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Malignant neoplasms of the vagina: A 30-year review from the Republic of Belarus

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ABSTRACT

Objective: To perform a retrospective review of patients diagnosed with vaginal malignant neoplasms (VMN) in the Republic of Belarus.
Methods: The Belarusian Cancer Registry was reviewed for patients diagnosed with VMN from 1990 to 2019. The data collected included age at diagnosis, demographic information, histology, stage, treatment modalities, and outcomes. Data were compared across decades (1990–1999, 2000–2009, and 2010–2019).
Results: A total of 868 patients were diagnosed with VMN in Belarus between 1990 and 2019. The estimated age-standardized incidence rate of VMN per 100,000 female population increased from 0.1 in 1999 to 0.4 in 2019 ($p < 0.05$). The mortality rate for this period was 0.0–0.2 per 100,000 female population. Of all newly diagnosed cases of VMN, 70.9% ($n = 615$) lived in urban centers and 29.1% (n = 253) lived in rural areas. The most common histological type was squamous cell carcinoma, accounting for 78.4% of cases. The median age at diagnosis was 63.4 years (range, 15.0–87.0 years). When compared across the three decades, the number of stage I cases increased slightly more than twofold (from 19.1% to 38.5% for 1990–1999 to 2010–2019). Furthermore, the number of stage III cases decreased from 30.3% to 13.0% from 1990 to 1999 to 2010–2019. There were no significant changes in the number of patients diagnosed with stage II or IV disease over time. The overall 5-year survival rate for the entire group was 68.7 ± 5.1%, with no statistically significant difference between women living in urban centers vs. rural areas (67.8 ± 5.1% vs. 65.8 ± 10.4%; $p = 0.99$). However, there was a 26.2% increase in the 5-year survival rate for the entire group over the study period. This increase was higher for women living in rural areas (+61.7%) than for those in urban centers (+51.3%); $p > 0.05$. Furthermore, a comparison of 5-year adjusted survival rates between 2000 and 2015 showed increased survival for stages I, II, and III, with the most significant increase noted for stage III disease (2.4-fold increase).
Conclusions: This retrospective study found that the survival rates of women with VMN in Belarus have improved over the past 30 years. This is likely due to improvements in early detection as well as improved approaches to treatment, particularly for those living in rural areas. Additional study is needed to further understand and improve the outcomes of women diagnosed with VMN in Belarus.

1. Introduction

Vaginal malignant neoplasms (VMN) are a rare entity and account for only 1–2% of all cases of cancer of the female reproductive system (Siegel et al., 2016; Eifel et al., 2019; Adams and Cuello, 2018). According to GLOBOCAN 2020, there are approximately 17,908 invasive vaginal cancers diagnosed annually globally with 7995 related deaths (https://gco.iarc.fr/today/data/factsheets/cancers/22-Vagina-fact-sheet.pdf). The global average incidence rate is 0.36 and the mortality rate is 0.16 per 100,000 women. The highest incidence rates of VMN are in African countries (≥0.48 per 100,000 women) and the lowest are in North America (0.29–0.37) and Latin America (0.16–0.29) (https://gco.iarc.fr/today/data/factsheets/cancers/22-Vagina-fact-sheet.pdf). In the European Region, the highest incidence rates are noted in France (0.57)

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and Latvia (0.47), the lowest in the Republic of Belarus (0.27), Sweden (0.26), and Poland (0.20). The highest mortality rates are in African countries (0.38) and the lowest mortality rates are in North America, Europe, and Asia (0.06–0.11). In the Republic of Belarus, it is estimated that 37 women are diagnosed with VMN, and 12 women die of this disease annually (Statistics of oncological diseases in the Republic of Belarus, 2018).

Due to the rarity of this disease, there is a paucity of literature describing the epidemiology and outcomes of vaginal cancer. To better understand this disease, we reviewed and analyzed population-based data on incidence, mortality, and survival rates of VMN from the Belarusian Cancer Registry over a 30-year period (1990–2019).

