3.1.6. Oncology, radiation therapy, 3.1.15. Cardiovascular surgery, 3.1.7. Dentistry, 3.1.2. Maxillofacial surgery /
3.1.6. Онкология, лучевая терапия, 3.1.15. Сердечно-сосудистая хирургия, 3.1.7. Стоматология, 3.1.2. Челюстно-лицевая хирургия

Multidimensional Determinants of Cardiovascular Mortality in Tongue Cancer Survivors: A Population - Based Cohort Study Leveraging SEER Data

Xinyi Yang [1], I.V. Reshetov [1], M.G. Poltavskaya [1], Y.S. Agakina [1],
N.P. Loginova [2], A.E. Kiseleva [1]

[1]Sechenov First Moscow State Medical University (Sechenov University), Ministry of Health of the Russian Federation, Moscow, Russia
[2]Federal Scientific and Clinical Center for Specialized Medical Care and Medical Technologies, Federal Medical-Biological Agency, Moscow, Russia
Contacts: Xinyi Yang – e-mail: yangxinyi0125@gmail.com

Многомерные детерминанты смертности в результате сердечно-сосудистых заболеваний у пациентов, переживших рак языка: популяционное когортное исследование на базе данных SEER

Ян Синьи [1], И.В. Решетов [1], М.Г. Полтавская [1], Ю.С. Агакина [1],
Н.П. Логинова [2], А.Э. Киселева [1]

[1]ФГАОУ ВО Первый Московский государственный медицинский университет имени И. М. Сеченова Министерства здравоохранения Российской Федерации (Сеченовский Университет), Москва, Россия
[2]ФГБУ «Федеральный научно-клинический центр специализированных видов медицинской помощи и медицинских технологий» Федерального медико-биологического агентства, Москва, Россия
Контакты: Синьи Ян – e-mail: yangxinyi0125@gmail.com

舌癌幸存者心血管疾病死亡率的多维决定因素：基于SEER数据库的人群队列研究

Xinyi Yang [1], I.V. Reshetov [1], M.G. Poltavskaya [1], Y.S. Agakina [1],
N.P. Loginova [2], A.E. Kiseleva [1]

[1]俄罗斯联邦卫生部莫斯科国立第一医科大学（谢切诺夫大学），俄罗斯莫斯科
[2]联邦医疗生物署“联邦专业医疗类型和医疗技术科学临床中心”联邦国家预算机构，俄罗斯莫斯科
联系方式：Yang Xinyi 邮箱：yangxinyi0125@gmail.com

Background. Tongue cancer (TC) is a prevalent head and neck malignancy with significant morbidity and mortality. Epidemiological studies indicate that mortality causes in TC patients shift over time: cancer-related deaths dominate early stages, while long-term survivors face increasing non-cancer mortality, primarily cardiovascular disease (CVD). Treatment modalities such as radiotherapy (RT) and chemotherapy may exacerbate CVD risks, compounded by sociodemographic and tumor-related heterogeneity.

Objective. This study aimed to quantify CVD-related mortality risk in TC survivors, identify high-risk subgroups, and explore multidimensional determinants using population-level data.

Methods. A retrospective cohort study was conducted using the Surveillance, Epidemiology, and End Results (SEER) database (2000–2021). A total of 7,691 TC patients were included after applying exclusion criteria.Standardized mortality ratios (SMRs) and excess risks were calculated by comparing observed CVD deaths to expected rates in age-, sex-, and race-matched general populations. Nelson-Aalen cumulative hazard curves and Poisson regression were employed for risk stratification.

Results. CVD-related mortality in TC survivors was significantly elevated (SMR = 3.16, 95% CI: 3.15–3.17), with pronounced heterogeneity across subgroups. Radiotherapy-exposed patients (SMR = 11.48), those with distant metastases (SMR = 7.05), and socially vulnerable populations – Black individuals (SMR =5.76) and widowed/separated patients (SMR = 15.92–16.18) – faced the highest risks. Ischemic heart disease dominated CVD deaths (42.9%, SMR =15.61), followed by cerebrovascular diseases (17.3%, SMR = 13.69). Non-chemotherapy patients exhibited elevated risks (SMR = 7.33), potentially due to comorbidities or unmeasured treatment interactions.

Conclusion. TC survivors face a substantially increased CVD mortality burden, driven by treatment toxicity, tumor biology, and sociodemographic disparities. Integrating cardiovascular surveillance into survivorship care is critical, particularly for irradiated patients and socially vulnerable groups. Future research should prioritize mechanistic studies, risk prediction models, and equity-focused interventions to mitigate dual cancer-CVD burdens.

Key words: TC SEER Cardiovascular Disease

Conflict of interest. The authors declare that there is no conflict of interest.

Funding. The study has not received any funding.

For citation: Xinyi Yang, Reshetov I.V., Poltavskaya M.G., Agakina Y.S., Loginova N.P., Kiseleva A.E. Multidimensional Determinants of Cardiovascular Mortality in Tongue Cancer Survivors: A Population - Based Cohort Study Leveraging SEER Data. Head and neck. Head and Neck. Russian Journal. 2025;13(4):27–35

Doi: 10.25792/HN.2025.13.4.27-35

The authors are responsible for the originality of the data presented and the possibility of publishing illustrative material – tables, drawings, photographs of patients.

Введение. Рак языка (РЯ) является распространенной злокачественной опухолью головы и шеи с высокой заболеваемостью и смертностью. Эпидемиологические исследования показывают, что структура причин смерти у пациентов с РЯ изменяется со временем: в ранние сроки преобладает смертность по причине онкологического заболевания, тогда как у долгожителей возрастает доля причин не связанных с онкологическим заболеванием, в первую очередь сердечно-сосудистых заболеваний (ССЗ). Лечебные подходы, такие как лучевая и химиотерапия, могут дополнительно увеличивать сердечно-сосудистые риски.

Цель. Определить риск смертности от сердечно-сосудистых заболеваний у пациентов, переживших рак языка, выявить группы высокого риска и проанализировать многомерные детерминанты на популяционном уровне.

