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## Aims and Scope

### *Aims*

**The Indonesian Journal of Cancer Control** aims to contribute towards better knowledge as a result of scientific studies that can be accessed by academic circles and researchers.

### *Scope*

**The Indonesian Journal of Cancer Control** is a scientific quadrimester journal, managed by the Indonesian Society of Oncology. This journal is designed as a place of dissemination of information and scientific knowledge. It publishes original articles, case reports or case series, and review articles. These comprise of biomedical science, clinical medicine, public health science, and medical science education in the cancer field.

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The InaJCC with its distinguished, diverse, and Indonesian & International-wide team of editors, reviewers, and readers, ensure the highest standards of research communication within the cancer control community across Indonesia as well as globally. The InaJCC accepts manuscripts on the whole spectrum of cancer control.

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Editorial

# Is 5-Fluorouracil Cream Chemoprevention for Actinic Keratoses

According to the National Population-Based Cancer Registry, skin cancer accounted for 2.5% of all malignancies in Indonesia between 2013 and 2017. Non-melanoma skin cancer (NMSC) is more common than melanoma.[1] Sunscreen is essential for preventing skin cancer as a primary chemopreventive measure, while secondary chemoprevention helps suppress and reverse carcinogenesis (agents could be administered topically or systemically). Tertiary chemoprevention aims to reduce recurrence and metastasis.[2]

Actinic keratosis (AK) is a very common neoplastic intraepidermal squamous proliferative lesion associated with ultraviolet radiation exposure and characterized by squamous dysplasia. AKs may remain stable, regress spontaneously, or progress to invasive squamous cell carcinoma (SCC). According to the ICD-O coding of skin tumours, AK is a premalignant keratosis and a precursor of skin tumours.[3] Currently, topical 5-fluorouracil (5-FU) cream, diclofenac sodium gel, imiquimod cream, ingenol mebutate gel, and tirbanibulin have been approved by the FDA for the treatment of AK.[2]

Compared with other targets of secondary chemoprevention, the skin is easily accessible. 5-FU is a chemotherapeutic drug that acts as a pyrimidine analogue by being misincorporated into RNA and DNA in place of uracil or thymine, thereby causing the death of rapidly proliferating cells. The topical use of fluorouracil has a selective cytotoxic effect on actinically damaged skin, while normal skin is relatively unaffected.[4] Walker JL et al. (2017) found that topical 5-FU for AKs remained effective after treatment was discontinued, with more than a 60% decrease in the number of new AKs on the face and ears at 6 months, and the effect persisted for at least 2 years.[5] Weinstock MA et al. (2018) conducted a study of 5-FU treatment for AKs on the face and ears and found that it reduced the need for surgery for SCC for 1 year without significantly increasing the risk of BCC.[6]

Further studies are needed to provide evidence that 5-FU could be used as chemoprevention for AK, since 5-FU is efficacious, inexpensive, practical, and has manageable adverse effects. Therefore, any treatment that reduces the development of SCC or other keratinocyte carcinomas could be cost-effective and decrease the tumour burden.

***Aida SD Hoemardani***

References

1. Suzanna E. Dharmais Cancer Registration (internet). Jakarta: Hospital Based Cancer Registration;2024 (Downloaded March 15th, 2025). Available from: https://cancerreg.rskdharmais.go.id/
2. Ren J, Yan G, Yang L, Kong L, Guan Y, Sui H et al. Cancer chemopreventions: signalling pathways and strategic approaches. Signal Transduct. Target Ther. 2025;10:113
3. WHO Classification of Tumours Editorial Board. Skin Tumours. 5th ed. Lyon: International Agency for Research on Cancer;2025.p.30-1
4. Cassale J, Patel P. Fluorouracyl. StatPearls . NCBI Bookself-file (Internet).2024.
5. Walker JK, Siegel JA, Sachar M, Pomerantz H, Chen SE, Swetter SM et al. 5-Fluorouracil for actinic keratosis treatment and chemoprevention: A randomized controlled trial. J Invest Dermatol.2017;1367-70.
6. Weinstock MA, Thwin SS, Siegel JA, Marcolivio K, Means AD, Leader NF et al. Chemoprevention of basal and squamous cell carcinoma with a single course of fluorouracil, 5%, cream. JAMA Dermatol.2018;154(2):167-74.

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Original Article

# The effectiveness of chemopreventive therapies in reducing non-melanoma skin cancer

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## Abstract

**Introduction:** Non-melanoma skin cancer (NMSC) is the most common type of skin cancer and has a significant impact on patient quality of life. Effective prevention of NMSC is essential to reduce the incidence of skin cancer. One approach that has been developed is chemopreventive therapy, which uses pharmacological agents to inhibit or delay the development of cancer.
**Objective:** To assess the effectiveness of various chemopreventive therapies, such as nonsteroidal anti-inflammatory drugs (NSAID), difluoromethylornithine (DFMO), vitamin D3, nicotinamide, and acitretin, in reducing the incidence of NMSC.
**Methods:** Systematic literature review with a search for articles in the PubMed and Google Scholar databases, using the keywords "chemopreventive" and "non melanoma skin cancer". The inclusion criteria were that articles had the same objectives and results as the objectives of this study. Five articles that met the inclusion criteria were used in this analysis.
**Results:** This study showed that NSAIDs, DFMO, vitamin D3, nicotinamide, and acitretin significantly reduced the incidence of NMSC. The use of NSAIDs reduced the risk of BCC, DFMO showed a decrease in the incidence of new NMSC, vitamin D3 reduced BCC recurrence, nicotinamide reduced the incidence of new NMSC, and acitretin was effective in preventing invasive SCC.
**Conclusion:** Chemopreventive therapy can be an effective strategy in reducing the incidence of non-melanoma skin cancer.

***Keywords:*** *basal cell carcinoma, chemopreventive, non-melanoma skin cancer, squamous cell carcinoma.*

## Abstrak

**Pendahuluan:** Kanker kulit non-melanoma merupakan jenis kanker kulit yang paling sering ditemukan dan memiliki dampak signifikan terhadap kualitas hidup pasien. Upaya pencegahan yang efektif sangat penting untuk menurunkan insidens kanker kulit. Salah satu pendekatan yang telah dikembangkan adalah terapi kemopreventif, yaitu penggunaan agen farmakologis untuk menghambat atau menunda perkembangan kanker.
**Tujuan:** Menilai efektivitas berbagai terapi kemopreventif, seperti NSAID, DFMO, vitamin D3, nikotinamid, dan asitretin, dalam menurunkan insidens kanker kulit non-melanoma.
**Metode:** Tinjauan pustaka sistematis dengan penelusuran artikel pada basis data PubMed dan Google Scholar menggunakan kata kunci *"chemopreventive"* dan *"non melanoma skin cancer"*. Kriteria inklusi meliputi artikel yang memiliki tujuan dan luaran yang sesuai dengan tujuan penelitian ini. Sebanyak lima artikel yang memenuhi kriteria inklusi dianalisis dalam penelitian ini.
**Hasil:** Hasil penelitian menunjukkan bahwa NSAID, DFMO, vitamin D3, nikotinamid, dan asitretin secara signifikan menurunkan insidens kanker kulit non-melanoma. Penggunaan NSAID menurunkan risiko terjadinya BCC, DFMO menunjukkan penurunan insidens NMSC baru, vitamin D3 menurunkan kekambuhan BCC, nikotinamid menurunkan insidens NMSC baru, serta asitretin efektif dalam mencegah terjadinya SCC invasif.
**Kesimpulan:** Terapi kemopreventif dapat menjadi strategi yang efektif dalam menurunkan insidens kanker kulit non-melanoma.

***Keywords:*** *kanker kulit non-melanoma, karsinoma sel basal, karsinoma sel skuamosa, kemopreventif*

## Background

Cancer Non-melanoma skin cancer or Non-Melanoma Skin Cancer (NMSC) is the most commonly diagnosed type of malignant skin tumor throughout the world. This disease is mostly caused by exposure to ultraviolet (UV) radiation.[1] More than 95% of NMSC cases appear in the head and neck area, such as the nose, ears, eyelids, and lips. NMSC consists of two main types, namely squamous cell carcinoma (SCC) and basal cell carcinoma (BCC).[2]

According to the Surveillance, Epidemiology, and End Results (SEER) program, NMSC, although it does not have a significant impact on the number of cancer deaths, its incidence continues to increase with age.[2] As of 2019, it was found that globally there were more than 6 million new cases of NMSC, of which 4 million were BCC and the rest were SCC.[3,4] Based on other data from the Global Cancer Observatory (GLOBOCAN), the highest incidence of NMSC is in North America (49%) and the highest mortality is in Asia (43.6%).[2]

In Indonesia, there has not been much research on the prevalence of skin cancer, but according to one researcher at Dr. Cipto Mangunkusumo General Hospital, of the 263 cases of skin cancer studied, the most common skin cancer was BCC 66.9%, followed by SCC 27.4% and malignant melanoma 5.7%.[5] Therefore, an effective prevention strategy is needed to reduce the incidence of skin cancer. One approach developed in the prevention of skin cancer is chemopreventive therapy, namely the use of pharmacological agents to inhibit, delay or fight the development of cancer cells.[6,7]

Some chemopreventive agents that have been studied include non-steroidal anti-inflammatory drugs (NSAIDs), difluoromethylornithine (DFMO), vitamin D3, nicotinamide, and vitamin A.[8,9] Some chemopreventive agents work by inhibiting the development of precancerous enzymes in cells, inhibiting inflammation, cancer cell proliferation, and increasing apoptosis so that they can suppress the development of NMSC.[1,10] However, no recent studies have been found that examine all of these chemopreventive therapies. Therefore, this systematic review was conducted with the aim of evaluating the effectiveness of various chemo-preventive therapies in reducing the incidence of non-melanoma skin cancer. This study also examines scientific evidence related to the role of chemopreventive in suppressing the rate of NMSC development and its implications in clinical practice.

## Methods

The search for this article is a systematic literature review to determine the benefits of chemopre-ventive in reducing cases of non-melanoma skin cancer. The literature search was conducted on the electronic databases PubMed and Google Scholar using the keywords "chemopreventive" and "non-melanoma skin cancer". With the inclusion criteria, namely articles that have the same objectives and results as the objectives of this study, articles are available in full text for free, articles are written in English with a publication time of the last 15 years. Exclusion criteria were articles with quantitative data that were not included, and literature that was not fully accessible or duplicated.

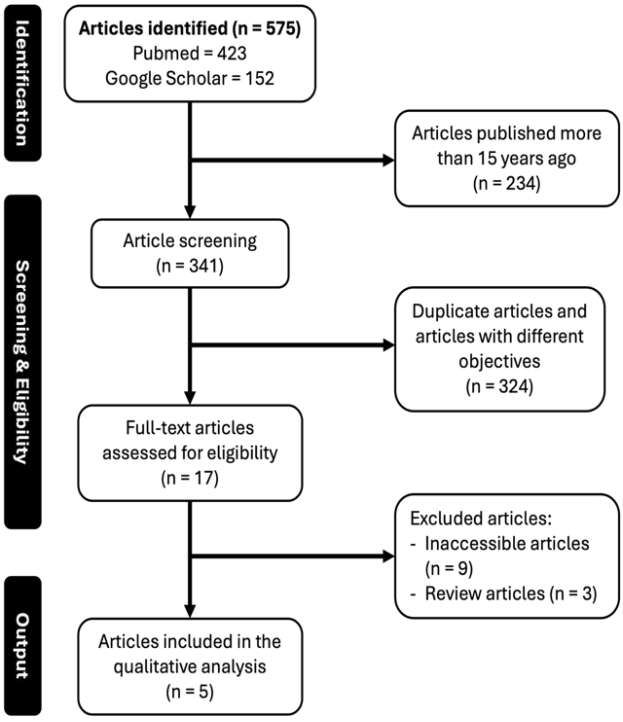


**Figure 1.** Systematic review extraction scheme.

## Results

A total of 5 articles were used in this study. These articles have met the specified criteria. The following are the extraction results of the 5 articles used in this study:

**Table 1.** Characteristics of research studies

| Author | Study Design | Chemopreventive Agent | Average Age (years) | Number of Subjects | Study Duration |
|---|---|---|---|---|---|
| Reinau D, et al. 2014.[7] | Case Control | NSAID | 66 | 73,262 | 19 years |
| Kreul, et al. 2012.[11] | RCT | DMFO | 61 | 291 | 5 years |
| Ince B, et al. 2019.[12] | Prospective Cohort | Vitamin D | 69 | 496 | 3 years |
| Chen AC, et al. 2015.[13] | RCT | Nicotinamide | 66 | 386 | 1 year |
| Bhullar S, et al. 2023.[14] | Retrospective Cohort | Vitamin A | 71 | 34 | 2 years |

**Table 2.** Summary of extracted articles

| Author | Study Subjects | Results |
|---|---|---|
| Reinau D, et al. 2014.[7] | 65,398 cases of BCC and 7,864 cases of SCC with NSAID use | The risk of BCC with long-term ibuprofen use decreased (OR: 0.61, 95% CI: 0.48-0.78). The reduction in SCC risk was statistically significant only for naproxen use (OR: 0.84, 95% CI: 0.70-0.99). |
| Kreul, et al. 2012.[11] | 291 patients with a history of NMSC, divided into intervention with 500 mg/day DFMO (144 participants) vs. placebo (147 participants) | The incidence of new NMSC during the study was lower in the DFMO intervention group compared to placebo (0.444 vs. 0.701, p = 0.012). The incidence of new BCC was also lower in the DFMO group compared to placebo (0.294 vs. 0.466, p = 0.014). |
| Ince B, et al. 2019.[12] | A total of 496 BCC patients: 239 in the first stage, 114 in the second stage, and 143 in the third stage. In the third stage, 50,000 IU oral vitamin D3 was administered weekly for 6 weeks. | The average serum 25-OH vitamin D3 level after replacement therapy was 40.1 ng/mL, and recurrence rates dropped to 3.49%. Recurrence rates in stage 2 were statistically higher than in stage 3 (P < 0.05). |
| Chen AC, et al. 2015.[13] | 386 non-melanoma patients receiving 500 mg of nicotinamide twice daily for 12 months | The incidence of new non-melanoma skin cancer was 23% lower (95% CI, 4 to 38) in the nicotinamide group compared to placebo (P = 0.02). The incidence of new BCC (20% lower [95% CI, -6 to 39], P = 0.12) and new SCC (30% lower [95% CI, 0 to 51], P = 0.05). |
| Bhullar S, et al. 2023.[14] | 34 SCC patients: 20 immunocompetent, 9 immunosuppressed, and 5 immunodeficient, treated with 14.1 mg/day acitretin for 1.8 years | A 68% reduction in invasive SCC incidents during acitretin therapy compared to no therapy (P < 0.0001). SOTR and immunocompetent patients showed reductions of 73% and 76% in invasive SCC incidents with acitretin therapy, respectively. |

## Discussion

Based on the research results that we obtained from 5 articles that met our inclusion criteria, there are several chemopreventive agents that can significantly reduce the incidence of NMSC.
According to Sari M, et al, several studies have shown that UV exposure is associated with increased expression of cyclooxygenase-2 (COX-2) in human skin. COX-2 is found in actinic keratosis (AK), SCC, and is expressed in the parenchyma and stroma of BCC tissue. Increased expression of COX-2 triggers the production of prostaglandins (PG) and vascular epidermal growth factor (VEGF), which accelerate tumor proliferation.[15,16]

According to Janicka N, et al, parenteral administration of naproxen (nonselective COX) to mice at a dose of 1 mg in 100 µL phosphate-buffered saline (PBS) increases apoptosis and inhibits tumor growth, which has potential therapeutic implications.[17] Literature review conducted by Sari, et al. stated a cohort study of 92,125 Caucasian women found that aspirin or ibuprofen use was associated with a lower risk of SCC tumors that were positive for p53 (by immunohistochemistry or TP53 mutation analysis) or with PTCH loss.[15]

A study by Taznin T, et al. in the lightest Caucasians often had lower vitamin D levels than other races.[18] This is partly due to their increased photosensitivity. Vitamin D insufficiency contributes to tumorigenesis, more specifically a worse prognosis related to drug resistance. Vitamin D3 hydroxyderivatives can suppress the development of skin cancers induced by ultraviolet B or chemical exposure.[19] In addition, vitamin D3 can also inhibit the hedgehog signaling pathway associated with several types of cancer, making it a target for research into skin cancer treatments, including SCC and BCC.[2]

In a study by Lappe J, et al. Among 2303 women with a mean age of 65 years, the mean baseline serum 25-hydroxyvitamin D level was 32.8 ng/ml. At year 1, serum 25-hydroxyvitamin D levels were 43.9 ng/ml in the vitamin D3 + calcium group versus 31.6 ng/ml in the placebo group. A new cancer diagnosis was confirmed in 109 participants, 45 (3.89%) in the vitamin D3 + calcium group and 64 (5.58%) in the placebo group (difference, 1.69% [95% CI, -0.06% - 3.46%]; P=0.06).[20] A literature review by Gorgojo AM, et al, suggested that taking 1500 IU of vitamin D3 daily may reduce the risk of cancer death in men in the United States by 30%. This suggests that adequate vitamin D intake may have a protective effect against cancer.[21]

Based on a literature review by Russomanno K, et al, the risk of developing SCC and BCC in the solid organ transplant recipient (SOTR) population is estimated to be 40–250 and 5–10 times higher than the general population, respectively. Systemic retinoid administration can reduce the risk of developing SCC and BCC.[22] A study by Kadakia C, et al, involving 70 non-SOTR patients who took acitretin 25 mg orally for five days a week showed an equivalent level of effectiveness in preventing NMSC.[23]

A randomized control trial (RCT) study, conducted by Bailey, et al, showed that oral DFMO administration at a dose of 500 mg/day for 5 years was safe and well tolerated and resulted in significant inhibition of Ornithine decarboxylase (ODC) activity.[24] There was a significant decrease in the incidence of NMSC developing into BCC in patients taking DFMO compared to placebo. A total of 69 subjects taking DFMO developed 163 new BCCs compared to 77 subjects taking placebo who developed 245 new BCCs. The incidence of BCC in the placebo group (0.40 events/patient-year) was significantly greater (P=0.03) than the rate in subjects taking DFMO (0.28 events/patient-year).[24]

In accordance with research conducted by Schneider, et al, conducted a survey of 50 skin cancer patients undergoing Moh's surgery in 2019 who consumed nicotinamide 2x500 mg compared to sunscreen on the perceived risk reduction of skin cancer. In the subgroup of respondents who consumed nicotinamide had a significantly higher risk reduction of 41.2% in BCC and 38.3% in SCC ($p<0.05$) and was positively correlated with nicotinamide use. In addition, 15.6% of respondents believed that nicotinamide was more effective than sunscreen in preventing skin cancer.[25]

## Limitations

This study has several limitations. One of them is that although the data collection aimed to gather relevant studies from databases, some references included are older than five years. Furthermore, the inclusion and exclusion criteria for this systematic review only considered sources written in English and excluded studies published in other languages, which could potentially lead to bias. The small

number of articles included in analysis potentially leads to overestimation of results.

## Conclusion

This study demonstrates that chemopreventive agents such as NSAIDs (particularly ibuprofen and naproxen), DFMO, vitamin D3, nicotinamide, and acitretin can reduce the incidence of NMSC, including BCC and SCC. Various studies highlight the protective effects of these agents through mechanisms such as the inhibition of inflammation, suppression of cancer cell proliferation, and enhancement of apoptosis. High-risk populations, such as organ transplant recipients, exhibit higher incidences, making chemopreventive interventions highly relevant. While the efficacy of these agents is significant, further research is needed to confirm their long-term benefits and determine optimal dosages, positioning chemoprevention as a promising adjunct strategy in NMSC prevention.

## References


1. Cives M, Mannavola F, Lospalluti L, Sergi MC, Cazzato G, Filoni E, et al. Non-melanoma skin cancers: Biological and clinical features. *Int J Mol Sci.* 2020;21(15):5394.
2. Roky AH, Islam MM, Ahasan AMF, Mostaq MS, Mahmud MZ, Amin MN, et al. Overview of skin cancer types and prevalence rates across continents. *Cancer Pathog Ther.* 2024;08:1-12.
3. Huang S, Jiang J, Wong H-shiwn, Zhu P, Ji X, Wang D. Global burden and prediction study of cutaneous squamous cell carcinoma from 1990 to 2030: A systematic analysis and comparison with China. *J Glob Health.* 2024;14:04093.
4. Zhang W, Zeng W, Jiang A, He Z, Shen X, Dong X, et al. Global, regional and national incidence, mortality and disability-adjusted life-years of skin cancers and trend analysis from 1990 to 2019: An analysis of the Global Burden of Disease Study 2019. *Cancer Med.* 2021;10(14):4905–22.
5. Wibawa LP, Andardewi MF, Ade Krisanti I, Arisanty R. The epidemiology of skin cancer at Dr. Cipto Mangunkusumo National Central General Hospital from 2014 to 2017. *J Gen-Proced Dermatol Venereol Indones.* 2019;4(1):11–6.
6. Jiminez V, Yusuf N. An update on clinical trials for chemoprevention of human skin cancer. *J Cancer Metastasis Treat.* 2023;9(1):4.
7. Reinau D, Surber C, Jick SS, Meier CR. Nonsteroidal anti-inflammatory drugs and the risk of nonmelanoma skin cancer. *Int J Cancer.* 2015;137(1):144–53.
8. Sutedja EK, Arianto TR, Lesmana R, Suwarsa O, Setiabudiawan B. The chemoprotective role of vitamin D in skin cancer: A systematic review. *Cancer Manag Res.* 2022;14:3551–65.
9. Tosti G, Pepe F, Gnagnarella P, Silvestri F, Gaeta A, Queirolo P, et al. The role of nicotinamide as chemo-preventive agent in NMSCs: A systematic review and meta-analysis. *Nutrients.* 2024;16(1):100.
10. Koulmi K, Cattelan L, Litvinov IV. Evaluating difluoromethylornithine safety and efficacy for non-melanoma skin cancer chemoprevention: A systematic review. *J Cutan Med Surg.* 2024;12034754241302818.
11. Kreul SM, Havighurst T, Kim K, Mendonça EA, Wood GS, Snow S, et al. A phase III skin cancer chemoprevention study of DFMO: Long-term follow-up of skin cancer events and toxicity. *Cancer Prev Res Phila Pa.* 2012;5(12):1368–74.
12. Ince B, Yildirim MEC, Dadaci M. Assessing the effect of vitamin D replacement on basal cell carcinoma occurrence and recurrence rates in patients with vitamin D deficiency. *Horm Cancer.* 2019;10(4–6):145–9.
13. Chen AC, Martin AJ, Choy B, Fernández-Peñas P, Dalziell RA, McKenzie CA, et al. A phase 3 randomized trial of nicotinamide for skin-cancer chemoprevention. *N Engl J Med.* 2015;373(17):1618–26.
14. Bhullar S, Christensen SR. Effectiveness of acitretin for skin cancer prevention in immunosuppressed and nonimmunosuppressed patients: A retrospective cohort study. *J Am Acad Dermatol.* 2024;90(4):821–2.
15. Sari M, Misalina K, Listiawan Y, Listiawan Y. The role of cyclooxigenase-2 inhibitor in basal cell carcinoma: A literature review. *Pharmacogn J.* 2023;15(1):233–8.
16. Wong RSY. Role of nonsteroidal anti-inflammatory drugs (NSAIDs) in cancer prevention and cancer promotion. *Adv Pharmacol Sci.* 2019;2019:1–10.
17. Janicka N, Sałek A, Sawińska M, Kuchar E, Wiela-Hojeńska A, Karłowicz-Bodalska K. Effects of non-opioid analgesics on the cell membrane of skin and gastrointestinal cancers. *Int J Mol Sci.* 2022;23(13):7096.
18. Taznin T, Tabassum T, Haque SN, Hasan MR, Amin ASMA, Khan S. Impact of vitamin D in different skin cancer pathogenesis and treatment modalities. 2023;01–21.
19. Tang JY, Xiao TZ, Oda Y, Chang KS, Shpall E, Wu A, et al. Vitamin D3 inhibits hedgehog signaling and proliferation in murine basal cell carcinomas. *Cancer Prev Res Phila Pa.* 2011;4(5):744–51.
20. Lappe J, Watson P, Travers-Gustafson D, Recker R, Garland C, Gorham E, et al. Effect of vitamin D and calcium supplementation on cancer incidence in older women: A randomized clinical trial. *JAMA.* 2017;317(12):1234–43.
21. Martin-Gorgojo A, Gilaberte Y, Nagore E. Vitamin D and skin cancer: An epidemiological, patient-centered update and review. *Nutrients.* 2021;13(12):4292.

