e-ISSN 2797-457X

THE INDONESIAN JOURNAL OF CANCER CONTROL

Official Journal of The Indonesian Society of Oncology

InaJCC Vol.04 No.01 Page: 1-48

Jakarta, Jan – Apr 2025

e-ISSN 2797-457X

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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.

The Indonesian Journal of Cancer Control (InaJCC) is a quadrimester electronic journal, publishing papers in a wide spectrum of cancer control. The journal was launched in 2021 as the official publication of the Indonesian Society of Oncology and its first volume was published in 2021.

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.

e-ISSN 2797-457X

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Editorial

Bridging science, humanity, and system: toward a more integrated cancer care

Burden of cancer care and fast growing of landscape technology in cancer management giving it's own challenge for the oncologist. The *Indonesian Journal of Cancer Care (InaJCC)*, in this issue present a rich collection of manuscripts that reflect both the scientific complexity and the real word experience of cancer care across disciplines, faith, and frontiers. These articles exemplify the growing maturity of oncology practice in Indonesia and globally—where scientific precision meets multidisciplinary collaboration and as well as an obstacle in it's daily practice.

The **Special Article**, *"Bridging the Complexity of Triple-Negative Breast Cancer Care through an MDT Approach,"* underscores the importance of the *multidisciplinary team (MDT)* model in addressing one of the most aggressive and biologically heterogeneous subtypes of breast cancer. Triple-negative breast cancer (TNBC) poses therapeutic challenges due to its lack of hormonal or HER2 targets; thus, coordinated care involving oncologists, pathologists, surgeons, molecular biologists, and palliative experts becomes essential. The article reinforces the message that complexity in cancer care is best countered by collective expertise—bridging clinical, molecular, and psychosocial dimensions for optimal outcomes.

Our **Original Article** from the *Dharmais Cancer Center*, *"Five-Year Layer by Layer: Mohs Micrographic Surgery Insight from Indonesia Cancer Center,"* brings valuable local evidence on precision cutaneous oncology. Through meticulous "layer-by-layer" histopathologic control, Mohs surgery offers maximal tumor clearance while sparing healthy tissue—an approach particularly relevant in the era of personalized surgical oncology. This also showed a long-term insight from a national cancer center demonstrates Indonesia's commitment to evidence-based refinement of oncologic surgery.

Another **Original Article**, *"Knowledge, Attitude and Practices of Islamic Scholars on Cancer Care and Preventive Measures in Ile-Ife, Nigeria: Implication for Policy Action,"* reflects the vital intersection between health literacy, faith, and community leadership. Religious scholars often hold pivotal influence in shaping perceptions toward prevention, early detection, and treatment adherence. This study highlights the untapped potential of faith-based engagement as a vector for public health communication and policy formulation in cancer prevention—an approach highly relevant for culturally diverse nations.

Two **Case Reports** in this issue remind us that the practice of oncology remains deeply rooted in clinical vigilance and diagnostic precision. The first, *"Rare Delayed Tracheal Perforation after Total Thyroidectomy,"* draws attention to the delicate balance between surgical intervention and delayed complications in endocrine oncology. The second, *"Misdiagnosis of Lung Adenocarcinoma Mimicking Pulmonary Tuberculosis,"* reflects a diagnostic challenge prevalent in many developing regions, where infectious diseases and malignancies may clinically overlap. Both reports emphasize that clinical acumen, supported by histopathological confirmation and multidisciplinary review, remains indispensable.

Finally, the **Review Article**, *"Mechanism of Target Therapy Resistance in NSCLC,"* provides a timely and comprehensive overview of molecular pathways that underpin treatment failure in non-small cell lung cancer. Understanding these resistance mechanisms—from EGFR and ALK mutations to MET amplification and tumor microenvironment adaptation—guides future strategies for overcoming therapeutic resistance and achieving durable remission.

These contributions embody the spirit of *InaJCC*: fostering scientific exchange that not only informs but also transforms cancer care practice. They remind us that effective oncology lies at the intersection of molecular insight, clinical precision, systemic coordination, and human compassion. As cancer care advances, integration—of science, system, and soul—remains our ultimate bridge.

Cosphiadi Irawan
The Indonesian Society of Oncology

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Original Article

Five years, layer by layer: Mohs micrographic surgery insight from Indonesia Cancer Center, Dharmais Cancer Hospital

Raissa P Raspati, Adeline Jaclyn, Danang T Wahyudi, Aida SD Hoemardani, Agassi S Sutarjo, Fadhli A Mughni, Inadia P Chairista, Nuril Ilmi

e-ISSN 2797-457X
DOI: 10.52830/inajcc.v1i1.109

Received: October 10th, 2024
Accepted: November 27th, 2024

Authors' affiliations:
Dermatology and Venereology Department, Dharmais National Cancer Hospital, Jakarta, Indonesia

Corresponding author:
E-mail: raissaraspati@gmail.com

Abstract

Background: Mohs micrographic surgery (MMS) is the gold standard for treating high-risk non-melanoma skin cancer (NMSC). However, epidemiological data on MMS in Indonesia remain limited. This study aims to evaluate MMS use, tumor characteristics, and surgical outcomes at a single center in Indonesia.
Methods: A retrospective review of 83 MMS cases at Dharmais Cancer Hospital (2020–2024) was conducted. Data on demographics, tumor characteristics, and surgical outcomes were analyzed. Tumor locations were classified into high-risk (H area), moderate-risk (M area), and low-risk (L area) anatomical zones.
Results: Most tumors were located in the H area (57.8%). Basal cell carcinoma (BCC) was the most common diagnosis (79.5%), with infiltrative BCC as the predominant subtype (41.0%). A surgical margin of ≥3 mm was significantly associated with achieving tumor clearance in a single stage (p = 0.018). Multiple-stage MMS was required in 15.0% of cases. Defect closure was primarily performed using grafts or flaps (69.9%), with dermatologists performing most reconstructions (83.1%).
Conclusion: MMS is effective for treating high-risk NMSC in Indonesia, with findings comparable to global data. The study highlights the importance of appropriate surgical margins and the need for further research, particularly in Asian countries. Establishing a national skin cancer registry would enhance future epidemiological studies.

