ISSN 0029–540X
e-ISSN 2300–2115

Volume 73 | Number 3 | Year 2023

NOWOTWORY. Journal of Oncology 2023, Volume 73, Number 3, 111–199

# Nowotwory

## Journal of Oncology



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# Nowotwory

## Journal of Oncology

established in 1923
as the *Bulletin of the Polish Anti-Cancer Committee*
renamed *NOWOTWORY* in 1928
renamed *NOWOTWORY Journal of Oncology* in 2001

bimonthly

official organ of the

POLISH ONCOLOGICAL SOCIETY

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RESEARCH INSTITUTE OF ONCOLOGY

journal of the

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22-6132.003.001

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Journal of Oncology



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VM Media Group sp. z o.o.
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e-mail: viamedica@viamedica.pl, www.viamedica.pl

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*NOWOTWORY Journal of Oncology*
is indexed in: Biochemistry & Biophysics Citation Index, CAS, CrossRef, EMBASE, Free Medical Journals, Google Scholar, Index Copernicus (120.58), MEiN (100), Polska Bibliografia Lekarska, Scopus, SJR and Ulrich's Periodicals Directory

Editorial policies and author guidelines are published on journal website:
www.nowotwory.edu.pl

ISSN: 0029–540X
e-ISSN: 2300–2115

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VIA MEDICA

Original article

NOWOTWORY Journal of Oncology
2023, volume 73, number 3, 111–116
DOI: 10.5603/NJO.a2023.0023

ISSN: 0029–540X, e-ISSN: 2300-2115
www.nowotwory.edu.pl

# The molecular portrait of triple-negative breast cancer: the *LAG3* gene single nucleotide polymorphism rs2365094 has no impact on the clinical picture

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**Introduction.** Triple-negative breast cancer (TNBC) is characterized by a lack of oestrogen, progesterone and human epidermal growth factor receptors. It is the one of most heterogeneous and highly-aggressive breast cancers, resulting in fast progression. In humans, the lymphocyte activation gene 3 (*LAG3*) is located on chromosome 12p13 and encodes an immune-regulatory molecule. The aim of the study was to perform a molecular analysis of *LAG3* gene polymorphisms.
**Material and method.** The presence of single-nucleotide polymorphisms (SNPs) at rs2365094 was determined in 30 TNBC patients and 30 healthy controls using a polymerase chain reaction (PCR) and commercially-available TaqMan SNP Genotyping Assays. SNP status was then compared with the clinical outcome.
**Results.** The allelic alterations in *LAG3* gene SNP in rs2365094 appear to have no influence on the clinicopathological picture among TNBC patients. The carriage rate for a single allele did not differ significantly between patients and controls.
**Conclusions.** No significant relationship was observed between the rs2365094 SNP status and clinicopathological determinants.

**Key words:** *LAG3*, triple negative breast cancer, immune checkpoints, immunotherapy

## Introduction

Triple-negative breast cancer (TNBC) is an aggressive condition that is negative for hormone-receptor and human epidermal growth factor receptor 2. TNBC accounts for 20% of overall breast cancers [1]. A key prognostic factor for this type of breast cancer comprises a complete pathological response to first-line neoadjuvant therapy and primary chemosensitivity [2] but high risk of recurrence [3]. Even so, unlike other breast cancers, TNBC demonstrates a much higher likelihood of metastasis to the brain or lung rather than bone.

The 2016 Lehmann et al. classification [4] divides TNBC into four subgroups based on genomic analysis of *BRCA1/2, STAT4, TP53, APC, BRAF, MAP2, MAPK13, MDC1, PTEN, RB1, CDKN2A, UTX,*

**How to cite:**
Boguszewska-Byczkiewicz K, Wow T, Szymańska B, Kośny M, Kołacińska-Wow A. ***The molecular portrait of triple-negative breast cancer: the LAG3 gene single nucleotide polymorphism rs2365094 has no impact on the clinical picture.*** *NOWOTWORY J Oncol* 2023; 73: 111–116.

*CTNNA, DDX18, HUWE1, NFKBIA, PIK3CA, KRAS, HRAS*: basal-like immunosuppressed, basal-like immune-activated, luminal androgen receptor and mesenchymal types [3]. The classification of TNBC decides on the treatment strategy [4, 5]. Individual patients have distinctive molecular portraits for breast cancer, and a better understanding of the gene expression patterns of triple negative breast cancer is likely to improve therapeutic strategies with targeted agents. Jurj et al. [6] published a comprehensive study of SNPs in TNBC that may be used as potential prognostic biomarkers for early-stage TNBC, predicting the presence of TNBC and prognosis. These include rs3817198(LSP1), rs1436904(CHST9), rs1219648(FGFR2), rs4415084(locus 5p12), rs799917(BRCA1), rs8100241(ANKLE1), rs201360779(PDE4D), rs201654150/ rs149590841(FBXL22).

Of all breast cancers, TNBC is considered to be one of the most immunogenic. Briefly, the expression of immune checkpoint members in the tumor microenvironment boosts tumor growth, making the tumor invisible to the defense mechanisms of the innate immune reaction. Immune checkpoint inhibitors reverse this mechanism, thus inducing removal of tumor tissue by the immune system. The components of the peritumoral and intratumoral microenvironment may serve as surrogate biomarkers for treatment qualification, and such aberrations may facilitate the action of chemotherapy [7]. Anti-immune checkpoint treatments are the backbone for many clinical trials in breast cancer, including TNBC. These drugs are often combined with chemotherapeutics [8], angiogenesis inhibitors and recently, with other immune checkpoint inhibitors [9]. The individual schedule of the bispecific antibodies CTLA4, PD-1/PD-L1 and LAG3 plays a crucial role in tumor immunospecification [10].

Lymphocyte-activation gene 3 (*LAG3*, *CD223*), known since 1990 [11], is a non-cellular component of the tumor microenvironment, a transmembrane protein consisting of 489 amino acids and a member of the IgG group. The LAG3 protein is integrally expressed by tumor cells and immune cells and has been associated with a clinical response [12]. The ligand of LAG3 is FGL1 [13]. Although it is expressed on the surface of breast cancer cells, LAG3 can also be found in the cytoplasm in non-small cell lung cancer (NSCLC) [13, 14]. LAG3, together with PD-1, inhibits anti-tumor immunity by interacting with MHC-II on activated T cells [9], LAG3 inhibits CD8+ and CD4+ T cell proliferation [15]. *LAG3* signaling blockade restores anti-tumor activity. Although LAG3 has been introduced for immunotherapy in TNBC, insufficient response has been noted [16].

TNBC and hormone-receptor-positive breast cancer cells have been found to co-express LAG3 and PD-1 or PD ligand 1 (PD-L1), known as double-positive expression [17, 18]. In addition, approximately half of PD-L1+ TNBC cells have been found to demonstrate LAG3 and PD-1 co-expression [18, 19]. Such co-expression reinforces cytokine production by LAG3/FGL1 ligand conjugation [13]. Resistance to immune checkpoints can be mutually mediated and co-targeting of PD-L1 and LAG3 could provide a new therapeutic approach [9, 20, 21].

In bispecific antibodies, the presence of a single nucleotide polymorphism (SNP) could result in variation in their biological properties and effector functions [22]. The *LAG3* gene is a key predictive factor associated with the LAG3 protein network. The gene is located on chromosome 12 (12p13.32) [23]. Current findings indicate significant correlations between the status of eight SNPs, *viz.* rs1922452, rs951818, rs870849, rs188255, rs11227, rs2365094, rs3782735 and rs2365095 and multiple myeloma, sepsis, Parkinson's disease, HDL-cholesterol and multiple sclerosis as origin-of-inflammation cascades [22, 24–28].

The status of the *LAG3* gene SNP rs1922452 was found to be associated with multiple sclerosis co-morbidity [24]. In addition, the T allele of rs2365095 in the *LAG3* gene was found to be less frequent in multiple sclerosis cases, and the C allele could be considered a risk factor [27]. Furthermore, the T allele of *LAG3* rs870849 was found to be a protective factor against primary immune thrombocytopenia [22], and SNP rs951818 may be involved in the neuroinflammatory mechanisms of disease pathogenesis in Parkinson's disease [25].

In patients with sepsis, those with the *LAG3* rs951818 AA-homozygote showed significantly increased 28-day mortality (17.3%) compared to carriers of the C-allele (23.7%) [26]. A study of *LAG3* gene rs2365094 and rs3782735 found that rs2365094 has an association with multiple myeloma risk [28]. Also, a positive association was identified between the *LAG3* rs3782735 variant allele G and plasma LAG3 protein level in a study of HDL-C, coronary heart disease and all-cause mortality [23]. However, no data exists on the functional significance of any *LAG3* gene SNPs in TNBC. Hence, the present paper examines the influence of *LAG3* gene SNP rs2365094 on triple negative breast cancer (TNBC) and its potential interactions with clinical features that can be used to stratify cancer patients.

## Material and methods

A total of 30 TNBC breast cancer cases were analyzed for *LAG3* rs2365094 SNP. The description of the clinical features of TNBC patients is shown in table I. The study included 30 TNBC patients (n = 30) and 30 healthy controls (n = 30) treated in the Department of Surgical Oncology, Copernicus Provincial Multidisciplinary Centre of Oncology and Traumatology in Lodz, Poland. The study was conducted with the approval of the Independent Ethics Commission of the Medical University of Lodz (study number RNN/298/19/KE) and all participants gave their written consent to take part in the study.

Sixty samples of whole blood in ethylenediaminetetraacetic acid (EDTA) were obtained from peripheral veins according to standard procedures and stored at –20°C. The cancer patients did not receive preoperative chemotherapy or radiotherapy before blood collection. The medical records of the patients, including age of diagnosis, grading, tumor size,

**Table I.** The clinicopathological characteristics of breast cancer patients participating in the study (N = 30)

| Characteristics | Parameter |
|---|---|
| age, years median (range) | 67.5 years (38–84 years) |
| side of involved breast | left – 14<br>right – 17 |
| tumor size (T in TNM classification 2021) | Tx – 1<br>T1a – 1<br>T1b – 1<br>T1c – 9<br>T2 – 12<br>T3 – 1<br>T4 – 6 |
| node status (N in TNM classification 2021) | Nx – 1<br>N0 – 15<br>N1 – 3<br>N2 – 5<br>N3 – 6 |
| Ki-67(%) | <20% – 3<br>≥20% – 27 |
| histological grade | grade 1 – 1<br>grade 2 – 14<br>grade 3 – 15 |

lymph node status, Ki-67 (%) level and histological subtype are presented in table I.

Genomic DNA was isolated from 200 µL of frozen blood using the GeneMATRIX Quick Blood DNA Purification Kit (EURex) according to the manufacturer's protocol. DNA was quantified using the PicoDrop spectrophotometer (Picodrop Limited) and immediately used for PCR reaction or stored at –20°C.

The status of the rs2365094 SNP in the *LAG3* gene was determined using a polymerase chain reaction (PCR) and commercially-available TaqMan SNP Genotyping Assays (Applied Biosystems): Context Sequence GGAGAAGACAAGTCTAAAGCCAGGT [C/G]CCTGTTTCCAGGAGCTTCCGGCTTG (table II). PCR was performed using the GeneAmp PCR System 9700 (Applied Biosystems) in a 20 µl reaction volume containing 10 ng DNA, 10 µl TaqMan® Universal PCR Master Mix and 0.5 µL (40x) appropriate TagMan® SNP Genotyping Assay. The following PCR cycle was performed: initial denaturing at 95°C for 10 min; 40 cycles of 92°C for 15 s and 60°C for 1 min. Each 96-well plate contained the test samples and three reaction mixtures without DNA template (no-template control). End-point fluorescent intensities of each probe were monitored using the 7900HT Fast Real-Time PCR System (Applied Biosystems). The genotypes were determined automatically and verified visually using Sequence Detection System 2.3 Software.

### *Statistical analysis*

Patient data and the SNP status of the gene coding for the *LAG3* gene were analyzed using the chi2 test with Fisher's exact test (taking into consideration the small sample size); the aim was to determine the significance of the co-occurrence between the minor allele and the clinicopathological picture. The addition of Fisher's exact test provides more reliable results with the smaller studied group. Furthermore, logistic regression was performed to determine the impact of **minor allele load** (i.e. the number of minor allele variants – 0, 1 or 2) on the risk of cancer development and certain clinical aspects. The odds ratio (OR) with 95% confidence interval (CI) was also calculated to evaluate the risk associated with allele frequency of rs2365094 (C/G). Statistical significance was assumed for p = 0.05. The analysis was performed using the Statistica v.13 TIBCO Software Inc.

## Results

The study examines the status of potential polymorphic changes in *LAG3* at rs2365094 (C/G) in 30 TNBC patients and 30 healthy controls. The rs2365094 reference allele is G, present in the population at a level of 0.71091 (G = 0.71091) [29].

In the TNBC group, 18 (60%) were found to be rs2365094 GG carriers, 11 were CG carriers (36.7%), one (3.3%) was a CC carrier. Regarding the healthy controls, 13 (43.3%) were GG carriers, 14 (47.7%) CG carriers, and three (10.0%) CC carriers. Additionally, most genotypes were homozygous GG; these were found at a slightly higher frequency in the patients than the controls (60% vs. 43,3%), but this was not significant (p = 0.3634).

Our findings do not indicate any association between the status of the rs2365094 polymorphism and the risk of cancer progression. Also, no correlation was observed between rs2365094 minor allele distribution and the risk of TNBC (OR 0.5319; CI 95%; 0.2257–1.2535; p = 0.1489). In addition, the rs2365094 SNP did not appear to have any significant relationship with the TNBC phenotype, nor with the tested clinicopathological parameters (tumor size, lymph node invasion, grade, Ki-67 status or age of diagnosis). Evaluation was included for 60 samples (table III, fig. 1 and 2).

## Discussion

Immune checkpoints are immunotherapeutic targets and have often yielded remarkable outcomes in treating advanced malignancies. The LAG3 protein is involved in the activation of T cells and in maintaining immune homeostasis. LAG3 activation is used by tumor cells to evade the host immune system.

**Table II.** Characteristics of lymphocyte activating 3 gene (LAG3) rs2365094 sequence, primer and chromosomal location

| Gene name | SNP (rs) number | Chromosomal location | Primer sequence | Polymorphism | Minor allele |
|---|---|---|---|---|---|
| *LAG3* | rs2365094 | chr.12:6774504 on build GRCh38 | context sequence [VIC/FAM] GGAGAAGACAAGTCTAAAGCCAGGT_ [C/G]CCTGTTTCCAGGAGCTTCCGGCTTG | C/G, transversion substitution | G = 0.71091 |

**Table III.** Summary of statistical analysis for association between minor allele presentation in study group (chi2 test with Fisher's exact test)

| Minor allele presentation | | OR (odds ratio) for minor allele presentation | Lower limit of 95% confidence interval for OR | Upper limit of 95% confidence interval for OR | p value |
|---|---|---|---|---|---|
| study group (triple negative breast cancer presentation) | | 0.5319 | 0.2257 | 1.2535 | 0.1489 |
| clinicopathological determinants | G3 | 0.9718 | 0.2690 | 3.5104 | 0.9652 |
| | N | 0.5647 | 0.1476 | 2.1607 | 0.4039 |
| | Ki-67 (%) >20 | 0.3484 | 0.0354 | 3.4281 | 0.3660 |
| | T ≤ 3 | 0.9803 | 0.2148 | 4.4728 | 0.9795 |
| | T = 4 | 0.6509 | 0.1157 | 36614 | 0.6261 |

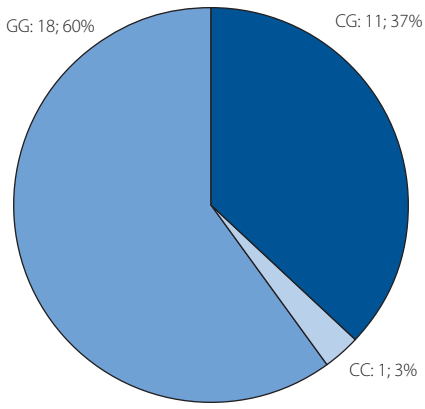


**Figure 1.** Genotype frequencies of *LAG3* rs2365094 in the study group

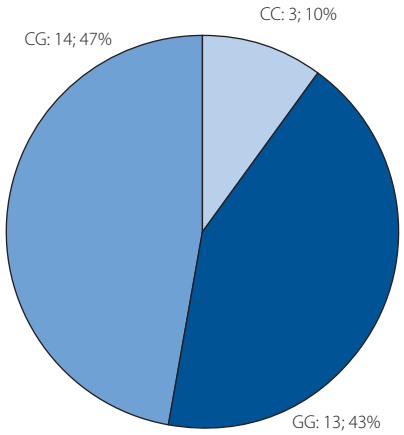


**Figure 2.** Genotype frequencies of *LAG3* rs2365094 in the control group

Recently, a number of studies have examined the potential of anti-LAG3, either alone or in combination with PD-1/PD-L1 blockade, for treating cancer. So far, three LAG3-targeted immunotherapeutics have been identified:

- a phase I clinical trial examined the use of a first-in-class biospecific molecule binding LAG3 and PD-1(MDG013) [20] together with NCT03219268, FS118 [21] in TNBC,
- soluble LAG3Ig (IMP321,clinically tested in metastatic breast carcinoma [30]),
- antagonistic LAG3 antibodies (immunotherapeutics drug named; LAG525, BMS-986016, REGN3767, TSR-033).

Among known molecular biomarkers, the TNBC subtype is considered to be one of the most immunogenic. LAG3 and PD-1/PD-L1 are mutually expressed within TNBC tumor-infiltrating cells and tumor cells. As a result, LAG3-targeted immunotherapeutics designed to coordinately block PD-1 and LAG3 are almost perfect for treatment. A study of tumor-infiltrating lymphocytes, co-expressing PD-L1 and LAG3 in TNBC patients, found all LAG3-positive cases to be PD-L1-positive, but not *vice versa* [18]. A combined blockade of PD-1 and LAG3 could yield survival benefits exclusively in PD-L1 and LAG3-positive TNBC patients. Although immunohistochemical testing for PD-1 expression has been approved by the US Food and Drug Administration (FDA), no reliable or precise LAG3 marker is available to guide the clinical use of anti-LAG3 therapy.

It is noteworthy that the incorporation of immunocheckpoint expression into a basic diagnostic panel can yield significant benefits for TNBC patients. LAG3 transmembrane protein expression has been found to demonstrate prognostic value in a large series of breast cancer patients and LAG3 expression correlated with crucial biomarkers. It has been found that the level of infiltration of LAG3-positive basal-like breast cancer cells in the tumor microenvironment appears to be significantly associated with increased survival, and that LAG3 and PD-1 are co-expressed on tumor infiltrating lymphocytes (TIL) [2]. For tumor therapy, Shi et al. [12] note that LAG-3 protein expression appears to influence anti-PD-1, EGFR-TKI and gefitinib therapy resistance.

Tumor-associated stromal cells support and increase tumor metastatic potential. Studies on metastatic TNBC immunotherapy suggest that the formation of the tumor microenvironment may influence drug resistance: out of all breast cancers, TNBC has been found to have the highest amounts of tumor-infiltrating lymphocytes [31]. However, no data exists on the functional significance of any *LAG3* gene SNPs in the immune-environmental network of various macromolecules.

To our knowledge, there are no studies that investigate the *LAG3* gene polymorphism in breast cancer. In whole genome sequencing (WGS) of the *LAG3* gene, Manichaikul et al. examined the polymorphism of the *LAG3* locus to identify those associated with plasma LAG3 protein concentrations and clinical outcomes [22]. Finally, they reported that a common SNP in the intone region of the *LAG3* gene (rs3782735, allel G) is positively associated with plasma LAG3 protein levels [22].

The *LAG3* in intronic regions was previously examined in women with multiple myeloma by Lee et al. The two SNPs in the *LAG3* gene (rs2365094 and rs3782735) were significantly associated with a risk of multiple myeloma [28].

However, there are no available data on the functional significance of any *LAG3* SNPs in any subtype of breast cancer. Further study is warranted to elucidate the molecular mechanisms of the *LAG3* gene polymorphism with regard to TNBC characteristics.

## Conclusions

TNBC displays poor prognosis. However, the observation that both LAG3 and PD-1 inhibit anti-tumor activity has led to a significant growth in therapeutic strategies aimed at the tumor microenvironment. Than immunocheckpoint-based therapeutic regimens require a better understanding of the underlying mechanisms of LAG3 presentation, which *LAG3* gene sequencing . The sequence analysis of the *LAG3* gene found rs2365094 status may be a predictor of TNBC patient outcome. Our present findings based on a group of Polish patients with the TNBC *LAG3* gene, genotyped for the first time, identify no significant difference in allelic distribution between TNBC patients and group of healthy controls in rs2365094. In addition, SNP status does not appear to be significantly associated with clinicopathological determinants. Although this work was intended as a pilot study towards a future randomized trial with a larger group, its findings provide a better understanding of the genetic basis of TNBC.

**Conflict of interest:** none declared

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*Received: 17 Jan 2023*
*Accepted: 17 May 2023*

## References

1. Li X, Yang J, Peng L, et al. Triple-negative breast cancer has worse overall survival and cause-specific survival than non-triple-negative breast cancer. Breast Cancer Res Treat. 2017; 161(2): 279–287, doi: 10.1007/s10549-016-4059-6, indexed in Pubmed: 27888421.
2. Burugu S, Gao D, Leung S, et al. LAG-3+ tumor infiltrating lymphocytes in breast cancer: clinical correlates and association with PD-1/PD-L1+ tumors. Ann Oncol. 2017; 28(12): 2977–2984, doi: 10.1093/annonc/mdx557, indexed in Pubmed: 29045526.
3. Nowecki Z, Jagiełło-Gruszfeld A, Pogoda K, et al. Leczenie przedoperacyjne chorych na raka piersi i jego wpływ na postępowanie operacyjne oraz radioterapeutyczne (część 2.). Nowotwory. Journal of Oncology. 2021; 71(2): 79–93, doi: 10.5603/njo.2021.0021.
4. Lehmann BD, Jovanović B, Chen Xi, et al. Refinement of Triple-Negative Breast Cancer Molecular Subtypes: Implications for Neoadjuvant Chemotherapy Selection. PLoS One. 2016; 11(6): e0157368, doi: 10.1371/journal.pone.0157368, indexed in Pubmed: 27310713.
5. Yin Li, Duan JJ, Bian XW, et al. Triple-negative breast cancer molecular subtyping and treatment progress. Breast Cancer Res. 2020; 22(1): 61, doi: 10.1186/s13058-020-01296-5, indexed in Pubmed: 32517735.
6. Jurj MA, Buse M, Zimta AA, et al. Critical Analysis of Genome-Wide Association Studies: Triple Negative Breast Cancer . Int J Mol Sci. 2020; 21(16), doi: 10.3390/ijms21165835, indexed in Pubmed: 32823908.
7. Maruhashi T, Sugiura D, Okazaki IM, et al. LAG-3: from molecular functions to clinical applications. J Immunother Cancer. 2020; 8(2), doi: 10.1136/jitc-2020-001014, indexed in Pubmed: 32929051.
8. Schmid P, Adams S, Rugo HS, et al. IMpassion130 Trial Investigators. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. N Engl J Med. 2018; 379(22): 2108–2121, doi: 10.1056/NEJMoa1809615, indexed in Pubmed: 30345906.
9. Jiang H, Ni H, Zhang P, et al. PD-L1/LAG-3 bispecific antibody enhances tumor-specific immunity. Oncoimmunology. 2021; 10(1): 1943180, doi: 10.1080/2162402X.2021.1943180, indexed in Pubmed: 34239776.
10. Andrews LP, Marciscano AE, Drake CG, et al. LAG3 (CD223) as a cancer immunotherapy target. Immunol Rev. 2017; 276(1): 80–96, doi: 10.1111/imr.12519, indexed in Pubmed: 28258692.
11. Triebel F, Jitsukawa S, Baixeras E, et al. LAG-3, a novel lymphocyte activation gene closely related to CD4. J Exp Med. 1990; 171(5): 1393–1405, doi: 10.1084/jem.171.5.1393, indexed in Pubmed: 1692078.
12. Shi AP, Tang XY, Xiong YL, et al. Immune Checkpoint LAG3 and Its Ligand FGL1 in Cancer. Front Immunol. 2021; 12: 785091, doi: 10.3389/fimmu.2021.785091, indexed in Pubmed: 35111155.
13. Ma C, Sun X, Shen D, et al. Ectopic expression of LAG-3 in non-small-cell lung cancer cells and its clinical significance. J Clin Lab Anal. 2020; 34(6): e23244, doi: 10.1002/jcla.23244, indexed in Pubmed: 32077528.
14. Workman CJ, Cauley LS, Kim IJ, et al. Lymphocyte activation gene-3 (CD223) regulates the size of the expanding T cell population following antigen activation in vivo. J Immunol. 2004; 172(9): 5450–5455, doi: 10.4049/jimmunol.172.9.5450, indexed in Pubmed: 15100286.
15. Schöffski P, Tan DSW, Martín M, et al. Phase I/II study of the LAG-3 inhibitor ieramilimab (LAG525) ± anti-PD-1 spartalizumab (PDR001) in patients with advanced malignancies. J Immunother Cancer. 2022; 10(2), doi: 10.1136/jitc-2021-003776, indexed in Pubmed: 35217575.
16. Du H, Yi Z, Wang L, et al. The co-expression characteristics of LAG3 and PD-1 on the T cells of patients with breast cancer reveal a new therapeutic strategy. Int Immunopharmacol. 2020; 78: 106113, doi: 10.1016/j.intimp.2019.106113, indexed in Pubmed: 31841754.
17. Stovgaard ES, Kümler I, List-Jensen K, et al. Prognostic and Clinicopathologic Associations of LAG-3 Expression in Triple-negative Breast Cancer. Appl Immunohistochem Mol Morphol. 2022; 30(1): 62–71, doi: 10.1097/PAI.0000000000000954, indexed in Pubmed: 34081635.
18. Wu S, Shi X, Wang J, et al. Triple-Negative Breast Cancer: Intact Mismatch Repair and Partial Co-Expression of PD-L1 and LAG-3. Front Immunol. 2021; 12: 561793, doi: 10.3389/fimmu.2021.561793, indexed in Pubmed: 33717059.
19. Luke J, Patel M, Hamilton E, et al. A phase I, first-in-human, open-label, dose-escalation study of MGD013, a bispecific DART molecule binding PD-1 and LAG-3, in patients with unresectable or metastatic neoplasms. Journal of Clinical Oncology. 2020; 38(15_suppl): 3004–3004, doi: 10.1200/jco.2020.38.15_suppl.3004.
20. Yap T, Wong D, Hu-Lieskovan S, et al. 395 A first-in-human study of FS118, a tetravalent bispecific antibody targeting LAG-3 and PD-L1, in patients with advanced cancer and resistance to PD-(L)1 therapy. Regular and young investigator award abstracts. 2020, doi: 10.1136/jitc-2020-sitc2020.0395.
21. Wang S, Zhang X, Leng S, et al. Immune Checkpoint-Related Gene Polymorphisms Are Associated With Primary Immune Thrombocytopenia. Front Immunol. 2020; 11: 615941, doi: 10.3389/fimmu.2020.615941, indexed in Pubmed: 33584705.
22. Manichaikul A, Lin H, Kang C, et al. Lymphocyte activation gene-3-associated protein networks are associated with HDL-cholesterol

and mortality in the Trans-omics for Precision Medicine program. Commun Biol. 2022; 5(1): 362, doi: 10.1038/s42003-022-03304-0, indexed in Pubmed: 35501457.
23. Wang M, Du Qi, Jin J, et al. LAG3 and its emerging role in cancer immunotherapy. Clin Transl Med. 2021; 11(3): e365, doi: 10.1002/ctm2.365, indexed in Pubmed: 33784013.
24. Al-Eitan L, Qudah MAl, Qawasmeh MAl. Association of Multiple Sclerosis Phenotypes with Single Nucleotide Polymorphisms of and Genes in a Jordanian Population: A Genotype-Phenotype Study. Biomolecules. 2020; 10(3), doi: 10.3390/biom10030356, indexed in Pubmed: 32111053.
25. Guo W, Zhou M, Qiu J, et al. Association of LAG3 genetic variation with an increased risk of PD in Chinese female population. J Neuroinflammation. 2019; 16(1): 270, doi: 10.1186/s12974-019-1654-6, indexed in Pubmed: 31847878.
26. Mewes C, Alexander T, Büttner B, et al. Effect of the Lymphocyte Activation Gene 3 Polymorphism rs951818 on Mortality and Disease Progression in Patients with Sepsis-A Prospective Genetic Association Study. J Clin Med. 2021; 10(22), doi: 10.3390/jcm10225302, indexed in Pubmed: 34830585.
27. Al-Eitan L, Al Qudah M, Al Qawasmeh M. Candidate gene association analysis of multiple sclerosis in the Jordanian Arab population: A case-control study. Gene. 2020; 758: 144959, doi: 10.1016/j.gene.2020.144959, indexed in Pubmed: 32683075.
28. Lee KM, Baris D, Zhang Y, et al. Common single nucleotide polymorphisms in immunoregulatory genes and multiple myeloma risk among women in Connecticut. Am J Hematol. 2010; 85(8): 560–563, doi: 10.1002/ajh.21760, indexed in Pubmed: 20568250.
29. Smigielski EM, Sirotkin K, Ward M, et al. dbSNP: a database of single nucleotide polymorphisms. Nucleic Acids Res. 2000; 28(1): 352–355, doi: 10.1093/nar/28.1.352, indexed in Pubmed: 10592272.
30. Brignone C, Gutierrez M, Mefti F, et al. First-line chemoimmunotherapy in metastatic breast carcinoma: combination of paclitaxel and IMP321 (LAG-3Ig) enhances immune responses and antitumor activity. J Transl Med. 2010; 8: 71, doi: 10.1186/1479-5876-8-71, indexed in Pubmed: 20653948.
31. Fertal SA, Poterala JE, Ponik SM, et al. Stromal Characteristics and Impact on New Therapies for Metastatic Triple-Negative Breast Cancer. Cancers (Basel). 2022; 14(5), doi: 10.3390/cancers14051238, indexed in Pubmed: 35267548.

VIA MEDICA

Original article

NOWOTWORY Journal of Oncology
2023, volume 73, number 3, 117–121
DOI: 10.5603/NJO.a2023.0024

ISSN: 0029–540X, e-ISSN: 2300-2115
www.nowotwory.edu.pl

# Efficacy of the mRNA SARS-CoV-2 vaccine in cancer patients during systemic therapy. A single-centre experience

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**Introduction.** A novel coronavirus, causing severe acute respiratory syndrome 2 (SARS-CoV-2) has spread globally since its emergence in December 2019. The mRNA SARS-CoV-2 vaccines have been proven to be an efficient and safe disease control means among adult patients without immunocompromising conditions. However, cancer patients were among the group of people that was initially excluded from the registration trials.

**Material and methods.** 60 patients, enrolled to this study, had been voluntarily vaccinated either with the BNT162b2 or mRNA-1273 SARS-CoV-2 vaccine between March and June 2021 and have been undergoing systemic treatment in the Clinical Oncology Unit of the University Clinical Center of the Medical University of Silesia in Katowice, Poland. Patients received 2 injections of vaccine 21 days apart and were tested with Elecsys® Anti-SARS-CoV-2 immunoassay (Roche Diagnostics, France) for the presence of anti-S-protein antibodies in the patients' serum. The serum samples were collected 2 to 8 weeks after receiving the second dose of vaccine.

**Results.** The BNT162b2 vaccine was administered to 57 patients, while the mRNA-1273 vaccine – to 3 patients. Seroconversion was achieved in 83.33% of patients. The median amount of anti-S-protein antibodies was 75,9 U/ml.There were no statistically significant differences in terms of age between the group with seroconversion and the group without seroconversion (Mann-Whitney U-test $p = 0.762$). There was no statistically significant correlation between neither the BMI (Spearman test, $p = 0.079$) norage (Spearman test, $p = 0.762$) and anti-S-protein antibody levels. Just as the diagnosis (primary tumor localization), clinical stage, type of modality (chemotherapy, chemoradiotherapy, immunotherapy) and the goal of treatment (radical, palliative) were not statistically significant in terms of anti-S-protein antibody levels.

**Conclusions.** Due to the high number of unresponsive or poorly responsive results, patients undergoing systemic therapy should be advised to maintain other measures of disease control such as distancing, usage of masks. Nevertheless, implementing mRNA SARS-CoV-2 vaccinesinimmunocompromised patientsduring systemic therapyis reasoned, valuable and safe.

**Key words:** cancer patients, systemic therapy, SARS-CoV-2, COVID-19, SARS-CoV-2 vaccine

**How to cite:**

Wnuk JS, Bobola A, Pietrzyński Ł, Gisterek I. *Efficacy of the mRNA SARS-CoV-2 vaccine in cancer patients during systemic therapy. A single-centre experience.* *NOWOTWORY J Oncol* 2023; 73: 117–121.

## Introduction

A novel coronavirus, causing severe acute respiratory syndrome 2 (SARS-CoV-2) has spread globally since its emergence in December 2019, affecting our lives dramatically [1]. Until now it has infected 650 million people worldwide [2]. Since then, governments have applied several control measures such as distancing, usage of masks, testing of exposed or symptomatic patients, isolation of symptomatic patients and vaccination programs.

The mRNA SARS-CoV-2 vaccines have been proven to be an efficient and safe disease control means among adult patients without immunocompromising conditions. Their effectiveness has been reported to oscillate around 95%. However, cancer patients were among the group of people that was initially excluded from the registration trials [3, 4]. Therefore, vaccine efficacy among patients in this group remains unclear.

What is more, cancer patients are also at greater risk of COVID-19 infection and worse outcomes of treatment [5, 6]. Therefore, it is implied that SARS-CoV-2 vaccination of patients treated with antineoplastic drugs should be prioritized [7, 8]. That is why the Ministry of Health in Poland in 05.03.2021 implemented guidelines encouraging cancer patients to be the first group of patients vaccinated in Poland, beside elderly citizens and health care workers [9].

## Material and methods

There were 60 patients who were enrolled in this study. We have included the patients who were voluntarily vaccinated either with BNT162b2 or mRNA-1273 SARS-CoV-2 vaccine between March and June 2021, according to the Polish SARS-CoV-2 vaccination program conducted by the Polish Ministry of Health and were currently undergoing systemic treatment in the Clinical Oncology Unit of the University Clinical Center of the Medical University of Silesia in Katowice, Poland [9]. According to the vaccination program, patients undergoing chemotherapy were vaccinated between the third and seventh day from the last received chemotherapy infusion. Patients undergoing immunotherapy could be vaccinated at any time during their treatment.

Patients received 2 vaccine injections 21 days apart and were tested with Elecsys® Anti-SARS-CoV-2 immunoassay (Roche Diagnostics, France) for the presence of anti-S-protein antibodies in their serum. The serum samples were collected 2 to 8 weeks after receiving the second dose of the vaccine. The test used to determine levels of anti-S-protein antibodies was an electrochemiluminescent immunoassay. Its positive cutoff value was set at 0.80 U/mL, according to procedures guidelines.

We have collected demographic data such as the patients' sex, age, height, weight. Data concerning the oncologic treatment included the diagnosis, clinical stage, type of therapy carried out (chemotherapy, chemoradiotherapy, immunotherapy) and the goal of treatment (radical, palliative) were included in the analysis. We measured the time of receiving the second injection of the vaccine after the last dose of systemic treatment.

The Mann-Whitney U-test for comparing two groups or the Kruskal-Wallis ANOVA test for multi-group comparisons was used to compare quantitative variables. The relationships between quantitative variables were analyzed using the Spearman's rank correlation coefficient. The $Chi^2$ test and its variants were used to compare the qualitative data. The analysis was performed using STATISTICA 13.3 software (TIBCO software). The $p < 0.05$ values were considered significant.

## Results

There were 60 patients included in the statistical analysis – 36 women and 24 men. Demographic details are presented in table I.

The BNT162b2 vaccine was administered to 57 patients, while the mRNA-1273 vaccine – to 3 patients. Seroconversion, defined as the amount of anti-S-protein antibodies above 0.80 U/ml was achieved in 83.33% of patients. The median amount of anti-S-protein antibodies was 75.9 U/ml, (min.

**Table I.** Demographic data

| Parameter | Total | Females | Males |
|---|---|---|---|
| sex | 60 | 36 | 24 |
| age (years) | • median: 63<br>• min.–max.: 33–78<br>• interquartile range: 54.5–67.5 | • median: 62<br>• min.–max.: 35–78<br>• interquartile range: 51–67 | • median: 63.5<br>• min.–max.: 33–78<br>• interquartile range: 59–68 |
| weight (kg) | • median: 71<br>• min.–max.: 47–137<br>• interquartile range: 59–81.5 | • median: 66<br>• min.–max.: 47–121<br>• interquartile range: 58.5–76.5 | • median: 74<br>• min.–max.: 50–137<br>• interquartile range: 68–86.5 |
| BMI ($kg/m^2$) | • median: 25.36<br>• min.–max.: 17.47–54.5<br>• interquartile range: 22.32–28.84 | • median: 25.39<br>• min.–max.: 17.47–54.5<br>• interquartile range: 22.02–29.39 | • median: 25.04<br>• min. –max.: 17.96–39.18<br>• interquartile range: 23.22–27.53 |

**Table II.** Antibody levels and vaccination efficacy according to patient diagnosis

| Diagnostic group (nr of patients) | Anti-S-protein antibody level [U/ml] | % of levels above 0.8 U/ml |
|---|---|---|
| breast cancer (14) | • median: 64.86<br>• min.–max.: 0.4–1,200 | 71.4% |
| lung cancer (9) | • median: 76.08<br>• min.–max.: 0.25–2,500 | 77.7% |
| gastrointestinal cancers (24) | • median: 39.77<br>• min.–max.: 0.4–2,500 | 91.67% |
| gynecologic cancers (7) | • median: 39.77<br>• min.–max.: 0.4–168.3 | 71.43% |

*There were 2 cases of head and neck cancers, 2 cases of NET, 1 case of seminoma and 1 case of AB type metastatic thymoma that are not shown in the table

**Table III.** Antibody levels and vaccination efficacy according to clinical stage of the diseases

| Clinical stage (number of patients) | Anti-S-protein antibody level [U/ml] | % of levels above 0.8 U/ml |
|---|---|---|
| I (6) | • median: 75.9<br>• min.–max.: 0.4–2,500 | 83.33% |
| II (9) | • median: 47.6<br>• min.–max.: 0.4–1,200 | 66.67% |
| III (18) | • median: 55.3<br>• min.–max.: 0.5–2,500 | 88.89% |
| IV (27) | • median: 96.8<br>• min.–max.: 0.2–2500 | 85.18% |

**Table IV.** Antibody levels and vaccination efficacy according to treatment modality

| Treatment modality (number of patients) | Anti-S-protein antibody level [U/ml] | % of levels above 0.8 U/ml |
|---|---|---|
| chemotherapy (42) | • median: 71.1<br>• min.–max.: 0.4–2,500 | 80.92% |
| chemoradiotherapy (2) | • median: 16.3<br>• min.–max.: 8.7–23.9 | 100% |
| immunotherapy (12) | • median: 79.1<br>• min.–max.: 0.25–2,500 | 83.33% |
| chemotherapy with concurrent immunotherapy (4) | • median: 561.6<br>• min.–max.: 39.7–2,500 | 100% |

–max. range: 0.4–2500 U/ml). There were no statistically significant differences in terms of age between the group with seroconversion and the group without seroconversion (Mann-Whitney U-test, p = 0.762). There was no statistically significant correlation between the body-mass index (BMI) and anti-S-protein antibody levels (Spearman test, p = 0.079) or age and anti-S-protein antibody levels (Spearman test, p = 0.762). Data concerning differences in anti-S-protein antibody levels among different diagnostic groups are presented in table II. The differences were not statistically significant (ANOVA Kruskal-Wallis, p = 0.125). The difference in vaccination efficacy between patients diagnosed with gastrointestinal cancers and other patients is not statistically significant (Fisher's exact test, p = 0.144) (tab. II). There were no statistically significant differences between groups with different clinical stages of the disease in terms of antibody levels. Details of this analysis is presented in table III.

The difference in vaccination efficacy between patients in II stage of the disease and other patients is not statistically significant (Fisher's exact test, p = 0.166). There were no statistically significant differences in terms of anti-S-protein antibody levels between patients with palliative and radical intention of treatment (Mann-Whitney U-test, p = 0.326). Table IV presents data regarding different modalities of treatment. There were no statistically significant differences between those groups (ANOVA Kruskal-Wallis, p = 0.268).

The median time between receiving a second injection of the vaccine and the last course of systemic therapy was 10 days (mean: 10.05, min.–max.: 0–46 days). This parameter was not correlated with any level of detected antibodies (Spearman test, p = 0.09). There were no severe adverse events connected with mRNA SARS-CoV-2 vaccinations reported by patients.

## Discussion

According to registration trials, the mRNA SARS-CoV-2 vaccine is an effective and safe mean of disease control. Its efficacy was determined at to be 95% (BNT162b2 vaccine) and 94.1% (mRNA-1,273 vaccine).

Those studies as the primary end points had serologic or virologic evidence of SARS-CoV-2 infection or presence of COVID-19 symptoms [3, 4]. We have based our study on detecting seroconversion after at least 2 weeks of receiving the second dose of the vaccination. It was detected in 83.33% of tested patients and there were no statistically significant differences within secondary analyses performed in this study. This stands in accordance with other studies conducted on patients with immunocompromised conditions. In Barrière's et al. study, 47.5% of patients had anti-S-seroconversion after 3 to 4 weeks, and 95.2% after 6 to 8 weeks after the second dose of the vaccination. What is more, antibody levels were significantly lower compared to the control group consisting of people with no known immunocompromising condition [10].

In Monin's et al. study, seroconversion after the first dose of the vaccination was observed in 35% of cancer patients and in 95% after the booster – 21 days after the 1st injection [11]. According to Addeo et al., seroconversion was observed in 94% of patients after the receipt of two doses of vaccine [12].

Differences between our study and the cited examples may be caused by used methodology. We did not differentiate between patients tested after 2 or 8 weeks after

**Table V.** Comparison of study results

| Author | Year | Seroconversion in cancer patients | Seroconversion in the control group | Malignancy |
|---|---|---|---|---|
| Addeo et al. [12] | 2021 | 94% | – | solid tumor and hematologic malignancies |
| Ariamanesh et al. [15] | 2021 | 86.9% | – | hematologic malignancies |
| Barrière et al. [10] | 2021 | 95.2% | – | solid tumor |
| Cai et al. [16] | 2022 | 83.3% | 96.3% | solid tumor |
| Massarweh et al. [17] | 2021 | 90% | 100% | solid tumor |
| Monin et al. [11] | 2021 | 95% | 100% | solid tumor |
| Schmueli et al. [18] | 2021 | 84.1% | 98.9% | solid tumor |
| Waldhorn [19] | 2021 | 79% | 84% | solid tumor |
| Yasin et al. [20] | 2022 | 85.2% | 97.5% | solid tumor |
| this study | 2023 | 83.33% | – | solid tumor |

the 2nd dose of the vaccine. Agbarya et al. provided data suggesting that up to 23.3% of patients were seronegative after the second dose of the vaccination [13]. Those results are also compliant with a systemic review by Tran et al. In their study, there were 21 works included providing data from a total of 2,309 patients with solid cancer. Seroconversion after the second dose of the vaccine was observed in 91–97% of patients [14]. The comparison of study results are presented in table V.

We did not observe any association between the seroconversion rate and age or chemotherapy in our study, which stands in contrast with a study by Yasim et al. [20]. This may be due to differences in the patient population size enrolled in the studies, which was larger in Yasim's study. Similar effects were also detected in studies by Massarweh et al., Ariamanesh et al. and Buttiron Webber et al. [15, 17, 21]. The results of this study are also similar to studies on the influenza vaccination in patients undergoing chemotherapy [22, 23]. The goal of treatment (radical or palliative) or the patients' age did also not affect the results of the vaccination [23]. In our study there was no correlation between BMI and the amount of anti-S antibodies detected. In the large prospective study by Nilles et al., after adjusted analysis there was no evidence of increased seroprevalence with increasing BMI among tested patients. There was also no statistically significant differences between seropositive obese and non-obese patients in terms of peak SARS-CoV-2 IgG titters [24].

Unfortunately, some patients did not follow the Ministry of Health recommendations and had themselves vaccinated within 2 days of finishing the last dose of systemic treatment. There were seven cases of such practice in our study, but only in one case was anti-S-protein antibodies undetectable (a 68-year-old male patient, treated with chemotherapy due to CS III lung cancer, sequential chemoradiation).

## Conclusions

Due to the high number of unresponsive or poorly responsive results, patients undergoing systemic therapy should be advised to maintain other measures of disease control such as social distancing and the use of masks. Swab testing of asymptomatic patients should be considered before admission to the hospital. The duration of immunity after receiving a 2-dose regimen remains unknown and requires further studies.

**Conflict of interest:** none declared. Elecsys® Anti-SARS-CoV-2 immunoassay tests were provided by Roche.

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*Received: 24 Jan 2023*
*Accepted: 24 May 2023*

## References

1. Dykas P, Wisła R. The Socioeconomic Impact of COVID-19 on Eastern European Countries. 2021, doi: 10.4324/9781003211891.
2. Coronavirus Resource Center John Hopkins University & Medicine. https://coronavirus.jhu.edu/map.html (13.12.2022).
3. Absalon J, Koury K, Gruber WC, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2021; 384(16): 1576–1577, doi: 10.1056/NEJMc2036242, indexed in Pubmed: 33596348.
4. Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med. 2021; 384(5): 403–416, doi: 10.1056/NEJMoa2035389, indexed in Pubmed: 33378609.
5. Wang QQ, Berger NA, Xu R. Analyses of Risk, Racial Disparity, and Outcomes among US Patients with Cancer and COVID-19 Infection. JAMA Oncol. 2021; 7(2): 220–227, doi: 10.1001/jamaoncol.2020.6178, indexed in Pubmed: 33300956.
6. Sharafeldin N, Su J, Madhira V, et al. Outcomes of COVID-19 in cancer patients: Report from the National COVID Cohort Collaborative (N3C). J Clin Oncol. 2021; 39(15_suppl): 1500–1500, doi: 10.1200/jco.2021.39.15_suppl.1500.

7. Desai A, Gainor J, Hegde A, et al. Author Correction: COVID-19 vaccine guidance for patients with cancer participating in oncology clinical trials. Nature Reviews Clinical Oncology. 2021; 18(5): 320–320, doi: 10.1038/s41571-021-00503-2.
8. Hwang JK, Zhang T, Wang AZ, et al. COVID-19 vaccines for patients with cancer: benefits likely outweigh risks. J Hematol Oncol. 2021; 14(1): 38, doi: 10.1186/s13045-021-01046-w, indexed in Pubmed: 33640005.
9. Wspólne wytyczne dla pacjentów z grupy 1B i personelu medycznego w zakresie szczepienia przeciwko COVID-19 - Ministerstwo Zdrowia. https://www.gov.pl/web/szczepimysie/wspolne-wytyczne--dla-pacjentow-z-grupy-1b-i-personelu-medycznego-w-zakresie-szczepienia-przeciwko-covid-19.
10. Barrière J, Chamorey E, Adjtoutah Z, et al. Impaired immunogenicity of BNT162b2 anti-SARS-CoV-2 vaccine in patients treated for solid tumors. Ann Oncol. 2021; 32(8): 1053–1055, doi: 10.1016/j.annonc.2021.04.019, indexed in Pubmed: 33932508.
11. Monin L, Laing AG, Muñoz-Ruiz M, et al. Safety and immunogenicity of one versus two doses of the COVID-19 vaccine BNT162b2 for patients with cancer: interim analysis of a prospective observational study. Lancet Oncol. 2021; 22(6): 765–778, doi: 10.1016/S1470-2045(21)00213-8, indexed in Pubmed: 33930323.
12. Addeo A, Shah PK, Bordry N, et al. Immunogenicity of SARS-CoV-2 messenger RNA vaccines in patients with cancer. Cancer Cell. 2021; 39(8): 1091–1098.e2, doi: 10.1016/j.ccell.2021.06.009, indexed in Pubmed: 34214473.
13. Agbarya A, Sarel I, Ziv-Baran T, et al. Efficacy of the mRNA-Based BNT162b2 COVID-19 Vaccine in Patients with Solid Malignancies Treated with Anti-Neoplastic Drugs. Cancers (Basel). 2021; 13(16), doi: 10.3390/cancers13164191, indexed in Pubmed: 34439346.
14. Tran S, Truong TH, Narendran A. Evaluation of COVID-19 vaccine response in patients with cancer: An interim analysis. Eur J Cancer. 2021; 159: 259–274, doi: 10.1016/j.ejca.2021.10.013, indexed in Pubmed: 34798454.
15. Ariamanesh M, Porouhan P, PeyroShabany B, et al. Immunogenicity and Safety of the inactivated SARS-CoV-2 vaccine (BBIBP-CorV) in patients with malignancy. Cancer Invest. 2022; 40(1): 26–34, doi: 10.1080/07357907.2021.1992420.
16. Cai SW, Chen JY, Wan R, et al. Efficacy and safety profile of two-dose SARS-CoV-2 vaccines in cancer patients: An observational study in China. World J Clin Cases. 2022; 10(31): 11411–11418, doi: 10.12998/wjcc.v10.i31.11411, indexed in Pubmed: 36387801.
17. Massarweh A, Eliakim-Raz N, Stemmer A, et al. Evaluation of Seropositivity Following BNT162b2 Messenger RNA Vaccination for SARS--CoV-2 in Patients Undergoing Treatment for Cancer. JAMA Oncol. 2021; 7(8): 1133–1140, doi: 10.1001/jamaoncol.2021.2155, indexed in Pubmed: 34047765.
18. Shmueli ES, Itay A, Margalit O, et al. Efficacy and safety of BNT162b2 vaccination in patients with solid cancer receiving anticancer therapy - a single centre prospective study. Eur J Cancer. 2021; 157: 124–131, doi: 10.1016/j.ejca.2021.08.007, indexed in Pubmed: 34508994.
19. Waldhorn I, Holland R, Goshen-Lago T, et al. Six-Month Efficacy and Toxicity Profile of BNT162b2 Vaccine in Cancer Patients with Solid Tumors. Cancer Discov. 2021; 11(10): 2430–2435, doi: 10.1158/2159-8290.CD-21-1072, indexed in Pubmed: 34475136.
20. Yasin AI, Aydin SG, Sümbül B, et al. Efficacy and safety profile of COVID-19 vaccine in cancer patients: a prospective, multicenter cohort study. Future Oncol. 2022; 18(10): 1235–1244, doi: 10.2217/fon-2021-1248, indexed in Pubmed: 35081732.
21. Buttiron Webber T, Provinciali N, Musso M, et al. Predictors of poor seroconversion and adverse events to SARS-CoV-2 mRNA BNT162b2 vaccine in cancer patients on active treatment. Eur J Cancer. 2021; 159: 105–112, doi: 10.1016/j.ejca.2021.09.030, indexed in Pubmed: 34742157.
22. Lo W, Whimbey E, Elting L, et al. Antibody response to a two-dose influenza vaccine regimen in adult lymphoma patients on chemotherapy. Eur J Clin Microbiol Infect Dis. 1993; 12(10): 778–782, doi: 10.1007/BF02098469, indexed in Pubmed: 8307050.
23. Nordøy T, Aaberge IS, Husebekk A, et al. Cancer patients undergoing chemotherapy show adequate serological response to vaccinations against influenza virus and Streptococcus pneumoniae. Med Oncol. 2002; 19(2): 71–78, doi: 10.1385/MO:19:2:71, indexed in Pubmed: 12180483.
24. Nilles EJ, Siddiqui SM, Fischinger S, et al. Epidemiological and Immunological Features of Obesity and SARS-CoV-2. Viruses. 2021; 13(11), doi: 10.3390/v13112235, indexed in Pubmed: 34835041.