Материалы и методы. Проведено ретроспективное когортное исследование на основе базы SEER (2000–2021 гг.). В анализ включено 7691 пациент с РЯ после применения критериев исключения. Стандартизованные коэффициенты смертности (SMR) и избыточный риск определялись путем сравнения наблюдаемой смертности от ССЗ с ожидаемой в сопоставимых по возрасту, полу и расе группах населения. Для стратификации риска использовали кривые накопленного риска Нельсона—Алена и пуассоновскую регрессию.

Результаты. Риск смертности от ССЗ у пациентов с РЯ был существенно выше (SMR = 3,16; 95% ДИ: 3,15–3,17), с выраженной гетерогенностью между подгруппами. Наивысший риск зафиксирован у пациентов, подвергшихся лучевой терапии (SMR = 11,48), с отдалёнными метастазами (SMR = 7,05), а также среди социально уязвимых групп — афроамериканцев (SMR = 5,76) и вдов/разведённых (SMR = 15,92–16,18). Основной причиной ССЗ стала ишемическая болезнь сердца (42,9%, SMR = 15,61), далее следовали цереброваскулярные заболевания (17,3%, SMR = 13,69). У пациентов, не получавших химиотерапию, также отмечен повышенный риск (SMR = 7,33), что может быть связано с сопутствующей патологией либо не описанными методами лечения.

Заключение. Выжившие после рака языка имеют значительно повышенное бремя смертности от сердечно-сосудистых заболеваний, обусловленное токсичностью терапии, особенностями опухоли и социально-демографическими неравенствами. Необходима интеграция сердечно-сосудистого мониторинга в наблюдение за такими пациентами, особенно после лучевой терапии и в группах с социальной уязвимостью. Дальнейшие исследования должны быть направлены на механистические аспекты, создание прогностических моделей риска и разработку интервенций, ориентированных на уменьшение двойного бремени онкологических и сердечно-сосудистых заболеваний.

Ключевые слова: рак языка; SEER (Surveillance, Epidemiology, and End Results); сердечно-сосудистые заболевания (ССЗ)

Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.

Финансирование. Работа выполнена без спонсорской поддержки.

Для цитирования: Синьи Ян, Решетов И.В., Полтавская М.Г., Агакина Ю.С., Логинова Н.П., Киселева А.Э. Многомерные детерминанты смертности в результате сердечно-сосудистых заболеваний у пациентов, переживших рак языка: популяционное когортное исследование на базе данных SEER. Head and neck. Голова и шея. Российский журнал. 2025;13(4):27–35

Doi: 10.25792/HN.2025.13.4.27-35

Авторы несут ответственность за оригинальность представленных данных и возможность публикации иллюстративного материала – таблиц, рисунков, фотографий пациентов.

引言：舌癌是一种常见的头颈部恶性肿瘤，具有高发病率和高死亡率的特点。流行病学研究表明，舌癌患者的死因结构随时间而变化：早期以癌症相关死亡为主，而在长期生存者中，非癌症相关死因的比例增加，其中首要的是心血管疾病。放射治疗和化学治疗等治疗方式可能进一步增加心血管风险。

目的：确定舌癌幸存者心血管疾病死亡风险，识别高风险人群，并在人群水平上分析其多维决定因素

材料与方法：基于SEER数据库（2000−2021年）进行了一项回顾性队列研究。应用排除标准后，共纳入7691例舌癌患者进行分析。通过比较观察到的死亡率与年龄、性别和种族匹配人群中的预期死亡率，计算了标准化死亡率（SMR）和超额风险。使用Nelson–Aalen累积风险曲线和泊松回归进行风险分层。

结果：合并心血管疾病的舌癌患者的死亡风险显著升高（SMR = 3.16; 95% CI: 3.15—3.17），且各亚组间存在明显的异质性。最高风险见于接受过放射治疗的患者（SMR = 11.48）、存在远处转移的患者（SMR = 7.05），以及社会弱势群体—非裔美国人（SMR = 5.76）和丧偶/离异人群（SMR = 15.92—16.18）。其主要死因是缺血性心脏病（42.9%, SMR = 15.61），其次是脑血管疾病（17.3%, SMR = 13.69）。未接受化疗的患者也观察到风险升高（SMR = 7.33），这可能与合并症或未记录的治疗方法有关。

结论：舌癌幸存者面临着显著升高的心血管疾病死亡负担，这归因于治疗的毒性、肿瘤特征以及社会人口学不平等。有必要将心血管监测整合到此类患者的随访中，特别是在放射治疗后和社会弱势群体中。未来的研究应关注机制方面、建立风险预测模型以及制定旨在减轻癌症和心血管疾病双重负担的干预措施。

关键词：舌癌；SEER（监测、流行病学和最终结果数据库）；心血管疾病

利益冲突声明: 作者声明不存在利益冲突。 资助声明: 本研究由作者团队资助。

引用格式: **Xinyi Yang, Reshetov I.V., Poltavskaya M.G., Agakina Y.S., Loginova N.P., Kiseleva A.E. Multidimensional Determinants of Cardiovascular Mortality in Tongue Cancer Survivors: A Population-Based Cohort Study Leveraging SEER Data. Head and neck. Russian Journal. 2025;13(4):27–35**

Doi: 10.25792/HN.2025.13.4.27-35

作者声明：作者对所提供数据的原创性及插图（表格、图片、患者照片）的发表合法性负责。

Background

TC (TC) is one of the most common head and neck malignancies globally, with significant morbidity and mortality rates [1, 2]. Epidemiological studies indicate that causes of death in TC patients exhibit distinct time-dependent patterns: cancer-related deaths dominate during early follow-up periods, while long-term survivors face a gradual shift in mortality risk toward non-cancer factors, particularly cardiovascular disease (CVD) [3,4]. Treatment modalities, including surgery, radiotherapy, and chemotherapy, may substantially elevate non-cancer mortality risks due to treatment-related toxicities. Additionally, TC mortality risk demonstrates marked heterogeneity influenced by multidimensional factors such as age, race, marital status, and tumor stage [5].

Despite advancements in therapeutic strategies and improved prognoses, TC patients remain at high risk of mortality, especially from CVD, which significantly exceeds rates observed in the general population. This study aimed to comprehensively analyze mortality patterns and associated risk factors in TC patients, with a focus on the incidence and determinants of CVD-related deaths [6,7,8].

