International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

Vol. 31 No. 2 March 2022, pp. 43-48

Effect of Age at Diagnosis on Cervical Cancer Patient Prognoses in Georgia

Gabrichidze T [1].,Mchedlishvili I[1].,Mebonia N [1.2]., Didbaridze T [1]., Gamkrelidze A[2].

[1]Tbilisi State Medical University, Georgia; [2]National Center for Disease Control and Public

Abstract – The current incidence of cervical cancer varies around 17.0/100,000 women per year. The study aims to describe the effect of age at diagnosis on CC patient prognosis in Georgia. Methods. Univariable and Multivariable survival analysis using Cox's regression model was constructed. All women aged ≤80 years, diagnosed with invasive CC (ICD10-site code C53) from 2015 to 2019, were eligible for inclusion in the analysis. During analysis a hazard (mortality) ratio for the patients, who were diagnosed at different ages was estimated. Survival period was determined from the date of diagnosis until the date of death or the date of last follow up visit. High risk of death was defined as a mortality of CC patients whose survival period was less than 5 years.The level of statistical significance of the study findings is estimated by using p-value andthe 95% of confidence interval (95%CI). A p value < 0.05 was considered as statistically significant. In estimation of hazard ratio, the patients under 41 years were selected as a reference group. Data was analyzed using Statistical Package of SPSS version 23. Results.Totally 1646 CC patients were enrolled in the study. The median age at diagnosis was 54years and age range was 25 - 80 years. Univariable statistical analysis has revealed that cancer diagnosed over 60 years of age had a higher death hazard (HR=1.80, p<0.001), compared to cancer detected under 60 years (HR=3.30, p<0.001). Multivariable statistical analysis has detected that stage and age at diagnosis are independent, statistically significant predictors for high mortality in patients diagnosed with cervical cancer, while the role of histological grade has not been revealed. In addition, older age generally is related to a high prevalence of comorbidities. The reasons for the unfavourable cervical cancer prognosis in older patients that was detected during statistical analysis might be explained by tumor stage at diagnoses and with higher ratesof comorbidity among the elderly. Conclusions: Finally, our study results are in concordance with numerous studies, which confirm that the age of patients at the moment of diagnosis is an independent predictor for cervical cancer early mortality.

Keywords – Cervical Cancer, Survival, Age At Diagnosis, Hazard Ratio.

I. INTRODUCTION

Annually, more than 570,000 new cases of cervical cancer (CC) and 311,000 deaths occur globally; the vast majority of these incident cases and deaths occur in low-, lower-middle- and upper-middle-income countries, where accessibility to the effective cervical cancer prevention and management services – such as, HPV vaccination, cervical screening and quality treatment is low.The World Health Assembly in May 2020 adopted the Global Strategy to Accelerate the Elimination of Cervical Cancer as a Public Health Problem, with the goal of reaching an incidence rate below 4 per 100,000 women (11).

Georgia still has to work extensively to reach the elimination threshold of cervical cancer; the current incidence of cervical cancer is 16.7/100,000 women per year. During the period of 2011-2018 the number of annual deaths fluctuated inconsistently between 121 and 185 cases, that composed variation of mortality rates from 6.1 to 9.5 per 100 000 women. This slight increase in CC mortality could be related to the improvement of death registration. Comparatively stable median age of deaths, indicates that, there is no tendency of cervical cancer early mortality reductionin Georgia.

The study aims to describe the effect of age at diagnosis on CC prognosis among patients diagnosed during the period of 2015 and 2019 in Georgia.

Corresponding Author: Didbaridze T

II. Methods

Univariable and Multivariable survival Analysis using Cox's regression model was constructed to analyze the effect of age at diagnosis on CC patients' early mortality.CC patients' data for analysis was obtained from the national population based cancer registry. All women aged ≤80 years, diagnosed with invasive CC (ICD10-site code C53) from 2015 to 2019 and registered in the population-based cancer registry database, were eligible for inclusion in the analysis. In order to investigate the correlation between age at diagnosis and hazard of mortality, the study participants were divided into the following three groups: a young group (under 41 years), a middle age group (41-59 years), and an elderly group (60 years and over). During analysis a hazard (mortality) ratio for the patients, who were diagnosed at different ages was estimated.The level of statistical significance of the study findings is estimated by using *p-value* andthe 95% of confidence interval (95%CI). A *p value* < 0.05 was considered as statistically significant. In estimation of hazard ratio, the patients under 41 years were selected as a reference group. Survival period was determined from the date of diagnosis until the date of death or the date of last follow up visit. Any cause of death of CC patients was considered as the end point, therefore the overall (and not cervical cancer specific) survival period is examined. The cut-off point of data for the survival analysis was set at December 31ST, 2019. Patients who were alive after the cut-off date were considered as censored. High risk of death was defined as a mortality of CC patients whose survival period was less than 5 years. Data were analyzed using Statistical Package of *SPSS version 23*.