2. Methods

2.1. Data extraction

Women diagnosed with VMN between 1990 and 2019 were identified through the Belarusian Cancer Registry. The information collected by the registry included demographic characteristics for each patient (age, gender, city of residence), location and histological type of tumor according to the International Classification of Diseases for Oncology [ICD-O] site codes C52 (WHO Library Cataloguing-in-Publication, xxxx), as well as the date of confirmation of the diagnosis.

Survival information was obtained from mortality statistics and active surveillance based on vital status checks from current residence registers. We included only the first primary vaginal lesions to calculate the 5-year relative survival rate. Vaginal neoplasms that were identified solely on the basis of a death certificate or diagnosed at autopsy were excluded from the survival analysis. The vital status of each registered case was confirmed by June 30, 2021.

This study was approved by the Ethics Committee of the NN Alexandrov National Cancer Centre (Protocol No. 17), Minsk, Belarus on 17 January 2020.

2.2. Statistical analysis

Data were summarized using basic descriptive statistics. The main outcome of the studywas survival time. The time period was calculated from the time of diagnosis to death. Survival measures were calculated using the Kaplan–Meier method. Comparison of survival in two groups was performed according to the log rank test, and in groups of three or more using the χ^2 criterion. Differences were considered statistically significant at $p < 0.05$. All p values were two-sided. The calculations were performed using the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows version 23.0, Armonk, NY).

3. Results

In Belarus, 868 new cases of VMN were reported during the 30-year period from 1990 to 2019. In the structure of the incidence of malignant neoplasms among the female population of Belarus for the entire 30-year period, VMN represented 0.1–0.17%. Over the 30-year period, there was an increase in the number of newly diagnosed cases of VMN from 11 cases in 2009 to 37 cases in 2019 (Fig. 1).

The changes of VMN incidence rates in the female population of Belarus over time are shown in Fig. 2. Analysis of these data showed an increase in both the VMN incidence rate and the World standardized indicator (from 0.1 to 0.7 per 100,000 female population, and from 0.1 to 0.4, respectively). However, the age-standardized incidence rate increased more slowly, which reflects a greater impact of demographic changes on the increase in the incidence rate. The number of deaths from VMN had a slight upward trend and varied from 6 to 20 cases per year (Fig. 1). VMN incidence rate was at the level of 0.1–0.4 per 100,000 female population, World standardized 0–0.2.

The median age of patients was 69.0 years (range 40.0–84.0) in 1990, 69.8 (range 30.0–87.0) in 2010, and 62.0 (range 35.0–87.0) in 2019. Fig. 3 shows the age-specific incidence rate of VMN in Belarus for three 5-year periods (1990–1994, 2000–2004, and 2015–2019). Fig. 3 shows a pronounced peak of incidence rate for the age group 70–84 years. An increase in the incidence is noted for women over 50 years old. No change in the incidence peaks was observed during the study period.

The most common histological type identified was squamous cell carcinoma (SCC), ranging from 81.8% in 1990 to 78.4% in 2019 (Fig. 4). Analysis of the distribution by stage showed that the proportion of cases of VMN detected in stage I doubled (from 19.1% to 38.5%), while neoplasms diagnosed in stages II and IV practically did not change, and the frequency of stage III sharply decreased (from 30.3% to 13.0%). In general, the proportion of cases with early stage at diagnosis (I and II) has increased by 37.1% over 10 years, and the proportion of cases with

