] show no difference in survival rates by stage between squamous cell carcinoma and adenocarcinoma. In our study the overall 5-year survival for squamous cell carcinoma and adenocarcinoma was almost the same. Different are the data of Bulk et al. [15] who in 2003 found better survival in women with squamous cell cancer than in those with adenocarcinoma and they recommended closer follow-up of those women. In their article in 2006 Chung et al. [10] stated that patients with adenosquamous carcinoma had higher survival than women with nonkeratinizing squamous cell cervical carcinoma.

According to the 24th FIGO annual report stage showed a direct correlation with survival [4]. Our re-

sults over survival for stages I and II are lower than those reported by most authors which varies from 94.4 to 55.4, respectively [8,9,14-17] and confirm better survival for early-stage disease. Better survival of cases with unknown stage in this country suggests that probably this group included women with early-stage disease.

The data of Coker et al. [12] demonstrate that women undergoing radical hysterectomy vs. no surgery or any other treatment had significantly better survival. Houvenaeghel et al. [18] using multivariate analysis found that only the type of surgery affected overall survival. According to the data of Hwang et al. [19] neoadjuvant chemotherapy followed by radical hysterectomy in locally advanced cervical cancer seemed to improve long-term survival.

Our results from the relative risk analysis showed that significant poor prognostic factors include patients with advanced clinical stage, age over 65 years, living in villages, patients with rare histological types and those receiving symptomatic treatment only.

Similar to our results concerning the influence of age are those of Shepherd et al. [20]. They reported that age over 69 is among the most significant poor prognostic factors. Other factors including histology and initial stage were not significant in the multivariate analysis of these authors.

According to the data of Bielska-Lasota et al. [8] stage is the most important prognostic factor. Similar are our results about the influence of disease stage on survival and also the data of Chung et al. [10] who reported that clinical stage and histological type are the most significant independent prognostic factors for survival.

In the analysis performed by Kim et al. [13], age, cell type and lymph node metastases were independent predictors of survival. Patients who had positive lymph nodes, adenocarcinoma and were older than 50 had a poorer survival rate.

Eralp et al. [21] also found that stage at presentation was an independent prognostic factor with a significant impact on overall survival.

Conclusions

According to these results, Bulgaria is among the countries with low 5-year cervical cancer cumulative survival. Lower survival was found in older women, in village population, in patients with advanced disease and with rare histological types. Surgical treatment and surgery combined with radiotherapy give better survival. Among the most significant poor prognostic factors are age over 65, village population, patients with rare histological types, with advanced clinical stage and those receiving symptomatic therapy only. Survival at the population level depends on several factors, the most important among them being the absence of an organized cervical screening.

References

1. Welch HG, Schwartz LM, Woloshin S. Are increasing 5-year survival rates evidence of success against cancer? JAMA 2000; 283: 2975-2978.
2. Black RJ, Sankaranarayanan R, Parkin DM. Interpretation of population-based cancer survival data. In: Sankaranarayanan R, Black RJ, Parkin DM (Eds): Cancer survival in developing countries (IARC Scientific Publications No 145), Lyon. IARC Press 1998, pp 13-17.
3. IARC Handbooks of Cancer Prevention. Vol. 10: Cervix Cancer Screening. IARC Press, Lyon, 2005, pp 8-9.
4. FIGO Annual Report on the Results of Treatment in Gynecological Cancer (Vol. 24). Pecorelli S, Beller U, Peter A et al. (Eds). J Epidemiol Biostat 2001; 6: 42-43.
5. Zlatkov V, Kostova-Zlatkova P (Eds). Prophylaxis, screening and vaccines for precancer and cancer of the uterine cervix. Bulgarian Publ House, Sofia, Bulgaria, 2006.
6. Danon S. Survival of most curable cancers. 6th Natl Oncol Congr, 19-20 November 1999, Sofia, Bulgaria. Proceedings book, pp 31-32.
7. Yeole BB, Kumar AV, Kurkure A et al. Population-based survival from cancers of breast, cervix and ovary in women in Mumbai, India. Asian Pac J Cancer Prev 2004; 5: 308-315.
8. Bielska-Lasorta M, Krynicki R, Rabszenko D et al. Survival of cervical cancer patients in selected regions of Poland in 1990-1996, in relation to some prognostic factors. Przegl Epidemiol 2004; 58: 523-536 (in Polish with Engl abstr).
9. Zheng XK, Chen LH, Li J. Radiotherapeutic effect and prognosis of bulky exophytic cervical cancer. Di Yi Jun Yi da Xue Xue Bao 2005; 25: 332-334 (in Chinese with Engl abstr).
10. Chung HH, Jang MJ, Jung KW et al. Cervical cancer incidence and survival in Korea: 1993-2002. Int J Gynecol Cancer 2006; 16: 1833-1838.
11. Wang H, Chia KS, Du WB et al. Population based survival for cervical cancer in Singapore, 1968-1992. Am J Obstet Gynecol 2003; 188: 324-329.
12. Coker AL, Du XL, Fang S et al. Socioeconomic status and cervical cancer survival among older women; Findings from the SEER-Medicare linked data cohorts. Gynecol Oncol 2006; 102: 278-284.
13. Kim SK, Choi HS, Byun JS. Overall 5-year survival rate and prognostic factors in patients with stage IB and IIA cervical cancer treated by radical hysterectomy and pelvic lymph node dissection. Int J Gynecol Cancer 2000; 10: 305-312.
14. Ioka A, Tsukuma H, Ajiki W et al. Influence of age on cervical cancer survival in Japan. Jpn J Clin Oncol 2005; 35: 464-469.
15. Bulk S, Visser O, Rosendaal L et al. Incidence and survival rate of women with cervical cancer in the Greater Amsterdam area. Br J Cancer 2003; 89: 834-839.
16. Dupont G, Lauszus FF, Guttorm E et al. Survival rate after radical hysterectomy for cervical cancer performed in a central hospital. Ugeskr Laeger 2005; 167: 4367-4371.
17. Papp Z, Csapo Z, Mayer A et al. Wertheim-operation: 5-year

survival of 501 consecutive cases of cervical cancer. Orv Hetil 2006; 147: 537-545.
18. Houvenaeghel G, Lelievre L, Gonzague-Casabianca L et al. Long-term survival after concomitant chemoradiotherapy prior to surgery in advanced cervical carcinoma. Gynecol Oncol 2006; 100: 338-343.
19. Hwang YY, Moon H, Cho SH et al. Ten-year survival of patients with locally advanced, stage Ib-IIb cervical cancer after neoadjuvant chemotherapy and radical hysterectomy. Gynecol Oncol 2001; 82: 88-93.
20. Shepherd JH, Ngan HYS, Neven P et al. Multivariate analysis of factors affecting survival in pelvic exenteration. Int J Gynecol Cancer 1994; 4: 361-370.
21. Eralp Y, Saip P, Sakar B et al. Prognostic factors and survival in patients with metastatic or recurrent carcinoma of the uterine cervix. Int J Gynecol Cancer 2003; 13: 497-504.