III. Results

Totally 1646 CC patients were enrolled in the study. The median age at diagnosis was 54 years and age range was 25 - 80 years. Tables1& 2 summarises tumor stage at diagnosis and grade status of patients with CC by age at diagnosis. There were some age-specific differences in both variables: for example, 56.0% of patients aged under 41 years were detected at early stages (the first and second) compared with 52.0% in patients aged 41-59 years, and 47.7% in patients aged ≥60 years old. Younger women were less likely to have histologically poorly differentiated tumor; it was 23.2%, 27.1%, and 27.6% in patients aged under 41 years, 41-59 years, and over 59 years old accordingly.

Table 1. Tumor stage at diagnosis by age groups for patients with cervical cancer (total number of patients: n=1646)

Stage at diagnosis		Age at diagnosis			Total
		under 41	41-59 yy	≥ 60 yy	
first	**Count**	**78**	**251**	**107**	**436**
	% within Stage	17.9%	57.6%	24.5%	100.0%
	% within age	37.7%	27.5%	20.3%	26.5%
second	**Count**	**38**	**225**	**144**	**407**
	% within Stage	9.3%	55.3%	35.4%	100.0%
	% within age	18.4%	24.6%	27.4%	24.7%
third	**Count**	**37**	**237**	**139**	**413**
	% within Stage	9.0%	57.4%	33.7%	100.0%
	% within age	17.9%	26.0%	26.4%	25.1%
fourth	**Count**	**17**	**108**	**87**	**212**
	% within Stage	8.0%	50.9%	41.0%	100.0%
	% within age	8.2%	11.8%	16.5%	12.9%
unknown	**Count**	**37**	**92**	**49**	**178**

	% within #Stage	20.8%	51.7%	27.5%	100.0%
	% within age	17.9%	10.1%	9.3%	10.8%
Total	**Count**	**207**	**913**	**526**	**1646**
	% within #Stage	12.6%	55.5%	32.0%	100.0%
	% within age	100.0%	100.0%	100.0%	100.0%

Table 2. Tumor's histological differentiation by age groups for patients with cervical cancer (total number of patients: n=1646)

Tumor grade		Age at diagnosis			Total
		under 41	41-59 yy	≥ 60 yy	
well differentiated	**Count**	**16**	**46**	**20**	**82**
	% withinGrade	19.5%	56.1%	24.4%	100.0%
	% within age	7.7%	5.0%	3.8%	5.0%
moderately differentiated	**Count**	**53**	**229**	**110**	**392**
	% within Grade	13.5%	58.4%	28.1%	100.0%
	% within age	25.6%	25.1%	20.9%	23.8%
poorly differentiated	**Count**	**48**	**247**	**145**	**440**
	% within Grade	10.9%	56.1%	33.0%	100.0%
	% within age	23.2%	27.1%	27.6%	26.7%
undifferentiated	**Count**	**0**	**6**	**3**	**9**
	% within Grade	0.0%	66.7%	33.3%	100.0%
	% within age	0.0%	0.7%	0.6%	0.5%
Unknown	**Count**	**90**	**385**	**248**	**723**
	% within Grade	12.4%	53.3%	34.3%	100.0%
	% within age	43.5%	42.2%	47.1%	43.9%
Totally	**Count**	**207**	**913**	**526**	**1646**
	% within Grade	12.6%	55.5%	32.0%	100.0%
	% within age	100.0%	100.0%	100.0%	100.0%

Univariable statistical analysis has revealed that cancer diagnosed over 60 years of age had a higher death hazard compared to cancer detected under 59 years (table #3).