VIA MEDICA

Original article

NOWOTWORY Journal of Oncology
2023, volume 73, number 3, 122–128
DOI: 10.5603/NJO.a2023.0025

ISSN: 0029–540X, e-ISSN: 2300-2115
www.nowotwory.edu.pl

# Implementation of a population-based breast cancer prevention program in Poland before, during and after the COVID-19 pandemic. Poland in comparison with other countries

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**Introduction.** Breast cancer is the most common malignant tumor in women in Poland and in the world. It accounts for about 24% of all cancer cases in Polish women. The aim of this study was to analyze the coverage of the population eligible for a population-based breast cancer prevention program in Poland before, during and after the COVID-19 pandemic, and to compare the Polish data with data from other countries around the world.

**Material and methods.** The study was based on epidemiological data related to the performance of mammography examinations among Polish women under the breast cancer prevention program. The results were compared with data from other countries around the world.

**Results.** In the years 2014–2022, a significant decrease was observed in the number of mammography examinations among Polish women under the population-based breast cancer prevention program.

**Conclusions.** A continuous decrease in the number of preventive examinations in Poland is related not only to the COVID-19 pandemic, but also to the discontinuation of sending paper invitations for mammography under the breast cancer prevention program.

**Key words:** breast cancer, prevention, cancer

## Introduction

Breast cancer is the most common malignant tumor in women in Poland and in the world [1, 2]. It accounts for about 24% of all cancer cases in Polish women [1]. It is more common after menopause than before. The risk of developing the disease increases after the age of 50. An analysis of incidence rates in individual age groups showed a significant increase in the group of patients aged 50–69 years [3]. Risk factors for breast cancer include:

- age 50–69,
- breast cancer in the family (the degree of risk depends on the number of cases in the family and the degree of relatedness with the ill person),
- mutations found in the *BRCA1* and/or *BRCA2* genes,

**How to cite:**

Borowska MW, Religioni U, Augustynowicz A. ***Implementation of a population-based breast cancer prevention program in Poland before, during and after the COVID-19 pandemic. Poland in comparison with other countries.*** *NOWOTWORY J Oncol* 2023; 73: 122–128.

- early menarche – before the age of 12,
- late menopause – after the age of 55,
- having a child after the age of 35,
- childlessness,
- alcohol consumption,
- obesity among postmenopausal [2, 4, 5].

The etiology of breast cancer is still not sufficiently clear. The same cancer can be induced by several or even a dozen or so carcinogenic factors. More and more frequently, genetic determinants are indicated as risk factors for developing breast cancer: about 10% of breast cancer cases in Poland occur in women with mutations in genes, most often in *BRCA1* [6–8]. It is of key importance to detect cancer at the earliest stage of its development. Mammography is a medical examination that allows the diagnosis of pathological changes in the breast tissue. Its sensitivity is the highest of all tests, and it is estimated at 90–95% in postmenopausal women. In the group of women aged 50–69 who had mammography examinations every year or every 2 years, there was a 25–30% reduction in mortality. It is recommended to perform a mammography in 2 projections: every 2 years in women from the low-risk group who are aged 50–69, and every year in women from the high-risk group I.

In populations where preventive examinations are not performed, there is a high mortality rate due to advanced invasive breast cancer. Invasive breast cancer requires costly treatment. Depending on the clinical stage of advancement, surgical treatment (breast amputation), radiotherapy or systemic treatment (chemotherapy, hormone therapy) is applied. All these treatment methods are very expensive [9].

In the USA and in the countries of the European Union, it was recognized that the most effective method to reduce breast cancer incidence and to improve the results of malignant tumor treatment are national cancer control programs. These programs are financed from the state budget, and apart from population screening, they involve the purchase of modern diagnostic and therapeutic equipment and educational activities among the general population and medical staff [10–12].

According to data from the World Health Organization, the incidence of cancer is mainly influenced by three factors: lifestyle, genes and the environment. The World Health Organization's estimates on the possibility of cancer prevention suggest that even 30% to 50% of cancer cases can be prevented by avoiding risk factors. These factors include:

- smoking,
- excessive body weight (obesity),
- improper diet,
- alcohol,
- low physical activity,
- lack of vaccinations [2, 5].

According to the latest report published in November 2022 by the Sarcoma Association for Sarcomas and Melanomas, as many as 39% of Polish women and men do not know that free of charge, National Health Fund-financed, preventive examinations detecting cancer at an early stage are available in Poland. Almost half of Polish men and women cannot name any preventive examination for cancer. As many as 2 out of 3 people do not perform regular preventive examinations for cancer. Unfortunately, the report also shows that every fifth Pole believes that prophylaxis will not save their life [13].

The prevention program for early detection of breast cancer in Poland, which is financed by the National Health Fund, has been developed for women aged 50–69 who have not had a mammography examination in the last 24 months and for those who have received a written recommendation to repeat the mammography examination after 12 months. The reason to repeat the mammography may be risk factors: breast cancer in family members (mother, sister or daughter) and mutations in the *BRCA1* and/or *BRCA2* genes. A mammography examination is free of charge and does not require a doctor's referral. The aim of the program is to reduce the mortality rate due to breast cancer to the level achieved in the leading European Union countries, to increase the level of knowledge among women about breast cancer prevention and to introduce rules of diagnostic procedures across the country [14, 15].

The aim of the study was to analyze the coverage of the population eligible for the population-based breast cancer prevention program in Poland before, during and after the COVID-19 pandemic, and to compare Polish data with data from other countries around the world.

## Material and methods

The material consists of epidemiological data on the performance of mammography examinations in Polish women under the population breast cancer prevention program in the years 2014–2022. The data are obtained from monthly reports published by the National Health Fund [15]. The prevention program for early breast cancer detection is addressed to women aged 50–69 who have not had a mammography examination in the last 24 months and to those who have received a written recommendation to repeat a mammography examination after 12 months.

The aim of the program is to reduce the mortality rate due to breast cancer to the level achieved in the leading European Union countries. The study is also based on epidemiological data on preventive screenings for early detection of breast cancer in other countries around the world, obtained from the Health at Glance 2021 Organization for Economic Cooperation and Development report (OECD) [2].

## Results

Every year, a population of over five million women aged 50–69 is eligible for a preventive mammographic examination under the Population Breast Cancer Prevention Program (tab. I).

The highest percentage of the population was covered by preventive mammography examinations in 2014 (over

**Table I.** Population coverage in women aged 50–69 by prophylactic mammography as part of the Population-based Breast Cancer Prevention Program 2014–2022 in Poland

| Year | Females | | |
|---|---|---|---|
| | eligible | excluded from the program | who took part in the research |
| 2014 | 5,337,265 | 2,389,269 | 44.77% |
| 2015 | 5,404,594 | 2,381,783 | 44.07% |
| 2016 | 5,428,839 | 2,270,033 | 41.81% |
| 2017 | 5,425,011 | 2,141,972 | 39.27% |
| 2018 | 5,393,354 | 2,092,405 | 38.51% |
| 2019 | 5,378,866 | 2,057,447 | 37.78% |
| 2020 | 5,352,470 | 1,848,381 | 34.89% |
| 2021 | 5,334,865 | 1,771,513 | 33.72% |
| 2022 | 5,401,858 | 2,016,543 | 35.90% |

Source: Narodowy Fundusz Zdrowia

44% population coverage). In the following years, a decrease in the percentage of women aged 50–69 was observed with regard to the performance of mammography examinations. The lowest percentage was observed in the years 2020 and 2021, during the COVID-19 pandemic. Then, in 2022, about 36% of eligible women were examined under the Population Breast Cancer Prevention Program. One of the most probable and impactful factors for the systematic decrease in the percentage of women reporting for mammography examinations under the population breast cancer prevention program is the discontinuation of sending paper invitations to patients, among other reasons. The lowest values were reported during the COVID-19 pandemic due to the limited access to medical facilities, patient isolation and patient fear related not only to the examination itself, but also to the possibility of contracting the SARS-CoV-2 virus during the examination.

Polish women can do mammography examinations not only under the population-based breast cancer prevention program that is addressed to women aged 50–69, but also under outpatient specialist care and under health policy programs implemented by local government units at all levels, which are developed, implemented and financed by provinces, districts and communes. Health policy programs for breast cancer prevention involve not only mammography but also ultrasound examinations for younger women, educational activities addressed to all age groups, and therapeutic programs addressed to women who suffer from cancer and often have already had a mastectomy.

The total percentage of mammography examinations that are performed in Poland and OECD countries is presented in table II, which includes data from the years 2009 and 2019, and in the case of several countries, data from the year 2020, and the average of 61.7% in OECD countries in 2019.

**Table II.** Mammography screening in women aged 50–69 within the past 2 years, 2009, 2019 (or nearest years) and 2020

| Location | 2009 | 2019 | 2020 |
|---|---|---|---|
| Sweden[2] | 90.4% | 95.2% | |
| Denmark[1] | 77.4% | 83.2% | |
| Spain[2] | 73.3% | 81.5% | 73.8% |
| Finland[1] | 85.5% | 81.3% | |
| Portugal[2] | 84.2% | 80.2% | |
| Slovenia[1] | 85.1% | 76.8% | 74.3% |
| United States[2] | 80.4% | 76.5% | |
| Netherlands[1] | 82.2% | 76.1% | |
| United Kingdom[1] | 76.8% | 75.1% | |
| Austria[2] | 72.7% | 74.5% | |
| Israel[1] | 68.6% | 72.1% | |
| Ireland[1] | 75.7% | 71.6% | |
| Norway[1] | 71.9% | 71.6% | |
| New Zealand[1] | 66.9% | 71.5% | 68.3% |
| Korea[1] | 55.1% | 70.2% | |
| Greece[2] | 49.6% | 65.7% | |
| Canada[1] | 52.8% | 62.0% | |
| **OECD36** | **58.2%** | **61.7%** | |
| Czech Republic[1] | 48.4% | 60.9% | |
| Italy[1] | 60.0% | 60.7% | |
| Belgium[1] | 62.5% | 60.2% | |
| Iceland[1 3] | 60.7% | 60.0% | 62.0% |
| Estonia[1] | 52.0% | 55.9% | |
| Luxembourg[1 3] | 63.6% | 55,1% | |
| Australia[1] | 56.2% | 54.5% | |
| **Poland[2]** | **57.1%** | **53.7%** | |
| Lithuania[1] | 25.6% | 52.9% | 45.3% |
| Germany[1] | 54.4% | 50.1% | |
| Switzerland[2] | 47.4% | 49.0% | |
| France[1] | 52.7% | 48.8% | |
| Mexico[1] | 17.8% | 45.4% | |
| Japan[2] | 36.4% | 44.6% | |
| Chile[1] | 19.3% | 40.1% | 36.3% |
| Latvia[1] | 21.1% | 39.1% | |
| Hungary[1] | 47.0% | 39.1% | |
| Turkey[1] | 30.2% | 36.0% | 26.9% |
| Slovakia[1] | 34.9% | 31.0% | |

[1] programme data; [2] survey data; * 3 year average. Source: OECD Health Statistics 2021

The average performance of preventive mammography among women aged 50–69 in OECD countries was 61.7% in 2019. The highest percentage of mammography examinations was carried out in Sweden (95.2%), Denmark, Spain, Finland and Portugal (values above 80%: 83.2%, 81.5%, 81.3%, 80.2%, respectively). The lowest percentage of mammography examinations was carried out in Latvia, Hungary, Turkey and Slovakia (39.1%, 39.1%, 36.0%, 31.0%, respectively). Data for the year 2020 are incomplete due to the lack of reporting related to the COVID-19 pandemic. Countries that gathered data that were later developed by the OECD were: Spain, Slovenia, New Zealand, Iceland, Lithuania, Chile and Turkey. The highest percentage was reported in Slovenia (74.3%) and Spain (73.8%), and the lowest in Turkey (26.9%). Comparison of the data from 2019 and 2020 showed a decrease in the performance of mammography examinations among women of all countries except Iceland (a different method of reporting). Regarding Poland, the coverage value of 53.7% that was reported by the OECD in 2019 was lower than the OECD average.

The availability of preventive mammography is also related to the number of mammograms available in Poland. Table III presents the number of mammography machines in OECD countries per million inhabitants as of 2021, broken down by outpatient care facilities and hospitals, as well as the summary results.

The biggest number of mammograms in the OECD countries was reported in the United States of America (7,720 per 1,000,000 inhabitants), Greece (68,790 per 1,000,000 inhabitants) and Korea (65,090 per 1,000,000 inhabitants). This is also related to the availability of examinations and the percentage of women who regularly perform preventive mammography examinations. The lowest percentage (in total) was reported in Mexico (9,570 per 1,000,000 inhabitants), Poland (10,260 per 1,000,000 inhabitants) and the Czech Republic (10,560 per 1,000,000 inhabitants).

## Discussion

The report *Health at a Glance 2021* shows that the cancer incidence rate in Poland is still relatively low and on average it amounts to 267 persons per 100,000 inhabitants. This rate is lower than in the majority of OECD countries, where the average is 294 persons/100,000. In turn, the cancer mortality rate in Poland is one of the highest in OECD countries and amounts to 228 deaths per 100,000 inhabitants, with an average of 191 deaths per 100,000 population. Poland lags behind other OECD countries with regard to breast cancer diagnosis and treatment [2].

Since breast cancer is the cancer with the highest incidence among women in all OECD countries and the second most common cause of cancer-related deaths among women, a separate section of the *Health at a Glance 2021* report is devoted to this disease. Many OECD countries have implemented breast cancer screening programs, which led to an increase in the proportion of women having mammography examinations from 58.2% in 2009 to 61.7% in 2019. In Poland, an opposite trend can be observed: the share of women aged 50–69 who underwent mammography examinations in the last two years decreased from 57.1% in 2009 to 53.7% in 2019 (survey data).

According to data from the report, the COVID-19 pandemic reduced the popularity of breast cancer screening tests, which may have had a negative impact on the results of breast cancer treatment in the OECD countries. This can already be seen in the Netherlands, where screening tests were suspended during the first wave of COVID in 2020 and a higher percentage of patients diagnosed with advanced breast cancer was recorded, as compared to data from the equivalent time period in the previous two years [2]. According to data from OECD countries from the years 2010–2014, 51.5% of women with breast cancer were diagnosed at an early stage of the disease, and 8.6% were diagnosed at an advanced stage. In Poland, the rate of early detection of breast cancer is unfortunately low, and it amounts to 41.3%, which is more than 10 percentage points below the average for the OECD countries [2].

Studies conducted in many countries indicate that the level of health behavior is influenced by various socio-demographic factors, such as age, education, marital status, family situation, social origin and material status [16, 17]. In a study on the socio-demographic profile of women participating in mammography screening tests in Lower Silesia Province, reasons for the low performance of mammography examinations were indicated. They included factors such as place of residence, age, education and professional status. Women aged 55–59, with at least secondary education, mostly pensioners, underwent mammography examinations more frequently than the representatives of other age groups [18]. In 2010, the opinion of women living in villages in the Kuyavian-Pomeranian Province were examined with regards to the importance of breast cancer prevention. More than half of the respondents had never participated in preventive examinations. Most of the respondents admitted that knowledge about the importance of mammography checks, the occurrence of disturbing breast symptoms or medical recommendations did not sufficiently motivate them to participate in screening tests. The only factor that pushed them to do a mammography examination were disturbing changes in the mammary gland [19]. The population-based breast cancer prevention program is a relatively young program. It has been carried out since 2007 with no restrictions on the number of examinations and sending out invitations (paper invitations for examinations stopped being sent out in 2015) [20].

In Sweden, where the population coverage is very high (the highest in the OECD countries), preventive examinations are paid. In another Scandinavian country, if a woman fails to attend the examination after the third invitation, she receives information about an increase in the health insurance premi-

**Table III.** Mammography machines in ambulatory care providers / total / in hospitals, per 1,000,000 inhabitants, 2021 or latest available

| Location | In ambulatory care providers | In hospitals | Total |
|---|---|---|---|
| Australia | data not available | data not available | 20,590 |
| Austria | 19,290 | 2,360 | 21,640 |
| Belgium | 16,700 | 19,590 | 36,400 |
| Canada | data not available | data not available | 17,470 |
| Colombia | data not available | 22,310 | data not available |
| Costa Rica | data not available | 8,720 | 8,720 |
| Czechia | 4,860 | 5,700 | 10,560 |
| Denmark | 1,030 | 14,900 | 15,920 |
| Estonia | 3,010 | 8,270 | 11,280 |
| Finland | 0.000 | 30,920 | 30,920 |
| France | data not available | 6,970 | data not available |
| Germany | data not available | 4,870 | data not available |
| Greece | 54,870 | 13,930 | 68,790 |
| Iceland | 16,370 | 0.000 | 16,370 |
| Ireland | data not available | data not available | 16,850 |
| Israel | 5,770 | 5,020 | 10,780 |
| Italy | 16,090 | 19,190 | 35,280 |
| Japan | data not available | data not available | 33,780 |
| Korea | 41,920 | 23,170 | 65,090 |
| Latvia | 16,310 | 11,580 | 27,890 |
| Lithuania | 7,510 | 10,370 | 17,880 |
| Luxembourg | 0.000 | 11,030 | 11,030 |
| Mexico | 2,100 | 7,470 | 9,570 |
| New Zealand | data not available | data not available | 20,730 |
| Norway | data not available | data not available | 11,870 |
| Poland | 4,380 | 5,880 | 10,260 |
| Slovak Republic | 6,230 | 9,890 | 16,120 |
| Slovenia | 5,690 | 9,010 | 14,700 |
| Spain | 2,600 | 13,980 | 16,570 |
| Switzerland | data not available | data not available | 29,640 |
| Sweden | data not available | 19,120 | data not available |
| United Kingdom | data not available | 11,220 | data not available |
| United States | data not available | data not available | 70,720 |

Source: https://data.oecd.org/healtheqt/mammography-machines.htm

um. Information about the breast cancer prevention program effectively reached the group of women aged 50–69, but did not affect the number of examinations. The reasons behind this phenomenon should be sought in the attitude of the media to negative statistics and in impersonal messages. A personal invitation or recommendation from a doctor or friend was more encouraging than other forms of communication. It seems advisable to continue sending personal invitations to women, e.g. *via* the Online Patient Account. Considering that 41% of respondents in the Millward Brown study declared that it

was not their own choice to perform the examination, there is a need to educate this particular group on the possibilities of effective treatment of early detected breast cancer. These women also need information about easy access to medical care if cancer is detected. Women should be convinced that preventive examinations should be performed when a woman is healthy, that is, before the disease manifests itself clinically, and lesions can be detected in advance in a mammography examination [20–24].

In the Millward Brown study from 2015 on the attitudes towards the breast cancer prevention program, attention was drawn to the role of the media and representatives of medical staff in encouraging women to perform preventive mammography examinations. Considering the media, the respondents were of the opinion that instead of providing information on the number of deaths, it is better to talk and write about successfully treated patients who have had a mammography examination [27]. In this study, 83% of respondents were well acquainted with the Population Program for Early Detection of Breast Cancer. According to the respondents, the best source of information about it was the mass media (television, press and radio – 42.5%) [25]. An important role was also played by personal invitations (28.3%), leaflets and posters in health care facilities (23.5%). As many as 41% of women who did not make the decision about the mammography examination on their own knew about free of charge mammography examinations. This attitude resulted from harmful stereotypes about cancer, such as "let sleeping dogs lie" (24% of responses); "it's better not to know" (24% of responses); "better leave it" (21% of responses) [25]. A different approach to mammography was represented by Polish women who had a mammography performed as part of the breast cancer prevention program in the population. They believed that "examination guarantees access to treatment" (32% of responses), there is a possibility of further diagnosis (28% of responses), and "cancer that is detected early can be cured" (32% of responses) [27]. The study also shows that as many as 72% of Polish women aged 50–69 visit a family doctor at least once a year, and the respondents trust their doctors, which is why they would like primary health care physicians to control the health of their patients on their own initiative and remind them about the schedule of preventive examinations [25].

It is important for women to have a positive attitude towards medical examinations, as British analyzes show that 63% of patients with a positive attitude to mammography examinations participated in the screening tests on time, and 72% of those with a negative attitude did not undergo the examinations on time [26].

In Europe, the best rates of cancer control are achieved in the Nordic countries, where conditions for easier access to medical examinations have been created, and methods of persuading women to systematically participate in screening tests have been developed. This is important because the detection of cancer in the early, preclinical phase is more prognostic than any combination of treatment methods in the later phase of the disease [27–29].

With regards to the modification of the age of women eligible for preventive mammography examinations under a population-based breast cancer prevention program, the latest American College of Physicians (ACP) guidelines on mammography screening, which were published in the Annals of Internal Medicine, should be considered. These guidelines were created based on the analysis of the recommendations of 7 English-speaking societies (USPSTF, ACS, ACR, American College of Obstetricians and Gynecologists, Canadian Task Force on Preventive Health Care, National Comprehensive Cancer Network and the World Health Organization). They suggest having a discussion with women aged 40–49 about the potential benefits and disadvantages of an early mammography. In this age group, the risks outweigh the benefits. The recommendations also indicate that women aged 50–74 should undergo preventive mammography examinations every 2 years. Preventive examinations should be stopped when a woman reaches the age of 75 or if life expectancy is less than 10 years. Clinical breast examinations should not be used as a screening test in any age group. These guidelines are dedicated to women with an average risk of breast cancer, without mutations in the *BRCA* genes, or a history of breast cancer in the family [30].

## Conclusions

Both the data on the population-based breast cancer prevention program reported by the National Health Fund and the overall data reported by the OECD indicate a low percentage of performance of mammography examinations in Poland. Among other factors, the decrease in the percentage of women reporting for mammography examinations under the population breast cancer prevention program can be related to the discontinuation of sending paper invitations out to patients. It should be considered to reintroduce the sending out of paper invitations. The COVID-19 pandemic had little impact on the decline in women's performance of mammography examinations under the population-based breast cancer prevention program, which had been observed for several years.

Although the number of breast cancer cases in Poland is relatively low compared to OECD countries, the number of deaths is definitely high. This is related to the detection of cancer at a late stage of the disease. It is worth considering the inclusion of women up to 74 years of age into the screening tests under the population-based breast cancer prevention program. Among the possible solutions which could be taken in order to address the challenge of low participation in breast cancer screenings in Poland, it is worth considering reintroducing sending out paper invitations and introducing invitations by e-mail or telephone.

In addition, breast cancer screening promotion should be used in social media and with the participation of opinion leaders and authorities in the medical community. Reaching out to young people who are users of social media should create agility and influence of young people on close elderly people, especially grandmothers. Employers should be also involved in creating the optimum conditions for taking care of their employees' health and carrying out preventive measures, as well as encouraging female staff to carry out examinations.

**Conflict of interest:** none declared

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*Received: 30 Jan 2023*
*Accepted: 27 Apr 2023*

## References

1. Wojciechowska U, Barańska K, Michałek I, et al. Nowotwory złośliwe w Polsce w 2020 roku. Ministerstwo Zdrowia, Warszawa 2022.
2. Health at a Glance 2021. https://www.oecd.org/health/health-at-a-glance/ (15.01.2023).
3. Duffy SW, Vulkan D, Cuckle H, et al. Effect of mammographic screening from age 40 years on breast cancer mortality (UK Age trial): final results of a randomised, controlled trial. Lancet Oncol. 2020; 21(9): 1165–1172, doi: 10.1016/S1470-2045(20)30398-3, indexed in Pubmed: 32800099.
4. https://onkologia.org.pl/pl/epidemiologia/nowotwory-zlosliwe-w-polsce (15.01.2023).
5. Kozierkiewicz A. Biała Księga. Zwalczanie raka jelita grubego i raka piersi w Polsce na tle wybranych krajów europejskich. Ośrodek Analiz Uniwersyteckich, Warszawa-Kraków 2011.
6. Brożek I, Limon J. Poradnictwo genetyczne w dziedzicznym raku piersi. In: Jassem J, Krzakowski M. ed. Rak piersi. Praktyczny przewodnik dla lekarzy. Via Medica, Gdańsk 2009: 20–31.
7. Paluch-Shimon S, Cardoso F, Sessa C, et al. ESMO Guidelines Committee. Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening. Ann Oncol. 2016; 27(suppl 5): v103–v110, doi: 10.1093/annonc/mdw327, indexed in Pubmed: 27664246.
8. De Felice F, Marchetti C, Musella A, et al. Bilateral risk-reduction mastectomy in BRCA1 and BRCA2 mutation carriers: a meta-analysis. Ann Surg Oncol. 2015; 22(9): 2876–2880, doi: 10.1245/s10434-015-4532-1, indexed in Pubmed: 25808098.
9. Kuhl C, Schrading S, Leutner C, et al. Mammography, Breast Ultrasound, and Magnetic Resonance Imaging for Surveillance of Women at High Familial Risk for Breast Cancer. J Clin Oncol. 2005; 23(33): 8469–8476, doi: 10.1200/jco.2004.00.4960.
10. Wolff A, Hammond M, Allison K, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. Arch Pathol Lab Med. 2018; 142(11): 1364–1382, doi: 10.5858/arpa.2018-0902-sa.
11. Mann RM, Balleyguier C, Baltzer PA, et al. European Society of Breast Imaging (EUSOBI), with language review by Europa Donna–The European Breast Cancer Coalition. Breast MRI: EUSOBI recommendations for women's information. Eur Radiol. 2015; 25(12): 3669–3678, doi: 10.1007/s00330-015-3807-z, indexed in Pubmed: 26002130.
12. Sardanelli F, Fallenberg EM, Clauser P, et al. European Society of Breast Imaging (EUSOBI), with language review by Europa Donna–The European Breast Cancer Coalition. Mammography: an update of the EUSOBI recommendations on information for women. Insights Imaging. 2017; 8(1): 11–18, doi: 10.1007/s13244-016-0531-4, indexed in Pubmed: 27854006.
13. Dlaczego się nie badamy? Profilaktyka nowotworowa Polek i Polaków Raport Sarcoma. Stowarzyszenie Pomocy Chorym na Mięsaki i Czerniaki Sarcoma 2022.
14. https://www.nfz-szczecin.pl/hxavi_wczesne_wykrywanie_raka_piersi.htm (15.01.2023).
15. https://www.nfz.gov.pl/dla-pacjenta/programy-profilaktyczne/dane-o-realizacji-programow/ (15.01.2023).
16. Ostrowska A. Profilaktyka raka szyjki macicy i raka piersi: Wiedza, postawy i zachowania kobiet. Wybrane wyniki badań. Instytut Filozofii i Socjologii PAN, Warszawa 2010.
17. Padoan M, Ferrante D, Pretti G, et al. Study of socio-economic characteristics, diagnosis and outcome of women participating or not participating in mammogram screening. Ann Ig. 2014; 26(6): 518–526, doi: 10.7416/ai.2014.2010, indexed in Pubmed: 25524076.
18. Garwacka-Czachor E, Maciejczyk A, Bębenek M. Profil społeczno-demograficzny kobiet biorących udział w skriningu mammograficznym na Dolnym Śląsku. Biuletyn Polskiego Towarzystwa Onkologicznego NOWOTWORY. 2017; 2(2): 119–126.
19. Koper A, Kalisz Z, Mierzwa T. et.al. Znaczenie profilaktyki raka piersi w opinii kobiet wiejskich w woj. kujawsko- pomorskim. Probl Hig Epidemiol. 2010; 91(Supl. 1): 54–55.
20. Dyzmann-Sroka A, Trojanowski M. Dlaczego Polki nie robią badań profilaktycznych? Nowiny Lekarskie. 2012; 81(3): 258–264.
21. Perry N, Broeders M, de Wolf C. European guidelines for quality assurance in breast cancer screening and diagnosis; fourth edition. European Comission, Belgia 2006: 3–49.
22. Verdecchia A, Francisci S, Brenner H, et al. EUROCARE-4 Working Group. Recent cancer survival in Europe: a 2000-02 period analysis of EUROCARE-4 data. Lancet Oncol. 2007; 8(9): 784–796, doi: 10.1016/S1470-2045(07)70246-2, indexed in Pubmed: 17714993.
23. Dyzmann-Sroka A, Jędrzejczak A, Kubiak A, et al. Wiedza o nowotworach i profilaktyce. Raport dla województwa wielkopolskiego. Wielkopolskie Centrum Onkologii, Poznań 2008: 3–34.
24. Wronkowski Z, Zwierko M, Nowacki M. Zasady i wyniki programu modelowego skryningu raka piersi i raka szyjki macicy w Polsce, 1999-2000. Nowotwory, Warszawa 2002: 1–157.
25. SMG/KRC – Instytut Millward Brown „Postawy wobec programu profilaktyki raka piersi" 2015.
26. Smith SM, Ford JS, Rakowski W, et al. Inconsistent mammography perceptions and practices among women at risk of breast cancer following a pediatric malignancy: a report from the Childhood Cancer Survivor Study. Cancer Causes Control. 2010; 21(10): 1585–1595, doi: 10.1007/s10552-010-9587-5, indexed in Pubmed: 20506037.
27. Klint A, Engholm G, Storm HH, et al. Trends in survival of patients diagnosed with cancer of the digestive organs in the Nordic countries 1964-2003 followed up to the end of 2006. Acta Oncol. 2010; 49(5): 578–607, doi: 10.3109/02841861003739330, indexed in Pubmed: 20491524.
28. Kozierkiewicz A, Bochenek T, Gilewski D, et al. Biała Księga. Zwalczanie raka jelita grubego i raka piersi w Polsce na tle wybranych krajów europejskich. Prognozy zapadalności na raka piersi. Ośrodek Analiz Uniwersyteckich, Polskie Towarzystwo Onkologiczne, Warszawa–Kraków 2011.
29. Storm HH, Engholm G, Hakulinen T, et al. Survival of patients diagnosed with cancer in the Nordic countries up to 1999-2003 followed to the end of 2006. A critical overview of the results. Acta Oncol. 2010; 49(5): 532–544, doi: 10.3109/02841861003801148, indexed in Pubmed: 20491522.
30. https://www.acpjournals.org/doi/abs/10.7326/AITC201606070 (15.01.2023).

VIA MEDICA

Special article

NOWOTWORY Journal of Oncology
2023, volume 73, number 3, 129–145
DOI: 10.5603/NJO.2023.0026

ISSN: 0029–540X, e-ISSN: 2300-2115
www.nowotwory.edu.pl

# Cancer incidence and mortality in Poland in 2020

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**Introduction.** Morbidity due to malignant neoplasms has been growing steadily during the last three decades, and cancer has become the second most widespread cause of death. The aim of this article is to present a summary of the epidemiological indicators of malignant neoplasms in Poland in 2020.

**Material and methods.** In the following report, we present the latest estimates of morbidity and mortality from cancer in Poland in 2020–2022 and a wide range of information on the occurrence of registered cancer cases and deaths in 2020, according to sex, age, cancer site, or Polish administrative division. Cancer data was collected by the National Cancer Registry and the Central Statistical Office.

**Results.** The PNCR received information about 146,181 new cases and 99,871 thousand cancer deaths in 2020. Compared to the previous year, the number of cancer cases decreased by about 12,000 in both sexes.

**Conclusions.** An important phenomenon that appeared in 2020 was the COVID-19 pandemic. It more than likely significantly influenced cancer cases under-registration.

**Key words:** mortality, morbidity, neoplasms, Poland

## Introduction

Cancer is an increasing health problem in Poland. The number of cases has been growing steadily during the last three decades, and cancer has become the second most common cause of death, constituting nearly one-fifth of deaths (21% of deaths in 2020 [1]). At the beginning of the 2nd decade of the the 21st century, over 1.3 million Poles were living with a cancer diagnosis and it was estimated that in 2020, for every 100,000 inhabitants – 381 people were diagnosed with cancer [2]. The aim of the article is to present a summary of the epidemiological indicators of malignant neoplasms in Poland in 2020.

## Material and methods

### *Source of data and identification of cancer cases*

Data on cancer cases are derived from the Polish National Cancer Registry. The data is collected on the basis of a unified protocol valid in the whole country, which allows us to maintain the same cancer registration rules in Poland. The source of data on deaths from cancer is the Central Statistical Office. All presented data are collected following the 10th Revision of the International Classification of Diseases and Health Problems [3].

**How to cite:**
Wojciechowska U, Barańska K, Miklewska M, Didkowska JA. ***Cancer incidence and mortality in Poland in 2020.*** *NOWOTWORY J Oncol* 2023; 73: 129–145.

### *Statistical analysis*

In this report, the basic statistical indicators were used: absolute numbers, percentages, crude and age-standardized the World Standard Population (ASW, Segi's standard [4]), revised European Standard Population (ESP2013 [5]) rates, and 5-years survival rates. Projected data for 2020–2022 were estimated based on linear regression.

## Results

### *Overall national analysis*

In Poland, cancer is still a growing social problem and is both an economic and health challenge. The most common cancers in men in 2020 were (listed as the most common):

- prostate (20%),
- lung (16%),

**Table I.** Cancer incidence in Poland in 2020

| Cancer site | ICD-10 | Absolute number | Crude rate | Stand. rate (ESP2013) | Absolute number | Crude rate | Stand. rate (ESP2013) |
|---|---|---|---|---|---|---|---|
| | | males | | | females | | |
| **all cancers** | **C00–D09** | **72,651** | **391.6** | **466.6** | **73,530** | **371.3** | **351.5** |
| oral cavity and pharynx | C00–C14 | 2,792 | 15.0 | 16.4 | 1 ,108 | 5.6 | 5.2 |
| • lip | C00 | 168 | 0.9 | 1.2 | 78 | 0.4 | 0.4 |
| • tongue | C01–C02 | 560 | 3.0 | 3.2 | 237 | 1.2 | 1.1 |
| • pharynx | C10–C13 | 668 | 3.6 | 3.8 | 154 | 0.8 | 0.7 |
| digestive organs | C15–C26 | 16,111 | 86.8 | 104.3 | 12,415 | 62.7 | 58.9 |
| • oesophagus | C15 | 976 | 5.3 | 5.9 | 343 | 1.7 | 1.6 |
| • stomach | C16 | 2,856 | 15.4 | 18.8 | 1,649 | 8.3 | 7.8 |
| • small intestine | C17 | 181 | 1.0 | 1.1 | 166 | 0.8 | 0.8 |
| • colon | C18 | 4,978 | 26.8 | 33.1 | 4,366 | 22.0 | 20.7 |
| • rectosigmoid junction | C19 | 823 | 4.4 | 5.4 | 592 | 3.0 | 2.8 |
| • rectum | C20 | 3,126 | 16.9 | 19.9 | 1,931 | 9.8 | 9.2 |
| • anus and anal canal | C21 | 83 | 0.4 | 0.5 | 192 | 1.0 | 0.9 |
| • colorectum | C18–C21 | 9,010 | 48.6 | 58.9 | 7,081 | 35.8 | 33.6 |
| • liver | C22 | 759 | 4.1 | 4.8 | 505 | 2.6 | 2.4 |
| • gallbladder and biliary tract | C23–C24 | 506 | 2.7 | 3.4 | 761 | 3.8 | 3.6 |
| • pancreas | C25 | 1,747 | 9.4 | 11.0 | 1,808 | 9.1 | 8.6 |
| respiratory system | C30–C39 | 13,318 | 71.8 | 83.7 | 7,776 | 39.3 | 36.4 |
| • larynx | C32 | 1,499 | 8.1 | 8.9 | 260 | 1.3 | 1.2 |
| • trachea and lung | C33–C34 | 11,534 | 62.2 | 73.1 | 7,309 | 36.9 | 34.2 |
| bone and articular cartilage | C40–C41 | 167 | 0.9 | 0.9 | 145 | 0.7 | 0.7 |
| neoplasms of skin | C43–C44 | 6,702 | 36.1 | 48.4 | 7,135 | 36.0 | 33.9 |
| • melanoma | C43 | 1 565 | 8.4 | 9.9 | 1,680 | 8.5 | 8.1 |
| • other neoplasms of skin | C44 | 5,137 | 27.7 | 38.5 | 5,455 | 27.5 | 25.7 |
| mesothelial and soft tissue | C45–C49 | 792 | 4.3 | 4.9 | 679 | 3.4 | 3.3 |
| breast | C50 | 113 | 0.6 | 0.7 | 17,511 | 88.4 | 84.4 |
| female genital organs | C51–C58 | – | – | – | 10,912 | 55.1 | 52.4 |
| • vulva and vagina | C51–C52 | – | – | – | 547 | 2.8 | 2.6 |
| • cervix uteri | C53 | – | – | – | 1,920 | 9.7 | 9.2 |

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**Table I. cont.** Cancer incidence in Poland in 2020

| Cancer site | ICD-10 | Absolute number | Crude rate | Stand. rate (ESP2013) | Absolute number | Crude rate | Stand. rate (ESP2013) |
|---|---|---|---|---|---|---|---|
| | | males | | | females | | |
| • corpus uteri | C54 | – | – | – | 5,238 | 26.5 | 25.1 |
| • ovary | C56 | – | – | – | 3,012 | 15.2 | 14.6 |
| male genital organs | C60–C63 | 15,691 | 84.6 | 99.3 | – | – | – |
| • penis | C60 | 273 | 1.5 | 1.8 | – | – | – |
| • prostate | C61 | 14,244 | 76.8 | 91.7 | – | – | – |
| • testis | C62 | 1,156 | 6.2 | 5.6 | – | – | – |
| urinary tract | C64–C68 | 7,826 | 42.2 | 51.0 | 3,466 | 17.5 | 16.5 |
| • kidney and renal pelvis | C64–C65 | 2,892 | 15.6 | 17.7 | 1,878 | 9.5 | 9.0 |
| • urinary bladder | C67 | 4,815 | 26.0 | 32.5 | 1,516 | 7.7 | 7.1 |
| eye | C69 | 206 | 1.1 | 1.2 | 219 | 1.1 | 1.1 |
| central nervous system | C70–C72 | 1,353 | 7.3 | 7.9 | 1,229 | 6.2 | 6.0 |
| • brain | C71 | 1,293 | 7.0 | 7.5 | 1,156 | 5.8 | 5.6 |
| endocrine glands | C73–C75 | 648 | 3.5 | 3.6 | 2,788 | 14.1 | 13.7 |
| • thyroid gland | C73 | 574 | 3.1 | 3.1 | 2,699 | 13.6 | 13.3 |
| ill-defined, secondary and unspecified sites | C76–C80 | 1 494 | 8.1 | 10.0 | 1,402 | 7.1 | 6.6 |
| lymphoid, haematopoietic and related tissue | C81–C96 | 4,235 | 22.8 | 26.3 | 3,896 | 19.7 | 18.9 |
| • Hodgkin lymphoma | C81 | 340 | 1.8 | 1.8 | 341 | 1.7 | 1.7 |
| • non-Hodgkin lymphoma | C82–C85 | 1,525 | 8.2 | 9.4 | 1,439 | 7.3 | 6.9 |
| • immunoproliferative diseases | C88 | 28 | 0.2 | 0.2 | 32 | 0.2 | 0.2 |
| • multiple myeloma | C90 | 714 | 3.8 | 4.6 | 730 | 3.7 | 3.5 |
| • lymphoid leukaemia | C91 | 949 | 5.1 | 6.1 | 712 | 3.6 | 3.5 |
| • myeloid leukaemia | C92 | 550 | 3.0 | 3.4 | 505 | 2.6 | 2.4 |
| • all leukaemias | C91–C95 | 1,610 | 8.7 | 10.2 | 1,322 | 6.7 | 6.4 |
| • other and unspecified neoplasms of lymphoid, haematopoietic and related tissue | C96 | 18 | 0.1 | 0.1 | 32 | 0.2 | 0.1 |
| primary multiple sites | C97 | 0 | 0.0 | 0.0 | 0 | 0.0 | 0.0 |
| cancers *in situ* | D00–D09 | 1,203 | 6.5 | 8.1 | 2,849 | 14.4 | 13.7 |

- colon (7%),
- bladder cancers (7%).

In women, these were:

- breast (24%),
- lung (10%),
- corpus uteri (7%),
- colon (6%),
- ovarian (4%),
- thyroid cancers (4%) (tab. I).

Among the main causes of death, the most common cancer sites were lung cancer (26% in men and 18% in women), prostate cancer (11%) in men and breast cancer in women (15%) (tab. II). Detailed data on morbidity and mortality in women and men are presented in tables I and II, respectively.

### *Predictions for 2020 and 2022*

The precise number of cancer cases in 2022 is still unknown due to collecting data method (a 2 year delay to ensure completeness of data). The prediction of the incidence in 2020 and 2022 was made based on the trend from 2010–2019. The results of the morbidity and mortality are presented in tables III and IV, respectively.

**Table II.** Cancer deaths in Poland in 2020

| Cancer site | ICD-10 | Absolute number | Crude rate | Stand. rate (ESP2013) | Absolute number | Crude rate | Stand. rate (ESP2013) |
|---|---|---|---|---|---|---|---|
| | | males | | | females | | |
| **all cancers** | **C00–D09** | **54,370** | **293.1** | **377.7** | **45,501** | **229.8** | **213.9** |
| oral cavity and pharynx | C00–C14 | 2,253 | 12.1 | 13.4 | 764 | 3.9 | 3.6 |
| • lip | C00 | 79 | 0.4 | 0.6 | 37 | 0.2 | 0.2 |
| • tongue | C01–C02 | 430 | 2.3 | 2.5 | 141 | 0.7 | 0.7 |
| • pharynx | C10–C13 | 609 | 3.3 | 3.6 | 137 | 0.7 | 0.6 |
| digestive organs | C15–C26 | 16,133 | 87.0 | 111.3 | 12,066 | 60.9 | 56.7 |
| • oesophagus | C15 | 1,227 | 6.6 | 7.6 | 355 | 1.8 | 1.7 |
| • stomach | C16 | 3,115 | 16.8 | 21.6 | 1,657 | 8.4 | 7.8 |
| • small intestine | C17 | 126 | 0.7 | 0.8 | 105 | 0.5 | 0.5 |
| • colon | C18 | 4,415 | 23.8 | 32.3 | 3,535 | 17.9 | 16.6 |
| • rectosigmoid junction | C19 | 424 | 2.3 | 3.0 | 326 | 1.6 | 1.5 |
| • rectum | C20 | 2,213 | 11.9 | 15.6 | 1,345 | 6.8 | 6.3 |
| • anus and anal canal | C21 | 129 | 0.7 | 0.9 | 115 | 0.6 | 0.5 |
| • colorectum | C18–C21 | 7,181 | 38.7 | 51.8 | 5,321 | 26.9 | 24.9 |
| • liver | C22 | 1,265 | 6.8 | 8.3 | 875 | 4.4 | 4.1 |
| • gallbladder and biliary tract | C23–C24 | 592 | 3.2 | 4.1 | 988 | 5.0 | 4.7 |
| • pancreas | C25 | 2,431 | 13.1 | 15.7 | 2,542 | 12.8 | 12.0 |
| respiratory system | C30–C39 | 15,926 | 85.8 | 104.3 | 8,404 | 42.4 | 39.2 |
| • larynx | C32 | 1,409 | 7.6 | 8.9 | 195 | 1.0 | 0.9 |
| • trachea and lung | C33–C34 | 14,229 | 76.7 | 93.5 | 8,009 | 40,4 | 37.3 |
| bone and articular cartilage | C40–C41 | 167 | 0.9 | 1.1 | 145 | 0.7 | 0.7 |
| neoplasms of skin | C43–C44 | 1,432 | 7.7 | 11.5 | 1,401 | 7.1 | 6.4 |
| • melanoma | C43 | 762 | 4.1 | 5.4 | 668 | 3.4 | 3.1 |
| • other neoplasms of skin | C44 | 670 | 3.6 | 6.1 | 733 | 3.7 | 3.3 |
| mesothelial and soft tissue | C45–C49 | 570 | 3.1 | 3.7 | 460 | 2.3 | 2.2 |
| breast | C50 | 77 | 0.4 | 0.6 | 6,956 | 35.1 | 32.9 |
| female genital organs | C51–C58 | – | – | – | 6,811 | 34.4 | 32.3 |
| • vulva and vagina | C51–C52 | – | – | – | 409 | 2.1 | 1.9 |
| • cervix uteri | C53 | – | – | – | 1,511 | 7.6 | 7.2 |
| • corpus uteri | C54 | – | – | – | 1,811 | 9.1 | 8.5 |
| • ovary | C56 | – | – | – | 2,688 | 13.6 | 12.8 |
| male genital organs | C60–C63 | 6,010 | 32.4 | 48.4 | – | – | – |
| • penis | C60 | 110 | 0.6 | 0.8 | – | – | – |
| • prostate | C61 | 5,748 | 31.0 | 46.7 | – | – | – |
| • testis | C62 | 137 | 0.7 | 0.7 | – | – | – |
| urinary tract | C64–C68 | 4,802 | 25.9 | 35.4 | 1,967 | 9.9 | 9.3 |
| • kidney and renal pelvis | C64–C65 | 1,521 | 8.2 | 10.4 | 1,001 | 5.1 | 4.8 |

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**Table II. cont.** Cancer deaths in Poland in 2020

| Cancer site | ICD-10 | Absolute number | Crude rate | Stand. rate (ESP2013) | Absolute number | Crude rate | Stand. rate (ESP2013) |
|---|---|---|---|---|---|---|---|
| | | males | | | females | | |
| • urinary bladder | C67 | 3,202 | 17.3 | 24.4 | 915 | 4.6 | 4.3 |
| eye | C69 | 57 | 0.3 | 0.4 | 54 | 0.3 | 0.3 |
| central nervous system | C70–C72 | 1,621 | 8.7 | 10.0 | 1,432 | 7.2 | 6.8 |
| • brain | C71 | 1,571 | 8.5 | 9.7 | 1,365 | 6.9 | 6.5 |
| endocrine glands | C73–C75 | 187 | 1.0 | 1.2 | 283 | 1.4 | 1.4 |
| • thyroid gland | C73 | 125 | 0.7 | 0.8 | 222 | 1.1 | 1.1 |
| ill-defined, secondary and unspecified sites | C76–C80 | 1,768 | 9.5 | 12.5 | 1,775 | 9.0 | 8,2 |
| lymphoid, haematopoietic and related tissue | C81–C96 | 3,304 | 17.8 | 23.5 | 2,945 | 14.9 | 13.9 |
| • Hodgkin lymphoma | C81 | 102 | 0.5 | 0.6 | 65 | 0.3 | 0.3 |
| • non-Hodgkin lymphoma | C82–C85 | 921 | 5.0 | 6.5 | 769 | 3.9 | 3.6 |
| • immunoproliferative diseases | C88 | 27 | 0.1 | 0.2 | 13 | 0.1 | 0.1 |
| • multiple myeloma | C90 | 680 | 3.7 | 4.8 | 770 | 3.9 | 3.7 |
| • lymphoid leukaemia | C91 | 706 | 3.8 | 5.3 | 578 | 2.9 | 2.7 |
| • myeloid leukaemia | C92 | 666 | 3.6 | 4.6 | 586 | 3.0 | 2.8 |
| • all leukaemias | C91–C95 | 1,509 | 8.1 | 11.0 | 1,280 | 6.5 | 6.0 |
| • other and unspecified neoplasms of lymphoid, haematopoietic and related tissue | C96 | 65 | 0.4 | 0.4 | 48 | 0.2 | 0.2 |
| primary multiple sites | C97 | 60 | 0.3 | 0.4 | 37 | 0.2 | 0.2 |
| cancers *in situ* | D00–D09 | 3 | 0.0 | 0.0 | 1 | 0.0 | 0.0 |

**Table III.** Cancer cases in Poland in 2019 and estimates for 2022. Data for 2022 is estimated on the basis of the trend from 2010–2019

| Cancer site | ICD-10 | 2019 observed | | | 2022 expected | | |
|---|---|---|---|---|---|---|---|
| | | Absolute number | Crude rate | Standardized rate (ESP2013) | Absolute number | Crude rate | Standardized rate (ESP2013) |
| | | males | | | | | |
| **all cancers** | **C00–D09** | **85,559** | **460.75** | **563.73** | **89,699** | **490.7** | **575.4** |
| oesophagus | C15 | 1,139 | 6.13 | 6.95 | 1,214 | 6.6 | 7.2 |
| stomach | C16 | 3,230 | 17.39 | 21.59 | 3,063 | 16.8 | 20.1 |
| colorectum | C81–C21 | 10,397 | 55.99 | 69.92 | 11,155 | 61.0 | 73.2 |
| pancreas | C25 | 1,920 | 10.34 | 12.16 | 1,868 | 10.2 | 11.7 |
| larynx | C32 | 1,688 | 9.09 | 10.19 | 1,638 | 9.0 | 9.8 |
| lung | C33–C34 | 13,819 | 74.42 | 89.24 | 12,659 | 69.2 | 79.8 |
| melanoma | C43 | 1,749 | 9.42 | 11.28 | 2,073 | 11.3 | 13.1 |
| prostate | C61 | 17,638 | 94.98 | 117.93 | 21,093 | 115.4 | 133.5 |
| kidney | C64 | 3,214 | 17.31 | 19.71 | 3,372 | 18.4 | 20.3 |
| urinary bladder | C67 | 5,482 | 29.52 | 38.04 | 5,696 | 31.2 | 38.3 |
| brain | C71 | 1,382 | 7.44 | 8.24 | 1,291 | 7.1 | 7.6 |
| Hodgkin lymphoma | C81 | 365 | 1.97 | 1.98 | 346 | 1.9 | 1.9 |