Keywords: *Basal cell carcinoma, H area, Indonesia, Mohs micrographic surgery, surgical margin*.

Abstrak

Latar Belakang: *Mohs micrographic surgery* (MMS) merupakan baku emas dalam penatalaksanaan kanker kulit non-melanoma (NMSC) berisiko tinggi. Namun, data epidemiologi mengenai pelaksanaan MMS di Indonesia masih terbatas. Penelitian ini bertujuan untuk mengevaluasi penerapan MMS, karakteristik tumor, serta hasil pembedahan di satu pusat layanan kanker di Indonesia.
Metode: Tinjauan retrospektif dilakukan terhadap 83 kasus MMS di Rumah Sakit Kanker Dharmais selama periode 2020–2024. Data demografi pasien, karakteristik tumor, dan hasil pembedahan dianalisis. Lokasi tumor dikategorikan berdasarkan zona anatomi berisiko tinggi (area H), berisiko sedang (area M), dan berisiko rendah (area L).
Hasil: Sebagian besar tumor ditemukan pada area H (57,8%). *Basal cell carcinoma* (BCC) merupakan diagnosis tersering (79,5%), dengan subtipe infiltratif sebagai bentuk paling dominan (41,0%). Tepi bedah ≥3 mm secara signifikan berhubungan dengan keberhasilan pembersihan tumor dalam satu tahap (p = 0,018). Prosedur MMS dengan lebih dari satu tahap dibutuhkan pada 15,0% kasus. Defek pasca-bedah paling sering ditutup menggunakan cangkok atau flap (69,9%), dan sebagian besar rekonstruksi dilakukan oleh dokter spesialis kulit (83,1%).
Kesimpulan: MMS terbukti efektif untuk menangani NMSC berisiko tinggi di Indonesia, dengan hasil yang sebanding dengan data internasional. Penelitian ini menekankan pentingnya penentuan tepi bedah yang adekuat serta perlunya penelitian lanjutan, khususnya di negara-negara Asia. Pembentukan registri nasional kanker kulit akan sangat mendukung pengembangan penelitian epidemiologi di masa mendatang.

Kata Kunci: *Area H, Indonesia, karsinoma sel basal, Mohs micrographic surgery, tepi bedah.*

Background

Mohs micrographic surgery (MMS) is a specialized technique offering the highest cure rates for many types of skin cancer. MMS involves precise, visible tumor resection while minimizing the removal of healthy tissue.[1] Excision is followed by a complete histopathological analysis of the peripheral and deep surgical margins under microscope by the systematic use of frozen sections to ensure eradication of the neoplasm by mapping the tumor extension and margin clearance.[2,3] Following tumor clearance, the defect areas are repaired by primary closure or reconstruction.[4,1] Approximately 75% of skin cancer are basal cell carcinoma (BCC), whereas cutaneous squamous cell carcinoma (SCC) represent approximately 20%, and the remaining are melanomas (4%) and other rare tumors.[1] According to Global Cancer Observatory (GLOBOCAN) in 2022, it is estimated 1,234,533 cases of Non-melanoma skin cancers (NMSC) occur worldwide.[5] NMSC can cause significant morbidity from local compression and invasion.[6,7] MMS is preferred for high-risk tumors, particularly in cosmetically sensitive areas such as the H area, which includes the face, eyelids, periorbital region, nose, lips, and ears, and is the most common site of recurrence.[8] Study in Brazil on the use of MMS for BCC has shown 87.1% of BCC case were located in the H area.[9] According to guideline from National Comprehensive Cancer Network (NCCN), BCC is considered high risk for recurrence if any of major risk is present.[10] It is considered high risk when BCC is in the H area, larger than 2 cm, a recurrent rumor, has ill-defined borders, perineural invasion, or has aggressive histological subtype.[11] For high-risk lesions exceeding 2 cm, a 4–6 mm margin is advised to ensure complete tumor removal. However, research indicates that a 4 mm margin is often unfeasible on the face due to cosmetic and functional limitations. Some studies suggest that a 2 mm margin may be sufficient for small, well-defined BCCs in the head and neck, though a 3 mm margin is often recommended for more reliable results.[12] According to data from the national Spanish Mohs registry, MMS offers a 5-year cure rate of 98.7% for BCC and 95.5% for SCC.[13]. A retrospective review of patients who underwent MMS for BCC in Singapore from 2019 – 2024 showed 79.7% of BCC subtype was nodular followed by infiltrative subtype by 12.5%.[14] There is a paucity of data in Asia, with use of MMS reported in less than 20% of Asian countries.[14] Epidemiological studies on the incidence and use of MMS are limited in Indonesia. Therefore, this study aims to review the epidemiological features and identify significant correlations between various parameters of MMS cases and enhancing our understanding of skin cancer treatment. The newly established registry may also serve as a valuable resource for future MMS research, particularly in Asian countries.

Methods

We conducted a retrospective review of patients who underwent MMS in a single center in Indonesia, Dharmais Cancer Hospital from January 2020 to December 2024. Data were retrospectively collected for patients' demographics, tumor characteristics, and MMS aspects. Outcomes included need for multiple-stage of MMS and referral to other specialties for closure. Tumors were classified as being located on either areas H, M, or L: The H Area such as the mask area of the face, the M Area encompasses the cheeks, the forehead, the scalp, the neck, the jawline, and pretibial surfaces. Finally, the L Area includes the rest of the body (i.e., trunk and extremities).

All statistical analyses were conducted using the Statistical Package for the Social Sciences software (SPSS) version 25. Categorical variables were explored and summarized using frequency and percentage. Chi-square test was used to test association between MMS stages and surgical characteristics and Fisher's exact test was applied to ensure result accuracy. Variables with a p value less than 0.05 on bivariate analysis were used.

Results

A total number of 83 cases were reviewed.