The Surveillance, Epidemiology, and End Results (SEER) database, a publicly accessible cancer registry encompassing over 8 million cancer cases across multiple U.S. states, was utilized for this study. Renowned for its large sample size and comprehensive follow-up information, the SEER database has been widely employed to investigate cancer incidence, prognosis, and mortality risks, including assessments for colorectal and breast cancers [9,10]. Leveraging this population-based cohort, we systematically evaluated mortality risks in TC patients, emphasizing the characteristics of CVD-related deaths and high-risk subgroups to provide robust evidence for clinical practice.

Materials and methods

This study extracted data from the Surveillance, Epidemiology, and End Results (SEER) database for all TC patients diagnosed between January 1, 2000, and December 31, 2021. For comparison, general population mortality data from the same period (2000–2021) were obtained from the National Center for Health Statistics (NCHS) [11]. A total of 10,728 patients diagnosed with TC were initially identified. Inclusion criteria required histologically confirmed tongue malignancies, while exclusion criteria removed patients who received no antitumor therapy, those with secondary or multiple primary tumors, and cases with incomplete diagnostic/survival information or tumors identified solely via death certificates. After applying these criteria, 7,691 eligible patients were included, of whom 492 died from cardiovascular disease (CVD) [12]. CVD-related deaths, defined by SEER codes for six conditions – (1) cerebrovascular diseases, (2) diseases of arteries/arterioles/capillaries, (3) hypertension, (4) ischemic heart disease, (5) pulmonary heart disease, and (6) other/unspecified circulatory disorders – served as the primary endpoint. Competing risks included TC-related deaths, deaths from metastatic complications, and non-CVD/non-cancer deaths. This retrospective study utilized de-identified clinical data and adhered to SEER ethical guidelines, exempting informed consent.

This multicenter retrospective cohort study analyzed demographic and clinical variables: age at diagnosis, race, sex, diagnosis year, histological type, tumor stage, radiotherapy/chemotherapy status, marital status, median household income, and follow-up information (survival time and cause of death). Causes of death were categorized as: (1) TC-related, (2) metastatic/complication-related, (3) CVD-related, or (4) other non-cancer causes. CVD-related deaths were specifically coded using SEER-defined terms: hypertensive disease, ischemic heart disease, cerebrovascular diseases, pulmonary heart disease, diseases of arteries/arterioles/capillaries, and other/unspecified circulatory system disorders [13].

The primary outcome was CVD-related death. Patients not deceased due to CVD at the last follow-up were censored. Follow-up duration was calculated from the date of diagnosis to death or censoring. Survival times recorded as 0 months were converted to 0.5 months per epidemiological conventions.

Statistical Analysis

CVD mortality rates were calculated by dividing CVD-related deaths by the total number of TC patients. Standardized mortality ratios (SMRs) were derived by comparing observed CVD deaths in TC subgroups to expected deaths in age-, sex-, and race-matched general populations (reference data from the National Cancer

Institute). Poisson regression was used to estimate 95% confidence intervals (CIs) for SMRs. Excess risk was defined as:

Nelson-Aalen cumulative hazard curves were plotted to assess temporal trends in CVD-related mortality across subgroups. Statistical significance was set at p<0.05p<0.05. Analyses were performed using SEER*STAT, Python, and Microsoft Excel 2019.

Results

The study included 7,691 eligible TC patients with a mean age of 62.83 years and a median follow-up duration of 38 months. The majority of patients were aged 40–59 years (35.3%), White (n=6,252, 81.2%), male (n=4,333, 56.3%), married (n=4,249, 55.24%), and had localized tumor invasion (n=4,866, 63.26%). Median household income exceeded $70,000 in 79.88% of cases. Histologically, squamous cell carcinoma predominated (n=7,561, 98.3%), while other pathological types accounted for 1.69% (n=130). Radiotherapy and chemotherapy were administered to 27.42% (n=2,109) and 17.38% (n=1,331) of patients, respectively.

Overall survival analysis revealed significant time-dependent patterns in all-cause mortality. Among 3,761 deaths during follow-up, mortality peaked in early follow-up periods: 34.69% (n=1,305) occurred within <1 year, followed by 33.98% (n=1,278) in the 1–3 year interval. A dynamic shift in causes of death was observed: cancer-related deaths declined from 56.8% in the <1-year period to 15.3% in the >10-year period (χ^2 trend test, p<0.001), while non-cancer-related deaths increased from 41.9% to 80.2%, indicating a transition toward non-oncological mortality risks in long-term survivors (Figure 1). Among non-cancer deaths, cardiovascular disease (CVD) was the leading cause (n=491, 13.06%), with significant heterogeneity in CVD subtypes (p<0.05): ischemic heart disease predominated (42.9%), followed by other/unspecified circulatory disorders (23.6%), cerebrovascular diseases (17.3%), hypertensive disease (10.7%), and pulmonary heart disease/arterial disorders (2.6% each).

A total of 491 TC patients died from cardiovascular disease (CVD). Compared to an age-, sex-, and race-matched general population cohort (expected deaths = 155.2), the standardized mortality ratio (SMR) was 3.16 (95% CI: 3.15–3.17, p<0.0001), with an excess risk of 335.8 per 10,000 person-years. Baseline characteristics and subgroup-specific SMRs are detailed in Table 1.

This study demonstrates that CVD-related mortality risk in TC patients is significantly elevated compared to the general population (overall SMR = 3.16, 95% CI: 3.15–3.17), with marked heterogeneity across demographic and clinical subgroups. Age exhibited a nonlinear inverse association with SMR: middle-aged to older patients (60–69 years: SMR = 3.55; 70–79 years: SMR = 3.59) had the highest risks, whereas younger (15–39 years: SMR = 1.08) and elderly (⩾80 years: SMR = 2.95) patients showed lower risks (all p<0.05). Racial disparities were pronounced, with Black patients facing the highest risk (SMR = 5.76, 95% CI: 4.00–8.10), followed by Asian or Pacific Islander patients (SMR = 5.51, 95% CI: 4.19–7.25). Social support deficits further amplified risk, as separated patients exhibited an exceptionally high SMR of 16.18 (p<0.05). Tumor-related factors also influenced outcomes: distant metastases (SMR = 7.05, 95% CI: 4.61–10.36) and radiotherapy exposure (SMR = 11.48 vs. 2.03 in non-irradiated patients) were associated with substantially elevated CVD mortality.