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**Table III. cont.** Cancer cases in Poland in 2019 and estimates for 2022. Data for 2022 data is estimated on the basis of the trend from 2010–2019

| Cancer site | ICD-10 | 2019 observed | | | 2022 expected | | |
|---|---|---|---|---|---|---|---|
| | | Absolute number | Crude rate | Standardized rate (ESP2013) | Absolute number | Crude rate | Standardized rate (ESP2013) |
| | | males | | | | | |
| non-Hodgkin lymphomas | C82–C85 + C96 | 1,682 | 9.06 | 10.71 | 1,732 | 9.5 | 11.0 |
| leukaemias | C91–C95 | 1,995 | 10.74 | 13.06 | 2,044 | 11.2 | 13.1 |
| | | females | | | | | |
| **all cancers** | **C00–D09** | **85,659** | **432.25** | **413.26** | **89,815** | **459.50** | **425.99** |
| stomach | C16 | 1,870 | 9.44 | 9.01 | 1,862 | 9.53 | 8.77 |
| colorectum | C81–C21 | 8,117 | 40.96 | 39.04 | 8,554 | 43.76 | 40.39 |
| gallbladder | C23–C24 | 892 | 4.50 | 4.24 | 746 | 3.82 | 3.45 |
| pancreas | C25 | 1,932 | 9.75 | 9.20 | 1,990 | 10.18 | 9.28 |
| lung | C33–C34 | 8,480 | 42.79 | 40.15 | 9,198 | 47.06 | 41.97 |
| melanoma | C43 | 1,940 | 9.79 | 9.41 | 2,282 | 11.67 | 10.95 |
| breast | C50 | 19,620 | 99.01 | 95.23 | 20,413 | 104.44 | 97.79 |
| cervix uteri | C53 | 2,407 | 12.15 | 11.58 | 2,085 | 10.67 | 9.87 |
| corpus uteri | C54 | 6,023 | 30.39 | 29.16 | 6,581 | 33.67 | 31.30 |
| ovary | C56 | 3,710 | 18.72 | 18.12 | 3,786 | 19.37 | 18.30 |
| kidney | C64 | 2,000 | 10.09 | 9.75 | 2,108 | 10.78 | 9.95 |
| urinary bladder | C67 | 1,851 | 9.34 | 8.76 | 2,083 | 10.66 | 9.60 |
| brain | C71 | 1,172 | 5.91 | 5.72 | 1,115 | 5.70 | 5.42 |
| thyroid gland | C73 | 3,490 | 17.61 | 17.19 | 4,206 | 21.52 | 20.83 |
| Hodgkin lymphoma | C81 | 334 | 1.69 | 1.70 | 333 | 1.71 | 1.73 |
| non-Hodgkin lymphomas | C82–C85+C96 | 1,702 | 8.59 | 8.21 | 1,722 | 8.81 | 8.18 |
| leukaemias | C91–C95 | 1,567 | 7.91 | 7.67 | 1,637 | 8.37 | 7.86 |

**Table IV.** Cancer deaths in Poland in 2019 and estimates for 2022. Data for 2022 is estimated on the basis of the trend from 2010–2019

| Cancer site | ICD-10 | 2019 observed | | | 2022 expected | | |
|---|---|---|---|---|---|---|---|
| | | Absolute number | Crude rate | Standardized rate (ESP2013) | Absolute number | Crude rate | Standardized rate (ESP2013) |
| | | males | | | | | |
| **all cancers** | **C00–D09** | **54,370** | **292.8** | **382.6** | **54,601** | **298.7** | **382.2** |
| oesophagus | C15 | 1,311 | 7.1 | 8.2 | 1,262 | 6.9 | 7.7 |
| stomach | C16 | 3,116 | 16.8 | 21.7 | 2,816 | 15.4 | 19.5 |
| colorectum | C81–C21 | 7,047 | 37.9 | 51.9 | 7,357 | 40.2 | 53.6 |
| pancreas | C25 | 2,435 | 13.1 | 16.1 | 2,455 | 13.4 | 16.2 |
| larynx | C32 | 1,267 | 6.8 | 7.9 | 1,327 | 7.3 | 8.4 |
| lung | C33–C34 | 14,921 | 80.4 | 99.7 | 14,383 | 78.7 | 95.0 |
| melanoma | C43 | 788 | 4.2 | 5.8 | 812 | 4.4 | 6.1 |
| prostate | C61 | 5,618 | 30.3 | 46.4 | 6,202 | 33.9 | 50.5 |

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**Table IV. cont.** Cancer deaths in Poland in 2019 and estimates for 2022. Data for 2022 data is estimated on the basis of the trend from 2010–2019

| Cancer site | ICD-10 | 2019 observed | | | 2022 expected | | |
|---|---|---|---|---|---|---|---|
| | | Absolute number | Crude rate | Standardized rate (ESP2013) | Absolute number | Crude rate | Standardized rate (ESP2013) |
| | | males | | | | | |
| kidney | C64 | 1,504 | 8.1 | 10.5 | 1,524 | 8.3 | 10.6 |
| urinary bladder | C67 | 3,131 | 16.9 | 24.2 | 3,305 | 18.1 | 25.6 |
| brain | C71 | 1,462 | 7.9 | 9.3 | 1,511 | 8.3 | 9.5 |
| Hodgkin lymphoma | C81 | 89 | 0.5 | 0.5 | 88 | 0.5 | 0.5 |
| non-Hodgkin lymphomas | C82–C85 + C96 | 1,022 | 5.5 | 7.2 | 1,134 | 6.2 | 8.0 |
| leukaemias | C91–C95 | 1,553 | 8.4 | 11.5 | 1,555 | 8.5 | 11.4 |
| | | females | | | | | |
| **all cancers** | **C00–D09** | **45,954** | **231.9** | **219.3** | **47,467** | **242.8** | **221.0** |
| stomach | C16 | 1,716 | 8.7 | 8.2 | 1,653 | 8.5 | 7.7 |
| colorectum | C81–C21 | 5,343 | 27.0 | 25.5 | 5,478 | 28.0 | 25.6 |
| gallbladder | C23–C24 | 1,176 | 5.9 | 5.6 | 1,026 | 5.2 | 4.7 |
| pancreas | C25 | 2,633 | 13.3 | 12.5 | 2,663 | 13.6 | 12.4 |
| lung | C33–C34 | 8,215 | 41.5 | 38.9 | 9,133 | 46.7 | 41.8 |
| melanoma | C43 | 676 | 3.4 | 3.2 | 720 | 3.7 | 3.3 |
| breast | C50 | 6,951 | 35.1 | 33.3 | 7,549 | 38.6 | 35.5 |
| cervix uteri | C53 | 1,569 | 7.9 | 7.5 | 1,484 | 7.6 | 6.9 |
| corpus uteri | C54 | 1,859 | 9.4 | 8.9 | 2,214 | 11.3 | 10.3 |
| ovary | C56 | 2,777 | 14.0 | 13.4 | 2,845 | 14.6 | 13.5 |
| kidney | C64 | 947 | 4.8 | 4.5 | 909 | 4.7 | 4.2 |
| urinary bladder | C67 | 1,017 | 5.1 | 4.8 | 1,082 | 5.5 | 5.0 |
| brain | C71 | 1,288 | 6.5 | 6.3 | 1,312 | 6.7 | 6.2 |
| thyroid gland | C73 | 181 | 0.9 | 0.9 | 231 | 1.2 | 1.1 |
| Hodgkin lymphoma | C81 | 84 | 0.4 | 0.4 | 74 | 0.4 | 0.4 |
| non-Hodgkin lymphomas | C82–C85+C96 | 882 | 4.5 | 4.2 | 951 | 4.9 | 4.5 |
| leukaemias | C91–C95 | 1,308 | 6.6 | 6.3 | 1,357 | 6.9 | 6.3 |

It is estimated that in 2022 the number of cancer cases will increase and the most frequently diagnosed cancer in men will be:

- prostate (24%),
- lung (14%),
- colorectal cancer (C18–C21 – 12%),

and in women:

- breast (23%),
- lung (10%),
- colorectal cancer (C18–C21 – 10%).

There will be cancers, which will also be the main causes of death. Estimated incidence and death rates for the most common cancers in 2022 are presented in table V. However, a noticeable reduction in the incidence of stomach, lung and brain cancers in men and gallbladder, cervix uteri and brain cancers in women is expected. Unfortunately, in man, colorectal, prostate and bladder and in woman, lung, breast, and corpus uteri cancer-related mortality is expected to increase in 2020.

The observed number of cancer cases in 2020 compared to the predicted values is lower in all cancer groups (tab. VI). Comparing the observed mortality rates in 2020 to the expected ones, it can be seen that they are lower in almost all presented cancer groups (except for laryngeal cancer in men and brain cancer in both sexes) – table VII. Therefore, there is a noticeable change in the trend of both morbidity and mortality in 2020.

**Table V.** Estimated cancer cases and deaths numbers in 2022 from the most common cancers in women and men

| Cancer site | Cancer cases | | Cancer deaths | | |
|---|---|---|---|---|---|
| | males | | | | |
| **all cancers** | **89,699** | **100%** | **all cancers** | **54,370** | **100%** |
| prostate | 21,093 | 24% | lung | 14,921 | 27% |
| lung | 12,659 | 14% | colorectum | 7,047 | 13% |
| colorectum | 11,155 | 12% | prostate | 5,618 | 10% |
| urinary bladder | 5,696 | 6% | urinary bladder | 3,131 | 6% |
| kidney | 3,372 | 4% | stomach | 3,116 | 6% |
| stomach | 3,063 | 3% | leukaemias | 1,553 | 3% |
| melanoma | 2,073 | 2% | kidney | 1,504 | 3% |
| leukaemias | 2,044 | 2% | larynx | 1,267 | 2% |
| non-Hodgkin lymphomas | 1,732 | 2% | non-Hodgkin lymphomas | 1,022 | 2% |
| larynx | 1,638 | 2% | melanoma | 788 | 1% |
| | females | | | | |
| **all cancers** | **89,815** | **100%** | **all cancers** | **47,467** | **100%** |
| breast | 20,413 | 23% | lung | 9,133 | 19% |
| lung | 9,198 | 10% | breast | 7,549 | 16% |
| colorectum | 8,554 | 10% | colorectum | 5,478 | 12% |
| corpus uteri | 6,581 | 7% | ovary | 2,845 | 6% |
| ovary | 3,786 | 4% | corpus uteri | 2,214 | 5% |
| melanoma | 2,282 | 3% | stomach | 1,653 | 3% |
| kidney | 2,108 | 2% | cervix uteri | 1,484 | 3% |
| cervix uteri | 2,085 | 2% | leukaemias | 1,357 | 3% |
| urinary bladder | 2,083 | 2% | urinary bladder | 1,082 | 2% |
| stomach | 1,862 | 2% | non-Hodgkin lymphomas | 951 | 2% |
| non-Hodgkin lymphomas | 1,722 | 2% | kidney | 909 | 2% |
| leukaemias | 1,637 | 2% | melanoma | 720 | 2% |

**Table VI.** The incidence of the most common cancers in 2020 – observed and expected values (estimation based on the trend from 2010–2019)

| Cancer site | ICD–10 | 2020 observed | | | 2020 expected | | |
|---|---|---|---|---|---|---|---|
| | | Absolute number | Crude rate | Standardized rate (ESP2013) | Absolute number | Crude rate | Standardized rate (ESP2013) |
| | | males | | | | | |
| **all cancers** | **C00–D09** | **72,651** | **391.6** | **466.6** | **88,772** | **478.5** | **573.5** |
| oesophagus | C15 | 976 | 5.3 | 5.9 | 1,203 | 6.5 | 7.2 |
| stomach | C16 | 2,856 | 15.4 | 18.8 | 3,252 | 17.5 | 21.5 |
| colorectum | C81–C21 | 9,010 | 48.6 | 58.9 | 11,049 | 59.6 | 73.1 |
| pancreas | C25 | 1,747 | 9.4 | 11.0 | 1,887 | 10.2 | 11.9 |
| larynx | C32 | 1,499 | 8.1 | 8.9 | 1,762 | 9,5 | 10.5 |

→

**Table VI. cont.** The incidence of the most common cancers in 2020 – observed and expected values (estimation based on the trend from 2010–2019)

| Cancer site | ICD–10 | 2020 observed | | | 2020 expected | | |
|---|---|---|---|---|---|---|---|
| | | Absolute number | Crude rate | Standardized rate (ESP2013) | Absolute number | Crude rate | Standardized rate (ESP2013) |
| | | males | | | | | |
| lung | C33–C34 | 11,534 | 62.2 | 73.1 | 13,508 | 72.8 | 85.6 |
| melanoma | C43 | 1,565 | 8.4 | 9.9 | 1,963 | 10.6 | 12.4 |
| prostate | C61 | 14,244 | 76.8 | 91.7 | 19,333 | 104.2 | 125.0 |
| kidney | C64 | 2,727 | 14.7 | 16.6 | 3,340 | 18.0 | 20.2 |
| urinary bladder | C67 | 4,815 | 26.0 | 32.5 | 5,720 | 30.8 | 38.8 |
| brain | C71 | 1,293 | 7.0 | 7.5 | 1,340 | 7.2 | 7.9 |
| Hodgkin lymphoma | C81 | 354 | 1.9 | 1.9 | 354 | 1.9 | 1.9 |
| non-Hodgkin lymphomas | C82–C85 + C96 | 1,543 | 8.3 | 9.5 | 1,726 | 9.3 | 10.9 |
| leukaemias | C91–C95 | 1,610 | 8.7 | 10.2 | 2,023 | 10.9 | 13.0 |
| | | females | | | | | |
| **all cancers** | **C00–D09** | **73,530** | **371.3** | **351.5** | **88,162** | **445.21** | **419.8** |
| stomach | C16 | 1,649 | 8.3 | 7.8 | 1,911 | 9.65 | 9.1 |
| colorectum | C81–C21 | 7,081 | 35.8 | 33.6 | 8,508 | 42.96 | 40.4 |
| gallbladder | C23–C24 | 761 | 3.8 | 3.6 | 894 | 4.5 | 4.2 |
| pancreas | C25 | 1,808 | 9.1 | 8.6 | 1,965 | 9.9 | 9.2 |
| lung | C33–C34 | 7,309 | 36.9 | 34.2 | 8,759 | 44.23 | 40.5 |
| melanoma | C43 | 1,680 | 8.5 | 8.1 | 2,157 | 10.89 | 10.4 |
| breast | C50 | 17,511 | 88.4 | 84.4 | 19,907 | 100.53 | 95.7 |
| cervix | C53 | 1,920 | 9.7 | 9.2 | 2,288 | 11.55 | 10.9 |
| uterus | C54 | 5,238 | 26.5 | 25.1 | 6,451 | 32.58 | 30.8 |
| ovary | C56 | 3,012 | 15.2 | 14.6 | 3,798 | 19.18 | 18.4 |
| kidney | C64 | 1,755 | 8.9 | 8.4 | 2,093 | 10.57 | 10.0 |
| urinary bladder | C67 | 1,516 | 7.7 | 7.1 | 1,983 | 10.01 | 9.2 |
| brain | C71 | 1,156 | 5.8 | 5.6 | 1,179 | 6.0 | 5.7 |
| thyroid | C73 | 2,699 | 13.6 | 13.3 | 3,848 | 19.4 | 18.9 |
| Hodgkin lymphoma | C81 | 341 | 1.7 | 1.7 | 343 | 1.7 | 1.7 |
| non-Hodgkin lymphomas | C82–C85 + C96 | 1,471 | 7.4 | 7.1 | 1,694 | 8.56 | 8.1 |
| leukaemias | C91–C95 | 1,322 | 6.7 | 6.4 | 1,619 | 8.17 | 7.8 |

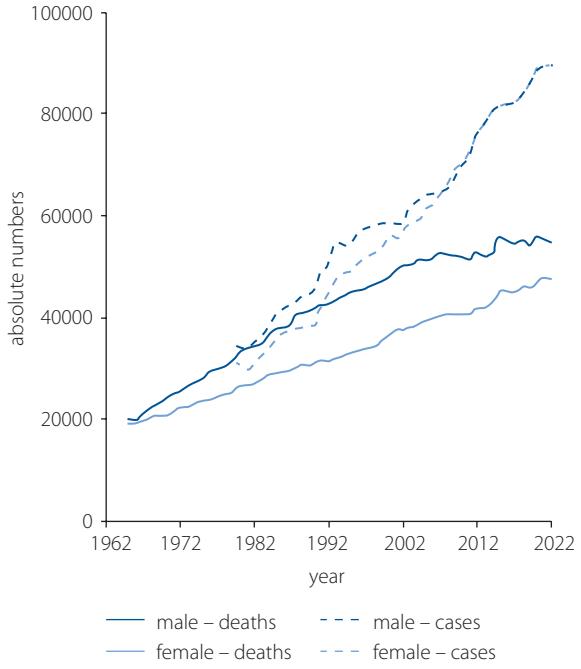
### *Incidence time-trends*

The number of cases in men for the first three analyzed decades was higher than the number of cases in women. In 2007, this changed and the number of cases in both sexes is similar. The number of deaths in men had an upward trend until 2012, after which it stabilized. For women, the number of deaths has been steadily increasing since 1965.

The standardized rate of incidence in women and men shows an upward trend throughout the observed period. Since 1992, the trend has been flattening for men. The standardized rate of death in men had been increasing until 2002, after which it has begun to decrease. Among women throughout the observed period, the standardized death rate remains at a similar level without any particular deviations (fig. 1).

**Table VII.** Deaths from the most common cancers in 2020 – observed and expected values (estimation based on the trend from 2010–2019)

| Cancer site | ICD-10 | 2020 observed | | | 2020 expected | | |
|---|---|---|---|---|---|---|---|
| | | Absolute number | Crude rate | Standardized rate (ESP2013) | Absolute number | Crude rate | Standardized rate (ESP2013) |
| | | males | | | | | |
| **all cancers** | **C00–D09** | **54,370** | **293.1** | **377.7** | **55,999** | **301.9** | **390.1** |
| oesophagus | C15 | 1,227 | 6.6 | 7.6 | 1,275 | 6.9 | 7.8 |
| stomach | C16 | 3,115 | 16.8 | 21.6 | 3,062 | 16.5 | 21.2 |
| colorectum | C81–C21 | 7,181 | 38.7 | 51.8 | 7,342 | 39.6 | 53.4 |
| pancreas | C25 | 2,431 | 13.1 | 15.7 | 2,500 | 13.5 | 16.5 |
| larynx | C32 | 1,409 | 7.6 | 8.9 | 1,370 | 7.4 | 8.6 |
| lung | C33–C34 | 14,229 | 76.7 | 93.5 | 15,242 | 82.2 | 100.6 |
| melanoma | C43 | 762 | 4.1 | 5.4 | 809 | 4.4 | 5.9 |
| prostate | C61 | 5,748 | 31.0 | 46.7 | 6,010 | 32.4 | 48.8 |
| kidney | C64 | 1,434 | 7.7 | 9.8 | 1,589 | 8.6 | 11.0 |
| urinary bladder | C67 | 3,202 | 17.3 | 24.4 | 3,284 | 17.7 | 25.2 |
| brain | C71 | 1,571 | 8.5 | 9.7 | 1,535 | 8.3 | 9.7 |
| Hodgkin lymphoma | C81 | 102 | 0.5 | 0.6 | 94 | 0.5 | 0.6 |
| non-Hodgkin lymphomas | C82–C85 + C96 | 986 | 5.3 | 6.9 | 1,105 | 6.0 | 7.7 |
| leukaemias | C91–C95 | 1,509 | 8.1 | 11.0 | 1,595 | 8.6 | 11.6 |
| | | females | | | | | |
| **all cancers** | **C00–D09** | **45,501** | **229.8** | **213.9** | **47,325** | **239.0** | **221.4** |
| stomach | C16 | 1,657 | 8.4 | 7.8 | 1,743 | 8.8 | 8.2 |
| colorectum | C81–C21 | 5,321 | 26.9 | 24.9 | 5,529 | 27.9 | 25.9 |
| gallbladder | C23–C24 | 988 | 5.0 | 4.7 | 1,117 | 5.6 | 5.2 |
| pancreas | C25 | 2,542 | 12.8 | 12.0 | 2,652 | 13.4 | 12.4 |
| lung | C33–C34 | 8,009 | 40.4 | 37.3 | 8,719 | 44.0 | 40.3 |
| melanoma | C43 | 668 | 3.4 | 3.1 | 719 | 3.6 | 3.3 |
| breast | C50 | 6,956 | 35.1 | 32.9 | 7,305 | 36.9 | 34.4 |
| cervix | C53 | 1,511 | 7.6 | 7.2 | 1,549 | 7.8 | 7.3 |
| uterus | C54 | 1,811 | 9.1 | 8.5 | 2,039 | 10.3 | 9.5 |
| ovary | C56 | 2,688 | 13.6 | 12.8 | 2,832 | 14.3 | 13.5 |
| kidney | C64 | 946 | 4.8 | 4.5 | 948 | 4.8 | 4.4 |
| urinary bladder | C67 | 915 | 4.6 | 4.3 | 1,025 | 5.2 | 4.7 |
| brain | C71 | 1,365 | 6.9 | 6.5 | 1,351 | 6.8 | 6.5 |
| thyroid | C73 | 222 | 1.1 | 1.1 | 226 | 1.1 | 1.1 |
| Hodgkin lymphoma | C81 | 65 | 0.3 | 0.3 | 75 | 0.4 | 0.4 |
| non-Hodgkin lymphomas | C82–C85 + C96 | 817 | 4.1 | 3.9 | 938 | 4.7 | 4.4 |
| leukaemias | C91–C95 | 1,280 | 6.5 | 6.0 | 1,364 | 6.9 | 6.4 |



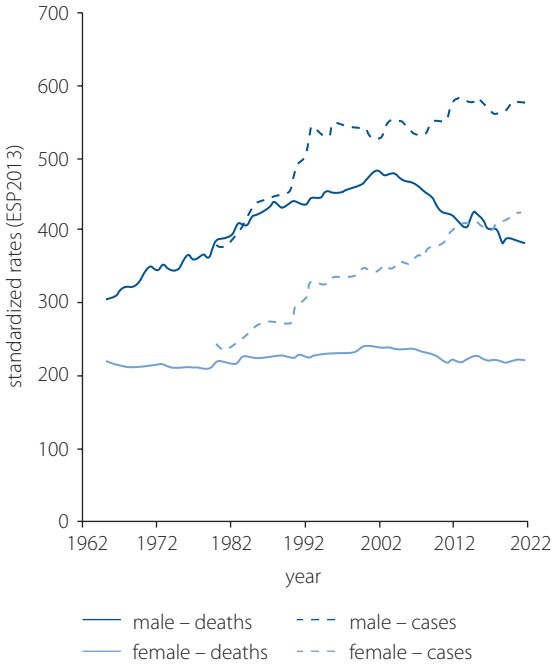




**Figure 1.** Cancer morbidity and mortality trends in Poland in 1965–2022*

*Values for 2021–2022 estimated based on trends in 2010–2019

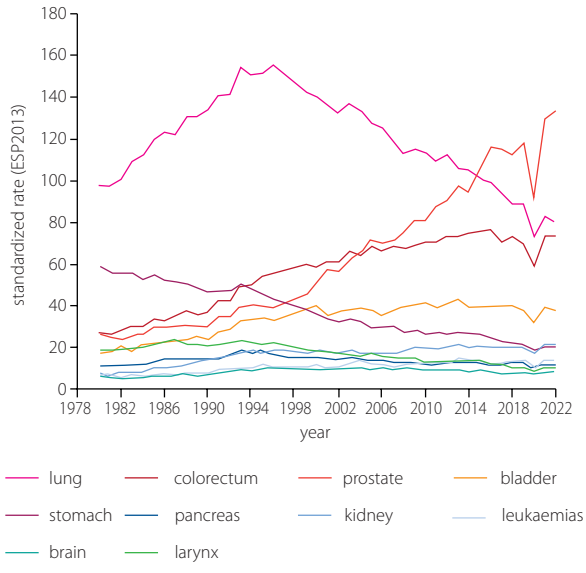



**Figure 2.** Incidence trends of the leading cancer sites for males, Poland 1980–2022 (2021–2022 estimation)

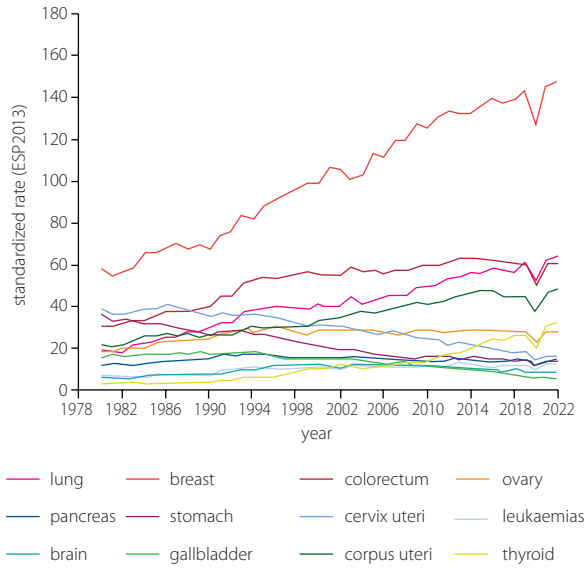



**Figure 3.** Incidence trends of the leading cancer sites for females, Poland 1980–2022 (2021–2022 estimation)

Until 2013, lung cancer was the leading cancer among men. After changing from an ascending to a declining trend in the 1990s, the continued decline led to the prostate becoming the first cancer in 2016. In third place for most of the observed time is colorectal cancer (fig. 2).

Throughout the observed period, breast cancer has been the main cancer among women. In the last 2–3 years, colorectal cancer and lung cancer rank second ex aequo; previously, colorectal cancer had a higher morbidity than lung cancer (fig. 3).

Lung cancer is the most common single cause of death in men. Lung cancer mortality had been increasing in the second part of the 20$^{th}$ century, but since the start of the 21$^{st}$, the death rate has been declining. Colorectal cancer, the second most common cause of death, was characterized by an increasing mortality trend until the mid-first decade of the 21$^{st}$ century,

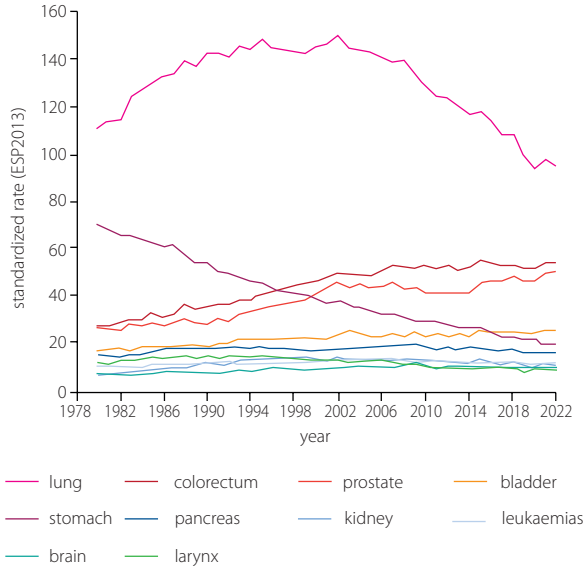



**Figure 4.** Mortality trends of the leading cancer sites for males, Poland 1980–2022 (2021–2022 estimation)

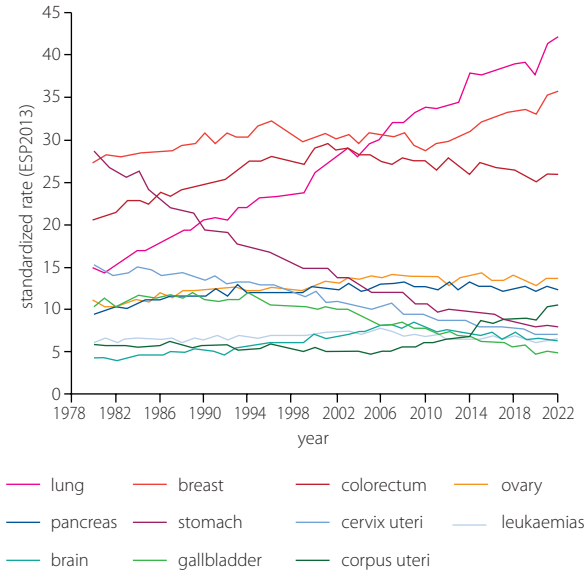



**Figure 5.** Mortality trends of the leading cancer sites for females, Poland 1980–2022 (2021–2022 estimation)

after which there was a clear slowdown in the growth rate. The third common cancer cause of death since the beginning of the 21st century is prostate cancer, with stabilized level of mortality (fig. 4).

Breast cancer was the most frequent cancer-related cause of death in the female population from the middle of the 1970s through the middle of the 2000s. Since 2007, cancer deaths have been most often caused by lung cancer. It is noteworthy that the decreased trend in breast cancer mortality was reversed in 2010. Lung cancer has replaced breast cancer as the top cause of cancer-related fatalities in women for more than ten years. Since the beginning of the twentieth century, the mortality rate for colorectal cancer in women has been decreasing. In the past 50 years, the mortality rate from stomach cancer has fallen by a factor of four. Additionally, over this time period, there is a declension in cervical cancer mortality (fig. 5). Stomach cancer is characterized by downward trend in both mortality and incidence throughout the observed period (about 40 years) (fig. 2–5).

### *Age group analysis*

The incidence and mortality of malignant tumors varies with the age of the patient. In children, both among girls and boys, leukaemia is the main diagnosis. In second place are cancers of the brain and central nervous system.

In men, the incidence varies with age. Testicular cancer is the most common cancer diagnosed in young men. In the age group 45–64, the main diagnosis was lung cancer, and in older men over 65, prostate cancer. In men over 45, lung cancer remains the most common cause of death. In women over 20 years of age, the most frequently diagnosed cancer was breast cancer. Between the ages of 20 and 44, it was also the leading cause of cancer death. The highest morbidity and mortality for this cancer site were noted in patients over 65 years of age.

In adult women and men, cancers of the lungs and the second intestine were among the most frequently diagnosed causes of cancer-related deaths, regardless of age. The exact incidence and mortality values for the most common cancers by sex and age are presented in tables VIII and IX, respectively.

### *Spatial analysis and clustering*

In 2020, among men and women, the highest cancer morbidity rates were observed in the western part of Poland, and the lowest cancer morbidity occurred in the southeastern area. In 2020, in most voivodships, the most frequent cancer in men was prostate cancer. In 15 voivodships the most lethal cancers among men are lung cancer, colorectal cancer and prostate cancer (tab. X).

Among women in all voivodships, the leading cancer site is the breast. Two patterns can be identified among the incidences. The first pattern present in mainly central and northern Poland is characterized by the second and third sites of lung cancer and colorectal cancer, respectively. Colorectal cancer takes second place and lung cancer is third in the second pattern found in the rest of Poland.

Among cancer deaths in women, two patterns also noted. In the first pattern, the most lethal is breast cancer, followed by lung cancer and it concerns the southern part of Poland and one voivodship from the eastern-northern part. In the second pattern, in the rest of the country, the situation is reversed – among cancer mortality, lung cancer leads, followed by breast cancer. In both cases, colorectal cancer ranks third among cancer deaths in women (tab. XI).

**Table VIII.** The incidence of the 5 most common cancer sites in Poland in 2020, depending on sex and age

| Males | | | | | | | |
|---|---|---|---|---|---|---|---|
| **age: 0–19** | | **age: 20–44** | | **age: 45–64** | | **age: 65+** | |
| **number** | **%** | **number** | **%** | **number** | **%** | **number** | **%** |
| **all cancers** | | **all cancers** | | **all cancers** | | **all cancers** | |
| **550** | | **3,578** | | **21,625** | | **46,898** | |
| leukaemias (C91–C95) | | testis (C62) | | lung (C33–C34) | | prostate (C61) | |
| 173 | 31% | 914 | 26% | 3,599 | 17% | 10,684 | 23% |
| brain and CNS (C71–C72) | | colorectum (C18–C21) | | prostate (C61) | | lung (C33–C34) | |
| 85 | 15% | 254 | 7% | 3,540 | 16% | 7,840 | 17% |
| non-Hodgkin lymphomas (C82–C85 + C96) | | melanoma (C43) | | colorectum (C18–C21) | | colorectum (C18–C21) | |
| 44 | 8% | 238 | 7% | 2,774 | 13% | 5,975 | 13% |
| Hodgkin lymphoma (C81) | | non-Hodgkin lymphomas (C82–C85 + C96) | | urinary bladder (C67) | | urinary bladder (C67) | |
| 40 | 7% | 231 | 6% | 1,157 | 5% | 3 ,008 | 8% |
| connective and soft tissue (C49) | | brain and CNS (C71–C72) | | kidney (C64) | | stomach (C16) | |
| 32 | 6% | 233 | 6% | 1,065 | 5% | 1,911 | 4% |
| **Females** | | | | | | | |
| **age: 0–19** | | **age: 20–44** | | **age: 45–64** | | **age: 65+** | |
| **aumber** | **%** | **number** | **%** | **number** | **%** | **number** | **%** |
| **all cancers** | | **all cancers** | | **all cancers** | | **all cancers** | |
| **532** | | **7,421** | | **25,083** | | **40,494** | |
| leukaemias (C91–C95) | | breast (C50) | | breast (C50) | | breast (C50) | |
| 151 | 28% | 2,170 | 29% | 7,790 | 31% | 7,551 | 19% |
| brain and CNS (C71–C72) | | thyroid gland (C73) | | lung (C33–C34) | | lung (C33–C34) | |
| 59 | 11% | 1,160 | 16% | 2,160 | 9% | 5,071 | 13% |
| Hodgkin lymphoma (C81) | | cervix uteri *in situ* (D06) | | corpus uteri (C54) | | colorectum (C18–C21) | |
| 53 | 10% | 758 | 10% | 2,154 | 9% | 4,848 | 12% |
| thyroid gland (C73) | | melanoma (C43) | | colorectum (C18-C21) | | corpus uteri (C54) | |
| 46 | 9% | 416 | 6% | 1 ,987 | 8% | 2,920 | 7% |
| kidney (C64) | | cervix uteri (C53) | | ovary (C56) | | ovary (C56) | |
| 29 | 5% | 378 | 5% | 1,344 | 5% | 1,313 | 3% |

In addition to differences in morbidity and mortality at the level of voivodeships, differences in 5-year net survival rates were also observed in Poland (diagnosis from 2015 to 2019, end point of observation on December 31, 2019). The 5-year cancer net survival rate for the whole country was 55.5%, with the highest values recorded in central and eastern Poland. In women, compared to men, higher values were found in all voivodeships (tab. XII).

## Discussion

Malignant neoplasms are the second leading cause of mortality in Poland. The Polish National Cancer Registry received information about 146,181 new cases and 99,871 thousand cancer deaths in 2020. Compared to the previous year, the number of cases decreased by about 12,000 in both sexes. Mortality in men did not change compared to 2019, and in women it was decreased by about 400 events.

**Table IX.** The mortality of the 5 most common cancer sites in Poland in 2020, depending on sex and age

| Males | | | | | | | |
|---|---|---|---|---|---|---|---|
| age: 0–19 | | age: 20–44 | | age: 45–64 | | age: 65+ | |
| number | % | number | % | number | % | number | % |
| all cancers | | all cancers | | all cancers | | all cancers | |
| 113 | | 1,038 | | 13,917 | | 39,302 | |
| brain and CNS (C71–C72) | | brain and CNS (C71–C72) | | lung (C33–C34) | | lung (C33–C34) | |
| 47 | 42% | 146 | 14% | 4,001 | 29% | 10,151 | 26% |
| leukaemias (C91–C95) | | colorectum (C18–C21) | | colorectum (C18–C21) | | colorectum (C18–C21) | |
| 23 | 20% | 100 | 10% | 1,550 | 11% | 5,531 | 14% |
| connective and soft tissue (C49) | | lung (C33–C34) | | stomach (C16) | | prostate (C61) | |
| 9 | 8% | 77 | 7% | 839 | 6% | 5,249 | 13% |
| bone and articular cartilage (C40–C41) | | testis (C62) | | pancreas (C25) | | urinary bladder (C67) | |
| 6 | 5% | 73 | 7% | 798 | 6% | 2,679 | 7% |
| peripheral nerves and autonomic nervous system (C47) | | stomach (C16) | | brain and CNS (C71–C72) | | stomach (C16) | |
| 6 | 5% | 70 | 7% | 599 | 4% | 2,206 | 6% |
| **Females** | | | | | | | |
| age: 0–19 | | age: 20–44 | | age: 45–64 | | age: 65+ | |
| number | % | number | % | number | % | number | % |
| all cancers | | all cancers | | all cancers | | all cancers | |
| 78 | | 1,133 | | 10,500 | | 33,790 | |
| brain and CNS (C71–C72) | | breast (C50) | | lung (C33–C34) | | lung (C33–C34) | |
| 24 | 31% | 328 | 29% | 2,097 | 20% | 5,869 | 17% |
| leukaemias (C91–C95) | | colorectum (C18–C21) | | breast (C50) | | breast (C50) | |
| 21 | 27% | 105 | 9% | 1,881 | 18% | 4,747 | 14% |
| connective and soft tissue (C49) | | cervix uteri (C53) | | colorectum (C18–C21) | | colorectum (C18–C21) | |
| 12 | 15% | 99 | 9% | 972 | 9% | 4,244 | 13% |
| bone and articular cartilage (C40–C41) | | ovary (C56) | | ovary (C56) | | pancreas (C25) | |
| 6 | 8% | 88 | 8% | 916 | 9% | 1,952 | 6% |
| kidney (C64) | | brain and CNS (C71–C72) | | cervix uteri (C53) | | ovary (C56) | |
| 4 | 5% | 86 | 8% | 568 | 5% | 1,683 | 5% |

The most common male cancer is prostate cancer (almost 20% of all male cancers). The death rate for prostate cancer has been increasing year by year since 2004.

The second most common cancer among men is lung cancer (16% of all cases), despite the fact that they have been showing a decreasing trend in mortality and morbidity rates for 15 years. Right behind colorectal cancer, in third place is colorectal cancer (11% of all cases). The decrease in incidence and mortality of lung cancer can be attributed to the noticeable reduction of smoking prevalence among Polish men, which has been observed in recent decades. Despite the decrease in the mortality rate, lung cancer is still the dominant cause of male cancer death (26% of all cases), significantly affecting the all cancer mortality curve.

Among women, the three most common cancer sites are: breast, lung and colorectum. The most fatal cancer for this group was lung cancer (18%), followed by breast cancer (15%), which for the last 10 years has been on an upward trend.

**Table X.** Standardized rates of morbidity and mortality for the most common malignant neoplasms in men in Poland in 2020 by voivodships

| Voivodship | All cancers | Stomach | Colorectum[1] | Pancreas | Lung | Melanoma | Prostate | Kidney | Bladder | non-Hodgkin lymphomas[2] | Leukaemias[3] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | incidence rates (ESP2013) | | | | | | | | | | |
| Dolnośląskie | 516.4 | 20.3 | 66.9 | 14.2 | 80.2 | 11.3 | 94.4 | 19.6 | 43.0 | 9.9 | 12.6 |
| Kujawsko-pomorskie | 540.2 | 22.0 | 68.6 | 11.8 | 101.0 | 10.5 | 101.0 | 23.6 | 40.9 | 9.0 | 6.4 |
| Lubelskie | 448.0 | 16.7 | 58.0 | 10.5 | 62.8 | 9.0 | 89.2 | 17.3 | 35.6 | 8.6 | 10.9 |
| Lubuskie | 421.5 | 16.6 | 55.3 | 10.1 | 60.7 | 5.6 | 94.3 | 18.2 | 42.7 | 6.7 | 8.5 |
| Łódzkie | 430.0 | 20.2 | 57.2 | 10.1 | 69.4 | 12.1 | 78.3 | 13.3 | 22.5 | 9.9 | 17.6 |
| Małopolskie | 406.0 | 15.8 | 45.6 | 8.7 | 67.5 | 8.5 | 81.0 | 10.9 | 22.3 | 8.5 | 9.1 |
| Mazowieckie | 401.3 | 16.4 | 51.1 | 10.8 | 63.7 | 11.2 | 71.9 | 15.0 | 24.3 | 11.1 | 7.4 |
| Opolskie | 458.8 | 15.4 | 55.3 | 10.6 | 65.2 | 7.7 | 89.0 | 16.3 | 37.2 | 7.1 | 7.5 |
| Podkarpackie | 467.8 | 22.4 | 60.9 | 11.2 | 60.9 | 10.7 | 84.5 | 17.1 | 26.3 | 11.0 | 13.0 |
| Podlaskie | 420.7 | 17.8 | 65.0 | 9.7 | 58.1 | 9.8 | 92.7 | 18.5 | 32.1 | 7.9 | 6.7 |
| Pomorskie | 465.5 | 15.7 | 48.5 | 9.1 | 77.4 | 7.8 | 103.6 | 19.7 | 39.8 | 10.2 | 6.5 |
| Śląskie | 522.0 | 22.9 | 65.2 | 11.4 | 82.1 | 8.6 | 117.1 | 16.4 | 33.9 | 9.5 | 10.7 |
| Świętokrzyskie | 479.3 | 15.6 | 52.4 | 12.3 | 72.2 | 11.7 | 93.3 | 13.6 | 42.0 | 11.9 | 15.2 |
| Warmińsko-mazurskie | 480.1 | 22.5 | 65.6 | 9.4 | 88.6 | 10.1 | 79.8 | 14.8 | 36.1 | 9.1 | 15.3 |
| Wielkopolskie | 545.7 | 18.9 | 75.0 | 13.8 | 79.4 | 10.0 | 105.4 | 20.4 | 32.0 | 10.4 | 10.1 |
| Zachodniopomorskie | 430.2 | 17.6 | 50.6 | 7.7 | 67.1 | 11.4 | 83.2 | 13.8 | 38.4 | 5.2 | 7.5 |
| **Poland** | **466.6** | **18.8** | **58.9** | **11.0** | **73.1** | **9.9** | **91.7** | **16.6** | **32.5** | **9.5** | **10.2** |
| | mortality rates (ESP2013) | | | | | | | | | | |
| Dolnośląskie | 419.6 | 24.7 | 58.8 | 17.0 | 105.9 | 4.8 | 53.5 | 14.8 | 28.3 | 6.8 | 11.0 |
| Kujawsko-pomorskie | 416.6 | 24.4 | 62.7 | 16.0 | 106.0 | 6.0 | 49.8 | 8.8 | 29.3 | 7.7 | 11.7 |
| Lubelskie | 350.4 | 21.2 | 45.1 | 14.1 | 95.4 | 4.2 | 40.8 | 9.8 | 19.0 | 7.1 | 11.6 |
| Lubuskie | 396.2 | 23.8 | 53.9 | 16.9 | 101.9 | 6.8 | 53.0 | 10.3 | 29.2 | 5.7 | 6.5 |
| Łódzkie | 365.4 | 20.7 | 47.5 | 13.1 | 91.5 | 7.9 | 42.7 | 8.7 | 24.8 | 5.0 | 13.0 |
| Małopolskie | 367.0 | 21.6 | 47.5 | 14.4 | 85.6 | 6.1 | 43.2 | 9.9 | 25.1 | 6.5 | 11.8 |
| Mazowieckie | 363.3 | 18.5 | 48.5 | 15.1 | 92.0 | 5.8 | 47.4 | 8.7 | 22.2 | 7.3 | 9.3 |
| Opolskie | 351.5 | 17.4 | 56.1 | 15.3 | 75.9 | 3.7 | 38.0 | 10.7 | 25.6 | 5.5 | 10.6 |
| Podkarpackie | 323.8 | 21.1 | 44.0 | 16.3 | 65.0 | 5.0 | 48.4 | 7.5 | 20.7 | 8.2 | 11.5 |
| Podlaskie | 351.5 | 15.8 | 52.8 | 14.4 | 93.5 | 6.1 | 44.7 | 10.7 | 22.0 | 5.3 | 11.9 |
| Pomorskie | 383.8 | 21.5 | 49.1 | 18.4 | 100.0 | 4.9 | 48.4 | 10.8 | 24.7 | 7.8 | 9.0 |
| Śląskie | 373.4 | 23.2 | 52.9 | 15.5 | 84.3 | 4.8 | 46.4 | 9.5 | 22.6 | 6.1 | 10.8 |
| Świętokrzyskie | 350.8 | 20.5 | 44.1 | 14.6 | 92.1 | 5.2 | 42.3 | 7.4 | 21.1 | 6.7 | 10.6 |
| Warmińsko-mazurskie | 391.7 | 25.4 | 53.2 | 13.1 | 97.1 | 3.1 | 49.2 | 10.6 | 26.0 | 12.1 | 12.0 |
| Wielkopolskie | 429.9 | 24.9 | 63.4 | 18.2 | 112.5 | 5.2 | 49.9 | 10.2 | 28.4 | 7.8 | 11.6 |
| Zachodniopomorskie | 389.9 | 20.3 | 51.3 | 18.0 | 100.0 | 5.1 | 44.8 | 9.4 | 26.0 | 5.6 | 12.4 |
| **Poland** | **377.7** | **21.6** | **51.8** | **15.7** | **93.5** | **5.4** | **46.7** | **9.8** | **24.4** | **6.9** | **11.0** |

[1] colorectum C18–C21; [2] non-Hodgkin lymphomas C82–C85 + C96; [3] leukaemias C91–C95

**Table XI.** Standardized rates of morbidity and mortality for the most common malignant neoplasms in women in Poland in 2020 by voivodships

| Voivodship | All cancers | Colorectum[1] | Lung | Breast | Cervix uteri | Corpus uteri | Ovary | Kidney | Bladder | non-Hodgkin lymphomas[2] | Leukaemias[3] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | incidence rates (ESP2013) | | | | | | | | | | |
| Dolnośląskie | 388.4 | 38.8 | 42.0 | 90.4 | 10.6 | 26.1 | 15.3 | 8.0 | 8.6 | 7.4 | 8.8 |
| Kujawsko-pomorskie | 421.1 | 38.4 | 45.5 | 89.8 | 8.6 | 28.0 | 17.1 | 11.8 | 8.0 | 8.5 | 4.3 |
| Lubelskie | 322.3 | 32.6 | 24.8 | 74.2 | 9.2 | 25.9 | 14.3 | 7.2 | 6.3 | 6.5 | 5.7 |
| Lubuskie | 319.9 | 32.2 | 36.9 | 77.0 | 10.3 | 22.0 | 17.2 | 10.1 | 9.2 | 3.8 | 4.8 |
| Łódzkie | 343.0 | 31.2 | 33.2 | 91.3 | 9.6 | 24.5 | 16.5 | 6.1 | 5.0 | 7.3 | 12.1 |
| Małopolskie | 293.7 | 24.2 | 25.4 | 60.8 | 9.0 | 26.1 | 12.9 | 6.1 | 4.0 | 6.8 | 5.7 |
| Mazowieckie | 322.4 | 26.2 | 32.5 | 92.2 | 6.9 | 20.9 | 10.5 | 7.5 | 5.5 | 7.8 | 4.0 |
| Opolskie | 308.8 | 32.4 | 27.3 | 67.5 | 10.7 | 24.6 | 13.6 | 8.2 | 7.9 | 4.,4 | 5.6 |
| Podkarpackie | 335.4 | 31.1 | 21.0 | 70.3 | 6.0 | 28.9 | 15.7 | 8.5 | 4.6 | 7.4 | 8.1 |
| Podlaskie | 343.0 | 35.7 | 22.4 | 84.4 | 11.0 | 27.2 | 15.8 | 8.6 | 9.0 | 5.5 | 5.4 |
| Pomorskie | 328.5 | 28.9 | 40.3 | 80.9 | 8.3 | 15.9 | 13.2 | 9.2 | 10.1 | 5.8 | 3.0 |
| Śląskie | 382.4 | 43.0 | 38.2 | 88.4 | 11.8 | 32.8 | 18.5 | 9.3 | 8.6 | 7.2 | 7.0 |
| Świętokrzyskie | 336.5 | 33.4 | 26.9 | 75.0 | 9.3 | 24.8 | 14.2 | 7.8 | 8.2 | 6.1 | 8.3 |
| Warmińsko-mazurskie | 360.0 | 35.3 | 42.4 | 79.9 | 10.0 | 19.7 | 14.2 | 10.0 | 7.2 | 7.3 | 9.1 |
| Wielkopolskie | 408.2 | 41.3 | 37.0 | 101.3 | 9.7 | 26.4 | 14.2 | 10.1 | 7.3 | 9.1 | 7.0 |
| Zachodniopomorskie | 364.0 | 32.1 | 42.6 | 92.2 | 8.8 | 19.1 | 13.2 | 9.5 | 10.3 | 5.1 | 4.5 |
| **Poland** | **351.5** | **33.6** | **34.2** | **84.4** | **9.2** | **25.1** | **14.6** | **8.4** | **7.1** | **7.1** | **6.4** |
| | mortality rates (ESP2013) | | | | | | | | | | |
| Dolnośląskie | 233.1 | 27.5 | 46.9 | 32.1 | 7.3 | 7.7 | 12.3 | 4.1 | 5.4 | 3.1 | 6.4 |
| Kujawsko-pomorskie | 234.5 | 27.9 | 47.2 | 36.1 | 7.2 | 10.1 | 14.0 | 4.9 | 6.7 | 4.7 | 5.7 |
| Lubelskie | 179.0 | 21.3 | 29.7 | 24.3 | 5.6 | 6.4 | 11.1 | 4.5 | 3.1 | 3.9 | 6.3 |
| Lubuskie | 234.2 | 26.5 | 49.9 | 34.0 | 8.4 | 7.7 | 12.0 | 6.6 | 3.7 | 3.5 | 6.5 |
| Łódzkie | 219.1 | 24.8 | 37.2 | 36.1 | 7.2 | 8.8 | 14.9 | 3.8 | 4.1 | 3.2 | 6.9 |
| Małopolskie | 205.3 | 25.6 | 29.0 | 31.4 | 6.1 | 8.2 | 11.7 | 3.7 | 4.9 | 4.1 | 5.1 |
| Mazowieckie | 215.1 | 24.4 | 37.6 | 34.5 | 6.7 | 10.6 | 12.4 | 3.8 | 3.7 | 4.1 | 5.9 |
| Opolskie | 187.3 | 25.2 | 28.2 | 25.3 | 8.6 | 6.1 | 12.6 | 4.7 | 3.0 | 2.7 | 5.0 |
| Podkarpackie | 172.2 | 20.7 | 21.3 | 26.0 | 5.9 | 8.5 | 12.4 | 3.8 | 3.0 | 3.8 | 6.1 |
| Podlaskie | 197.1 | 23.2 | 30.2 | 30.5 | 6.3 | 8.0 | 14.3 | 6.6 | 3.6 | 3.3 | 5.8 |
| Pomorskie | 211.6 | 23.3 | 45.0 | 28.5 | 6.6 | 7.3 | 11.1 | 3.5 | 4.6 | 3.4 | 6.4 |
| Śląskie | 223.9 | 25.7 | 35.3 | 35.9 | 8.2 | 8.7 | 14.3 | 4.8 | 3.6 | 3.9 | 5.9 |
| Świętokrzyskie | 186.9 | 21.4 | 31.8 | 27.4 | 6.4 | 8.3 | 12.7 | 4.3 | 4.2 | 2.9 | 4.8 |
| Warmińsko-mazurskie | 216.2 | 24.5 | 37.9 | 34.6 | 11.0 | 6.9 | 10.6 | 6.1 | 3.5 | 7.6 | 6.8 |
| Wielkopolskie | 242.2 | 28.3 | 42.5 | 40.9 | 7.7 | 9.2 | 13.8 | 5.6 | 5.6 | 4.0 | 6.5 |
| Zachodniopomorskie | 211.2 | 23.8 | 44.4 | 31.0 | 8.0 | 8.2 | 11.8 | 5.6 | 4.7 | 3.4 | 6.3 |
| **Poland** | **213.9** | **24.9** | **37.3** | **32.9** | **7.2** | **8.5** | **12.8** | **4.5** | **4.3** | **3.9** | **6.0** |

[1] colorectum C18–C21; [2] non-Hodgkin lymphomas C82–C85 + C96; [3] leukaemias C91–C95

**Table XII.** Geographical distribution of 5-year cancer rate in both sexes (2015–2019)

| Voivodship | Geographical distribution of 5-year cancer survival rate (%) | |
|---|---|---|
| | males | female |
| Dolnośląskie | 48.8% | 57% |
| Kujawsko-pomorskie | 50.5% | 55.3% |
| Lubelskie | 53.4% | 60.8% |
| Lubuskie | 51.8% | 58.7% |
| Łódzkie | 51.1% | 61.6% |
| Małopolskie | 53% | 59.4% |
| Mazowieckie | 55.1% | 61.5% |
| Opolskie | 49% | 58.7% |
| Podkarpackie | 55% | 61.5% |
| Podlaskie | 50.7% | 60% |
| Pomorskie | 57.3% | 61.8% |
| Śląskie | 48.9% | 55.6% |
| Świętokrzyskie | 50.8% | 58.8% |
| Warmińsko-mazurskie | 47.3% | 57% |
| Wielkopolskie | 48.9% | 56.7% |
| Zachodniopomorskie | 50.3% | 59.8% |
| **Poland** | **51.6%** | **58.9%** |

Poland's cancer incidence and death trends are influenced by the population's age distribution and exposure to carcinogens, particularly cigarette smoking (female population) and poor diet. In 2020, there were more than 1000 more female lung cancer deaths than breast cancer deaths.