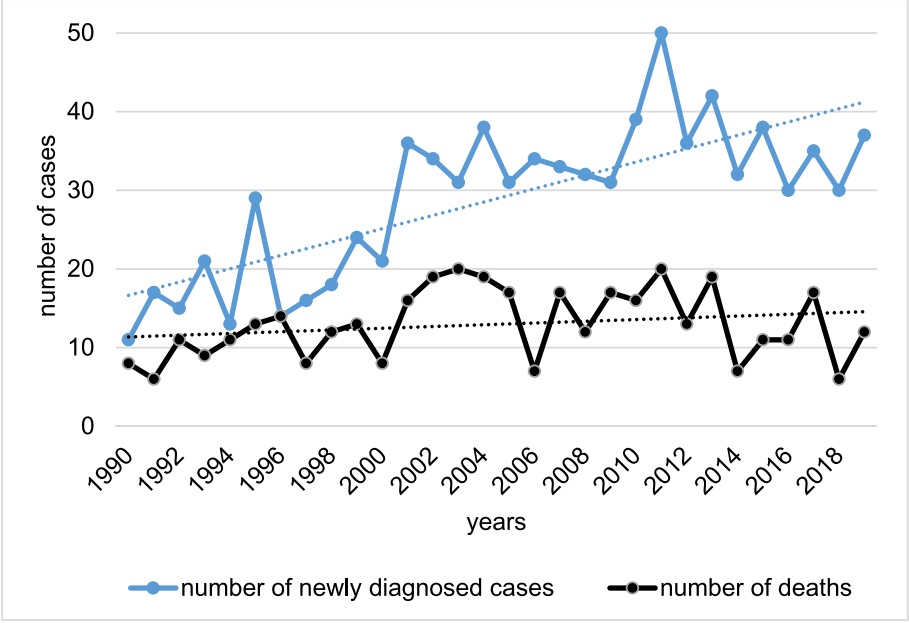

Fig. 1. The number of newly diagnosed cases of VMN and the number of deaths from VMN among women in Belarus for 1990–2019.

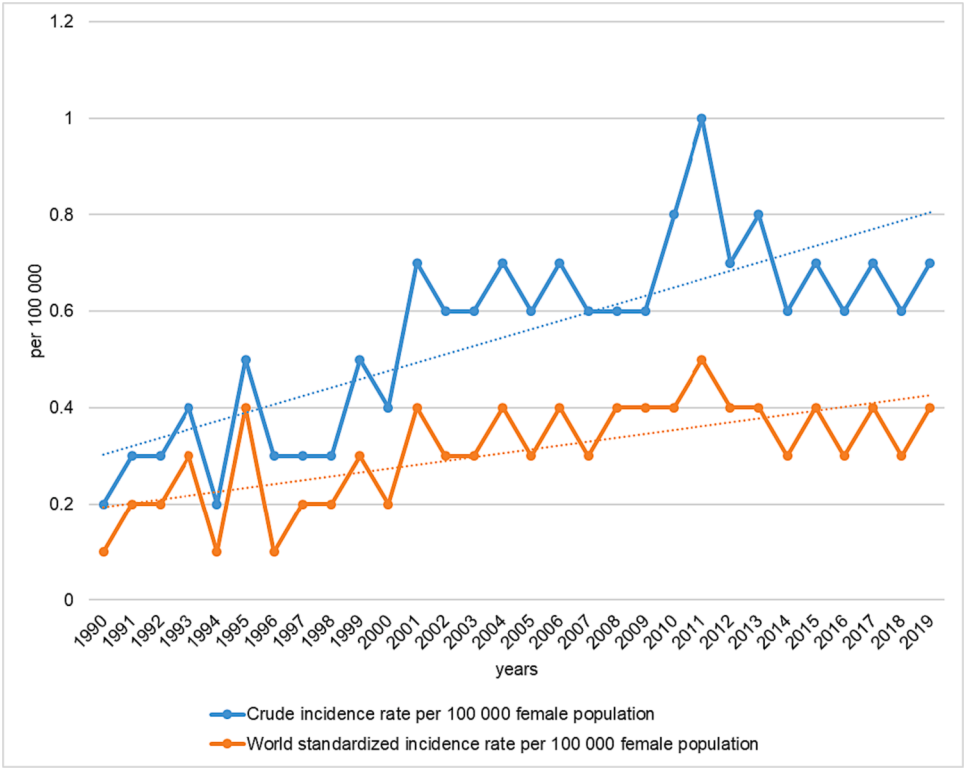

Fig. 2. Dynamics of VMN incidence rate in the female population of Belarus (incidence rate per 100,000 female population, World standardized incidence rate per 100,000 population), 1990–2019.