22. Russomanno K, Abdel Azim S, Patel VA. Immunomodulators for non-melanoma skin cancers: Updated perspectives. *Clin Cosmet Investig Dermatol.* 2023;16:1025–45.
23. Kadakia KC, Barton DL, Loprinzi CL, Sloan JA, Otley CC, Diekmann BB, et al. Randomized controlled trial of acitretin versus placebo in patients at high-risk for basal cell or squamous cell carcinoma of the skin (North Central Cancer Treatment Group Study 969251). *Cancer.* 2012;118(8):2128–37.
24. Bailey H, Kim K, Verma A, Sielaff K, Larson P, Snow S, et al. A randomized, double-blind, placebo-controlled phase 3 skin cancer prevention study of DFMO in subjects with previous history of skin cancer. *Cancer Prev Res Phila Pa.* 2010;3(1):35–47.
25. Schneider JG, Majidian M, Moy RL. Patient perception of skin cancer reduction by nicotinamide correlates with use. *Cureus.* 2023;15(8):e44403.

InaJCC The Indonesian Journal of Cancer Control

Original Article

# Efficacy and safety of neoadjuvant nivolumab and ipilimumab for resectable melanoma

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## Abstract

**Introduction:** Neoadjuvant immunotherapy is an emerging strategy in the management of resectable melanoma, aiming to improve long-term outcomes by inducing early immune responses before surgery. The combination of nivolumab (PD-1 inhibitors) and ipilimumab (anti–CTLA-4) has shown promise.
**Objective:** To systematically review the efficacy and safety of neoadjuvant nivolumab and ipilimumab regimens in resectable melanoma patients.
**Methods:** A systematic search of databases was conducted following PRISMA 2020 guidelines. Studies were screened and selected based on the use of neoadjuvant nivolumab and ipilimumab combination for resectable melanoma. Risk of bias was assessed. Key outcomes included relapse-free survival (RFS), event-free survival (EFS), overall survival (OS), pathological response and grade ≥3 adverse events (AE). Seven studies comprising five randomized controlled trials (RCT), non-RCT and one retrospective cohort study with a total of 530 patients were included.
**Results:** The combination of neoadjuvant nivolumab and ipilimumab showed high efficacy, with RFS from 70% to 96%, EFS ≥90%, and OS ≥95% over median follow-up of 8-28 months. The most favorable outcomes were observed with low-dose ipilimumab (1 mg/kg) plus high-dose nivolumab (3 mg/kg). Pathological response rates were high, major/complete responses ≥70% of patients. Grade ≥3 treatment-related AE were common, including rash, colitis, elevated liver enzyme.
**Conclusion:** Neoadjuvant nivolumab with ipilimumab shows strong clinical and pathological response in resectable melanoma, with a potential to improve long-term outcomes. However, its use is limited by a significant risk of severe immune-related adverse events. Optimizing the dosing, lowering ipilimumab dosage, may enhance the risk-benefit profile.

***Keywords:*** *Ipilimumab; melanoma; neoadjuvant therapy; nivolumab*

## Abstrak

**Pendahuluan:** Imunoterapi neoadjuvan merupakan strategi yang sedang berkembang dalam penatalaksanaan melanoma yang dapat direseksi, dengan tujuan meningkatkan luaran jangka panjang melalui induksi respons imun dini sebelum pembedahan. Kombinasi nivolumab (inhibitor PD-1) dan ipilimumab (anti-CTLA-4) telah menunjukkan hasil yang menjanjikan.
**Tujuan:** Meninjau secara sistematis efektivitas dan keamanan regimen neoadjuvan nivolumab dan ipilimumab pada pasien melanoma yang dapat direseksi.
**Metode:** Penelusuran sistematis terhadap basis data dilakukan sesuai pedoman PRISMA 2020. Studi diseleksi berdasarkan penggunaan kombinasi neoadjuvan nivolumab dan ipilimumab pada melanoma yang dapat direseksi. Risiko bias dinilai secara sistematis. Luaran utama meliputi *relapse-free survival* (RFS), *event-free survival* (EFS), *overall survival* (OS), respons patologis, serta kejadian efek samping terkait terapi derajat ≥3. Sebanyak tujuh studi yang terdiri atas lima uji klinis teracak terkontrol (RCT), satu studi non-RCT, dan satu studi kohort retrospektif dengan total 530 pasien diikutsertakan dalam analisis.
**Hasil:** Kombinasi neoadjuvan nivolumab dan ipilimumab menunjukkan efektivitas yang tinggi, dengan RFS berkisar antara 70–96%, EFS ≥90%, dan OS ≥95% pada median tindak lanjut 8–28 bulan. Luaran terbaik ditemukan pada regimen ipilimumab dosis rendah (1 mg/kgBB) yang dikombinasikan dengan nivolumab dosis tinggi (3 mg/kgBB). Angka respons patologis tergolong tinggi, dengan respons mayor/komplet pada ≥70% pasien. Efek samping terkait terapi derajat ≥3 cukup sering dijumpai, termasuk ruam kulit, kolitis, dan peningkatan enzim hati.
**Kesimpulan:** Pemberian neoadjuvan nivolumab yang dikombinasikan dengan ipilimumab menunjukkan respons klinis dan patologis yang kuat pada melanoma yang dapat direseksi, serta berpotensi memperbaiki luaran jangka panjang. Namun, penggunaannya dibatasi oleh risiko efek samping imunologis berat yang signifikan. Optimalisasi regimen dosis, khususnya dengan penurunan dosis ipilimumab, berpotensi meningkatkan rasio manfaat–risiko terapi.

## Background

Melanoma is a highly aggressive skin cancer that develops from melanocytes, the cells in the deepest layer of the skin responsible for producing melanin. Although it makes up just about 1% of all skin cancers, melanoma is responsible for more than 80% of deaths from skin cancer.[1] For individuals with resectable melanoma at stage IIIB or higher, the standard of care was surgery followed by adjuvant therapy.[2] Over the past decade, melanoma treatment has undergone significant transformation. To further improve clinical outcomes, neoadjuvant strategies (NAS) are now being explored.[3] Neoadjuvant therapy, especially immunotherapy, can change the way treatment works. It not only shrinks lesions but also makes surgery less necessary by boosting the body's immune response more effectively than adjuvant therapy. It also allows for more frequent monitoring, enabling timely assessment of treatment response and early detection of disease progression.[4] The International Neoadjuvant Melanoma Consortium (INMC) also highlighted several advantages of the NAS therapy approach. This helps identify good responders, potentially reducing the extent of surgery and need for further therapy.[3]

Previous studies have shown that adjuvant PD-1 inhibitors, such as nivolumab and pembrolizumab, improve relapse-free survival (RFS) when compared to ipilimumab or placebo. Despite of adjuvant therapy, patients still experience recurrence after surgery, and no approved adjuvant immunotherapies have demonstrated a significant benefit in overall survival (OS) after long-term follow-up.[5] A combination of immunotherapy drugs tends to offer superior long-term outcomes, particularly in terms of recurrence-free and OS.[6] Pre-clinical and phase 1 studies suggest neoadjuvant immune checkpoint inhibitors may be more effective than adjuvant therapy. The nivolumab ipilimumab combination shows strong potential in activating immune responses against tumor cells.[3,7]

The nivolumab–ipilimumab combination shows strong promise in neoadjuvant treatment for resectable melanoma, achieving high rates of pathological remission linked to improved long-term survival.[8] Despite promising results, no comprehensive review currently exists on this topic. Previous reviews have focused on adjuvant therapy or lacked synthesis of recent high-quality neoadjuvant trials. This study aims to evaluate the efficacy and safety of neoadjuvant nivolumab and ipilimumab in resectable melanoma.

## Methods

This systematic review was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 statement. The protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO) on April 18th, 2025, with the following registration number: CRD420251033496. The study aimed to evaluate the efficacy and safety of nivolumab and ipilimumab as neoadjuvant for patients with resectable melanoma.

The review included all studies published in English up to April 2025, whether interventional or observational studies. Research that were classified as reviews, case reports, case series, conference abstracts, book sections, commentaries/editorials, or in vitro or in silico investigations were not included. The included studies focused on resectable melanoma patients who underwent therapy with Nivolumab and Ipilimumab as neoadjuvant. Patients with metastatic or unresectable melanoma and adjuvant only therapies were excluded. The primary outcomes of interest are relapse-free survival (RFS), event-free survival (EFS), overall survival (OS), pathological response and grade ≥3 adverse events (AE). Relevant studies were identified through searches on MEDLINE, EBSCO, ScienceDirect, ProQuest. Four independent authors searched for articles using the following keyword combination: ((“Nivolumab”) AND (“ipilimumab”) AND (“neoadjuvant”)) AND ((“melanoma” OR “cutaneous melanoma” OR “skin melanoma” OR “malignant melanoma”)).

All studies were imported into Rayyan software to remove duplicates. Titles and abstracts were independently screened by the authors, and studies that did not match the review objective were excluded. Full-text articles were then assessed based on the eligibility criteria. The authors independently extracted key information from each study. Due to the variety in study designs and reported outcomes, the limited data made a meta-analysis unfeasible.

## Results

The systematic review process began with 662 potentially relevant articles, from which 559 remained after duplicates were removed. After screening titles and abstracts, 19 studies were selected for full-text review. Of these, 11 were excluded due to reasons such as wrong population (n = 2), outcomes (n = 3), interventions (n = 3),

study design (n = 2), and one ongoing study (Figure 1). Ultimately, 7 studies were included in the final analysis. Study quality was evaluated using the modified Newcastle-Ottawa Scale for cohort studies (Table 1), RoB 2 for RCT (Table 2), and ROBINS-I for non-RCT studies (Table 3). Overall, the included studies demonstrated a low risk of bias. These studies, published between 2018 and 2024, were conducted across diverse regions including Australia, Sweden, the Netherlands, Europe, and Brazil. The review comprised randomized controlled trials and a retrospective cohort study, involving a total of 530 patients. Patient performance status was assessed using either the Eastern Cooperative Oncology Group (ECOG) or World Health Organization (WHO) criteria. Key demographic data, as well as survival outcomes including RFS, EFS, DMFS, OS and median follow-up duration, are detailed in **Table 4.**

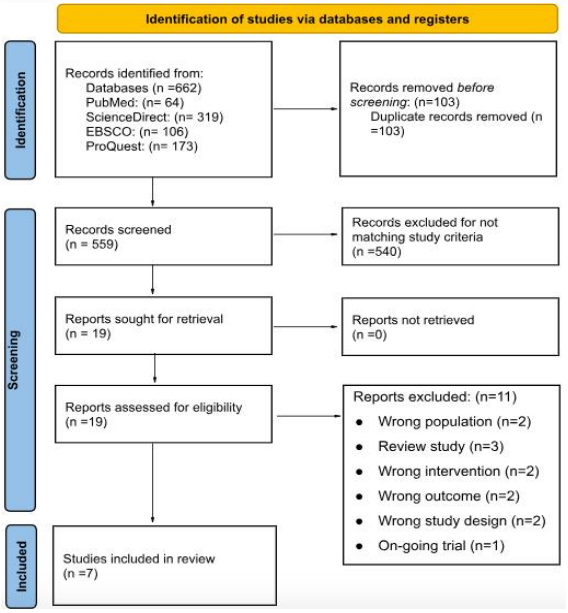


**Figure 1.** PRISMA 2020 flowchart

Neoadjuvant treatment with nivolumab and ipilimumab showed promising survival outcomes in resectable stage III melanoma. RFS rates were favorable across studies: the NADINA Phase 3 trial reported RFS of 95.1% in patients with major pathological response (MPR).[5] The OPACIN Phase 1B trial found 80% of patients relapse-free at a median follow-up of 25.6 months. The PRADO trial observed 85% RFS at 28.1 months.[9] Another cohort study reported a 96% RFS at 16 months, suggesting that relapse can be effectively prevented.10 Reijers et al. reported an 80% EFS, and the OpACIN and OpACIN-neo protocols showed 70% and 82% EFS, respectively.[9]

DMFS outcomes were also favorable. OS rates were consistently high: the PRADO trial reported 95% OS at 24 months, the OpACIN trial showed 90% 5-year OS (95% CI, 73% to >99%), and the OpACIN-neo trial demonstrated 92% 3-year OS (95% CI, 86% to 98%) across all arms.[9,13,14] In Blank et al. (2024), 90% of patients were alive at 25.6 months, reflecting durable long-term benefits.[5] Pathological responses to neoadjuvant immuno-therapy were also strong. The OpACIN-neo trial identified ipilimumab 1 mg/kg plus nivolumab 3 mg/kg for two cycles as the optimal regimen, achieving a 74% total pathological response, including a high rate of complete responses.[11]

Treatment-related toxicity, especially grade ≥3 AEs, remains a significant concern. OPACIN trial reported a 90% incidence of severe AEs, while PRADO trial observed only 22%.[9,14] Immune-related AEs (irAEs) such as rash, elevated liver enzymes and colitis were common, due to T-cell activation from checkpoint inhibitors.[16] While neoadjuvant ipilimumab and nivolumab are effective, careful management of irAEs is essential.

**Table 1.** Risk of bias for included Cohort Study

| Journal | Selection (4 stars) | | | | Comparability (2 stars) | Outcome (3 stars) | | | Total |
|---|---|---|---|---|---|---|---|---|---|
| | Represen-tativeness of the exposed cohort | Selection of the non-exposed cohort | Ascertain-ment of exposure | Demonstration that outcome of interest was not present at start of study | Comparability of cohorts based on the design or analysis | Assessment of outcome | Was follow-up long enough for outcomes to occur | Adequacy of follow up of cohorts | |
| Silva et al, 2024 | * | - | * | * | - | * | * | * | Satisfactory Studies |

Very Good Studies: 9-10 stars
Good Studies: 7-8 stars
Satisfactory Studies: 5-6 stars
Unsatisfactory Studies: 0-4 stars

**Table 2.** Risk of bias for included Randomized Controlled Trials

| Study | Randomization Process | Deviations from Intended Interventions | Missing Outcome Data | Measurement of the Outcome | Selection of the Reported Result |
|---|---|---|---|---|---|
| Blank et al., 2024 | Low | Some | Low | Low | Low |
| Blank et al., 2018 | Low | Some | Low | Some | Low |
| Versluis et al., 2023 | Low | Low | Some | Low | Some |
| Rozeman et al., 2019 | Low | Low | Low | Low | Low |
| Rozeman et al., 2021 | Low | Low | Some | Low | Low |

**Table 3.** Risk of bias for included Non-randomized Controlled Trials

| Study | Bias due to confounding | Bias in classifi-cation of inter-ventions | Bias in selection of participants into the study (or into the analysis) | Bias due to deviations from intended interventions | Bias due to missing data | Bias arising from measurement of the outcome | Bias in selection of the reported result |
|---|---|---|---|---|---|---|---|
| Reijers et al., 2022 | Moderate | Low | Moderate | Moderate | Low | Moderate | Moderate |

**Table 4.** Study Characteristics and Survival Outcome

| Author, year | Study/ Registration | Patients (M/F) | Median Age | Perfu-sion Status | Stage | BRAF Status | Lymph Node | Previous Treatment | Inter-vention | RFS | EFS | DMFS | OS | MPR | pCR | Near-pCR | Partial Response | Non-Response | Non-Evalua-tion | Follow-up (months) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Blank et al., 2018 | OPACIN (NCT0243 7279) | 6/4 | 54 | 0=10* | IIIB=7, IIIC=3 | V600=6 | N/A | SND=2, LND=0, ST=0 | IPI3+NIV O1 x2 pre/post-op | 80% | N/A | N/A | 90% | N/A | 3 | 3 | 1 | 2 | 1 | 25.6 |
| Rozeman et al., 2019 | OpACIN-neo (NCT0297 7052) | 49/37 | N/A | 0=85, 1=1* | T1a= 22 T1b= 7 T2a=6 T2b= 3 T3a= 7 T3b= 7 T4a= 2 T4b=8 Unkno wn=24 | N/A | Neck= 14 Axilla=44 Axilla and Neck= 3 Groin=24 Epitrochle ar= 1 | SND=26, LND=5 | Arms A=IPI3 + NIVO1 x3 Arms B=IPI1 + NIVO3 x3 Arms C=IPI3 x3 + NIVO3 x2 | PR=1 00% Non= 57% | Not reach ed | N/A | N/A | N/A | 37 | 15 | 12 | 21 | 1 | 8.3 |
| Rozeman et al., 2021 | OpACIN-neo (NCT0297 7052) | 49/37 | N/A | 0=85, 1=1* | Idem Rozeman 2019 | N/A | N/A | N/A | Follow-up from 2019 study | 84% | 82% | N/A | 95% | N/A | N/A | N/A | N/A | N/A | N/A | 24.6 |
| Reijers et al., 2022 | PRADO (NCT0297 7052) | 65/34 | 58 | 0=94, 1=5† | T1a/b = 17 T2a/b = 26 T3a/b = 20 T4a/b = 21 Tx = 2 Unknown = 13 | Yes = 45 No = 43 VE1 - = 9 Unknown = 2 | Neck=24 Axilla=39 Groin=36 | SND=24, LND=2 | IPI1+NIV O3 week 0 & 3 | 85% | 80% | 89% | 95% | 61 | 48 | 12 | 11 | N/A | N/A | 28.1 |
| Versluis et al., 2023 | OpACIN / OpACIN-neo | 55/41 | 57 | N/A | N/A | V600=43 | Neck=14 Axilla=49 Groin=29 Epitrochle ar=1 | N/A | OPACIN = 2 cycles neoadjuv ant OpACIN-neo-Arms A=IPI3 + NIVO1 x3 Arms B=IPI1 + NIVO3 x3 Arms C=IPI3 x3 + NIVO3 x2 | 70 - 82% | 70– 87% | 80– 88% | 90– 92% | 58 | N/A | N/A | 13 | 23 | 2 | OpACIN =69 OpACIN -neo = 47 |

| | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Blank et al., 2024 | NADINA (NCT04949113) | 71/141 | 60 | 0=192, 1=20* | T1= 25 T2= 41 T3= 41 T4= 52 Tx = 7 Unknown = 46 | V600E=95 V600K=17 Other = 5 Wild type = 95 | Neck=55 Axilla=86 Groin=66 | SND = 75 LND = 1 None = 136 | IPI80mg + NIVO240 mg x3 | MPR = 95,7% | N/A | N/A | N/A | 125 | 100 | 25 | 17 | 56 | 14 | 9.9 |
| Silva et al., 2024 | Retrospective cohort | 25/12 | 58 | N/A | IIIB=23, IIIC=12, IIID=2 | V600=25 | N/A | N/A | IPI1+NIVO3 x2, surgery + adj. | 96% | 73% | N/A | N/A | 23 | N/A | N/A | 12 | 2 | N/A | 16.1 |

† Eastern Cooperative Oncology Group (ECOG) Performance Status; * World Health Organization (WHO) Performance Status; SND= Sentinel Node Procedure ; LNP= Lymph Node Dissection; ST= Systemic Therapy; F= female; M = male; RFS=Relapse-Free Survival; EFS=Event-Free Survival; DMFS=Distant Metastasis-Free Survival; OS=Overall Survival; IPI=Ipilumumab; NIVO=Nivolumab; MPR=Major Pathological Response; N/A=Not Available; pNR=Pathological Non-Response; pCR=pathological complete response; pPR=pathological partial response

## Discussion

This systematic review provides a comprehensive summary of the efficacy and safety of neoadjuvant nivolumab and ipilimumab in patients with resectable melanoma. The included studies consistently reported high OS and RFS rates, with durable responses over extended follow-up periods. These findings suggest that the combination therapy may significantly improve long-term outcomes. However, the treatment is also associated with a high rate of grade ≥3 treatment-related adverse events (AEs), such as rash, elevated liver enzyme and colitis as the highest. The exact pathophysiology of immune-mediated colitis is unknown, however, the hyperproliferation and hyperactivation of T cells and lymphocyte infiltration are proposed mechanisms. Studies by Rozeman et al. and Silva et al. highlighted the need to balance efficacy with toxicity. Lowering the dose of ipilimumab, particularly the 1 mg/kg ipilimumab plus 3 mg/kg nivolumab regimen used in Arm B of several trials, was found to reduce toxicity.[10,12]

Standard treatment for resectable stage III melanoma typically involves surgery, but recurrence and metastasis remain concerns. Neoadjuvant immunotherapy offers several advantages: it allows assessment of treatment efficacy, reduces tumor size preoperatively, and uses pathological response as a surrogate marker for long-term survival outcomes.[5] Wolchok et al. confirmed the clinical feasibility and benefit of this approach. PD-1, found on T cells, downregulates immune activity when binding to PD-L1/PD-L2 on antigen-presenting cells. In cancer, tumor-expressed PD-L1 suppresses PD-1+ T cells, helping tumors evade the immune system. Nivolumab blocks PD-1, restoring T-cell activity and enabling tumor destruction. Ipilimumab targets CTLA-4, preventing its interaction with B7 and allowing continued CD28-mediated costimulation. This enhances T-cell activation and proliferation, promoting an antitumor immune response, making their combination particularly effective.[16]

This is the first systematic to provide an overview focused specifically on neoadjuvant nivolumab and ipilimumab for resectable melanoma. It includes all relevant studies to date and presents a detailed analysis of efficacy and grade ≥3 safety outcomes. However, limitations include the inability to conduct a meta-analysis due to insufficient pooled data, exclusion of ongoing trials, and incomplete pathological response reporting in some studies. Future research should focus on directly comparing different dosing strategies especially reduced-dose ipilimumab regimens to optimize the balance between efficacy and tolerability. Long-term follow-up data are essential. Additionally, studies involving more diverse populations and real-world clinical environments are needed to enhance the generalizability of current findings.

## Conclusion

This systematic review highlights the promise of neoadjuvant nivolumab and ipilimumab in resectable melanoma, with high response rates and improved survival, especially in high-risk patients. However, significant grade ≥3 immune-related adverse events may impact adherence and quality of life. Lower-dose ipilimumab (1 mg/kg) with higher-dose nivolumab (3 mg/kg) appears to offer a better safety-efficacy balance. Further randomized trials are needed to confirm the optimal dosing strategy.

### Conflict of Interests

All the authors declare no conflict of interest..