The Polish National Cancer Registry has received fewer incident cancer cases in 2020 than in 2019 as a result of the COVID-19 pandemic, there was a decrease of 15% for men and 14% for women. The COVID-19 pandemic (ICD-10 U07.1, U07.2) caused 41,451 deaths in Poland in 2020. 7,043 (17%) of COVID-19 deaths were related to cancer, with men accounting for 61% of these deaths [6]. The COVID-19 pandemic has resulted in limitations in performing planned procedures and diagnostic possibilities in both screening and early diagnosis [6]. It can be seen that the COVID-19 pandemic has significantly changed the trend of cancer detection in Poland, and further effects of this phenomenon will be observed in the coming years.

## Conclusions

The decrease in the incidence of cancer in 2020 was probably related to the occurrence of the COVID-19 pandemic. At that time, access to public health care was limited due to the reduction of patient admission in clinics, the development of telemedicine instead of a conventional doctor's visit, and the transformation of hospitals into specialist hospitals treating only COVID-19, which could have influenced the postponement of the diagnosis of cancer.

Malignant neoplasms constitute a significant health problem, especially in young and middle-aged individuals (25–64 years old). In 2020, the most frequently diagnosed cancers among men in Poland were prostate, lung and colorectal cancers. In the female population, leading cancer sites still remain: breast, lung and colorectum. The highest mortality was observed due to lung cancer, colorectal cancer and, depending on sex, prostate or breast cancer.

### *Strengths and limitations of the report*

The analysis covers the entire population of Poland and is the best source of data on the incidence of cancer. Registration of cancers in the Polish National Cancer Registry (PNCR) is obligatory, which allows for high completeness of data. Unfortunately, the year 2020 caused disturbances in the functioning of health care facilities, which was reflected in the number of applications to the PNCR.

## Data availability

The presented data come from the Polish National Cancer Registry (PNCR) and is available at https://onkologia.org.pl/.

**Conflict of interest:** none declared

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*Received and accepted: 7 Apr 2023*

## References

1. https://stat.gov.pl/obszary-tematyczne/ludnosc/statystyka-przyczyn-zgonow/umieralnosc-i-zgony-wedlug-przyczyn-w-2020-roku,10,1.html.
2. Wojciechowska U, Barańska K, Michalek IM, Olasek P, Miklewska M, Didkowska J. Nowotwory Złośliwe w Polsce w 2020 roku. Krajowy Rejestr Nowotworów 2022.
3. World Health Organization. International Statistical Classification of Diseases and Related Health Problems. World Health Organization; 2015. https://apps.who.int/iris/handle/10665/246208 (22.03.2023).
4. Ahmad OB, Boschi-Pinto C, Lopez AD, et al. Age Standardization of Rates: A new WHO Standard.
5. European Commission. Eurostat. Revision of the European Standard Population: Report of Eurostat's Task Force : 2013 Edition. Publications Office; 2013. https://data.europa.eu/doi/10.2785/11470 (25.10.2022).
6. Bakouny Z, Paciotti M, Schmidt AL, et al. Cancer Screening Tests and Cancer Diagnoses During the COVID-19 Pandemic. JAMA Oncol. 2021; 7(3): 458–460, doi: 10.1001/jamaoncol.2020.7600, indexed in Pubmed: 33443549.

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Editorial

NOWOTWORY Journal of Oncology
2023, volume 73, number 1, 146
DOI: 10.5603/NJO.2023.0027

ISSN: 0029–540X, e-ISSN: 2300-2115
www.nowotwory.edu.pl

Photo: archives

# *The Liver tumors* section

Liver oncology is a rapidly growing field that constantly brings about unexpected developments. It will therefore come as no surprise that we have decided to start a new section of *Nowotwory. Journal of Oncology*, devoted to this fascinating aspect of cancer therapy.

Modern approaches to primary and secondary liver tumors, which include surgery, ablation, systemic therapy, targeted treatment, radiotherapy and transplantation, all bring something to exemplary customized contemporary treatment. We hope that this section will allow our readership to stay at the front line of cutting-edge approaches to liver tumors. And that this will eventually translate into better outcomes for our patients which, of course, should always be the ultimate goal of our actions.

Andrzej L. Komorowski
Section Editor
*Liver Tumors*

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Liver tumors

NOWOTWORY Journal of Oncology
2023, volume 73, number 3, 147–153
DOI: 10.5603/NJO.a2023.0019

ISSN: 0029–540X, e-ISSN: 2300-2115
www.nowotwory.edu.pl

# Novel systemic treatment for hepatocellular carcinoma: a step-by-step review of current indications

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Hepatocellular carcinoma (HCC) is the most common primary liver cancer and the main cause of cancer-related death worldwide. The available treatment options for HCC include liver transplant, locoregional therapy (such as ablation, embolization, and radiotherapy), and systemic treatment. The latter encompasses targeted therapy, immunotherapy, and angiogenesis inhibitors, alone or in combination. The introduction of immune checkpoint inhibitors and targeted drug therapy has been one of the most significant advances in HCC treatment. These therapies were shown to prolong overall survival and progression-free survival in clinical trials including patients with advanced HCC. In recent years, the systemic treatment of advanced HCC has vastly improved, with a median survival of 19.2 months in the IMbrave150 trial. However, further research is needed to determine the optimal sequence of treatment.

**Key words:** hepatocellular carcinoma, targeted therapy, immunotherapy, systemic treatment

## Epidemiology and pathogenesis of hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy. It is diagnosed in 75% to 80% of cases of primary liver cancer [1, 2]. In 2020, there were more than 900,000 new cases of HCC worldwide, and more than 800,000 patients died of HCC [3]. It is the fifth most common malignancy and the fourth most common cause of cancer-related death in the world. The highest prevalence of HCC was reported in south-east Asia. It is more common in men than in women and is usually diagnosed between the age of 60 to 75 years [2, 3].

In 90% of cases, HCC is caused by chronic liver disease, most often liver cirrhosis. The risk factors for liver cirrhosis include viral hepatitis (hepatitis B and C virus infection), alcohol use disorder, nonalcoholic fatty liver disease, aflatoxin exposure, and genetic factors (alpha-1-antitrypsin deficiency, autoimmune hepatitis, hemochromatosis, tyrosinemia type 1, glycogen storage disease, porphyria, and Wilson disease) [1, 2, 4].

The stages of liver cirrhosis are similar irrespective of the etiology. Initially, exposure to the risk factor triggers an acute inflammatory response and liver damage. Acute inflammation progresses into a chronic inflammatory state, leading to liver fibrosis and, ultimately, cirrhosis. These cirrhotic changes underlie the development of HCC [1].

## Current approach to diagnosis of hepatocellular carcinoma

The histological subtypes of HCC according to the World Health Organization classification are presented in table I [5–7]. At the initial stage, HCC is asymptomatic. Therefore, it is usually an incidental finding. In patients with liver cirrhosis, it is usually diagnosed during routine follow-up tests. Patients with

**How to cite:**

Lompart J, Sałek-Zań A, Puskulluoglu M, Grela-Wojewoda A. ***Novel systemic treatment for hepatocellular carcinoma: a step-by-step review of current indications.*** *NOWOTWORY J Oncol* 2023; 73: 147–153.

**Table I.** Histological subtypes of hepatocellular carcinoma (HCC) [5–7]

| Subtype* | Characteristics |
|---|---|
| fibrolamellar HCC | • a rare subtype of HCC,<br>• often occurs in young patients,<br>• less common in patients with liver cirrhosis,<br>• presents as a single large mass, well demarcated, no hepatic infiltration,<br>• tumor composed of large polygonal cells separated into liver cords or sheets of cells by dense bands of collagen; another characteristic feature is dense intratumoral fibrosis,<br>• associated with a better prognosis |
| scirrhous HCC | • a rare subtype of HCC,<br>• associated with poor prognosis,<br>• dense intratumoral fibrosis that separates small nests of tumor cells,<br>• tumor cells are small and arranged into cords or nests,<br>• occurs in patients with liver cirrhosis |
| clear cell HCC | • a rare subtype of HCC,<br>• characterized by cytoplasmic clearing that may be a consequence of glycogen or lipid accumulation in tumor cells,<br>• risk factors include liver cirrhosis, hepatitis B or C, alcohol use disorder, and nonalcoholic fatty liver disease |
| steatohepatitic HCC | • common HCC subtype,<br>• arises in the background of nonalcoholic or alcoholic steatohepatitis,<br>• associated with liver fibrosis and cirrhosis,<br>• may be accompanied by inflammation and liver necrosis,<br>• tumor cells with a large clear cytoplasm and a high degree of nuclear atypia,<br>• associated with poor prognosis |
| macrotrabecular HCC | • characterized by macrotrabecular structures that are thicker than the three layers of tumor cells arranged into trabeculae or nests and surrounded by intratumoral fibrosis,<br>• associated with poor prognosis and aggressive tumor progression,<br>• more common in the background of liver cirrhosis |
| chromophobe HCC | • a rare subtype of HCC,<br>• considered to be a variant of conventional HCC,<br>• characterized by large, polygonal cells with pale eosinophilic cytoplasm,<br>• tumor cells arranged into trabeculae or nests; intratumoral fibrosis is common,<br>• associated with a better prognosis,<br>• cirrhotic background less common |
| neutrophil rich HCC | • a rare subtype of HCC,<br>• characterized by large neutrophil infiltrates within the tumor, a high degree of necrosis and inflammation,<br>• associated with a worse prognosis and a higher risk of recurrence and metastases |
| lymphocyte rich HCC | • characterized by dense lymphoid infiltrate,<br>• usually occurs in young patients,<br>• associated with a better prognosis |

* Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) was not included in this list

advanced HCC present with progressive cachexia, abdominal pain, ascites, leg swelling, jaundice, and fever [8].

Laboratory workup is based primarily on liver function tests. The previous gold standard in HCC diagnosis was an alpha-fetoprotein (AFP) test. However, in current clinical practice, its role is considered controversial. Increased AFP levels are neither sensitive nor specific for HCC. About 40% of patients with HCC have normal AFP levels, while elevated levels are seen also in other benign or malignant tumors [8–10].

If imaging tests of the liver reveal a lesion that is likely to be HCC, multiphase computed tomography or contrast-enhanced magnetic resonance imaging of the abdomen should be performed. Lesions should be assessed using the Liver Imaging Reporting and Data System (LI-RADS), which includes 5 categories. A lesion that is assigned to category LR-5 is considered as definitely HCC [8, 10–12]. If HCC cannot be determined on the basis of imaging tests or if another etiology of the lesion is suspected, a tumor biopsy should be considered. However, it is not indicated in patients with a suspicion of HCC who are referred for liver transplant [8, 11].

If the diagnosis of HCC is confirmed, liver function should be assessed using the Child-Pugh score. The score was originally developed by Child in 1964 for patients undergoing portocaval shunt surgery. It was then modified in 1973 by Pugh to replace the criterion of nutritional status with prothrombin time or international normalized ratio. Currently, it is a widely used tool for assessing liver function and predicting mortality in patients with chronic liver disease [8, 13]. The score is presented in table II.

## Treatment of hepatocellular carcinoma

The choice of treatment strategy depends on cancer stage, liver function, and the patient's general condition. There are

**Table II.** Child-Pugh score [8, 13]

| Parameter | 1 point | 2 points | 3 points |
|---|---|---|---|
| total bilirubin (μmol/L) | <34 | 34–50 | >50 |
| serum albumin (g/L) | >35 | 28–35 | <28 |
| INR or PT | <1.7 (<4) | 1.71–2.30 (4–6) | >2.3 (>6) |
| ascites | none | mild (or medically suppressed) | moderate to severe (or refractory) |
| encephalopathy | none | grade I–II (or suppressed with medication) | grade III–IV (or refractory) |
| | **Class A** | **Class B** | **Class C** |
| total points | 5–6 | 7–8 | 10–15 |
| 1-year survival | 100% | 80% | 45% |
| 2-year survival | 85% | 57% | 35% |

INR – international normalization ratio; PT – prothrombin ratio

18 different scoring systems available in HCC (e.g., the Okuda system, Cancer of the Liver Italian Program, tumor node metastasis (TNM) system, and Barcelona Clinic Liver Cancer [BCLC]). Each system has its advantages and limitations [1, 8]. Because HCC is a heterogeneous malignancy, in some cases, a molecular classification is additionally used (gene signature-based, metabolic, immune, or chromosome classification of HCC) [1]. In Western countries, a standard approach is to use the BCLC staging system to guide the management of patients with HCC. The BCLC system assesses the performance status, liver function based on the Child-Pugh score, the number and size of tumors in the liver, and the presence and severity of comorbidities (fig. 1) [8, 14, 15].

## *Locoregional therapy*

HCC can be cured completely by liver resection or transplant. However, in clinical practice, this strategy is rarely feasible. Liver resection can be done at an early stage provided that enough functioning parts of the liver can be spared. On the other hand, liver transplant options are limited because many patients are not eligible for the procedure. Another problem is the insufficient number of donors and a limited availability of liver transplant centers [13]. In patients with locally advanced cancer, so called locoregional therapies are an important part of treatment. Locoregional therapies are minimally invasive procedures for localized disease. They can be applied before systemic therapy to reduce tumor mass or as a palliative treatment option when systemic therapy is not possible [10, 16, 17]. Locoregional therapies for HCC, together with indications, are presented in table III.

## *Systemic therapy*

Systemic therapy is used only as a palliative treatment in patients with advanced HCC, corresponding to BCLC stage C (patients with very good or good functional status, with preserved liver function, that is Child-Pugh class A, and tumor invasion of the portal veins or extrahepatic spread) [19]. According to European Association for the Study of the Liver guidelines, which summarize efficacy data for available HCC treatments, there is no evidence to support the efficacy of standard cytostatic drugs in this indication [20].

### *First-line palliative systemic therapy*

Until 2008, there were no medical treatments available with proven efficacy in patients with HCC. However, a breakthrough in the treatment of HCC occurred in 2008, when the results of the phase 3 SHARP trial were published, which compared a multikinase inhibitor, sorafenib, with a placebo [21]. The primary outcomes were overall survival (OS) and the time to symptomatic progression. Sorafenib was shown to prolong the median OS by 2.8 months (median OS, 10.7 months *vs.* 7.9 months in the sorafenib and placebo arms, respectively), while it had no effect on the time to symptomatic progression. Thus, sorafenib became the standard first-line treatment for patients with advanced HCC. For the next 10 years, no new therapy had been developed that would offer better outcomes. Around that time, the efficacy of sorafenib was confirmed in a similar study in the Asian population [22]. However, in a meta-analysis by Zhang et al. [23], a subgroup analysis of these two trials showed a limited therapeutic effect of sorafenib in patients with extrahepatic spread. Based on these findings, sorafenib was not reimbursed in Poland in the treatment of patients with extrahepatic spread, even though it was a standard treatment worldwide. However, a modified drug program was introduced in May 2022, and since then sorafenib has been reimbursed for this indication.

After sorafenib efficacy was confirmed in the treatment of advanced HCC, studies were undertaken to investigate its use as adjuvant therapy after radical local therapy (resection or ablation). However, the phase 3 STORM trial showed no

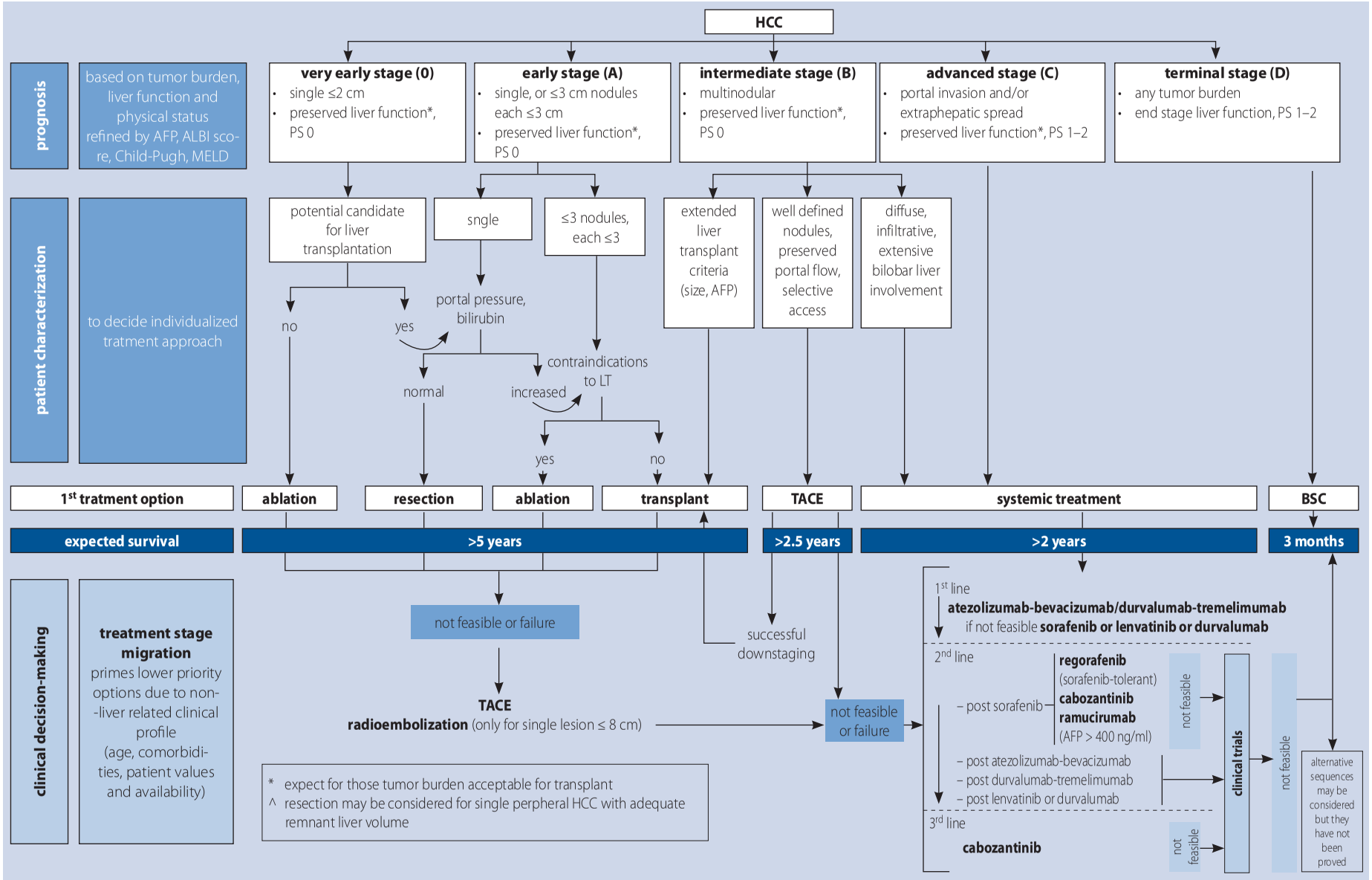


**Figure 1.** Barcelona Clinic Liver Cancer (BCLC) staging system [14, 15]

**Table III.** Locoregional therapies in hepatocellular carcinoma [10, 17, 18]

| Type | Indications |
|---|---|
| ablative therapies:<br>• RFA<br>• microwave ablation<br>• laser-induced interstitial thermotherapy<br>• high-intensity focused ultrasound<br>• cryoablation<br>• percutaneous ethanol injection<br>• irreversible electroporation | BCLC-A patients |
| transarterial embolization:<br>• conventional TACE<br>• chemoembolization with drug-eluting beads,<br>transarterial radioembolization – commonly yttrium-90 microspheres | BCLC-B patients without portal vein tumor thrombus |
| combined therapy (RFA + TACE) | selected BCLC-A/B patients |
| selective internal radiation therapy | selected cases of BCLC-B/C patients ineligible for TACE or systemic treatment |

RFA – radiofrequency ablation; TACE – transarterial chemoembolization; BCLC – Barcelona Clinic Liver Cancer

difference in recurrence-free survival between the sorafenib and placebo groups (33.3 months *vs.* 33.7 months, respectively; HR, 0.940; 95% CI 0.780–1.134; p = 0.26) [24].

The phase 3 CALGB 80802 trial assessed whether the addition of a cytostatic drug, doxorubicin, enhanced the effect of palliative treatment with sorafenib, but the results were not satisfactory [25]. There was strong evidence that the combination of doxorubicin and sorafenib therapy does not improve survival (median OS, 9.3 months in the combination arm *vs.* 9.4 months in the sorafenib arm; HR 1.05; 95% CI, 0.83–1.31) [25].

In 2018, the results of the noninferiority REFLECT trial comparing lenvatinib with sorafenib as first-line systemic therapy were published, marking a positive shift in the treatment of HCC [26]. It was assumed that lenvatinib should retain at least 60% of the sorafenib effect on OS *vs.* placebo. The median OS was 13.6 months for lenvatinib *vs.* 12.3 months for sorafenib (HR, 0.92; 95% CI, 0.79–1.06). Thus, lenvatinib was proven to be noninferior to the standard first-line treatment with sorafenib. In Poland, lenvatinib is not reimbursed in the treatment of patients with HCC.

Around this time, it was suggested for the first time that immunotherapy may be effective in HCC. However, studies on immunotherapy alone did show promising results. The CheckMate 459 study compared nivolumab *vs.* sorafenib as first-line treatment in systemic therapy-naive patients with advanced HCC [27]. The primary endpoint was OS. The median OS was 16.4 months (95% CI, 13.9–18.4) for nivolumab and 14.7 months (95% CI, 11.9–17.2) for sorafenib (HR, 0.85 [95% CI 0.72–1.02]; p = 0.075; minimum follow-up, 22.8 months). The protocol-defined significance level of p = 0.0419 was not reached [27].

A breakthrough in the treatment of HCC occurred in 2020. Improved efficacy was achieved by combining immunotherapy with angiogenesis inhibitors. The development of HCC is a complex and multiphase process, with tumor growth dependent on pathological vascularization. The proliferation of cancer cells and neoangiogenesis are induced by numerous factors, including the vascular endothelial growth factor (VEGF). Bevacizumab inhibits the microvascular growth of tumor blood vessels by increasing T-lymphocyte infiltration, reducing the activity of immunosuppressive cells and acting synergistically with anti-programmed death ligand 1 (PD-L1) inhibitors [28, 29].

The results of the IMbrave150 trial provided the basis for developing a new first-line standard of care in the treatment of HCC. In this study, a combination of the PD-L1 inhibitor atezolizumab, 1200 mg, with the VEGF inhibitor bevacizumab, 15 mg/kg, was compared with the standard of care (sorafenib) [30]. Patients were randomly assigned in a 2:1 ratio to receive either atezolizumab plus bevacizumab or sorafenib. The study included 501 patients from Asia (excluding Japan) and the rest of the world. Patients with extrahepatic spread constituted 60% of the study population. The primary endpoints were OS and progression-free survival (PFS).

The results were promising, with a median OS of 19.2 months in patients who received the combination therapy *vs.* 13.4 months in the sorafenib group. The PFS was 6.8 months and 4.3 months, respectively. Of note, the objective response rate was 30%, including 10% of total remission cases. Combination therapy prolonged the time to symptomatic progression by 7 months. In contrast, while sorafenib improved survival, it had no effect on the time to symptomatic progression. Sorafenib prolonged survival, but it was associated with a shorter time to deterioration of the quality of life compared with the atezolizumab–bevacizumab group. Atezolizumab plus bevacizumab also showed an acceptable safety profile. Serious toxic effects were reported in 38% of patients receiving the combination therapy *vs.* 31% of those receiving sorafenib [30].

The most recent area of research into the efficacy of treatment for advanced HCC has focused on the use of dual immunotherapy, The phase 3 HIMALAYA trial evaluated the efficacy and safety of tremelimumab (anti-CTLA-4) plus durvalumab (anti-PD-L1) or durvalumab alone *vs.* sorafenib as the first-line treatment in patients with unresectable HCC [31]. The study showed that the STRIDE (single tremelimumab regular interval durvalumab) regimen, that is, a single dose of tremelimumab at 300 mg added to 1500 mg of durvalumab on the same day, followed by durvalumab, 1500 mg, every 4 weeks, is more effective than sorafenib alone. The median OS was 16.4 months for STRIDE *vs.* 13.8 months for sorafenib. Durvalumab alone was noninferior to sorafenib, with a median OS of 16.6 months *vs.* 13.8 months. The results of the HIMALAYA trial were positive, but in the light of findings from the IMbrave150 trial, it seems that dual immunotherapy might be used in patients with

**Table IV.** Summary of clinical trials on first-line palliative systemic treatment [21, 26, 30, 31]

| Study | Therapy | Primary endpoints | Median OS |
|---|---|---|---|
| therapies reimbursed in Poland | | | |
| SHARP | sorafenib *vs.* placebo | OS, TTSP | longer by 2.8 months |
| IMbrave150 | atezolizumab + bevacizumab *vs.* sorafenib | OS, PFS | longer by 5.8 months |
| therapies not reimbursed in Poland | | | |
| REFLECT | lenvatinib *vs.* sorafenib | OS | NA |
| HIMALAYA | tremelimumab + durvalumab *vs.* sorafenib | OS | longer by 2.6 months |

NA – not available; OS – overall survival; PFS – progression-free survival; TTSP – time to symptomatic progression

contraindications to antiangiogenic therapy. Clinical trials on first-line treatments for patients with HCC are summarized in table IV.

*Second-line systemic therapy*

Until 2017, there was no second-line therapy with confirmed efficacy available for patients with cancer progression after sorafenib therapy. However, in recent years, there have been significant advances also in this field. Three multikinase inhibitors were shown to be effective in the second-line setting. The first drug to show promising effects in clinical trials was regorafenib. The phase 3 RESORCE trial included 843 patients with HCC who showed disease progression on sorafenib treatment [32]. Patients were randomly assigned in a 2:1 ratio to receive either regorafenib or placebo. The primary endpoint was OS. Regorafenib improved OS: the median OS was 10.6 months for regorafenib *vs.* 7.8 months for placebo (HR, 0.63; 95% CI, 0.50–0.79) [32]. In Poland, regorafenib is not reimbursed for this indication.

In 2018, the CELESTIAL trial was published, which assessed the efficacy and safety of another multikinase inhibitor, cabozantinib, in previously treated patients with advanced HCC [33]. The study included 707 patients after up to 2 previous lines of systemic treatments, one of which had to be sorafenib. Patients were randomly assigned in a 2:1 ratio to receive either cabozantinib or a placebo. Patients in the study arm received cabozantinib at a dose of 60 mg/d. To manage adverse events, treatment interruptions and dose reductions to 40 mg/d and then 20 mg/d were used. The primary endpoint was OS, and the secondary endpoints were the objective response rate and PFS. The study showed promising results, with a significantly higher median OS in the cabozantinib *vs.* placebo arm (10.2 *vs.* 8 months). There were also significant differences in PFS between groups (5.2 months in the cabozantinib arm *vs.* 1.9 months in the placebo arm) [33]. In Poland, cabozantinib is available within the drug program of the Ministry of Health.

The most modest, but still significant, effect on survival was shown for ramucirumab in the second-line setting in patients with HCC and AFP levels higher than 400 ng/ml. Patients were randomized in a 2:1 ratio to receive ramucirumab or placebo. The primary endpoint was OS. The median OS was significantly higher in the ramucirumab group *vs.* placebo (8.5 *vs.* 7.3 months; HR, 0.710; 95% CI, 0.531–0.949; $p = 0.0199$. Also, PFS was higher in patients receiving ramucirumab *vs.* those receiving placebo (2.8 *vs.* 1.6 months; HR, 0.452; 95% CI, 0.339–0.603; $p < 0.0001$) [34]. Clinical trials on second-line treatments for patients with HCC are summarized in table V.

**Table V.** Summary of clinical trials on second-line palliative systemic treatment [32–34]

| Study | Therapy | Primary endpoints | Median OS |
|---|---|---|---|
| therapies reimbursed in Poland | | | |
| CELESTIAL | cabozantinib *vs.* placebo | OS | longer by 2.2 months |
| therapies not reimbursed in Poland | | | |
| RESORCE | regorafenib *vs.* placebo | OS | longer by 2.8 months |
| REACH-2 | ramucirumab *vs.* placebo | OS | longer by 1.2 months |

OS – overall survival

## Conclusions

Over the past 5 years, there have been significant advances in the systemic treatment of advanced HCC. The median OS increased from 10.7 months in the SHARP trial to 19.2 months in the IMbrave150 trial. However, all therapies that were effective in the second-line setting were investigated in patients with disease progression on sorafenib treatment. Therefore, the sequence of treatment lines is an issue that remains to be addressed in future studies.

**Conflict of interest:** none declared

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*Received: 29 Mar 2023*
*Accepted: 7 Apr 2023*

## References

1. Chidambaranathan-Reghupaty S, Fisher PB, Sarkar D. Hepatocellular carcinoma (HCC): Epidemiology, etiology and molecular classification. Adv Cancer Res. 2021; 149: 1–61, doi: 10.1016/bs.acr.2020.10.001, indexed in Pubmed: 33579421.
2. Frager SZ, Schwartz JM. Hepatocellular carcinoma: epidemiology, screening, and assessment of hepatic reserve. Curr Oncol. 2020; 27(Suppl 3): S138–S143, doi: 10.3747/co.27.7181, indexed in Pubmed: 33343207.
3. International Agency for Research on Cancer. https://gco.iarc.fr/projects#database (10.03.2023).
4. Renne SL, Sarcognato S, Sacchi D, et al. Hepatocellular carcinoma: a clinical and pathological overview. Pathologica. 2021; 113(3): 203–217, doi: 10.32074/1591-951X-295, indexed in Pubmed: 34294938.
5. El Jabbour T, Lagana SM, Lee H. Update on hepatocellular carcinoma: Pathologists' review. World J Gastroenterol. 2019; 25(14): 1653–1665, doi: 10.3748/wjg.v25.i14.1653, indexed in Pubmed: 31011252.
6. Digestive System Tumours. WHO Classification of Tumours. Ed. 5. 2019.
7. Lo RL. An update on the histological subtypes of hepatocellular carcinoma. Hepatoma Research. 2019; 2019, doi: 10.20517/2394-5079.2019.021.
8. Abraham J, Gulley JL. The Bethesda Handbook of Clinical Oncology. Ed. 6. Wolters Kluwer Health 2022.
9. Piñero F, Dirchwolf M, Pessôa MG. Biomarkers in Hepatocellular Carcinoma: Diagnosis, Prognosis and Treatment Response Assessment. Cells. 2020; 9(6), doi: 10.3390/cells9061370, indexed in Pubmed: 32492896.
10. Benson AB, Abbott DE, Ahmed A. et al.. Hepatobiliary Cancers. NCCN Guidelines Version 5. 2023.
11. Kulik L, El-Serag HB. Epidemiology and Management of Hepatocellular Carcinoma. Gastroenterology. 2019; 156(2): 477–491.e1, doi: 10.1053/j.gastro.2018.08.065, indexed in Pubmed: 30367835.
12. Liver Reporting & Data System. American College of Radiology. https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/LI-RADS (10.03.2023).
13. Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973; 60(8): 646–649, doi: 10.1002/bjs.1800600817, indexed in Pubmed: 4541913.
14. Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis. 1999; 19(3): 329–338, doi: 10.1055/s-2007-1007122, indexed in Pubmed: 10518312.
15. Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. J Hepatol. 2022; 76(3): 681–693, doi: 10.1016/j.jhep.2021.11.018, indexed in Pubmed: 34801630.
16. Lurje I, Czigany Z, Bednarsch J, et al. Treatment Strategies for Hepatocellular Carcinoma ¯ a Multidisciplinary Approach. Int J Mol Sci. 2019; 20(6), doi: 10.3390/ijms20061465, indexed in Pubmed: 30909504.
17. Inchingolo R, Posa A, Mariappan M, et al. Locoregional treatments for hepatocellular carcinoma: Current evidence and future directions. World J Gastroenterol. 2019; 25(32): 4614–4628, doi: 10.3748/wjg.v25.i32.4614, indexed in Pubmed: 31528090.
18. Kung J, Ng K. Role of locoregional therapies in the management of patients with hepatocellular carcinoma. Hepatoma Research. 2022; 8: 17, doi: 10.20517/2394-5079.2021.138.
19. Krzakowski M, Reguła J, Cichoż-Lach H, et al. Wytyczne postępowania diagnostyczno-terapeutycznego w raku wątrobowokomórkowym. Onkol Prakt Klin Edu. 2022; 8(2): 81–124.
20. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu, European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol. 2018; 69(1): 182–236, doi: 10.1016/j.jhep.2018.03.019, indexed in Pubmed: 29628281.
21. Llovet JM, Ricci S, Mazzaferro V, et al. SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008; 359(4): 378–390, doi: 10.1056/NEJMoa0708857, indexed in Pubmed: 18650514.
22. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2009; 10(1): 25–34, doi: 10.1016/S1470-2045(08)70285-7, indexed in Pubmed: 19095497.
23. Zhang X, Yang XR, Huang XW, et al. Sorafenib in treatment of patients with advanced hepatocellular carcinoma: a systematic review. Hepatobiliary Pancreat Dis Int. 2012; 11(5): 458–466, doi: 10.1016/s1499-3872(12)60209-4, indexed in Pubmed: 23060390.
24. Bruix J, Takayama T, Mazzaferro V, et al. STORM investigators. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2015; 16(13): 1344–1354, doi: 10.1016/S1470-2045(15)00198-9, indexed in Pubmed: 26361969.
25. Abou-Alfa GK, Shi Q, Knox JJ, et al. Assessment of Treatment With Sorafenib Plus Doxorubicin vs Sorafenib Alone in Patients With Advanced Hepatocellular Carcinoma: Phase 3 CALGB 80802 Randomized Clinical Trial. JAMA Oncol. 2019; 5(11): 1582–1588, doi: 10.1001/jamaoncol.2019.2792, indexed in Pubmed: 31486832.
26. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet. 2018; 391(10126): 1163–1173, doi: 10.1016/S0140-6736(18)30207-1, indexed in Pubmed: 29433850.
27. Yau T, Park JW, Finn RS, et al. CheckMate 459: A randomized, multi--center phase III study of nivolumab (NIVO) vs sorafenib (SOR) as first-line (1L) treatment in patients (pts) with advanced hepatocellular carcinoma (aHCC). Ann Oncol. 2019; 30: v874–v875, doi: 10.1093/annonc/mdz394.029.
28. Fukumura D, Kloepper J, Amoozgar Z, et al. Enhancing cancer immunotherapy using antiangiogenics: opportunities and challenges. Nat Rev Clin Oncol. 2018; 15(5): 325–340, doi: 10.1038/nrclinonc.2018.29, indexed in Pubmed: 29508855.
29. Gabrilovich DI, Chen HL, Girgis KR, et al. Production of vascular endothelial growth factor by human tumors inhibits the functional maturation of dendritic cells. Nat Med. 1996; 2(10): 1096–1103, doi: 10.1038/nm1096-1096, indexed in Pubmed: 8837607.
30. Cheng AL, Qin S, Ikeda M, et al. IMbrave150 Investigators. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med. 2020; 382(20): 1894–1905, doi: 10.1056/NEJMoa1915745, indexed in Pubmed: 32402160.
31. Abou-Alfa G, Chan S, Kudo M, et al. Phase 3 randomized, open-label, multicenter study of tremelimumab (T) and durvalumab (D) as first-line therapy in patients (pts) with unresectable hepatocellular carcinoma (uHCC): HIMALAYA. J Clin Oncol. 2022; 40(4_suppl): 379–379, doi: 10.1200/jco.2022.40.4_suppl.379.
32. Bruix J, Qin S, Merle P, et al. RESORCE Investigators. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017; 389(10064): 56–66, doi: 10.1016/S0140-6736(16)32453-9, indexed in Pubmed: 27932229.
33. Abou-Alfa G, Meyer T, Cheng AL, et al. Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma. N Engl J Med. 2018; 379(1): 54–63, doi: 10.1056/nejmoa1717002.
34. Zhu AX, Kang YK, Yen CJ, et al. REACH-2 study investigators. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2019; 20(2): 282–296, doi: 10.1016/S1470-2045(18)30937-9, indexed in Pubmed: 30665869.

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NOWOTWORY Journal of Oncology
2023, volume 73, number 3, 154–161
DOI: 10.5603/NJO.a2023.0021

ISSN: 0029–540X, e-ISSN: 2300-2115
www.nowotwory.edu.pl

# Epithelioid sarcoma

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Epithelioid sarcoma (ES) is a very rare sarcoma characterized by loss of *INI1*. Enzinger first described ES in 1970, but the histopathologic differential diagnosis of ES remains challenging. There are two ES subtypes, the classical type with spindle epithelioid to the central pseudogranulomatous cells, and the proximal type, which is predominantly composed of epithelioid and rhabdoid cells. ES symptoms and signs are not specific and depend on tumor localization. The only treatment for ES is radical excision with a microscope-radical margin. In general, the best treatment for ES in extremes is radical resection with a wide margin or amputation with or without lymph node dissection. Surgery may be followed by adjuvant chemotherapy and/or radiation therapy. Referral of patients with ES to a sarcoma center that offers hypofractionation RT trials and multidisciplinary clinical trials should be considered upfront. Neoadjuvant chemotherapy with ifosfamide and doxorubicin with / or without radiation therapy must be used after a multidisciplinary team discussion. On 23 January 2020, the US Food and Drug Administration (FDA) first approved tazemetostat – an inhibitor of zeste homolog 2 enhancer – therapy for metastatic ES or locally advanced ES not eligible for radical resection.

**Key words:** sarcoma, epithelioid sarcoma, Enzinger, tazemetostat

## Introduction

Epithelioid sarcoma is a very rare (less than 1% of all soft tissue sarcomas) high-grade soft tissue sarcoma (STS) with a known propensity for locoregional recurrence and dissemination [1]. In general, ES tumors are built by spindled and epithelioid cells that circumscribe areas of central hyalinization and necrosis. Although ESs are of mesenchymal origin, their mixed differentiation makes their histopathological differential diagnosis challenging. The incidence in the EU and the United States is less than 0.2 and 0.5 new cases per million inhabitants per year, respectively. Enzinger first described epithelioid sarcoma (ES) in 1970 as a rare tumor of the distal extremities with epithelioid cytomorphology on pathological examination [2, 3]. The 5- and 10-year survival rates for ES are approximately 68% and 61%, respectively. No survival advantage was found for any gender, race, or ethnic group [4]. In the course of the natural history of ES, local failure occurs in approximately 25%, lymph node involvement in 30% and distant metastases are found in more than 40% of patients [5]. However, ES is commonly initially diagnosed as a benign condition, thus delaying definitive treatment. ES can also be misdiagnosed as another subtype of sarcoma:

- clear cell sarcoma,
- fibrosarcoma,
- synovial sarcoma,
- peripheral nerve sheath tumor,
- spinal cell sarcoma,
- fibrous histiocytosarcoma or other fibrohistiocytic tumor,
- nodular tenosynovitis or fasciitis,

**How to cite:**
Czarnecka AM. ***Epithelioid sarcoma.*** *NOWOTWORY J Oncol* 2023; 73: 154–161.

- squamous cell carcinoma,
- Dupuytren's disease,
- necrotising granuloma,
- rheumatoid nodule [6, 7].

There are two typical ES morphologies:

- the classical type, which is a spindle-epithelioid to central pseudogranulomatous cells, and
- the proximal type, which is predominantly composed of epithelioid and rhabdoid cells.

Proximal ES is also known as the large cell subtype. The classic ES type is epidemiologically more common than the proximal type. Furthermore, the classic subtype is most commonly diagnosed in adolescents and young adults (10 to 40 years of age), while the proximal one in adults between 20 and 65 years of age. Classic ES is usually diagnosed in locations of the distal upper extremities with more than 50% developing in the hand and fingers. Proximal ESs develop more often in the hip, trunk, pelvis, peritoneal cavity, or inguinal and genital area. Proximal ES type is built of large cells with prominent nucleoli that resemble a poorly differentiated carcinoma and a frequent rhabdoid phenotype. In ES, periosteal bone invasion may also occur, as well as central necrosis of the tumor, its hemorrhage or ulceration [8].

Epithelioid sarcoma symptoms and signs are not specific and depend on tumor location, therefore include a lump or swelling in the area, with masses greater than 20 cm, slightly mobile tumors, painful on palpation and without skin changes, or ulcerated and indurated lesions, but also rectum bleeding, vaginal bleeding, epistaxis, hemoptysis, nausea, vomiting, abdominal pain, abdominal fullness, ptosis, headaches, neck pain, eye pain and swelling, diarrhea or constipation, depression, anorexia, weight loss, or fever [2]. Regional spread of ES through lymphatic drainage and/or direct infiltration results in lymph node metastases, while distant metastases arise with hematogenous spread mainly in the lungs or liver [9]. Indolent tumor growth along with distal location may also lead to inappropriate primary diagnosis and subsequent surgical procedures prior to referral to the reference sarcoma clinic [10, 11]. Most often, at first, ES presents as a slowly growing, painless, and firm nodule, but the course of ES is unpredictable, including rapid progression with extensive lymph node or distant metastasis development. Furthermore, the natural history of ES is characterized by a high risk of multiple recurrences. ES tends to spread along the fascia and muscles, resulting in multifocality of the tumor [10, 12–14]. The 5-year risk of recurrence after radical treatment is high, up to 70% [5, 13, 15, 16]. The ES tends to have regional lymphatic spread by more than 20% [6, 17, 18]. Patients with proximal-type tumor, ES tumor diameter >5 cm, multifocal tumors, nodal involvement, ES tumor necrosis, vascular invasion, and high mitotic index have shorter 5-year disease-specific survival (DSS) [14].

Epithelioid sarcoma has a complex genome with a high mutational rate that is comparable to that of ovarian carcinoma. More than 90% of ES cases are characterized by the loss of function of integrase interactor 1 (*INI1; SMARCB1/* hSNF5 – chromatin regulator, subfamily B, member 1 or malignant rhabdoid tumor suppressor) [11, 19]. The INI1 protein is a core component of the SWItch/ sucrose non-fermentable (SWI/SNF) chromatin remodeling complex that alters the structure of chromatin and facilitates transcription, replication, and DNA repair. *INI1* is located on chromosome 22q11.2 [20]. Other key SWI/SNF complex subunits are *BRG1* (SMARCA4), *BRM* (SNF2L2, SMARCA2), *PBRM1* (hPB1, BAF180), and *BAF155* (SMARCC1) that can all be lost in ES [21]. In ES, multiple mechanisms lead to inactivation of *SMARCB1*, including homozygous deletions, monoallelic deletion, nonsense point mutations, epigenetic mechanisms, and microRNA down-regulation of mRNA [22]. INI1 signals regulate chromosomal stability by signaling through the p16INK4a-Rb-E2F pathway. At the same time, in tumors with the *INI1* gene, zeste homolog 2 (EZH2) signaling is up-regulated [23]. As a result, EZH2 is recruited to Polycomb targets and trimethylation of histone 3 lysine 27 in these regions leads to repression of target genes [24]. The loss of INI1 expression is characteristic for both conventional ES and proximal ES [20].

Epithelioid sarcoma is characterized by the expression of carcinoma markers (e.g. cytokeratin and EMA) and sarcoma markers (e.g. vimentin), as well as CD34, while negative for: S-100, and CD31 [14]. Other alterations found in ES cells include activation of PI3K/AKT/mTOR, overexpression of EGFR, and activation of *MET* [11]. In an animal model, it was proven that smarcb1 deficiency with concordant *TP53* mutation is sufficient to induce the development of ES [25]. In ES cells, it was shown that *SMARCB1* negatively controls the expression of cyclin D1, E2F, and AURKA. As a result of the loss of *SMARCB1* in these tumors, cyclin D1, E2F, and AURKA are upregulated and stimulate the cell cycle. In normal cells, *SMARCB1/INI1* suppresses tumor progression by p16INK4a signaling to pRb (retinoblastoma), a tumor suppressor that negatively regulates cell cycle progression from G0/G1 to the S phase. At the same time, enhanced MYC activity and increased DNA replication are found in cells with *SMARCB1* loss. Importantly, SMARCB1 interacts with the BRCA1, BARD1 and XPC proteins responsible for nucleotide excision repair. It also regulates chromosomal stability [26]. As a result, *SMARCB1* loss results in the fast proliferation of cells and mutation accumulation. SMARCB1 also inhibits the signaling of the sonic hedgehog (SHH) pathway, and this pathway is important in the development of radio and chemo-resistance [27, 28]. Next-generation sequencing (NGS) may enable further insights into the pathogenesis of ES, allowing genetic classification and biomarker discovery. NGS may also be used to verify diagnoses [29, 30].

## Radical treatment

The curative treatment of ES is radical excision with wide R0 margins. In general, the best treatment for ES in the extre-

mities is *en bloc* excision. In cases with large tumors, amputation must often be performed in order to obtain radical resection with tumor-free margins. Primary tumor resection may be accompanied by lymph node dissection. After MDT adjuvant chemotherapy and/or radiation therapy can also be used in high-risk patients [31–33]. MDT should consider neoadjuvant chemotherapy for ES patients based on prognostic stratification with Sarculator nomogram for STS (https://www.sarculator.com/) [32, 34, 35].

The proximal subtype of ES is more aggressive, has higher rates of recurrence and metastases, and generally worse prognosis and higher mortality compared to classical ES [36]. In ES treatment, a sophisticated and well-planned surgical reconstruction can be performed with microsurgery, including free flap reconstruction or tendon transfers. In general practice, most ESs are extracompartmental and infiltrate surrounding tissues, including the neurovascular plexus. Consequently, due to anatomical constraints, conservative surgery is not always possible in the case of locally advanced tumors. Furthermore, due to a common location in the distal part of the extremities, in cases of extensive infiltration of the soft tissues that limits the possibility of reconstruction, amputation can also be required [10, 12, 13]. In centrally located ES tumors, the complex anatomy surrounding the spine further complicates the treatment and often makes complete resection R0 extremely difficult or impossible [37]. If lymph node metastases occur, therapeutic lymph node dissection (LND) should be performed [6, 10, 38]. The high rate of nodal involvement may justify performing a sentinel node biopsy (SLNB) in selected cases of ES, but a low percentage of occult metastases was reported in this subtype of sarcoma. However, SLNB should be considered as a minimally invasive N disease staging procedure [17, 39–41].

Neodjuvant chemotherapy and radiotherapy (RT) can be considered in patients with ES after multidisciplinary team evaluation (MDT) [42]. In fact, radiation therapy has been reported to reduce the risk of local recurrence, but not overall survival (OS) [43]. At this point in time, radical surgery with conventionally fractionated perioperative RT is considered the standard of care in ES [44], while patients should be referred to trials with RT hypofractionation and combined therapy clinical trials when available in a sarcoma center. There are no phase III data on the role of RT in recurrent and metastatic ES. If RT was not used in radical treatment, perioperative RT may be considered in recurrent ES. In the event of a local recurrence in the field, re-irradiation should be considered only in selected cases. Patients with a limited volume of local ES recurrence can be treated with perioperative or definitive brachytherapy in sarcoma centers [45]. Select ES patients with oligometases may receive definitive radiation therapy [46, 47]. Patients with large recurrent ES tumors may receive multidisciplinary treatment with chemotherapy with RT with/without hyperthermia after MDT [48]. Palliative RT can be used for symptomatic ES metastases (palliative single fraction) [11].