Table 1. The patient demographics, tumor and surgical characteristics

Variable	N = 83
Age	66.05 (±11.8)
Sex, *n* (%)	
Female	44 (53%)
Male	38 (45.8%)
Diagnosis	
Basal cell carcinoma (BCC)	66 (79.5%)
Superficial	7 (8.4%)
Nodular	8 (9.6%)
Infiltrative	34 (41.0%)
Micronodular	8 (9.6%)
Morpheaphorm	1 (1.2%)
Basosquamous	1 (1.2%)
Squamous cell carcinoma (SCC)	5 (6.0%)
Bowen's Disease	9 (10.8%)
Dermatofibrosarcoma	2 (2.4%)
Protuberans	
Lentigo Maligna	1 (1.2%)
Tumor location, *n* (%)	
L Area	16 (19.3%)
M Area	19 (22.9%)
H Area	48 (57.8%)
Tumor Risk Group	
Low-Risk Group	5 (7.6%)
High-Risk Group	61 (92.4%)
Tumor size, cm^2	
Mean (SD)	2.2 (1.9)
Minimum	0.5
Maximum	15.0
MMS Stage, *n* (%)	
I	68 (81.9%)
Multiple Stages	15 (18.1%)
II	12 (14.5%)
III	3 (3.6%)
Surgical margin, *n* (%)	
< 3 mm	33 (39.8%)
≥ 3 mm	50 (60.2%)
Intervention, *n* (%)	
Primary closure	25 (30.1%)
Reconstruction	58 (69.9%)
Defect closure specialty, *n* (%)	
Dermatologist	69 (83.1%)
Plastic surgeon	14 (16.9%)

A chi-square test was conducted to assess the association between intraoperative surgical margin size and the number of Mohs surgery stages required for tumor clearance. The results revealed a significant association between margin size and the number of stages (p = 0.018) Patients with intraoperative margins larger than 3 mm were more likely to achieve tumor clearance in a single stage of MMS (88.0%), whereas patients with margins smaller than 3 mm were more likely to require multiple stages for complete tumor removal (33.3%). Fisher's Exact Test confirmed the significance of this association (p = 0.026). Additionally, a linear-by-linear association test showed a significant linear trend (p = 0.020), indicating that smaller intra-operative margins were progressively associated with a higher likelihood of requiring additional stages (Table 2.)

Table 2. Bivariate analysis comparing surgical margin to MMS stages.

Surgical Margin	MMS		Total	*p* value
	Stage I	Multiple Stages		
< 3 mm	22 (66.7%)	11 (33.3%)	33	0.018
≥ 3 mm	44 (88.0%)	6 (12.0%)	50	

Discussion

Mohs micrographic surgery (MMS) remains the gold standard for treating non-melanoma skin cancer (NMSC). This study evaluated MMS use in a single center in Indonesia, reviewing 83 cases retrospectively. Findings revealed that females were more likely to undergo MMS (53%), which contrasts with previous literature where males are more commonly treated with MMS. The average tumor size in this study was 2.2 cm^2, aligning with findings from a Brazilian study that reported an average tumor diameter exceeding 2 cm^2. Most tumors were located H area (57.8%), followed by the M area (22.9%) and the L area (19.3%). Other studies have reported a higher percentage of tumors in the H area (87%). Regarding tumor diagnosis, basal cell carcinoma (BCC) was the most common, accounting for 66 cases (79.5%), reflecting global NMSC incidence patterns. Histopathological confir-mation identified BCC subtypes in 57 cases, with infiltrative BCC being the most prevalent (41%), followed by nodular BCC (8.4%). This differs from a retrospective study in Singapore, where nodular BCC was the most common (79.7%), with infiltrative BCC accounting for only 12.5%. NCCN guidelines on BCC recurrence risk factors, most BCC cases in this study (92.4%) were classified as high risk. Multiple MMS stages were required in 15% of cases, a slightly higher percentage than the 11% reported by Fantini et al. for BCC. The mean surgical margin used was 2.63 mm, with most cases (60.2%) utilizing a margin of ≥3 mm. Defect closure was primarily performed using grafts or flaps (69.9%), with dermatologists performing of these procedures (83.1%). A surgical margin of ≥3 mm was more likely

to achieve tumor clearance in a single-stage MMS. This finding aligns with a global guidelines review, which recommends a 3 mm margin for complete tumor excision in 85% of cases. Using this margin may also help reduce the risk of tumor recurrence, particularly in H area.

Conclusion

This study highlights the importance of MMS in treating NMSC, particularly BCC, which was the most common diagnosis. Using a safe and recommended surgical margin is crucial, as it can reduce the need for multiple MMS stages and may help lower the risk of tumor recurrence. A limitation of this study is the small sample size, which may not be representative of Indonesia's population. Additionally, the absence of a national skin cancer registry and the limited availability of MMS in Indonesia hinder nationwide comparisons with our center. Therefore, our study may serve as a foundation for future research and as a registry for MMS cases. Further studies, particularly those focusing on 5-year follow-up data on MMS recurrence risk and cure rates are needed to expand our understanding of MMS outcomes especially in Asian countries like Indonesia.