## References

1. Saginala K, Barsouk A et al. Epidemiology of melanoma. Med Sci (Basel). 2021 Oct 20;9(4):63.
2. Ellebaek E, Donia M, Svane IM. Neoadjuvant or perioperative immunotherapy for resectable melanoma: The need for biomarkers. Eur J Cancer. 2025 Feb 25;217:115257.
3. Kuijpers AMJ, van Akkooi ACJ. Neo-adjuvant therapy for metastatic melanoma. Cancers (Basel). 2024 Mar 22;16(7):1247.
4. Bushara O, Tidwell J, Wester JR, Miura J. The current state of neoadjuvant therapy in resectable advanced stage melanoma. Cancers (Basel). 2023 Jun 26;15(13):3344.
5. Blank CU, Lucas MW, Scolyer RA, Van de Wiel BA, Menzies AM et al. Neoadjuvant nivolumab and ipilimumab in resectable stage III melanoma. N Engl J Med. 2024 Nov 7;391(18):1696-1708.
6. Menzies AM, Amaria RN, Rozeman EA et al. Pathological response and survival with neoadjuvant therapy in melanoma: A pooled analysis from the International Neoadjuvant Melanoma Consortium (INMC). Nat Med. 2021 Feb;27(2):301-309.
7. Sharon CE, Karakousis GC. Neoadjuvant therapy for resectable melanoma. Clin Exp Metastasis. 2024 Aug;41(4):461-464.
8. Hieken TJ, Kreidieh F, Aedo-Lopez V et al. Neoadjuvant immunotherapy in melanoma: The paradigm shift. Am Soc Clin Oncol Educ Book. 2023 Jan;43:e390614.
9. Reijers ILM, Menzies AM, van Akkooi ACJ et al. Personalized response-directed surgery and adjuvant therapy after neoadjuvant ipilimumab and

nivolumab in high-risk stage III melanoma: the PRADO trial. Nat Med. 2022 Jun;28(6):1178-1188.
10. Silva MJ, Tavares MC, Lima JPSN, et al. Analysis of neoadjuvant nivolumab and ipilimumab for clinical stage III melanoma using the SWOG S1801 event-free survival definition. J Clin Oncol. 2024;42(16_suppl):e21563.
11. Rozeman EA, Menzies AM, van Akkooi AC et al. Identification of the optimal combination dosing schedule of neoadjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma (OpACIN-neo): A multicentre, phase 2, randomised, controlled trial. The lancet oncology. 2019;20(7):948–60.
12. Rozeman EA, Hoefsmit EP, Reijers ILM et al. Survival and biomarker analyses from the OpACIN-neo and OpACIN neoadjuvant immunotherapy trials in stage III melanoma. Nat Med. 2021 Feb;27(2):256–63.
13. Versluis JM, Menzies AM et al Survival update of neoadjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma in the OpACIN and OpACIN-neo trials. Ann Oncol. 2023 Apr;34(4):420-430.
14. Blank CU, Rozeman EA et al. Neoadjuvant versus adjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma. Nat Med. 2018 Nov;24(11):1655-1661.
15. Coutzac C, Adam J, Soularue E, et al. Colon immune-related adverse events: anti-CTLA-4 and anti-PD-1 blockade induce distinct immunopathological entities. J Crohns Colitis. 2017;11:1238–1246.
16. Wolchok JD, Chiarion-Sileni V et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med. 2017 Oct 5;377(14):1345-1356. doi: 10.1056/NEJMoa1709684. Epub 2017 Sep 11. Erratum in: N Engl J Med. 2018 Nov 29;379(22):218.

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Case Report

# A rare adnexal tumor: desmoplastic trichilemmoma

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## Abstract

**Background:** Desmoplastic trichilemmoma (DT) is a rare benign cutaneous adnexal tumor originating from the outer root sheath of hair follicles. Histologically, it is chacularly basal cell carcinoma, making accurate diagnosis is essential to avoid overtreatment. DT most frequently arises in sun-exposed areas of elderly population and is rarely found on the eyelid.
**Case Illustration:** A 66-year-old male with a 1 cm, skin-colored, dome-shaped nodule on the left upper eyelid, present for four years. Histopathological examination revealed a well-circumscribed dermal tumor composed of clear cells arranged in nests and cords with peripheracterized by a prominent desmoplastic stroma that may resemble invasive malignancies, partiral palisading, embedded in dense, hyalinized stroma. No atypia or mitotic activity was noted. The diagnosis of DT was confirmed.
**Discussion:** DT is a variant of trichilemmoma with unique histologic features that can resemble infiltrative neoplasms. Eyelid involvement is particularly challenging due to cosmetic and functional considerations. Immunohistochemistry may assist in distinguishing DT from basal cell carcinoma, with CD34 positivity and BerEP4 negativity supporting the diagnosis.
**Conclusions:** DT should be included in the differential diagnosis of benign-appearing eyelid lesions that demonstrate histologic features suggestive of malignancy. Proper identification is crucial to ensure appropriate surgical management and to prevent unnecessary aggressive treatment.

***Keywords:*** *desmoplastic, eyelid tumor, trichilemmoma*

## Abstrak

**Latar Belakang:** Desmoplastic trichilemmoma (DT) merupakan tumor adneksa kulit jinak yang jarang, berasal dari selubung akar luar folikel rambut. Secara histologis, lesi ini ditandai oleh stroma desmoplastik yang menonjol yang dapat menyerupai keganasan invasif, terutama karsinoma sel basal, sehingga diagnosis yang akurat sangat penting. DT paling sering muncul pada area kulit yang terpapar sinar matahari pada populasi usia lanjut dan jarang ditemukan pada kelopak mata.
**Ilustrasi Kasus:** Seorang laki-laki berusia 66 tahun dengan nodul sewarna kulit, berbentuk kubah, berukuran 1 cm pada kelopak mata atas kiri, yang telah ada selama empat tahun. Pemeriksaan histopatologi menunjukkan tumor dermal berbatas tegas yang tersusun atas sel-sel jernih yang membentuk sarang dan kord, dengan palisade perifer, tertanam dalam stroma padat yang mengalami hialinisasi. Tidak ditemukan atipia maupun aktivitas mitosis. Diagnosis DT pun ditegakkan.
**Diskusi:** DT merupakan varian dari trichilemmoma dengan karakteristik histologis khas yang dapat menyerupai neoplasma infiltratif. Keterlibatan kelopak mata menjadi tantangan tersendiri karena pertimbangan kosmetik dan fungsional. Pemeriksaan imunohistokimia dapat membantu membedakannya dari karsinoma sel basal, di mana ekspresi CD34 positif dan BerEP4 negatif mendukung diagnosis DT.
**Kesimpulan:** DT perlu dipertimbangkan pada lesi kelopak mata yang tampak jinak namun menunjukkan gambaran histologis yang menyerupai keganasan. Identifikasi yang tepat sangat penting untuk memastikan tata laksana bedah yang sesuai serta mencegah tata laksana yang tidak diperlukan.

***Kata kunci:*** *desmoplastik, trichilemmoma, tumor kelopak mata*

## Background

Desmoplastic trichilemmoma (DT) is a rare cutaneous adnexal tumor originating from the outer root sheath of the pilosebaceous unit. It was first characterized as a distinct histopathologic entity by Hunt et al. in 1990. DT is considered a histologic variant of trichilemmoma, distinguished by a prominent desmoplastic stroma that can lead to diagnostic confusion with invasive malignancies such as basal cell carcinoma (BCC) or desmoplastic squamous cell carcinoma (SCC). The tumor most frequently arises in sun-exposed areas of elderly individuals, particularly the face, and rarely, the eyelids.[1,2]

Given the overlapping clinical and histopathological features with malignant neoplasms, identifying this rare tumor is essential to avoid misdiagnosis and overtreatment. The rarity of DT on the eyelid poses a diagnostic challenge for clinicians and dermato-logists.[2,3] In this report, we present a case of DT arising on the left upper eyelid in a 66-year-old male, along with a review of its diagnostic features and clinical significance.

## Case Illustration

A 66-year-old male presented to the dermato-oncology clinic with a skin-colored, dome-shaped nodule on his left upper eyelid, which had progressively enlarged over the past four years. The lesion was asymptomatic, non-pruritic, and non-tender. Physical examination revealed a 1 cm soft, flesh-colored nodule with a smooth surface and well-defined borders (Figure 1)

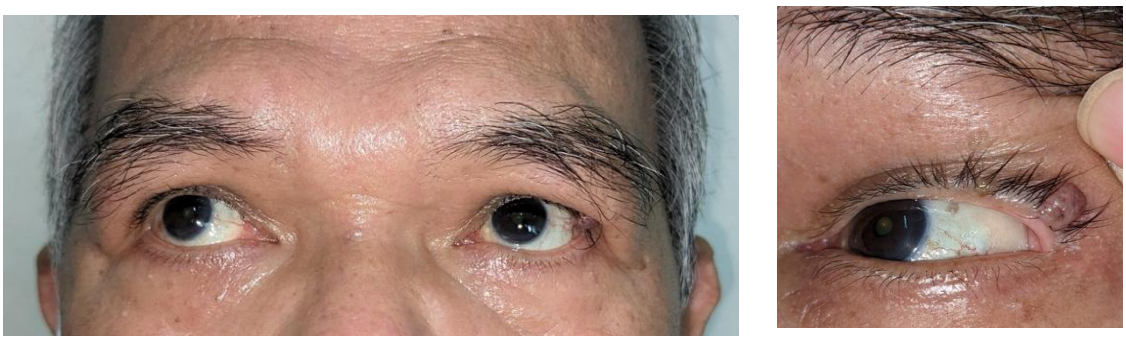

**Figure 1.** A mass lesion on the left upper eyelid of a 66-year-old man

There were no signs of ulceration, telangiectasia, or pigmentation (Figure 2). The differential diagnosis included basal cell carcinoma, epidermal inclusion cyst, and adnexal tumor.

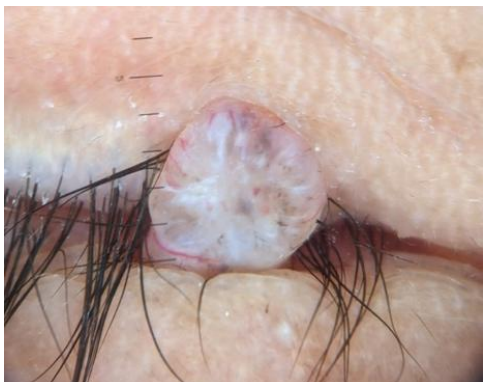

**Figure 2.** Dermoscopic feature of the mass show blue ovoid dots, multiple linear branching vessels

The patient's comorbidities included type 2 diabetes mellitus, stage 3 chronic kidney disease (CKD), coronary artery disease (CAD) post-percutaneous coronary intervention (PCI), hypertension, and dyslipidemia. Excisional biopsy was performed (Figure 3). Histopathological examination showed a well-circumscribed lobulated tumor in the dermis, partially connected to the epidermis and extending from the outer root sheath of a hair follicle. The tumor was composed of pale-staining cells with clear cytoplasm arranged in nests and cords. Peripheral palisading of nuclei was evident. The surrounding stroma was prominently desmoplastic, hyalinized, and showed dense collagenization. No significant nuclear atypia, necrosis, or abnormal mitotic activity was observed (Figure 4).

Clinicopathological conference was conducted with dermatopathology and pathology department, histopathological reading revealed that given the lack of significant nuclear atypia and the absence of mitotic activity, the differential diagnosis of basal cell carcinoma was conveniently excluded. The histopathology revealed a tumor composed of palisading basaloid cells with a central sclerotic stroma containing interspersed nests of tumor cells, leading to a diagnosis of desmoplastic trichilemmoma.

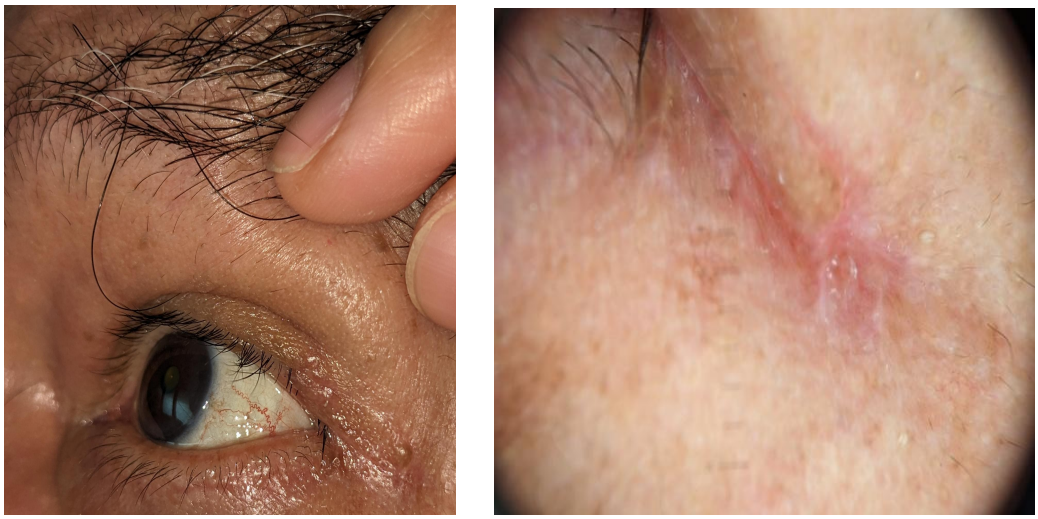

**Figure 3.** Skin lesion 1 month post excisional biopsy, show linear scar with erythematous background

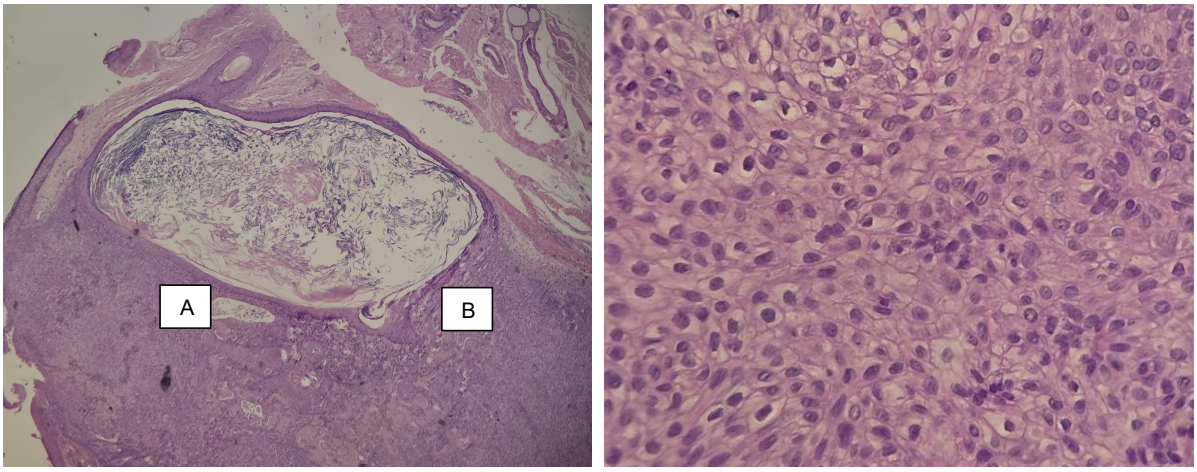


**Figure 4.** A) Well-circumscribed lobulated tumor in the dermis, partially connected to the epidermis and extending from the outer root sheath of a hair follicle, B) Pale-staining cells with clear cytoplasm arranged in nests and cords

## Discussion

Trichilemmoma is a benign adnexal neoplasm that differentiates toward the outer root sheath of the hair follicle. The desmoplastic variant is histologically characterized by lobules or cords of glycogen-rich clear cells embedded within a dense, sclerotic stroma. Unlike classic trichilemmoma, the desmoplastic variant exhibits a fibrous background that may simulate the appearance of infiltrative carcinomas, notably BCC and desmoplastic SCC.[1,4]

The eyelid, abundant in pilosebaceous units, is a recognized but uncommon location for DT. The differential diagnosis is particularly important in this area due to the functional and cosmetic implications of surgical intervention. The desmoplastic stroma and structural irregularities can resemble invasive malignancies, potentially leading to overly aggressive treatment if not accurately diagnosed.[2,3]

Histopathological features of DT over malignancy include symmetry, circumscription, peripheral palisading, and the absence of cytologic atypia or perineural invasion. Immunohistochemical studies may aid in diagnosis; CD34 is often positive in trichilemmoma, especially at the periphery, while BerEP4 is usually negative, distinguishing it from

BCC. PAS-positive, diastase-sensitive staining of the cytoplasm supports the presence of intracellular glycogen, a characteristic of outer root sheath differentiation.[3,4]

Treatment of DT is primarily surgical. Complete excision is both diagnostic and curative. Recurrency is rare if the excision is adequate. No malignant transformation has been reliably documented in DT, although rare cases of trichilemmal carcinoma may share overlapping features and must be considered in ambiguous cases.[5]

This case underlines the importance of considering DT in the differential diagnosis of eyelid tumors, particularly when the lesion exhibits benign clinical behavior but alarming histologic features. Awareness of this entity can prevent misdiagnosis and avoid unnecessary radical procedures.

## Conclusion

Desmoplastic trichilemmoma is a rare, benign neoplasm of follicular origin that may clinically and histologically mimic malignant cutaneous tumors. It poses a diagnostic challenge, particularly when located on the eyelid. Accurate histopathological evaluation, supported by immunohistochemistry, when necessary, is essential to establish the correct diagnosis and avoid unnecessary aggressive treatment. Recognition of DT is crucial in dermatologic practice to ensure appropriate patient management and favorable outcomes.

### References

1. Keskinbora KH, Buyukbabani N, et al. Desmoplastic trichilemmoma: a rare tumor of the eyelid. *Eur J Ophthalmol.* 2004;14(6):562–4.
2. Sano DT, Tebcherani AJ, et al. A rare clinical presentation of desmoplastic trichilemmoma mimicking invasive carcinoma. *An Bras Dermatol.* 2014;89(5):796–8.
3. Zhong S, Wang L, et al. Desmoplastic trichilemmoma of the scalp: case report and literature review of immunohistochemical staining features. *J Int Med Res.* 2019;47(8):3918–25.
4. Sharma R, Sirohi D, et al. Desmoplastic trichilemmoma of the facial region mimicking invasive carcinoma. J. Maxillofac. Oral Surg. 2011;10(1):71-3.
5. Afshar M, Lee RA, et al. Desmoplastic trichilemmoma—a report of successful treatment with Mohs micrographic surgery and a review an update of the literature. Dermatol Surg. 2012;38(11):1867-71.

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Case Report

# Mixed type basal cell carcinoma: Clinical correlation of dermoscopy and histopathology

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## Abstract

**Background**: Basal cell carcinoma (BCC) is a skin cancer that arising from the basal layer of the epidermis. If left untreated, it may cause significant tissue destruction and morbidity. The gold standard for diagnosing BCC involves clinical examination, dermoscopy, and histopathology. Mixed type BCC poses challenges due to its aggressive behavior and higher recurrence risk.
**Case Illustration**: A 56-year-old Caucasian male presented with a gradually enlarging lump on his forehead over the past year. Clinical examination revealed a pigmented nodule (6.5 × 9 × 4 mm) on the temporalis dextra. Dermoscopy features including blue-gray ovoid nests, arborizing telangiectasias, and blue-gray globules were found. Complete excisional biopsy confirmed mixed-type BCC.
**Discussion**: Ultraviolet light exposure plays an important role in the development of BCC, in addition to genetic predisposition factors. The patient had Fitzpatrick skin type II with occupational sun exposure as a significant risk factor. Dermoscopy enhanced the preliminary diagnosis, revealing characteristic features including blue-gray ovoid nests, arborizing telangiectasias, and blue-gray globules, which correlated with histopathological findings. In this case, mixed type BCC (aggressive type) was confirmed through histopathological examination following complete excisional biopsy.
**Conclusion**: The accurate diagnosis of BCC requires integration of clinical examination, dermoscopy, and histopathology. Dermoscopy enables early detection while histopathology remains the gold standard for definitive diagnosis and risk stratification. In this case, mixed-type BCC poses challenges due to its aggressive behavior and higher recurrence risk, which requires complete excision.
***Keywords**: dermoscopy, histopathology, mixed-type basal cell carcinoma*

## Abstrak

**Latar Belakang**: Karsinoma sel basal (KSB) merupakan kanker kulit yang berasal dari lapisan basal epidermis. Jika tidak ditangani, penyakit ini dapat menyebabkan destruksi jaringan yang bermakna dan meningkatkan morbiditas. Standar emas untuk diagnosis KSB meliputi pemeriksaan klinis, dermoskopi, dan histopatologi. KSB tipe campuran (*mixed-type*) memberikan tantangan tersendiri karena memiliki karakteristik yang lebih agresif dan risiko kekambuhan yang lebih tinggi.
**Ilustrasi Kasus:** Seorang laki-laki Kaukasia usia 56 tahun datang dengan keluhan benjolan pada dahi yang membesar secara perlahan selama satu tahun terakhir. Pemeriksaan klinis menunjukkan nodul berpigmen berukuran 6,5 × 9 × 4 mm pada regio temporalis dekstra. Pada pemeriksaan dermoskopi ditemukan gambaran berupa *blue-gray ovoid nests*, *arborizing telangiectasias*, dan *blue-gray globules*. Biopsi eksisional lengkap menegakkan diagnosis KSB tipe campuran.
**Diskusi:** Pajanan sinar ultraviolet berperan penting dalam perkembangan KSB, selain faktor predisposisi genetik. Pasien memiliki tipe kulit Fitzpatrick II dengan pajanan sinar matahari akibat pekerjaan sebagai faktor risiko yang bermakna. Dermoskopi membantu menegakkan diagnosis awal dengan menunjukkan gambaran khas berupa *blue-gray ovoid nests*, *arborizing telangiectasias*, dan *blue-gray globules*, yang berkorelasi dengan temuan histopatologi. Pada kasus ini, KSB tipe campuran dikonfirmasi melalui pemeriksaan histopatologi setelah dilakukan biopsi eksisional lengkap.
**Kesimpulan:** Diagnosis KSB yang akurat memerlukan integrasi pemeriksaan klinis, dermoskopi, dan histopatologi. Dermoskopi memungkinkan deteksi dini, sedangkan histopatologi tetap menjadi standar emas untuk diagnosis definitif dan stratifikasi risiko. Pada kasus ini, KSB tipe campuran memberikan tantangan karena perilakunya yang agresif dan risiko kekambuhan yang lebih tinggi, sehingga memerlukan eksisi yang lengkap.
***Kata kunci:** dermoskopi, histopatologi, karsinoma sel basal tipe campuran*

## Introduction

Basal cell Carcinoma (BCC) is the most common type of skin cancer worldwide, accounting 80-90% of skin cancer.[1] BCC mostly occur on sun exposed area, predominantly on head and neck. It arises from the basal layer of the skin, with characteristic of slow growth, locally aggressive but rarely metastasize. The destructive effects of BCC often lead to morbidity if left untreated.[2]

The incidence of BCC is higher in Caucasian population. Prolonged Ultraviolet (UV) exposure is one of the predisposition factors that causing BCC. The earliest lesions of basal cell carcinoma are generally seen as a small papule or nodule, with variety size and can easily bleeds on minor trauma or friction. BCC clinically can be either pigmented or nonpigmented. Dermoscopy has been widely used for early detection of cancerous lesions. Dermoscopy able to visualize the skin condition that couldn't be seen with naked eye. However, histophatology remains the gold standard for definitive diagnosis.[2,3]

Clinicopathologically, BCC has several forms, including nodular, infiltrative, fibroepithelial, morpheaform and superficial. When more than one subtype is present in the same lesion, the BCC is classified as mixed.[1,3] Mixed type BCC may have aggressive behavior and potentially to have local reccurences. This study aims to assess the correlation between clinical findings, dermoscopy and histophatology to establish a definitive diagnosis and determine further treatment.

### Case Illustration

A Male, 56 years old, Caucasian, presented with a lump on his forehead for almost 1 year. It had begun with a small, pigmented lump, then it slowly enlarged. It was painless, but slightly itchy. No history of bleeding or previous skin cancer. Patient works as an architect, most of the time working outdoor. He rarely applies sunscreen during daytime.

A complete cutaneous examination was performed. A pigmented nodule with 2 color was found on the temporalis sinistra regio, with size 6,5mm x 9mm x 4mm, non-tenderness upon palpation. Dermoscopy examination found to be asymmetrical, with multiple large blue gray ovoid nests, multiple blue gray globules, multiple arborizing talengiectasias on erythematous background.

Diagnosis of pigmented nodular BCC suspected after clinical and dermoscopy examination. The lesion was completely excised for further histophatology examination. Microscopic evaluation of the tissue specimen showed several basaloid cell proliferations in lobular formation, varying shapes and sizes with focal necrosis and peripheral palisading. Narrow cleft and mucin-like material were found between the tumor lobules. Melanin pigment and melanin-laden macrophages were noted within the tumor nests connected to the basal epidermis. Ephitelioid, lymphocytic and multinucleated giant cell were found on the dermis area, without mitotic activity. Correlation between clinical presentation, dermoscopy and phatology findings established the diagnosis of mixed type of BCC (nodular, pigmented, infiltrative and pleomorphic type).