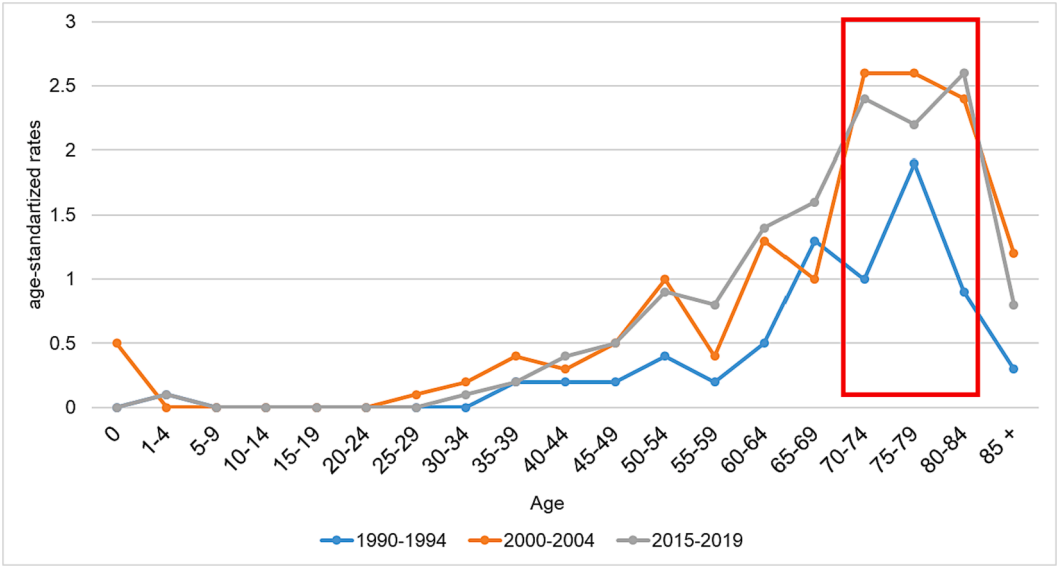

Fig. 3. The age-specific VMN incidence rates in Belarus for three 5-year periods (1990–1994, 2000–2004 and 2015–2019).

late stage at diagnosis (III and IV) has decreased by 60% (Fig. 5).

Analysis of 5-year adjusted survival rate by stage showed that the survival rate of patients with stage I, II, and III disease increased over time, with stage III being the most significant with a 2.4-fold increase. Patients with stage IV did not survive the 5-year milestone; however, over the last 5 years, the survival rate for patients with stage IV was 16.8% (Supplementary Fig. 1). Analysis of the cumulative 5-year adjusted survival rates in patients with VMN showed a significant increase in survival over the observed period. In 1990, the survival rate was 42.5 months ± 8.4, while by 2015, it increased to 68.7 months ± 5.1% ($p = 0.001$) (Supplementary Fig. 2).

3.1. Subgroup analysis

In total, there were 615 (70.9%) patients living in urban centers and 253 (29.1%) living in rural areas. The results of the analysis of the incidence rates of VMN based on residence type showed that the number of cases of newly diagnosed VMN was significantly higher among women living in urban centers. However, the analysis of crude and age-standardized incidence rates, leveling the differences in the number and