In some cases, after MDT, perioperative chemotherapy can be considered [5, 13, 49, 50]. According to the current ESMO–EURACAN–GENTURIS Clinical Practice Guidelines, neoadjuvant treatment of operable localized STS of the extremities and the trunk wall is not yet standard treatment, although it can be proposed for fit patients with high-risk disease [51]. In patients with ES, MDT may advise perioperative chemotherapy for patients with large, high-grade tumors. After surgery with incomplete resection, as well as in cases of up-front metastases, chemotherapy is also considered [42, 52]. In studies by NIO-PIB, the Royal Marsden Hospital, Japan, and the French Sarcoma Group, doxorubicin with ifosfamide (AI) was the most commonly used [13, 49, 53, 54]. After neoadjuvant chemotherapy, objective and/or pathological responses are expected in 15% of cases [13, 49, 55]. Chemotherapy regimens used in radical and / or first-line treatment should be based on doxorubicin. In addition to the AI regimen and doxorubicin monotherapy, the use of CyVADIC (cyclofosfamide, vincristine, doxorubicin, and dacarbazine) and VAIA (vincristine, doxorubicin, ifosfamide, actinomycin-D) have also been reported [11, 50]. Most recently, ES patients were recruited into a trial of radiation therapy with or without combination chemotherapy or pazopanib prior to surgery to treat patients with newly diagnosed nonrhabdomyosarcoma soft tissue sarcomas that can be removed by surgery. There are no reports on the association between perioperative chemotherapy and OS, DMFS, or LRFS [5, 42, 50, 52].

## Systemic therapies in advanced epithelioid sarcoma

Epithelioid sarcoma metastasizes most frequently to the lungs or pleura [6, 12, 15, 56]. High-risk epithelioid sarcomas are patients with large tumors, high tumor grade, inadequate tumor resection, and metastatic disease, predicting a relatively poor clinical outcome [57]. There are no specific guidelines based on high-quality evidence on systemic therapy in advanced ES [58]. Patients treated at Royal Marsden Hospital benefit from significantly longer OS when treated with palliative chemotherapy versus BSC (mOS: 16.8 *vs.* 8.7 months, p = 0.044) [50]. Most available data on systemic ES therapy are reported as retrospective studies, case series, and case reports. Only a small number of patients with ES were treated in clinical trials. 27 ES patients were treated in EORTC trials 62012, 62043, 62072 and 62091. Among these cases, objective responses were reported for those treated with doxorubicin with ifosfamide (12.5 – 1/8), pazopanib (objective respons rate [ORR] 100% – 2/2), or trabectedin (33.3% – 1/3), but without OR when treated with doxorubicin monotherapy. The median progression-free survival (PFS) for patients treated first-line was 4.04 months. The median OS of these patients was only 10.93 months [59]. The analysis of 74 patients with ES has shown that patients receiving first-line systemic therapy have ORR of 15%, desease control rate (DCR) of 20%, and a median duration of

response (DOR) of 3.3 months (95% CI: 2.1–5.2 months). In these patients, the mPFS was 2.5 months (95% confidence interval [CI]: 1.7–6.9 months), and the mOS was 15.2 months (95% CI: 11.4–21.7 months). More than half of these patients were treated with regimens based on doxorubicin [60]. In general, the most extensive evidence on the use of chemotherapy in ES comes from a recently published series of 115 patients with advanced or metastatic ES. These patients were not treated with chemotherapy in a perioperative setting before treatment was reported. This analysis has shown that there is no difference in response rates between patients treated with monotherapy anthracycline or with anthracycline combined with ifosfamide [61]. In clinical practice, anthracyclines can be combined not only with ifosfamide, but also vincristine, dacarbazine, actinomycin D, cyclofosfamide, or carboplatin [38, 49, 50, 55, 62]. Anthracycline-based therapy results in favorable disease control. In reported studies, ORR for anthracycline-based regimens is 22% (1 complete response [CR], 18 partial response [PR]), while DCR – 75%. The response rate was numerically higher in proximal ES cases than in classical ES (26% *vs.* 19%, p = 0.44). The median PFS was 6.76 months (95%CI: 23–35). The median OS from the beginning of palliative chemotherapy was only 12 months (95% CI: 29–73). The six-month OS was 79% and the 12-month OS rate was 46% [49].

Another common regimen used in ES treatment is gemcitabine with docetaxel (GD) [50, 61, 63]. In 12 patients treated with gemcitabine-based chemotherapy, the ORR and DCR rates were 58% and 83%, respectively. When gemcitabine was used, the median PFS was 9 months in patients treated first-line and 8 months in the mixed population [63]. In another report on the use of gemcitabine in ES, the ORR was reported to be 27%, while the DCR was reported to be 66% with the median PFS of 4 months. Interestingly, a trend toward higher response rates has been reported in the classical ES subtype (30% *vs.* 22%; p = 0.72) and the location of the distal tumor (40% *vs.* 14%; p = 0.08). No differences in ORR were reported between patients treated with gemcitabine monotherapy and GD chemoregimen [61]. Recently, albumin-bound paclitaxel (nab-paclitaxel) 300 mg/m$^2$ *via* intravenous bolus on day 1, and gemcitabine 1250 mg/m$^2$ gemcitabine *via* intravenous bolus on days 1 and 8 chemoregimen was used in ES therapy and has been shown to be safe and moderately effective [64].

Only case reports on other chemotherapy agents in ES have been published and include high-dose ifosfamide, trofosfamide, gemcitabine with cisplatin, dacarbazine, and trabectedin [63, 65]. An interesting case report was published showing complete remission (CR) of ES pulmonary metastases treated with vinorelbine (17–30 mg/m$^2$ every 2 to 4 weeks) therapy. In this case, the response CR was 4 years long [66]. Another ES case achieved a partial response (PR) with a duration of 27.4 months [67].

Targeted therapies for ES are still in development. **Pazopanib** is the first tyrosine kinase inhibitor (TKI) approved for ES therapy [50, 61]. In a case series of 18 pazopanib patients treated, no ORRs were reported, 50% of the patients benefited with stable diseases (SD), but PFS was only 3 months. However, PR case reports on pazopanib treatment in patients with metastatic ES have also been published [68, 69]. In the pulled analysis of the EORTC trial, pazopanib was used in patients with ES in the second line and resulted in ORR 11.1% (1/9) and a median PFS of 2.73 months [59]. A case report on **sunitinib** therapy in ES was published. This patient achieved long-term stabilization of the disease (>32 months) after progression in two lines of chemotherapy [70]. Sunitinib in combination with nivolumab was found to improve PFS in patients with advanced epithelioid sarcoma [71].

Another therapy that has shown some benefit in case series is another TKI, anlotinib, in combination with PD-1 inhibitors [72]. Some data on **dasatinib** activity in ES are also available. In an open-label single-arm SARC0009 study 2/7 patients achieved objective tumor responses according to Choi's criteria. The mPFS was 7.9 months and the PFS rate at 6 months was 57%. However, the OS was poor with a 2-year OS rate of 21% [73]. Another study investigates ipilimumab in combination with dasatinib in patients with refractory and/or unresectable GIST or other STS, including epithelioid sarcoma [74].

As ES sarcoma was reported to have a relatively high mutation rate, it is a candidate for **immune checkpoint inhibitor** therapies [75]. ES patient were recruited in a KEYNOTE-051 study of **pembrolizumab** in patients with PD-L1 positive, advanced, refractory, or refractory solid tumors, but no subgroup ORR was reported until now [76]. Case reports of the efficacy of pembrolizumab in advanced ES in adults have also been published. Pembrolizumab was used in the second line of palliative therapy, after chemotherapy with doxorubicin-ifosfamide [77]. In the study of **nivolumab**, a 24-year-old male ES metastatic lung patient had PR after 4 immunotherapy cycles, but the response was not durable as the patient progressed after the next 4 cycles [78]. An interesting case of long-term response to camrelizumab was recently published. This patient had high expression of PD-L1 and a high number of tumor-infiltrating lymphocytes in the tumor [79]. Currently, patients with ES are enrolled in a study of nivolumab and ipilimumab in children and young adults with *INI1* negative cancers and tigolumab and atezolizumab for the treatment of *SMARCB1* or *SMARCA4* deficient tumors.

On 23 January 2020, the US Food and Drug Administration (FDA) approved the first EZH2 methyltransferase inhibitor – **tazemetostat** – for the treatment of patients with locally advanced and metastatic epithelioid sarcoma not eligible for complete resection in patients older than 16 years. In a phase I trial (NCT02601937) for patients with tazemetostat ES, they achieved SD and continued treatment for >20 months [80]. Later, FDA approval was granted based on the results of a phase 2 trial (NCT02601950 ). In the analyzed ES cohort (cohort 5), 62 patients were treated, 24 in the first line and 38 in the second

or further lines. In the trial, patients were treated with 800 mg of tazemetostat twice daily. In the phase 2 trial, ORR was 15% (95% CI: 6.9–25.8), while DCR was 26% (95% CI: 15.5–38.5). In particular, ORR was 25% in patients treated in the first line, but only 8% in patients treated in other lines [81]. In this trial, 26% of the patients had disease control at 32 weeks and 21% remained progression-free at 1 year. The median response duration (DOR) was 16.1 months [82]. After FDA approval, the results of the treatment of patients from an additional cohort of ES (cohort 6) were reported. In cohort 6, ORR was 11.4% and DCR – 50% [82]. The final pooled analysis confirmed mPFS of 3.7 months and mOS – 18.0 months. The toxicity profile of tazemetostat is favorable. The most common AE are nausea and fatigue (in 40% of patients). Grade 3 treatment-related AEs were reported in 16% of the patients [81, 82]. Currently, in the next trial, tazemetostat is tested with doxorubicin in the Phase 1b/3 trial as the first-line therapy for patients with advanced epithelioid sarcoma [83]. Furthermore, potential synergism between prior radiotherapy and TAZ requires further investigation [84]. A phase II study of temozolomide and olaparib for the treatment of advanced uterine leiomyosarcoma is ongoing [85]. ES patients are enrolled in cohort D of the CAIRE: A multicenter open-label phase 2 basket study evaluating the EZH2 inhibitor tazemetostat in combination with durvalumab in patients with advanced solid tumors [86].

## Conclusions

Epithelioid sarcoma is built by pleomorphic epithelioid cells and the proximal subtype is more aggressive than the classical subtype, as it has higher recurrence and metastasis rates, and shorter overall survival. ES occurs more frequently in adolescents and young adults with a slight predominance of men. Loss of expression of SWI/SNF chromatin-remodeling complex proteins plays an important role in ES development. At initial diagnosis, the tumor stage should be evaluated not only with clinical and radiological examination, but also with imaging focused on regional lymph nodes and the chest (pulmonary metastases). Surgical resection of primary tumors may be curative. The patient should be treated with wide local excision or with surgery plus lymphadenectomy. Radiation therapy should be considered after MDT to decrease the local recurrence rate. Currently hypofractionated preoperative RT may be advised [87, 88]. Referral to a sarcoma center for hypofractionated radiotherapy with hyperthermia may be considered in patients with marginally resectable or unresectable ES and in patients who are not eligible for chemotherapy [89]. Adjuvant radiation therapy is recommended in cases with positive margins (R1/R2 resections). Local recurrences are common in ES and most often develop within six months after radical treatment. Up to 75% of cases with local recurrence also develop distant metastases [9]. However, most patients have an advanced stage at first diagnosis with lymph node and / or lung metastases. Chemotherapy may provide palliation in patients with metastatic and unresectable epithelioid sarcoma, but responses are short and there is still an unmet need for more effective novel targeted therapies. Immunotherapy may be an alternative option for patients with metastatic ES. Most recently, tazemetostat showed activity in advanced ES with loss of *INI1/SMARCB1*. Tazemetostat therapy is a new treatment option for patients with ES approved by the FDA [90, 91].


## Acknowledgements

The authors thank Prof. Ewa Bartnik for her expertise and assistance in the language editing of the manuscript. This work was supported by a NCN 2019/35/O/NZ2/03761 grant.

**Conflict of interest:** none declared



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*Received: 23 Mar 2023*
*Accepted: 28 Mar 2023*


## References


1. Gliński B, Dymek P, Ryś J, et al. Epithelioid sarcoma – a case report and literature review. Contemporary Oncology/Współczesna Onkologia. 2008; 12(2): 95–98.
2. Fisher C. Epithelioid sarcoma of Enzinger. Adv Anat Pathol. 2006; 13(3): 114–121, doi: 10.1097/00125480-200605000-00002, indexed in Pubmed: 16778474.
3. Enzinger FM. Epithelioid sarcoma.A sarcoma simulating a granuloma or a carcinoma. Cancer. 1970; 26(5): 1029–1041, doi: 10.1002/1097-0142(197011)26:5<1029::aid-cncr2820260510>3.0.co;2-r.
4. Jawad MU, Extein J, Min ES, et al. Prognostic factors for survival in patients with epithelioid sarcoma: 441 cases from the SEER database. Clin Orthop Relat Res. 2009; 467(11): 2939–2948, doi: 10.1007/s11999-009-0749-2, indexed in Pubmed: 19224301.
5. Baratti D, Pennacchioli E, Casali PG, et al. Epithelioid sarcoma: prognostic factors and survival in a series of patients treated at a single institution. Ann Surg Oncol. 2007; 14(12): 3542–3551, doi: 10.1245/s10434-007-9628-9, indexed in Pubmed: 17909905.
6. Sobanko JF, Meijer L, Nigra TP. Epithelioid sarcoma: a review and update. J Clin Aesthet Dermatol. 2009; 2(5): 49–54, indexed in Pubmed: 20729965.
7. Alexander L. Epithelioid Sarcoma of Upper Extremity: Diagnostic Dilemma With Therapeutic Challenges. Cureus. 2021; 13(3): e14156, doi: 10.7759/cureus.14156, indexed in Pubmed: 33936870.
8. Hasegawa T, Matsuno Y, Shimoda T, et al. Proximal-type epithelioid sarcoma: a clinicopathologic study of 20 cases. Mod Pathol. 2001; 14(7): 655–663, doi: 10.1038/modpathol.3880368, indexed in Pubmed: 11454997.
9. Zegarra Buitron E, Vidal Panduro DA, Morales Luna D. Clinicopathological Characteristics, Treatment, and Survival in Patients Diagnosed With Proximal-Type Epithelioid Sarcoma: A Case Report and Systematic Review. Cureus. 2022; 14(12): e32962, doi: 10.7759/cureus.32962, indexed in Pubmed: 36712724.
10. Pradhan A, Grimer RJ, Abudu A, et al. Epithelioid sarcomas: How important is loco-regional control? Eur J Surg Oncol. 2017; 43(9): 1746–1752, doi: 10.1016/j.ejso.2017.07.002, indexed in Pubmed: 28756018.
11. Czarnecka AM, Sobczuk P, Kostrzanowski M, et al. Epithelioid Sarcoma-From Genetics to Clinical Practice. Cancers (Basel). 2020; 12(8), doi: 10.3390/cancers12082112, indexed in Pubmed: 32751241.
12. Rutkowski P. Soft Tissue Sarcomas. Via Medica, Gdańsk 2016.

13. Levy A, Le Péchoux C, Terrier P, et al. Epithelioid sarcoma: need for a multimodal approach to maximize the chances of curative conservative treatment. Ann Surg Oncol. 2014; 21(1): 269–276, doi: 10.1245/s10434-013-3247-4, indexed in Pubmed: 24046109.
14. Regalbuto A, Tudosie A, Klenotic E. A metastatic distal-type epithelioid sarcoma: Case report and review. Int J Surg Case Rep. 2020; 71: 144–146, doi: 10.1016/j.ijscr.2020.04.096, indexed in Pubmed: 32450373.
15. Guzzetta AA, Montgomery EA, Lyu H, et al. Epithelioid sarcoma: one institution's experience with a rare sarcoma. J Surg Res. 2012; 177(1): 116–122, doi: 10.1016/j.jss.2012.04.030, indexed in Pubmed: 22575361.
16. Thway K, Jones RL, Noujaim J, et al. Epithelioid Sarcoma: Diagnostic Features and Genetics. Adv Anat Pathol. 2016; 23(1): 41–49, doi: 10.1097/PAP.0000000000000102, indexed in Pubmed: 26645461.
17. Daigeler A, Kuhnen C, Moritz R, et al. Lymph node metastases in soft tissue sarcomas: a single center analysis of 1,597 patients. Langenbecks Arch Surg. 2009; 394(2): 321–329, doi: 10.1007/s00423-008-0371-x, indexed in Pubmed: 18594854.
18. Andreou D, Boldt H, Werner M, et al. Sentinel node biopsy in soft tissue sarcoma subtypes with a high propensity for regional lymphatic spread--results of a large prospective trial. Ann Oncol. 2013; 24(5): 1400–1405, doi: 10.1093/annonc/mds650, indexed in Pubmed: 23372051.
19. Jamshidi F, Bashashati A, Shumansky K, et al. The genomic landscape of epithelioid sarcoma cell lines and tumours. J Pathol. 2016; 238(1): 63–73, doi: 10.1002/path.4636, indexed in Pubmed: 26365879.
20. Hornick JL, Dal Cin P, Fletcher CDM. Loss of INI1 expression is characteristic of both conventional and proximal-type epithelioid sarcoma. Am J Surg Pathol. 2009; 33(4): 542–550, doi: 10.1097/PAS.0b013e3181882c54, indexed in Pubmed: 19033866.
21. Li Li, Fan XS, Xia QY, et al. Concurrent loss of INI1, PBRM1, and BRM expression in epithelioid sarcoma: implications for the cocontributions of multiple SWI/SNF complex members to pathogenesis. Hum Pathol. 2014; 45(11): 2247–2254, doi: 10.1016/j.humpath.2014.06.027, indexed in Pubmed: 25200863.
22. Ngo C, Postel-Vinay S. Immunotherapy for SMARCB1-Deficient Sarcomas: Current Evidence and Future Developments. Biomedicines. 2022; 10(3), doi: 10.3390/biomedicines10030650, indexed in Pubmed: 35327458.
23. Le Loarer F, Zhang L, Fletcher CD, et al. Consistent SMARCB1 homozygous deletions in epithelioid sarcoma and in a subset of myoepithelial carcinomas can be reliably detected by FISH in archival material. Genes Chromosomes Cancer. 2014; 53(6): 475–486, doi: 10.1002/gcc.22159, indexed in Pubmed: 24585572.
24. Kohashi K, Oda Y. Oncogenic roles of SMARCB1/INI1 and its deficient tumors. Cancer Sci. 2017; 108(4): 547–552, doi: 10.1111/cas.13173, indexed in Pubmed: 28109176.
25. Oppel F, Shao S, Gendreizig S, et al. p53 Pathway Inactivation Drives SMARCB1-deficient p53-wildtype Epithelioid Sarcoma Onset Indicating Therapeutic Vulnerability Through MDM2 Inhibition. Mol Cancer Ther. 2022; 21(11): 1689–1700, doi: 10.1158/1535-7163.MCT-21-0770, indexed in Pubmed: 36099437.
26. Kohashi K, Oda Y. Oncogenic roles of SMARCB1/INI1 and its deficient tumors. Cancer Sci. 2017; 108(4): 547–552, doi: 10.1111/cas.13173, indexed in Pubmed: 28109176.
27. Carballo GB, Honorato JR, de Lopes GP, et al. A highlight on Sonic hedgehog pathway. Cell Commun Signal. 2018; 16(1): 11, doi: 10.1186/s12964-018-0220-7, indexed in Pubmed: 29558958.
28. Del Savio E, Maestro R. Beyond SMARCB1 Loss: Recent Insights into the Pathobiology of Epithelioid Sarcoma. Cells. 2022; 11(17), doi: 10.3390/cells11172626, indexed in Pubmed: 36078034.
29. Szurian K, Kashofer K, Liegl-Atzwanger B. Role of Next-Generation Sequencing as a Diagnostic Tool for the Evaluation of Bone and Soft-Tissue Tumors. Pathobiology. 2017; 84(6): 323–338, doi: 10.1159/000478662, indexed in Pubmed: 28817827.
30. Rutkowski P, Prochorec-Sobieszek M, Wągrodzki M, et al. Diagnostyka z wykorzystaniem sekwencjonowania następnej generacji (NGS) w mięsakach — rekomendacje. Onkol Prakt Klin Edu. 2020; 6(1): 1–8.
31. Spunt SL, Francotte N, De Salvo GL, et al. Clinical features and outcomes of young patients with epithelioid sarcoma: an analysis from the Children's Oncology Group and the European paediatric soft tissue Sarcoma Study Group prospective clinical trials. Eur J Cancer. 2019; 112: 98–106, doi: 10.1016/j.ejca.2019.02.001, indexed in Pubmed: 30954717.
32. Pasquali S, Palmerini E, Quagliuolo V, et al. Neoadjuvant chemotherapy in high-risk soft tissue sarcomas: A Sarculator-based risk stratification analysis of the ISG-STS 1001 randomized trial. Cancer. 2022; 128(1): 85–93, doi: 10.1002/cncr.33895, indexed in Pubmed: 34643947.
33. Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults: meta-analysis of individual data. Sarcoma Meta-analysis Collaboration. Lancet. 1997; 350(9092): 1647–1654, indexed in Pubmed: 9400508.
34. Bonvalot S, Wunder J, Gronchi A, et al. Complete pathological response to neoadjuvant treatment is associated with better survival outcomes in patients with soft tissue sarcoma: Results of a retrospective multicenter study. Eur J Surg Oncol. 2021; 47(8): 2166–2172, doi: 10.1016/j.ejso.2021.02.024, indexed in Pubmed: 33676792.
35. Pasquali S, Colombo C, Bottelli S, et al. The sarculator predicted risk of distant metastasis and overall survival in patients with high-risk soft tissue sarcoma treated with perioperative chemotherapy in a randomised controlled trial. Eur J Surg Oncol. 2018; 44(10): e2, doi: 10.1016/j.ejso.2018.07.012, indexed in Pubmed: 29475197.
36. Thway K, Jones RL, Noujaim J, et al. Epithelioid Sarcoma: Diagnostic Features and Genetics. Adv Anat Pathol. 2016; 23(1): 41–49, doi: 10.1097/PAP.0000000000000102, indexed in Pubmed: 26645461.
37. Hu W, Wu X, Ma H, et al. Systematic Review of Published Cases of Primary Epithelioid Sarcoma of the Spine. Med Sci Monit. 2023; 29: e938416, doi: 10.12659/MSM.938416, indexed in Pubmed: 36604864.
38. de Visscher SA, van Ginkel RJ, Wobbes T, et al. Epithelioid sarcoma: Still an only surgically curable disease. Cancer. 2006; 107(3): 606–612, doi: 10.1002/cncr.22037, indexed in Pubmed: 16804932.
39. Maduekwe UN, Hornicek FJ, Springfield DS, et al. Role of sentinel lymph node biopsy in the staging of synovial, epithelioid, and clear cell sarcomas. Ann Surg Oncol. 2009; 16(5): 1356–1363, doi: 10.1245/s10434-009-0393-9, indexed in Pubmed: 19259743.
40. Seal A, Tse R, Wehrli B, et al. Sentinel node biopsy as an adjunct to limb salvage surgery for epithelioid sarcoma of the hand. World J Surg Oncol. 2005; 3: 41, doi: 10.1186/1477-7819-3-41, indexed in Pubmed: 15987509.
41. Blazer DG, Sabel MS, Sondak VK. Is there a role for sentinel lymph node biopsy in the management of sarcoma? Surg Oncol. 2003; 12(3): 201–206, doi: 10.1016/s0960-7404(03)00030-6, indexed in Pubmed: 12957624.
42. Callister MD, Ballo MT, Pisters PW, et al. Epithelioid sarcoma: results of conservative surgery and radiotherapy. Int J Radiat Oncol Biol Phys. 2001; 51(2): 384–391, doi: 10.1016/s0360-3016(01)01646-7, indexed in Pubmed: 11567812.
43. Regalbuto A, Tudosie A, Klenotic E. A metastatic distal-type epithelioid sarcoma: Case report and review. Int J Surg Case Rep. 2020; 71: 144–146, doi: 10.1016/j.ijscr.2020.04.096, indexed in Pubmed: 32450373.
44. Casali PG, Abecassis N, Bauer S, et al. Soft tissue and visceral sarcomas: ESMO–EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018; 29: iv51–iv67, doi: 10.1093/annonc/mdy096, indexed in Pubmed: 29846498.
45. Naghavi AO, Fernandez DC, Mesko N, et al. American Brachytherapy Society consensus statement for soft tissue sarcoma brachytherapy. Brachytherapy. 2017; 16(3): 466–489, doi: 10.1016/j.brachy.2017.02.004, indexed in Pubmed: 28342738.
46. Stragliotto CL, Karlsson K, Lax I, et al. A retrospective study of SBRT of metastases in patients with primary sarcoma. Med Oncol. 2012; 29(5): 3431–3439, doi: 10.1007/s12032-012-0256-2, indexed in Pubmed: 22815154.
47. Lindsay AD, Haupt EE, Chan CM, et al. Treatment of Sarcoma Lung Metastases with Stereotactic Body Radiotherapy. Sarcoma. 2018; 2018: 9132359, doi: 10.1155/2018/9132359, indexed in Pubmed: 29808081.
48. de Jong MAA, Oldenborg S, Bing Oei S, et al. Reirradiation and hyperthermia for radiation-associated sarcoma. Cancer. 2012; 118(1): 180–187, doi: 10.1002/cncr.26252, indexed in Pubmed: 21713762.
49. Jones RL, Constantinidou A, Olmos D, et al. Role of palliative chemotherapy in advanced epithelioid sarcoma. Am J Clin Oncol. 2012; 35(4): 351–357, doi: 10.1097/COC.0b013e3182118cf7, indexed in Pubmed: 21422990.
50. Kim C, Yoo KH, Kim MH, et al. Different subtypes of epithelioid sarcoma and their clinical implication: long-term multi-institutional experience with a rare sarcoma. APMIS. 2017; 125(3): 223–229, doi: 10.1111/apm.12656, indexed in Pubmed: 28233450.
51. Casali PG, Blay JY, Abecassis N, et al. ESMO Guidelines Committee, EURACAN and GENTURIS. Electronic address: clinicalguidelines@esmo.org, ESMO Guidelines Committee, EURACAN and GENTURIS. Electronic address: clinicalguidelines@esmo.org. Soft tissue and visceral sarcomas: ESMO-EURACAN-GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2021; 32(11): 1348–1365, doi: 10.1016/j.annonc.2021.07.006, indexed in Pubmed: 34303806.

52. Rekhi B, Gorad BD, Chinoy RF. Clinicopathological features with outcomes of a series of conventional and proximal-type epithelioid sarcomas, diagnosed over a period of 10 years at a tertiary cancer hospital in India. Virchows Arch. 2008; 453(2): 141–153, doi: 10.1007/s00428-008-0639-0, indexed in Pubmed: 18607629.
53. Outani H, Imura Y, Tanaka T, et al. Clinical outcomes of patients with epithelioid sarcomas: impact and management of nodal metastasis. Int J Clin Oncol. 2018; 23(1): 181–188, doi: 10.1007/s10147-017-1179-x, indexed in Pubmed: 28799063.
54. Spillane AJ, Thomas JM, Fisher C. Epithelioid sarcoma: the clinicopathological complexities of this rare soft tissue sarcoma. Ann Surg Oncol. 2000; 7(3): 218–225, doi: 10.1007/BF02523657, indexed in Pubmed: 10791853.
55. Casanova M, Ferrari A, Collini P, et al. Italian Soft Tissue Sarcoma Committee. Epithelioid sarcoma in children and adolescents: a report from the Italian Soft Tissue Sarcoma Committee. Cancer. 2006; 106(3): 708–717, doi: 10.1002/cncr.21630, indexed in Pubmed: 16353216.
56. Ross HM, Lewis JJ, Woodruff JM, et al. Epithelioid sarcoma: clinical behavior and prognostic factors of survival. Ann Surg Oncol. 1997; 4(6): 491–495, doi: 10.1007/BF02303673, indexed in Pubmed: 9309338.
57. Tang F, Tie Y, Wei YQ, et al. Targeted and immuno-based therapies in sarcoma: mechanisms and advances in clinical trials. Biochim Biophys Acta Rev Cancer. 2021; 1876(2): 188606, doi: 10.1016/j.bbcan.2021.188606, indexed in Pubmed: 34371128.
58. Rutkowski P, Koseła-Paterczyk H, Kozak K, et al. Postępowanie diagnostyczno-terapeutyczne u chorych na mięsaki tkanek miękkich u dorosłych — zalecenia ekspertów. Onkol Prakt Klin Edu. 2022.
59. Touati N, Schöffski P, Litière S, et al. European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Experience with Advanced/Metastatic Epithelioid Sarcoma Patients Treated in Prospective Trials: Clinical Profile and Response to Systemic Therapy. Clin Oncol (R Coll Radiol). 2018; 30(7): 448–454, doi: 10.1016/j.clon.2018.02.065, indexed in Pubmed: 29550245.
60. Gounder MM, Merriam P, Ratan R, et al. Real-world outcomes of patients with locally advanced or metastatic epithelioid sarcoma. Cancer. 2021; 127(8): 1311–1317, doi: 10.1002/cncr.33365, indexed in Pubmed: 33296083.
61. Frezza AM, Jones RL, Lo Vullo S, et al. Anthracycline, Gemcitabine, and Pazopanib in Epithelioid Sarcoma: A Multi-institutional Case Series. JAMA Oncol. 2018; 4(9): e180219, doi: 10.1001/jamaoncol.2018.0219, indexed in Pubmed: 29800950.
62. Tsakonas GP, Kallistratos MS, Balamoti EK, et al. Rare and aggressive metastatic, axial multifocal local epithelioid sarcoma associated with paraneoplastic granulocytosis and hypoglycaemia. Lancet Oncol. 2007; 8(1): 82–84, doi: 10.1016/S1470-2045(06)71015-4, indexed in Pubmed: 17196515.
63. Pink D, Richter S, Gerdes S, et al. Gemcitabine and docetaxel for epithelioid sarcoma: results from a retrospective, multi-institutional analysis. Oncology. 2014; 87(2): 95–103, doi: 10.1159/000362602, indexed in Pubmed: 25011671.
64. Tian Z, Zhang F, Li Po, et al. Albumin-bound paclitaxel and gemcitabine combination therapy in soft tissue sarcoma. BMC Cancer. 2020; 20(1): 698, doi: 10.1186/s12885-020-07199-0, indexed in Pubmed: 32723378.
65. Palmerini E, Sanfilippo R, Grignani G, et al. Transcription regulators and ultra-rare and other rare translocation-related sarcomas treated with trabectedin: A proof of principle from a analysis. Front Oncol. 2022; 12: 1042479, doi: 10.3389/fonc.2022.1042479, indexed in Pubmed: 36568164.
66. Tariq Z, Ghose A, Bawany MZ, et al. A case report of complete remission of pulmonary metastases from epithelioid sarcoma to navelbine chemotherapy. Am J Ther. 2012; 19(2): e95–e97, doi: 10.1097/MJT.0b013e3181e70a50, indexed in Pubmed: 20634676.
67. Anderson SE, Keohan ML, D'Adamo DR, et al. A retrospective analysis of vinorelbine chemotherapy for patients with previously treated soft-tissue sarcomas. Sarcoma. 2006; 2006: 15947, doi: 10.1155/SRCM/2006/15947, indexed in Pubmed: 17496991.
68. Nakamura T, Matsumine A, Kawai A, et al. The clinical outcome of pazopanib treatment in Japanese patients with relapsed soft tissue sarcoma: A Japanese Musculoskeletal Oncology Group (JMOG) study. Cancer. 2016; 122(9): 1408–1416, doi: 10.1002/cncr.29961, indexed in Pubmed: 26970174.
69. Irimura S, Nishimoto K, Kikuta K, et al. Successful Treatment with Pazopanib for Multiple Lung Metastases of Inguinal Epithelioid Sarcoma: A Case Report. Case Rep Oncol. 2015; 8(3): 378–384, doi: 10.1159/000439427, indexed in Pubmed: 26500539.
70. Penot P, Bouaziz JD, Battistella M, et al. Stabilization of multiple metastatic epithelioid sarcoma under treatment with sunitinib malate. Br J Dermatol. 2013; 168(4): 871–873, doi: 10.1111/bjd.12038, indexed in Pubmed: 22963050.
71. Broto J, Hindi N, Grignani GE, et al. IMMUNOSARC: A collaborative Spanish (GEIS) and Italian (ISG) sarcoma groups phase I/II trial of sunitinib plus nivolumab in advanced soft tissue and bone sarcomas: Results of the phase II- soft-tissue sarcoma cohort. Ann Oncol. 2019; 30: v684, doi: 10.1093/annonc/mdz283.002.
72. Yao W, Du X, Wang J, et al. Long-Term Efficacy and Safety of Anlotinib as a Monotherapy and Combined Therapy for Advanced Sarcoma. Onco Targets Ther. 2022; 15: 669–679, doi: 10.2147/OTT.S365506, indexed in Pubmed: 35726279.
73. Schuetze SM, Bolejack V, Choy E, et al. Phase 2 study of dasatinib in patients with alveolar soft part sarcoma, chondrosarcoma, chordoma, epithelioid sarcoma, or solitary fibrous tumor. Cancer. 2017; 123(1): 90–97, doi: 10.1002/cncr.30379, indexed in Pubmed: 27696380.
74. D'Angelo SP, Shoushtari AN, Keohan ML, et al. Combined KIT and CTLA-4 Blockade in Patients with Refractory GIST and Other Advanced Sarcomas: A Phase Ib Study of Dasatinib plus Ipilimumab. Clin Cancer Res. 2017; 23(12): 2972–2980, doi: 10.1158/1078-0432.CCR-16-2349, indexed in Pubmed: 28007774.
75. Clemente O, Ottaiano A, Di Lorenzo G, et al. Is immunotherapy in the future of therapeutic management of sarcomas? J Transl Med. 2021; 19(1): 173, doi: 10.1186/s12967-021-02829-y, indexed in Pubmed: 33902630.
76. Geoerger B, Kang HJ, Yalon-Oren M, et al. Pembrolizumab in paediatric patients with advanced melanoma or a PD-L1-positive, advanced, relapsed, or refractory solid tumour or lymphoma (KEYNOTE-051): interim analysis of an open-label, single-arm, phase 1-2 trial. Lancet Oncol. 2020; 21(1): 121–133, doi: 10.1016/S1470-2045(19)30671-0, indexed in Pubmed: 31812554.
77. Wang J, Lu C, Tang Xi. Response to immunotherapy in a patient with advanced epithelioid sarcoma of adrenal gland: A case report. Exp Ther Med. 2022; 24(5): 659, doi: 10.3892/etm.2022.11595, indexed in Pubmed: 36168426.
78. Paoluzzi L, Cacavio A, Ghesani M, et al. Response to anti-PD1 therapy with nivolumab in metastatic sarcomas. Clin Sarcoma Res. 2016; 6: 24, doi: 10.1186/s13569-016-0064-0, indexed in Pubmed: 28042471.
79. Gong TJ, Tang F, Zheng CX, et al. Case Report: Pulmonary Metastases From Epithelioid Sarcoma in Extremity Favourably Responding to Immunotherapy With Camrelizumab. Front Oncol. 2021; 11: 728437, doi: 10.3389/fonc.2021.728437, indexed in Pubmed: 34692503.
80. Italiano A, Soria JC, Toulmonde M, et al. Tazemetostat, an EZH2 inhibitor, in relapsed or refractory B-cell non-Hodgkin lymphoma and advanced solid tumours: a first-in-human, open-label, phase 1 study. Lancet Oncol. 2018; 19(5): 649–659, doi: 10.1016/S1470-2045(18)30145-1, indexed in Pubmed: 29650362.
81. Stacchiotti S, Schoffski P, Jones R, et al. Safety and efficacy of tazemetostat, a first-in-class EZH2 inhibitor, in patients (pts) with epithelioid sarcoma (ES) (NCT02601950). J Clin Oncol. 2019; 37(15_suppl): 11003–11003, doi: 10.1200/jco.2019.37.15_suppl.11003.
82. Gounder M, Stacchiotti S, Schoffski P, et al. Efficacy, safety, and immune priming effect of tazemetostat in patients with epithelioid sarcoma. J Clin Oncol. 2020; 38(15_suppl): 11564–11564, doi: 10.1200/jco.2020.38.15_suppl.11564.
83. Sen S, McKean M, Sierra L, et al. A phase Ib/III randomized, double--blind, placebo-controlled study of tazemetostat plus doxorubicin as frontline therapy for patients with advanced epithelioid sarcoma. J Clin Oncol. 2020; 38(15_suppl): TPS11573–TPS11573, doi: 10.1200/jco.2020.38.15_suppl.tps11573.
84. Chi S, Bourdeaut F, Casanova M, et al. Update on phase 1 study of tazemetostat, an enhancer of zeste homolog 2 inhibitor, in pediatric patients with relapsed or refractory integrase interactor 1–negative tumors. J Clin Oncol. 2022; 40(16_suppl): 10040–10040, doi: 10.1200/jco.2022.40.16_suppl.10040.
85. Bose S, Ingham M, Chen Li, et al. Correlative results from NCI protocol 10250: A phase II study of temozolomide and olaparib for the treatment of advanced uterine leiomyosarcoma. J Clin Oncol. 2022; 40(16_suppl): 11509–11509, doi: 10.1200/jco.2022.40.16_suppl.11509.
86. Italiano A, Isambert N, Metges JP, et al. CAIRE: A basket multicenter open-label phase 2 study evaluating the EZH2 inhibitor tazemetostat in combination with durvalumab in patients with advanced solid tumors. J Clin Oncol. 2022; 40(16_suppl): TPS2703–TPS2703, doi: 10.1200/jco.2022.40.16_suppl.tps2703.
87. Spałek MJ, Koseła-Paterczyk H, Borkowska A, et al. Combined Preoperative Hypofractionated Radiotherapy With Doxorubicin-Ifosfamide

Chemotherapy in Marginally Resectable Soft Tissue Sarcomas: Results of a Phase 2 Clinical Trial. Int J Radiat Oncol Biol Phys. 2021; 110(4): 1053–1063, doi: 10.1016/j.ijrobp.2021.02.019, indexed in Pubmed: 33600887.
88. Spałek M, Borkowska A. Current advances in radiotherapy for soft tissue sarcomas. Nowotwory. Journal of Oncology. 2020; 70(6): 288–295, doi: 10.5603/njo.2020.0056.
89. Spałek MJ, Borkowska AM, Telejko M, et al. The Feasibility Study of Hypofractionated Radiotherapy with Regional Hyperthermia in Soft Tissue Sarcomas. Cancers (Basel). 2021; 13(6), doi: 10.3390/cancers13061332, indexed in Pubmed: 33809547.
90. Simeone N, Frezza AM, Zaffaroni N, et al. Tazemetostat for advanced epithelioid sarcoma: current status and future perspectives. Future Oncol. 2021; 17(10): 1253–1263, doi: 10.2217/fon-2020-0781, indexed in Pubmed: 33289402.
91. Dudzisz-Śledź M, Rogala P. Advances in systemic treatment of advanced soft tissue sarcomas. Oncol Clin Pract. 2019; 14(6): 377–391, doi: 10.5603/ocp.2018.0051.

VIA MEDICA

Cancer prevention and public health

NOWOTWORY Journal of Oncology
2023, volume 73, number 3, 162–167
DOI: 10.5603/NJO.a2023.0022

ISSN: 0029–540X, e-ISSN: 2300-2115
www.nowotwory.edu.pl

# Novel tobacco and nicotine products and youth in the European Union

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In recent years, there has been a rapid proliferation of novel tobacco and nicotine products in the market, which have gained in popularity among adolescents. The prevalence of ever users of electronic cigarettes (e-cigs) in Europe among those aged 10–24 ranges from 5.5% to 56.6%, with significant variations across countries. Adolescents have reported several reasons for e-cig use initiation, including low harm perception, social acceptability, novelty, and peer influence. Despite being marketed as safe alternatives, e-cigs are not risk-free and have already been associated with respiratory diseases. A major concern is their potential to renormalize smoking among non-smokers and to foster nicotine dependence, leading to the initiation of conventional cigarette smoking, which would reverse actual declining trends in tobacco consumption. Hence, to prevent a setback on the progress made in tobacco control, there is a pressing need for more comprehensive regulation, with a particular focus on adolescents, given that the teenage years are pivotal in determining future smoking behavior.

**Key words:** tobacco, novel products, youth, European Union, tobacco control

## Introduction

Tobacco use remains a major public health problem worldwide. In the European region, the prevalence of tobacco use among adults is the highest globally, and one of the highest among adolescents. Accordingly, the proportion of all-cause mortality attributable to tobacco use is also higher in the region (16% in adults ≥30 years old) than the global average (12%) [1]. Hence, accelerating the decline of tobacco use in all population groups should continue to be a high priority across the region [2].

Implementation of comprehensive evidence-based tobacco control policies has the potential to reduce tobacco-related diseases across Europe [2]. These policies have shown to significantly decrease tobacco use prevalence and increase smoking cessation rates in the region [3, 4]; especially, when implemented at the highest level. The European Union (EU) has ratified the WHO Framework Convention on Tobacco Control (FCTC) [5] and, subsequently, over the last decades all EU Member States (MS) have implemented key tobacco control policies; however, considerable differences still exist across the EU [6].

**How to cite:**
Feliu A, Espina C, Martinez C, Fernandez E. ***Novel tobacco and nicotine products and youth in the European Union.*** *NOWOTWORY J Oncol* 2023; 73: 162–167.

Smoking prevalence in the EU has declined considerably, from 32.0% in 2007 [7] to 23.0% in 2020 [8]. New forms of tobacco and nicotine products – electronic cigarettes (e-cigs), heated-tobacco products (HTPs), and smokeless tobacco – have been aggressively introduced in the market to attract new customers, retain users, and re-engage those that have already quit [9]. Although the prevalence of e-cig use and smoking HTPs are currently relatively low in the general population in the EU, these products, especially e-cigs, have rapidly gained in popularity among adolescents and have become the most commonly used tobacco products in some countries [10–12]. Their popularity may respond to aggressive marketing to children and youth, accessibility, appealing flavors, high nicotine delivery, and lower risk perceptions [13]. All in all, despite the progress made since the ratification of WHO FCTC, the emergence of novel tobacco products continues to challenge tobacco control efforts globally.

The aim of this work is to review the use and trends of novel tobacco and nicotine products in the EU, as well as their potential harm for bystanders. Additionally, this manuscript will discuss the challenges the new products pose for tobacco control, and provide recommendations for policymakers and other stakeholders to move forward to a tobacco and nicotine-free generation by 2040, as outlined in the Europe's Beating Cancer Plan [14].

## Prevalence of ever use of novel tobacco and nicotine products in the EU

According to Tehrani et al., the worldwide prevalence of ever users of e-cigs was 23.0% with a higher prevalence among men (22%) than women (16%). Current e-cig users were 11.0%, with a higher prevalence in men (12%) than in women (8%). Among adolescents and college students, the prevalence of e-cig ever users was even higher – up to 25% [10]. Even more alarming, an upward trend of lifetime e-cig use in the youngest segments of the population has been reported.

In the EU, in 2020, 14.0% of EU citizens had used an e-cig at least once or twice, meeting the criteria for ever use [8]. The proportion of ever users varied widely between countries, ranging from 6.0% in Poland up to 29.0% in Ireland. Young adults (15–24 years old) and current smokers of conventional tobacco were more likely to have tried e-cigs in their lifetime, compared to older groups (over 55 years old) and never or former smokers[8]. These findings are in line with previous studies in the region showing higher odds of ever use among the younger population [15]. Finally, although only 5% of EU citizens reported being daily users of e-cigs, this proportion has critically increased by 12% between 2017 and 2020 [8], showing an upward trend for both current and lifetime e-cigarette use in Europe [10].

There are scant global data regarding the use of HTPs. Data from the United States (US), Japan and Korea report prevalence of ever use of 2.2% [16], 15.0% [17] and 10.7% [18], respectively, among adults from 2017 to 2020. Ever use of HTPs in EU Member States (MS) in 2020 was lower than for e-cigs (6.5%) in citizens 15 years or older [8]; however, this prevalence has considerably increased since 2017 according to previous data in the region reaching 1.8% [19]. Overall, 1.3% were current users and 0.7% reported a daily use. As with e-cigs, in most EU MS, the use of HTPs is mostly occasional. Czech Republic was the MS with the highest prevalence of ever users of HTPs (14.6%), followed by Latvia (13.8%) and Ireland (12.3%). Conversely, France had the lowest prevalence (2.8%), followed by Poland (3.8%) and Malta (3.9%). Similarly to e-cigs, an inverse association between age and HTPs use was observed as people aged 15–24 years old were significantly more likely to report ever, current, and daily use compared to older age groups [19, 20].

Data on the prevalence of e-cigs and HTP ever use in children and adolescents is limited and difficult to compare since authors define youth with different age ranges. A recent narrative review by Kapan et al. [21] reported that the highest prevalence of having tried e-cigs was found among those aged 10–24, ranging from 5.5% to 56.6%. A study among school students in England reported that 19.2% of the respondents (aged 14–17 years old) had tried e-cigs; among them 35.8% were regular users and 15.8% had never used them [22]. Another study in Denmark found that 26.5% of respondents aged 15–17 years had at least tried e-cigs and 1.1% HTPs. Finally, a recent survey from Poland [23] reported that 57.8% of respondents (aged 15–19 years old) have used e-cigs and about 44% HTPs, from which 37.9% and 12.6%, respectively, were never smokers of conventional cigs.

Differences in the prevalence of ever e-cigs and HTP use across EU MS, both in adults and adolescents, may be partially explained by variations in their prevalence of combustible cigarette smoking (e.g., manufactures, cigarettes, cigars, roll-your-own tobacco, pipe), as current smokers are more likely to have tried these products [15]. Other explanations could be, first, differences in the local tobacco market and the market penetration of these products [20], since the date of their first commercialization varies widely across countries [19]. Second, availability and access to smoking cessation programs may play a role, as e-cigs are often sold as quitting tools (such as in the UK where guidelines recommend them for smoking cessation) [24]. And, finally, other legal or regulatory factors such as affordability, advertising, promotion and sponsorship, restricting flavors, and enforcement of smoke-free laws in public settings, may also contribute to differences in use [15, 25].

## Characteristics of e-cigarette and novel tobacco products' users

The vulnerability of adolescents to using e-cigs and other novel tobacco products may be influenced by various characteristics. Adolescents who have a low risk perception may be

particularly susceptible to using these products. According to Perikleous et al. [12], determinants of e-cig use among students include male gender, low school performance, high school grade, daily smoking, having household members and peers who smoke, and ever-use of other tobacco products (such as waterpipe smoking). Moreover, other studies have found strong associations between ever e-cig use and alcohol use, both with a moderate and binge drinking pattern [22] as well as cannabis use [26]. These associations suggest that adolescents who access e-cigarettes are also more likely to experiment or use other psychoactive substances and engage in risk-taking behavior.

## Health hazards associated with the use of novel tobacco and nicotine products

Novel tobacco and nicotine products have been commonly marketed as "safer" alternatives to traditional combustible cigs and smoking cessation tools. Although these products often produce lower levels of some carcinogens and toxic chemicals compared to conventional cigarettes, they are not risk free [19]. A recent review on the health consequences of e-cig use found a moderate association with increased risk of myocardial infarction and stroke in daily users, and with asthma exacerbation, chronic bronchitis, and e-cig use-association lung injury (EVALI) in adolescents and younger users [27]. Moreover, e-cigs are especially toxic to children and adolescents due to the impact of nicotine on the development of their brains [28]. Regarding HTPs, little data on the short- and middle-term health consequences of using HTPs is available; however, they also raise concerns about their safety since, similarly to e-cigs, they produce new substances (such as emission of metals, and volatile organic compounds) not generated by conventional cigarettes, whose impact on health has not yet been evaluated [19]. The long-term effects for both of these products are still unknown since they were first introduced in the market only a few years ago.

### *Exposure to secondhand aerosols from tobacco and nicotine products*

The potential passive exposure to the aerosol exhaled by e-cig and HTP users, as their use has increased in indoor places including those with tobacco smoke-free bans, is also under investigation. A systematic review indicated that second-hand aerosols (SHA) exhaled by e-cig users contain potential toxic compounds such as nicotine, carbonyls, metals, and organic volatile compounds, besides particulate matter [29]. E-cig exposure to SHA among non-users at home have been less frequently reported (i.e., 5.8% among 12 European countries) than in other public places (16.0%) [30]. Yet, exposure to SHA in homes is linked with significantly higher levels of cotinine, 3'-OH-cotinine and 1,2-propanediol in saliva, and cobalt in urine among exposed bystanders residing with e-cigarette users [31, 32].

## Reasons to start using novel tobacco and nicotine products

Subjective perceptions and beliefs about these products direct consumer behavior, particularly among young populations [33]; therefore, understanding the reasons why adolescents start using these novel products is key to counteract tobacco industry marketing strategies and implement and enforce a robust regulatory framework for these products [20].

Common reasons to start using e-cigs in all population groups include perceived safety [23, 34], novelty and curiosity [12], peer influences, avoidance of smoking regulations [34], and social acceptability [9, 35]. However, some generational differences exist. While adults are commonly also attracted by the potential of these products to help them quit smoking or reduce their daily conventional cigarette consumption; teenagers and young adults are charmed by their appealing flavors (mostly candy) [9, 21, 36], low price, and perceived "coolness" [34]. Similarly, HTPs are also perceived to be less harmful or risk-free [20] and more socially acceptable. Although available data on adolescents' perceptions in the EU is scarce, most of the beliefs and perceptions for e-cigarettes may be also true for HTPs [9].

## Main challenges for global tobacco control globally

### *Gateway for tobacco smoking initiation among adolescents*

The teenage years are a critical period in establishing future smoking behaviors. A key public health concern with novel tobacco and nicotine products is their potential to recruit never smokers, especially adolescents, to nicotine dependence [37]. The tobacco industry is promoting the substitution of conventional cigarettes by e-cigarettes, as a key-element of what the industry (and some tobacco control advocates) calls the "tobacco harm reduction" strategy [38]. However, e-cig use is increasing especially among nonsmokers and experimental smokers [39]. Indeed, among teenagers, unlike adult populations in which e-cig users are current or former smokers [22], the proportion that had tried e-cigs who had never smoked conventional cigarettes is noteworthy. For example, data from Poland and Wales (UK) show a high proportion of adolescents reporting ever use of e-cigarettes among those who were never smokers (37.9% and 43.2%, respectively) [21, 40].