Ischemic heart disease was the leading cause of cardiovascular disease (CVD)-related deaths, accounting for 42.9% of CVD mortality (Standardized Mortality Ratio [SMR] = 15.61, 95% CI: 13.46–18.00).

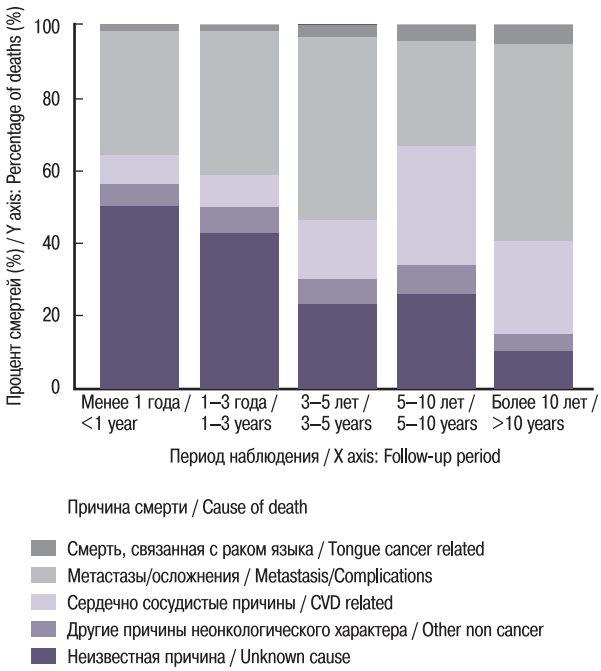

Рис. 1. Доля причин смерти у пациентов с раком языка по периодам наблюдения

Fig. 1. Proportion of causes of death in tongue cancer patients by follow up period

Other CVD subtypes also exhibited significantly elevated risks: cerebrovascular diseases (17.3% of CVD deaths, SMR = 13.69), other/unspecified circulatory disorders (23.6%, SMR = 13.52), and hypertensive disease (10.7%, SMR = 11.25) (all P<0.05). Notably, despite fewer deaths from pulmonary heart disease (SMR = 13.68) and diseases of arteries/capillaries (SMR = 12.50), their risks remained significantly higher than those in the general population (P<0.05).

Figure 2 displays Nelson-Aalen cumulative hazard curves for cardiovascular disease (CVD)-related mortality in TC patients, stratified by subgroups including age, race, sex, marital status, household income, tumor stage, radiotherapy, and chemotherapy. The analysis demonstrates that cumulative CVD mortality risks significantly increased with prolonged follow-up in high-risk subgroups, such as older patients (e.g., ⩾70 years), those with distant metastases, individuals receiving radiotherapy, Black and Asian/Pacific Islander populations, and widowed or separated patients. Key determinants of elevated CVD mortality included advanced tumor stage (e.g., distant metastasis: SMR = 7.05), treatment modalities (e.g., radiotherapy: SMR = 11.48), race (e.g., Black patients: SMR = 5.76), marital status (e.g., separated individuals: SMR = 16.18), and older age (60–79 years: SMR = 3.55–3.59). These factors exhibited strong associations with CVD-related mortality (P<0.05 for all), underscoring the multifactorial nature of cardiovascular risk in this population.

Discussion

TC is one of the most common head and neck malignancies worldwide, with significant prognostic disparities across disease stages. Advanced-stage patients exhibit substantially lower survival rates compared to early-stage counterparts. While advancements

Таблица 1. Риск смерти от сердечнососудистых заболеваний у пациентов с раком языка в разрезе демографических и опухолевых характеристик
Table 1:The cardiovascular disease (CVD) mortality risk among TC patients stratified by demographics and tumor characteristics

		Наблюдаемые смерти от ССЗ/ *Observed CVD deaths*	Ожидаемые смерти/ *Expected deaths*	СМР/ *SMR*	95%ДИ /*95%CI*	Р-значение/ *P-value*	Избыточный риск/ *Excess Risk*	Всего случаев / *Total cases*	Общие персоны-годы выживания/ *Total person-years of survival*
		491	155.2	3.16	3.15-3.17	P< 0.0001	335.8	7691	45459.25
Возраст/ *Age*	15-39	2	1.85	1.08	0.13-3.92	P>0.05	0.31	490	3712.25
	40-59	78	38.01	2.05	1.60,2.51	P<0.05	14.73	2716	19007.58
	60-69	103	28.98	3.55	2.87,4.24	P<0.05	36.64	2023	12073.33
	70-79	155	43.21	3.59	3.02,4.15	P<0.05	77.78	1440	7202.00
	80+	153	51.91	2.95	2.48,3.41	P<0.05	98.99	1021	3460.42
Пол/*Sex*	Мужкой/*male*	308	62.87	4.90	4.38-5.48	P<0.05	56.57	4333	25146.42
	Женский/*female*	183	36.56	5.01	4.33-5.78	P<0.05	43.61	3358	20312.83
Раса/*Race*	Белые/*White*	403	82.72	4.87	4.42-5.37	P<0.05	51.17	6252	37599.42
	Черные/*Black*	33	5.73	5.76	4.00-8.10	P<0.05	80.12	341	1432.08
	Азиаты или уроженцы тихоокеанских островов/*Asian or Pacific Islander*	51	9.25	5.51	4.19- 7.25	P<0.05	39.81	1050	6167.67
	Американские индейцы/коренные жители Аляски/ *American Indian/ Alaska Native*	4	0.91	4.40	1.20-11.30	P<0.05	67.39	46	260.08
Семейное положение/*Marital Status*	Разведены/*Divorced*	55	8.79	6.26	4.74-8.23	P<0.05	53.97	854	4624.17
	Состоит в браке/ *Married*	228	41.37	5.51	4.83-6.27	P<0.05	43.94	4249	27580.88
	В раздельном проживании/*Separated*	11	0.68	16.18		P<0.05	119.77	86	379.75
	Не состоит в браке/ *Single*	72	14.77	4.87	3.84-6.06	P<0.05	36.47	1568	8951.25
	Вдовец/вдова/ *Widowed*	125	7.85	15.92	13.27-18.96	P<0.05	125.37	934	3924.00
Стадия опухоли / *Tumor stage*	Только локализованная/*Localized only*	345	61.81	5.58	5.02-6.20	P<0.05	58.19	4866	34338.08
	Отдалённые очаги и/или лимфоузлы вовлечены/*Distant site(s)/node(s) involved*	26	3.69	7.05	4.61-10.36	P<0.05	36.57	610	1677.25
	Регионарное поражение только прямым распространением/ *Regional by direct extension only*	24	3.76	6.38	4.10-9.51	P<0.05	62.63	322	1505.42
	Регионарное поражение с прямым распространением и поражением лимфатических узлов/*Regional by both direct extension and lymph node involvement*	20	3.16	6.33	3.87-9.78	P<0.05	46.89	360	1052.33
	Поражены только регионарные лимфатические узлы/ *Regional lymph nodes involved only*	66	21.58	3.06	2.39-3.85	P<0.05	34.38	1291	6165.92
	Неизвестно/не стадировано/не уточнено/данные из свидетельства о смерти (DCO)/ *Unknown/unstaged/ unspecified/DCO*	10	1.44	6.94	3.33-12.77	P<0.05	35.54	242	720.25
Лучевая терапия/ *Radiotherapy*	Да/*Yes*	387	33.72	11.48	10.36-12.71	P<0.05	411.92	858	11238.58
	Нет/*No*	104	51.29	2.03	1.66-2.47	P<0.05	1.54	433	34193.75
Химиотерапия/ *Chemotherapy*	Да/*Yes*	54	17.20	3.14	2.37-4.12	P<0.05	66.67	552	5734.75
	Нет/*No*	437	59.60	7.33	6.66-8.06	P<0.05	511.91	739	39734.5

