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Lung cancer mortality due to delayed treatment: Literature review

Relevance: Lung cancer is still leading in the structure of cancer incidence and mortality worldwide. Delay in appropriate treatment increases the probability of death from this disease.

Purpose: to study foreign scientific publications of recent years on the mortality from lung cancer due to delayed treatment.

Results: The analysis of global literature for 2010–2020 shows that any delay in lung cancer treatment after establishing the diagnosis reduces the survival rates. Recent studies provide a qualitative assessment of the effect of delay in treatment on cancer mortality for prioritization and modeling. The indications for surgery, systemic treatment, and radiation therapy in seven types of cancer, including lung cancer, evidence a significant association between delay in treatment and increased mortality. The researchers believe that early diagnostics increase the treatment efficacy.

Conclusion: Analyzing the barriers to timely treatment for lung cancer can help clarify and assess the impact of delayed treatment on survival. Policies designed to minimize delays in treatment can improve survival outcomes.

Keywords: lung cancer, non-small cell lung cancer (NSCLC), delayed treatment, survival.

Introduction

Noncommunicable diseases, including lung cancer, are currently the cause of most deaths worldwide [1]. According to GLOBOCAN, in 2020 have been registered more than 19.2 million new cases of malignant neoplasms and more than 9.9 million deaths from this disease. Lung cancer ranks second in incidence (11.4%) and first in mortality (18.0%) among all cancers [2].

Delaying cancer treatment can have adverse consequences for the patient. However, despite the fundamental importance of cancer treatment, there are no standardized estimates of the effect of delayed treatment on survival for most treatment indications. The article shares the meta-analyses that contain evidence of a regular relation between delayed treatment and mortality [3]. Examining the impact of treatment delays on mortality and other outcomes such as relapses or financial considerations is of great importance for developing cancer treatment systems, ways and models of providing care to ensure affordable and efficient results [4].

The need for a better understanding of the impact of delayed treatment on outcomes has skyrocketed during the COVID-19 pandemic. In this period, planned cancer surgery and radiation therapy were delayed, and the provision of systemic treatment was reduced in many countries [5, 6] since the healthcare resources were reallocated to ensure readiness for the pandemics [7].

Purpose: to study foreign scientific publications of recent years on the mortality from lung cancer due to delayed treatment.

Materials and methods:

This review included the results of foreign studies on the influence of treatment delays on lung cancer mortality in 2010–2020. The review covered publications in English indexed in PubMed, Science Direct, Google Scholar, and the World Health Organization (WHO) library databases. The search utilized such keywords as lung cancer, non-small cell lung cancer (NSCLC), treatment delay, and survival rate.

Results and Discussion:

According to most researchers, access to comprehensive quality medical services is an important factor in promoting health, prevention, and treatment of diseases. The literature consistently highlights the necessity for the prompt provision of medical care to achieve the best results [8–12].

Research shows that the cancer burden is growing mainly in low-income countries, where inefficient lung cancer treatment can lead to negative health outcomes [13–16]. However, in many cases, the differences in outcomes result from the differences in the quality of medical care, including the time of diagnosis, the type of diagnostic methods used, the stage of disease, start, and type of treatment [15, 17–18]. Recognition, analysis, and communication of these barriers form the basis for quality improvement, as well as the development and evaluation of effective corrective interventions in existing lung cancer treatment processes [19].

U.S. scientists showed the extreme importance of timely surgical intervention for the survival of patients with early-stage NSCLC. They reported that a patient of 60 years diagnosed with stage IIB NSCLC with a 4+ cm tumor has a 50% chance of survival for five years if the treatment starts within two weeks after diagnosis. The start of treatment within four weeks after diagnosis reduces the 5-year survival rate up to 47%. This is equivalent to living for another 0.4 years. For a 30-year-old patient, the start of treatment within four weeks after diagnosis is associated with a 71% 5-year survival rate [20]. The scientists believe that primary care providers and specialists shall ensure surgical treatment of patients with early stages of lung cancer as a most effective approach in this case [21].

According to Samson et al. [22], delays in surgical intervention for patients with early-stage NSCLC are quite common and are often associated with socioeconomic and clinical factors. According to the authors, significant delays in providing medical care result in unfavorable short-term and long-term outcomes for patients.