References

1. Bittner GC, Cerci FB, Kubo EM, Tolkachjov SN. Mohs micrographic surgery: a review of indications, technique, outcomes, and considerations. An Bras Dermatol. 2021 Jul 26;96(3):263–77.
2. Mohs FE. Mohs Micrographic Surgery: A Historical Perspective. Dermatol Clin. 1989 Oct 1;7(4):609–12.
3. Berjawi A, Saade N, Tannous Z. Nonmelanoma Skin Cancer in the Heart of the Middle East : Analysis of Mohs Micrographic Surgery Cases From a Tertiary Care Center in Lebanon. 2024;2024.
4. Nazzaro G, Minuti A, Quattri E, Passoni E. Mohs micrographic surgery: the experience of the Dermatology Unit of the University of Milan confirms the superiority over traditional surgery in high-risk non-melanoma skin cancers. Dermatology Reports. 2022 Jul 14;15(1).
5. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229–63.
6. Aggarwal P, Knabel P, Fleischer AB. United States burden of melanoma and non-melanoma skin cancer from 1990 to 2019. J Am Acad Dermatol [Internet]. 2021;85(2):388–95. Available from: https://doi.org/10.1016/j.jaad.2021.03.109
7. Walker HS, Hardwicke J. Non-melanoma skin cancer. Surg. 2022 Jan 1;40(1):39–45.
8. Marzuka AG, Book SE. Basal Cell Carcinoma: Pathogenesis, Epidemiology, Clinical Features, Diagnosis, Histopathology, and Management. Yale J Biol Med. 2015 Jun 1;88(2):167.
9. Fantini B de C, Bueno Filho R, Chahud F, Souza C da S. Appropriate use criteria for basal cell carcinoma Mohs surgery at a single center in the face of high-burden skin cancer: a retrospective cohort study. J Dermatolog Treat [Internet]. 2019 Jan 2 [cited 2025 Feb 16];30(1):74–80. Available from: https://pubmed.ncbi.nlm.nih.gov/29727201/
10. Miller SJ, Alam M, Andersen J, Berg D, Bichakjian CK, Bowen G, et al. Basal Cell and Squamous Cell Skin Cancers. J Natl Compr Cancer Netw. 2010 Aug 1;8(8):836–64.
11. Puig S, Berrocal A. Management of high-risk and advanced basal cell carcinoma. Clin Transl Oncol. 2015;17(7):497–503.
12. Quazi SJ, Aslam N, Saleem H, Rahman J, Khan S. Surgical Margin of Excision in Basal Cell Carcinoma: A Systematic Review of Literature. Cureus. 2020 Jul 15;12(7):e9211.
13. Tomás-Velázquez A, Sanmartin-Jiménez O, Garcés JR, Rodríguez-Prieto MA, Ruiz-Salas V, Eusebio-Murillo E De, et al. Risk Factors and Rate of Recurrence after Mohs Surgery in Basal Cell and Squamous Cell Carcinomas: A Nationwide Prospective Cohort (REGESMOHS, Spanish Registry of Mohs Surgery). Acta Derm Venereol. 2021;101(11):1–7.
14. Lua ACY, Oh DAQ, See Tow HX, Por RH, Koh HY, Oh CC. Mohs Micrographic Surgery for Basal Cell Carcinoma in an Asian Medical Centre in Singapore - A Retrospective Review. JAAD Int. 2024;17:167–9

InaJCC The Indonesian Journal of Cancer Control

Original Article

Knowledge, attitude and practices of islamic scholars on cancer care and preventive measures in Ile-Ife, Nigeria: Implication for policy action

Khadijat Y Lawal[1], Samuel A Olowookere[1], Abdulfatah K Makinde[2], Abdulakeem A Ahmed[3], Ajibola Idowu[4], Emmanuel Folami[5], Ismaheel A Azeez[6], Fatai A Olaniyan[7]

e-ISSN 2797-457X
DOI: 10.52830/inajcc.v1i1.104

Received: January 6th, 2025
Accepted: March 10th, 2025

Authors' affiliations:
[1]Department of Community Health, Obafemi Awolowo University, Ile-Ife, Nigeria
[2]Department of Religious Studies, Obafemi Awolowo University, Ile-Ife, Nigeria
[3]Department of Family Medicine, Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Nigeria
[4]Department of Community Medicine, Bowen University, Iwo, Nigeria
[5]Department of Anaesthesia, Osun State University, Osogbo, Nigeria
[6]Department of Family Medicine, Afe Babalola University, Ado-Ekiti, Nigeria
[7]Department of Family Medicine, University College Hospital, Ibadan, Nigeria

Corresponding author:
E-mail:
abdulakeem.ahmed@npmcn.edu.ng

Abstract

Background: Cancer is currently one of the leading causes of morbidity and mortality, especially among adults globally. It is important to understand the perspectives of religious leaders on cancer prevention and care since their doctrines have tremendous impacts on the behaviour of their followers. This study assessed the knowledge, attitudes, and practices of Islamic scholars/clerics on cancer care and prevention.
Methods: A cross-sectional design using a mixed-method approach and a two-stage sampling technique was used to recruit 128 consenting Islamic scholars. An interviewer-administered questionnaire and focus group discussion guide were used for data collection. Quantitative data were analysed using the SPSS software version 20 with $p \leq 0.05$ taken as significant. Qualitative data from 36 participants with the results analysed using thematic content analysis.
Results: The majority of the respondents had heard of cancer, and 60% of them had poor knowledge of cancer care and prevention. The statistically significant predictors of good practice among the respondents include being not married (AOR 3.64; 95%CI 1.26-10.47; p=0.017), being new members of an Islamic congregation (AOR 6.00; 95%CI 2.22-16.19; p=0.0001) and having good knowledge (AOR 4.85; 95%CI 1.66-14.11; p=0.004). The FGD sessions revealed several myths and misconceptions about cancer.
Conclusion: This study revealed predominantly poor cancer knowledge, negative preventive attitude, and poor cancer care/preventive practices. It underscores the need for an educational intervention targeting Islamic scholars to equip them with the right cancer-related information, which can be passed down to their followers.
Keywords: *attitude, cancer awareness, islamic scholars, knowledge, practice*

Abstrak

Latar Belakang: Kanker saat ini merupakan salah satu penyebab utama morbiditas dan mortalitas, khususnya pada populasi dewasa di seluruh dunia. Pemahaman terhadap perspektif para pemuka agama terhadap pencegahan dan perawatan kanker sangat penting, mengingat ajaran mereka memiliki pengaruh besar terhadap perilaku para pengikutnya. Penelitian ini bertujuan untuk menilai pengetahuan, sikap, dan praktik para ulama atau cendekiawan Islam mengenai perawatan dan pencegahan kanker.
Metode: Penelitian ini menggunakan desain potong lintang dengan pendekatan *mixed-method* dan teknik pengambilan sampel dua tahap untuk merekrut 128 ulama Islam. Pengumpulan data menggunakan kuesioner wawancara terstruktur dan panduan *focus group discussion* (FGD). Data kuantitatif dianalisis menggunakan perangkat lunak SPSS versi 20 dengan tingkat signifikansi $p \leq 0,05$. Data kualitatif dari 36 peserta dianalisis menggunakan analisis isi tematik.
Hasil: Sebagian besar responden pernah mendengar tentang kanker, namun 60% di antaranya memiliki tingkat pengetahuan rendah terkait perawatan dan pencegahan kanker. Prediktor yang berhubungan bermakna dengan praktik baik di antara responden meliputi status tidak menikah (AOR 3,64; 95% CI 1,26–10,47; p = 0,017), menjadi anggota baru dalam komunitas Islam (AOR 6,00; 95% CI 2,22–16,19; p = 0,0001), serta memiliki pengetahuan yang baik (AOR 4,85; 95% CI 1,66–14,11; p = 0,004). Sesi FGD mengungkap berbagai mitos dan kesalahpahaman mengenai kanker.
Kesimpulan: Sebagian besar ulama Islam memiliki pengetahuan yang rendah tentang kanker, sikap pencegahan yang negatif, serta praktik perawatan dan pencegahan yang kurang memadai. Diperlukan intervensi edukatif kepada para pemuka agama Islam untuk membekali mereka dengan informasi yang benar mengenai kanker, agar dapat disampaikan secara efektif kepada para pengikutnya.
Kata Kunci: sikap, kesadaran kanker, ulama Islam, pengetahuan, praktik.