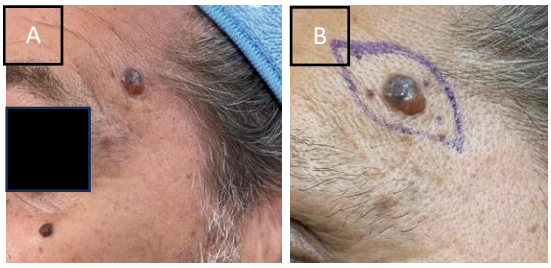


**Figure 1**. (A) Clinical appearance of the skin lesions as an asymetrical nodule with 2 color. (B) In closer view, and the eliptical excisional biopsy site was design.

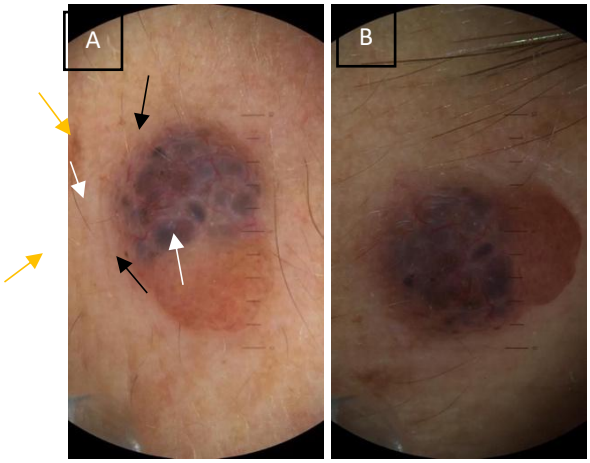


**Figure 2**. (A) Dermoscopy appearance of the lesion in vertical view, length 9mm. Multiple large blue gray ovoid nest noticed (black arrow) with arborizing talengiectasias (white arrows) and multiple blue gray globules (yellow arrow). (B) dermoscopy appearance in horizontal view, width 6,5mm.

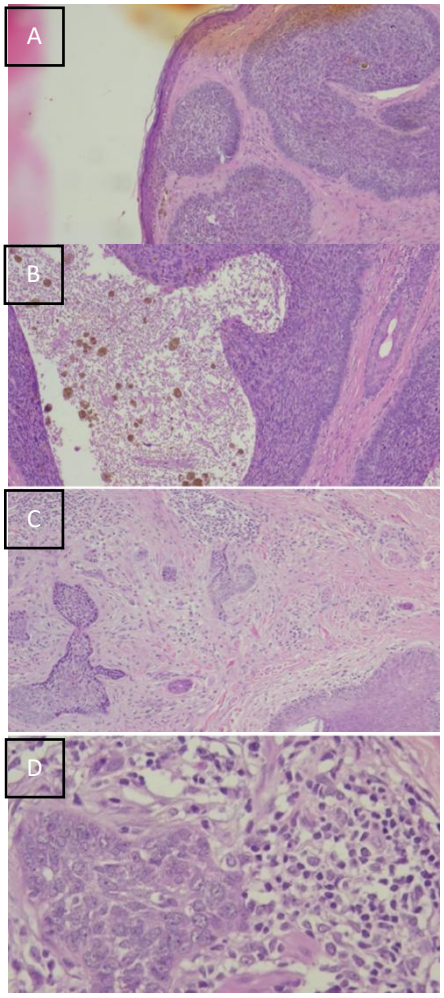


**Figure 3**. Histophatology finding of the patient (A) nodular type, (B) Pigmented type, (C) Infiltrative type, (D) Pleomorphic type.

## Discussion

BCC is the most common type of skin cancer. BCC originates from the basal layer of the epidermis, in the interfollicular or follicular bulges. It characterizes as a slow growing lesion, locally invasive with infrequent rate of metastasis. Many various factors have been describing as the predisposition factors of BCC such as genetic, chronic exposure to arsenic, photosensitizing drugs, or immunosuppression, however sun exposure (UV rays) particularly since childhood, is the main caused for the development of BCC. The severe and intermittent UV exposure during childhood is strongly linked to BCC. The UV exposure may cause DNA damage, mutagenesis and decrease immune surveillance.[1,2,7]

People who have type 1 and II Fitzpatrick skin type have a higher risk of developing BCC with a lifetime risk as 30%. People with red hair, light eye color and freckles are associated with higher risk of BCC. There are many clinical features of BCC. The most common form of BCC is nodular, start with a small lesion that is slowly growing. Unhealling ulcer may develop on the lesion, also called rodent ulcer. It is typically fragile and easy to bleed. This solid nodule may extent into subcutaneous tissue. The lesion may also pigment or pink-red color, macule or patch, scally.[1,7]

In this case, the patient is Caucasian with skin type II Fitzpatrick, who has no history of previous skin cancer, however the risk factor is prolonged UV light exposure without sun protection. The lesion started as a small, pigmented nodule that slowly enlarged and itchy. All these finding, support the diagnosis of BCC.

Dermoscopy has become an essential tool in dermatologic practice. It provides the skin imaging of the skin lesions, that can visualize microstructure of the skin that are not visible to naked eye. This noninvasive technique aids in the early detection of skin cancer.[8] Recent evidence suggests that dermoscopy is also useful in BCC management, providing information on the histological subtype, the presence of pigmentation or ulceration, as well as the response rate to non-ablative therapies.[8,9]

Dermoscopy diagnosis in BCC is based mainly in the presence of typical vascular structure, pigmented structure, ulceration and in the absence of pigmented network. BCC has a specific arborizing telangiectasias structure that characterized by bright red vessels, that branch irregularly into finer capillaries. They are sharply focused as they are located on the surface of the tumor Histologically, this finding corresponds to tumor neovascularization in the form of dilated vessels in the dermis. The most common pigmented structure observe in BCC is the large blue gray ovoid nest. Histologically, it is related to large tumor nest with pigment aggregates invading the dermis. Blue gray globules also give similar dermoscopy but smaller, round to oval structure, which correlates to small tumor nest in the papillary dermis and/or reticular dermis histologically. Blue-gray dots are seen as randomly distributed dots in sharp focus. Histologically, they correspond to small tumor aggregates at the dermo-epidermal junction or in the superficial dermis. Other pigmented structures such as maple leaf-like areas, spoke-wheel structures, and concentric structures all correspond to pigmented nests at the dermo-epidermal junction

and in the superficial papillary dermis. Ulceration under dermoscopy examination appears as orange and red structureless area, which corresponds to a total loss of epidermis and partial loss of dermis.[4,6,8] In our case, dermoscopy finding in this patient are blue gray ovoid nest, arborizing telangiectasias, and blue gray globules, which support the clinical diagnosis of BCC.

The histopathology subtypes of BCC are classified as low risk of recurrence (nodular, pigmented, superficial, infundibulocystic and fibroepithelial) and high risk of recurrence (micronodular, infiltrative, morphea and basosquamous). Some other rare variants of BCC including pleomorphic, signet, granular and clear cell BCC. Mixed types of BCC have been associated with tumor aggressiveness and high risk or recurrence. There is different treatment method of BCC, ranging from medical to surgical therapy. Complete surgical removal with histopathological confirmation is the first treatment of choice especially in mixed type BCC.[3,7,9] In our case, the histopathology findings were nodular, pigmented, infiltrative and pleomorphic. The patient underwent complete excisional removal and biopsy.

## Conclusions

To establish an accurate diagnosis of BCC, a comprehensive evaluation of clinical presentation, dermoscopic features, play an important role in guiding therapy, allowing clinicians to select the most effective treatment option with minimal side effect and optimal aesthetic outcome. A confirmation of histopathological examinations remains the gold standard for definitive diagnosis, and to reduce the recurrence rate, particularly in high-risk case such as mixed type BCC.

## References

1. Naik, PP, Desai MB. Basal cell carcinoma: a narrative review on contemporary diagnosis and management. Oncol Ther. 2022;10(2): 317-335
2. Ghanadan A, Abbasi A, Rabet M, Abdollahi P, Abbasi MA. Characteristics of mixed type basal cell carcinoma in comparison to other BCC subtypes. Indian J Dermatol 2014;59:56-9
3. Cerci FB, Kubo EM, Werner B.Comparison of basal cell carcinoma subtypes observed in preoperative biopsy and Mohs micrographic surgery. An Bras Dermatol 2020;95(5):594-601
4. Reiter O, Mimouni I, Dusza S, Halpern AC, Leshem YA, Marghoob AA. Dermoscopic Features of Basal Cell Carcinoma and its Subtypes: A systematic Review. J Am Acad Dermatol. 202;85(3):653–664. doi:10.1016/j.jaad.2019.11.008
5. Bartoš V, Kullová M. Basal cell carcinoma of the skin with mixed histomorphology: a comparative study. Cesk Patol 2016;52(4): 222–226
6. Álvarez-Salafranca M, Ara M, Zaballos P. Dermatoscopia del carcinoma basocelular: revisión actualizada. Actas Dermosifiliogr. 2021;112:330-338.
7. Jagtap SV, Jagtap SS, Shingh R et all. Basal Cell Carcinoma Mixed Histological Subtype: case report and Review of Literature. Indr Jr Path: Res and Practice 2024;13(2)61-66
8. Ungureanu L, Cosgarea I, S enilaˇ S and Vasilovici A. Role of Dermoscopy in the Assessment of Basal Cell Carcinoma. Front Med (Lausanne).2021;8:718855. doi: 10.3389/fmed.2021.718855
9. Niculet E, Craescu M, Rebegae L,Bobeica C, Nastase F, Lupasteanu G, Stan DJ, Chioncel V, Abfel L, Lungu M, Tatu AL. Basal cell carcinoma: Comprehensive clinical and histophatological aspects, novel imaging tools, and therapeutic approaches. . Exp Ther Med 2022 . Jan 23(1):60.

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Review Article

# Tuberculosis Co-Infection in Lung Cancer

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**Abstract**

Lung cancer and tuberculosis are two diseases with large numbers of cases and high mortality rates. Pulmonary tuberculosis is an infection in the lungs caused by the bacterium Mycobacterium tuberculosis. Pulmonary tuberculosis and lung cancer often present with similar clinical symptoms, and there is often a delay in diagnosis. Tuberculosis co-infection in lung cancer patients is found to be approximately 2. Several studies have shown a positive correlation between pulmonary tuberculosis and lung cancer. A person with a history of tuberculosis has a 1.7-2 times greater risk of developing lung cancer. Co-infection of tuberculosis and lung cancer can occur sequentially or simultaneously. The mechanism of lung cancer with a history of tuberculosis is due to chronic inflammation, scarring or epidermal growth factor receptor (EGFR) mutation. While comorbid tuberculosis in lung cancer may occur with two mechanisms, due to tumorigenesis caused by tuberculosis or tuberculosis induced cancer. Proper and rapid diagnosis of comorbid tuberculosis in lung cancer is a challenge so that patients receive appropriate treatment.

***Keywords:*** *co-infection, lung cancer, tuberculosis*

**Abstrak**

Kanker paru dan tuberkulosis merupakan dua penyakit dengan jumlah kasus yang besar serta angka mortalitas yang tinggi. Tuberkulosis paru adalah infeksi pada paru yang disebabkan oleh bakteri *Mycobacterium tuberculosis*. Tuberkulosis paru dan kanker paru sering kali menunjukkan gejala klinis yang serupa, sehingga kerap terjadi keterlambatan diagnosis. Ko-infeksi tuberkulosis pada pasien kanker paru ditemukan sekitar 2%. Beberapa studi menunjukkan adanya korelasi positif antara tuberkulosis paru dan kanker paru. Seseorang dengan riwayat tuberkulosis memiliki risiko 1,7–2 kali lebih tinggi untuk mengalami kanker paru. Ko-infeksi tuberkulosis dan kanker paru dapat terjadi secara berurutan maupun simultan. Mekanisme terjadinya kanker paru pada pasien dengan riwayat tuberkulosis diduga berkaitan dengan inflamasi kronis, jaringan parut (scarring), atau mutasi *epidermal growth factor receptor* (EGFR). Sementara itu, tuberkulosis sebagai komorbid pada kanker paru dapat terjadi melalui dua mekanisme, yaitu akibat proses tumorigenesis yang dipicu oleh tuberkulosis atau kanker yang menginduksi terjadinya tuberkulosis. Diagnosis yang tepat dan cepat terhadap komorbid tuberkulosis pada kanker paru masih menjadi tantangan, agar pasien dapat memperoleh terapi yang sesuai.

***Kata kunci:*** *kanker paru, ko-infeksi, tuberkulosis*

## Background

Lung cancer is the leading cause of cancer death and is estimated to have 2.2 million new cases with 1.8 million deaths by 2020.[1,2] Tuberculosis (TB) is the leading cause of death from infection in the world, with an estimated 1.3 million deaths by 2022.[3] It is known that TB increases the risk of lung cancer and affects its prognosis.[4] Patients with lung cancer and TB will have a higher mortality compared to those without TB.[5] Coexistence of TB and lung cancer is rare but can occur with an incidence of coexistence of about 2%.[6] From several studies, the risk of lung cancer increases 1.7-2 times in people with a history of tuberculosis.[7]

There is some evidence that TB can coexist with cancer, where TB is a susceptibility factor for cancer and cancer can increase the risk of TB incidence.[8] The mechanism of copathogenesis remains unclear, but it is thought to be primarily due to chronic inflammation of the lung, in cases of lung cancer with prior TB.[9] Long-term TB creates long-standing scarring that leads to lung epithelial metaplasia.[10] Another mechanism of coexistence is tumorigenesis due to tuberculosis or cancer-induced tuberculosis.[8] The clinical symptoms of TB are very similar to those of lung cancer, hence the need for caution and care when diagnosing patients with symptoms of TB or lung cancer. Diagnosis and treatment of the coexistence of pulmonary TB and lung cancer remains a challenge in TB-endemic countries. Early detection is needed before the disease reaches an advanced stage.[11]

## Content

### Tuberculosis

Pulmonary tuberculosis is a lung infection caused by the bacterium Mycobacterium tuberculosis. Tuberculosis is a significant public health problem in Indonesia, with a high prevalence rate. In 2022, Indonesia reported an estimated 10.6 million new TB cases, ranking second globally after India.[12] The incidence of pulmonary tuberculosis in Indonesia (10%) is second only to India (27%).[3] In 2021, the incidence rate of TB in Indonesia was 354 per 100,000 population with a TB mortality rate of 52 per 100,000 population.[13] The prevalence of pulmonary TB in Indonesia in the population aged 15 years and over is approximately 759 cases per 100,000 population.[14]

### Lung Cancer

Lung cancer is a serious disease that affects 2.4 million people in 2022 (12.4% of all cancers), killing 1.8 million people, approximately 18.7% of all cancer deaths in the world.[15] In 2018, lung cancer was the leading cause of cancer death in Indonesia, accounting for approximately 12.6% of all cancer deaths and 8.6% of all incidents. The total number of cases per year is expected to almost double from 30,023 in 2018 to 54,983 cases in 2040.[16] This type of cancer has a poor prognosis and poor clinical outcomes, mainly due to late diagnosis, ineffective treatment, and tumor cell resistance. There are currently about 2.09 million of lung cancer and 1.76 million deaths each year.[17]

### Co-infection with tuberculosis and lung cancer

A study found that 7.3% of lung cancer patients in Indonesia had a history of tuberculosis (TB).18 Coexistence of TB and lung cancer complicates diagnosis and worsens prognosis due to similar clinical and radiologic features.18) Patients diagnosed with lung cancer along with pulmonary tuberculosis have a higher mortality rate compared to lung cancer patients without TB.[5] Coexistence of TB and lung cancer is rarely described in the literature, but the incidence of coexistence is about 2%[6,19], as found by Cicėnas et al, about 2.1% of lung cancer patients are diagnosed with pulmonary tuberculosis.[19]

Co-infection with tuberculosis (TB) and lung cancer are two diseases that occur simultaneously or sequentially in the same individual. Co-infection is divided into two, simultaneous or sequential. Simultaneous is when both tuberculosis and lung cancer are diagnosed simultaneously, usually within a short period of time (less than two months). Sequential is where one condition precedes the other, with patients diagnosed with tuberculosis first and then lung cancer or lung cancer and then lung tuberculosis. [20-21]

### Correlation of tuberculosis and lung cancer

Several studies have shown a positive correlation between tuberculosis incidence and lung cancer, Tuberculosis patients have a 50% greater chance of developing lung cancer. Those with a history of tuberculosis for more than 20 years are 2.5 times more likely develop cancer.[22] It is reported that the risk of lung cancer increases 1.7-fold in people with TB.[7] A cohort study also found that the incidence of lung cancer in TB patients was 269 per 100,000 people per year, which is higher than in the normal population (153 per 100,000 people per year).[4]

A large body of epidemiologic data has shown that pulmonary TB is closely associated with lung cancer (shown in Table 1).[23]

**Table 1.** Epidemiologic Data of Pulmonary TB and Lung Cancer

| Researcher (Year) | Cohort size (Number of Controls) | Methods | Results | Conclusion |
|---|---|---|---|---|
| **Leung (2020)** | 52,480 cancer cases | Meta-analysis | Lung cancer RR 1.7 (95% CI: 1.5-2.0) against TB | TB is linked to lung cancer. |
| **Everatt (2016)** | 21,986 TB patients | Retrospective study | 477 TB patients developed lung cancer, a 3.5 times increased risk of cancer lung in subjects with a history of TB. | The increased risk of lung cancer in the TB cohort is associated with many factors. |
| **Oh (2020)** | 2,640 patients with pre-existing TB, 17,612 controls | Retrospective cohort study | HR of lung cancer 3.2 (95% CI: 1.9-5.6) in patients with pulmonary TB. | A higher risk of lung cancer was found in patients with a previous history of TB. |
| **Wu (2011)** | 5,657 pre-existing TB patients, 23,984 controls | Retrospective cohort study | Lung cancer IRR 1.8 (95% CI: 1.3-2.3) in patients with pulmonary TB. | Pulmonary TB is associated with an increased risk of lung cancer. |
| **Yu (2011)** | 4,480 TB patients, 712.392 control | Prospective longitudinal study | The incidence of lung cancer in TB patients is almost 11 times higher than in controls (26.3 vs. 2.4 /10,000) people/year | TB patients have an increased risk of lung cancer. |
| **Zheng (1987)** | 1,405 lung cancer patients, 1,495 controls | Prospective longitudinal study | The OR of lung cancer was 1.5 in the TB cohort and remained 2.5 times higher after TB diagnosis in the last 20 years. | TB may predispose to lung cancer |
| **Shiels (2011)** | 1,403 male smokers with TB, 28,860 male non-smokers with TB | Prospective longitudinal study | HR of lung cancer 2 in TB patients (95% CI: 1.5- 2.7), and the risk of lung cancer was highest around 2 years after TB diagnosis (HR: 5.0: 95% CI: 3.0-8.5), but the risk remained elevated at longer latencies (HR: 1.5; 95% CI:1.1-2.2). | TB is associated with an increased risk of lung cancer in male smokers. |
| **Liang (2009)** | 19,143 TB cases, 118.191 controls | Meta-analysis | Lung cancer RR 1.7 in patients with TB and passive smoking or exposure to environmental smoke (RR 1.8; 95% confidence interval (95% CI: 1.4-2.2 and 2.9; 95% CI: 1.6-5.3). | TB has a direct association with lung cancer, especially adenocarcinoma. |
| **Brenner (2011)** | 30 studies, 82,716 cases | Meta-analysis | The RR of lung cancer was 1.8 (95% CI: 1.5-2.1) in patients with previous TB. | Pulmonary TB is associated with an increased risk of lung cancer. |

Note:TB: *Tuberculosis*; HR : *Hazard Ratio*; CI: *Confidence Interval*; IRR: *Incidence Rate Ratio*; OR: *Odds Ratio*, RR: *Relative Risk*; LTBI: *Latent Tuberculosis Infection*

Source: Xiong K, Sun W, He Y, Fan L. Advances in molecular mechanisms of interaction between Mycobacterium tuberculosis and lung cancer: A narrative review. Vol. 10, Translational Lung Cancer Research. AME Publishing Company; 2021. p. 4012-26.

Everatt et al found out of 21,986 pulmonary TB patients in Lithuania, 477 TB patients developed lung cancer and patients with a history of TB had a 3.5 times higher risk of lung cancer.[24] Liang et al conducted a systematic review and meta- analysis of 37

case-control studies and 4 cohort studies to assess the association between lung cancer risk and pre-existing tuberculosis.[7] The results showed pre- existing TB significantly increased the risk of lung cancer [ (RR): 1.7; 95% confidence interval (CI): 1,5-2,0). The increase in cancer risk was 2-fold until more than two decades after TB was diagnosed.[7] Brenner et al conducted a meta- analysis of 30 studies, a significantly increased risk of lung cancer was found in patients with a history of TB compared to those without TB (RR: 1.8; 95% CI: 0.5-2.1).[25] Leung et al covering 52,480 cancer cases showed tuberculosis associated lung cancer.[26]

A retrospective cohort study in China showed that lung cancer mortality was higher in patients with a history of TB (25 per 1,000 person-years) than without lung TB (3.1 per 1,000 person-years) in the first 5 years HR ranged from 6.7 to 13), at 5-9.9 years (HR: 3,4; 95% CI: 1.3-9.1), or at ≥10 years (HR: 3.0; 95% CI: 1.3-7.3).27 Based on research conducted by Heuvers et al showed that 13 of 214 lung cancer patients had a history of pulmonary tuberculosis, and the survival of lung cancer patients with previous pulmonary TB was significantly shorter (HR: 2.4, 95% CI: 1.1-4.9) with a difference of± 311 days.[28] So from some of these studies it can be said that a history of pulmonary tuberculosis increases the risk of lung cancer and increases the mortality rate of patients.