Anggondowati et al. have analyzed data from the U.S. National Cancer Database on adult patients with newly diagnosed NSCLC. They concluded that longer treatment times did not improve survival. However, delayed treatment had no negative impact on patients with more advanced stages. The treatment for 4 to 6 weeks reduced the risk of death for patients with early-stage cancer, locally advanced cancer, or metastatic cancer compared to the treatment started one day to 4 weeks after the diagnosis. A longer treatment for more than six weeks was associated with a lower death risk in patients with any cancer stage at the time of diagnosis. However, the analysis of patients who received surgery in the early stages of the disease showed that a long time before surgery was associated with a higher risk of death. Comprehensive examination and preparation are of use for the patients but do not accelerate the treatment. However, it is important not to delay the treatment of patients with resectable cancers. According to the authors [23], future research should focus on identifying clinical characteristics of patients that predict the optimal time to treatment for better results. This would benefit the patients and would serve to improve clinical standards. Such studies would be relevant given the discrepancy in NSCLC treatment initiation timing guidelines [23].

The mentioned study supports the idea that even if allowing time for optimal planning of treatment might postpone the start of treatment, it is likely to increase the survival rates of patients. It seems reasonable to initiate treatment of patients with resectable early lung cancer within four weeks after diagnosis. This is due to an expected increase in patients with early stages of the disease after improving screening programs and recent recommendations issued by the U.S. Preventive Services Task Force. Despite various factors leading to treatment delays, attempts should be made to reduce delays caused by systemic factors [23].

Meta-analyses conducted by several researchers evidence a relationship between the treatment delay and mortality. The studies have covered seven types of cancer, which together account for 44% of all cancer cases in the world [3]. These were the five most common cancers (bladder, breast, colon, rectum, and lung cancer), as well as cervical cancer (ranks fourth globally among female cancers) and head and neck cancer (the main cancer burden in middle-income countries). The studies were limited to English-language publications of 2010-2020, which reported specifically on treatment delays and survival. The authors found that a four-week delay in treatment was associated with an increased risk of death for all three treatment modalities (surgery, systemic treatment, and radiation therapy). Every four weeks of delay in surgery increased the risk of death by 6-8% [24-30].

Conclusions:

Thus, the analyzed studies show that delays in lung cancer treatment after diagnosis reduce the survival of patients. Further study of the factors hindering the timely initiation of treatment and searching for ways to overcome these barriers is required.