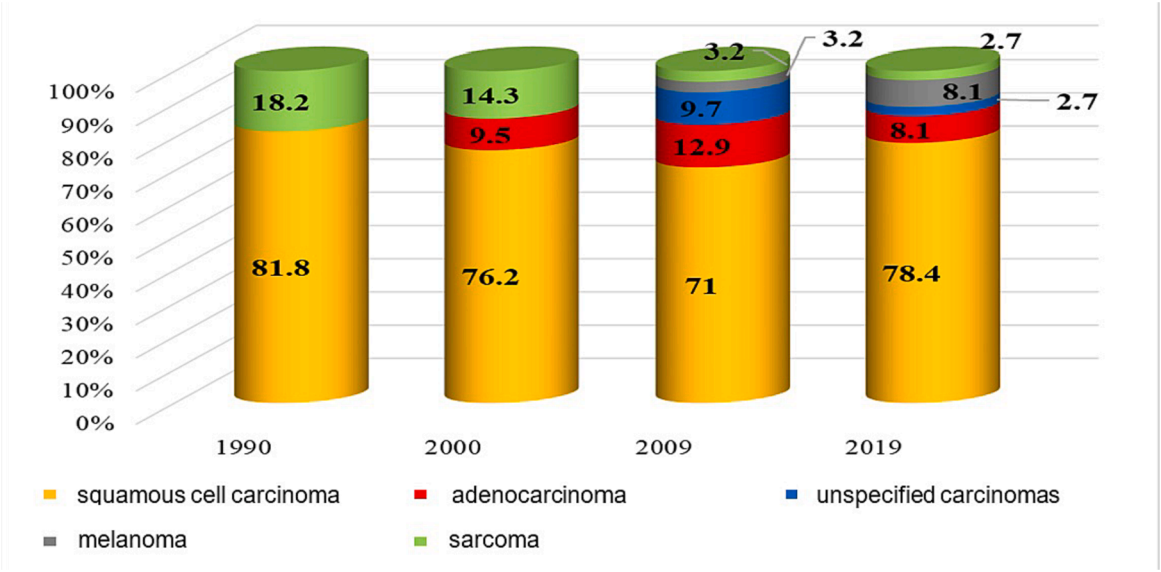

Fig. 4. Distribution of newly diagnosed cases of VMN in Belarus by the tumor histological type (%) for 1990, 2000, 2009, 2019.

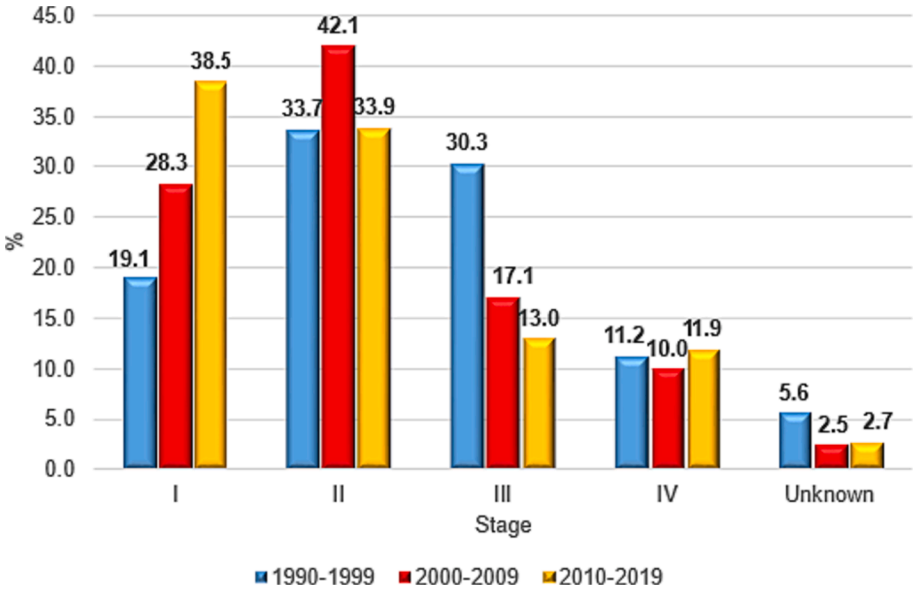

Fig. 5. Distribution of newly diagnosed cases of VMN by stages of the disease (%) for three 10-year periods: 1990–1999, 2000–2009, 2010–2019.

age composition, showed that women living in urban centers and rural areas are diagnosed with VMN with the same frequency (Supplementary Fig. 3).

When the changes over time of stage at diagnosis for three time periods (1990–1999, 2000–2009, and 2010–2019) were compared, we noted that the number of women with stage I disease almost doubled among women living in urban centers (from 21.8% to 38.8%) and almost tripled among women living in rural areas (from 13.6% to 37.4%). There was also an increase in the portion of women with stage IV disease living in urban centers (from 10.9% to 12.9%) and a decrease in the proportion of women with stage IV disease living in rural areas (from 11.9% to 8.8%). There were no significant changes in women with stage II and III disease based on residence type (Supplementary Fig. 4). Analysis of survival in the subgroups of urban and rural residents did not show a difference in 2015–2019 (67.8 ± 5.1% and 65.8 ± 10.4%, respectively, $p = 0.99$), while the increase in survival in comparison with 1990–1994 among rural residents turned out to be more significant than that among urban residents (+51.3% and + 61.7%, respectively, $p > 0.05$).