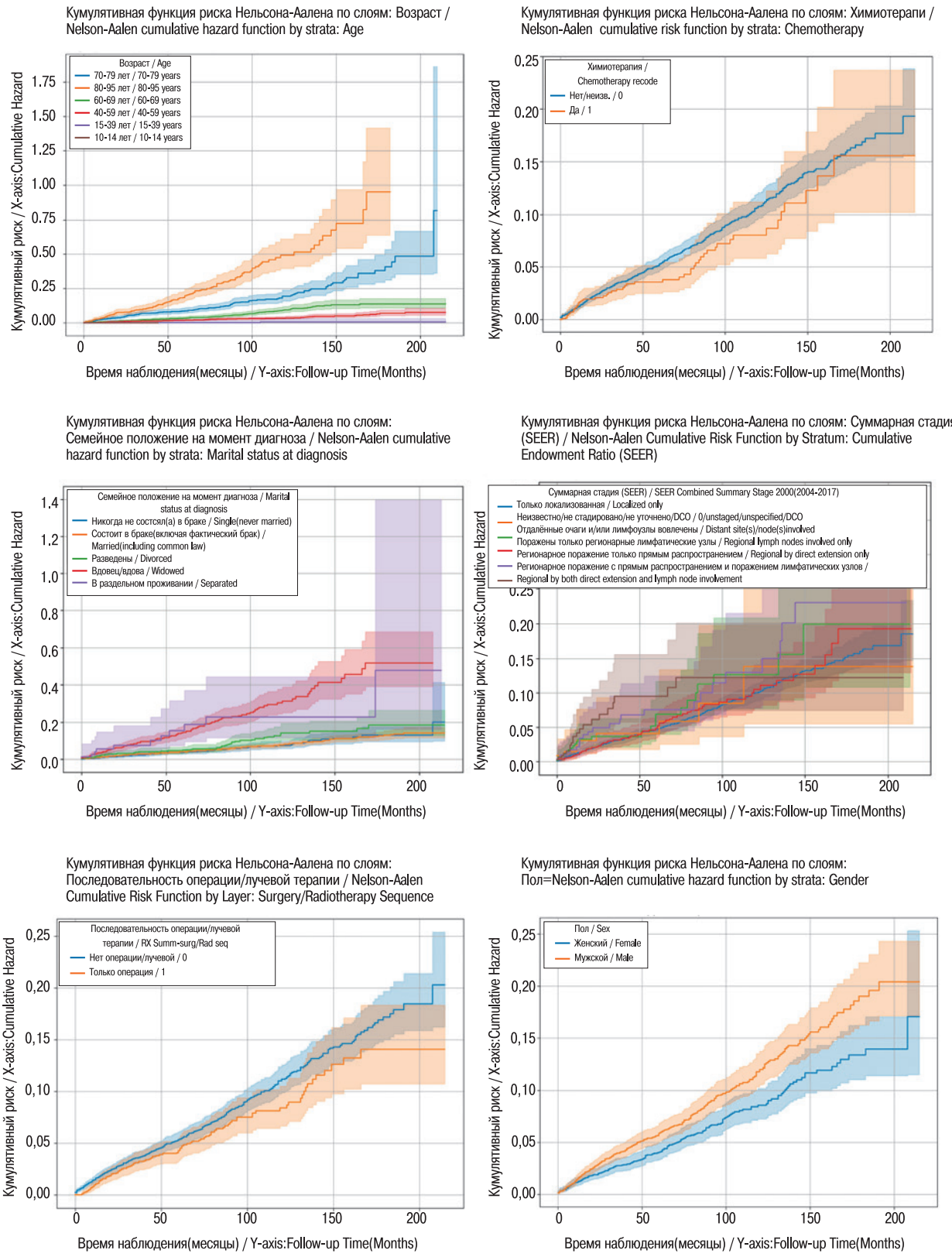

Рисунок 2. Кумулятивные кривые риска Нельсона–Аалена для смертности от сердечно сосудистых заболеваний у пациентов с раком языка

Figure 2. Nelson-Aalen Cumulative Hazard Curves for CVD-Related Mortality in TC Patients

Таблица 2. Риск смерти от различных типов ССЗ у пациентов с раком языка
Table2:The mortality risk of different types of CVD among TC patients