Background

Like in other developing nations, cancer is still a major public health concern in Nigeria, where high death rates are a result of late-stage diagnosis and inadequate health-seeking practices. Cancer is a group of diseases emanating from abnormal cellular growth which could spread to some other parts of the body and is a major cause of death all over the world.[1-3] Common types of cancer include breast cancer, skin cancer, lung cancer, cervical cancer and prostate cancer.[4,5] The Global Cancer Observatory (GCO) recorded 115,950 new cancer cases in Nigeria and 70,327 cancer deaths, of which 22.7% (26,310) were attributable to breast cancer.[6] The increasing global prevalence of these cancers makes them remain on the campaign list of various health organisations, ranging from governmental to non-governmental organisations.[7-9] The GCO statistics record that breast cancer cases increased by 37%, while cervical cancer increased by 21% among Nigerian women.[6] Once cancer is diagnosed, the patient may require medical treatment and specialised care such as surgery, radiotherapy, and chemotherapy for months and often years. Muslims are encouraged to seek treatment for illness and relief from distress.[10-12]

Breast cancer screening is the medical screening of asymptomatic women for breast cancer, and early detection of the tumour can be cured with appropriate treatment, which can reduce the morbidity and mortality rate.[13] Several screening tests have been employed, which include self-breast examination, clinical breast examination, mammography, ultrasound, and magnetic resonance imaging.[11,13] Self-breast examination should be done by every woman after their menstruation period, The American Cancer Society recommends mammograms be done yearly for women who are 40 years and above, and women between the ages of 20 and 30 should go through clinical breast examination (CBE) every 3 years.[3-5] Screening mammography is the most acceptable and effective screening procedure adopted for the early detection of breast cancer, and it is prominently practised in developed countries but less practised in Nigeria and other developing countries.[8,12] Early detection of breast cancer improves the chances of survival and lessens the need for invasive treatment[13-15]. Also, the uptake of cervical cancer screening tests is quite low among Nigerian women due to poor awareness and lack of cervical cancer screening centres, especially in the rural areas of Nigeria, which therefore results in increased morbidity and mortality.[16,17]

The most common cancer found among men according to GOBOCAN 2018 is prostate cancer with 13,078 new cases recorded.[6] The awareness and knowledge of prostate cancer and screening uptake are very low among people living in rural communities in Nigeria compared to urban communities.[18]

Religious leaders play a significant role in influencing the health practices and beliefs of their communities. The Islamic scholars are individuals who have vast knowledge of the Qur'an and teachings of Prophet Muhammad, who practice and teach the ethics of Islam and who hold esteemed positions in the mosques. In Nigeria, Faith-Based Organisations have since inception delivered educational, social, and health services globally.[19-22] Few studies, nevertheless, have looked at their knowledge of cancer, attitudes toward prevention, and capacity to promote early detection and treatment. This study explores a critical yet under-researched area of public health by assessing the knowledge, attitudes and practices of Islamic scholars on cancer care and preventive measures. These are factors that influence their role in shaping community perspectives on cancer awareness, prevention, and treatment.

This research provides baseline information which can be used by policymakers to design cost-effective cancer prevention awareness campaigns for religious leaders which can be disseminated to their followers. It also offers insightful information about the misunderstandings and knowledge gaps that could affect how the community behaves regarding cancer care and prevention. By emphasising these areas, our research can help develop culturally aware and cost-effective health education initiatives and cancer prevention awareness campaigns for religious leaders which can be disseminated to their followers to improve cancer awareness and outcomes.

Methods and Material

Description of Study Site: The study was conducted in Ile-Ife, Nigeria. It consists mainly of the Yoruba ethnic group. It is made up of two Local Government Areas (LGA), namely Ife Central and Ife East. Major religions practised are Christianity, Islam, and Traditional religion. Cancer screening services and care are available at the Obafemi Awolowo University Teaching Hospital Complex, Ile-Ife (OAUTHC). Islamic scholars comprised the Imam,

deputy Imam, Mufasir (paraphraser), deputy Mufasir, and others working in the Mosque.
Study design: The study employed a descriptive cross-sectional design using a mixed-method approach.
Study population: Islamic scholars in Ile-Ife, Osun State.
Inclusion criteria: Islamic scholars aged ≥18 years working at the selected mosques.
Exclusion criteria: The respondents that were not available or not willing to participate in the study.
Sample size determination: One hundred and twenty-eight Islamic scholars participated in the quantitative aspect of the study after sample size calculation using the statistical formula for descriptive health studies ($n=Z^2pq/d^2$) with 91.7% of Islamic scholars having poor knowledge of cancer preventive care and non-response/attrition rate taken into consideration.[23] Thirty-six Islamic scholars participated in the qualitative aspect.

Sampling technique

The study respondents were selected using a multi-stage sampling technique.

1. **First stage**: The list of the mosques in Ile-Ife was obtained from the Chief Imam of the Ife Land Muslim Community. Fifty-nine mosques were purposively selected from the list based on viability and attracting a large number of worshippers at the Jumat service.
2. **Second stage**: Fourteen out of the 59 mosques were selected with seven mosques selected per LGA based on the number of Islamic scholars higher than Ratib (district mosques),
3. **Third stage:** A simple random sampling technique (balloting method) was used to select respondents proportionately based on the number of Islamic scholars from each selected mosque. Each participant was then approached to participate in the study.