4. Discussion

Compared with cervical cancer, which is closest in etiology and localization, vaginal cancer is more likely to occur among older women. According to Huang et al. (2020), the median age at diagnosis for invasive cervical cancer was 47 years, whereas the median age for invasive vaginal cancer was 68 years (Huang et al., 2020). In our study, the median age was roughly the same at 69.0 years in 1990, 69.8 in 2010, and 62.0 in 2019, respectively.

SCC, the most common VMN histology, is reported to account for 79–85% of VMN and usually occurs in elderly women, followed by adenocarcinoma (5–14%) and melanoma (1–5%) (William et al., 1998; Tasaka et al., 2017). The most common histology type in our study was SCC, accounting for 81.8% of cases in 1990 and 78.4% in 2019. Similarly to previous reports, we noted that approximately 10% of cases were adenocarcinomas and 8% were melanomas.

The majority of vaginal cancer cases are diagnosed as stage I disease, as has been described previously in the literature (William et al., 1998). It was also found in our study that 38.5% of patients were stage I, occupying the largest proportion in the last study period (2010–2019).

Reports of 5-year survival rates for vaginal cancer vary from 24% to 77.3% but mostly remain low (Lian et al., 2008; Tjalma et al., 2001; Ghia et al., 2011; Trétarre et al., 2023; Banas et al., 2015). Prognosis correlates strongly with disease stage. Five-year survival in larger series ranges from 64% to 84% for stage I, 53 to 75% for stage II, 36 to 46% for stage III, and 3 to 36% for stage IV (Frank et al., 2005; de Crevoisier et al., 2007; Shah et al., 2009). In our study, 5-year adjusted survival rate for all patients in 2015 was 68.7%, in contrast to 1990, when it was 42.5% ($p = 0.001$): 92.0% (stage I), 67.8% (stage II), 62.6% (stage III), and 16.8% (stage IV).

In the United States, the observed associations between urbanicity and breast and cervical cancer incidence are partly mediated by county-level socioeconomic status and the density of primary care providers, both of which tend to be higher in urban areas. The urban/rural differences in cancer incidence can be partly (for breast cancer) or completely (for cervical cancer) explained by these latter variables. The relationships observed for cervical cancer were slightly different from those for breast cancer. The main effect between urbanicity and cancer was reversed: breast cancer incidence was higher, while cervical cancer incidence was lower in urban areas compared with rural areas (Moss et al., 2017). Despite consistently declining mortality rates, both white and black women in nonmetropolitan areas experienced higher mortality risks than their metropolitan counterparts. In both 1969 and 2007, white as well as black women in nonmetropolitan areas had an approximately 24–29% higher cervical cancer mortality than their counterparts in metropolitan areas (Singh, 2012; Toboni et al., 2022).

In our observations throughout three time periods, the detection of VMN as a stage I disease increased from 21.8% to 38.0% in urban residents and from 13.6% to 37.4% in rural residents. This is likely due to cervical cancer screening, close anatomical localization with the cervix, and similar etiology, such as HPV infection.

Throughout the studied time period, greater increase in the incidence of VMN was observed in women living in rural areas than in urban centers. The most likely reason for this is improved access for screening for the patients who reside in rural areas, because in Belarus there have been consistent efforts to strengthen the role of primary care in rural areas over the study period (Toboni et al., 2022; Richardson et al., 2013).