Показатель / *Indicator*	Наблюдаемые смерти от ССЗ / *Observed CVD deaths*	Ожидаемые смерти / *Expected deaths*	СМР / *SMR*	95% ДИ / *95% CI*	Рзначение / *Pvalue*	Избыточный риск / *Excess Risk*	Персоныгоды выживания, связанные со смертностью от ССЗ / *Total personyears of survival related to CVD mortality*
Итого / *Total*	491	155.2	3.16	3.15–3.17	P<0.05	335.8	1432.26
Ишемическая болезнь сердца / *Ischemic heart disease*	211	13.52	15.61	13.46–18.00	P<0.05	197.48	901.42
Заболевания артерий, артериол и капилляров / *Diseases of arteries, arterioles and capillaries*	13	1.04	12.50	7.14–21.87	P<0.05	11.96	69.42
Цереброваскулярные заболевания / *Cerebrovascular diseases*	85	6.21	13.69	11.09–16.87	P<0.05	78.79	413.92
Легочное сердце / *Pulmonary heart disease*	13	0.95	13.68	7.82–23.91	P<0.05	12.05	63.00
Гипертоническая болезнь / *Hypertensive disease*	53	4.71	11.25	8.65–14.63	P<0.05	48.29	314.00
Прочие и неуточненные заболевания системы кровообращения / *Other and unspecified disorders of the circulatory system*	116	8.58	13.52	11.34–16.08	P<0.05	107.42	571.92

in multimodal therapies – including surgery, radiotherapy, and chemotherapy – have modestly improved outcomes for advanced TC, overall prognosis remains suboptimal. Despite extensive research on treatment strategies and long-term survival in advanced disease, studies focusing on mortality risk determinants, particularly non-cancer causes such as cardiovascular disease (CVD), remain limited.

This study systematically evaluated CVD-related mortality risk in TC patients using the SEER database, revealing a significantly elevated standardized mortality ratio (SMR = 3.16, 95% CI: 3.15–3.17) compared to the general population, with marked multidimensional heterogeneity. First, age emerged as a critical determinant: middle-aged to older patients (60–79 years) faced the highest risk (SMR = 3.55–3.59), whereas younger (15–39 years, SMR = 1.08) and elderly (⩾80 years, SMR = 2.95) patients exhibited lower risks. This pattern may reflect age-related declines in baseline cardiovascular health and cumulative treatment toxicities. Second, tumor stage strongly influenced outcomes: distant metastases conferred the highest cumulative risk (SMR = 7.05), followed by locally advanced disease with nodal involvement, while localized tumors carried the lowest risk. These findings suggest that tumor burden exacerbates cardiovascular injury, potentially through systemic inflammation or metabolic dysregulation [14].

The impact of treatment modalities on cardiovascular disease (CVD) mortality risk is significant. Patients who underwent radiotherapy exhibited a substantially higher risk of CVD-related mortality compared to those who did not receive radiotherapy (SMR = 11.48 vs. 2.03). Similarly, patients who did not undergo chemotherapy also demonstrated a higher risk (SMR = 7.33). This finding may appear to deviate from general medical logic and could be attributed to several factors. Prior to initiating antitumor treatments, patients' cardiovascular health is thoroughly evaluated, and only those with relatively better cardiovascular conditions are deemed eligible for chemotherapy. Consequently, chemotherapy patients tend to benefit from longer survival times, which are closely associated with an increased likelihood of CVD-related mortality [15,16]. The chemotherapy regimens commonly used for tongue cancer patients include platinum-based agents and taxanes, both of which exert multifaceted effects on the cardiovascular system. Platinum-based chemotherapeutic agents (e.g., cisplatin, carboplatin, oxaliplatin) are widely utilized for their broad-spectrum antitumor efficacy, including the treatment of head and neck cancers, lung cancer, and breast cancer [17]. These agents interact with DNA, inducing cross-linking, disrupting DNA function, and ultimately leading to apoptosis. In a study of testicular cancer survivors, 53% of patients treated with cisplatin developed hypertension, with an incidence rate 2.3 times higher than that of the control group [18].

Sociodemographic disparities further stratified risk. Black (SMR = 5.76, 95% CI: 4.00–8.10) and Asian/Pacific Islander (SMR = 5.51, 95% CI: 4.19–7.25) patients faced disproportionately higher CVD mortality than White patients (SMR = 4.87), likely due to socioeconomic inequities, healthcare access barriers, or genetic predispositions. Marital status also significantly impacted outcomes: widowed (SMR = 15.92) or separated (SMR = 16.18) patients had exceptionally high risks compared to married counterparts (SMR = 5.51), highlighting the role of social support in mitigating cardiovascular morbidity [19,20].

Limitations

This study has several limitations. First, reliance on SEER data introduces potential biases from incomplete records (e.g., missing diagnostic/survival dates) and unmeasured confounders (e.g., lifestyle factors, comorbidities). Second, competing risks from complex mortality causes (e.g., cancer progression, non-CVD comorbidities) may overestimate CVD-specific mortality. Third, insufficient treatment details (e.g., radiotherapy doses, chemotherapy regimens) limit mechanistic insights into therapy-related cardiovascular toxicity. Finally, the 21-year study span introduces temporal heterogeneity, as evolving treatment protocols and CVD management guidelines may affect longitudinal risk patterns.

Future Directions

Prospective cohorts integrating granular treatment data, cardiovascular biomarkers (e.g., high-sensitivity troponin, inflammatory cytokines), and social determinants of health are needed

to clarify mechanisms – such as radiation-induced oxidative stress or tumor-derived endothelial damage – and refine risk prediction models. Interventions targeting high-risk subgroups (e.g., irradiated patients, socioeconomically disadvantaged populations) should prioritize cardioprotective strategies (e.g., statins, lifestyle modifications). Community-level initiatives to address healthcare access disparities, particularly for Black and uninsured groups, are equally critical to mitigate biological and structural CVD risks [21, 22].

By bridging oncology and cardiology disciplines, future efforts may reduce the dual burden of cancer and CVD, ultimately improving long-term outcomes for TC survivors.

Conclusion

This study underscores the imperative to integrate cardiovascular risk surveillance into survivorship care for TC patients, particularly those exposed to radiotherapy or experiencing social vulnerability. The multidimensional determinants of CVD-related mortality – spanning treatment toxicity, tumor biology, and sociodemographic disparities – highlight the need for interdisciplinary collaboration between oncology and cardiology. Future efforts should prioritize mechanistic research and equity-focused interventions to mitigate the dual burden of cancer and cardiovascular disease in this population.