## Pathophysiology of Tuberculosis

Mycobacterium tuberculosis (Mtb) is a large nonmotile rod-shaped obligate aerobic bacterium that requires oxygen to. Mtb is an intracellular pathogen capable of infecting human mononuclear phagocytes, spending most of its life cycle in macrophages.[29] Following transmission of Mtb to a new host via inhalation, the bacilli enter the lung and are digested by macrophages. Further immune cells are recruited to fortify the infected macrophages, leading to granuloma formation. Healthy individuals remain latently infected, and infection can be prevented at this stage, but are susceptible to the risk of reactivation (Figure 1).[30]

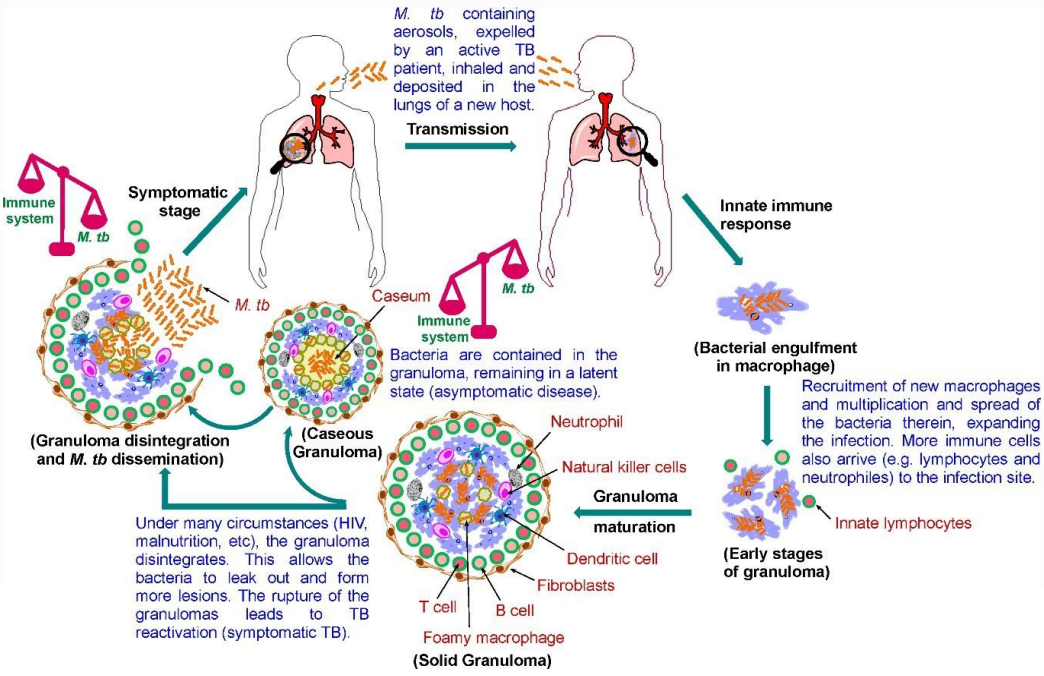


**Figure 1.** Pathophysiology of Pulmonary TB[30]

Foamy macrophages release their lipid content during necrosis, causing caseation (cheese-like structure). Caseum is the decay that occurs at the core of the granuloma that disrupts its rigid integrity. As the granuloma develops, bacilli begin to seep out of the macrophages into caseum layer. When reactivation occurs, Mtb proliferates and the bacterial count becomes so high, that the granuloma ruptures, spreading the bacteria into the airways. The bacilli are then expelled as infectious aerosolized droplets, restarting the cycle, and infecting others. [30]

**Sequential Tuberculosis - Lung Cancer Co-Infection**

Many studies have documented an association between TB and lung cancer (Table 1), but the mechanism remains unclear. It is difficult to identify a causal relationship between lung cancer and TB. The following are some possible mechanisms in the co-infection of lung cancer with a previous history of tuberculosis in patients, including due to chronic inflammation, Epidermal Growth Receptor EGFR gene mutation and scarring.[23,30]

a. Chronic inflammation
In the early phase of Mtb infection, bacilli are phagocytosed by alveolar macrophages (AM). These cells are then activated and adopt a pro-inflammatory phenotype, recruiting many immune cells to the infection site, including interstitial macrophages (IM). This decreases oxidative phosphorylation with energy from AM.[31] This type of energy gain is driven by fatty acid oxidation, making the environment more conducive for myco-bacterial infection.[32] IM also increases aerobic glycolysis, as in the Warburg effect, providing biosynthetic precursors necessary for rapid cell growth and proliferation.[33] This mechanism is part of the effort to eliminate infection, so if aerobic glycolysis is inhibited at this stage, the resulting immunological changes lead to increased Mtb survival, mainly due to decreased levels of pro-inflammatory IL-1β.[34]

Inflammatory cells produce many cytokines and chemokines that form an attractive environment for tumor progression, promoting the formation of new blood vessels from existing ones, in addition to facilitating genomic instability.[35] In chronic inflammation, by producing ROS and RNS, most phagocytic cells induce DNA damage in proliferating cells due to the resulting peroxynitrite production. If DNA damage occurs continuously and repeatedly, it may result in permanent genomic changes, such as mutations, deletions or rearrangements (Figure 2).[33-35]

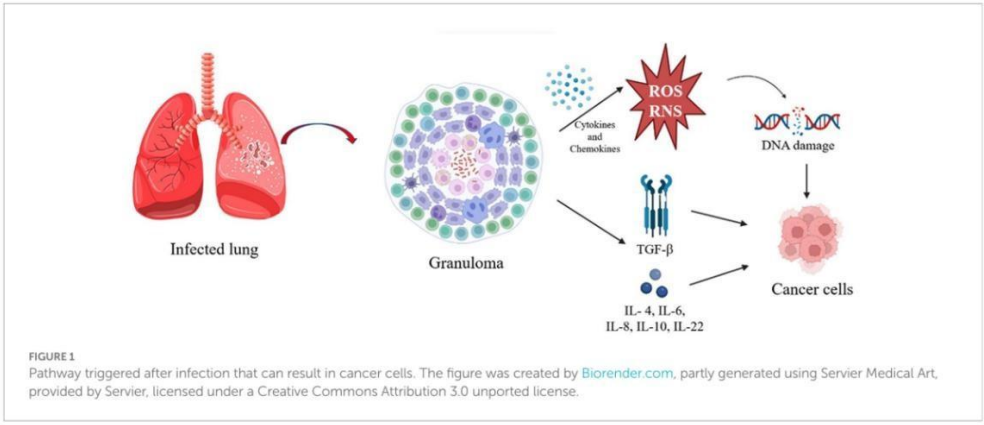


**Figure 2.** Pathways Triggered After Infection That Can Lead to Cancer Cells[30]

Lung cancer originating from chronic uncontrolled inflammation can also drive abundant expression of growth factors and cytokines, such as transforming growth factor beta (TGF-b) and interleukin (IL)-1b, IL-4, IL-6, IL-8, IL-10, and IL-22. This expression activates several tumori-genic pathways, such as cyclooxygenase 2 (COX-2) and nuclear factor kappa B (NF-kB) subunits to promote tumori-genesis.[36] TB also causes extensive pulmonary fibrosis, which is associated with the production of TGF-b, IL-4 and IL-13.[33] Conversely, lung cancer can decrease local immunity and reactivate latent infections, or even increase the likelihood of exogenous infections.[37]

Mtb-induced chronic inflammation may be involved in the development of lung cancer through the exhausted T cell phenotype, DNA damage and repair, production of reactive oxygen species (ROS), tuberculous granulomas, formation of tuber-culous fibrosis, and infiltration of IMs. In the early stages of infection, infected MTB that undergoes endocytosis escapes the phagosomes of alveolar macrophages leading to granuloma formation, which vascularizes surrounding tissues and recruits immune cells, contributing to prolonged inflammation. Exhausted T cells enriched with granulomas and chronic ROS-induced inflammation and

release of chemical irritants promote the occurrence of lung cancer. From several studies, it shows that several expressions of immune checkpoints plays a role in inhibiting T cell responses and facilitating tumor progression (Figure 3).[23]

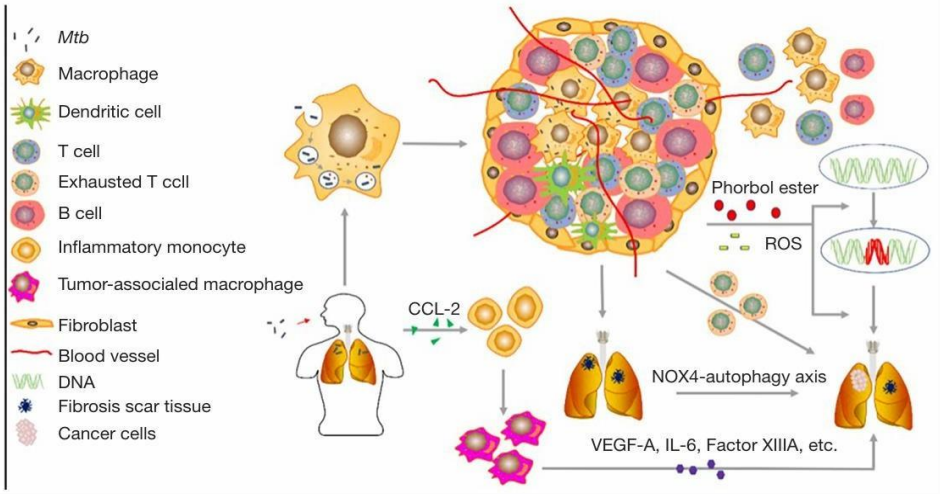


**Figure 3.** Chronic inflammation caused by Mycobacterium tuberculosis (MTB)[23]

b. Epidermal Growth Receptor (EGFR) Gene Mutation and Epiregulin Production. EGFR, a transmembrane glycoprotein belonging to the HER family (human EGFR-related family), participates in various biological processes, including cell proliferation and survival, and gene mutation. EGFR was the first driver mutation identified in lung cancer.[38,39] Gene amplification or mutation can result in continuously activated EGFR, leading to tumorigenesis.40 The prevalence of EGFR mutations in lung adenocarcinoma patients ranges from 10% to 78%, depending on ethnicity and geographic location, such as 30% to 40% in Asian patients and 15% in white patients.[41,42]

A study from South Korea showed that in patients with lung adenocarcinoma, pre-existing TB lesions were significantly associated with increased EGFR mutation rates, particularly exon 19 deletions.[43] In addition, patients treated with EGFR-TKIs in TB-associated adenocarcinoma had poorer treatment response and survival than patients without TB.43 Luo et al, EGFR mutation rates were significantly.[44]

Nalbandian et al. found that Mtb-infected macrophages induce DNA damage and produce a potent ligand for EGFR, epiregulin, to induce carcinogenesis.[45] Together, TB-induced EGFR mutation and epiregulin production may also contribute to carcino-genesis in the lung (Figure 4).[23]

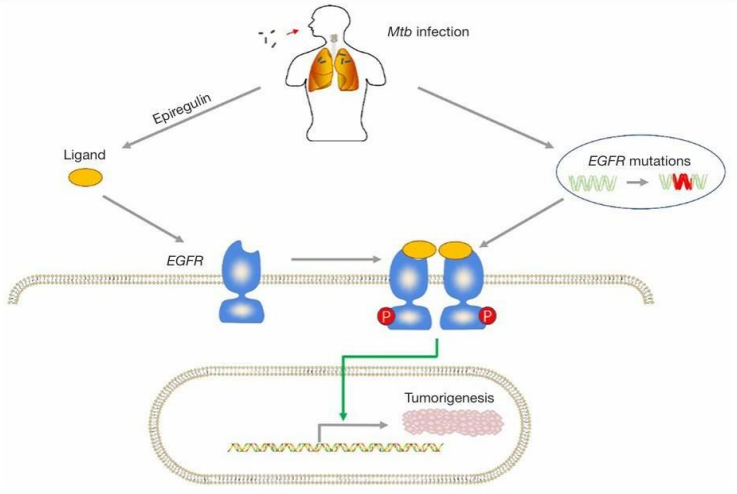


**Figure 4.** Epidermal growth factor receptor (EGFR) mutations induced by tuberculosis (TB) in lung cancer[23]

Tuberculosis (TB)-induced epidermal growth factor receptor (EGFR) mutations in lung cancer: EGFR autophosphorylates its tyrosine residues after binding to ligands. Activated EGFR will activate many downstream signaling pathways, such as cell proliferation, apoptosis, and survival. EGFR mutations can result in continuously activated EGFR, leading to tumorigenesis. Patients with pre- existing tuberculosis have an increased frequency of EGFR mutations, and Mtb- infected macrophages play a role in the production of epiregulin, the most potent ligand for EGFR, thus promoting lung cancer.[23]

c. Scarring/scar theory

Cancer can arise from previous pulmonary tuberculosis lesions.[46] Lung cancer can develop from fibrotic scarring caused by Mtb-induced chronic lung inflammation through mechanisms such as the NOX4 autophagy axis and this increases the tumorigenic potential of lung cells [23] Tuberculosis can cause persistent inflammation resulting in fibrosis, scarring, and destruction of host tissue. Fibrosis from old TB lesions can cause lymphadenopathy and increase carcinogen accumulation in the area. In addition, lung scarring, which results from an environment that favors spontaneous healing after recurrent pulmonary TB infection, favors tumor growth. Lung parenchyma may promote atypical epithelial cell proliferation and metaplasia in healed cavities.[46]

## Simultaneous co-infection of tuberculosis and lung cancer

Patients who get comorbid tuberculosis disease with lung cancer there are several mechanisms that may occur, namely the mechanism of tumorigenesis caused by tuberculosis and the mechanism of tuberculosis induced cancer. Both can cause disease at the same time. The mechanism of tumorigenesis caused by tuberculosis can be due to the activity of T cells, myeloid derived suppressor cells (MDSC), macrophages or EGFR signals. While the mechanism of cancer-induced tuberculosis can be due to tumor effects, chemotherapy and immunotherapy.[8]

Mechanisms of tumorigenesis caused by tuberculosis[8]

a. T cells

T cells play an important role in tumor growth and metastasis. CD4+ T cells can be divided into Th1, Th2, and regulatory T cells (Treg). Th1 increase the activity of nicotinamide adenine dinucleotide NAD)-dependent silence-message regulatory factor-associated enzyme 1 (SIRT1)[47] Th2 plays an antitumor role through the expression of eosinophilic chemotactic factor (ECF), and Th2 also plays a pro-tumor role through the secretion of cytokines IL-4 and IL-5. Th1/Th2 imbalance leads to impaired immune function and promotes tumor formation.[48] TB patients exhibit a reduced Th1 response and/or increased Th2 response, and disease severity is related to Th1 response, with the lower the Th1 response, the more severe the disease.[49]

Cao et al. demonstrated that MTB can inhibit Th1 immune responses through the programmed cell death 1 (PD-1)/ programmed cell death ligand 1 (PD-L1) protein signaling pathway, causing a Th1/Th2 imbalance and promoting lung cancer metastasis.[50] Treg can protect tumor cells by inhibiting apoptosis mediated by cytotoxic T lymphocytes (CTL).[47,48] Jie et al. showed that the percentage of Tregs in the peripheral blood of patients with active TB was significantly higher than that of the latent TB group or the control group.[51] Increased Treg activity may lead to immunosuppression and a decrease in the number of Th1 cells, which is conducive to the incidence and progression of skin cancer (Figure 5).[8]

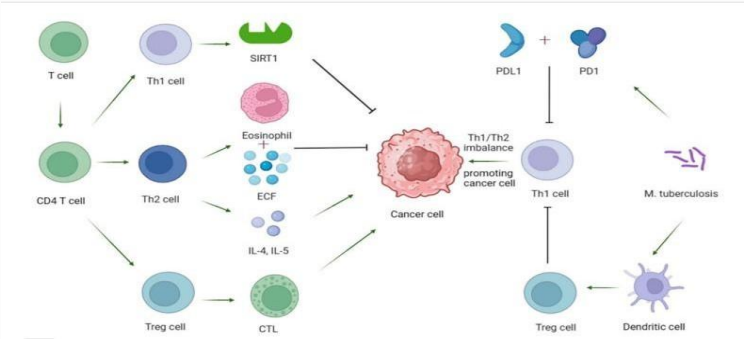


**Figure 5.** Mechanism of T cell influence on tumor cells and possible mechanism of MTB causing tumors.[8]

b. Myeloid derived suppressor cells (MDSC)
MDSCs are a heterogeneous group of cells from the bone marrow, which can inhibit immune cell responses through molecular reactive oxygen species (ROS) and other pathways, and have been shown to play a role in promoting malignant tumor growth and metastasis in tumor immunity.[52] This is because: in the tumor microenvironment, MDSCs inhibit excess ROS production, but MDSCs increase ROS production in a high concentration ROS environment. ROS can produce highly destructive hydroxyl radicals, resulting in damage to DNA, proteins, and lipids in the body. At the same time, jun and fos oncogenes are also activated, which even-tually leads to the occurrence of tumors.[8,53] On the other hand, maintaining an immunosup-pressor environment, MDSCs secrete a series of chemokines, thus playing a role in Treg recruitment, promoting tumor development.[48,54]

MDSCs also play an important role in chronic infectious diseases, such as TB. Studies have shown that under abnormal conditions of chronic infection such as TB, excessive production of MDSCs will lead to inhibition of host protective T lymphocyte responses.[55] The mechanism: MDSCs change the polarization direction of mono-cytes and macrophages by producing ROS, thereby inhibiting the anti-inflamma-tory response; on the other hand, studies have shown that MDSCs inhibit the immune responses of effector T cells and B cells by inducing Treg-like cells.[56] Therefore, it is very likely that MDSCs are produced after TB infection, and MDSCs ultimately promote the occurrence and progression of tumors through upregula-tion of ROS and recruitment of Treg.

c. Macrophages
Tumor-associated macrophages (TAMs) are one of the major immune cell types that infiltrate tumors and are generally divided into classically activated M1 macrophages and replacement-activated M2 macrophages. M1 functions anti- tumor, M2 promotes tumor cell formation and metastasis by inhibiting immune responses.

When the body is exposed to Mtb, macro-phages play an important role as the main innate immune cells.[8] The mechanism is likely as follows: First, it has been found that IL-37 induces macrophage polarization towards an M2-like phenotype during MTB infection.[57,58] Furthermore, it can promote the occurrence and metastasis of tumor cells.[8]

The second mechanism may be that Mtb toxic factor ESAT-6 can promote the polarization of macrophages toward pro-inflammatory M1 phenotype, and further toward anti-inflammatory M2 phenotype which also promotes the transformation of activated M1 phenotype into M2 phenotype.[59] This may play a role in promoting the development of cancer. In addition, in the inflammatory process, activated macro-phages will gather at the site of Mtb infection and produce a large amount of active nitrogen and ROS, etc. ROS promote tumor occurrence and progression by activating jun and fos oncogenes.[60]

d. Epidermal Growth Factor Receptor Signaling
EGFR signaling was shown to play an important role in regulating the prolife-ration, and differentiation of tumor cells, and is highly expressed in more than 60% of non-small cell lung cancers.[8] Mtb can cause tumors through the EGFR pathway, Nalbandian et al. found that Mtb-infected macrophages induce the production of epidermal regulatory hormone (EREG), activating the EGFR signaling pathway and promoting cancer development.45,61 Studies in mice have shown that Mtb infection stimulates EREG expression in a toll receptor 2 (TLR2)-dependent manner, and EREG binds to EGFR in a membrane or soluble form to stimulate downstream signal transduction, thereby inducing k-ras gene activation and mutation, leading to lung cancer[61] (Figure 6).

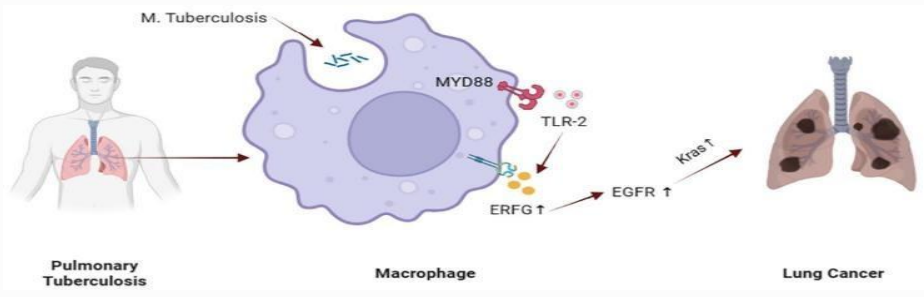


**Figure 6.** Possible mechanism of MTB causing tumors through the EGFR pathway[8]

A study in Taiwan evaluated the correlation of EGFR mutation outcomes in 275 TB patients, with 191 patients (69.5%) having elevated EGFR mutations in their study.[62] While it is certain that TB can induce EGFR mutations and increase the risk of tumor progression, the exact molecular mechanism remains to be further elucidated. TB not only affects EGFR mutation status, but also affects the treatment response of patients treated with EGFR tyrosine kinase inhibitors (TKIs). The concomitant use of antituberculosis drugs and TKIs in comorbid patients for EGFR-mutated lung cancer patients with active TB has shown to be a safe treatment strategy.

**Mechanisms of Tumor/Cancer-Induced Tuberculosis[8]**

a. Tumor effects
Currently, the mechanism of tumor-induced TB itself is not completely clear. Possible mechanisms are as follows: First, there are high levels of adenosine triphosphate (ATP) in the TME, and CD73 degrades ATP through dephosphorylation, and eventually produces adenosine.[63] Adenosine has a significant inhibitory effect on immune responses and may also play a protective role on extracellular bacteria and fungi, including MTB, by mediating type 3 immune effects.[64]

In addition, studies of lung cancer patients and mouse models have proved that lung cancer can cause a loss of microbial diversity, a reduction in the total number of bacteria, and a change in bacterial composition, which can lead to an imbalance in the microbial flora, resulting in a decrease in the stability of the body's immune homeostasis, and thus increase the host's susceptibility to various pathogens. 65 Studies have shown that up to 50%-70% of lung cancer patients develop pulmonary infectious complications during the course of the disease.[66]

b. Chemotherapy
Chemotherapy drugs have an effective killing effect on tumor cells, but affect the patient's immune system. Investigations in TB endemic areas found that TB infection is common in patients on systemic chemotherapy.[67] On the one hand, chemotherapy can produce immunosuppressive effects on cellular immunity and immunoglobulins, affecting immune function. Chemotherapy, can cause neutropenia and leukopenia leading to a severe immune deficiency state. Decreased immune deficiency makes it easier for patients to acquire infections, it also affects the normal immune defense function of the lung, thus increasing the susceptibility of the lung to bacteria including Mtb.[8] A study showed that cancer immunosuppression or anticancer chemotherapy increases the risk of TB reactivation, especially in cancer patients with previous TB.[8]

c. Immunotherapy
Immune checkpoint inhibitors (ICIs) one of the important immunotherapy therapies. ICIs mainly inhibit immune checkpoint proteins by blocking CTLA-4, PD-1, and PD-L1. ICIs affect immune function, which may increase susceptibility to Mtb infection: First, because ICIs work by blocking CTLA-4, PD-1, and PD-L1 to inhibit immune checkpoint proteins. Model studies in mice show that conditions in which CTLA-4 and PD-1 are absent can lead to homeostatic imbalanced immune system, resulting in reduced host immunity.[8,68]

Addition, pneumonia caused by ICI is the most common pulmonary toxic reaction, which may also be one of the reasons for the increased susceptibility to Mtb infection.[8] Macrophage apoptosis plays an important role in pneumonia. Through the mutual influence and stimulation of inflammation and apoptosis, macrophage apoptosis is accelerated while inflammation is aggravated.[69] After Mtb enters the body through the respiratory tract, the body mainly plays a defense role through macrophages and other cells. Therefore, macrophage apoptosis increases the risk of TB and reactivation of latent TB.[8]

**Risk Factors**

The following summarizes the risk factors for tuberculosis and lung cancer

**Table 2.** Risk factors for tuberculosis and lung cancer

| Tuberculosis | Lung Cancer |
|---|---|
| **1.** Have lived with or frequently interacted with people who have TB. The risk of transmission depends on the length of time in close proximity, air circulation in the room, and immune levels. | 1. Patients aged more than 40 years with a smoking history of 30 years or more and quit smoking within 15 years before the examination, or patients aged 20 years or more with a smoking history of 20 years. Years or older and the presence of at least one other risk factor. |
| **2.** Immunocompromized status (for example: People with HIV/AIDS, cancer, organ transplant recipients, or who take corticosteroid drugs for a long time are more susceptible to TB). | 2. Exposure to radiation/atmospheric substances and work with known carcinogens (such as radon, asbestos, arsenic, bichloro methyl ether, chromium, nickel, polycyclic aromatic compounds). |
| **3.** Substance abuse: People who inject drugs or alcohol are at higher risk | 3. Occupational exposure to chemical carcinogens |
| **4.** Everyone without access to adequate health services, especially children under 15 years old and young adults aged 15-44, are more vulnerable | 4. History of cancer in the patient or family |
| **5.** Pre-existing medical conditions or treatment from a specialist (for example: Diabetics, chronic kidney disease, malnutrition, or those undergoing dialysis or organ transplantation are at high risk | 5. Second-hand smoke environment. |
| **6.** Institutionalization: for example long- term health care facilities, mental hospitals, prisons. | 6. Exposure to certain metals (chromium, cadmium, arsenic), some organic chemicals, radiation, air pollution |
| **7.** Living in densely populated neighborhoods and uninhabitable housing | 7. Medical history of tuberculosis |
| **8.** Being a health worker with high-risk activities: Administration of pentamidine and other drugs, sputum induction procedures, bronchoscopy, suction, cough etiquette, managing patients with immunosuppression and administration of anesthesia and related procedures (e.g. intubation, suction) | 8. Cytogenetic studies have identified many chromosomal alterations in lung cancer with numerical abnormalities and structural deviations, including deletions and translocations. Small cell lung cancer is linked to oncogenes such as c-myc, L- myc, N-myc, c-raf, and tumor suppressor genes such as p53 and Rb. Non-small cell lung cancer is linked to K-ras, N-ras, H- ras, c-myc, c-raf, and tumor suppressor such as p16 and rb genes |

Source: Aribowo K, Medison I, Mizarti D, Fitrina DW. Co-Existence of tuberculosis and lung cancer. MAGNA MEDICA Berkala Ilmiah Kedokteran dan Kesehatan. 2022 Apr 9;9:51.