E-cig use is associated with the initiation of conventional cigarette smoking among adolescents, thereby increasing their probability of becoming tobacco addicts and suffering from tobacco-related harms in the medium and long run. In this regard, two recent systematic reviews and meta-analysis by O'Brien [37] and Adermark et al. [39] found that adolescents reporting ever e-cigarette use were four times more likely to start smoking tobacco cigarettes compared to those who had never used them at baseline. Findings, thereby, support an association between e-cig ever use and future conventional

cigarette smoking in never smokers and recurrence in experimental smokers even after adjusting for potential confounders, which indicates the robustness of the associations observed. These results pose an important public health threat as it undermines hard-won progress in tobacco control that has succeeded in preventing smoking initiation among the youth over the past decades.

### *Renormalization of the act of tobacco smoking*

Another public health problem associated with novel tobacco products is their potential to renormalize smoking. This can occur when adolescents view smoking as a socially accepted behavior due to the growing prevalence and visibility of these products. The renormalization hypothesis [41] suggests that the increasing extent to which smoking is perceived as a "normal" behavior and accepted by a non-smoking majority, including the youth, is challenging the success of tobacco control efforts in recent decades [26]. Particularly concerning are the high rates of ever use observed among never smokers in the EU, especially among adolescents [22, 23]. Factors such as social acceptability [9] and perceiving these products as "cool" were two of the main reasons reported for US teenagers to start using these products [34].

Harm perceptions of e-cigs and other novel tobacco products among adolescents may also contribute to the renormalization of smoking. These products are often perceived as a healthier alternative since they are thought to be less harmful than conventional cigarettes by both young [42] and adult populations [15, 20, 43]. Previous studies suggest that perceptions play a significant role in predicting their use among young people. A recent meta-analysis showed that adolescents, who believed e-cigs were less harmful and less addictive than conventional cigarettes, were twice as likely more likely to have tried these products [13]. Even more concerning is the finding that low harm perception predicts the initiation of e-cigarette use among youth non-smokers [44].

There is limited evidence available regarding the changes in attitudes towards smoking as a normative behavior among the youth. One of the first studies to address this question found limited evidence for the renormalization of youth smoking and suggested a "normalization" of e-cig use in the context of the denormalization of conventional cigarettes [26]. This is in line with previously described data. Meanwhile, whilst the renormalization hypothesis remains unclear, it has been suggested that the "normalization" of e-cigs leads to an increase in smoking prevalence since e-cig use has been associated with tobacco smoking initiation. Further research is needed to better understand the impact of e-cigarettes on youth smoking attitudes and behavior.

## Further regulating e-cigarettes and novel tobacco products

A precautionary approach is warranted given the many unknowns regarding these products. Indeed, the WHO recommends regulating e-cigarettes to prevent initiation by non-smokers and children, minimize potential health risks, and protect non-users from secondhand exposure to their emissions (SHA) [45]. Yet the legal and regulatory status of these products differs widely by country [9, 46]. In 2014, the European Commission enacted the Tobacco Products Directive (TPD) [47], to provide a framework of actions and goals for EU MS to meet the obligations under the WHO FCTC [48].

The TPD lays down rules for e-cigarettes as consumer products, including but not limited to, setting a maximum nicotine concentration and volume for cartridges, tanks, and nicotine liquid containers; mandating child-resistant containers; requiring text-only health warning messages advising consumers that they contain nicotine and should not be used by non-smokers; and providing instructions for use and information on adverse effects, risk groups, addictiveness, and toxicity (article 20) [47]. That said, under the TPD, HTPs are covered under the more general term "novel tobacco products", which allows manufacturers to self-categorize them either under the definition of tobacco products or smokeless tobacco, the latter being less restrictive (article 19.4) [47, 48]. Tobacco control policy progress in EU MS is lagging behind tobacco industry innovations [2]. Thereby, a more comprehensive regulation of novel nicotine and other tobacco products is needed in the EU. For example, it is necessary that EU MS adopt monitoring strategies over the usage and distribution of these products, and ban their use in public places to protect bystanders. In this regard, the 2nd Joint Action on Tobacco Control (www.jaotc.eu) [49], launched in October 2021, is aimed at strengthening the cooperation between the EU MS and the European Commission concerning the enforcement and improvement of the Tobacco Products Directive (TPD) and the Tobacco Advertising Directive (TAD), to develop a common ground for strategies on smoke-free environments and tobacco endgame strategies.

Novel tobacco and nicotine products have rapidity penetrated the adolescent market [22]. The lack of regulation governing these products in many European countries has led to unrestricted access to addictive products by children and adolescents. Governments should offer children and adolescents the same protection from these products as for conventional cigarettes through a well-enforced regulatory regime of measures including but not limited to the age restriction on purchase and promotion [22], restraint of availability through licensing outlets, limits to product visibility and attractiveness through savage marketing campaigns, and appropriate pricing through taxation [37]. Besides, it is urgent to incorporate novel tobacco and nicotine products in tobacco smoking prevention programs by targeting vulnerable groups through early intervention efforts [12].

Moreover, given their overwhelming acceptance and popularity among the youth, EU MS should design and implement prevention campaigns via social media [12] and educational interventions [23] in schools to raise the awareness of children and adolescents about these products. These strategies may also have the potential to revert potential misconceptions

young people may have regarding their associated health hazards, addictiveness, and harm level [37].

## Conclusions

Novel tobacco and nicotine and products have rapidly gained in popularity among children and adolescents across the EU, challenging tobacco control globally. Despite being marketed by the tobacco industry as "safe" alternatives to conventional cigarettes, these products are not risk-free [50]. The usage of these products, especially e-cigarettes, has been associated with an increase in the uptake of conventional cigarette smoking among adolescents, but also with the renormalization of smoking, making it more socially acceptable behavior, even by non-smokers. Therefore, to prevent setbacks in tobacco control efforts, EU MS should implement more stringent restrictions on these products to ensure they at least match the ones in place for conventional cigarettes and roll-your own tobacco.


## Acknowledgements

The authors alone are responsible for the views expressed in this manuscript. Where authors are identified as personnel of the International Agency for Research on Cancer / World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer / World Health Organization.

**Conflict of interest:** none declared



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*Received: 17 Mar 2023*
*Accepted: 18 Apr 2023*


## References


1. WHO Regional Office for Europe. Tobacco: data and statistics. https://www.who.int/europe/news-room/fact-sheets/item/tobacco (14.02.2023).
2. Willemsen MC, Mons U, Fernández E. Tobacco control in Europe: progress and key challenges. Tob Control. 2022; 31(2): 160–163, doi: 10.1136/tobaccocontrol-2021-056857, indexed in Pubmed: 35241582.
3. Feliu A, Filippidis FT, Joossens L, et al. Impact of tobacco control policies on smoking prevalence and quit ratios in 27 European Union countries from 2006 to 2014. Tob Control. 2019; 28(1): 101–109, doi: 10.1136/tobaccocontrol-2017-054119, indexed in Pubmed: 29472445.
4. Schaap MM, Kunst AE, Leinsalu M, et al. Effect of nationwide tobacco control policies on smoking cessation in high and low educated groups in 18 European countries. Tob Control. 2008; 17(4): 248–255, doi: 10.1136/tc.2007.024265, indexed in Pubmed: 18483129.
5. World Health Organization. WHO Framework Convention on Tobacco Control. Geneva: 2003. http://www.who.int/tobacco/framework/WHO_FCTC_english.pdf (7.05.2017).
6. Joossens L, Olefir L, Feliu A, et al. The Tobacco Control Scale 2021 in Europe. Brussels: 2022. http://www.tobaccocontrolscale.org/TCS2021 (20.02.2023).
7. European Commission. Special Eurobarometer 272c Report: Attitudes of Europeans towards Tobacco. Brussels: 2007.
8. European Commission. Attitudes of Europeans towards tobacco and electronic cigarettes. Brussels: 2021. https://europa.eu/eurobarometer/surveys/detail/2240 (20.02.2023).
9. O'Connor R, Schneller LM, Felicione NJ, et al. Evolution of tobacco products: recent history and future directions. Tob Control. 2022; 31(2): 175–182, doi: 10.1136/tobaccocontrol-2021-056544, indexed in Pubmed: 35241585.
10. Tehrani H, Rajabi A, Ghelichi-Ghojogh M, et al. The prevalence of electronic cigarettes vaping globally: a systematic review and meta-analysis. Arch Public Health. 2022; 80(1): 240, doi: 10.1186/s13690-022-00998-w, indexed in Pubmed: 36415010.
11. Gentzke AS, Wang TW, Cornelius M, et al. Tobacco Product Use and Associated Factors Among Middle and High School Students - National Youth Tobacco Survey, United States, 2021. MMWR Surveill Summ. 2022; 71(5): 1–29, doi: 10.15585/mmwr.ss7105a1, indexed in Pubmed: 35271557.
12. Perikleous EP, Steiropoulos P, Paraskakis E, et al. E-Cigarette Use Among Adolescents: An Overview of the Literature and Future Perspectives. Front Public Health. 2018; 6: 86, doi: 10.3389/fpubh.2018.00086, indexed in Pubmed: 29632856.
13. Aly AS, Mamikutty R, Marhazlinda J. Association between Harmful and Addictive Perceptions of E-Cigarettes and E-Cigarette Use among Adolescents and Youth-A Systematic Review and Meta-Analysis. Children (Basel). 2022; 9(11), doi: 10.3390/children9111678, indexed in Pubmed: 36360406.
14. European Parliament and the Council. Europe's Beating Cancer Plan Brussels, 2021.
15. Filippidis FT, Laverty AA, Gerovasili V, et al. Two-year trends and predictors of e-cigarette use in 27 European Union member states. Tob Control. 2017; 26(1): 98–104, doi: 10.1136/tobaccocontrol-2015-052771, indexed in Pubmed: 27220621.
16. Karim MA, Talluri R, Chido-Amajuoyi OG, et al. Awareness of heated tobacco products among US Adults - Health information national trends survey, 2020. Subst Abus. 2022; 43(1): 1023–1034, doi: 10.1080/08897077.2022.2060440, indexed in Pubmed: 35435808.
17. Tabuchi T, Gallus S, Shinozaki T, et al. Heat-not-burn tobacco product use in Japan: its prevalence, predictors and perceived symptoms from exposure to secondhand heat-not-burn tobacco aerosol. Tob Control. 2018; 27(e1): e25–e33, doi: 10.1136/tobaccocontrol-2017-053947, indexed in Pubmed: 29248896.
18. Yi J, Lee CM, Hwang SS, et al. Prevalence and predictors of heated tobacco products use among male ever smokers: results from a Korean longitudinal study. BMC Public Health. 2021; 21(1): 316, doi: 10.1186/s12889-021-10344-4, indexed in Pubmed: 33557796.
19. Gallus S, Lugo A, Liu X, et al. TackSHS Project Investigators. Use and Awareness of Heated Tobacco Products in Europe. J Epidemiol. 2022; 32(3): 139–144, doi: 10.2188/jea.JE20200248, indexed in Pubmed: 33456019.
20. Laverty AA, Vardavas CI, Filippidis FT. Prevalence and reasons for use of Heated Tobacco Products (HTP) in Europe: an analysis of Eurobarometer data in 28 countries. Lancet Reg Health Eur. 2021; 8: 100159, doi: 10.1016/j.lanepe.2021.100159, indexed in Pubmed: 34557853.
21. Kapan A, Stefanac S, Sandner I, et al. Use of Electronic Cigarettes in European Populations: A Narrative Review. Int J Environ Res Public Health. 2020; 17(6), doi: 10.3390/ijerph17061971, indexed in Pubmed: 32192139.
22. Hughes K, Bellis MA, Hardcastle KA, et al. Associations between e-cigarette access and smoking and drinking behaviours in teenagers. BMC Public Health. 2015; 15: 244, doi: 10.1186/s12889-015-1618-4, indexed in Pubmed: 25886064.
23. Wężyk-Caba I, Kaleta D, Zajdel R, et al. Do Young People Perceive E-Cigarettes and Heated Tobacco as Less Harmful Than Traditional Cigarettes? A Survey from Poland. Int J Environ Res Public Health. 2022; 19(22), doi: 10.3390/ijerph192214632, indexed in Pubmed: 36429359.
24. National Institute for Health and Care Excellence. Tobacco: preventing uptake, promoting quitting and treating dependence NICE guideline-and-conditions#notice-of-rights Your responsibility. London: 2021. www.nice.org.uk/guidance/ng209 (9.05.2023).
25. O'Connor RJ, Giovino GA, Kozlowski LT, et al. Changes in nicotine intake and cigarette use over time in two nationally representative cross-sectional samples of smokers. Am J Epidemiol. 2006; 164(8): 750–759, doi: 10.1093/aje/kwj263, indexed in Pubmed: 16887891.
26. Hallingberg B, Maynard OM, Bauld L, et al. Have e-cigarettes renormalised or displaced youth smoking? Results of a segmented regression analysis of repeated cross sectional survey data in England, Scotland

and Wales. Tob Control. 2020; 29(2): 207–216, doi: 10.1136/tobaccocontrol-2018-054584, indexed in Pubmed: 30936390.
27. Cao D, Aldy K, Hsu S, et al. Review of Health Consequences of Electronic Cigarettes and the Outbreak of Electronic Cigarette, or Vaping, Product Use-Associated Lung Injury. J Med Toxicol. 2020; 16(3): 295–310, doi: 10.1007/s13181-020-00772-w.
28. Goriounova NA, Mansvelder HD. Short- and long-term consequences of nicotine exposure during adolescence for prefrontal cortex neuronal network function. Cold Spring Harb Perspect Med. 2012; 2(12): a012120, doi: 10.1101/cshperspect.a012120, indexed in Pubmed: 22983224.
29. Fernández E, Ballbè M, Sureda X, et al. Particulate Matter from Electronic Cigarettes and Conventional Cigarettes: a Systematic Review and Observational Study. Curr Environ Health Rep. 2015; 2(4): 423–429, doi: 10.1007/s40572-015-0072-x, indexed in Pubmed: 26452675.
30. Amalia B, Liu X, Lugo A, et al. TackSHS Project Investigators. Exposure to secondhand aerosol of electronic cigarettes in indoor settings in 12 European countries: data from the TackSHS survey. Tob Control. 2021; 30(1): 49–56, doi: 10.1136/tobaccocontrol-2019-055376, indexed in Pubmed: 32123139.
31. Amalia B, Fu M, Tigova O, et al. TackSHS Project Investigators. Exposure to secondhand aerosol from electronic cigarettes at homes: A real-life study in four European countries. Sci Total Environ. 2022 [Epub ahead of print]: 158668, doi: 10.1016/j.scitotenv.2022.158668, indexed in Pubmed: 36099951.
32. Ballbè M, Martínez-Sánchez JM, Sureda X, et al. Cigarettes vs. e-cigarettes: Passive exposure at home measured by means of airborne marker and biomarkers. Environ Res. 2014; 135: 76–80, doi: 10.1016/j.envres.2014.09.005, indexed in Pubmed: 25262078.
33. McKelvey K, Baiocchi M, Halpern-Felsher B. PMI's heated tobacco products marketing claims of reduced risk and reduced exposure may entice youth to try and continue using these products. Tob Control. 2020; 29(e1): e18–e24, doi: 10.1136/tobaccocontrol-2019-055318, indexed in Pubmed: 32029537.
34. Nicksic NE, Snell LM, Barnes AJ. Reasons to use e-cigarettes among adults and youth in the Population Assessment of Tobacco and Health (PATH) study. Addict Behav. 2019; 93: 93–99, doi: 10.1016/j.addbeh.2019.01.037, indexed in Pubmed: 30703668.
35. Xu SS, Meng G, Yan Mi, et al. Reasons for Regularly Using Heated Tobacco Products among Adult Current and Former Smokers in Japan: Finding from 2018 ITC Japan Survey. Int J Environ Res Public Health. 2020; 17(21), doi: 10.3390/ijerph17218030, indexed in Pubmed: 33142757.
36. McKelvey K, Popova L, Kim M, et al. Heated tobacco products likely appeal to adolescents and young adults. Tob Control. 2018; 27(Suppl 1): s41–s47, doi: 10.1136/tobaccocontrol-2018-054596, indexed in Pubmed: 30352843.
37. O'Brien D, Long J, Quigley J, et al. Association between electronic cigarette use and tobacco cigarette smoking initiation in adolescents: a systematic review and meta-analysis. BMC Public Health. 2021; 21(1): 954, doi: 10.1186/s12889-021-10935-1, indexed in Pubmed: 34078351.
38. Dewhirst T. Co-optation of harm reduction by Big Tobacco. Tob Control. 2021; 30(e1): e1–e3, doi: 10.1136/tobaccocontrol-2020-056059, indexed in Pubmed: 32796080.
39. Adermark L, Galanti MR, Ryk C, et al. Prospective association between use of electronic cigarettes and use of conventional cigarettes: a systematic review and meta-analysis. ERJ Open Res. 2021; 7(3), doi: 10.1183/23120541.00976-2020, indexed in Pubmed: 34262971.
40. Moore G, Hewitt G, Evans J, et al. Electronic-cigarette use among young people in Wales: evidence from two cross-sectional surveys. BMJ Open. 2015; 5(4): e007072, doi: 10.1136/bmjopen-2014-007072, indexed in Pubmed: 25877272.
41. Sæbø G, Scheffels J. Assessing notions of denormalization and renormalization of smoking in light of e-cigarette regulation. Int J Drug Policy. 2017; 49: 58–64, doi: 10.1016/j.drugpo.2017.07.026, indexed in Pubmed: 28987929.
42. Sharma A, McCausland K, Jancey J. Adolescent's Health Perceptions of E--Cigarettes: A Systematic Review. Am J Prev Med. 2021; 60(5): 716–725, doi: 10.1016/j.amepre.2020.12.013, indexed in Pubmed: 33775514.
43. Wilson S, Partos T, McNeill A, et al. Harm perceptions of e-cigarettes and other nicotine products in a UK sample. Addiction. 2019; 114(5): 879–888, doi: 10.1111/add.14502, indexed in Pubmed: 30609154.
44. Cooper M, Loukas A, Case KR, et al. A longitudinal study of risk perceptions and e-cigarette initiation among college students: Interactions with smoking status. Drug Alcohol Depend. 2018; 186: 257–263, doi: 10.1016/j.drugalcdep.2017.11.027, indexed in Pubmed: 29626778.
45. WHO report on the global tobacco epidemic 2021: addressing new and emerging products. Geneva: 2021. https://www.who.int/publications/i/item/9789240032095 (2.08.2022).
46. Amalia B, Fu M, Feliu A, et al. Regulation of Electronic Cigarette Use in Public and Private Areas in 48 Countries Within the WHO European Region: A Survey to In-country Informants. J Epidemiol. 2022; 32(3): 131–138, doi: 10.2188/jea.JE20200332, indexed in Pubmed: 33342937.
47. European Parliament, Council. Tobacco Products Directive. European Union: 2014.
48. Vardavas CI. European Tobacco Products Directive (TPD): current impact and future steps. Tob Control. 2022; 31(2): 198–201, doi: 10.1136/tobaccocontrol-2021-056548, indexed in Pubmed: 35241588.
49. Straarup MS, O'Donovan F, Lambrou A, et al. The Joint Action on Tobacco Control: A cooperation project for strengthening tobacco control in Europe. Tob Prev Cessat. 2022; 8: 26, doi: 10.18332/tpc/151050, indexed in Pubmed: 35855292.
50. Peruga A, Rodríguez Lozano F, López MJ, et al. [Tobacco heated products: a new challenge in tobacco control]. Gac Sanit. 2022; 36(1): 57–59, doi: 10.1016/j.gaceta.2020.12.033, indexed in Pubmed: 33563478.

VIA MEDICA

Cancer epidemiology

NOWOTWORY Journal of Oncology
2023, volume 73, number 3, 168–173
DOI: 10.5603/NJO.a2023.0011

ISSN: 0029–540X, e-ISSN: 2300-2115
www.nowotwory.edu.pl

# Trends in cancer mortality among Poland's oldest old (aged 85 years and older)

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**Introduction.** The population of Poland's oldest old has increased substantially in recent decades. We evaluate mortality rates for all major cancers and their trend changes between 1999–2018.

**Material and methods.** Cancer death data (1999–2018) were extracted from the World Health Organization (WHO) database. Age-standardized rates, and annual percent changes (APC) were determined.

**Results.** Overall, 1 out of every 8 cancers are diagnosed over age 85+. Women are more often diagnosed than men at a ratio of 2.6 to 1. With regards to the cancers with the highest mortality rates, APCs increased for lung (0.9; 95% confidence interval [CI]: 0.1–0.9) and breast (2.3; 95% CI: 1.7–2.9) cancer among women. Colon cancer also increased among men (2.7; 95% CI: 1.7–2.2).

**Conclusions.** Substantial progress in cancer prevention has been made due to access to diagnostic testing, treatment, and a reduction of smoking. However, there is a need for comprehensive cancer centers that are equipped to administer and coordinate complex and personalized cancer care for the growing elderly population.

**Key words:** cancer, mortality, elderly, Poland

## Introduction

The world's population is aging and has tripled in size from 1950 to 2022 [1]. In Poland, the median age increased from 28.8 years in 1950 to 41.7 in 2020 [2] and it is projected to further increase to 51 years by 2050 [3]. The population of Poland may increase more than projected, as the conflict in Ukraine has displaced an estimated 7.8 million refugees as of November 2022, with millions crossing into Poland [4]. In addition, the emigration of the young Polish population has also increased the proportion of the old [2]. These exogenous events, in addition to increasing life expectancy, have been recently reported to pose a major challenge for cancer care [5].

Like other European countries, the proportion of the oldest old in Poland – here defined as individuals over the age of 85 years – is increasing. When statistics were first published on this population in 2002, the number of people aged 85 and over was 329,525 (0.9% of the total population), while in 2020, the population doubled to 798,726 (2.2%) [6]. As the number of oldest old in Poland increases, so does the risk of acquiring common chronic diseases such as cancer. Cancer mortality has been shown to reach its peak between the ages of 80 to 89 in Poland [7], putting the healthcare system face to face with the burgeoning challenge of meeting the needs of an aging population.

**How to cite:**
Kristjansson D, Mańczuk M. ***Trends in cancer mortality among Poland's oldest old (aged 85 years and older).*** *NOWOTWORY J Oncol* 2023; 73: 168–173.

To the best of our knowledge, there has been little research done to understand the epidemiology of cancer among the oldest old in Poland. In order to determine where to allocate healthcare resources in cancer care within this population, we evaluate mortality rates for all major cancers and their changes over two decades (1999–2018).

## Material and methods

Official death certification data from 1999 through 2018 were extracted from the World Health Organization (WHO) database for all cancers and 22 cancer sites by International Classification of Disease codes [8, 9]:

- lip, oral cavity and pharynx (C00–C14),
- oesophagus (C15),
- stomach (C16),
- colon (C18),
- rectum and anus (C19–C21),
- liver (C22),
- gallbladder and biliary tract (C23–C24),
- pancreas (C25),
- larynx (C32),
- lung (C33–C34),
- breast (C50),
- cervix uteri (C53),
- corpus uteri (C54),
- ovary (C56),
- prostate (C61),
- bladder (C67),
- kidney (C64–C65),
- brain and central nervous system (C70–C72),
- thyroid (C73),
- Hodgkin lymphoma (C81),
- non-Hodgkin lymphoma (C82–C88),
- multiple myeloma (C90),
- leukaemia (C91–C95),
- and all cancers excluding non-melanoma skin (C00–C96, excluding C44).

Age-specific mortality rates (2000–2014) were calculated for each 5-year age group from 61 and older compared to the standard population proposed by Doll et al. [10], as used in GLOBOCAN [11]. We computed the estimated age percent change (APC), defined as the percent change from one year to the next among individuals over 85+ years old over the two decades. Data on the population in Poland was abstracted from Statistics Poland [6].

## Results

From 1999 to 2018, there were a total of 64,644 and 91,361 cancer mortalities reported among persons over 85 years among men and women, respectively, with a total of 156,005 cancers. Considering that there was a total of 1,850,553 malignancies diagnosed in Poland, this amounts to 1 out of every 8 cancers diagnosed at age 85+.

The cancer types with the highest age-standardized mortality rates (ASR) (fig. 1) and proportion of all cancers for men were:

- prostate (510.1; 21.2%),
- lung (377.1; 15.6%),
- colon (220.7; 9.2%),
- bladder (207.0; 8.6%)

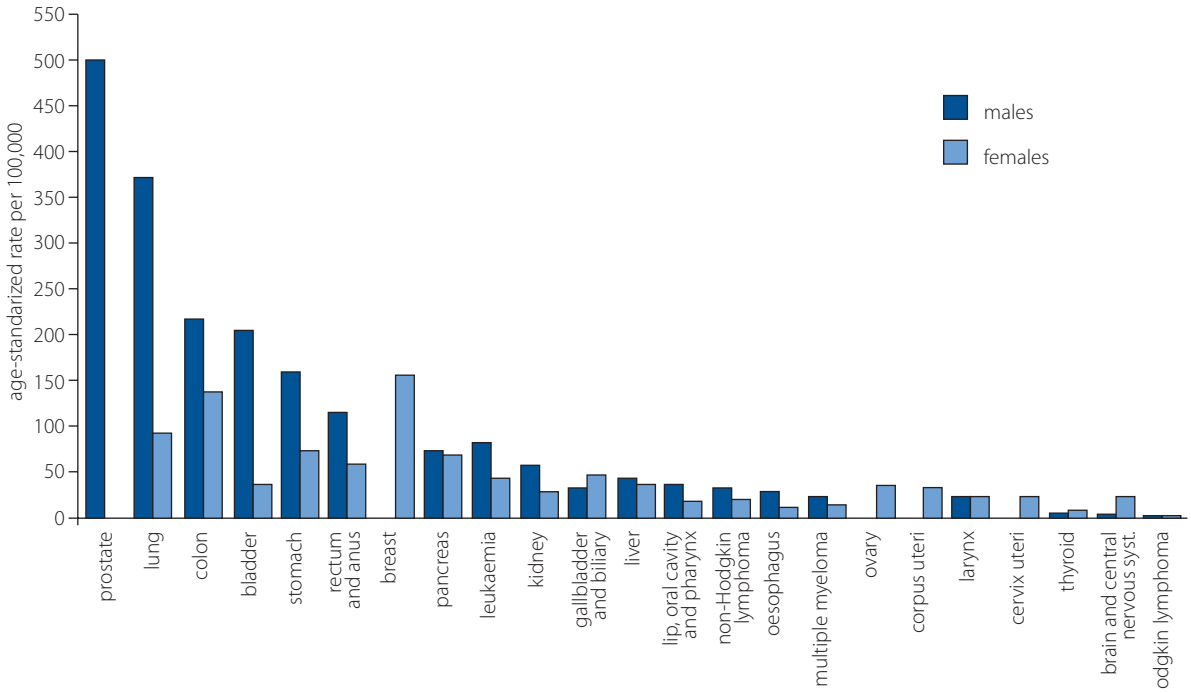


**Figure 1.** Mortality rate of major cancers occurring in those 85-years and older in Poland (1999–2018). Age-standardized according to world population

- stomach (162.2; 6.8%).

For women:

- the highest ASRs were found for breast (159.4; 12.7%),
- colon (139.6; 11.1%),
- lung (93.9; 7.5%),
- stomach (72.7; 5.8%)
- pancreas (70.3; 5.6%).

Among men, deaths due to prostate cancer are more frequent among those aged 85 years or older than for the general population (21.2% among the oldest old while 10.3% was reported among the general population) [12]. Breast cancers were similarly proportioned among both the general population and those 85 or older [12]. Conversely, for the general population, lung cancer accounted for the most deaths among both men and women [12].

According to the estimated APCs (fig. 2), mortality for all cancer sites remained stable for men (0.5; 95% CI: 0.4–0.7) and women (–0.1; 95% CI: –0.3–0.2). Mortality from cancers of the brain and central nervous system had the highest increase among the oldest old (6.0; 95% CI: 4.4–7.6 among men and 5.8; 95% CI: 3.0–6.6 among women). In addition, other cancers without established screening protocols – multiple myeloma, non-Hodgkin lymphoma, ovary, kidney, and bladder – showed the largest APC increases among those 85+ years old. While colon cancer mortality decreased among women, reaching 0.3 (95% CI: –0.3–1.0) APC, mortality rates have increased among men (2.7; 95% CI: 1.7–2.2).

While the APC for lung cancer among men is towards the null (0.3; 95% CI: –0.1–0.7), the APC is larger among women (0.9; 95% CI: 0.1–0.9), and is similar to global findings that reflect the tobacco smoking habits women had started decades after men [13]. In addition, breast cancer (2.3; 95% CI: 1.7–2.9) showed an increase. Prostate cancer (1.0; 95% CI: 0.6–1.3) did not show any changes. Stomach cancer decreased among both men and women (–2.0; 95% CI: –2.6 to –1.5) for men and –2.8 (95% CI: –3.7 to –2.0 for women).

The direction of the changes in cancer mortality rates by five-year age group (fig. 3) vary depending on the years of diagnosis. Among men, diagnoses occurring at earlier periods (from the period 1959–1963 until 1994–1998) show a decline or stabilization in cancers once they age beyond 81–85 years old. The highest cancer mortality rate occurred during 1999–2003 and 2004–2008. This was followed by a progressive decrease in mortality rates for periods after 2009.

The cohorts follow a similar trend among women with the mortality rates reaching a slower decline into the oldest

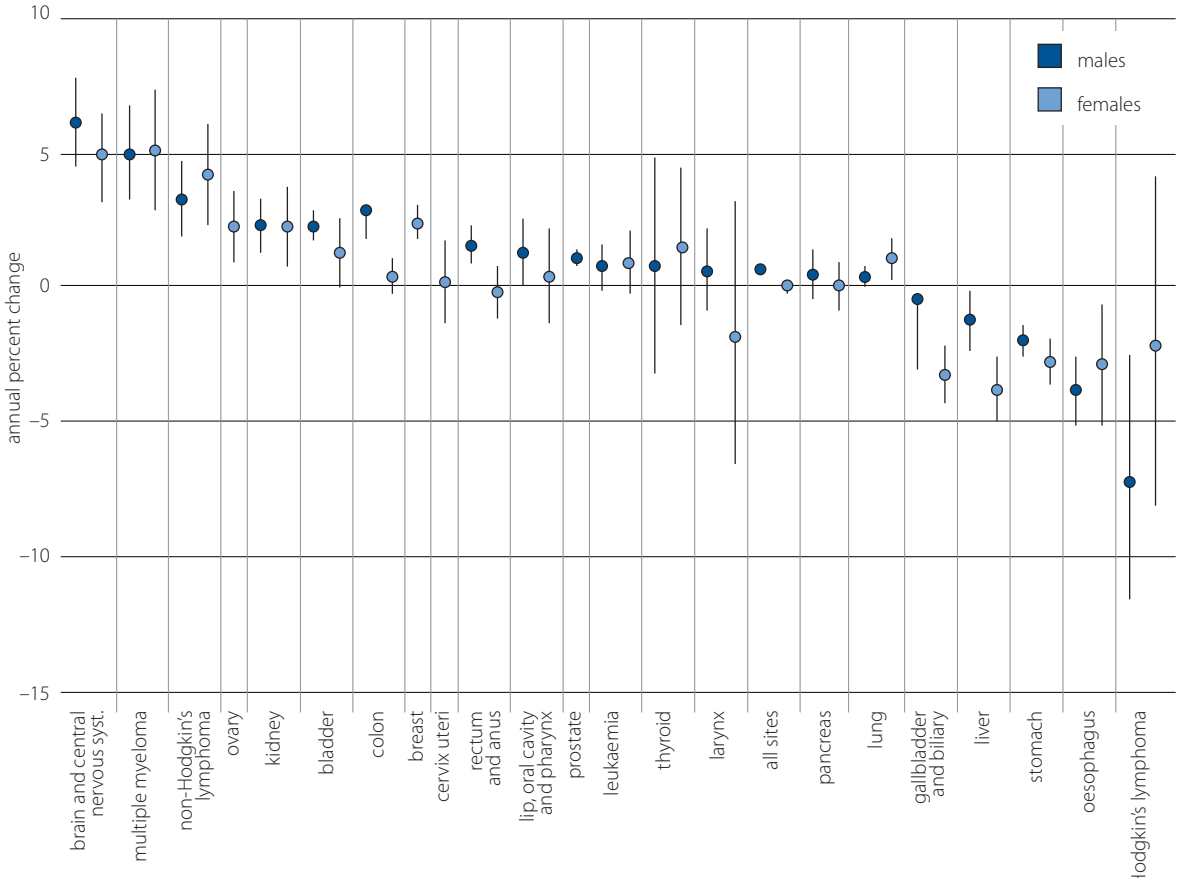


**Figure 2.** Annual percent change in mortality rates of major cancers occurring in those 85-years and older in Poland (1999–2018). Age-standardized according to world population

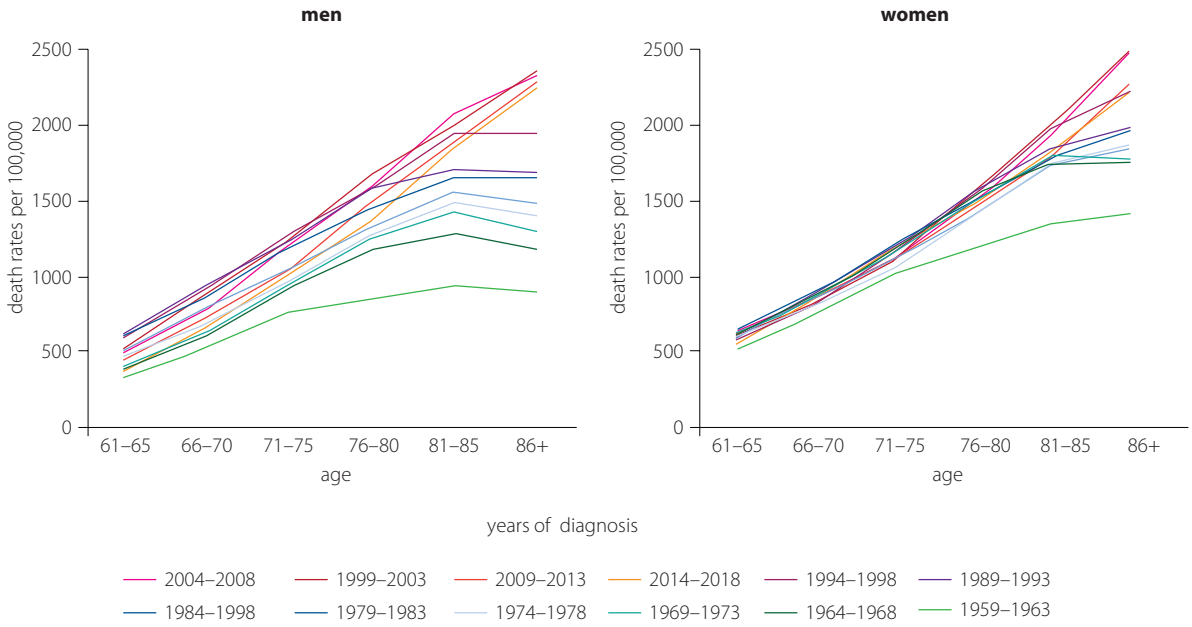


**Figure 3.** Age-specific mortality rates by year of diagnosis in Poland

ages for most of the time periods apart from those diagnosed in 1959–1963. The major difference between trends among men and women is there are fewer changes in cancer mortality rates after 1963 compared to the time-period changes observed among men.

## Discussion

This brief report of cancer mortality trends among the oldest old in Poland (1999–2018) showed that 59% of cancers occurred in women, outnumbering men by 2.6 to 1. Among women, there was a 2% increase in the annual mortality rates of breast cancer as well as an increasing trend for lung cancers. For men aged 85 and older, colon cancer is also increasing nearly 3% annually. Although prostate cancer rates are high among men 85+ years old, there has been little change in the past two decades. The data reveals a concerning trend in cancer mortality among men and women over the age of 85, indicating an increase during the late 1990s and early 2000s compared to previous decades. This was followed by a gradual decline in overall mortality after the 2004–2008 period. The direction of these trends suggests that the change in cancer mortality following the late 1990s may be influenced by exogenous events, including the introduction of cancer screening programs and access to treatment following the fall of the Soviet Union, as well as lifestyle habits.

Public health education in western countries between the 80s and 90s were marked by the encouragement of tobacco smoking cessation, moderation in alcohol consumption, reduction in weight, and a higher consumption of fruits and vegetables – lifestyle habits that have now been included as part of the European Prevention [14]. Lifestyle habits were much slower to change in the east, as a result of western information deprivation, increasingly available tobacco products, and consumer subsidies that kept meat and dairy prices quite low compared to western countries [15–17]. Prior to 1991, life expectancy was low; a 15-year-old boy in Poland had a life-expectancy of about 53.5 years [16]. It was not until the mid-1990s that life expectancy reached western standards, finally reaching 80.3 years in 2011 [18]. This has been partly attributed to reduced smoking, improved screening, and treatment advances, which led to a decline in mortality [19, 20].

Although a centralized cancer care management program is available at the Institute of Oncology, cancer care access and management in Poland has historically been and continues to be fragmented [21]. A 2016 study found that patients felt that their cancer care was not well-organized and lacked smooth and continuous care throughout diagnosis, treatment, and follow-up [22]. The national anticancer system in Poland, called the oncological package, attempted to transfer some of the cancer care onto general practitioners (GPs) [23]. However, not all institutions were found to be properly equipped. A 2015 study reported that only 28% of hospitals and 2% of specialist ambulatory providers participating were able to provide laboratory tests, CT and MRI scans, and endoscopy examinations; fewer than half of the audited providers could undertake the intraoperative pathology necessary to assess the margins of some tumor excisions [24].

The oldest old require particularly careful clinical evaluation due to multiple co-morbidities with multiple respective medication regimens, age-related physical and psychological changes, immunosuppression, and frailty [25, 26]. Cancer survival is lower among the oldest old compared to other age groups [27–29]. Comprehensive and interdisciplinary cancer

care centers, where several specialists can collaborate, evaluate risks-versus-benefits, plan, and deliver cancer care treatments is therefore especially vital for this vulnerable patient population.

Unfortunately, the focus of cancer care has mainly been on hospital care treatment, despite concerns that many cancers are detected too late and before they can be successfully treated [21]. Preventive care, which includes cancer diagnostic testing, is therefore of the utmost importance, but has not been funded as part of the oncological package. As a result, GPs are apprehensive about paying "out-of-pocket" for patient diagnostic testing, which has led to patient symptoms being downplayed [22].

Our findings have shown that cancers of that brain and central nervous system, multiple myeloma, non-Hodgkin's lymphoma, ovary, kidney, and bladder had the highest annual percent increases over the years. These are cancers for which there are no routine screening procedures, even during middle-age. In particular, brain, multiple myeloma and non-Hodgkin's lymphoma, and ovarian cancer have limited treatments, even if the cancer is detected early. Lung cancer, which was one of the most common cancers diagnosed among the oldest old, can benefit from the implementation of primary prevention programs. Smoking cessation is possible at an older age and has been shown to lower mortality rates even if the patient is over 65 years old [30].

The increase in breast cancer among women is particularly concerning. The national screening programs for breast, cervical, and colorectal cancers, were introduced as part of the National Program for Cancer Disease Control in 2006 and extended through 2015 and was later renewed for 2016–24 [31]. However, a pilot from 2018 reported 16% for breast, 20% for cervical, and 40% for colorectal cancer screening [24]. While the oldest old fall outside the boundaries of breast cancer screening, diagnostic testing of breast cancer should not be delayed. Older women with breast cancer are more likely to have large tumors and positive metastatic axillary nodes than their younger counterparts [32].

## Conclusions

Life expectancy increases mean that the burden of cancers in the oldest old age group will grow. In 2021, Poland spent 6.6% of its GDP on health which is one of the lowest in the EU [33]. Given the increasing growth of the older population with chronic health issues, expenditures are expected to increase [34]. Cancer risks such as smoking and obesity should be addressed by preventive programs as these issues are still prevalent among the older population in Poland [34]. In addition, more research is needed on Poland's oldest old in order to identify trends in time-to-diagnosis and survival, as well as pinpointing where the cancer healthcare system is most vulnerable. It is important to acknowledge that there is a wide variation of health status as individuals reach older ages, and comprehensive cancer centers that are equipped with diagnostic testing, resources, specialists will be best equipped to coordinate treatment for each patient. While substantial progress has been made, there is still a long way to go in terms of addressing and improving cancer care for the oldest old.

**Conflict of interest:** none declared

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*Received: 28 Dec 2022*
*Accepted: 9 Jan 2023*

## References

1. United Nations Department of Economic and Social Affairs, P.D., World Population Prospects 2022: Summary of Results. 2022, UN DESA/POP/2022/TR/NO .3.
2. Demographic Yearbook of Poland 2021. file:///C:/Users/danh/Downloads/demographic_yearbook_of_poland_2021.pdf (28.11.2022).
3. Devictor X. Poland: Aging and the Economy. 2012.
4. (UNHCR) Ukraine refugee situation. 2022. https://data.unhcr.org/en/situations/ukraine (28.11.2022).
5. Didkowska JA, Barańska K, Wojciechowska U, et al. War in Ukraine creates challenges for the cancer care system in Poland. Lancet Oncol. 2022; 23(10): 1239–1240, doi: 10.1016/S1470-2045(22)00384-9, indexed in Pubmed: 35785796.
6. Poland S. Data for year 2020: Population by sex and age group. 2022. https://bdl.stat.gov.pl/bdl/pomoc/stanzasilenia?active=0# (29.11.2022).
7. Hashim D, Carioli G, Malvezzi M, et al. Cancer mortality in the oldest old: a global overview. Aging (Albany NY). 2020; 12(17): 16744–16758, doi: 10.18632/aging.103503, indexed in Pubmed: 32882684.
8. WHO mortality database 2022. https://www.who.int/data/data-collection-tools/who-mortality-database (26.08.2022).
9. World Health Organization. International Classification of Disease: 10th revision. WHO, Geneva 1992.
10. Doll R, Payne P, Waterhouse J. Cancer Incidence in Five Continents: A Technical Report. Springer-Verlag, Berlin 1966.
11. Cancer, W.I.A.f.R.o. GLOBOCAN 2020: New Global Cancer Data 2020 . https://www.uicc.org/news/globocan-2020-new-global-cancer-data (29.11.2022).
12. Didkowska J, Wojciechowska U, Michalek IM, et al. Cancer incidence and mortality in Poland in 2019. Sci Rep. 2022; 12(1): 10875, doi: 10.1038/s41598-022-14779-6, indexed in Pubmed: 35760845.
13. Torre LA, Siegel RL, Ward EM, et al. International variation in lung cancer mortality rates and trends among women. Cancer Epidemiol Biomarkers Prev. 2014; 23(6): 1025–1036, doi: 10.1158/1055-9965.EPI-13-1220, indexed in Pubmed: 24836468.
14. Schüz J, Espina C, Villain P, et al. Working Groups of Scientific Experts. European Code against Cancer 4th Edition: 12 ways to reduce your cancer risk. Cancer Epidemiol. 2015; 39 Suppl 1: S1–10, doi: 10.1016/j.canep.2015.05.009, indexed in Pubmed: 26164654.
15. Zatonski W. Tobacco smoking in central European countries: Poland. In: Boyle P, Gray N, Henningfield J, et al. ed. Tobaccoand Public Health: Science and Policy. Oxford University Press, Oxford 2004: 235–252.
16. Zatoński WA. HEM project team. Epidemiological analysis of health situation development in Europe and its causes until 1990. Ann Agric Environ Med. 2011; 18(2): 194–202, indexed in Pubmed: 22324071.
17. Zatoński WA, Przewoźniak K. Zdrowotne następstwa palenia tytoniu w Polsce. Ariel, Warszawa 1992.
18. Sagan A, Panteli D, Borkowski W, et al. Poland Health system review. Health Systems in Transition. 2013; 8(11): 1–193.
19. DeSantis CE, Miller KD, Dale W, et al. Cancer statistics for adults aged 85 years and older, 2019. CA Cancer J Clin. 2019; 69(6): 452–467, doi: 10.3322/caac.21577, indexed in Pubmed: 31390062.

20. Didkowska J, Wojciechowska U. Breast cancer in Poland and Europe—population and statistics. Nowotwory. Journal of Oncology. 2013; 63(2): 111–118.
21. Sagan A, Kowalska-Bobko I, Gałązka-Sobotka M, et al. Assessing Recent Efforts to Improve Organization of Cancer Care in Poland: What Does the Evidence Tell Us? Int J Environ Res Public Health. 2022; 19(15), doi: 10.3390/ijerph19159369, indexed in Pubmed: 35954721.
22. Godlewski D, Adamczak M, Wojtyś P. Experiences of cancer patients in Poland throughout diagnosis and treatment. Eur J Cancer Care (Engl). 2017; 26(2), doi: 10.1111/ecc.12436, indexed in Pubmed: 26764219.
23. Holecki T, Romaniuk P. The oncological package: a new source of concern in Poland's health system. Lancet Oncol. 2015; 16(3): e104, doi: 10.1016/S1470-2045(15)70030-6, indexed in Pubmed: 25752556.
24. Maciejczyk A. Edytorial. Biuletyn PTO Nowotwory. 2018; 3(4): 207–208.
25. Colloca G, Corsonello A, Marzetti E, et al. Treating cancer in older and oldest old patients. Curr Pharm Des. 2015; 21(13): 1699–1705, doi: 10.2174/1381612821666150130122536, indexed in Pubmed: 25633116.
26. Schonberg MA, Marcantonio ER, Li D, et al. Breast cancer among the oldest old: tumor characteristics, treatment choices, and survival. J Clin Oncol. 2010; 28(12): 2038–2045, doi: 10.1200/JCO.2009.25.9796, indexed in Pubmed: 20308658.
27. Quaglia A, Tavilla A, Shack L, et al. EUROCARE Working Group. The cancer survival gap between elderly and middle-aged patients in Europe is widening. Eur J Cancer. 2009; 45(6): 1006–1016, doi: 10.1016/j.ejca.2008.11.028, indexed in Pubmed: 19121578.
28. Colonna M, Bossard N, Remontet L, et al. FRANCIM Network. Changes in the risk of death from cancer up to five years after diagnosis in elderly patients: a study of five common cancers. Int J Cancer. 2010; 127(4): 924–931, doi: 10.1002/ijc.25101, indexed in Pubmed: 19998335.
29. Zeng C, Wen W, Morgans AK, et al. Disparities by Race, Age, and Sex in the Improvement of Survival for Major Cancers: Results From the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program in the United States, 1990 to 2010. JAMA Oncol. 2015; 1(1): 88–96, doi: 10.1001/jamaoncol.2014.161, indexed in Pubmed: 26182310.
30. Müezzinler A, Mons U, Gellert C, et al. Smoking and All-cause Mortality in Older Adults: Results From the CHANCES Consortium. Am J Prev Med. 2015; 49(5): e53–e63, doi: 10.1016/j.amepre.2015.04.004, indexed in Pubmed: 26188685.
31. Wasilewski P. Narodowy program zwalczania chorób nowotworowych–realizacja planów, sukces czy porażka? Kontrola Państwowa. 2014; 6(59): 73–86.
32. Bouchardy C, Rapiti E, Fioretta G, et al. Undertreatment strongly decreases prognosis of breast cancer in elderly women. J Clin Oncol. 2003; 21(19): 3580–3587, doi: 10.1200/JCO.2003.02.046, indexed in Pubmed: 12913099.
33. OECD Data: Health spending 2022. https://data.oecd.org/healthres/health-spending.htm (8.12.2022).
34. Leszko M, Zając-Lamparska L, Trempala J. Aging in Poland. Gerontologist. 2015; 55(5): 707–715, doi: 10.1093/geront/gnu171, indexed in Pubmed: 26315315.

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Guidelines and recommendations

NOWOTWORY Journal of Oncology
2023, volume 73, number 3, 174–186
DOI: 10.5603/NJO.2023.0028

ISSN: 0029–540X, e-ISSN: 2300-2115
www.nowotwory.edu.pl

# Molecular diagnostics of cancers – practical approach

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Introduction of targeted therapies based on monoclonal antibodies or small-cell kinase inhibitors in cancer treatment led to major improvements of treatment outcomes in selected patients. However, achievement of prolonged progression-free survival or overall survival involves necessity to test a range of molecular markers at the diagnostic stage. Their number is determined by provisions of drug programmes and leads to serious problems with the right selection of individual markers. It is also an important challenge in the process of financial settlement of the performed tests. The present paper summarises the major aspects of molecular cancer diagnosis recommended and available in clinical practice in Poland.

**Key words:** targeted therapies, genetic diagnostics in cancers, settlement of genetic tests

The dynamic development of molecular biology led to exploration of a range of phenomena underlying the process of neoplastic transformation and contributing to fast development of therapies based on monoclonal antibodies and small-cell kinase inhibitors. However, multiple analyses have shown that these drugs are effective only in selected patients, and therefore it is necessary to test multiple molecular markers at the diagnostic stage to allow identification of those patients who can achieve the greatest benefits with the applied treatment. The number of tests imposed by provisions of drug programmes leads to multiple questions concerning selection of the testing method, quality standards to be met by diagnostic laboratories, and the major ones – concerning the possibility to settle the funding of individual tests. The present paper summarises the major aspects of molecular cancer diagnosis recommended and available in clinical practice in Poland.

## Genetic testing at medical diagnostic laboratories

Genetic Diagnostics Departments/Labs at referential oncology centres should employ a staff of experienced lab diagnosticians and specialists in laboratory medical genetics. The basic role of these units is to perform diagnostic genetic tests designed to identify germinal mutations (constitutive mutations) and

**How to cite:**
Tysarowski A, Szumera-Ciećkiewicz A, Marszałek A, Kowalik A, Seliga K, Bidziński M, Senkus-Konefka E, Wyrwicz L, Mądry R, Płużański A, Sakowicz M, Krzakowski M, Rutkowski P, Kubiatowski T. ***Molecular diagnostics of cancers – practical approach.*** *NOWOTWORY J Oncol* 2023; 73: 174–186.

somatic mutations (genetic testing in acquired cancers). Genetic cancer diagnostics allows, above all, differential diagnosis, qualifying patients for targeted therapies, and also it enables monitoring of treatment course [1]. Within the diagnostic process, molecular analyses are also applied for assessing the development risk for the given cancer and as a basis for providing genetic counselling and prophylaxis for high-risk family members [2].