Thirty-six Islamic scholars were purposively selected for the focus group discussions (FGD) conducted.

Research instruments

Quantitative data were collected from the participants using a pretested, semi-structured interviewer-administered questionnaire. The questionnaire gathered information on the respondents' socio-demographic characteristics, awareness and knowledge of cancer, attitudes, and practices towards cancer care and prevention. Qualitative data were collected using an FGD guide to moderate the FGD sessions. The guide introduced the topic and its objectives; asked questions on awareness, knowledge, attitude, Islamic beliefs about cancer, spiritual means of cancer care and perception of Islamic scholars on cancer care and prevention; requested contributory information from the participants. This was conducted amongst respondents who were not included in the quantitative study.

Face validity of the questionnaire and FGD guide were undertaken by the authors to ensure that the questions asked answered the set objectives. The questionnaire and FGD guide were then piloted among Islamic scholars with ambiguous questions rephrased or removed. These Islamic scholars were not included in the main study. The questionnaire and FGD guide were written in English, translated to Yoruba for the non-English speaking population and back-translated to English to preserve the original meanings.

Data collection method:

Data were collected by the principal investigators and four trained research assistants who were undergraduate students. The training lasted four days and involved practical sessions. The questionnaire was administered to the selected Islamic scholars in the central mosques. The researcher explained the study to the respondents and the questionnaire was administered to those who consented. The data was collected over three weeks. Focus group discussion was conducted among four sets of participants, each set comprised of 8 participants, based on their age and gender differences in conducive environments within their central mosques after Jumat services. Each FGD session lasted one hour with a moderator and a notetaker. Permission was obtained from study participants to record each FGD session. Grounded theory was used in exploring information on each question asked. The information recorded by the notetaker was triangulated on the recorded ones.

Data analysis

The quantitative data were analysed using SPSS version 20.0 software. Simple and inferential statistics were done. Knowledge, attitude, and practice scores were computed with ''+1'' assigned for correct responses and ''0'' assigned for incorrect responses. These scores were graded as appropriate or inappropriate knowledge, positive or negative attitude, and good or poor practice using their mean score as the cut-off point. The bivariate analysis with chi-square statistics was used to establish the association between the outcome variables at $p \leq$

0.05 for all analyses and further multivariate analysis was done with binary logistic regression.

The qualitative data was transcribed and the result was analysed using detailed content analysis. All interviews were audio-recorded and transcribed verbatim. The first stage of analysis took place during data collection. This involved memo writing by the assistant researcher. Comments were written down following each discussion, after which the researcher listened to each audio to confirm the accuracy of the transcripts. These were then read through, and general notes were made. The final stage involved collating the data and presenting the findings.

Ethical consideration

A written informed consent was obtained from all participants and serial code numbers were used instead of names. Also, the Institute of Public Health Ethics and Research Committee granted permission to conduct the study with protocol number IPHOAU/12/1312. Confidentiality of collected data was maintained as only the investigators stored and accessed the data collected.

Results

Quantitative study

A total of 128 Islamic scholars participated. Their mean age (SD) was 37.2 (7.39) years. Most respondents were within the age group of 40 to 49 years (46.9%), male (69.5%), married (85.2%), Yoruba (89.8%), had secondary education (40.6%), Traders (41%), earned income <$1/day (69.5%) and worked as Islamic scholar for >5 years (70.3%) (Table 1).

Respondents' knowledge towards cancer care and prevention

Table 2 shows the respondents' knowledge towards cancer care and prevention. A total of 115 (89.8%) have heard about cancer with the main sources of information being the Radio (86%), Health workers (82.6%) and Hospitals (63.5%). The majority (53.9%) have heard of cancer screening services, with breast cancer (72.6%), cervical cancer (43.5%) and prostate cancer (24.2%) the types of cancer screened for. About one-fifth (20.9%) defined cancer correctly as an uncontrolled division of abnormal cells in a part of the body. The most common risk factor for cancer reported by the respondents was evil spirit (79.1%) followed by alcohol ingestion (55.7%). The majority of the respondents reported that cancer is preventable (82.6%) with preventive measures including prayers (54.7%), and fasting (23.4%). Only 18% reported cancer screening as a means of preventing cancer. Also, the respondents reported that the most effective ways to cure cancer include using Islamic medicines (100%), going to spiritual homes (90.4%), and fasting and praying (89.6%).

Table 1: Distribution of the Respondents' Socio-demographic Characteristics

Variable	Frequency (N=128)	%
Age (years)		
30-39	58	45.3
40-49	60	46.9
≥50	10	7.8
Sex		
Male	89	69.5
Female	39	30.5
Marital status		
Single	9	7.0
Married	109	85.2
Divorced	8	6.1
Widow	2	1.7
Qur'anic education	128	100
Level of formal education		
None	13	10.2
Primary	18	14.0
Secondary	52	40.6
Tertiary	45	35.2
Service period in mosque		
Full term	26	20.3
Part term	102	79.7
Other functions/occupation (n=102)		
Trader	52	51.0
Civil servant	25	24.5
Schooling (undergraduate/postgraduate)	25	24.5
Income (US$1/day)		
<1	89	69.5
≥1	39	30.5