Several factors have been found to be associated with TB and lung cancer, including smoking, age, gender, and chronic inflammation due to Mtb infection.[9,71] According to the American Thoracic Society (ATS), the age at high risk of lung cancer is around 50 years, while TB can occur at any age.[72] Smoking is a strong risk factor for both lung cancer and TB.[9,73] Silva et al. found that, in general, patients with coexisting pulmonary TB and lung cancer were men with a history of smoking or former smoking.[74] There was a statistically significant 1.78-fold increase in lung cancer incidence in TB patients without smoking exposure, increasing to 2.93 times in smokers.[7] The increased risk of lung cancer was greatest in the first five years after diagnosis, the risk remaining 1.99 times higher for more than 20 years.[7]

## Diagnostic Challenges of Lung Cancer with Tuberculosis Co-Infection

### Suspicion of Lung Cancer with Tuberculosis Infection

Suspicion of patients with lung cancer and tuberculosis infection comes from radiological evidence and corresponding clinical features, especially in TB endemic areas.[75] Clinical features of pulmonary TB and lung cancer include cough, sputum, fever, hemoptysis, weight loss, and shortness of breath.[23] Due to similar symptoms, lung cancer and TB are difficult to distinguish for diagnosis. Patients with lung cancer and pulmonary TB have a higher proportion of cough but fewer night sweats than patients with pulmonary TB alone.[22,76]

The radiologic features for pulmonary TB cases are highly variable, usually in the upper lobes with cavitary lesions. In newly diagnosed active pulmonary TB, it often difficult to see concurrent lung cancer, especially in the same lobe. In a Korean study of 21 patients with pulmonary TB and lung cancer occurring in the same lobe, the diagnosis of lung cancer was delayed by an average of 11.7 months, mostly due to the occlusion of the nodules.

by TB lesions and misinterpret new lesions as worsening TB infection.[20] Compared to patients with TB alone, patients with pulmonary TB and lung cancer on CT thorax show a higher proportion of lobulated signs, masses, nodular shadows, satellite lesions, small vacuole signs, vacuole signs, spicule signs and pleural indentations, but a lower proportion of rope-like shadows and hollow lesions. [20] Whereas in TB, the main manifestations are cavitation, pleural effusion, miliary disease, lymphadenopathy and parenchymal disease.[77,78] The most frequent radiographic finding in lung cancer is a mass with or without collapse.[77] The edges of malignant tumors are uneven and form radiating threads. Hilar protrusion, pulmonary nodules, mediastinal expansion, whole or partial segmental, lobar, or pulmonary atelectasis, unresolved consolidation, cavitation, raised diaphragm, or pleural effusion are further signs of lung cancer.[77]

In newly diagnosed early-stage lung cancer, the presence of cavitary lesions, tree-in-bud appearance (peripheral "y"-shaped shadow on CT scan) and fibrocalcific foci on thoracic CT scan are indicative of possible infective agents such as TB. [79] Now that there are more sophisticated examinations with (PET)- CT for clinical staging, there are many reports that TB lesions look like lung cancer metastases.75 In particular, false-positive mediastinal lymph node metastases indicated by F-fluorodeoxyglucose (FDG) uptake are relatively common in TB endemic areas, for which a definitive diagnosis requires tissue samples by transbronchial needle aspiration guided by endobronchial ultrasonography (EBUS-TBNA).[75] This leads to a clinical diagnosis of extensive metastatic involvement of the primary lung cancer to be discovered and resected.[75]

Combined diagnosis has higher diagnostic value in lung cancer and TB, a study showed CEA, CYFRA21-1, and NSE marker examinations had high diagnostic value in lung cancer and TB patients, with a specificity of 89.9% and sensitivity of 94.9%.[80] Another study showed combined biomarkers and CT had high diagnostic value.

better. And in recent years, RNA and proteomic technologies have also been widely used in the diagnosis of TB and tumors. Some studies have applied miRNA as a new biomarker for the diagnosis and prognosis of cancer diseases, and achieved good results.[8]
In general, the presence of active pulmonary TB leads to delayed diagnosis and treatment of lung cancer. It was previously reported that active pulmonary TB in high-endemic countries worsens treatment outcomes for lung cancer patients.[81] On the other hand, the significance of coexistence of pulmonary TB and lung cancer in low-endemic countries remains unclear, as there are few reports. Contrary to previous reports, the prognosis of lung cancer was somewhat improved in the study of Lee et al, when lung cancer and active lung TB were diagnosed at the same time, patients were carefully examined and aggressively treated.[82]

The co-occurrence of TB and lung cancer may lead to an overestimation of lung cancer stage, as it is difficult to distinguish between lung cancer and TB lesions and may worsen the prognosis of lung cancer patients with active pulmonary TB.[20] Several meta-analyses have recommended that IFN-γ releasing assay (IGRA) be performed as a screening procedure prior to the initiation of systemic chemotherapy, especially immune checkpoint inhibitors (ICIs).[37] On the other hand, patients with malignant tumors are more likely to have false-negative results and weaker responses to IGRAs due to immunosuppression.[83] This is still controversial, but can be taken into consideration.

**Microbiologic Confirmation of TB**

Intensive sampling of sputum or other airway specimens for microbiologic examination confirms TB in patients with TB. Classical microbiologic evidence of TB in clinical or respiratory specimens consists of positive BTA microscopy, culture and identification of Mycobacterium tuberculosis (MTB) complex, and nucleic acid amplification/NAAT of Mtb. BTA positivity direct sputum or broncho-alveolar lavage, although suggestive of possible TB infection, is not found in most active TB infections, while the presence of atypical mycobacteria or non-tuberculous mycobacteria (NTM) can also lead to sputum BTA positivity. Culture is still the gold standard of microbiologic confirmation of TB infection but it takes a long time (6-8 weeks) and not all TB cases can be proven by culture.[75]

More recently, the wider use of various tests (PCR) has enabled rapid molecular testing as well as the use of GeneXpert.[75] The clinical diagnosis of TB infection can also be derived from the characteristic granulomatous inflammation (caseate) in the tissue (usually lung), when bta and/or culture results are negative. Occasionally, the first clinical suspicion of comorbid TB in early-stage lung cancer comes from pathologic evidence of granulomatous inflammation in dissected lung cancer specimens, especially in TB-endemic areas.[75]

**Treatment Strategies for Lung Cancer Patients with Pulmonary TB**

Current anti-TB treatment is based on WHO guidelines for TB in patients with active TB, and a combination of isoniazid, rifampicin, and pyrazinamide is used for 6-9 months.[84] If the patient is drug-resistant, the treatment regimen needs to be adjusted, and 2-5 sensitive or unused anti-TB drugs should be selected.[84] Treatment of lung cancer is more diverse, including surgery, chemotherapy and radiation therapy, targeted therapy, immunotherapy, cell therapy, and other therapies that may provide significant benefit to patients.[85]

Reports on the effectiveness and safety of therapy for pulmonary TB patients during TB treatment are limited, and there is no clear evidence. However, some reports suggest that cancer treatment does not interfere with TB treatment. In a retrospective study conducted in Japan, 30 patients with malignant tumors and TB (including 15 patients with lung cancer) reported that concurrent administration of anti-TB drugs and cytotoxic chemotherapy[86] Similarly, in a retrospective case-control study in Korea, TB that developed during chemotherapy was not clinically different from usual TB and chemotherapy did not interfere with TB treatment.[67]

Recently, it has been reported that the conversion rate of negative sputum cultures with standard TB treatment after 2 months reached 94%, even in patients with lung cancer; no significant difference was observed in the outcome of lung cancer treatment between patients with and without TB complications.[87] There are several criteria for determining when to stop or continue lung cancer treatment in patients with active TB. We need to consider the risk of transmission to medical staff, so ideally, if chemotherapy can be delayed, prioritize TB treatment. However, the priority given to TB treatment should not lead to loss of opportunity for radical treatment, such as radiation chemotherapy, therefore if radical treatment is needed immediately the patient can be hospitalized in isolation for 2 months.

A retrospective study in Japan of 24 patients with TB-associated malignancies showed that resumption of cancer treatment 2 months after completion of TB treatment may worsen prognosis and cancer progression.[87] Several papers have provided suggestions for the timing of lung cancer treatment for patients with concurrent TB. Ho et al. recommend that surgery and cytotoxic therapy be administered 2-3 weeks after starting TB treatment and that targeted therapy should be initiated while assessing drug interactions with anti-TB drugs and liver function.[75] The Japanese Society of Tuberculosis suggests that surgery be performed 4 weeks after starting TB treatment, and once confirmed BTA negative, radiotherapy can be started at the same time as TB treatment, and chemotherapy can be started 2-3 weeks after starting TB treatment.[83]

Other studies have shown that anti-TB drugs (isoniazid) can cause a decrease in white blood cells and platelets, resulting in liver damage, and cause a chemotherapy response in tumor patients, which may act as a suppressor of the therapeutic effect.[85] For patients with latent TB with lung cancer, anti-TB therapy is generally not required, but only anti-tumor therapy. For patients with active TB, both anti-tumor chemotherapy and anti-TB therapy are required.[85] For patients who require surgical resection of the tumor, preoperative tumor chemotherapy and anti-TB treatment should be synchronized, and anti-TB drugs should be continued after surgery.[8]

The following treatment flow can be used for lung cancer patients with tuberculosis infection. (Figure 7).

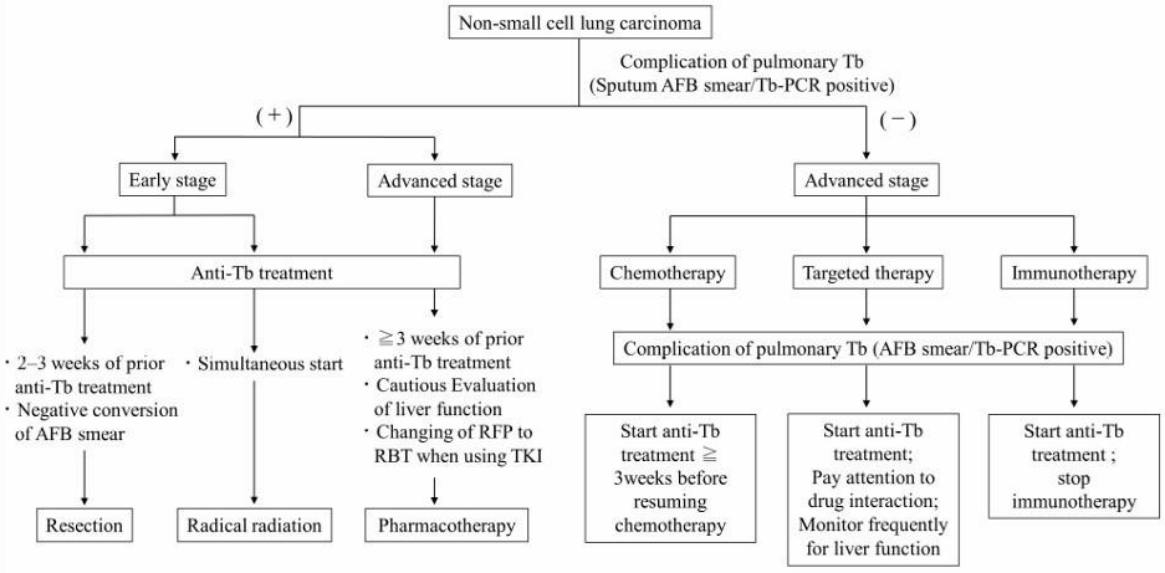


**Figure 7.** Suggested Algorithm for Lung Cancer Treatment Timing in Patients With Comorbid Sputum Smear/PCR Positive Active Pulmonary Tuberculosis[83]

In addition to the above algorithm there are other treatment algorithms, as follows:

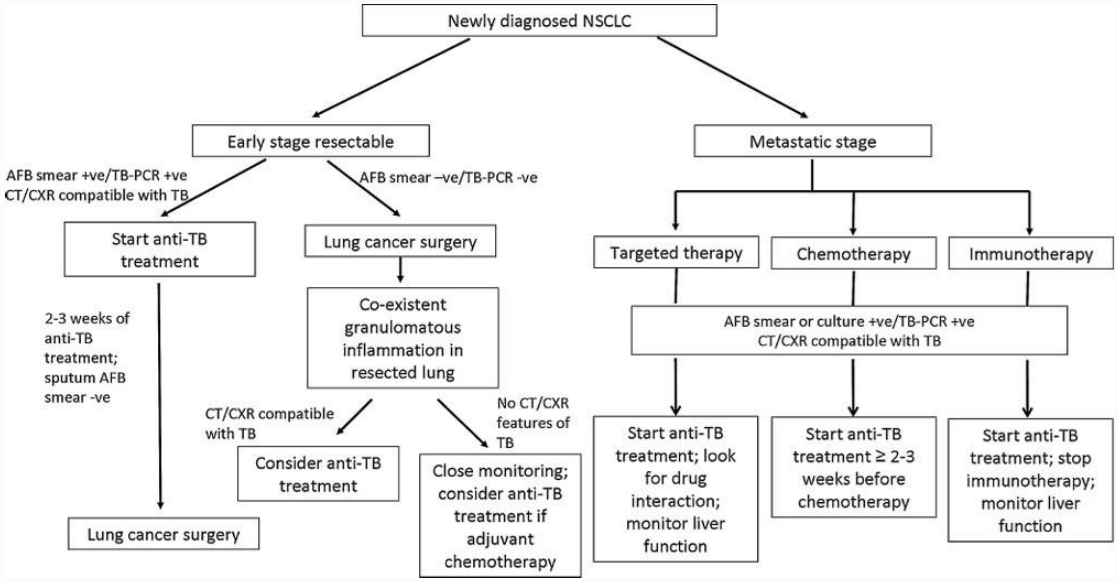


**Figure 8.** Suggested algorithm for diagnosis and management of tuberculosis disease and concurrent lung cancer in early stage and metastatic disease[75]

The use of immunotherapy in patients with tumors and TB should be cautious such as the use of Immune checkpoint inhibitors (ICI) or PD-1/PD-L1 treatment. Recent evidence suggests that tumor patients treated with ICIs may trigger reactivation of TB or accelerate the progression of TB infection.[88] Currently nanotechnology offers more possible strategies for the diagnosis and treatment of TCWT. Nano-dose inhalers have been developed for the treatment of lung cancer and TB, and can also be applied to patients with TB and lung cancer.[89] Clinical treatment of patients with tuberculosis comorbid lung cancer, it is necessary to consider comorbidities to develop a joint treatment strategy, and select appropriate treatment methods to play a synergistic or positive role in TB and tumors.

**Interactions Between Tuberculosis Drugs and Lung Cancer**

A doctor should pay attention to drug interactions when administering therapy to patients with lung cancer and tuberculosis. Among rifampicin is a strong inducer of cytochrome P450, which may reduce the effects of some anti-cancer drugs. In particular, rifampicin reduces the area under the concentration-time curve of most targeted therapies for cancer by 60-80%,[85] and caution should be exercised when using them together. Interactions between targeted therapy drugs and rifampicin are summarized in Table 3.[83]

**Table 3.** Drug Interactions Between Molecularly Targeted Drugs and Rifampicin

| Main target | Medicine | Mediator Metabolic | Decline AUC | Decline Cmax |
|---|---|---|---|---|
| **EGFR** | Gefitinib | CYP3A4 | 83% | 65% |
| | Erlotinib | CYP3A4 | 69% | 39% |
| | Ceritinib | P-glycoprotein | 34% | 22% |
| | Dacomitinib | CYP2D6 | no data | no data |
| | Osimertinib | CYP3A | 78% | 73% |
| **ALK** | Alectinib | CYP3A4 | 73% | 51% |
| | Lorlatinib | CYP3A, UGT1A4 | 85% | 76% |
| | Brigatinib | CYP2C8, CYP3A4 | 80% | 60% |
| | Ceritinib | CYP2C9, CYP3A4 | 70% | 44% |
| **ROS-1** | Crizotinib | CYP3A4 | 84% | 79% |
| **ROS- 1/NTRK** | Entrectinib | CYP3A | 77% | 55% |
| **BRAF** | Dabrafenib | CYP2C8/9, CYP3A4 | 34% | 27% |
| | Trametinib | CYP2B6, CYP3A4 | no data | no data |
| **MET** | Tepotinib | CYP2C8/9, CYP3A4 | no data | no data |
| | Capmatinib | CYP3A4 | 67% | 56% |
| **RET** | Selpercatinib | CYP3A4 | 87% | 70% |
| **KRAS** | Sotorasib | CYP3A | 51% | 35% |
| **HER2** | Trasruzumab | CYP3A | no data | no data |

Note: AUC*: area under the concentration-time curve. Cmax maximum plasma concentration,* EFGR*: epidermal growth factor receptor,* ALK*: anaplastic lymphoma kinase,* ROS-1, *c-ros oncogene 1;* NTRK*, neutrophic receptor tyrosine kinase,* BRAF*, B-raf proto-oncogene, serine/threonine kinase;* MET*: mesenchymal-epithelial transition,* RET*: rearranged during transfection,* KRAS*: v- Ki-ras2 Kirsten rat sarcoma viral oncogene homolog;* HER2*: human epidhermal growth factor type 2;* CYP*: cytochrome P450;* UGT, *UDP-glucoronosyl transferase*.

Source: Otoshi R, Ikeda S, Kaneko T, Sagawa S, Yamada C, Kumagai K, et al. Treatment Strategies for Non-Small-Cell Lung Cancer with Comorbid Respiratory Disease; Interstitial Pneumonia, Chronic Obstructive Pulmonary Disease, and Tuberculosis. Vol. 16, Cancers. Multidisciplinary Digital Publishing Institute (MDPI); 2024

## Conclusions

1. Tuberculosis and lung cancer are two diseases with high incidence and mortality rates, with similar clinical symptoms and radiological features.
2. Tuberculosis and lung cancer interact and influence each other, suggesting that TB and cancer should be diagnosed and treated holistically.
3. Integrated and individualized treatment protocols should be developed for patients with the aim of effectively enhancing therapeutic effects and improving prognosis.

## References


1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021 May;71(3):209-49.
2. Cabrera-Sanchez J, Cuba V, Vega V, Van der Stuyft P, Otero L. Lung cancer occurrence after an episode of tuberculosis: a systematic review and meta-analysis. Vol. 31, European Respiratory Review. European Respiratory Society; 2022.
3. WHO. Global tuberculosis report 2023. World Health Organization; 2023.
4. Oh CM, Roh YH, Lim D, Kong HJ, Cho H, Hwangbo B, et al. Pulmonary tuberculosis is associated with elevated risk of lung cancer in korea: the nationwide cohort study. J Cancer. 2020;11:1899-906.
5. Çakar B, Çiledağ A. Evaluation of coexistence of cancer and active tuberculosis; 16 case series. Respir Med Case Rep. 2018;23:33-7.
6. Byun HG, Yoo JY, Kim SJ, Lee OJ, Yoo MY. Coexistence of lung adenocarcinoma and pulmonary tuberculosis within a single lesion: A rare case report. Medicine (United States). 2019 Sep 1;98(39).
7. Liang HY, Li XL, Yu XS, Guan P, Yin ZH, He QC, et al. Facts and fiction of the relationship between preexisting tuberculosis and lung cancer risk: A systematic review. Vol. 125, International Journal of Cancer. 2009. p. 2936-44.
8. Wang C, Zou RQ, He GZ. Progress in mechanism-based diagnosis and treatment of tuberculosis comorbid with tumor. Vol. 15, Frontiers in Immunology. Frontiers Media SA; 2024.
9. Qin Y, Chen Y, Chen J, Xu K, Xu F, Shi J. The relationship between previous pulmonary tuberculosis and risk of lung cancer in the future. Vol. 17, Infectious Agents and Cancer. BioMed Central Ltd; 2022.
10. Cukic V. The association between lung carcinoma and tuberculosis. Med Arch. 2017 Jun 1;71:212-4.
11. Arliny Y, Yanifitri DB, Purqan M, Fachri M. Coexistence of pulmonary tuberculosis and small cell lung carcinoma: A significant problem in a tuberculosis-endemic country? Narra J. 2023 Aug 1;3.
12. Asmara OD, Tenda ED, Singh G, Pitoyo CW, Rumende CM, Rajabto W, et al. Lung cancer in Indonesia. Vol. 18, Journal of Thoracic Oncology. Elsevier Inc.; 2023. p. 1134-45.
13. Ministry of Health. Tuberculosis control in Indonesia 2022. https://tbindonesia.or.id/wp-content/uploads/ 2023/ 02/ Factsheet-Country Profile-Indonesia-2022.pdf.
14. Noviyani A, Nopsopon T, Pongpirul K. Variation of tuberculosis prevalence across diagnostic approaches and geographical areas of Indonesia. PLoS One. 2021 Oct 1;16(October 10).
15. Globocan. Number of new cases in 2022, both sexes, all ages. Glob. Cancer Obs. Available at: https://gco.iarc.fr/today (Accessed October 1, 2024).
16. Andarini S, Syahruddin E, Aditya N, Zaini J, Kurniawan FD, Ermayanti S, et al. Indonesian society of respirology (isr) consensus statement on lung cancer screening and early detection in Indonesia. Indonesian Journal of Respirology. Apr 19, 2023;43:144-50.
17. Arrieta O, Molina-Romero C, Cornejo-Granados F, Marquina-Castillo B, Avilés- Salas A, López-Leal G, et al. Clinical and pathological characteristics associated with the presence of the IS6110 Mycobacterim tuberculosis transposon in neoplastic cells from non-small cell lung cancer patients. Sci Rep. 2022 Dec 1;12.
18. Nastiti NP, Wulandari L, Sulistiawati S, Febriani A, Effendi WI. Prevalence of lung cancer with a history of tuberculosis. Respiratory Journal. May 31, 2023;9:87- 92.
19. Cicenas S, Vencevičius V. Lung cancer in patients with tuberculosis. World J Surg Oncol. 2007;5.
20. Uchida Y, Soejima K. Clinical characteristics of patients simultaneously diagnosed with lung cancer and active pulmonary tuberculosis in countries where tuberculosis is moderately endemic. Vol. 11, Translational Cancer Research. AME Publishing Company; 2022. p. 2480-2.
21. Rossato Silva D, Felipe Valentini Junior D, Mânica Müller A, Podalirio Borges de Almeida C, de Tarso Roth Dalcin P, et al. Pulmonary tuberculosis and lung cancer: simultaneous and sequential occurrence. Vol. 39, J Bras Pneumol. 2013.
22. Sun W, Zhang L, Liang J, Li X, Yang Y, Sun W, et al. Comparison of clinical and imaging features between pulmonary tuberculosis complicated with lung cancer and simple pulmonary tuberculosis: a systematic review and meta- analysis. Vol. 150, Epidemiology and Infection. Cambridge University Press; 2022.
23. Xiong K, Sun W, He Y, Fan L. Advances in molecular mechanisms of interaction between Mycobacterium tuberculosis and lung cancer: A narrative review. Vol. 10, Translational Lung Cancer Research. AME Publishing Company; 2021. p. 4012-26.