Genetic tests performed within a single medical centre allow introduction of integrated, interdisciplinary oncological diagnostics. The organisational structure and close multi-specialisation cooperation of lab diagnosticians, clinical physicians, pathomorphologists and geneticists enables specialist and comprehensive diagnostics in a single centre, without a need to send material to external cooperating units. Thus, the testing time is reduced to minimum, there is a possibility of consultation of the case with specialists in various medical specialties, and at the same time the risks involved in sample transport (e.g. sample loss or damage) are eliminated by application of consistent procedures for sample protection. Importantly, the material remains within the centre and if needed, it is available for re-analysis applying another technology. Further, if the result cannot be obtained, due to degradation of the genetic material or for other reasons, quick reaction is possible by re-harvesting a sample or using material harvested at another procedure or biopsy, if the archival material is representative [3].

Peripheral blood, drawn for assessment of germinal mutations or assessment of somatic mutations (referred to as liquid biopsy) on the level of extracellular nucleic acids – ctDNA (circulating tumour DNA) can be used material for genetic testing, if drawn upon prior written consent by the patient to diagnostic genetic testing. It should be referred directly to the genetics unit. Genetic testing of histopathology material (archival material fixed as paraffin blocks) performed upon acquisition of the patient's consent to diagnostic genetic testing, must be assessed by pathomorphologists to evaluate applicability of the material for molecular testing and to select the right sample (see: section about the role of pathomorphology in molecular diagnostics) [4].

A report of the completed genetic diagnostic test should include the test result, precise interpretation understandable for a clinical oncologist, clinical geneticist, pathomorphologist and the patient, as well as the scope and description of methods applied [5].

Genetic testing requires equipment with full technical documentation concerning repairs, validations and confirmation of annual inspections (Regulation of the Minister of Health of 21 March 2006 (Journal of Laws of 2006, no. 59, item 422, as amended). A genetic lab should hold experience of at least five years in working with peripheral blood material, tissue material, cytology material, extracellular nucleic acids; and it should have developed and implemented procedures, lab instructions, as well as internal quality control systems. It must be managed by a specialist in medical genetic diagnostics. The experience in testing germinal and somatic mutations should be documented by certificates of international quality control. The employed staff should be experienced and skilled in interpretation of the identified genetic variants based on medical databases, medical literature and bioinformatics analytical software *in silico*. All requirements set for diagnostic labs were described in the Regulation of the Minister of Health concerning quality standards for diagnostic labs and microbiology labs (Journal of Laws of 2019, item 1923).

A lab providing genetic testing for oncology diagnostics should ensure that the following tests are available at all times with no exceptions:

- **Sanger direct sequencing** – germinal and somatic mutations – testing of selected fragments of the DNA in genes where pathogenic variants can be located; targeted testing of selected genetic variants; verification of variants obtained by large-scale NGS methods. In assessment of histopathology material it is recommended that the tested preparations should contain no less than of 20% cancer tissue. Performance of macro- or micro-dissections is recommended to obtain the highest proportion of cancer tissue.
- **Next-generation sequencing (NGS)** – technology dedicated to comprehensive molecular diagnostics allowing parallel detection of multiple molecular markers and many classes of genetic mutations (point mutations, small deletions/insertions, big deletions, amplification, gene fusions), including genome signatures such as MSI (microsatellite instability), TMB (tumour mutational burden), HRD (homologous recombination deficiency). In testing germinal, as well as somatic mutations, panel (or targeted) next-generation sequencing can be applied, involving assessment of a selected pool of genes. In assessment of histopathology material it is recommended that the tested preparations should contain no less than of 20% cancer tissue (no less than 30% in the case of HRD testing). Performance of macro- or micro-dissections is recommended to obtain the highest share of cancer tissue.
- **qPCR** (modification of the PCR method referred to as quantitative real time PCR) –method dedicated to identification of only known genetic variants; quick method of high sensitivity of 1% to 0.2%. It allows identification of genetic mutations in material of scarce cancer tissue (5–15%) and ctDNA. Performance of macro- or micro-dissections is recommended to obtain the highest proportion of cancer tissue.
- **FISH** (fluorescent *in situ* hybridisation); **CISH** (chromogenic *in situ* hybridisation) – routine diagnosis of gene rearrangements, including gene fusions and gene amplifications.
- **MLPA** (multiplex ligation-dependent probe amplification) – method dedicated to assessment of large genetic rearrangements including deletions and duplications.

Dedicated mainly to assessment of germinal mutations. Frequently applied to verify mutations identified by large-scale techniques, such as NGS.

- **Other techniques: ddPCR** (droplet digital PCR) – one of the most sensitive techniques in molecular biology applied in testing selected genetic variants, especially on the ctDNA level. **Pyrosequencing** – method allowing assessment of methylation of selected DNA sequences. **aCGH** (array comparative genomic hybridisation) **–** cytogenetic method which involves detection of loss or amplification of chromosome regions or gene(s) characterised by very high resolution – for **SNP** assessment (single-nucleotide polymorphism) and evaluation of gene expression profile.

## Role of pathomorphology in molecular diagnostics

Tissue and cytology material is used for molecular biology testing mainly in order to determine the right pathomorphological diagnosis of the cancer according to the currently binding classifications of the World Health Organisation (WHO) and to identify patients who may benefit the most from personalised therapies. Such tests require involvement of a diagnostic team including physicians specialising in pathomorphology, lab diagnosticians specialising in medical genetic diagnosis, biologists, biotechnologists and lab technicians. Labs/departments of pathomorphology (units specialising in pathomorphology diagnostics) within the highly-specialist healthcare institutions should have guaranteed access to the listed types of tests performed either in their own specialist labs or within a close cooperation with diagnostic labs specialising in analyses associated with medical genetic lab diagnostics [6, 7].

The quality of the genetic material (least possible degree of DNA/RNA degradation) is determined by observance of the right procedures at particular stages of processing of the biological material. The most important factors allowing maintenance of high quality of the tissue material include:

- delivery of the harvested material to the pathomorphology lab as fast as possible;
- fixing in 10% buffered formalin (4% solution of formaldehyde, pH 7.2–7.4, ambient temperature at most),
- adaptation of the fixing time to the size of the material (small histology material: up to 24/48 h, big histology material: up to 48/72 h).

Further processing of the tissue material must be standardised according to norms/requirements approved by the Ministry of Health and procedures recommended by the Polish Pathology Society and their latest updates. Each sample (paraffin block and corresponding microscopic preparation stained with hemotoxylin and eosin) – originating from the selected material for pathomorphology testing and designed for molecular testing – must be assessed by a physician specialising in pathomorphology to confirm the diagnosis, determine presence of cancer tissue and describe the proportion of cancer cells in the preparation. A physician specialising in pathomorphology chooses the best sample (procedure of qualifying material for molecular testing) in the context of molecular testing, considering also the sequence of planned diagnostic stages. In the case of materials sent from other centres, it is reasonable to provide all paraffin blocks to ensure the right qualification for the molecular testing considering the necessity to choose the material of the highest quality. If there is no adequate material for molecular testing (e.g. the material is too scarce, the proportion of cancer cells is too low or the material is technically damaged), a physician specialising in pathomorphology may recommend re-harvesting of material from the patient. The technical requirements concerning harvesting material from a paraffin block for isolation of nucleic acids (cutting blocks, their storage and delivery for molecular testing) are described in detail in the quoted guidelines.

Cytology smears (material for exfoliative and aspiration cytology, in the form of smear on basic glassware, fixed with alcohol 95–96%) and cyto-blocks (material for exfoliative and aspiration cytology fixed and submerged in a paraffin block) may also serve as valuable material for molecular testing. The binding rules for qualification of samples by a physician specialising in pathomorphology are the same as described above with respect to tissue material. In the case of smears, digital archiving of materials is recommended before their delivery for molecular analysis, because the biological material is entirely and irreversibly used.

The result of molecular assessment, necessary either for pathomorphological diagnosis, or for personalised treatment, should be included in the final/comprehensive pathomorphology report (including a summary or so-called synoptic report) in the case if the medical diagnostic lab is a part of the pathomorphology diagnostic unit or it may be attached to the report. Regardless of the organisational relations, provision of material for molecular testing requires cooperation and efficient communication to ensure fluent and optimal process of diagnostics. In order to ensure the right pathomorphology diagnostics, introduction of a separate model of funding of these tests is expected, based on the JGPato model, currently in development.

## Funding of genetic diagnostic tests by the public payer

The right organisation of genetic diagnostics in oncology applying modern methods of molecular biology translates to improvement of the achieved outcomes of patient treatment, however, it requires additional funding [8]. Costs of genetic testing for oncologic patients vary depending on the applied testing technique and the number/type of procedures necessary to obtain an unequivocal, clinically useful result. There are several way of financial settlement of genetic tests within cancer diagnostics.

Considering the variable costs of genetic tests in oncology patients, the public payer introduced in 2017 a possibility to fund them within a hospitalisation agreement depending on ICD10 diagnosis, used diagnostic technology, number and type of the markets and moment of harvesting material for testing:

- archival material – provided from another centre or harvested at the given healthcare institution at a diagnostic procedure during earlier hospitalisation (fixed tissue and cytology material/paraffin blocks and preparations), or
- freshly harvested material sampled during hospitalisation (peripheral blood or material harvested during a surgical procedure and fixed as paraffin blocks or cytology material).

According to the Ordinance of the President of the National Health Fund concerning determination of terms of conclusion and implementation of agreements in the hospitalisation category (as amended), the possibility to settle diagnostic genetic testing in cancers was assigned to 15 areas both in conservative and surgical procedures (according to Attachment 1c to calculation): paediatric surgery, chest surgery, oncologic surgery, pulmonary disease / pulmonary disease in children, endocrinology, gastroenterology, oncologic gynaecology, haematology, neonatology, neurosurgery, paediatric oncology and haematology, clinical oncology, obstetrics and gynaecology, urology. It is not possible to settle genetic testing within general surgery.

For settlement of genetic testing in cancers within hospitalisation contracts, there are dedicated settlement products in catalogue 1c (for calculation) which allow funding of diagnostic genetic testing of material harvested during hospitalisation or archival material:

- basic genetic testing in cancers (code 5.53.01.0005001) – refund of **649 points**,
- complex genetic testing in cancers (code 5.53.01.0005002) – refund of **1,298 points**,
- advanced genetic testing in cancers (code 5.53.01.0005003) **–** refund of **2,434 points**.

Currently, this is the most favourable variant of settlement of genetic testing in cancers.

The basic condition of settlement of genetic testing in oncology within the hospitalisation agreement involves holding a contract with the National Health Fund concerning provision of healthcare services of the type "hospitalisation" in at least one area listed in catalogue 1c of the ordinance. Hospitalisation involving harvesting of material for genetic testing should be justified by medical considerations and correctly documented. Upon obtaining a result of a genetic test, the JGP group in catalogue 1a should be expanded by the correct settlement product as indicated by the genetics lab: simple, complex or advanced genetic testing in cancers.

Originally, reporting of genetic tests involved a necessity of hospitalisation of the patient, as harvesting of the material

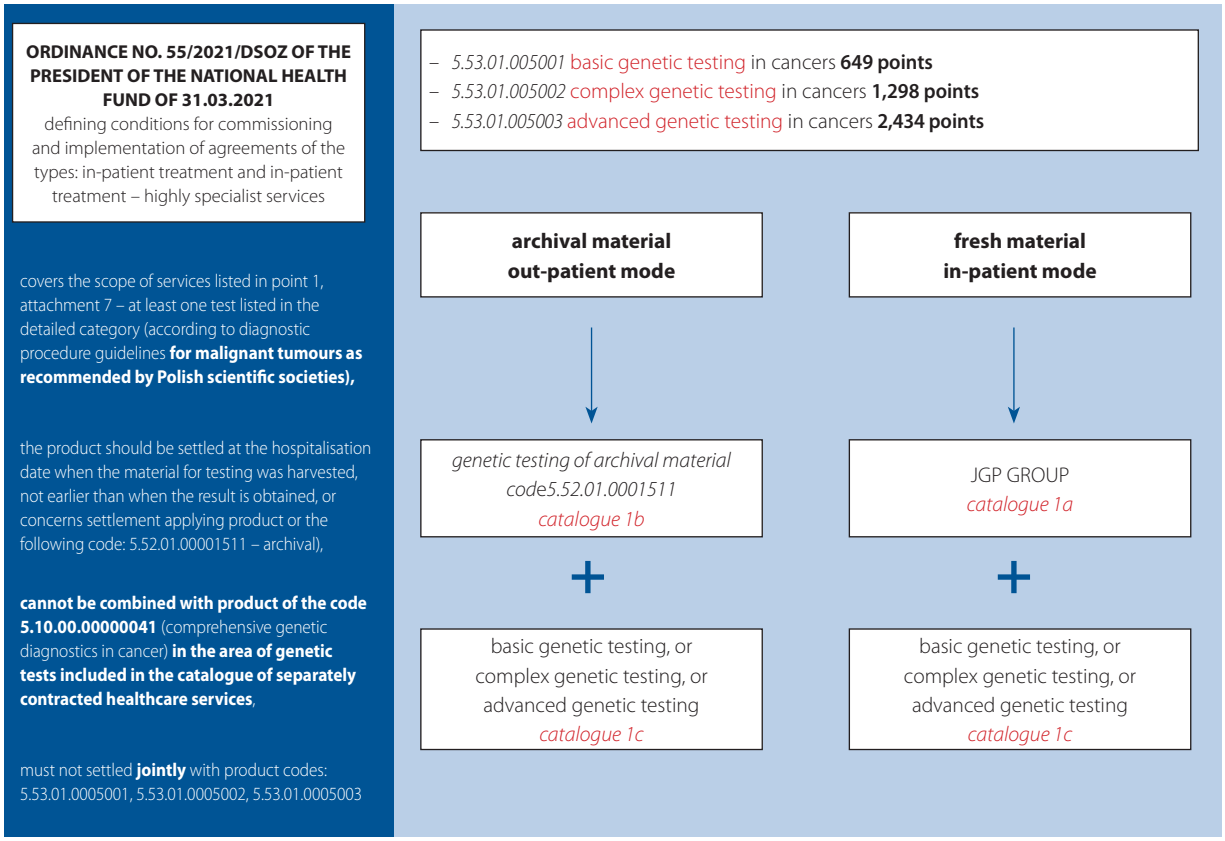


**Figure 1.** Settlement products in catalogue 1c (for calculation) which allow funding of diagnostic genetic testing of material harvested during hospitalisation or archival material

**Table I.** List of genetic tests in selected cancers (solid tumours) conisdering the type of material, testing technology and treatment method

| No. [1] | Name [2] | ICD 10 [3] | Objective of genetic testing [4] | Genetic testing basic profile minimum requirements [5] | Testing methods [6] | Material [7] | Funding method / settlement product [8] | Recommended extended profile (including genes of the basic profile and additional recommended genes), including markers significant for clinical trials [9] | Testing method [10] | Funding method [11] | Drug programme drugs as on 01.03.2023 [12] | Ministry of Health attachment no. [13] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. | treatment of gastrointestinal Stromal Tumours (GIST) | C15, C16, C17, C18, C20, C48 | qualification for targeted therapies[1] differential diagnosis[2] | *(KIT, PDGFRA)*[1,2] | sanger sequencing or NGS panel | • tissue – paraffin block<br>• peripheral blood – in rare selected cases for assessment of germinal mutations | • 5.53.01.0005001 simple or 5.53.01.0005002 complex genetic tests in cancers (material harvested during hospitalisation or archival out-patient material) – in-patient treatment contract, or<br>• 5.10.00.000041 comprehensive genetic diagnostics of cancers – separately contracted services | *(KIT, PDGFRA)*[1,2] *(KRAS, NRAS, PIK3CA)2, BRAF*[1,2]*, SDHA/B/C/D*[2]*, NTRK3 (fusions)*[1,2]*, FGFR1 (fusions)*[1,2]*, BRAF (fusions)*[1,2] | • NGS panel<br>• FISH (fluorescent in situ hybridisation),<br>• MLPA,<br>• aCGH micromatrices | • 5.53.01.0005003 advanced genetic tests in cancers on archival material (out-patient mode) – in-patient agreement | imatinib<br>sunitinib<br>sorafenib | B.3 |
| 2. | treatment of soft-tissue sarcomas | C48, C49 | qualification for targeted therapies[1] differential diagnosis[2] | basic panel: *EWSR1, SS18, FOXO1, FUS, PDGFB, MDM2* (amplification), USP6, DDIT3 | FISH (fluorescence *in situ* hybridisation), NGS panel recommended methods:<br>• typical cases are covered by FISH method testing (individual rearrangements),<br>• NGS panel – in the case of complex differential diagnostics | • tissue – paraffin block<br>• peripheral blood – in rare selected cases for assessment of germinal mutations | • 5.53.01.0005001 simple or 5.53.01.0005002 complex genetic tests in cancers (material harvested during hospitalisation or archival out-patient material) – in-patient treatment contract, or<br>• 5.10.00.000041 comprehensive genetic diagnostics of cancers – separately contracted services | diagnostics: *(BCOR; CAMTA1; CIC; CSF1; CTNNB1; EPC1; ERG; ESR1; EWSR1; FOS; FOSB; FOXO1; FUS; GLI1; HMGA2; JAZF1)*[2] *(MDM2)*[1,2]*; (MEAF6; MET; MGEA5; MKL2; MYOD1; NCOA1; NCOA2; NR4A3; NUTM1; PAX3)*[2]*; (PDGFB)*[1,2]*; (PHF1; PLAG1; PRKCA; PRKCB; PRKCD; RAF1; SS18; STAT6; TAF15; TCF12; TFE3; TFG; USP6; VGLL2; YAP1; YWHAE, and others)*[2] targeted therapy: *(ALK; BRAF)*[1,2]*; EGFR2; (FGFR1, FGFR2, FGFR3)*[1]*, (NTRK1; NTRK2)*[2]*; NTRK3*[1,2]*; (RET; ROS1 and others)*[1] | • NGS panel (gene fusions), or<br>• in selected cases comprehensive genome profiling (CGP): SNP, CNV, gene fusions, amplifications, gene signatures – MSI, TMB | no refund by the National Health Fund | trabectedin<br>pazopanib<br>sunitinib | B.8 |
| 3. | treatment of non-small-cell lung cancer and mesothelioma of the pleura | C34 C45 | qualification for targeted therapies[1] differential diagnosis[2] | *(EGFR, KRAS* (p.Gly12Cys), *ALK, ROS1)*[1] immunohistochemistry testing | qPCR, FISH (fluorescence *in situ* hybridization), sanger sequencing, NGS panel recommended method: NGS panel | • tissue – paraffin block<br>• peripheral blood – in rare selected cases for assessment of germinal mutations | • 5.53.01.0005001 simple or 5.53.01.0005002 complex or 5.53.01.0005003 advanced genetic tests in cancers (material harvested during hospitalisation or archival out-patient | *(EGFR, KRAS , BRAF, HER2, ALK, ROS1, RET, NTRK1-3, MET,* and other, gene signatures TMB)[1] | • NGS panel (gene fusions), or<br>• in selected cases comprehensive genome | NGS panel of tissue or cytology preparation:<br>• 5.53.01.0005003 advanced genetic tests in cancers on | crizotinib<br>osimertinib<br>nivolumab<br>pembrolizumab | B.6 |

**Table I. cd.** List of genetic tests in selected cancers (solid tumours) conisdering the type of material, testing technology and treatment method

| [1] | [2] | [3] | [4] | [5] | [6] | [7] | [8] | [9] | [10] | [11] | [12] | [13] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | (e.g. PD-1 or PD-L1 expression degree) | | • cytology preparations (cyto-blocks or smears on glass)<br>• ctDNA:<br>1. *EGFR* testing selected mutations in exons 18,19,20,21 – in the case of nondiagnostic material or no material,<br>2. treatment monitoring – testing mutations of p.Thr790Met in *EGFR*,<br>3. complex genetic profiling with ctDNA (extended profile) | material) – in-patient treatment contract, or<br>• 5.10.00.000041 comprehensive genetic diagnostics of cancers – separately contracted services | | profiling (CGP): SNP, CNV, gene fusions, amplification, gene signa tures – MSI, TMB | archival material (out-patient mode) – in-patient agreement,<br>• comprehensive genome profiling (CGP) – no refund | dacomitinib<br>lorlatinib<br>entrectinib<br>cemiplimab<br>ipilimumab<br>durvalumab<br>brigatinib<br>ceritinib<br>nintedanib<br>alectinib<br>atezolizumab<br>afatinib | |
| 4. | treatment of bone cancers | C48-C49 | qualification for targeted therapies[1] differential diagnosis[2] | *TP53*[2], *CDK4*[2], *(MDM2)*[1,2], *RB1*[2], *IDH1/2*[2], *GNAS*[2], *(H3.3A)*[1,2], *H3.3B*[2], *BCOR*[2], *NR4A3*[2] | FISH (fluorescence *in situ* hybridization), NGS panel <u>recommended methods</u>:<br>• FISH technique – typical cases, individual tests,<br>• NGS panel – complex differential diagnosis | • tissue – paraffin block<br>• peripheral blood – in rare selected cases for assessment of germinal mutations | • 5.53.01.0005001 simple or 5.53.01.0005002 complex genetic tests in cancers (material harvested during hospitalisation or archival out-patient material) – in-patient treatment contract,<br>• 5.10.00.000041 comprehensive genetic diagnostics of cancers – separately contracted services | (*PTEN, FOS, FOSB, TF3, CAMTA1, NCOA2, PHF1, CSF1*)[2], TMB[1] | • extended NGS panel (gene fusions), or<br>• in selected cases comprehensive genome profiling (CGP): SNP, CNV, gene fusions, amplification, gene signatures – MSI, TMB | no refund by the National Health Fund | | |
| 5. | treatment of melanoma of the skin or mucosa | C43 | qualification for targeted therapies[1] differential diagnosis[2] | *BRAF*[1] 600 codon mutations, *NRAS*[2], *KIT*[1,2], (*GNAQ, GNA11*)[2], *TERT2* promoter gene | sanger sequencing, NGS panel <u>recommended methods:</u><br>• qPCR for quick diagnosis of mutations in 600 codon of the BRAF gene in the tissue and ctDNA; | • tissue – paraffin block<br>• peripheral blood – in rare selected cases for assessment of germinal mutations<br>• cytology preparations (cyto-blocks) | • 5.53.01.0005001 simple tests in cancers (material harvested during hospitalisation or archival out-patient material) – in-patient treatment contract,<br>• in the case of testing multiple genes possible application of 5.53.01.0005002 complex genetic tests in | *BRAF*[1], *NRAS*, *KIT*[1,2], *(GNAQ, GNA11, CTNNB1, MAP2K1, NF1, PIK3CA, PTEN, TP53)*[2], *NTRK1-3*[1], genome signature TMB[1] | • NGS panel (gene fusions), or<br>• in selected cases comprehensive genome profiling (CGP): SNP, CNV, gene fusions, amplification, | • 5.53.01.0005003 advanced genetic tests in cancers on archival material (out-patient mode) – in-patient agreement, | ipilimumab<br>nivolumab<br>pembrolizumab<br>vemurafenib<br>cobimetinib<br>dabrafenib<br>trametinib | B.59 |

**Table I. cd.** List of genetic tests in selected cancers (solid tumours) conisdering the type of material, testing technology and treatment method

| [1] | [2] | [3] | [4] | [5] | [6] | [7] | [8] | [9] | [10] | [11] | [12] | [13] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | • Val600 variant verification by Sanger sequencing | • ctDNA liquid biopsy | cancers (material harvested during hospitalisation or archival out-patient material) – in-patient treatment contract,<br>• 5.10.00.000041 comprehensive genetic diagnostics of cancers – separately contracted services | | gene signatures – MSI, TMB | • comprehensive genome profiling (CGP) – no refund | encorafenib<br>binimetinib | |
| 6. | treatment of patients with ovarian cancer, fallopian tube cancer or peritoneal cancer | C56, C57, C48 | qualification for targeted therapies[1]<br>differential diagnosis[2]<br>prophylaxis[3] | *BRCA*[1]<br>*BRCA2*[1]<br>*HRD*[1] | *BRCA1, BRCA2* – NGS panel results verification by Sanger sequencing. **Note!** When a pathogenic variant is identified in tissue material of neoplastic origin, the genetic testing result should be delivered to the genetics office for verification in peripheral blood, if the variant is somatic or germinal. This is especially significant for prophylaxis for the patient's family. Genetic testing for a drug programme is requested by a clinical oncologist. If the patient has already had a genetic test result from a genetics office, it may be used for verifying eligibility for the drug programme | • tissue – paraffin block<br>• peripheral blood – verification or no tissue | • 5.53.01.0005003 advanced genetic tests in cancers (material harvested during hospitalisation or archival out-patient material) – in-patient treatment contract, or<br>• in the case of HRD: comprehensive genetic profiling (CGP) – no refund | (*BRCA1, BRCA2*)[1] HRD[1], (*BRAF, KRAS, PDGFRA, FOXL2,TP53*)[2] | • NGS panel, or<br>• in selected cases comprehensive genome profiling (CGP): SNP, CNV, gene fusions, amplification, gene signatures – HRD, TMB | • 5.53.01.0005003 advanced genetic tests in cancers on archival material (out-patient mode) – in-patient agreement,<br>• in the case of HRD: comprehensive genome profiling (CGP) – no refund | olaparib<br>niraparib | B.50 |

**Table I. cd.** List of genetic tests in selected cancers (solid tumours) conisdering the type of material, testing technology and treatment method

| [1] | [2] | [3] | [4] | [5] | [6] | [7] | [8] | [9] | [10] | [11] | [12] | [13] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 7. | treatment of the renal cancer | C64 | qualification for targeted therapies[1] differential diagnosis[2] | • somatic: (*VHL*, *TSC1*, *TFE3* (fusions), *TFEB* (fusions), *ELOC*)[2], *ALK* (fusions)[1,2], *SMARCB1*[2], • germinal: *VHL*,*FH* , *TSC1*/*TSC2*, *SDHB*/*C*/*D*, *PTEN*, *BAP1*, *MET*, *FLCN* | NGS panel, small targeted panels to assess mutations and fusions NGS panel of peripheral blood, <u>recommended method</u>: NGS panel | • tissue – paraffin block • peripheral blood in selected cases of suspicion of genetic form | • 5.53.01.0005003 advanced genetic tests in cancers (material harvested during hospitalisation or archival out-patient material) – in-patient treatment contract | (*PRBM1*, *BAP1*, *SET2D*, *KDMC5*, *TP53*, *PTEN*, *TET*, *ARID1A*, *TERT* promoter, *FOXI1*, *RHCG*, *MET*)[2] | • NGS panel | • 5.53.01.0005003 advanced genetic tests in cancers on archival material – in-patient agreement | sunitinib<br>everolimus<br>sorafenib<br>pazopanib<br>axitinib<br>nivolumab<br>ipilimumab<br>temsirolimus<br>cabozantinib | B.10 |
| 8. | treatment of castrate-resistant prostate cancer | C61 | qualification for targeted therapies[1] differential diagnosis[2] prophylaxis[3] | *BRCA1*[1] *BRCA2*[1] | <u>recommended methods</u>: • NGS panel to assess the status of genes BRCA1, BRCA2BRCA1, BRCA2 – verification of results by Sanger sequencing **Note!** For the purposes of targeted therapy in the drug programme, *BRCA1*, *BRCA2* testing is recommended by a clinical oncologist and based on archival material. If the tissue material is unavailable or non-diagnostic, *BRCA1*, *BRCA2* testing by liquid biopsy should be | • tissue – paraffin block • ctDNA – no tissue • peripheral blood - verification | • 5.53.01.0005003 advanced genetic tests in cancers (material harvested during hospitalisation or archival out-patient material) – in-patient treatment contract, or • 5.10.00.000041 comprehensive genetic diagnostics of cancers – separately contracted services | *BRCA1*[1] , *BRCA2*[1] *PTEN*[2], *AR*[1] | • NGS panel of cancer tissue, or • in the case of no material available or non-diagnostic material, the NGS panel should be used applying ctDNA | ctDNA – no refund | olaparib<br>enzalutamide<br>radium dichloride Ra 223<br>apalutamide<br>cabazitaxel<br>daratumumab | B.56 |

**Table I. cd.** List of genetic tests in selected cancers (solid tumours) conisdering the type of material, testing technology and treatment method

| [1] | [2] | [3] | [4] | [5] | [6] | [7] | [8] | [9] | [10] | [11] | [12] | [13] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | recommended (ctDNA). Currently liquid biopsy tested is not funded by the National Health Fund | | | | | | | |
| 9. | treatment of patient with urothelial cancer (urinary bladder) | C67 | qualification for targeted therapies[1] differential diagnosis[2] | *FGFR1/2/3*[1] | recommended methods: NGS panel to assess nucleotide level mutations, gene fusions, amplifications | • tissue – paraffin block | • 5.53.01.0005003 advanced genetic tests in cancers (material harvested during hospitalisation or archival out-patient material) – in-patient treatment contract | (*RB1, CDKN2A, TP53, KDM6A, ELF3, ERCC2, CDKN2B, PIK3CA, EGFR, ERBB2/3/4*)[2], TMB[1] | • NGS panel | • 5.53.01.0005003 advanced genetic tests in cancers (out-patient or in-patient harvesting of material) – in-patient agreement | avelumab | B.141 |
| 10. | treatment of the breast cancer | C50 | qualification for targeted therapies[1] prophylaxis[3] | *BRCA1*[1;2] *BRCA2*[1;2] *PIK3CA*[1] *HER2*[1] | *BRCA1, BRCA2* – NGS panel result verification by Sanger sequencing *PIK3CA* – recommended qPCR panel *HER2* – IHC method (in selected cases verification by FISH) **Note!** Genetic testing of *BRCA1; BRCA2* in peripheral blood (germinal mutations) for a drug programme is requested by a clinical oncologist. If a pathogenic variant is identified, the patient should be referred to a genetics office so that the patient's family is covered | • peripheral blood – *BRCA1, BRCA2, PALB2, CHEK2*<br>• tissue or ctDNA – PIK3CA<br>• tissue – NTRK1-3 – paraffin block<br>• tissue – gene signature TMB | • 5.10.00.000041 comprehensive genetic diagnostics of cancers – separately contracted services,<br>• 5.53.01.0005003 advanced genetic tests in cancers (material harvested during hospitalisationl) – in-patient treatment contract, or<br>• testing mutations in *BRCA1, BRCA2, PALB2, CHEK2* genes with NGS technique – separately contracted services | (*BRCA1, BRCA2, HER2, PIK3CA, ESR1, PALB2, CHEK2, NTRK,*)[1,3] | • NGS panel | • 5.10.00.000041 comprehensive genetic diagnostics in cancers – separately contracted services<br>• no refund of advanced panels or out-patient material harvesting | trastuzumab emtansine<br>lapatinib<br>pertuzumab<br>palbociclib<br>ribociclib<br>abemaciclib<br>alpelisib<br>talazoparib<br>sacituzumab govitecan | B.9 |

**Table I. cd.** List of genetic tests in selected cancers (solid tumours) conisdering the type of material, testing technology and treatment method

| [1] | [2] | [3] | [4] | [5] | [6] | [7] | [8] | [9] | [10] | [11] | [12] | [13] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | by prophylactic care. If the patient already has a genetic test result from a genetics office, it may be used for verifying eligibility for the drug programme | | | | | | | |
| 11. | treatment of the advanced colon cancer | C18, C19, C20 | qualification for targeted therapies[1] differential diagnosis[2] | (*KRAS, NRAS, BRAF, MSI* – microsatellite instability)[1] | sanger sequencing, qPCR, recommended method: qPCR | • tissue – paraffin block<br>• in rare selected cases peripheral blood can be applied for assessment of germinal mutations<br>• ctDNA | • 5.53.01.0005002 complex genetic tests in cancers (material harvested during hospitalisation or archival out-patient material) – in-patient treatment contract, or<br>• 5.10.00.000041 comprehensive genetic diagnostics of cancers – separately contracted services, or<br>• in the case of peripheral blood material – ctDNA: *KRAS, NRAS, BRAF* | gene status assessment: (*ALK, BRAF*)[1], *BRCA1/2, EGFR, ERBB2 (HER2)*[1], *FGFR1, MET, MLH1, MSH2, MSH6, NRG1, PIK3CA, PMS2, POLE, PTEN, RET, ROS1, KRAS, NRAS* | • NGS panel | • 5.53.01.0005003 advanced genetic tests in cancers (out-patient archival material) – in-patient agreement,<br>• comprehensive genome profiling (CGP) – no refund | cetuximab<br>panitumumab<br>aflibercept<br>trifluridine + tipiracil<br>ipilimumab<br>nivolumab<br>pembrolizumab | B.4 |
| 13. | treatment of the pancreatic cancer | C25.4 | qualification for targeted therapies[1] differential diagnosis[2] prophylaxis[3] | *BRCA1*[1,3] *BRCA2*[1,3] | recommended methods: NGS panel to assess the status of *BRCA1, BRCA2* genes **Note!** Genetic testing of *BRCA1; BRCA2* in peripheral blood (germinal mutations) for a drug programme is requested by a clinical oncologist. If a pathogenic variant is identified, the patient should be referred to a genetics office so | • peripheral blood – *BRCA1, BRCA2* | • 5.10.00.000041 comprehensive genetic diagnostics of cancers – separately contracted services | (*KRAS, SMAD4, FGFR1/2/3*)[2] (*GNAS, CDKN2A*)[2] | • NGS panel | • 5.53.01.0005003 advanced genetic tests in cancers (material harvested during hospitalisation or out-patient archival material) – in-patient agreement | everolimus<br>sunitinib | B.53 |

**Table I. cd.** List of genetic tests in selected cancers (solid tumours) conisdering the type of material, testing technology and treatment method

| [1] | [2] | [3] | [4] | [5] | [6] | [7] | [8] | [9] | [10] | [11] | [12] | [13] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | that the patient's family is covered by prophylactic care | | | | | | | |
| 14. | treatment of the advanced oesophageal and gastric cancer | C15, C16, C17, C18, C20, C48 | qualification for targeted therapies[1] differential diagnosis[2] | *HER2* assessment[1] | FISH (fluorescence *in situ* hybridization) | • tissue – paraffin block | • 5.53.01.0005001 simple genetic tests in cancers (material harvested during hospitalisation or archival out-patient material) – in-patient treatment contract, or<br>• 5.10.00.000041 comprehensive genetic diagnostics of cancers – separately contracted services | *BRAF, EGFR, HER2*[1], *FGFR2, KIT, KRAS, MET, NRG1, PIK3CA, PDGFR, TP53* | • NGS panel | • 5.53.01.0005003 advanced genetic tests in cancers (material harvested during hospitalisation or out-patient archival material) – in-patient agreement | nvolumab<br>pembrolizumab<br>ramucirumab | B.58 |
| 15. | central nervous system | C71 | qualification for targeted therapies[1] differential diagnosis[2] | (*IDH1, IDH2*)[2], *MGMT* promoter methylation[1], 1p/19q2 co-deletion | sanger sequencing, qPCR, FISH (fluorescence *in situ* hybridization), pyrosequencing | • tissue – paraffin block | • 5.53.01.0005003 advanced genetic tests in cancers (material harvested during hospitalisation or archival out-patient material) – in-patient treatment contract, or<br>• 5.10.00.000041 comprehensive genetic diagnostics of cancers – separately contracted services | (*IDH1, IDH2*)[2], promoter methylation MGMT[1], co-deletion 1p/19q[2], EGFR (amplification)[1,2], (*CDKN2A/B* (homozygotic deletion), mutation in the TERT gene promoter, *H3.3* (mutation), cytogenetic assessment of chromosome +7/–10)[2], fusions of BRAF, EGFR, (ROS1, ALK, NTRK1/2/3)[1, 2], and other fusions associated with neoplasms of the central nervous system | • NGS panel<br>• FISH (fluorescent in situ hybridisation),<br>• MLPA,<br>• aCGH micromatrices | • 5.53.01.0005001 simple, 5.53.01.0005002 complex, or 5.53.01.0005003 advanced genetic tests in cancers (material harvested during hospitalisation or out-patient archival material) – in-patient agreement,<br>• comprehensive genome profiling (CGP) – no refund | | |
| 16. | thyroid cancers | C73 | qualification for targeted therapies[1] differential diagnosis[2] *prophylaxis*[3] | *BRAF*[1,2], (*KRAS, NRAS, PIK3CA, TERT*)[2], (*RET, NTRK3*)[1] *RET*[3] DNA level mutations | qPCR, NGS panel <u>recommended methods</u>:<br>• NGS panels | • tissue – paraffin block<br>• peripheral blood – germinal | • 5.53.01.0005003 advanced genetic tests in cancers (material harvested during hospitalisation or archival out-patient material) – in-patient treatment contract, or | none | | | | |

**Table I. cd.** List of genetic tests in selected cancers (solid tumours) conisdering the type of material, testing technology and treatment method

| [1] | [2] | [3] | [4] | [5] | [6] | [7] | [8] | [9] | [10] | [11] | [12] | [13] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | • qPCR recommended for fast *BRAF* diagnostics | mutations (in some cases) | • 5.10.00.000041 comprehensive genetic diagnostics of cancers – separately contracted services | | | | | |
| 17. | neoplasms of unknown primary origin | C80 | qualification for targeted therapies[1] differential diagnosis[2] | (*EGFR, KRAS, BRAF, NTRK1/2/3, ALK, ROS1*)[1,2] | NGS panel | • tissue – paraffin block<br>• ctDNA | • 5.10.00.000041 comprehensive genetic diagnostics of cancers – separately contracted services<br>• the test is not funded within the hospitalisation agreement due to lack of C80 diagnosis in attachment no. 7 | | | • comprehensive genome profiling (CGP) – no refund | | |
| 18. | treatment of the endometrial cancer | C54 | qualification of molecular subtype associated with prognosis and treatment[2] | *POLE*[2], *MSI*[2] | sanger sequencing, capillary electrophoresis | • tissue – paraffin block | • 5.53.01.0005001 simple genetic tests in cancers (material harvested during hospitalisation or archival out-patient material) – in-patient treatment contract, or<br>• 5.53.01.0005002 ccomplex genetic tests in cancers (material harvested during hospitalisation or archival out-patient material) – in-patient treatment contract | (*POLE, TP53, MSH2, MSH6, MLH1, PMS2, BRCA1, BRCA2, CTNNB1, MSI* signature)[2] | • NGS panel | • 5.53.01.0005003 advanced genetic tests in cancers (material harvested during hospitalisation or out-patient archival material) – in-patient agreement | dostarlimab not included in any drug programme | none |
| 19. | treatment of patients with solid tumours with neurotrophic receptor tyrosine kinase (NTRK) fusions | ICD10 in solid tumours with *NTRK* fusion, tested upon qualification by a Coordination Team for Treatment of Solid Tumour Patients | qualification for targeted therapies[1] | (*NTRK1, NTRK2, NTRK3* – gene fusions)[1] | recommended method: NGS (RNA-seq) | • tissue – paraffin block | • 5.53.01.0005003 advanced genetic tests in cancers (material harvested during hospitalisation or archival out-patient material) – in-patient treatment contract, or<br>• 5.10.00.000041 comprehensive genetic diagnostics of cancers – separately contracted services | *NTRK1, NTRK2, NTRK3* – gene fusions on the ctDNA level | • NGS panel with ctDNA | • comprehensive genome profiling (CGP) with ctDNA – no refund | larotrectinib | B.144 |

for diagnostic testing was an in-patient procedure. A change was introduced early in 2018 with introduction of a possibility to settle out-patient genetic diagnostic tests in cancers performed on archival material which could have been harvested by other providers. In this case, we apply product 5.52.01.0001511: genetic testing of archival material. The product's value is 0, but it allows reporting and settlement of genetic tests: simple, complex and advanced ones, if the treatment plan has to be modified. The service concerning genetic testing of archival material (code 5.52.01.0001511) is meant for out-patient procedures, but it is settled within an in-patient agreement. It is also obligatory to report the original date of harvesting of the material for testing.

Further, reimbursement of costs of genetic testing in cancers can be based on other agreements concluded between service providers and the National Health Fund:

1. Agreements concerning separately contracted services (SOK), which may fund tests on material harvested during an out-patient or in-patient diagnostic procedure as product (5.10.00.000041) – complex genetic diagnostics of cancers – 534 points.
2. The least favourable financial settlement involves an agreement concerning out-patient specialist care with settlement product (5.03.00.000021) – RNA/DNA detection with molecular tests (PCR/PFGE) – 300 points.
3. In the case of haemato-oncological drug programmes, it is admissible to settle genetic testing during qualification for drug programmes with so-called diagnostic lump amount.
4. Additionally, since September 2022 some service providers may perform specific genetic tests within a programme of care for families with high risk of hereditary breast cancer or ovarian cancer, as well as colon cancer or endometrial cancer.

Table I presents discussion of genetic diagnostics for particular cancers along with methods and type of funding.

**Conflict of interests:** Andrzej Tysarowski, Anna Szumera-Ciećkiewicz, Andrzej Marszałek, Artur Kowalik, Katarzyna Seliga, Mariusz Bidziński, Lucjan Wyrwicz, Radosław Mądry, Adam Płużański, Magdalena Sakowicz, Maciej Krzakowski – non reported. Elżbieta Senkus-Konefka obtained remuneration from: AstraZeneca, Cancérodigest, Curio Science, Egis, Eli Lilly, Exact Sciences, Gilead, high5md, MSD, Novartis, Oncompass Medicine, Pfizer, Pierre Fabre, Roche; travel support: Amgen, Egis, Gilead, Novartis, Pfizer, Roche; contracted research: Amgen, AstraZeneca, Eli Lilly, Novartis, OBI Pharma, Pfizer, Roche, Samsung; medical writing: AstraZeneca, Eli Lilly; royalties: Springer; president of: Stowarzyszenie Różowy Motyl; stock: AstraZeneca, Eli Lilly, Pfizer. Piotr Rutkowski obtained remuneration for lectures and participation in advisory boards: BMS, MSD, Novartis, Pierre Fabre, Sanofi, Merck, Philogen i AstraZeneca (no impact on the content of the paper). Tomasz Kubiatowski obtained remuneration for lectures: BMS, Novartis, Gilead (no impact on the content of the paper).
Funding: AstraZeneca grant

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*Received: 21 Mar 2023*
*Accepted: 28 Mar 2023*

## References

1. Sąsiadek M, Łaczmańska I, Maciejczyk A, et al. Fundamentals of personalised medicine in genetic testing-based oncology. Nowotwory. Journal of Oncology. 2020; 70(4): 144–149, doi: 10.5603/njo.2020.0029.
2. Stembalska A, Pesz K. The role of genetic counselling in oncology. Nowotwory. Journal of Oncology. 2022; 72(3): 207–210, doi: 10.5603/njo.2022.0030.
3. Viana RV, Wallis CL. Good Clinical Laboratory Practice (GCLP) for Molecular Based Tests Used in Diagnostic Laboratories. Wide Spectra of Quality Control. 2011, doi: 10.5772/23963.
4. Pieńkowska-Grela B, Chorostowska-Wynimko J, Cybulski C, et al. Wytyczne dla laboratoriów genetyki nowotworów litych. Biuletyn PTO NOWOTWORY. 2016; 1(2): 184–189.
5. Richards S, Aziz N, Bale S, et al. ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015; 17(5): 405–424, doi: 10.1038/gim.2015.30, indexed in Pubmed: 25741868.
6. Langfort R, Marszałek A, Ryś A (ed.). Patomorfologia: standardy i przykłady dobrej praktyki oraz elementy diagnostyki różnicowej. Wytyczne dla zakładów/pracowni patomorfologii. http://pol-pat.pl/index.php/2020/08/29/standardy-i-wytyczne-w-patomorfologii/.
7. Kutaj-Wąsikowska H, Marszałek A (ed.). Program akredytacji. Jednostki Diagnostyki Patomorfologicznej – zestaw standardów. https://www.cmj.org.pl/patomorfologia/04_zestaw-standardow-akredytacyjnych--dla-jdp.pdf.
8. Walewski J, Dziurda D, Bidziński M, et al. Consensus on methods of development of clinical practice guidelines in oncology under the auspices of Maria Sklodowska-Curie National Research Institute of Oncology and the Agency for Health Technology Assessment and Tariff System. Nowotwory. Journal of Oncology. 2022; 72(1): 44–50, doi: 10.5603/njo.2022.0005.

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Guidelines and recommendations

NOWOTWORY Journal of Oncology
2023, volume 73, number 3, 187–197
DOI: 10.5603/OCP.2023.0018

ISSN: 0029–540X, e-ISSN: 2300-2115
www.nowotwory.edu.pl

# Expert opinion on adjuvant treatment with osimertinib in patients with non-small cell lung carcinoma after radical tumor resection

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## Introduction

Lung cancer is the most common cause of cancer-related deaths in Poland, accounting for approximately 18% of deaths in women and 26% in men [1]. Non-small cell lung cancer (NSCLC) accounts for 80–85% of all primary lung cancers. Improving the effectiveness of treatment of NSCLC patients is important to reduce the total absolute number of deaths due to malignancies. The diagnosis of NSCLC in its early stages enables radical resection, which is the most effective treatment method. This is reflected in the 5-year survival rates, which for stages I–III are: I 73–90%, II 56–65%, and III 12–41% [2]. Surgical treatment achieves significantly better results than other methods, but it is not curative in all patients. The reason is the appearance of local recurrences and distant metastases, the frequency of which (25–50%) depends on cancer stage and other factors [3]. The above data justify the use of adjuvant treatment in NSCLC patients undergoing complete resection. Until recently, systemic adjuvant treatment consisted solely of chemotherapy with platinum-based regimens (3–4 cycles). The value of adjuvant chemotherapy was confirmed by the results of the LACE (lung adjuvant cisplatin evaluation) meta-analysis. The use of chemotherapy was associated with a reduction in the risk of death by 11% and an increase in the probability of 5-year survival by 5.3% [4]. Adjuvant postoperative chemotherapy is currently recommended in patients after resection of NSCLC in stages II and III, while adjuvant radiotherapy is only recommended in the case of incomplete tumor resection [5].

Breakthrough discoveries of the last two decades including the identification of specific molecular targets in NSCLC cells, evaluation of tumor cell expression of molecules that block anticancer T-cell activity, and introduction of targeted drugs significantly improved the prognosis of patients with locally advanced (stage IIIB) and disseminated (stage IV) NSCLC. These drugs are more effective and associated with a lower risk of side effects than chemotherapy. One of the most important groups is the next generation of tyrosine kinase inhibitors (TKI) targeting the epidermal growth factor receptor (EGFR) [6]. Demonstrating the effectiveness of TKI-EGFR in patients with advanced NSCLC naturally raised the question of the possibility of using

**How to cite:**

The article is a reprint. The original version should be quoted: Langfort R, Krzakowski M, Kowalski DM, Krenke R, Orłowski T, Rzyman W, Wasąg B. ***Expert opinion on adjuvant treatment with osimertinib in patients with non-small cell lung carcinoma after radical tumor resection.*** *Oncol Clin Pract.* DOI: 10.5603/OCP.2023.0018.

these drugs in adjuvant treatment in patients with stage I–IIIA undergoing radical surgical resection. To clarify this issue, a multicenter Phase III study was planned and conducted to evaluate the efficacy of adjuvant treatment with osimertinib (ADAURA, Adjuvant Therapy for EGFR Mutant Early-Stage NSCLC). The highest quality of the study (placebo-controlled, randomized, double-blinded) allowed for obtaining reliable and convincing results that are extremely important for clinical practice. In the group of patients with stage II–IIIA, in whom the presence of an activating *EGFR* gene mutation was confirmed in the postoperative material, treatment with osimertinib was associated with a significant increase in the percentage of patients who survived 24 months without recurrence of the disease (osimertinib 90% versus placebo 44%) [7]. A similar result was obtained for a wider group with stage IB–IIIA (89% and 49%, respectively) [8].

The unequivocal results of the ADAURA study justified a positive opinion of the Food and Drug Administration (FDA) issued in December 2020 regarding the use of osimertinib in the adjuvant treatment of patients with NSCLC with adenocarcinoma morphology or NSCLC with a predominant adenocarcinoma component undergoing radical resection, with confirmed *EGFR* gene mutations. In April 2021, the European Medicines Agency (EMA) also issued a positive decision.

From January 1, 2023, the National Health Fund introduced reimbursement of osimertinib treatment in the above indication under therapeutic drug program B.6. "Treatment of patients with lung cancer and pleural mesothelioma".

This document presents four key aspects for obtaining a positive therapeutic effect after adjuvant treatment with osimertinib in patients with lung adenocarcinoma or NSCLC with a predominant adenocarcinoma component undergoing surgical resection, such as:

1. surgical treatment and securing postoperative material for further examinations;
2. pathomorphological assessment of postoperative material;
3. identification of activating mutations in the *EGFR* gene;
4. recommendations for adjuvant treatment with osimertinib in the postoperative period.

## Surgical treatment of patients with NSCLC. Securing surgical material for further evaluation

Resection of lung parenchyma is the treatment of choice in NSCLC patients in stages I and II and selected patients in stage III, in whom the functional state of the respiratory and cardiovascular systems allows for radical surgery. The recommended type of surgery for patients in stages I–IIIA who are eligible for surgical treatment is lobectomy.

A smaller resection than a lobectomy is indicated only in patients with limited respiratory reserves or with other comorbidities that do not allow for a more extensive procedure. According to the recommendations of the International Association for the Study of Lung Cancer (IASLC), each anatomical resection should be supplemented with the resection of appropriate hilar and mediastinal lymph node stations [9]. The impact of the extent of lymphadenectomy on the results of surgical treatment has not been definitively established, but a more extensive excision of the lymphatic system allows for a more complete postoperative tumor staging and facilitates qualification for adjuvant treatment [9, 10].

Regional lymph nodes for lung cancer include 14 nodal stations located above the diaphragm, in the chest, as well as subscalene and supraclavicular nodes.

**The postoperative material should contain at least 6 lymph nodes, including 3 mediastinal (N2) lymph nodes, among them bifurcation (subcarinal) lymph nodes, and 3 hilar and intrapulmonary (N1) lymph nodes.**

**The required number of removed nodes is related to the assessment of the radicality of the resection.**

The main principles of lung cancer radical resection are presented in table I.

### *Principles of sending postoperative material for pathomorphological examination*

Postoperative material sent to the Pathomorphological Diagnostics Unit (PDU) requires appropriate protection enabling good fixation of the material and a properly completed referral form.

The material covering a lobe, lobes, a lung, or a fragment of a lung and lymph nodes should be placed in disposable plastic containers intended for this purpose, meeting the requirements of an *in vitro* diagnostic (IVD) medical device adapted to the size of the collected material and enabling proper fixation.

The required fixative is a 10% buffered formalin solution with a neutral pH (7.2–7.4). Depending on the rules agreed with PDU regarding the submission of material for pathomorphological evaluation, it is also possible to send unfixed material immediately after collection.