Table 2: Respondents' knowledge towards cancer care and prevention

Variable	Frequency	%
Have heard of cancer		
Yes	115	89.8
No	13	10.2
*Sources of information about cancer (n=115)		
Radio	99	86.0
Health workers	95	82.6
Hospital	73	63.5
Newspaper	46	40.0
Internet	39	34.0
Have heard of cancer screening services (n=115)		
Yes	62	53.9
No	53	46.1
*Type of cancer screening services heard (n=62)		
Breast cancer	45	72.6
Cervical cancer	27	43.5
Prostate cancer	15	24.2
Definition of cancer (n=115)		
Cancer is a curse	65	56.5
Cancer is sexually transmitted	26	22.6
Cancer is uncontrolled cell division in any part of the body	24	20.9
*Risk factor of cancer (n=115)		
Evil spirit	91	79.1
Alcohol	64	55.7
Poor diet	52	45.2
Promiscuity	52	45.2
*Common types of cancer (n=115)		
Breast cancer	58	45.3
Cervical cancer	48	37.5
Prostate cancer	12	9.4
Lung cancer	10	7.8
Cancer is preventable (n=115)		
Yes	95	82.6
No	20	17.4
*Preventive measures of cancer (n=115)		
Prayer	70	54.7
Fasting	30	23.4
Uptake of cancer screening service	23	18.0
Healthy diet	19	14.8
Lifestyle	19	14.8
How to cure cancer (n=115)		
Use Islamic medicine	115	100
Go to spiritual home	104	90.4
Fasting and prayer	103	89.6
Use local herbs	101	87.8
Go to Hospital	58	50.4

*Multiple response

Respondents' attitudes and practices towards cancer care and prevention

Table 3 shows respondents' attitudes and practices towards cancer care and prevention. Islamic scholars agreed that only Allah cures and prevents cancer through fasting and prayers (100%), agreed that cancer is a spiritual problem that is curable spiritually (91.3%), and a dead sentence from almighty Allah (84.3%). The respondents agreed that Islamic medicines cure and prevent cancer (100%) and that herbs (91.3%) and antibiotics (88.7%) cure cancer. They agreed that cancer only affects older women (91.3%), and disagreed that men can also have breast cancer (77.4%). They disagreed that it was a family disease (88.7%). They agreed that cancer screening wastes time (86.1%).

The respondents' practice shows that 33% knew someone who has/had cancer. The majority of the cancer patients sought care at Islamic spiritual homes (47.4%). The most commonly diagnosed cancer among the said patients was breast cancer (39.5%). Regular use of local herbs, Islamic medicines, and prayer were considered to be the most effective ways of cancer prevention. Only female respondents had undergone cancer screening services for the breast (57.1%) and cervix (42.9%).

Predictors of practice towards cancer care and preventive measures

Table 4 shows the predictors of practice towards cancer care and preventive measures. The statistically significant predictors of good practice among the respondents include being not married (AOR 3.64; 95%CI 1.26-10.47; p=0.017), being new members of the congregation (AOR 6.00; 95%CI 2.22-16.19; p=0.0001) and having good knowledge (AOR 4.85; 95%CI 1.66-14.11; p=0.004).

Qualitative study

Thirty-two respondents participated in the FGD conducted two days after Jumat. Ages ranged from 18 to 65 years; 10 participants were new congregation members. All had Arabic and formal education.

Awareness and knowledge about cancer

It was observed that even though the participants had heard about cancer, their knowledge of cancer was inadequate. Causes of cancer mentioned include eating roasted and canned foods, wearing tightly fitted clothes, keeping money in a bra, and stress especially in the elderly. Other causes include silver coating on the recharge cards, cosmetics and lightening cream which are linked to skin cancer while multiple sexual partners could cause cervical cancer.

Table 3: Respondents' beliefs, attitudes and practices towards cancer care and prevention

Variable	Frequency	%
Beliefs		
Only Allah cures and prevents cancer	115	100
Cancer can be cured by fasting and prayers	115	100
Cancer is a spiritual problem cured by spiritual means (agree)	105	91.3
Cancer is a merciful test of faith by Almighty Allah (agree)	105	91.3
Cancer is a death sentence from the almighty (agree)	97	84.3
Cancer is an affliction from evil spirits (agree)	91	79.1
Attitude		
Islamic medicine cure cancer (agree)	115	100
Islamic medicines prevent cancer (agree)	115	100
Herbs cure cancer (agree)	105	91.3
Cervical cancer only affects older women (agree)	105	91.3
Antibiotics cure cancer (agree)	102	88.7
Cancer is a family disease (disagree)	102	88.7
Cancer screening is a waste of time (agree)	99	86.1
Early breast development can lead to breast cancer (agree)	97	84.3
Men can have breast cancer (disagree)	89	77.4
Practice		
Know anyone who have/had cancer (n=115)		
Yes	38	33.0
No	77	67.0
*Relationship with the person who has/had cancer (n=38)		
Member of the mosque congregation	18	47.4
Family	12	31.6
None	12	31.6
Type of cancer (n=38)		
Breast cancer	15	39.5
Lung cancer	13	34.2
Cervical cancer	10	26.3
Place of diagnosis		
Hospital	38	100
Referral care centre (n=38)		
Islamic spiritual home	18	47.4
Hospital	12	31.6
Traditionalist	8	21.0
*Advise given to congregation members on cancer care and preventive measures (n=115)		
Praying regularly	115	100
Regular use of Islamic medicines	106	92.2
Regular use of local Herbs	104	90.4
A regular visit to the hospital for a check-up	78	67.8
Ever undergone any cancer screening services (n=115)		
Yes	28	24.3
No	87	75.7
Sex of respondents that undergone cancer screening (n=28)		
Female	28	100
*Type of cancer screening undergone (n=28)		
Breast	16	57.1
Cervix	12	42.9

*Multiple Responses

Table 4: Predictors of practice towards cancer care and preventive measures

Variable	Practice		Test statistic χ^2; p-value	AOR; 95%CI; p-value
Marital status	Poor (%)	Good (%)		
Not married	11(57.9)	8 (42.1)	6.215; 0.013	3.64; 1.26-10.47; 0.017
Married (Ref.)	80(83.3)	16 (16.7)		1
Level of education				
No formal education (Ref.)	11 (91.7)	1 (8.3)	1.275; 0.455	1
Had formal education	80 (77.7)	23 (22.3)		3.16; 0.39-25.80; 0.282
Duration in congregation (years)				
<5	13 (52.0)	12 (48.0)	14.238; 0.0001	6.00; 2.22-16.19; 0.0001
≥5 (Ref.)	78 (86.7)	12 (13.3)		1
Knowledge				
Poor (Ref.)	51 (91.1)	5 (8.9)	9.424; 0.002	1
Good	40 (67.8)	19 (32.2)		4.85; 1.66-14.11; 0.004