24. Everatt R, Kuzmickiene I, Davidaviciene E, Cicenas S. Incidence of lung cancer among patients with tuberculosis: a nationwide cohort study in Lithuania. Int J Tuberc Lung Dis. 2016 Jun;20(6):757-63. doi: 10.5588/ijtld.15.0783. PMID: 27155178.
25. Brenner DR, McLaughlin JR, Hung RJ. Previous lung diseases and lung cancer risk: A systematic review and meta-analysis. PLoS One. 2011;6.
26. Leung CY, Huang HL, Rahman MM, Nomura S, Krull Abe S, Saito E, et al. Cancer incidence attributable to tuberculosis in 2015: Global, regional, and national estimates. BMC Cancer. 2020 May 12;20.
27. Emgels EA, Min S, Chapman RS, Pfeiffer RM, Yu YY, Xingzhou H, et al. Tuberculosis and subsequent risk of lung cancer In Xuanwei, China. Int J Cancer. 2009 Mar 1;124:1183-7.
28. Heuvers ME, Aerts JGJV, Hegmans JP, Veltman JD, Uitterlinden AG, Ruiter R, et al. History of tuberculosis as an independent prognostic factor for lung cancer survival. Lung Cancer. 2012 Jun 1;76:452-6.
29. Vasava MS, Bhoi MN, Rathwa SK, Borad MA, Nair SG, Patel HD. Drug development against tuberculosis: past, present and future. Indian Journal of Tuberculosis. 2017 Oct 1;64:252-75.
30. Alsayed SSR, Gunosewoyo H. Tuberculosis: Pathogenesis, current treatment regimens and new drug targets. Vol. 24, International Journal of Molecular Sciences. Multidisciplinary Digital Publishing Institute (MDPI); 2023.
31. Tukiman MH, Norazmi MN. Immunometabolism of immune cells in mucosal environment drives effector responses against Mycobacterium tuberculosis. Vol. 23, International Journal of Molecular Sciences. MDPI; 2022.
32. Sheedy FJ, Divangahi M. Targeting immunometabolism in host defense against Mycobacterium tuberculosis. Vol. 162, Immunology. Blackwell Publishing Ltd; 2021. p. 145-59.
33. Polinário G, Primo LMDG, Rosa MABC, Dett FHM, Barbugli PA, Roque- Borda CA, et al. Antimicrobial peptides as drugs with double response against Mycobacterium tuberculosis coinfections in lung cancer. Vol. 14, Frontiers in Microbiology. Frontiers Media S.A.; 2023.
34. Gleeson LE, Sheedy FJ, Palsson-McDermott EM, Triglia D, O'Leary SM, O'Sullivan MP, et al. Cutting edge: Mycobacterium tuberculosis induces aerobic glycolysis in human alveolar macrophages that is required for control of intracellular bacillary replication. The Journal of Immunology. 2016 Mar 15;196:2444-9.
35. Coussens LM, Werb Z. Inflammation and cancer. Vol. 420, Nature. 2002. p. 860- 7.
36. Dubinett, S. M. Inflammation and lung cancer. New York, NY: Springer New York; 2015
37. Dobler CC, Cheung K, Nguyen J, Martin A. Risk of tuberculosis in patients with solid cancers and haematological malignancies: A systematic review and meta- analysis. Vol. 50, European Respiratory Journal. European Respiratory Society; 2017.
38. Jett JR, Carr LL. Targeted therapy for non-small cell lung cancer. Vol. 188, American Journal of Respiratory and Critical Care Medicine. 2013. p. 907-12.
39. Pao W, Miller V, Zakowski M, Doherty J, Politi K, Sarkaria I, et al. EGF receptor gene mutations are common in lung cancers from "'never smokers"' and are associated with sensitivity of tumors to gefitinib and erlotinib [Internet].2004. Available from: www.pnas.orgcgidoi10.1073pnas.0405220101
40. Liu H, Zhang B, Sun Z. Spectrum of EGFR aberrations and potential clinical implications: insights from integrative pan-cancer analysis. Cancer Commun. 2020 Jan 1;40:43-59.
41. Shi Y, Au JS, Thongprasert S, Srinivasan S, Tsai CM, Khoa MT, et al. A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER). J Thorac Oncol. 2014 Feb;9:154-62. doi: 10.1097/JTO.0000000000000033. PMID: 24419411; PMCID: PMC4132036.
42. Tfayli A, Fakhri G, Al Assaad M. Prevalence of the epidermal growth factor receptor mutations in lung adenocarcinoma patients from the Middle East region. Vol. 14, Annals of Thoracic Medicine. Wolters Kluwer Medknow Publications; 2019. p. 173-8.
43. Hwang K, Paik SS, Lee SH. Impact of pulmonary tuberculosis on the EGFR mutational status and clinical outcome in patients with lung adenocarcinoma. Cancer Res Treat. 2019 Jan 1;51:158-68.
44. Luo YH, Wu CH, Wu WS, Huang CY, Su WJ, Tsai CM, et al. Association between tumor epidermal growth factor receptor mutation and pulmonary tuberculosis in patients with adenocarcinoma of the lungs. Journal of Thoracic Oncology. 2012;7:299-305.
45. Nalbandian A, Yan BS, Pichugin A, Bronson RT, Kramnik I. Lung carcinogenesis induced by chronic tuberculosis infection: The experimental model and genetic control. Oncogene. 2009 Apr 30;28:1928-38.
46. Byun HG, Yoo JY, Kim SJ, Lee OJ, Yoo MY. Coexistence of lung adenocarcinoma and pulmonary tuberculosis within a single lesion: A rare case report. Medicine (United States). 2019 Sep 1;98.
47. Chatterjee S, Daenthanasanmak A, Chakraborty P, Wyatt MW, Dhar P, Selvam SP, et al. CD38-NAD+ Axis Regulates immunotherapeutic anti-tumor t cell response. Cell Metab. 2018 Jan 9;27:85-100.e8.
48. Duan MC, Zhong XN, Liu GN, Wei JR. The treg/Th17 paradigm in lung cancer. Vol. 2014, Journal of Immunology Research. Hindawi Publishing Corporation; 2014.
49. Barak V, Kidon MI. Article in The Israel Medical Association journal - [Internet]. 2007. Available from: https://www.researchgate.net/publication/6196974

50. Cao S, Li J, Lu J, Zhong R, Zhong H. Mycobacterium tuberculosis antigens repress Th1 immune response suppression and promote lung cancer metastasis through PD-1/PDl-1 signaling pathway. Cell Death Dis. 2019 Feb 1;10.
51. Luo J, Zhang M, Yan B, Zhang K, Chen M, Deng S. Imbalance of Th17 and Treg in peripheral blood mononuclear cells of active tuberculosis patients. Brazilian Journal of Infectious Diseases. 2017 Mar 1;21:155-61.
52. Gabrilovich DI. Myeloid-derived suppressor cells. Cancer Immunol Res. 2017 Jan 1;5:3-8.
53. Corzo CA, Condamine T, Lu L, Cotter MJ, Youn JI, Cheng P, et al. HIF-1α regulates function and differentiation of myeloid-derived suppressor cells in the tumor microenvironment. Journal of Experimental Medicine. 2010 Oct 25;207:2439-53.
54. Dyck L, Mills KHG. Immune checkpoints and their inhibition in cancer and infectious diseases. Vol. 47, European Journal of Immunology. Wiley-VCH Verlag; 2017. p. 765-79.
55. Ray A, Chakraborty K, Ray P. Immunosuppressive MDSCS induced by TLR signaling during infection and role in resolution of inflammation. Vol. 4, Frontiers in Cellular and Infection Microbiology. 2013.
56. Munansangu BSM, Kenyon C, Walzl G, Loxton AG, Kotze LA, Plessis N du. Immunometabolism of myeloid-derived suppressor cells: implications for Mycobacterium tuberculosis infection and insights from tumor biology. Vol. 23, International Journal of Molecular Sciences. MDPI; 2022.
57. Ward PS, Thompson CB. Metabolic reprogramming: a cancer hallmark even warburg did not anticipate. Vol. 21, Cancer Cell. Cell Press; 2012. p. 297-308.
58. Huang Z, Gao C, Chi X, Hu YW, Zheng L, Zeng T, et al. IL-37 expression is upregulated in patients with tuberculosis and induces macrophages towards an m2-like phenotype. Scand J Immunol. 2015 Oct 1;82:370-9.
59. Refai A, Gritli S, Barbouche MR, Essafi M. Mycobacterium tuberculosis virulent factor ESAT-6 drives macrophage differentiation toward the pro-inflammatory M1 phenotype and subsequently switches it to the anti- inflammatory M2 phenotype. Front Cell Infect Microbiol. 2018 Sep 18;8(SEP).
60. Zhai W, Wu F, Zhang Y, Fu Y, Liu Z. The immune escape mechanisms of Mycobacterium Tuberculosis. Vol. 20, International Journal of Molecular Sciences. MDPI; 2019.
61. Cheng WL, Feng PH, Lee KY, Chen KY, Sun WL, Van Hiep N, et al. The role of ereg/egfr pathway in tumor progression. Vol. 22, International Journal of Molecular Sciences. MDPI; 2021.
62. Xie Y, Su N, Zhou W, Lei A, Li X, Li W, et al. Concomitant pulmonary tuberculosis impairs survival in advanced epidermal growth factor receptor (Egfr) mutant lung adenocarcinoma patients receiving egfr-tyrosine kinase inhibitor. Cancer Manag Res. 2021;13:7517-26.
63. Pansy K, Uhl B, Krstic J, Szmyra M, Fechter K, Santiso A, et al. Immune regulatory processes of the tumor microenvironment under malignant conditions. Int J Mol Sci. 2021 Dec 1;22.
64. Haskó G, Antonioli L, Cronstein BN. Adenosine metabolism, immunity and joint health. Vol. 151, Biochemical Pharmacology. Elsevier Inc.; 2018. p. 307-13.
65. Goto T. Microbiota and lung cancer. Vol. 86, Seminars in Cancer Biology. Academic Press; 2022. p. 1-10.
66. Gadgeel SM. enrolled 482 patients with completely resected stage IB and II NSCLC, and these patients were role of chemotherapy and targeted therapy in early-stage non-small cell lung cancer. 2024.
67. Kim DK, Lee SW, Yoo CG, Kim YW, Han SK, Shim YS, et al. Clinical characteristics and treatment responses of tuberculosis in patients with malignancy receiving anticancer chemotherapy. Chest. 2005 Oct 1;128:2218- 22.
68. Tivol EA, Borriello F, Nicola Schweitzer A, Lynch WP, Bluestone JA, Sharpe AH. Loss of ctla-4 leads to massive lymphoproliferation and fatal multiorgan tissue destruction, revealing a critical negative regulatory role of CTLA-4. Vol. 3, Immunity. 1995.
69. Fan EKY, Fan J. Regulation of alveolar macrophage death in acute lung inflammation. Vol. 19, Respiratory Research. BioMed Central Ltd.; 2018.
70. Aribowo K, Medison I, Mizarti D, Fitrina DW. Co-Existence of tuberculosis and lung cancer. MAGNA MEDICA Berkala Ilmiah Kedokteran dan Kesehatan. 2022 Apr 9;9:51.
71. Ho LJ, Yang HY, Chung CH, Chang WC, Yang S Sen, Sun CA, et al. Increased risk of secondary lung cancer in patients with tuberculosis: A nationwide, population-based cohort study. PLoS One. 2021 May 1;16(May 5).
72. Park HY, Kang D, Shin SH, Choi H, Jang SH, Lee CH, et al. Pulmonary tuberculosis and the incidence of lung cancer among patients with chronic obstructive pulmonary disease. Ann Am Thorac Soc. 2022 Apr 1;19:640-8.
73. Shiels MS, Albanes D, Virtamo J, Engels EA. Increased risk of lung cancer in men with tuberculosis in the alpha-tocopherol, beta-carotene cancer prevention study. Cancer Epidemiology Biomarkers and Prevention. 2011 Apr;20:672-8.
74. Rossato Silva D, Felipe Valentini Junior D, Mânica Müller A, Podalirio Borges de Almeida C, de Tarso Roth Dalcin P, Rossato Silva Rua Ramiro D. Pulmonary tuberculosis and lung cancer: simultaneous and sequential occurrence. Vol. 39, J Bras Pneumol. 2013.

75. Ho JC man, Leung CC. Management of co-existent tuberculosis and lung cancer. Vol. 122, Lung Cancer. Elsevier Ireland Ltd; 2018. p. 83-7.
76. Uchida Y, Soejima K. Clinical characteristics of patients simultaneously diagnosed with lung cancer and active pulmonary tuberculosis in countries where tuberculosis is moderately endemic. Vol. 11, Translational Cancer Research. AME Publishing Company; 2022. p. 2480-2.
77. Bhatt MLB, Kant S, Bhaskar R. Pulmonary tuberculosis as differential diagnosis of lung cancer. South Asian J Cancer. 2012 Jul;1:36-42.
78. Mahler B, De Vries G, Van Hest R, Gainaru D, Menezes D, Popescu G, et al. Use of targeted mobile X-ray screening and computer-aided detection software to identify tuberculosis among high-risk groups in Romania: Descriptive results of the E-DETECT TB active case-finding project. BMJ Open. 2021 Aug 24;11.
79. Skoura E, Zumla A, Bomanji J. Imaging in tuberculosis. Vol. 32, International Journal of Infectious Diseases. Elsevier; 2015. p. 87-93.
80. Jia H, Zhang L, Wang B. The value of combination analysis of tumor biomarkers for early differentiating diagnosis of lung cancer and pulmonary tuberculosis [Internet]. 2019. Available from: www.annclinlabsci.org
81. Christopoulos A, Saif MW, Sarris EG, Syrigos KN. Epidemiology of active tuberculosis in lung cancer patients: A systematic review. Clinical Respiratory Journal. 2014 Oct 1;8:375-81.
82. Lee HY, Kang HS, Kang JY, Kim JW, Lee SH, Kim SJ, et al. Clinical characteristics and survival of patients concurrently diagnosed with lung cancer and active pulmonary tuberculosis. Transl Cancer Res. 2022 Aug 1;11:2671-80.
83. Otoshi R, Ikeda S, Kaneko T, Sagawa S, Yamada C, Kumagai K, et al. Treatment Strategies for Non-Small-Cell Lung Cancer with Comorbid Respiratory Disease; Interstitial Pneumonia, Chronic Obstructive Pulmonary Disease, and Tuberculosis. Vol. 16, Cancers. Multidisciplinary Digital Publishing Institute (MDPI); 2024.
84. WHO consolidated guidelines on tuberculosis Module 5: Management of tuberculosis in children and adolescents [Internet]. 2022. Available from: http://apps.who.int/bookorders.
85. Ye MF, Su S, Huang ZH, Zou JJ, Su DH, Chen XH, et al. Efficacy and safety of concurrent anti-tuberculosis treatment and chemotherapy in lung cancer patients with co-existent tuberculosis. Ann Transl Med. Sep 2020;8:1143- 1143.
86. Hirashima T, Tamura Y, Han Y, Hashimoto S, Tanaka A, Shiroyama T, et al. Efficacy and safety of concurrent anti-cancer and anti-tuberculosis chemotherapy in Cancer patients with active Mycobacterium tuberculosis: A retrospective study. BMC Cancer. 2018 Oct 12;18.
87. Fujita T, Endo M, Gu Y, Sato T, Ohmagari N. Mycobacterium tuberculosis infection in cancer patients at a tertiary care cancer center in Japan. Journal of Infection and Chemotherapy. 2014 Mar 1;20:213-6.
88. Morelli T, Fujita K, Redelman-Sidi G, Elkington PT. Infections due to dysregulated immunity: an emerging complication of cancer immunotherapy. Vol. 77, Thorax. BMJ Publishing Group; 2022. p. 304-11.
89. Kumar R, Mehta P, Shankar KR, Rajora MAK, Mishra YK, Mostafavi E, et al. Nanotechnology-assisted metered-dose inhalers (mdis) for high-performance pulmonary drug delivery applications. Vol. 39, Pharmaceutical Research. Springer; 2022. p. 2831-55.

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Review Article

# The Role of Proinflammatory Cytokines in Lung Cancer

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## Abstract

Lung cancer is one of the deadliest types of cancer worldwide, with high morbidity and mortality rates. In the progression of lung cancer, pro-inflammatory cytokines play a crucial role in chronic inflammatory processes that can facilitate the growth and spread of cancer cells. Pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α have been extensively studied due to their association with the pathogenesis of lung cancer. IL-1 triggers inflammatory responses and modulates the tumor microenvironment, IL-6 is involved in cancer cell proliferation and resistance to apoptosis, while TNF-α contributes to and metastasis. The relationship between these pro-inflammatory cytokines and lung cancer indicates that increased levels of these cytokines in the body can worsen cancer conditions by supporting tumor growth, evading immune responses, and promoting metastatic spread. Further research on the specific mechanisms of these pro-inflammatory cytokines is expected to pave the way for the development of more effective new therapies in tackling lung cancer.

***Keywords:*** *interleukin-1, interleukin-6, lung cancer, pro-inflammatory cytokines, tumor necrosis factor alpha*

## Abstrak

Kanker paru merupakan salah satu jenis kanker paling mematikan di dunia, dengan angka morbiditas dan mortalitas yang tinggi. Dalam progresi kanker paru, sitokin proinflamasi memainkan peran penting dalam proses inflamasi kronis yang dapat memfasilitasi pertumbuhan dan penyebaran sel kanker. Sitokin proinflamasi seperti IL-1, IL-6, dan TNF-α telah banyak diteliti karena kaitannya dengan patogenesis kanker paru. IL-1 memicu respons inflamasi dan memodulasi mikro lingkungan tumor, IL-6 berperan dalam proliferasi sel kanker dan resistensi terhadap apoptosis, sedangkan TNF-α berkontribusi terhadap invasi dan metastasis. Hubungan antara sitokin proinflamasi tersebut dengan kanker paru menunjukkan bahwa peningkatan kadar sitokin ini di dalam tubuh dapat memperburuk kondisi kanker dengan mendukung pertumbuhan tumor, menghindari respons imun, serta meningkatkan penyebaran metastasis. Penelitian lebih lanjut mengenai mekanisme spesifik sitokin proinflamasi ini diharapkan dapat membuka jalan bagi pengembangan terapi baru yang lebih efektif dalam penatalaksanaan kanker paru.

***Kata kunci:*** *interleukin-1, interleukin-6, kanker paru, sitokin proinflamasi, tumor necrosis factor alpha*

## Background

Lung cancer is one of the most common and deadly types of cancer in the world. Based on histology, *lung cancer* is classified into two main types: *small cell* lung cancer (SCLC=KPKSK) and *non-small cell* lung *cancer* (NSCLC=KPKBSK) (Figure 1). KPKSK is rarer in incidence but is known to be highly aggressive and fast-spreading, while KPKBSK is more common and has several subtypes such as adenocarcinoma, squamous cell carcinoma and large cell carcinoma. Major risk factors for lung cancer include smoking, exposure to cigarette smoke, air pollution, and exposure to harmful chemicals such as asbestos and radon. Diagnosis is often delayed due to non-specific symptoms in the early stages, resulting in a poor prognosis for many patients.

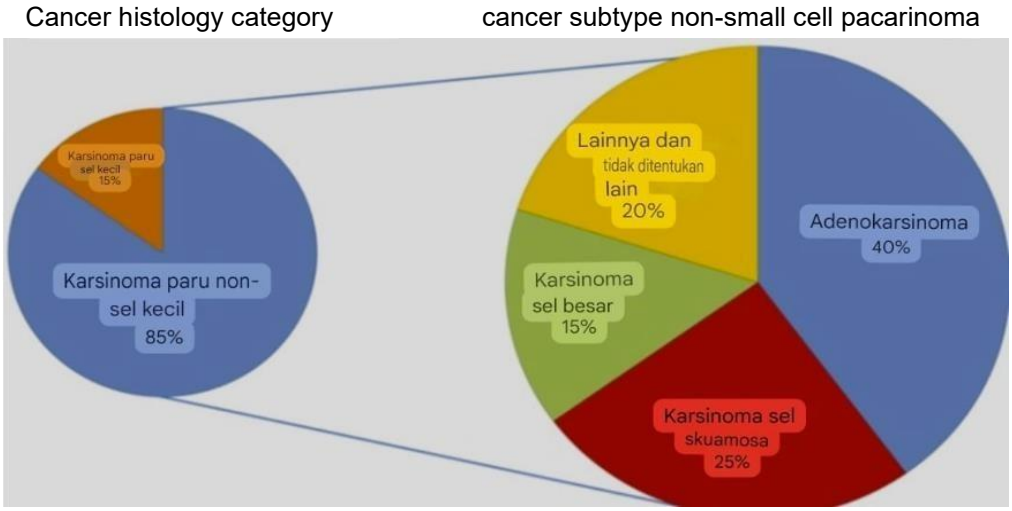


**Figure 1.** Proportion of lung cancer by type[2]

Molecular mechanisms in lung cancer involve various genetic and epigenetic alterations that trigger uncontrolled cell proliferation, evasion of apoptosis, angiogenesis and metastasis. Major signaling pathways often involved include mutations in the *Epidermal Growth Factor Receptor* (EGFR), *Kirsten Rat Sarcoma Viral Oncogene Homolog* (KRAS) and *Anaplastic Lymphoma Kinase* (ALK) genes (figure 2). Findings about these specific mutations have enabled the development of targeted therapies, such as EGFR and ALK inhibitors, which have shown significant success in prolonging patient survival. More extensive research on these molecular mechanisms may pave the way for the discovery of new therapies and a more personalized approach in the treatment of lung cancer.[1,3]

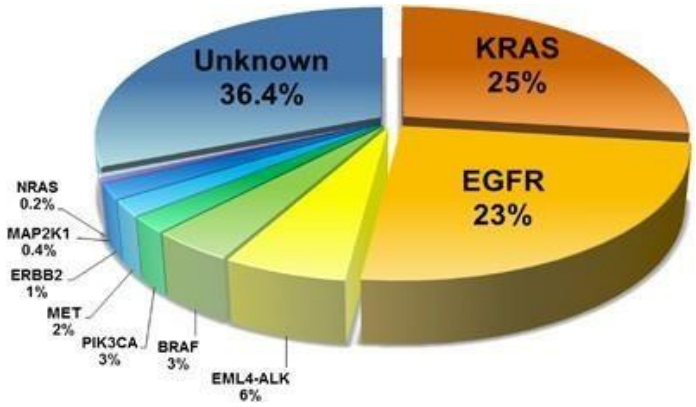


**Figure 2.** Proportion of genetic mutations in adenocarcinoma based on data from the *National Cancer Institute* Lung *Cancer* Mutation Consortium[4]

Inflammation is the body's natural response to infection or injury, but chronic inflammation can contribute to the development of various chronic diseases, including cancer. In cancer, chronic inflammation can create an environment that is support cancer cell proliferation, invasion and

metastasis. Proinflammatory cytokines such as Interleukin-1 (IL-1), Interleukin-6 (IL-6) and Tumor Necrosis Factor Alpha (TNF-α) play a key role in mediating this inflammatory process. These cytokines can induce changes in the tumor microenvironment, promote angiogenesis, and inhibit the body's anti-tumor defense mechanisms. Research shows that uncontrolled chronic inflammation contributes to the initiation and progression of many cancers, including lung cancer (figure 3).[5,6]

Several pro-inflammatory cytokines have also been reported to increase the progressivity of lung cancer and facilitate drug resistance. Therefore, targeting inflammatory pathways may be an effective strategy for the prevention and treatment of lung cancer. The main objective of this literature review is to comprehensively examine the role of pro-inflammatory cytokines in the development and progression of lung cancer and explore the specific mechanisms potential therapeutic interventions targeting the inflammatory pathway in the treatment of lung cancer. Due to the large number of cytokines involved in the inflammatory process, this literature review is limited to discussing three proinflammatory cytokines that are widely recognized and have important functions, namely IL-1, IL-6 and TNF-α.[6]

## Lung Cancer

### Lung Cancer Epidemiology

Lung cancer is the leading cause of cancer death worldwide, with incidence and prevalence varying globally and regionally. Globally, more than 2 million new cases are diagnosed each year, with a mortality rate approaching 1.8 million. In developing countries, the incidence of lung cancer is increasing with increased smoking and air pollution. In developed countries, despite a decline in incidence due to decreased smoking, mortality rates remain high. The main risk factors for lung cancer include smoking, which is responsible for about 85% of cases, as well as environmental exposures such as asbestos, radon and air pollution. Genetic factors also play an important role, with certain gene mutations increasing a person's risk of developing lung cancer.[1]