Table #3. Hazard (mortality) ratio of cervical cancer patients according to age at diagnosis

Age groups	*p-value*	Hazard Ratio (HR)	95.0% CI for HR	
			lower	upper
under 41 years	.000	*reference*		
41-59 years	.001	1.822	1.272	2.608
≥60 years	.000	3.322	2.312	4.773

Multivariable statistical analysis detected that stage and age at diagnosis are independent statistically significant predictors for high mortality in patients diagnosed with cervical cancer, while the role of histological grade has not been revealed to be statistically associated with the outcome (table #4).

Table #4. Hazard (mortality) ratio of cervical cancer patients according to age at diagnosis, tumor stage, and histological grade

Predictors	*p-value*	Hazard Ratio (HR)	95.0% CI for HR	
			Lower	Upper
first stage	.000	*referenc*		
second stage	.000	2.863	1.998	4.102
third stage	.000	5.599	3.990	7.856
fourth stage	.000	10.201	7.155	14.544
unknown	.004	2.044	1.251	3.339
age	.000	1.630	1.404	1.891
grade	.125	1.022	.994	1.052

IV. Discussion

A decline in cervical cancer mortality and increase of survival rates have been reported in most European countries over the last decades. However, there are large dissimilarities related to the mortality and survival and their trends between individual countries. These differences are mainly noticeable between EU15 Member States and other European countries. Particularly the lowest rates of deathwere observed in EU15 Member States, while the highest decreases were detected in Central and Eastern Europe (9,10).

One of the most important predictors in cancer survival is the age ofpatients at diagnosis, although the end result depends on a combination of multiple factors. The study conducted by *Castanon A.* et al. in England show that overall and relative survival for cervical cancer detected in younger women aged 20-29 years was correlated to tumor characteristic, such as, stage at diagnosisand it was excellent at 99.8% and 100%, respectively, if cancer has been detected at the stage of IA (2). The study from Japan underlines that the number of elderly patients with gynecological cancer is increasing in accordance with the aging of population. Five-year net survival of cervical cancer patients was higher (54.5%) in the younger age group (75-79 years old), it was medium (40.8%) in the older (80-84 years old) age group and lower (28.2%) in the oldest (85-99 years old) age group (4). The study by *Sutandyo N.* et al. conducted in Indonesia, confirms that advanced cancer stage was significant independent prognostic factor in female patients; this result highlights a crucial role of traditional prognostic factors in survival of elderly cancer patients (7).

Cervical cancer mortality has different tendencies in developedand developing countries. The study from Brazil conducted by *Vergas AC.* et al. demonstrated an increasing trend in cervical cancer mortality for younger womenaged 15 - 24 years, while between 25 - 64 and 65 years or older it remained stable, but high (8). Other investigation from Brazil - a time-series ecological study, in which more than 119,000 deaths due to cervical cancer in women aged 30 to 69 years during the period of 1998 and 2018 have been enrolled, revealed decline of mortality from cervical cancer. In addition, it was observed that death due to cervical cancer was higher among women over 60 years of age (5).

The large differences that exist between high- and low-income countries in terms of cervical cancer mortality and survival can be related to inequalities between countries according to their accessibility to different health care services, such as: cervical screening, HPV vaccination, and to the high-quality treatment of precancerous lesions. In the most EU15 Member countries, the large reduction in mortality occurred after the introduction of organised cervical screening, with the greatest reduction occurring in older women. In the countries where organized screening has not yet been introduced and only opportunistic screening is available, population participation in screening programs is low and mainly depends on people's general education andtheir awareness about the disease. Additional pattern of the target population, which defines their participation in screening programs is the age. For example, a case study from Kenya demonstrated that considerable proportion of young women are unaware of cervical cancer which is associated with a poor screening rates, while the study from Johannesburg shows that women who take up screening are older and more knowledgeable regarding cervical cancer and screening (3, 6). Adjusted multivariable logistic regression analysis performed in Swaziland revealed that women < 30 years of age were less likely to receive a cervical screening compared to women ≥30 years of age. Younger age, lower educational level, and lack of knowledge about disease and screening affected whether women obtained a cervical screening. Finally, several studies are demonstrating low participation of young women in screening programs, on the other hand, the age-specific morbidity and mortality of cervical cancer is highly related to the uptake in cancer screening by target population. This indicates the need for enhancing awareness raising programs for women, especiallyfor younger women, about the importance of cervical examinations (1).