References

1. World Health Organization. Global Health Estimates: Life expectancy and leading causes of death and disability // www.who.int/data/gho/data/themes/mortality-and-global-health-estimates. 03.06.2021;
2. International Agency for Research on Cancer. The Global Cancer Observatory Globocan 2020. All cancers // gco.iarc.fr/today/data/factsheets/cancers/39-All-cancers-fact-sheet.pdf. 03.06.2021;
3. Hanna T.P. et al. Mortality due to cancer treatment delay: A systematic review and meta-analysis // *BMJ*. – 2020. – № 371. – m4087. doi: 10.1136/bmj.m4087
4. Institute of Medicine (U.S.) Committee on Quality of Health Care in America. Crossing the Quality Chasm: A New Health System for the 21st Century. – National Academies Press (U.S.), 2001. doi: 10.17226/10027;
5. Sample I. More than 2m operations canceled as NHS fights COVID-19 // *Guardian*. – 26 Apr 2020.;
6. Harnett C.E. Clearing surgery backlog will take at least 17 months and cost millions, province says // *Times Colonist*. – 7 May 2020.;
7. Hanna T.P., Evans G.A., Booth C.M. Cancer, COVID-19, and the precautionary principle: prioritizing treatment during a global pandemic // *Nat. Rev. Clin. Oncol.* – 2020. – № 17(5). – P. 268-270. doi: 10.1038/s41571-020-0362-6;
8. Shankar A. et al. Feasibility of lung cancer screening in developing countries: challenges, opportunities, and way forward // *Transl. Lung Cancer Res.* – 2019. – № 8(Suppl. 1). – P. S106-S121. Doi: 10.21037/tlcr.2019.03.03;
9. Sullivan T., Sullivan R., Ginsburg O. M. Screening for cancer: considerations for low-and middle-income countries // In: *Cancer: Disease Control Priorities* / eds. Gelband H., Jha P., Sankaranarayanan R. et al. – Ed. 3. – Washington (D.C.): The International Bank for Reconstruction and Development / The World Bank, 2015. – Vol. 3. doi: 10.1596/978-1-4648-0349-9_ch12;
10. Sankaranarayanan R. Screening for cancer in low-and middle-income countries // *Annals Global Health*. – 2014. – №8(5). – P. 412-417. doi: 10.1016/j.aogh.2014.09.014;
11. Ambroggi M. et al. Distance as a barrier to cancer diagnosis and treatment: review of the literature // *Oncologist*. – 2015. – №20(12). – P. 1378-1385. doi: 10.1634/theoncologist.2015-0110;
12. Mills A. Health policy and systems research: defining the terrain; identifying the methods // *Health Policy Planning*. – 2012. – № 27(1). – P. 1-7. doi: 10.1093/heapol/czr006;
13. Bray F. et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries // *CA: Cancer J. Clin.* – 2018. – №68(6). – P. 394-424. doi: 10.3322/caac.21492;
14. Pakzad R., Mohammadian-Hafshejani A, Ghoncheh M, Pakzad I, Salehiniya H. The incidence and mortality of lung cancer and their relationship to development in Asia // *Transl. Lung Cancer Res.* – 2015. – №4(6). – P. 763-774. doi: 10.3978/j.issn.2218-6751.2015.12.01;
15. Walton L. et al. Patient perceptions of barriers to the early diagnosis of lung cancer and advice for health service improvement // *Family Practice*. – 2013. – № 30(4). – P. 436-444. doi:10.1093/fampra/cmt001;
16. Denny L., Anorlu R. Cervical cancer in Africa // *Cancer Epidemiol. Biomarkers. Prev.* – 2012. – №21(9). – P. 1434-1438. doi:10.1158/1055-9965.EPI-12-0334;
17. Urman A. et al. Burden of lung cancer and associated risk factors in Africa by region // *J. Pulm. Respir. Med.* – 2016. – №6(3). – P. 1000340. doi: 10.4172/2161-105X.1000340;
18. Winkler V., Mangolo N. J., Becher H. Lung cancer in South Africa: a forecast to 2025 based on smoking prevalence data // *BMJ open*. – 2015. – №5(3). – e006993. doi: 10.1136/bmjopen-2014-006993;
19. Carrillo J. E. et al. Defining and targeting health care access barriers // *J Health Care Poor Underserved*. – 2011. – №22(2). – P. 562-575. doi: 10.1353/hpu.2011.0037;
20. Kanarek N. F. et al. Survival after community diagnosis of early-stage non-small cell lung cancer // *Am. J. Med.* – 2014. – №127(5). – P. 443-449. doi: 10.1016/j.amjmed.2013.12.023;

21. Dovidio J. F., Fiske S. T. Under the radar: how unexamined biases in decision-making processes in clinical interactions can contribute to health care disparities // *Am. J. Public Health.* – 2012. – №102(5). – P. 945-952. doi: 10.2105/AJPH.2011.300601;
22. Samson P., Patel A., Garrett T., Crabtree T., Kreisel D., Krupnick A.S., Patterson G.A., Broderick S., Meyers B.F., Puri V. Effects of Delayed Surgical Resection on Short-Term and Long-Term Outcomes in Clinical Stage I Non-Small Cell Lung Cancer // *Ann. Thorac. Surg.* – 2015. – №99(6). – P. 1906-1913. doi:10.1016/j.athoracsurg.2015.02.022;
23. Anggondowati T., Ganti A. K., Islam K.M.M. Impact of time-to-treatment on overall survival of non-small cell lung cancer patients – an analysis of the national cancer database // *Transl. Lung Cancer Res.* – 2020. – №9(4). – P. 1202-1211. doi: 10.21037/tlcr-19-675;
24. Ferlay J. et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods // *Int. J. Cancer.* – 2019. – №144(8). – P. 1941-1953. doi: 10.1002/ijc.31937;
25. Chen Z. et al. The relationship between waiting time for radiotherapy and clinical outcomes: a systematic review of the lit-