The survival outcomes from our study showed no discrepancies in survival between women living in urban and rural areas. This was also confirmed in our previous study of a single cancer center (Matylevich et al., 2021). In our opinion, this is due to peculiarities of the health care system in Belarus, which is mostly provided through government-owned facilities, allowing citizens universal access to medical care, which is free at the point of use (Richardson et al., 2013). Besides, in Belarus, over the past 30 years, the centralization of oncological care has been maintained, which involves the provision of medical care in specialized oncological hospitals. Technological re-equipment of diagnostic equipment and devices for radiation therapy has occurred, which also, in our opinion, has contributed to an up trend of early-stage diagnoses and improved survival. An additional contribution to improved results may have been the implementation at the state level after the approval by the Ministry of Health in 2007 of algorithms for the diagnosis and treatment of oncological diseases, which became mandatory for use in all oncological institutions and unified the provision of oncological care throughout the country, where concurrent chemotherapy and radiation therapy for vaginal cancer was adopted ((АлгоритМы диагностики и лечения злокачественных новообразований: клинический протокол / Министерство здравоохранения Республики Беларусь. - Минск: «Профессиональные издания», 2019. - 616 с. In Russian.); Matylevich et al., 2016). The possible impact of HPV vaccination in Belarus cannot be traced, since it has not been included in the National Immunization Calendar and is only available for patients with private insurance. According to Trétarre et al., even in countries where it has been introduced, it is still too early to assess its positive impact, since vaginal cancer mainly affects older women and HPV vaccination has only been available since the early 2000s and only targets young girls (Trétarre et al., 2023).

5. Conclusion

Analysis of epidemiological data on vaginal malignant neoplasms in the Republic of Belarus revealed that the incidence rate has increased over the past three decades due to improvement in diagnostic approach and greater accessibility to medical services for the population. Disease-specific survival rate increased in rural and urban populations without significant differences between them, indicating that women throughout Belarus have the same access to diagnostic and medical care regardless of where they live.

Ethic approval

This study was approved by the Ethics Committee of the NN Alexandrov National Cancer Centre (Protocol No. 17), Minsk, Belarus on 17 January 2020.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gore.2023.101309.

References

Adams, T.S., Cuello, M.A., 2018. Cancer of the vagina. Int. J. Gynaecol. Obstet. 143 (Suppl 2), 14–21. https://doi.org/10.1002/ijgo.12610.

Banas, T., Pityński, K., Jach, R., Knafel, A., Ludwin, A., Juszczyk, G., Nieweglowska, D., 2015. Primary Vulvo-vaginal cancers: trends in incidence and mortality in Poland (1999–2012). Gynecol. Obstet. Invest. 80 (4), 240–245. https://doi.org/10.1159/000381770. Epub 2015 Jun 9 PMID: 26065364.

de Crevoisier, R., Sanfilippo, N., Gerbaulet, A., et al., 2007. Exclusive radiotherapy for primary squamous cell carcinoma of the vagina. Radiother. Oncol. 85, 362–370.

Eifel, P., Klopp, A.H., Berek, J.S., Konstantinopoulos, A., 2019. Chapter 74: cancer of the Cervix, Vagina, and Vulva. In: DeVita, V.T., Lawrence, T.S., Rosenberg, S.A. (Eds.), DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology, 11th ed. Lippincott Williams & Wilkins, Philadelphia, Pa, pp. 1171–1210.

Frank, S.J., Jhingran, A., Levenback, C., et al., 2005. Definitive radiation therapy for squamous cell carcinoma of the vagina. Int. J. Radiat. Oncol. Biol. Phys. 62, 138–147. https://doi.org/10.1016/j.ijrobp.2004.09.032.

Ghia, A.J., Gonzalez, V.J., Tward, J.D., et al., 2011. Primary vaginal cancer and chemoradiotherapy: a patterns-of-care analysis. Int. J. Gynecol. Cancer 21, 378–384.

АлгоритМы диагностики и лечения злокачественных новообразований: клинический протокол / Министерство здравоохранения Республики Беларусь. - Минск: «Профессиональные издания», 2019. - 616 с. In Russian.

https://gco.iarc.fr/today/data/factsheets/cancers/22-Vagina-fact-sheet.pdf.

Huang, J., Cai, M., Zhu, Z., 2020. Survival and prognostic factors in primary vaginal cancer: an analysis of 2004–2014 SEER data. Transl. Cancer Res. 9 (11), 7091–7102. https://doi.org/10.21037/tcr-20-1825. PMID: 35117314; PMCID: PMC8798963.