Although cervical cancer screening program was introduced in 2011 in Georgia, the proportion of cancerdetected at early-stagesis still low – it is slightly higher than 50%. It is essential to introduce well-organized screening program for early detection of CC with a high coverage of the women within target population. According to our study results cancer early detection was decreasing gradually with age and it was 56.0%, 52.0%, and 47.7% in patients under 41 years, between 41 and 59 years, and over 60 years old, accordingly; in addition, patients over 41 were more likely to have histologically poorly differentiated tumor (27.1% vs. 23.2%). Furthermore, older age generally is related to a high prevalence of comorbidities, which may increase the risk of early mortality that was detected in our study.Despite the fact that the cancer registry database does not include information about comorbidity and we were unable to analyze this variable, to assess overall outcome of CC in Georgia, high morbidity and mortality of cardio-vascular diseases and diabetes among older women should be taken into consideration.

V. Conclusion

Finally, our study results are in concordance with numerous studies that confirm that the age of patients at the moment of diagnosis is an independent predictor for cervical cancer early mortality. The reasons for the unfavourable cervical cancer prognosis in older patientsthat was detected during statistical analysis might be explained bytumor stage at diagnoses and with dissimilarities in comorbidity between different age groups.

References

[1] Aina IO, Raul SM, Padilla LA, Mthethwa-Hleta S, Preko PO, Jolly PE. **Sociodemographic factors, health seeking behaviors, reproductive history, and knowledge of cervical screening among women in Swaziland**. Infect Agent Cancer. 2020 Mar 5;15:16.

[2] Castanon A, Tataru D, Sasieni P. **Survival from Cervical Cancer Diagnosed Aged 20-29 Years by Age at First Invitation to Screening in England: Population-Based Study**. Cancers (Basel). 2020 Jul 28;12(8):2079.

[3] ChisaleMabotja M, Levin J, Kawonga M. **Beliefs and perceptions regarding cervical cancer and screening associated with Pap smear uptake in Johannesburg: A cross-sectional study**. PLoS One. 2021 Feb 10;16(2): e0246574.

[4] Inoue S, Ito H, Hosono S, Hori M, Matsuda T, Mizuno M, Kato K, Matsuo K. **Net Survival of Elderly Patients with Gynecological Cancer Aged Over 75 Years in 2006-2008**. Asian Pac J Cancer Prev. 2019 Feb 26; 20(2): p. 437-442.

[5] Nascimento SG, Carvalho CPAL, Silva RS, Oliveira CM, Bonfim CV. **Decline of mortality from cervical cancer.** Rev. Bras. Enferm [Internet]. 2018; 71(supl1): p. 585-90.

[6] Ngune I, Kalembo F, Loessl B, Kivuti-Bitok LW. **Biopsychosocial risk factors and knowledge of cervical cancer among young women: A case study from Kenya to inform HPV prevention in Sub-Saharan Africa**. PLoS One. 2020 Aug 20;15(8):e0237745.

[7] Sutandyo N, Kurniawati SA, Siregar NN, Sari NK. **Three Years Survival of Elderly Cancer Patients in Indonesia: Do We Need a Different Approach?** Acta Med Indones. 2020 Jan;52(1), p:39-46.

[8] Vargas AC, Dell Agnolo C, de Melo WA, Pelloso FC, Dos Santos L, Carvalho MDDB, Pelloso SM. **Trends in Cervical Cancer Mortality in Brazilian Women who are Screened and Not Screened.** Asian Pac J Cancer Prev. 2020 Jan 1;21(1) p:55-62.

[9] Wojtyla C, Ciebiera M, Kowalczyk D, Panek G. **Cervical Cancer Mortality in East-Central European Countries.** Int J Environ Res Public Health. 2020 Jun 28;17(13) p:4639.

[10] Wojtyla C, Janik-Koncewicz K, La Vecchia C. **Cervical cancer mortality in young adult European women.** Eur J Cancer. 2020 Feb;126: p.56-64.

[11] World Health Assembly adopts global strategy to accelerate cervical cancer elimination.WHO.www.who.int/news-room/detail/19-08-2020-world-health-assembly-adopts-global-strategy-to-acceleratecervical-cancer-elimination.