- erature // *Radiother. Oncology.* – 2008. – №87(1). – P. 3-16. doi: 10.1016/j.radonc.2007.11.016;
26. Jhawar S. et al. Adjuvant chemoradiation therapy for cervical cancer and effect of timing and duration on treatment outcome // *Int. J. Radiat. Oncol. Biol. Phys.* – 2017. – №98(5). – P. 1132-1141. doi: 10.1016/j.ijrobp.2017.03.045;
27. Booth C.M. et al. Time to adjuvant chemotherapy and survival in non-small cell lung cancer: A population-based study // *Cancer.* – 2013. – №119(6). – P. 1243-1250. doi: 10.1002/cncr.27823;
28. Salazar M.C. et al. Association of delayed adjuvant chemotherapy with survival after lung cancer surgery // *JAMA oncol.* – 2017. – №3(5). – P. 610-619. doi: 10.1001/jamaoncol.2016.5829;
29. Tsai C.H. et al. Effect of time interval from diagnosis to treatment for non-small cell lung cancer on survival: a national cohort study in Taiwan // *BMJ open.* – 2020. – №10(4). – e034351. doi: 10.1136/bmjopen-2019-034351;
30. McMillan M. et al. Radiation treatment time and overall survival in locally advanced non-small cell lung cancer // *Int. J. Radiat. Oncol. Biol. Phys.* – 2017. – №98(5). – P. 1142-1152. doi: 10.1016/j.ijrobp.2017.04.004.

ТҰЖЫРЫМ

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Емдеудің кешігуіне байланысты өкпе қатерлі ісігінен болатын өлім: Әдебиетке шолу

Өзектілігі: өкпенің қатерлі ісігі бүкіл әлемде онкологиялық аурулар мен өлім-жітім құрылымында жетекші орын алады. Өкпенің қатерлі ісігін тиісті емдеуді кешіктірген кезде өлім ықтималдығы болу мүмділігі жоғары.

Мақсаты: емдеудің кешігуіне байланысты өкпе қатерлі ісігінен болатын өлім туралы соңғы жылдардағы шетелдік ғылыми жарияланымдарды зерттеу.

Нәтижелер: 2010-2020 жылдардағы шетелдік зерттеулерді талдау нәтижелері өкпе қатерлі ісігі диагнозынан кейін емдеудің кез-келген кідірісі өмір сүрудің төмендеуіне әкелетінін көрсетеді. Соңғы жылдардағы зерттеулер басымдықты анықтау және модельдеу үшін емдеуді кешіктірудің қатерлі ісік ауруынан болатын өлімге әсері тигізетінін анықтауға мүмкіндік береді. Хирургиялық және жүйелі емдеу, сондай-ақ обьрдың жеті түрі, оның ішінде өкпе қатерлі ісігі бойынша сәулелік терапия көрсетілімдері бойынша емдеудің кешігуі мен өлім-жітімнің жоғарылауы арасында елеулі байланыстың болуы анықталды. Зерттеушілердің пікірінше, ең тиімді емдеу ерте диагнозбен байланысты.

Қорытынды: өкпенің қатерлі ісігін уақтылы емдеуге келергі келтіретін әртүрлі факторларды талдау кешіктірілген емнің өмір сүру деңгейіне әсерін анықтауға және оңтайлы бағалауға негіз болады. Емдеудің кідірістерін азайтуға бағытталған саясат өмір сүру нәтижелерін жақсартып алады.

Түйінді сөздер: өкпе қатерлі ісігі, кіші жасушалық емес өкпе қатерлі ісігі (NMRL), емдеуді кешіктіру, өмір сүру.

АННОТАЦИЯ

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Смертность от рака легкого из-за задержки лечения: Обзор литературы

Актуальность: Рак легких продолжает занимать лидирующие позиции в структуре онкологической заболеваемости и смертности во всем мире. При задержке соответствующего лечения рака легкого существует высокая вероятность летального исхода.

Цель: изучение зарубежных научных публикаций последних лет о смертности от рака легкого из-за задержки лечения.

Результаты: Результаты анализа зарубежных исследований за 2010-2020 годы показывают, что любая задержка лечения после постановки диагноза рака легкого приводит к снижению выживаемости. Исследования последних лет позволяют количественно оценить влияние задержки лечения на смертность от рака для определения приоритетов и моделирования. По показаниям хирургического и системного лечения, а также лучевой терапии по семи видам рака, в том числе рака легкого, установлено наличие значимой связи между задержкой лечения и повышенной смертностью. Как считают исследователи, наиболее эффективное лечение связано именно с ранней диагностикой.

Заключение: Анализ различных факторов, препятствующих своевременному лечению рака лёгких, послужит основой для уточнения и оптимальной оценки влияния отсрочки лечения на выживаемость. Политика, направленная на минимизацию задержек лечения, может улучшить результаты выживаемости.

Ключевые слова: рак легкого, немелкоклеточный рак легкого (НМРЛ), задержка лечения, выживаемость.