**Table I.** Principles of radical resection of lung cancer

| Principles of radical resection of lung cancer |
|---|
| tumor resection (lobectomy, bilobectomy, less often pneumonectomy or sublobar resection) together with the regional lymphatic system |
| block resection in cases of tumor infiltration of adjacent tissue structures with marking the margins, which is important for microscopic radicality assessment |
| lymphadenectomy involving at least 6 lymph nodes: hilar (N1) and mediastinal (N2) with marking the lymph node located highest in the mediastinum in relation to the tumor |

**The resected and secured material must be delivered to the PDU within 72 hours of the end of the surgical procedure, preferably within 48 hours [11–13].**

Tissue elements of importance for staging and assessment of surgery radicality (e.g. fragments of the pericardium, diaphragm, chest wall) or lesions that may be difficult to find during material preparation by a pathologist (e.g. ground-glass nodules, GGNs) should be marked in a way that allows for identification and proper collection of samples for microscopic evaluation [11, 12].

Each collected lymph node of a given station sent for pathomorphological examination should be placed in a separate container. This applies especially to fragmented material due to the risk of incorrect determination of the number of removed lymph nodes [14].

The attached referral form for pathomorphological examination should contain all data allowing for the identification of the patient and the material sent. Information on the type of procedure performed, the type of material collected, date and time of collection, and placement in the fixative is necessary. Clinical data on the current disease, location of lesions, and past medical history, especially regarding oncological diseases, including pathomorphological diagnosis and treatment, are also necessary [11–13].

Depending on the rules adopted at the center, it is possible to include information in the referral form about the need to provide material for *EGFR* gene status assessment, if required qualification criteria for adjuvant treatment with osimertinib are met.

### *Principles of sending surgical material for testing mutations in the* EGFR *gene*

In patients with primary lung adenocarcinoma or another morphological form of NSCLC diagnosed in the postoperative material with a predominance of adenocarcinoma tissue (≥ 50%) and meeting the eligibility criteria for treatment with osimertinib (disease stage IB–IIIA, radical surgery R0), *EGFR* gene status should be determined. The procedure for sending for *EGFR* gene status testing may vary, which results from different organizational protocols adopted in individual units. Possible protocols include sending for *EGFR* gene status testing by:

- the surgeon who operated, together with attached consent to perform the genetic test or information about consent expressed by the patient, obtained upon admission to the hospital;
- a designated person responsible for analysis of the results of all pathomorphological tests in the thoracic surgery center, together with attached consent to perform the genetic test or information about consent expressed by the patient, obtained upon admission to the hospital;
- a pathologist evaluating the postoperative material, provided that the information about the need to assess *EGFR* gene mutation was included in the referral form for pathomorphological examination.

## Pathomorphological examination of surgical material in patients qualified for osimertinib treatment

The pathomorphological examination of surgical material from lung cancer patients aims to determine its morphological form and histological differentiation grade as well as to assess prognostic factors, tumor stage (pTNM, tumor, nodes, metastasis), and radicality of surgical procedure.

A key prerequisite for establishing a pathomorphological diagnosis is compliance with the rules covering the initial preparation of the material and the phase of pathomorphological diagnosis in accordance with the recommendations of the Polish Society of Pathologists (PSP) and accreditation standards developed for PDU by PSP in 2021 in cooperation with the National Centre for Quality Assessment in Healthcare [11–13].

### *Macroscopic and microscopic examination of postoperative material*

The post-operative material submitted to the PDU requires preliminary processing, allowing for proper preservation and preparation for the collection of specimens.

Macroscopic assessment includes examining the tumor with three dimensions in millimeters, determining the exact location in relation to the bronchus and pleura and distance from the edges of bronchus and vessels cutoff and the pulmonary pleura. The assessment of the peripheral lung parenchyma for the presence of atelectasis and inflammation, determining their extent, and the presence of additional nodular lesions is also important for disease staging [11, 15–18].

The number of specimens to be taken for microscopic examination depends on the type of material sent and the size of the lesion. Due to the heterogeneity of lung cancers, especially adenocarcinomas, it is recommended to use the principle of collecting 1 biopsy/1 cm of tumor [15, 16]. Tumors up to 3 cm in diameter, which on computed tomography (CT) of the chest are described as GGN or ground-glass nodules with consolidation, suggesting the possibility of proliferation of adenocarcinoma *in situ* (AIS) or minimally invasive adenocarcinoma (MIA) require examination of the entire lesion.

The material should be taken both from all places that are important for cancer staging as well as from the areas constituting the edges of the surgical resection and, if relevant, also the margin covering the resection edge with the tumor [15–18].

In the material covering the lobe, lobes, or lung, it is important to find and assess the lymph nodes in the area of the bronchovascular border and intrapulmonary (station N1) [16–18].

### *Pathomorphological classification of lung adenocarcinoma*

More than 50% of non-small cell carcinomas are adenocarcinomas. The adenocarcinoma component is also present in adenosquamous NSCLC, which accounts for 2–3% of all

lung cancers; it can occur both in the so-called pleomorphic carcinomas (approximately 1%) and combined large-cell neuroendocrine carcinomas. The criteria for the diagnosis of individual morphological forms of lung cancer are strictly defined by the current 5th edition of 2021World Health Organization (WHO) classification (Thoracic Tumours) [19].

Pathomorphological diagnosis of lung adenocarcinoma should take into account all morphological components present in its structure and determine the degree of histological differentiation [grading – G].

**The microscopic diagnosis of lung adenocarcinomas is based on:**

- **finding morphological features of glandular differentiation (the presence of papillae, micropapillary and acinar structures visible on standard H+E staining) and/or**
- **the presence of mucus in tumor cells detected by histochemical examination (e.g. mucicarmine) and/or**
- **expression of immunohistochemical markers of glandular differentiation (TTF-1, napsin A) [19].**

The principles for determining the malignancy grade of lung adenocarcinomas refer to non-mucous forms and take into account the dominant morphological type and component of cancer tissue considered poorly differentiated, that is micropapillary, solid, with a complex glandular pattern. This term includes adenocarcinomas with the structure containing the so-called cribriform and fine-tubular, trabecular structures, often trapped in the fibrosing stroma [20].

The assessment of pleural infiltration is important in cancer staging. Therefore, in cancers located peripherally and adjacent to the pleura, it is necessary to perform an additional examination that stains the elastic fibers (e.g. elastic van Gieson method, EvG), enabling a precise assessment of the relationship of the tumor to elastic membranes of pleura, determining its possible infiltration (tab. II). The examination also visualizes blood vessels, which facilitates the identification of neoplastic emboli in the vessel lumen [21].

## *System of clinical (cTNM) and pathomorphological (pTNM) staging of lung cancer*

Selection of the optimal therapeutic option for patients with lung cancer requires accurate staging based on the classification system (8th edition) that includes three important elements:

- T (tumor) determination of tumor size and its localization in relation to anatomical structures (tab. III);
- N (nodes) assessment of the condition of lymph nodes;
- M (metastasis) information about the presence or absence of distant tumor metastases.

Clinical (c) and pathomorphological (p) TNM classifications do not differ from each other and are based on similar assumptions, and the final staging of the disease requires a correlation of both systems [2, 22].

*Additional morphological features affecting the assessment of tumor size pT*

- With regard to non-mucinous lepidic adenocarcinomas, the 8th edition of the TNM classification recommends assessment of the invasive component as corresponding to pT with the simultaneous specification of the total size of the lesion (invasive component/total tumor size). In the assessment of the invasive component and the determination of tumor size (pT), the correlation of microscopic changes with the CT image is helpful. The CT examination also facilitates the determination of tumor size in cases of fragmentation of the lesion and difficulties in distinguishing irregular foci that raise the suspicion of two separate foci [23].
- Multifocal lesions:
  - with similar morphology should be treated as a separate additional (satellite) lesion or metastasis (depending on the location);
  - with different morphology and different histological components, should be treated as separate primary (synchronous) lesions and classified separately;
  - multifocal adenocarcinoma with AIS, MIA, and lepidic foci should be classified based on the largest lesion with assessing the number of foci;
  - diffuse pneumonic-type adenocarcinoma is usually characterized by mucinous or mixed mucinous and serous adenocarcinoma foci (pT3 if unilateral; pT4 if multiple ipsilateral lobes; M1a if applies to the lobes on the opposite side).

*Assessment of regional lymph nodes (N)*

The assessment of regional lymph nodes (N disease) is presented in table IV.

Metastases in lymph nodes 10–14 on the primary tumor side are classified as N1.

Metastases limited to midline nodes and mediastinal lymph nodes on tumor side (stations 2–9) are classified as N2.

Involvement of lymph nodes on the primary tumor side and contralateral side within station 1 and stations 2, 4–6, and 8–14 on the contralateral side is classified as N3.

Pathomorphological evaluation of lymph nodes requires determination of the number of lymph nodes examined at a given station and size of individual nodes, assessment of the condition of the node capsule (including possible tumor infiltration), the extent of metastases, the identification of the so-called micrometastases and isolated tumor cells, and the presence of necrotic foci [16, 17]. Involvement of the lymph node(s) by neoplastic infiltration, the so-called "through-continuity" infiltration, is treated as a metastasis to the lymph node [2, 22].

According to the American Joint Committee on Cancer (AJCC) TNM recommendations specifying the required number of collected lymph nodes essential to determine the radica-

**Table II.** Microscopic assessment of pleural infiltration [21]

| Category | Definition |
|---|---|
| PL0 | no infiltration of pulmonary pleura<br>the tumor is separated from the pleura by the lung parenchyma or does not cross the elastic lamina of the pulmonary pleura |
| PL1 | the cancer infiltration exceeds the elastic lamina of the pulmonary pleura |
| PL2 | the cancer infiltration covers the entire thickness of the lung pleura and exceeds its surface |
| PL3 | the cancer infiltration penetrates the parietal pleura or chest wall |

**Table III.** Assessment of primary tumor (T feature)

| Category | Definition | |
|---|---|---|
| TX | primary tumor cannot be assessed, or tumor is indicated by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy | |
| T0 | no evidence of primary tumor | |
| Tis | carcinoma *in situ* | |
| T1 | tumor 3 cm or less in greatest dimension, surrounded by the lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e. not in the main bronchus) | |
| T1mi | minimally invasive adenocarcinoma (MIA) | solitary adenocarcinoma (≤3 cm) with a predominant lepidic pattern with an invasive component ≤5 mm in the greatest dimension, without necrosis, pleural infiltration, alveolar filling (STAS) |
| T1a | tumor 1 cm or less in greatest dimension | this includes superficially spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus |
| T1b | tumor more than 1 cm but not more than 2 cm in greatest dimension | |
| T1c | tumor more than 2 cm but not more than 3 cm in greatest dimension | |
| T2 | tumor more than 3 cm but not more than 5 cm<br>or<br>tumor with any of the following features:<br>• involves the main bronchus, regardless of distance to the carina, but without involvement of the carina<br>• invades the visceral pleura<br>• associated with atelectasis or obstructive pneumonitis that extends to the hilar region either involving part of or the entire lung | |
| T2a | tumor more than 3 cm but not more than 4 cm in greatest dimension | • infiltration of adjacent lobe through an interlobar fissure or directly if the fissure is not developed unless higher stage T criteria are met<br>• hilar adipose tissue infiltration unless higher stage T criteria are met |
| T2b | tumor more than 4 cm but not more than 5 cm in greatest dimension | |
| T3 | tumor more than 5 cm but not more than 7 cm in greatest dimension<br>or<br>one that directly invades any of the following:<br>• parietal pleura<br>• chest wall (including superior sulcus tumors)<br>• rib or ribs<br>• phrenic nerve<br>• parietal pericardium<br>or<br>separate tumor nodule(s) in the same lobe as the primary | |
| T4 | tumor more than 7 cm or of any size that invades any of the following:<br>• diaphragm, mediastinum, parietal pericardium, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, spine, carina<br>or<br>• tumor nodule(s) in a different ipsilateral lobe separate from that of the primary one | mediastinal adipose tissue infiltration<br>the term "great vessels" includes:<br>• aorta<br>• superior and inferior vena cava<br>• pulmonary trunk<br>• intrapericardial segments of the right/left pulmonary artery<br>• intrapericardial segments of the upper and lower pulmonary veins |

**Table IV.** Assessment of lymph nodes (N disease)

| Category | Definition |
|---|---|
| NX | regional lymph nodes cannot be assessed |
| N0 | no regional lymph node metastases |
| N1 | metastasis in the intrapulmonary lymph nodes, including involvement by direct extension (lymph nodes of 10–14 stations) |
| N2 | metastasis in the ipsilateral mediastinal and/or subcarinal lymph node(s) (lymph nodes of 2–9 stations) |
| N3 | metastasis in the:<br>• contralateral mediastinal<br>• or contralateral hilar<br>• or ipsilateral or contralateral scalene<br>• or ipsilateral or contralateral supraclavicular lymph node(s) (lymph nodes of 1 and 2, 4–6, and 8–14 contralateral stations) |

lity of the surgical procedure, it is necessary to find at least 3 lymph nodes of the N1 station in the surgical material covering the lobe, lobes, or lung.

Micrometastases are defined as neoplastic foci >0.2 to ≤2 mm in size, which in the pathomorphological examination report are described as "mi" (pNmi).

Single tumor cells or small clusters not larger than 0.2 mm detectable by standard hematoxylin and eosin (H+E) staining or immunohistochemistry (IHC) using mainly broad-spectrum cytokeratins or by other special methods, for example, flow cytometry or molecular testing, are referred to as isolated tumor cells (ITC). The finding of ITC does not adversely affect patient survival time and is defined as pN0 with information about their occurrence by marking as "i" or "mol" depending on the method of detection (pN0[i+], pN0[mol+]) [16, 22].

The neoplastic infiltration of the mediastinal lymph node capsule found in microscopic examination indicates a non-radical surgical procedure (pR1). The continuity of the capsule is not always trackable, depending to a large extent on the method of removing the nodes. While systematic lymphadenectomy allows excision of lymph nodes with a capsule, removal of node fragments (so-called sampling) usually does not allow for capsule assessment. The pathomorphological diagnosis then includes the information that "the evaluation of the node capsule is not possible, and the lymph node was removed in fragments".

*Assessment of distant metastases (M)*

Distant metastases include lesions other than the primary tumor and mediastinal lymph node lesions within the chest and outside the chest (tab. V).

The description of pM disease in the pathomorphological report requires confirmation by microscopic examination.

### *Evaluation of surgical radicality feature R*

The assessment of surgical radicality includes each margin of the performed resection and depends on the type of procedure performed. Most often, the margin consists of the bronchus/bronchi, blood vessels, lung parenchyma, mediastinal lymph nodes, and other elements of additionally removed tissues or organs. Surgical radicality is also specified as the absence of cancer cells in the fluid from the pleural and/or pericardial cavities collected during thoracotomy (pleural lavage cytology – PLC).

Surgical radicality is defined by the R feature (tab. VI) [2, 22, 24].

**The indicators of radical resection include [2, 22]:**

- **surgical cutoff margins free of neoplastic infiltration (R0);**
- **removal of the regional lymphatic system involving at least 6 lymph nodes (N1, N2), including lymph nodes of the tracheal bifurcation;**
- **absence of neoplastic infiltration beyond the lymph node capsule.**

The R0(un) feature includes an uncertain cutoff margin (uncertain resection) and applies to:

- estimated number of resected lymph nodes lower than required (<6);
- detection of cancer metastases in the superior resected mediastinal lymph node.

### *Pathomorphological diagnosis report*

The pathomorphological diagnosis report of surgical material with lung adenocarcinoma should include:

- diagnosis defining the morphological form of cancer, taking into account the percentage of individual tissue components, especially those considered to be less differentiated;
- ICD-O code;
- determination of the degree of cancer histological differentiation (G);
- type of material sent;
- macroscopic description;
- microscopic description, also taking into account prognostic factors: the presence of neoplastic emboli in the lymphatic and hematopoietic system, presence and extent of necrosis, infiltration of nerve fiber bands, stromal immunological reaction, stromal reaction, scar presence, spread through air spaces (STAS);
- assessment of surgical resection margins;

**Table V.** Assessment of metastasis (M disease)

| Category | Definition | |
|---|---|---|
| MX | distant metastasis cannot be assessed | |
| M0 | no distant metastasis | |
| M1 | distant metastasis | |
| M1a | nodule(s) in a contralateral lobe<br>nodule(s) in the ipsilateral pleura or parietal pleura<br>pericardial nodules or pericardium<br>malignant dissemination or neoplastic pleural or pericardial effusion[1] | nodule(s) located in the ipsilateral pulmonary and parietal pleura, unrelated to the primary tumor |
| M1b | single extrathoracic metastasis in a single organ | • this includes involvement of a single, distant, non-regional node<br>• metastatic lesion outside the parietal pleura in the chest wall |
| M1c | multiple extrathoracic metastases in a single or multiple organs | metastatic lesion not in contact with the primary tumor, outside the parietal pleura, located in the diaphragm |

[1]Pleural or pericardial fluid negative for cancer cells in cytological examination or blood admixture, non-exudative, should be classified as pM0

**Table VI.** Evaluation of surgical radicality (R feature)

| Category | Definition |
|---|---|
| Rx | surgical radicality cannot be assessed |
| R0 | no neoplastic infiltration in the dissection margins, radical surgery |
| R1 | microscopic examination reveals neoplastic infiltration:<br>• positive surgical margin[1]<br>• neoplastic infiltration exceeds the capsule of resected lymph nodes |
| R1(is) | carcinoma *in situ* at the surgical margin of the bronchus |
| R1(cy+) | no cancer infiltration at the surgical margin, cancer cells are present in the pleural or pericardial effusion collected during thoracotomy [pleural lavage cytology – PLC] |
| R2 | macroscopic neoplastic infiltration in the dissection margins |

[1]Malignant infiltration found in the margins of severed bronchi may occur as:
– infiltration of the bronchial wall;
– infiltration involving the peribronchial tissue (adventitia), also in continuity, spreading from nearby metastatic lymph nodes;
– cancer cells embolism in the lymphatic vessels of the bronchial mucosa

- assessment of margins covering the distance from resection margin to the neoplastic infiltration;
- assessment of the remaining lung parenchyma;
- evaluation of lymph nodes, including possible infiltration of the capsule;
- description of additional tests performed (histo- and immunohistochemical);
- information on qualification for *EGFR* gene mutation testing.

The report should end with the assessment of the pathomorphological stage of the tumor (pTNM) with additional prognostic features pV, pL, pR (pTNLVR) [16, 25]. It is advisable to attach the result of *EGFR* gene mutation testing to the pathomorphological diagnosis report.

### *Selection of material for the assessment of mutations in the* EGFR *gene*

The pathologist qualifies the material for testing using molecular biology methods, selecting the most reliable section containing an adequate number of cancer cells and, if possible, without necrosis and other changes that may adversely affect the test result.

The qualified material with a description of the pathomorphological diagnosis and information including the number of the selected paraffin block, and the adequacy of the material (number of cancer cells, number of cells in relation to other nucleated elements) is transferred to the molecular diagnostics department.

## Evaluation of activating mutations in the *EGFR* gene

According to the current recommendations, tests aimed at identifying mutations in the *EGFR* gene and analyzing PD-L1 protein expression level are the basis for the selection of adjuvant treatment methods in radically operated patients and should be performed in all NSCLC patients [26]. At the same time, there is a need to identify rearrangements in the *ALK* and *RET* genes and other rare molecular abnormalities that may have predictive and prognostic significance [27–31].

PD-L1 expression level is determined by immunohistochemistry. However, the identification of the *EGFR* gene variants can be performed using molecular biology techniques by quantitative polymerase chain reaction (qPCR) or next-generation sequencing (NGS). The tests used should detect all

mutations that have been reported, with a frequency of at least 1% in NSCLC patients with an *EGFR* gene variant [32].

Tests aimed at detecting deletions in exon 19 and p.L858R point mutations in exon 21 can be performed using the PCR technique [32]. Many commercial tests are now available, and the diagnostic process itself does not require advanced laboratory equipment. The advantage of the PCR test may be the short turnaround time (TAT) and the relatively low cost of the analysis. However, it should be remembered that these tests only detect specific variants in the *EGFR* gene.

According to the current guidelines of the European Society of Medical Oncology (ESMO), NGS should be used routinely in the diagnosis of advanced NSCLC [33]. The method not only allows for the simultaneous analysis of many biomarkers but is also a very effective tool for identifying *EGFR* gene variants. The results of the study conducted by Schrock et al. showed that the use of a specific NGS technique enables the detection of deletions in exon 19 of the *EGFR* gene in tissue material where previous standard diagnostic methods failed to identify these changes [34]. Another study by this group showed a higher efficiency of this technique compared to PCR in identifying not only deletions in exon 19 but also variants in the remaining exons (18, 20, and 21) of the *EGFR* gene [35].

Currently, studies (NCT04302025 and NCT04926831) are ongoing, which focus on identifying genetic variants in genes other than *EGFR* in radically operated patients. In the NCT04302025 study, molecular analyzes are conducted to detect rearrangements of the *ALK*, *NTRK1*, *RET*, and *ROS1* genes and point variants in the V600 codon of the *BRAF* gene [36]. In the latter study, patients were included in the study group based on exon 14 skipping mutation or *MET* gene amplification [37]. The need to identify various genetic variants (point mutations, deletions, insertions, rearrangements, or amplifications) in many genes is another argument for using the NGS method for routine diagnostics of all patients diagnosed with NSCLC. An additional justification is the fact that simultaneous biomarker analysis has been shown to be more effective than sequential testing using single-gene tests [38–41]. Sequential testing has been shown to produce more false positives (3.3%) than simultaneous analysis of several genes (1.4%), as each additional test increases the likelihood of a false positive result. At the same time, it was found that the sequential use of single-gene tests also increases the number of non-diagnostic results (sequential tests – 6.9% *vs.* NGS – 2.7%) [38]. The conducted studies have also shown that diagnostics using sequential tests have a negative impact on TAT or costs [38–40]. In addition, the use of multiple tests also increases the risk of material exhaustion before the end of the diagnostic process in individual patients [35, 38, 40].

## Osimertinib in adjuvant treatment after NSCLC radical resection

The value of osimertinib confirmed in patients with advanced NSCLC with the presence of activating mutations in the EGFR gene was the justification for conducting the phase III ADAURA study [7]. The ADAURA study involved 682 patients diagnosed with non-squamous cell lung cancer (adenocarcinoma 96%), who were randomly assigned to receive osimertinib 80 mg daily (n = 339) or placebo (n = 343) for 3 years. The study involved patients after radical resection of the lung parenchyma (pR0 in the postoperative pathomorphological examination), with confirmed an activating mutation in the *EGFR* gene (only a deletion in exon 19 or a substitution in exon 21). Adjuvant chemotherapy in the ADAURA study was allowed based on individually assessed indications before randomization, but radiotherapy was not allowed. The primary endpoint of the study was to assess disease-free survival in patients with stages IB–IIIA (secondary endpoints: assessment of benefits in individual postoperative stages and the overall population in terms of disease-free and overall survival, impact on quality of life and safety). Selected features of the assessed population are presented in table VII.

The first analysis of the ADAURA study results showed that endpoints were met – the use of osimertinib in the entire study population allowed for a significant reduction in the risk of death or disease recurrence by 80%. In postoperative stages II-IIIA, the rate was even more favorable and amounted to 83%. In the 2-year follow-up of patients with postoperative stages II–IIIA, 90% of patients receiving adjuvant treatment with osimertinib and 44% of patients receiving placebo were still alive without signs of disease recurrence (other results in tab. VIII) [7].

The cumulative risk of recurrence in the central nervous system (CNS) was significantly lower in the group of patients treated with osimertinib after a 24-month follow-up, 98% of patients receiving osimertinib had no brain metastases compared to 85% of patients in the placebo group (risk reduction by 82%; $p < 0.0001$). Local recurrences were reported in 7% of patients receiving osimertinib and 18% in the placebo group, and distant metastases in 4% and 28% of patients, respectively. Grade 3 or higher adverse reactions occurred in 20% of patients in osimertinib group and 13% in the placebo group. The most common adverse events (all grades) in the osimertinib arm versus placebo were diarrhea (46% *vs*. 20%), onychomycosis (25% *vs*. 1%), dry skin (19% *vs*. 6%), and pruritus (19% *vs*. 9%). The rate of treatment discontinuation due to adverse events was 11% and 3%, respectively [7].

Benefits associated with the use of osimertinib in terms of significant prolongation of disease-free survival were also noted in patients who received chemotherapy (84% risk reduction) and those who did not undergo chemotherapy (77% risk reduction) [8].

Longer follow-up of patients in the ADAURA study, presented during the ESMO Congress in 2022, confirmed the above-mentioned observations [8]. Median disease-free survival for patients with stage II and IIIA receiving osimertinib or placebo was 65.8 and 21.9 months, respectively, representing a 77% reduction in the risk of death or relapse. The percentage of pa-

**Table VII.** Characteristics of patients in the ADAURA study (selected features) [7]

| Features | Osimertinib [%] | Placebo [%] |
|---|---|---|
| postoperative stage – IB/II/IIIA | 32/34/35 | 32/34/34 |
| histological type – adenocarcinoma/other | 96/4 | 97/3 |
| performance status – 0/1 | 64/36 | 64/36 |
| *EGFR* gene mutation – ex19del/eks21sub/T790M | 55/45/1 | 55/45/1 |
| resection – lobectomy/other types | 97/3 | 94/6 |
| lymph nodes – N0/N1/N2 disease | 41/29/31 | 42/28/30 |
| adjuvant chemotherapy – yes/no | 60/40 | 60/40 |

ex19del – deletion in exon 19 of the *EGFR* gene; ex21sub – substitution in exon 21 of the *EGFR* gene; T790M – replacement of threonine with methionine in exon 20 of the *EGFR* gene

**Table VIII.** Phase III ADAURA study results [7]

| Index | Osimertinib | Placebo |
|---|---|---|
| median disease-free survival [months] | | |
| total patients (stages IB–IIIA) | not reached | 19.6 |
| patients in stages II and IIIA | not reached | 27.5 |
| reduction in the risk of death or recurrence [%] | | |
| total patients (stages IB–IIIA) | 80% ($p < 0.0001$) | |
| patients in stages II and IIIA | 83% ($p < 0.0001$ | |

tients living without recurrence of the disease reached 70% in the osimertinib group compared to 29% in the placebo group [42].

**The use of osimertinib in the adjuvant treatment after radical resection of the lung parenchyma (R0) is justified in patients with a diagnosis of adenocarcinoma or cancer with a predominance of adenocarcinoma in stages IB, II, and IIIA, with an activating mutation in the *EGFR* gene (only deletion in exon 19 or substitution in exon 21) independently of the expression of the programmed death ligand type 1 (PD-L1). This indication requires *EGFR* gene status testing in each patient with primary lung adenocarcinoma or NSCLC with a predominance of adenocarcinoma component undergoing complete resection (the assessment of PD-L1 status should be a second step after excluding the presence of mutations in the *EGFR* gene).**

Patients after incomplete resection (surgical margins with the presence of neoplastic cells R1 or R2) should receive chemotherapy (use of radiotherapy can be considered). In patients with stages II and IIIA after complete resection, apart from osimertinib, adjuvant postoperative chemotherapy should also be used, which should precede osimertinib (except for patients with real and documented contraindications to chemotherapy, which include, for example, kidney failure, neuropathy, and significant hearing impairment). In patients who do not receive adjuvant chemotherapy, the use of osimertinib should be started no later than 10 weeks after lung resection (it is advisable to start treatment as early as possible, provided that the result of *EGFR* gene status is known). In patients receiving adjuvant chemotherapy, osimertinib should be used no later than 26 weeks after surgery. Adjuvant treatment with osimertinib lasts up to 3 years. During the use of osimertinib, control tests should be performed (evaluation of treatment effectiveness and safety) in accordance with the summary of product characteristics (SmPC) and applicable B.6 program. Follow-up examinations after the completion of adjuvant treatment should be conducted in accordance with the currently applicable standard.

## Conclusions

New systemic therapies (molecularly targeted drugs and immune checkpoint inhibitors) are increasingly used in the radical management of cancer patients in combination with local treatment. The benefits of combining new drugs with surgery or radiotherapy also apply to NSCLC patients. The results of the ADAURA study, regardless of the lack of final OS results, justified the introduction of osimertinib to the standard of adjuvant postoperative treatment of NSCLC patients. The conditions for optimal use of osimertinib in adjuvant postoperative treatment include appropriate qualification for pulmonary parenchyma resection as well as pathomorphological and molecular diagnostics. Further studies are currently underway, the goals of which include, but are not limited to, identifying the optimal duration of osimertinib treatment, the use of anti-EGFR therapy in patients undergoing resection for very early stage (IA) NSCLC,

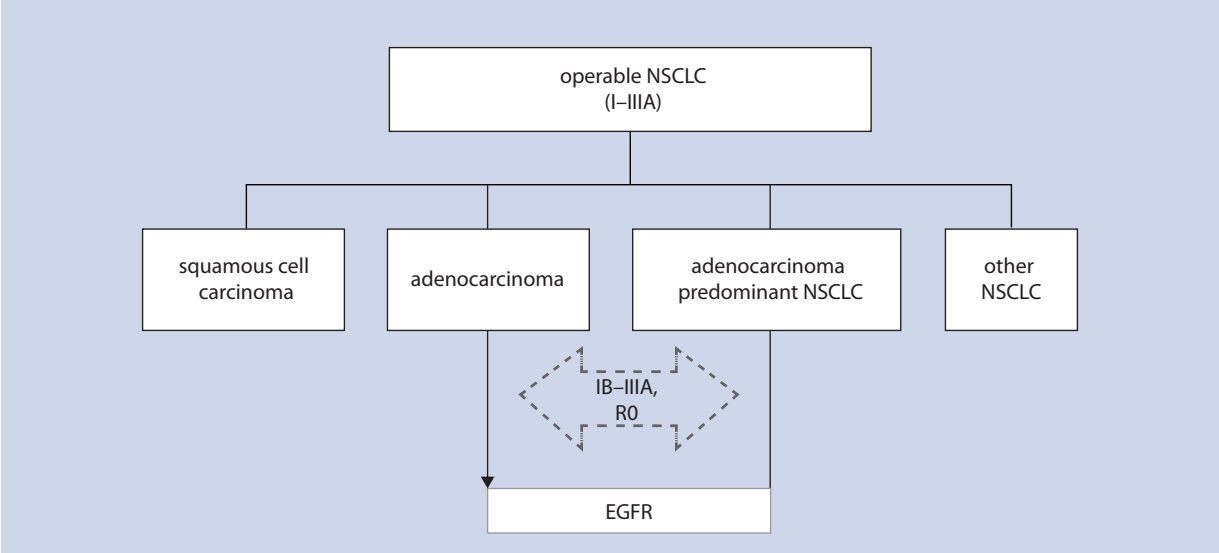


**Figure 1.** Qualification of patients treated surgically for adjuvant therapy with osimertinib; EGFR – epidermal growth factor receptor; NSCLC – non-small cell lung cancer

determining the value of longer use of osimertinib, and detecting resistance mechanisms and methods overcoming lower sensitivity to the drug (Fig. 1).

**Conflict of interest:** R.L.: advisory board or lecture fees from AstraZeneca, Roche, MSD, BMS, Takeda, Amgen, and Boehringer-Ingelheim. M.K.: lecture and consulting fees from AstraZeneca, Roche, Novartis, Eli Lilly, Pierre-Fabre, Gilead, and Boehringer-Ingelheim. D.K.: participation in advisory committees of AstraZeneca, BMS, MSD, Amgen, Pfizer, Takeda, Roche, Novartis, Sanofi-Aventis, Johnson&Johnson, and Boehringer-Ingelheim. R.K.: advisory board fees from AstraZeneca; for lectures from MSD and Boehringer-Ingelheim; covering the costs of participation in the WCLC (2022) and ELCC (2023) conferences by MSD. T.O.: participation in advisory committees or lectures for AstraZeneca, Roche, and Takeda. W.Rz.: participation in advisory committees for AstraZeneca, and Medtronic; travel grants from Siemens. B.W.: fees for attending advisory meetings or lectures from AstraZeneca, Amgen, Janssen, Roche, and Takeda.

Article funded by AstraZeneca.

*This article – by prior arrangement – was originally published in the journal "Oncology in Clinical Practice": Langfort R, Krzakowski M, Kowalski DM, et al. Expert opinion on adjuvant treatment with osimertinib in patients with non-small cell lung carcinoma after radical tumor resection. Oncol, Clin Pract. DOI: 10.5603/OCP.2023.0018.*

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## References

1. Wojciechowska U, Barańska K, Michałek I, et al. Nowotwory złośliwe w Polsce w 2020 roku. Krajowy Rejestr Nowotworów. Warszawa 2022. https://onkologia.org.pl/sites/default/files/publications/2023-01/nowotwory_2020.pdf.
2. Goldstraw P, Chansky K, Crowley J, et al. International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee, Advisory Boards, and Participating Institutions, International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee Advisory Boards and Participating Institutions. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2016; 11(1): 39–51, doi: 10.1016/j.jtho.2015.09.009, indexed in Pubmed: 26762738.
3. Karacz CM, Yan J, Zhu H, et al. Timing, Sites, and Correlates of Lung Cancer Recurrence. Clin Lung Cancer. 2020; 21(2): 127–135.e3, doi: 10.1016/j.cllc.2019.12.001, indexed in Pubmed: 31932216.
4. Pignon JP, Tribodet H, Scagliotti GV, et al. LACE Collaborative Group. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol. 2008; 26(21): 3552–3559, doi: 10.1200/JCO.2007.13.9030, indexed in Pubmed: 18506026.
5. Krzakowski M, Jassem J, Antczak A, et al. Thoracic neoplasms. Oncol Clin Pract. 2022; 18(1): 1–39, doi: 10.5603/OCP.2021.0022.
6. Sullivan I, Planchard D. Next-Generation Tyrosine Kinase Inhibitors for Treating -Mutant Lung Cancer beyond First Line. Front Med (Lausanne). 2016; 3: 76, doi: 10.3389/fmed.2016.00076, indexed in Pubmed: 28149837.
7. Wu YL, Tsuboi M, He J, et al. Osimertinib in Resected*EGFR*-Mutated Non–Small-Cell Lung Cancer. N Engl J Med. 2020; 383(18): 1711–1723, doi: 10.1056/nejmoa2027071.
8. Wu YL, John T, Grohe C, et al. Postoperative Chemotherapy Use and Outcomes From ADAURA: Osimertinib as Adjuvant Therapy for Resected EGFR-Mutated NSCLC. J Thorac Oncol. 2022; 17(3): 423–433, doi: 10.1016/j.jtho.2021.10.014, indexed in Pubmed: 34740861.
9. Lardinois D, De Leyn P, Van Schil P, et al. ESTS guidelines for intraoperative lymph node staging in non-small cell lung cancer. Eur J Cardiothorac Surg. 2006; 30(5): 787–792, doi: 10.1016/j.ejcts.2006.08.008, indexed in Pubmed: 16971134.
10. Darling GE, Allen MS, Decker PA, et al. Number of lymph nodes harvested from a mediastinal lymphadenectomy: results of the randomized, prospective American College of Surgeons Oncology Group Z0030 trial. Chest. 2011; 139(5): 1124–1129, doi: 10.1378/chest.10-0859, indexed in Pubmed: 20829340.
11. Patomorfologia: standardy i przykłady dobrej praktyki oraz elementy diagnostyki różnicowej. Wytyczne dla zakładów/pracowni patomorfologii 2020.
12. Standardy organizacyjne oraz standardy postępowania w patomorfologii. Wytyczne dla zakładów/pracowni patomorfologii 2020.
13. Program Akredytacji Jednostki Diagnostyki Patomorfologicznej. Zestaw standardów. CMJ, Kraków 2021.

14. Darling GE. Current status of mediastinal lymph node dissection versus sampling in non-small cell lung cancer. Thorac Surg Clin. 2013; 23(3): 349–356, doi: 10.1016/j.thorsurg.2013.05.002, indexed in Pubmed: 23931018.
15. Langfort R, Chyczewski L, Szołkowska M, et al. Płuco. Standardy oceny mikroskopowej materiału biopsyjnego i operacyjnego u chorych na nowotwory złośliwe. Pol J Pathol. 2015; 66(suppl. 1): 22–24.
16. Boyle DP, Allen DC. Histopathology reporting. Guidelines for surgical cancer. 4th ed. Springer. 2020.
17. Edge SB, Byrd DR, Compton CC. AJCC Cancer Staging Handbook. 7th ed. AJCC, Springer 2010.
18. Pfeifer JD, Humphrey PA, Ritter JH, Dehner LP. The Washington Manual of Surgical Pathology. 3rd ed. Wolters Kluwer, Philadelphia 2020.
19. WHO Clasification of Tumours Editorial Board. Thoracic tumours. In: WHO classification of tumours series, 5th ed.; vol. 5. International Agency for Research on Cancer, Lyon 2021.
20. Moreira AL, Ocampo PSS, Xia Y, et al. A Grading System for Invasive Pulmonary Adenocarcinoma: A Proposal From the International Association for the Study of Lung Cancer Pathology Committee. J Thorac Oncol. 2020; 15(10): 1599–1610, doi: 10.1016/j.jtho.2020.06.001, indexed in Pubmed: 32562873.
21. Travis WD, Brambilla E, Rami-Porta R, et al. International Staging Committee. Visceral pleural invasion: pathologic criteria and use of elastic stains: proposal for the 7th edition of the TNM classification for lung cancer. J Thorac Oncol. 2008; 3(12): 1384–1390, doi: 10.1097/JTO.0b013e31818e0d9f, indexed in Pubmed: 19057261.
22. Rami-Porta R. Staging Manual in Thoracic Oncology. 2nd ed. IASLC, North Fort Myers, FL 2016.
23. Travis WD, Asamura H, Bankier AA, et al. International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee and Advisory Board Members. The IASLC Lung Cancer Staging Project: Proposals for Coding T Categories for Subsolid Nodules and Assessment of Tumor Size in Part-Solid Tumors in the Forthcoming Eighth Edition of the TNM Classification of Lung Cancer. J Thorac Oncol. 2016; 11(8): 1204–1223, doi: 10.1016/j.jtho.2016.03.025, indexed in Pubmed: 27107787.
24. Rami-Porta R. The Evolving Concept of Complete Resection in Lung Cancer Surgery. Cancers (Basel). 2021; 13(11), doi: 10.3390/cancers13112583, indexed in Pubmed: 34070418.
25. Langfort R. Nowotwory klatki piersiowej. Rak płuca. In: Nasierowska-Guttmejer A, Górnicka B. ed. Zalecenia do diagnostyki histopatologicznej nowotworów. Centrum Onkologii, PTP 2013: 47–62.
26. Pisters K, Kris MG, Gaspar LE, et al. Adjuvant Systemic Therapy and Adjuvant Radiation Therapy for Stage I to IIIA NSCLC Guideline Expert Panel. Adjuvant Systemic Therapy and Adjuvant Radiation Therapy for Stage I-IIIA Completely Resected Non-Small-Cell Lung Cancer: ASCO Guideline Rapid Recommendation Update. J Clin Oncol. 2022; 40(10): 1127–1129, doi: 10.1200/JCO.22.00051, indexed in Pubmed: 35167335.
27. Solomon B, Ahn J, Barlesi F, et al. ALINA: A phase III study of alectinib versus chemotherapy as adjuvant therapy in patients with stage IB–IIIA anaplastic lymphoma kinase-positive (*ALK+*) non-small cell lung cancer (NSCLC). J Clin Oncol. 2019; 37(15_suppl): TPS8569–TPS8569, doi: 10.1200/jco.2019.37.15_suppl.tps8569.
28. Goldman J, Besse B, Wu Y, et al. P01.01 LIBRETTO-432: A Placebo-Controlled Phase 3 Study of Adjuvant Selpercatinib in Stage IB-IIIA RET Fusion-Positive NSCLC. J Thorac Oncol. 2021; 16(10): S975–S976, doi: 10.1016/j.jtho.2021.08.262.
29. https://www.clinicaltrials.gov/ct2/show/NCT04302025.
30. https://www.clinicaltrials.gov/ct2/show/NCT04926831.
31. Yuan M, Huang LL, Chen JH, et al. The emerging treatment landscape of targeted therapy in non-small-cell lung cancer. Signal Transduct Target Ther. 2019; 4: 61, doi: 10.1038/s41392-019-0099-9, indexed in Pubmed: 31871778.
32. Isla D, Lozano MD, Paz-Ares L, et al. New update to the guidelines on testing predictive biomarkers in non-small-cell lung cancer: a National Consensus of the Spanish Society of Pathology and the Spanish Society of Medical Oncology. Clin Transl Oncol. 2022 [Epub ahead of print], doi: 10.1007/s12094-022-03046-9, indexed in Pubmed: 36571695.
33. Mosele F, Remon J, Mateo J, et al. Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: a report from the ESMO Precision Medicine Working Group. Ann Oncol. 2020; 31(11): 1491–1505, doi: 10.1016/j.annonc.2020.07.014, indexed in Pubmed: 32853681.
34. Schrock AB, Frampton GM, Herndon D, et al. Comprehensive Genomic Profiling Identifies Frequent Drug-Sensitive EGFR Exon 19 Deletions in NSCLC not Identified by Prior Molecular Testing. Clin Cancer Res. 2016; 22(13): 3281–3285, doi: 10.1158/1078-0432.CCR-15-1668, indexed in Pubmed: 26933124.
35. Suh JH, Schrock AB, Johnson A, et al. Hybrid Capture-Based Comprehensive Genomic Profiling Identifies Lung Cancer Patients with Well-Characterized Sensitizing Epidermal Growth Factor Receptor Point Mutations That Were Not Detected by Standard of Care Testing. Oncologist. 2018; 23(7): 776–781, doi: 10.1634/theoncologist.2017-0493, indexed in Pubmed: 29540602.
36. https://www.clinicaltrials.gov/ct2/show/NCT04302025 (13.04.2023).
37. https://www.clinicaltrials.gov/ct2/show/NCT04926831 (13.04.2023).
38. Wolff HB, Steeghs EMP, Mfumbilwa ZA, et al. Cost-Effectiveness of Parallel Versus Sequential Testing of Genetic Aberrations for Stage IV Non-Small-Cell Lung Cancer in the Netherlands. JCO Precis Oncol. 2022; 6: e2200201, doi: 10.1200/PO.22.00201, indexed in Pubmed: 35834758.
39. Steeghs EMP, Groen HJM, Schuuring Ed, et al. PATH consortium. Mutation-tailored treatment selection in non-small cell lung cancer patients in daily clinical practice. Lung Cancer. 2022; 167: 87–97, doi: 10.1016/j.lungcan.2022.04.001, indexed in Pubmed: 35461050.
40. Dall'Olio FG, Conci N, Rossi G, et al. Comparison of Sequential Testing and Next Generation Sequencing in advanced Lung Adenocarcinoma patients - A single centre experience. Lung Cancer. 2020; 149: 5–9, doi: 10.1016/j.lungcan.2020.08.008, indexed in Pubmed: 32932213.
41. Kuang S, Fung AS, Perdrizet KA, et al. Upfront Next Generation Sequencing in Non-Small Cell Lung Cancer. Curr Oncol. 2022; 29(7): 4428–4437, doi: 10.3390/curroncol29070352, indexed in Pubmed: 35877212.
42. Tsuboi M, Wu YL, Grohe C, et al. Osimertinib as adjuvant therapy in patients with resected EGFR-mutated non-small-cell lung cancer: updated results from ADAURA. Ann Oncol. 2022; 33(suppl_7).

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NOWOTWORY Journal of Oncology
2023, volume 73, number 3, 198
DOI: 10.5603/NJO.a2023.0020

ISSN 0029–540X, e-ISSN: 2300-2115
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# Breast invasive carcinoma with a choriocarcinomatous pattern

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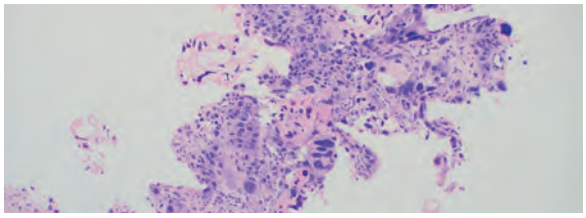

**Figure 1.** Core biopsy of breast carcinoma with a choriocarcinomatous pattern – both components of choriocarcinoma (cytotrophoblast-like and syncytiotrophoblast-like cells) are seen, staining H&E, x100 magnification

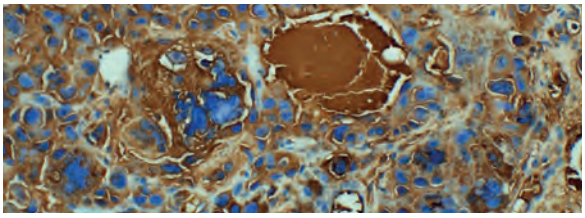

**Figure 2.** Core biopsy of breast carcinoma with choriocarcinomatous pattern – strong immunoreactivity for β-HCG in neoplasmatic cells, β-HCG immunostaining, x200 magnification

A 36-year old female was diagnosed with a breast infiltrating duct carcinoma, NOS, G2, luminal B *HER2*-neg, metastatic to the lymph nodes, lungs, liver and bones. She received ribociclib, fulvestrant and LHRH analog for 15 months with partial remission. For personal reasons the patient interrupted therapy for 4 months, but reported afterwards due to rapid progression. A core-biopsy revealed no presence of usual infiltrating duct carcinoma, but unequivocal choriocarcinomatous differentiation with mononuclear cytotrophoblast-like cells with hyperchromatic nuclei and multinucleated syncytiotrophoblast-like giant cells (fig. 1) and strong cytoplasmatic immunoreactivity for β-HCG (fig. 2). Pathologist suggested either a rare variant of invasive breast carcinoma with a choriocarcinomatous pattern or metastatic choriocarcinoma to the breast. Metastatic progression was seen; pregnancy, as well as primary choriocarcinoma were excluded; total β-HCG was 80,000 mU/ml. The patient received cisplatin plus etoposide with moderate clinical improvement and rapid decrease of β-HCG level. Invasive carcinoma of the breast with a choriocarcinomatous pattern is an extremely rare subtype of breast cancer listed in the WHO classification, with only few cases reported [1]. Systemic treatment was adjusted to the updated histopathological diagnosis. No optimal chemotherapy regimen is defined so far, and prognosis is unclear in advanced cases [3].

## References

1. WHO Classification of Tumours, Editorial Board. Breast Tumours, 5th edition. International Agency for Research on Cancer, Lyon 2019.
2. Jun SY, Yoon N, An S, et al. Clinicopathologic and Molecular Characteristics of and Diagnostic Dilemmas in Invasive Breast Carcinoma with Choriocarcinomatous Pattern apropos a New Case: A Literature Review with New Findings. Pathobiology. 2022; 89(6): 359–369, doi: 10.1159/000522621.

**How to cite:**

Wysocka JB, Lompart J, Pietruszka A, Puskulluoglu M, Grela-Wojewoda A. ***Breast invasive carcinoma with a choriocarcinomatous pattern***. *NOWOTWORY J Oncol* 2023; 73: 198.

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NOWOTWORY Journal of Oncology
2023, volume 73, number 3, 199
DOI: 10.5603/NJO.a2023.0010

ISSN 0029–540X, e-ISSN: 2300-2115
www.nowotwory.edu.pl



# Malignant neoplasm of the sigmoid colon found accidentally during a routine gynecological examination

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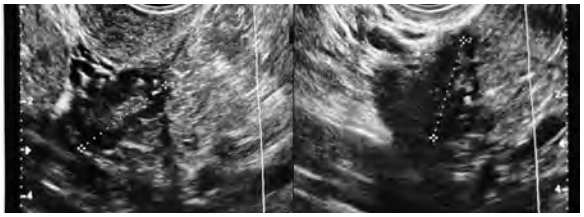

**Figure 1.** Transvaginal ultrasound, echopositive structure behind the uterus

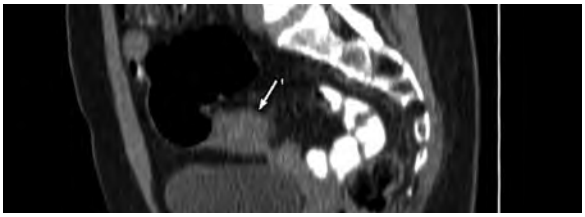

**Figure 2.** CT of the abdominal cavity of the pelvis without contrast, segmental thickening of the sigmoid colon

The patient underwent a routine gynecological examination with cytology every year. During 1 appointment, the gynecologist noticed and described a well-defined structure with a positive echo behind the uterus, measuring 22x24 mm in the transvaginal ultrasound (fig. 1). This structure aroused the oncological vigilance of the gynecologist performing the examination. Further diagnostics were recommended, during which a colonoscopy was performed, which revealed a tumor clamping the lumen of the sigmoid colon. In the next stage, a CT scan of the abdominal cavity and pelvis, without any contrasting agent, was performed (fig. 2). The examination revealed a thickening of the colon wall at the level of the initial segment of the sigmoid colon. The patient was qualified for surgical resection of the sigmoid colon. Histopathological examination of the excised tumor confirmed the diagnosis of pT3N1aM0 sigmoid adenocarcinoma. The patient underwent a cycle of adjuvant chemotherapy. This case shows that regardless of the medical specialty, attention should be paid to changes in other organs, including those that are not directly examined. Most colorectal cancers are diagnosed in older patients, over 70 years of age [1]. This patient was in her 50s at diagnosis, so it can be concluded that one should be vigilant for cancer, even if the patient is not directly in the high-risk age group. In this patient, the tumor was asymptomatic and accidental detection enabled the implementation of treatment that led to remission. If the gynecologist had ignored the lesion revealed in the transvaginal ultrasound, most likely the tumor would have been detected at the inoperable stage and, subsequently, only palliative treatment would be possible. In the available literature, one can find information that the only early detection of the disease presents an opportunity for remission [2].

## References

1. Kenig J. Colon cancer in the older population. Nowotwory. Journal of Oncology. 2021; 71(2): 119–121, doi: 10.5603/njo.2021.0025.
2. Salibasic M, Pusina S, Bicakcic E, et al. Colorectal Cancer Surgical Treatment, our Experience. Med Arch. 2019; 73(6): 412–414, doi: 10.5455/medarh.2019.73.412-414, indexed in Pubmed: 32082011.

**How to cite:**

Stopińska K, Marzec A, Olejek A. ***Malignant neoplasm of the sigmoid colon found accidentally during a routine gynecological examination***. *NOWOTWORY J Oncol* 2023; 73: 199.

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