Abbreviations

Abbreviation	Full Term
CI	Confidence Interval
CVD	Cardiovascular Disease
NCI	National Cancer Institute
SEER	Surveillance, Epidemiology, and End Results
SMR	Standardized Mortality Ratio
TC	Tongue Cancer

Competing interests

The authors declare no potential conflicts of interest.

ЛИТЕРАТУРА/REFERENCES

1. *Mody MD, Rocco JW, Yom SS, Haddad RI, Saba NF. Head and neck cancer. Lancet. 2021;398(10318):2289–2299. https://doi.org/10.1016/s0140-6736(21)01550-6*
2. *Chow LQM. Head and neck cancer. N Engl J Med. 2020;382(1):60–72. https://doi.org/10.1056/NEJMra1715715*
3. *Alterio D, Marvaso G, Ferrari A, Volpe S, Orecchia R, Jereczek-Fossa BA. Modern radiotherapy for head and neck cancer. Semin Oncol 2019;46(3):233–245. https://doi.org/10.1053/j.seminoncol.2019.07.002*
4. *Lee MS, Finch W, Mahmud E. Cardiovascular complications of radiotherapy. Am J Cardiol 2013;112(10):1688–1696. https://doi.org/10.1016/j.amjcard.2013.07.031*
5. *Sturgeon KM, Deng L, Bluethmann SM et al. A population-based study of cardiovascular disease mortality risk in US cancer patients. Eur Heart J 2019;40(48):3889–3897. https://doi.org/10.1093/eurheartj/ehz766*
6. *Sun L, Brody R, Candelieri D et al. Risk of cardiovascular events among patients with head and neck cancer. JAMA Otolaryngol Head Neck Surg 2023;149(8):717–725. https://doi.org/10.1001/jamaoto.2023.1342*
7. *Sindhu SK, Bauman JE. Current concepts in chemotherapy for head and neck cancer. Oral Maxillofac Surg Clin North Am 2019;31(1):145–154. https://doi.org/10.1016/j.coms.2018.09.003*
8. *Carnevale R, Lanzetta G, Biondi-Zoccai G, Frati G. Chemotherapy, cardiovascular disease and precision medicine: Toward truly individualized treatment for precision cardio-oncology? Int J Cardiol 2019;280:198–199. https://doi.org/10.1016/j.ijcard.2019.01.050*
9. *Roth GA, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, Abbastabar H, Abd-Allah F, Abdela J, Abdelalim A, Abdollahpour I. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392(10159):1736–1788. https://doi.org/10.1016/s0140-6736(18)32203-7*
10. *Sorrentino MF, Kim J, Foderaro AE, Truesdell AG (2012) 5-fluorouracil induced cardiotoxicity: review of the literature. Cardiol J 19(5):453–458. https://doi.org/10.5603/cj.2012.0084*
11. *Liao J, Zhou Z. Long-term cardiovascular mortality risk in patients with bladder cancer: a real-world retrospective study of 129,765 cases based on the SEER database. Front Cardiovasc Med 2023;10:1142417. https://doi.org/10.3389/fcvm.2023.1142417*
12. *Sun S, Wang W, He C. Cardiovascular mortality risk among patients with gastroenteropancreatic neuroendocrine neoplasms: a registry-based analysis. Oxid Med Cell Longev 2021;2021:9985814. https://doi.org/10.1155/2021/9985814*
13. *Yin X, Fan F, Zhang B, Hu Y, Sun C. Cardiovascular-specific mortality among multiple myeloma patients: a population-based study. Ther Adv Hematol 2022;13:20406207221086756. https://doi.org/10.1177/20406207221086755*
14. *Kivimaki M, Steptoe A. Effects of stress on the development and progression of cardiovascular disease. Nat Rev Cardiol, 2018;15(4):215–229. https://doi.org/10.1038/nrcardio.2017.189*
15. *Ferroni P, Della-Morte D, Palmirotta R et al. Platinum-based compounds and risk for cardiovascular toxicity in the elderly: role of the antioxidants in chemoprevention. Rejuvenation Res 2011;14(3):293–308. https://doi.org/10.1089/rej.2010.1141*
16. *Zhang S, Wang Y, Zhang P, et al. Cardiovascular outcomes in patients with colorectal cancer: A multi-registry-based cohort study of 197,699 cases in the real world. Front Cardiovasc Med. 2022;9:851833. https://doi.org/10.3389/fcvm.2022.851833*
17. *Srinivas US, Tan BWQ, Vellayappan BA, Jeyasekharan AD. ROS and the DNA damage response in cancer. Redox Biol 2019;25:101084. https://doi.org/10.1016/j.redox.2018.101084*
18. *Boer H, Proost JH, Nuver J, Bunskoek S, Gietema JQ, Geubels BM, Altena R, Zwart N, Oosting SF, Vonk JM, Lefrandt JD, Uges DR, Meijer C, de Vries EG, Gietema JA. Long-term exposure to circulating platinum is associated with late effects of treatment in testicular cancer survivors. Annals of Oncology, 2015;26(11):2305–2310. https://doi.org/10.1093/annonc/mdv369*
19. *Haier J, Schaefers J. Economic perspective of cancer care and its consequences for vulnerable groups. Cancers (Basel). 2022. https://doi.org/10.3390/cancers14133158*
20. *Jarroch R, Tajik B, Tuomainen TP, Kauhanen J. Economic recession and the risk of cancer: a cohort study from Eastern Finland. J Epidemiol 2022;32(8):384–390. https://doi.org/10.2188/jea.JE20200595*
21. *Macías Á, Díaz-Larrosa JJ, Blanco Y et al. Paclitaxel mitigates structural alterations and cardiac conduction system defects in a mouse model of Hutchinson-Gilford progeria syndrome. Cardiovasc Res 2022;118(2):503–516. https://doi.org/10.1093/cvr/cvab055*
22. *Bergom C, Bradley JA, Ng AK et al. Past, Present, and Future of Radiation-Induced Cardiotoxicity: Refinements in Targeting, Surveillance, and Risk Stratification. JACC CardioOncol 2021;3(3):343–359. https://doi.org/10.1016/j.jaccao.2021.06.007*

Поступила 22.07.2025
Получены положительные рецензии 01.09.25
Принята в печать 24.09.25
Received 22.07.2025