Lian, J., Dundas, G., Carlone, M., et al., 2008. Twenty-year review of radiotherapy for vaginal cancer: an institutional experience. Gynecol. Oncol. 111, 298–306. https://doi.org/10.1016/j.ygyno.2008.07.007.

Matylevich, V., Alimpiyeva, S., Mavrichev, S., 2016. Chapter 47. Belarus In: Klimaszewski, A.D., Bacon, M., Eggert, J.A., Ness, E., Westendorp, J.G., Willenberg, K., (Eds.), Manual or clinical trials nursing, third ed. Oncology Nursing Society Pittsburgh: Pennsylvania, 463-471.

Matylevich, O.P., Trukhan, H.V., Zubets, O.I., Mavrichev, S.A., 2021. Twenty years' experience of primary vaginal cancer treatment at one cancer centre: does residence status matter? Ecancermedicalscience. 15 (15), 1267. https://doi.org/10.3332/ecancer.2021.1267. PMID: 34567252; PMCID: PMC8426020.

Moss, J.L., Liu, B., Feuer, E.J., 2017. Urban/rural differences in breast and cervical cancer incidence: the mediating roles of socioeconomic status and provider density. Womens Health Issues. 27 (6), 683–691. https://doi.org/10.1016/j.whi.2017.09.008.

Richardson, E., Malakhova, I., Novik, I., Famenka, A., 2013. Belarus: health system review. HealthSyst. Transit. 15 (5), 1–118.

Shah, C.A., Goff, B.A., Lowe, K., et al., 2009. Factors affecting risk of mortality in women with vaginal cancer. Obstet. Gynecol. 113, 1038–1045.

Siegel, R.L., Miller, K.D., Jemal, A., 2016. Cancer statistics, 2016. CA Cancer J. Clin. 66 (1), 7–30. https://doi.org/10.3322/caac.21332.

Singh, G.K., 2012. Rural-urban trends and patterns in cervical cancer mortality, incidence, stage, and survival in the United States, 1950–2008. J. Commun. Health 37, 217–223. https://doi.org/10.1007/s10900-011-9439-6.

Statistics of oncological diseases in the Republic of Belarus (2008-2017) / A. E. Okeanov [et al]; ed. by O. G. Sukonko. - Minsk: N.N. Aleksandrov RNPC OMR, 2018. - 286 c. [In Russ].

Tasaka, R., Fukuda, T., Wada, T., et al., 2017. A retrospective clinical analysis of 5 cases of vaginal melanoma. Mol. Clin. Oncol. 6, 373–376. https://doi.org/10.3892/mco.2017.1158.

Tjalma, W.A., Monaghan, J.M., de Barros, L.A., et al., 2001. The role of surgery in invasive squamous carcinoma of the vagina. Gynecol. Oncol. 81, 360–365.

Toboni, M.D., Cohen, A., Gentry, Z.L., et al., 2022. Sociodemographic characteristics and cervical cancer survival in different regions of the United States: a National Cancer Database study. Int. J. Gynecol. Cancer. 32 (6), 724–731. https://doi.org/10.1136/ijgc-2021-003227.

Trétarre, B., Dantony, E., Coureau, G., Defossez, G., Guizard, A.V., Delafosse, P., Daubisse, L., Velten, M., Hammas, K., Barra, S., Lapotre, B., Plouvier, S., d'Almeida, T., Molinié, F., Woronoff, A.S., 2023. Trends in incidence of invasive vaginal cancer in France from 1990 to 2018 and survival of recently diagnosed women - a population-based study. Eur J Obstet Gynecol Reprod Biol. 283 (125–129) https://doi.org/10.1016/j.ejogrb.2023.02.003. Epub 2023 Feb 13. PMID: 36842246.

WHO Library Cataloguing-in-Publication Data. International classification of diseases for oncology (ICD-O) – 3rd edition, 1st revision. 1.Neoplams - classification. I.World Health Organization. II.ICD-O.

William, T.C., Phillips, J.L., Menck, H.R., 1998. The national cancer data base report on cancer of the vagina. Am. Cancer Soc. 83, 1033–1040.