### Pathogenesis and Progression of Lung Cancer

The pathogenesis of lung cancer involves various complex molecular and cellular mechanisms. Genetic mutations in oncogenes such as EGFR, KRAS, ALK as well as loss of function of tumor suppressor genes such as p53 contribute to uncontrolled cell proliferation, resistance to apoptosis and the ability to invade surrounding tissues. The development of lung cancer occurs through several stages, starting from basal cell hyperplasia, dysplasia, carcinoma in situ, to invasive carcinoma. In the early stages, cancer cells may be confined to the epithelial layer of the lung, but over time these cells can penetrate the basement membrane, enter the lymphatic and circulatory systems and eventually cause metastasis to other organs such as the brain, bone and liver. A deep understanding of these mechanisms is important for the development of more effective therapies and prevention strategies.[3]

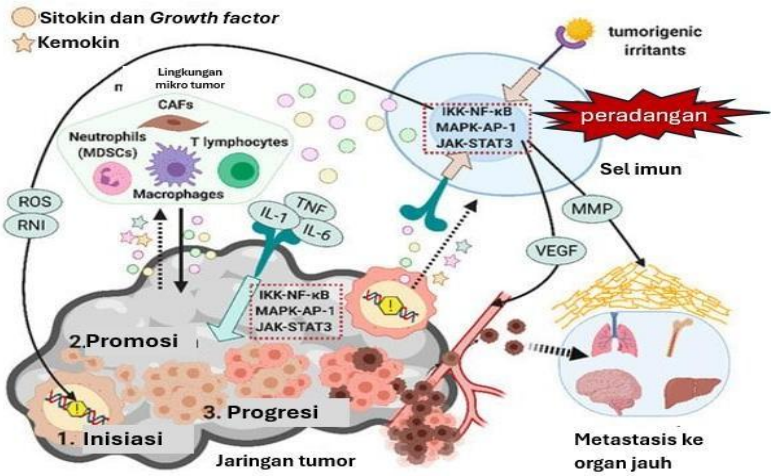


**Figure 3.** Role of proinflammatory cytokines in the tumor microenvironment[7]

## Cytokine Physiology

### Definition, Classification, and Mechanism of Action of Cytokines

Cytokines are small proteins secreted by immune system cells to communicate and mediate responses. Proinflammatory cytokines are a subgroup of cytokines that promote inflammation in response to infection or injury. These cytokines play an important role in triggering and maintaining the inflammatory response. The main classifications of proinflammatory cytokines include IL-1, IL-6 and TNF-α. Interleukin-1 is a key mediator in acute inflammatory responses, IL-6 has a role in the regulation of immune responses and chronic inflammation, while TNF-α is a powerful cytokine that can trigger apoptosis but also supports chronic inflammation that can contribute to carcinogenesis.[8]

Proinflammatory cytokines play a critical role in regulating immune and inflammatory responses by stimulating immune cells to migrate to sites of infection or injury, increasing vascular permeability and facilitating communication between immune cells. The mechanism of action of proinflammatory cytokines on target cells begins with binding to specific receptors on the cell surface that trigger various intracellular signaling pathways. These pathways can activate the transcription of genes involved in inflammation, cell proliferation and apoptosis. For example, IL-1 can activate *the Nuclear Factor Kappa B* (NF-κB) pathway involved in inflammatory responses, while IL-6 can activate the *Janus kinase-signal transducer and activator of transcription* (JAK/STAT) pathway involved in cell growth and differentiation. Tumor necrosis factor alpha through its receptor can trigger pathways that lead to apoptosis or in some cases support tumor cell survival and proliferation. [8]

### Inflammation and Cancer

The theory of inflammation as a cause of cancer suggests that chronic inflammation can create a favorable environment for cancer initiation and progression. Chronic inflammation causes oxidative stress, DNA damage and epigenetic changes that increase the risk of mutations and uncontrolled cell proliferation. In carcinogenesis, chronic inflammation plays a role in supporting a tumor microenvironment rich in proinflammatory cytokines, proteolytic enzymes and growth factors that can all promote cancer cell growth and spread. Therefore, chronic inflammation is not only a result of cancer but also contributes to the development and progression of cancer.[6]

## Specific Role of Proinflammatory Cytokines

### Interleukin-1 (IL-1)

Interleukin-1 is one of the major proinflammatory cytokines that plays an important role in the regulation of immune and inflammatory responses. Interleukin-1 consists of two main isoforms, namely IL-1α and IL-1β, which despite having similar functions are produced and regulated by different pathways. Interleukin-1α is usually found inside cells, whereas IL-1β is mainly released into the extra-cellular environment. Both are produced by various cell types such as macrophages, dendritic cells, fibroblasts, and some types of epithelial cells.

Interleukin-1 acts as a key mediator in the acute inflammatory response, helping the body fight infection and repair damaged tissue (figure 4).[9]

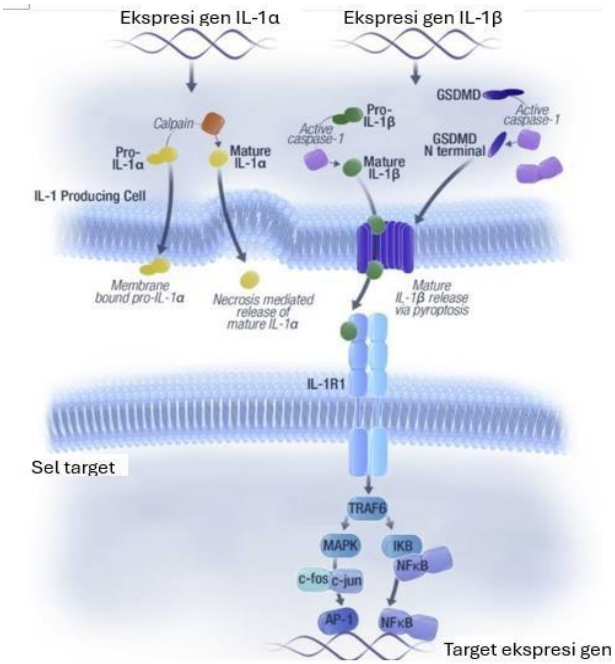


**Figure 4.** Mechanism of action of IL-1 molecules[10]

The role of IL-1 is not limited to acute inflamma-tory processes. In chronic inflammatory conditions, such as those in autoimmune diseases and cancer, IL-1 can contribute to tissue damage and worsen the disease. For example, in lung cancer, IL-1 plays an important role in tumor initiation and progression. IL-1 can facilitate cancer cell invasion and metastasis by increasing the expression of enzymes that break down the extracellular matrix, such as matrix metalloproteinases (MMPs). Interleukin-1 also stimulates angiogenesis and neovascularization

systems that facilitate metastasis, as well as inhibiting adaptive immune responses and promoting local immunosuppression.[9]
Excessive IL-1 activity can lead to detrimental effects. In chronic inflammation, IL-1 can trigger a sustained immune response, causing tissue damage and favoring the development of chronic diseases such as rheumatoid arthritis and inflammatory bowel disease. IL-1 may also play a role in the induction of fever as part of the body's response to infection. By increasing vascular permeability and stimulating the production of growth factors, IL-1 aids tissue healing, but if not properly regulated, can lead to damaging inflammation. Therefore, regulation of IL-1 activity is key in maintaining the balance between protective and pathological inflammatory responses. [9]

The mechanism of action of IL-1 begins with binding to the IL-1 receptor (IL-1R) located on the surface of target cells. This binding triggers a series of intracellular signaling pathways, including the NF-κB and MAPK pathways, which play a role in the transcription of proinflammatory genes. Activation of these pathways results in the production of more cytokines, proteolytic enzymes and adhesion molecules, all of which contribute to a more robust and sustained inflammatory response. In acute inflammation, these mechanisms help the body fight infection and repair damaged tissues. However, prolonged inflammation can trigger a range of diseases including lung cancer. [9]

In chronic inflammatory conditions, these activation mechanisms can become pathological. Excessive IL-1 activity can lead to sustained inflammation that damages healthy tissues and favors the development of chronic diseases, including cancer. In lung cancer, excessive IL-1 can increase the expression of enzymes such as MMPs, which break down the extracellular matrix and facilitate cancer cell invasion and metastasis. In addition, IL-1 can also promote angiogenesis, which is the formation of new blood vessels that nourish the tumor, thus supporting cancer growth and spread. Understanding IL-1' mechanism of action is important for the development of therapies that target inflammatory pathways in the treatment of chronic diseases and cancer. [9]

In lung cancer, IL-1 plays an important role in various stages of tumor development and progression. The recent *Canakinumab Anti-inflammatory Thrombosis Outcomes Study* (CANTOS) which evaluated the use of anti-interleukin-1β therapy in atherosclerotic disease revealed that interleukin-1β (IL-1β) blockade with canakinumab resulted in a lower incidence of lung cancer. This means that the use of canakinumab, which inhibits IL-1β, also has a positive effect in reducing the risk of developing lung cancer. Studies have also shown that high levels of IL-1 in tumor tissue or blood of lung cancer patients are often associated with a worse prognosis.[11]

Experimental studies have also shown that inhibition of the IL-1 pathway can reduce tumor growth and metastasis in experimental animal models. IL-1 inhibitors or IL-1 receptor antagonists have shown potential in suppressing the tumorigenic activity of IL-1. In addition, therapies targeting IL-1 can be used in conjunction with conventional therapies such as chemotherapy or immunotherapy to improve treatment effectiveness. Thus, IL-1 is not only an important target for basic research but also has meaningful clinical potential in the development of novel therapeutic strategies for lung cancer.[12]

**Interleukin-6 (IL-6)**

Interleukin-6 (IL-6) is a proinflammatory cytokine that plays an important role in the regulation of immune and inflammatory responses. Interleukin-6 is produced by various cell types, including macrophages, T cells, fibroblasts and endothelial cells, in response to infection, trauma or other stress. As one of the major mediators of inflammation, IL-6 mediates a variety of biological functions, including T and B cell differentiation, immunoglobulin production, and stimulation of hepatocytes to produce acute phase proteins. Interleukin-6 plays a central role in innate and adaptive immune responses, helping the body fight pathogens and repair damaged tissues. In, IL-6 also plays a role in various chronic inflammatory conditions and autoimmune diseases. For example, high levels of IL-6 have been associated with diseases such as rheumatoid arthritis, cardiovascular disease, and various cancers, including lung cancer.[13]

Interleukin-6 has several key functions in mediating the inflammatory process. One of its main functions is to induce hepatocytes to produce acute phase proteins such as *C- reactive* protein (CRP), which is important for systemic inflammatory responses. In addition, IL-6 plays a role in T cell differentiation into the T *helper* cell (Th17) subset, which is important for defense against infection but can also contribute to autoimmune diseases. Interleukin-6 also promotes the proliferation and differentiation of B cells, increasing the production of antibodies essential for humoral immune responses. Under these conditions, IL-6 can trigger a sustained inflammatory response and damage tissues. Therefore, IL-6 is an important target in the development of therapies to control chronic inflammation and prevent the

progression of more severe diseases.[13]

Excessive IL-6 activity can lead to detrimental effects. In chronic inflammation, IL-6 can trigger a prolonged inflammatory response, causing tissue damage and favoring the development of pathological conditions. Interleukin-6 can have detrimental effects on cancer through several mechanisms. Interleukin-6 is a proinflammatory cytokine that can affect the tumor microenviron-ment in various ways. First, IL-6 can increase cancer cell proliferation by activating signaling pathways that promote cell growth. Interleukin-6 can also inhibit apoptosis or programmed cell death, which is important for controlling cancer cell growth. Interleukin-6 also plays a role in promoting angiogenesis which facilitates tumors to get enough blood supply to grow and spread.[14]

The mechanism of action of IL-6 begins with binding to the IL-6 receptor (IL-6R) on the target cell surface, which consists of the IL-6Rα and gp130 subunits. This binding activates intracellular signaling pathways such as JAK/STAT, *mitogen-activated protein kinase* (MAPK) and Phosphoinositide 3-kinases (PI3K) pathways that play a role in transcription of proinflammatory and anti-apoptotic genes. Activation of these pathways results in increased expression of genes that support cell proliferation, differentiation and survival. For example, the JAK/STAT pathway plays a key role in the regulation of gene expression that controls proliferation and resistance to apoptosis (figure 5).[15]

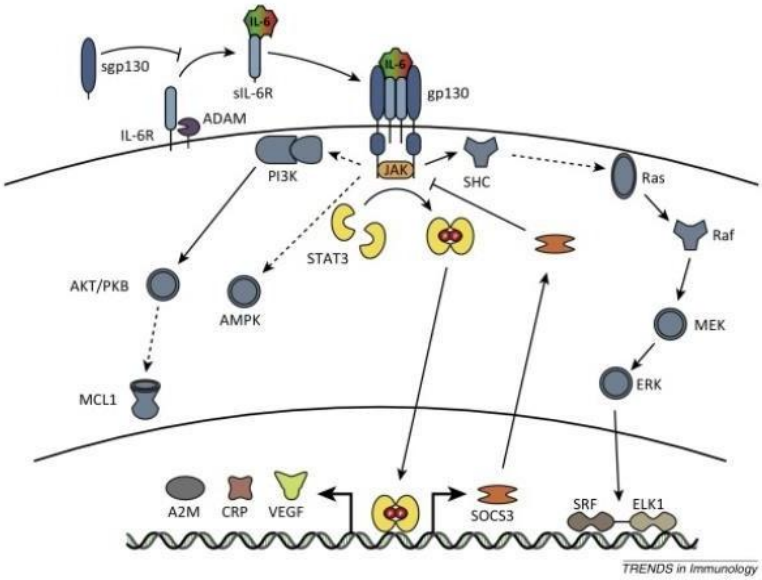


**Figure 5.** Interleukin 6 mechanism of action[16\]

Research shows that high levels of IL-6 in the serum of lung cancer patients are often associated with a worse prognosis. Interleukin-6 can activate the STAT3 signaling pathway, which plays an important role in cancer cell survival and metastatic ability. Activation of the STAT3 pathway by IL-6 leads to the expression of genes that favor cell proliferation, inhibit apoptotic mechanisms and increase the invasion and metastatic potential of cancer cells. In addition, IL-6 also contributes to the formation of new blood vessels (angiogenesis) around the tumor, providing the necessary nutrients for rapid tumor growth. IL-6 not only serves as an indicator of prognosis but also as a potential target for therapy in lung cancer.[15,17]
Experimental studies have also shown that inhibition of the IL-6 pathway can reduce tumor growth and metastasis in animal models of lung cancer. The use of monoclonal antibodies targeting IL-6 or the IL-6 receptor has shown potential in suppressing tumorigenic activity in cancer models. In addition, therapies targeting IL-6 can be used in conjunction with conventional therapies such as chemotherapy or immunotherapy to improve treatment effectiveness. Thus, IL-6 is not only an important target for basic research but also has meaningful clinical potential in the development of novel therapeutic strategies for lung cancer.[18,19]

### *Tumor Necrosis Factor Alpha* (TNF-α)

*Tumor Necrosis Factor- α* (TNF-α) is a proinflam-matory cytokine that plays an important role in the

regulation of immune and inflammatory responses. *Tumor Necrosis Factor-α* is produced by various cell types, including macrophages, T cells and NK cells, in response to infection, trauma or other pathological conditions. *Tumor Necrosis Factor- α* serves as a key mediator in acute inflammation, helping the body fight pathogens by stimulating a strong immune response. *Tumor Necrosis Factor- α* also induces apoptosis in infected cells or cancer cells, thus playing a role in the control of abnormal cell growth. However, in addition to its protective role, TNF-α is also involved in various chronic inflammatory conditions and autoimmune diseases. Excessive production of TNF-α can cause tissue damage and worsen disease conditions.[20]

*Tumor Necrosis Factor- α* has several key functions in the mediation of the inflammatory process. One of its main functions is to stimulate the expression of adhesion molecules on endothelial cells, which enhances the recruitment of immune cells to the site of infection or injury. In addition to that, TNF-α stimulates the production of chemokines and other cytokines, which amplifies inflammatory signals and helps attract more immune cells to the site of inflammation. TNF-α also plays a role in inducing fever and the production of acute- phase proteins by hepatocytes, which are part of the body's systemic response to infection. However, excessive TNF-α activity can lead to sustained inflammation that damages healthy tissue and favors the development of chronic diseases, such as rheumatoid arthritis and inflammatory bowel disease.[20]

The mechanism of action of TNF-α begins with binding to TNF receptors (TNFR1 and TNFR2) on the surface of target cells. This binding triggers the activation of a series of intracellular signaling pathways, including NF-κB and MAPK pathways that regulate the expression of proinflammatory and antiapoptotic genes. Activation of these pathways results in the production of more cytokines, chemokines and proteolytic enzymes, all of which contribute to a more robust and sustained inflammatory response. In chronic inflam-mation and cancer, excessive TNF-α activity through this pathway can support tumor growth and spread by creating a microenvironment that favors inflammation, angiogenesis and inhibits cancer cell apoptosis.[20,21]

In lung cancer, TNF-α supports tumor growth by increasing cancer cell proliferation, inhibiting apoptosis, and stimulating angiogenesis. Research shows that high TNF-α levels in the serum of lung cancer patients are often associated with a worse prognosis. *Tumor Necrosis Factor-α* can activate the NF-κB signaling pathway, which plays an important role in cancer cell survival and metastatic ability. Activation of the NF-κB pathway by TNF-α leads to the expression of genes that favor cell proliferation, inhibit apoptotic mechanisms, and increase the invasion and metastatic potential of cancer cells. addition, TNF-α also contributes to angiogenesis around the tumor, providing nutrients necessary for rapid tumor growth. Therefore, TNF-α not only serves as an indicator of prognosis but also as a potential target for therapy in lung cancer.[21]

## Conclusions

1. Proinflammatory cytokines such as IL-1, IL-6 and TNF-α play an important role in the development and progression of lung cancer. Interleukin-1 is known to promote cancer cell proliferation and angiogenesis, IL-6 supports tumor growth and metastasis through the STAT3 pathway, while TNF-α affects the tumor microenvironment and promotes chronic inflammation.
2. High levels of proinflammatory cytokines often correlate with poor prognosis in lung cancer patients. The specific mechanisms of how each cytokine affects molecular pathways in lung cancer still require further research for a more complete understanding.
3. Knowledge of proinflammatory cytokines can be applied in the diagnosis and therapy of lung cancer in several ways. Measurement of cytokine levels such as IL- 1, IL-6 and TNF-α in patient serum can be used as biomarkers for early diagnosis and prognosis of lung cancer. In addition, targeting proinflammatory cytokine pathways can be an effective therapeutic strategy. For example, inhibitors of IL-6 or TNF-α have shown potential in reducing cancer cell proliferation and metastasis in preclinical studies.
4. Potential new therapeutic targets based on proinflammatory cytokines pave the way the development of drugs that are more specific and less toxic than conventional chemotherapy.
5. Therapies targeting these cytokines can be used alone or in combination with other therapies such as immune *checkpoint* inhibitors or molecular targeted therapies. As we continue to develop our under-standing of the role of proinflammatory cytokines in lung cancer, it is hoped that more effective and personalized therapies can be found, ultimately improving clinical outcomes for patients.

## References


1. Thandra KC, Barsouk A, Saginala K, Aluru JS, Barsouk A. Epidemiology of Lung Cancer. Contemp Oncol (Pozn). 2021;25:45-52.
2. Schabath MB, Cote ML. Cancer Progress and Priorities: Lung Cancer. Cancer Epidemiol Biomarkers Prev. 2019;28:1563-79.
3. Thai AA, Solomon BJ, Sequist LV, Gainor JF, Heist RS. Lung Cancer. Lancet. 2021;398:535-54.
4. Cheng L, Alexander RE, Maclennan GT, Cummings OW, Montironi R, Lopez-Beltran A, et al. Molecular Pathology Of Lung Cancer: Key To Personalized Medicine. Mod Pathol. 2012;25:347-69.
5. Kiss AL. Inflammation In Focus: The Beginning And The End. Pathol Oncol Res. 2021;27:1610136.
6. Zhao H, Wu L, Yan G, Chen Y, Zhou M, Wu Y, et al. Inflammation And Tumor Progression: Signaling Pathways And Targeted Intervention. Signal Transduct Target Ther. 2021;6:263.
7. Hibino S, Kawazoe T, Kasahara H, Itoh S, Ishimoto T, Sakata-Yanagimoto M, et al. Inflammation-induced Tumorigenesis And Metastasis. Int J Mol Sci. 2021;22; 6009
8. Wautier JL, Wautier MP. Pro- and Anti-Inflammatory Prostaglandins And Cytokines In Humans: A Mini Review. Int J Mol Sci. 2023;24
9. Gelfo V, Romaniello D, Mazzeschi M, Sgarzi M, Grilli G, Morselli A, et al. Roles Of Il-1 In Cancer: From Tumor Progression To Resistance To Targeted Therapies. Int J Mol Sci. 2020;21
10. Garon EB, Chih-Hsin Yang J, Dubinett SM. The Role Of Interleukin 1beta In The Pathogenesis Of Lung Cancer. JTO Clin Res Rep. 2020;1:100001.
11. Zhang J, Veeramachaneni N. Targeting Interleukin-1beta And Inflammation In Lung Cancer. Biomark Res. 2022;10:5.
12. Yuan B, Clowers MJ, Velasco WV, Peng S, Peng Q, Shi Y, et al. Targeting IL-1beta As An Immunopreventive And Therapeutic Modality For K-ras-mutant Lung Cancer. JCI Insight. 2022;7
13. Hirano T. IL-6 in Inflammation, Autoimmunity And Cancer. Int Immunol. 2021;33:127-48.
14. Orange ST, Leslie J, Ross M, Mann DA, Wackerhage H. The Exercise IL-6 Enigma In Cancer. Trends Endocrinol Metab. 2023;34:749-63.
15. Uciechowski P, Dempke WCM. Interleukin-6: A Masterplayer In The Cytokine Network. Oncology. 2020;98:131-7.
16. Mauer J, Denson JL, Bruning JC. Versatile Functions For IL-6 In Metabolism And Cancer. Trends Immunol. 2015;36:92-101.
17. Silva EM, Mariano VS, Pastrez PRA, Pinto MC, Castro AG, Syrjanen KJ, et al. High Systemic IL-6 Is Associated With Worse Prognosis In Patients With Non-Small Cell Lung Cancer. PLoS One. 2017;12:e0181125.
18. Song L, Smith MA, Doshi P, Sasser K, Fulp W, Altiok S, et al. Antitumor Efficacy Of The Anti-Interleukin-6 (IL-6) Antibody Siltuximab In Mouse Xenograft Models Of Lung Cancer. J Thorac Oncol. 2014;9:974-82.
19. Ke W, Zhang L, Dai Y. The Role Of IL-6 In Immunotherapy Of Non-Small Cell Lung Cancer (NSCLC) With Immune-Related Adverse Events (irAEs). Thorac Cancer. 2020;11:835-9.
20. Kalliolias GD, Ivashkiv LB. TNF Biology, Pathogenic Mechanisms And Emerging Therapeutic Strategies. Nat Rev Rheumatol. 2016;12:49-62.
21. Gong K, Guo G, Beckley N, Zhang Y, Yang X, Sharma M, et al. Tumor Necrosis Factor In Lung Cancer: Complex Roles In Biology And Resistance To Treatment. Neoplasia. 2021;23:189-96.

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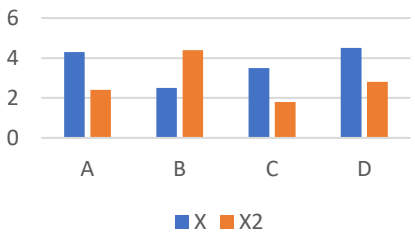


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