Positive reviews received 01.09.25
Accepted 24.09.25

Вклад авторов: *Синьи Ян: концепция и дизайн исследования; сбор и подготовка данных; статистический анализ; интерпретация результатов; написание первой версии рукописи. Решетов И.В.: научное руководство; критический пересмотр рукописи; утверждение окончательной версии к публикации. Полтавская М.Г.: интерпретация клинических данных; критический пересмотр рукописи; вклад в обсуждение результатов. Агакина Ю.С.: сбор клинической информации; контроль качества данных; участие в подготовке иллюстративного материала. Логинова Н.П.: методологическая поддержка; проверка статистической части; редакторская правка. Киселева А.Э.: обзор литературы; подготовка таблиц и рисунков; оформление рукописи в соответствии с требованиями журнала.*

Author contributions: *Xinyi Yan: study concept and design; data collection and preparation; statistical analysis; interpretation of results; drafting the first version of the manuscript. Igor V. Reshetov: scientific supervision; critical revision of the manuscript; approval of the final version for publication. Maria G. Poltavskaya: interpretation of clinical data; critical revision of the manuscript; contribution to the discussion of results. Yulia S. Agakina: collection of clinical information; data quality control; participation in the preparation of illustrative materials. Nina P. Loginova: methodological support; verification of the statistical section; editorial revision. Alevtina E. Kiseleva: literature review; preparation of tables and figures; formatting the manuscript in accordance with the journal's requirements.*

Информация об авторах:

Ян Синьи – аспирант, Первый Московский государственный медицинский университет им. И.М. Сеченова (Сеченовский Университет) Минздрава России. Адрес: 119991, Россия, Москва, ул. Трубецкая, д. 8, стр. 2. E-mail: yangxinyi0125@gmail.com. ORCID: https://orcid.org/0009-0009-2320-0834

Решетов Игорь Владимирович – Академик РАН, д.м.н., профессор, Первый МГМУ им. И.М. Сеченова (Сеченовский Университет) Минздрава России. Адрес: 119991, Россия, Москва, ул. Трубецкая, д. 8, стр. 2. E-mail: reshetov_i_v@staff.sechenov.ru. ORCID: https://orcid.org/0000-0002-0909-6278

Полтавская Мария Георгиевна – д.м.н., профессор, доцент по кафедре профилактической и неотложной кардиологии, Первый МГМУ им. И.М. Сеченова (Сеченовский Университет), Минздрава России. Адрес: 119991, Россия, Москва, ул. Трубецкая, д. 8, стр. 2. E-mail: poltavskaya_m_g@staff.sechenov.ru. ORCID: ORCID: https://orcid. org/0000-0003-4463-2897

Агакина Юлия Сергеевна – заведующая отделением, врач-онколог, Первый МГМУ им. И.М. Сеченова (Сеченовский Университет) Минздрава России. Адрес: 119991, Россия, Москва, ул. Трубецкая, д. 8, стр. 2. E-mail: y.agakina@gmail.com. ORCID: https://orcid. org/0000-0002-3556-2703

Логинова Нина Павловна– стажер-исследователь отдела современных биоматериалов Института регенеративной медицины Сеченовского университета, Федеральный научно-клинический центр специализированных видов медицинской помощи и медицинских технологий ФМБА России. Адрес: 115682, Москва, Ореховый бульвар, д. 28. E-mail: n.p.loginova@mail.ru. ORCID: https://orcid. org/0009-0002-7631-8149

Киселева Алевтина Эдуардовна – ассистент кафедры онкологии, радиотерапии и реконструктивной хирургии ФГАОУ ВО Первый МГМУ им. И.М. Сеченова Минздрава России (Сеченовский Университет). Адрес: 119991, Москва, ул. Трубецкая, д. 8, стр. 2. E-mail: kis-alevtina@yandex.ru. ORCID: https://orcid.org/0000-0002-6930-1261

Author information:

Xinyi Yan – PhD student, I.M. Sechenov First Moscow State Medical University (Sechenov University), Ministry of Health of Russia. Address: 8 Trubetskaya St., Bldg. 2, Moscow, 119991, Russia. E-mail: yangxinyi0125@gmail.com. ORCID: https://orcid.org/0009-0009-2320-0834

Igor Vladimirovich Reshetov – Academician of the Russian Academy of Sciences, MD, Professor, I.M. Sechenov First Moscow State Medical University (Sechenov University), Ministry of Health of Russia. Address: 8 Trubetskaya St., Bldg. 2, Moscow, 119991, Russia. E-mail: reshetov_i_v@staff.sechenov.ru. ORCID: https://orcid.org/0000-0002-0909-6278

Maria Georgievna Poltavskaya – MD, Professor, Associate Professor at the Department of Preventive and Emergency Cardiology, I.M. Sechenov First Moscow State Medical University (Sechenov University), Ministry of Health of Russia. Address: 8 Trubetskaya St., Bldg. 2, Moscow, 119991, Russia. E-mail: poltavskaya_m_g@staff.sechenov.ru. ORCID: https://orcid.org/0000-0003-4463-2897

Yulia Sergeevna Agakina – Head of Department, Oncologist, I.M. Sechenov First Moscow State Medical University (Sechenov University), Ministry of Health of Russia. Address: 8 Trubetskaya St., Bldg. 2, Moscow, 119991, Russia. E-mail: y.agakina@gmail.com. ORCID: https://orcid.org/0000-0002-3556-2703

Nina Pavlovna Loginova – Research Intern, Department of Advanced Biomaterials, Institute for Regenerative Medicine, Sechenov University; Federal Research and Clinical Center for Specialized Medical Care and Medical Technologies, FMBA of Russia. Address: 28 Orekhovy Boulevard, Moscow, 115682, Russia. E-mail: n.p.loginova@mail.ru. ORCID: https://orcid.org/0009-0002-7631-8149

Alevtina Eduardovna Kiseleva – Assistant, Department of Oncology, Radiotherapy and Reconstructive Surgery, I.M. Sechenov First Moscow State Medical University (Sechenov University), Ministry of Health of Russia. Address: 8 Trubetskaya St., Bldg. 2, Moscow, 119991, Russia. E-mail: kis-alevtina@yandex.ru. ORCID: https://orcid.org/0000-0002-6930-1261