The Islamic scholars had never heard of prostate cancer screening. Regarding the attitudes and practices of the Islamic scholars towards cancer care and preventive measures, some participants believe in using herbs to cure cancer. Due to the fear of the unknown, most participants will prefer not to undergo any cancer screening. The female discussants feel uncomfortable undressing or being examined by male health practitioners, and they cannot encourage their members to undergo clinical cancer screening either unless they are certain that they will be examined by a female. A participant sees cancer as a spiritual sin; hence, cancer patients need spiritual help. Faith, destiny and the will of Allah play crucial roles in the attitude and practice of the respondents

Discussion

The current study examined Islamic scholars' knowledge, attitudes and practices about cancer care and preventive measures. It showed that most participants were aware of cancer care and preventive measures. This was similarly reported by Narimah *et al.,* which implies that cancer awareness is high among Islamic scholars.[24]

Despite awareness, many Islamic scholars had poor knowledge, which is in contrast with previous studies among Muslim residents in developed countries that reported better knowledge.[21-23] This disparity could be due to differing education and exposure to cancer information. The current study revealed a high level of misconceptions and myths regarding the causes and prevention of cancer as the respondents believed that cancer is caused by evil spirits and could only be treated spiritually, believing that cancer screening is not preventive. These findings are in keeping with reports from previous studies.[15,25] Also, most Islamic scholars studied had negative attitudes towards cancer care and preventive measures. This finding is at variance with a report from a study conducted among Muslims in Jordan by Ahmad *et al*., which indicated positive attitudes among their study participants.[26] This underscores the need for educational interventions focusing on dispelling myths and misconceptions and improving cancer knowledge and attitude as better knowledge and positive attitude will motivate people to accept cancer screening, leading to early detection and prompt treatment.

Also, this study revealed that most Islamic scholars studied had poor practice towards cancer care and preventive measures. This was reported by Ahmed *et al.,* which indicated that most Islamic scholars studied had poor practices.[27] Improvement in cancer-related knowledge and attitudes will further improve practice regarding cancer prevention and care. Thus, the Nigerian Cancer Control Programme (CCP) needs to focus its attention on Islamic scholars who are key stakeholders in influencing the behaviour of their teeming followers. Due to the increasing burden of cancer in Nigeria, there is a need for the establishment of one-stop shops near Mosques and other religious centres where cancer-related information and preventive services can be readily accessed.

The current study reported that most Islamic scholars believed that cancer can be prevented and/or cured by prayers to Allah, Islamic medicines, herbal preparation and the use of antibiotics. Previous studies reported that the Islamic faith plays a crucial role such as religious values and beliefs influencing health behaviours significantly despite

racial and ethnic diversity.[22,26,28] Thus, Islamic Scholars who are well-trained by public health experts can be recruited as champions of cancer prevention through counselling cancer patients to accept orthodox care for better treatment outcomes.

Many of the respondents in the current study believed that food causes cancer and that some specific foods can cure cancer. This is similar to the findings of Norhasmilia *et al.* in their study on the Islamic healing approach to cancer treatment in Malaysia.[29] Cancer awareness campaigns should thus emphasise healthy eating. Adults should be counselled to eat more fresh fruits and vegetables. Some of these fruits and vegetables are promoted by Islamic doctrines. Nigerian adults should also desist from alcohol abuse, cigarette smoking and consumption of refined food products, which are some of the most predominant modifiable risk factors of cancers.

Limitation of the study

This study is limited by social desirability bias, which was reduced by the proper explanation of the study purpose.

Conclusion

Though the Islamic scholars studied were aware of cancer, they had poor knowledge, negative attitudes and poor practice towards cancer care and preventive measures. There is an urgent need for policymakers to design and implement a robust, cost-effective awareness campaign aimed at equipping Islamic scholars with the correct cancer-related information which can be passed down to their followers.

Acknowledgement: The authors acknowledged all Islamic scholars for their participation in this study.
Conflict of Interest: Authors declare none

References

1. Ojo J, Adeola M, Awe O, et al. Analyses and distribution of various types of cancers recorded in Ife-Ijesha Cancer Registry in the five years 2010-2014. IJS. 2016;18(4):1005-1017
2. El-Khodary MSM. Quranic Verse No. 8 of Surat Al-Jumu'ah Describes Cancer as a Complete and Accurate Description and Leads Us to Determine the True Cause of Cancer. Part-1. CellBio. 2018;7(1):1-11. doi: https://doi.org/10.4236/cellbio.2018.71001
3. Idowu A, Olowookere SA, Olumide A, et al. Breast cancer awareness, knowledge and screening practice among women resident in an urban local government area of Oyo State, Nigeria. J Cancer Policy. 2019;20:100179. doi:https://doi.org/10.1016/j.jcpo.2018.11.001
4. Idowu A, Olowookere SA, Fagbemi AT, Ogunlaja OA. Determinants of cervical cancer screening uptake among women in Ilorin, North Central Nigeria: a community-based study. J Cancer Epidemiol. 2016;2016(1):6469240. doi:http://dx.doi.org/10.1155/2016/6469240
5. Smith RA, Andrews KS, Brooks D, et al. Cancer screening in the United States, 2018: a review of current American Cancer Society guidelines and current issues in cancer screening. CA Cancer J Clin. 2018;68(4):297-316
6. Cancer IAfRo. GOBOCAN 2018: Estimated cancer incidence, mortality and prevalence worldwide in 2018. 2019
7. Sowunmi A, Alabi A, Fatiregun O, Olatunji T, Okoro US, Etti AFD. Trend of cancer incidence in an oncology centre in Nigeria. West Afr J Radiol. 2018;25(1):52-56
8. World Health Organization. WHO position paper on mammography screening. Geneva: World Health Organization; 2014
9. Ginsburg O, Bray F, Coleman MP, et al. The global burden of women's cancers: a grand challenge in global health. Lancet. 2017;389(10071):847-860
10. Mobin-Uddin A. An Islamic perspective: Suffering and meaning in cancer. Clin J Oncol Nurs. 2018;22(5):573-575
11. DeSantis CE, Fedewa SA, Goding Sauer A, Kramer JL, Smith RA, Jemal A. Breast cancer statistics, 2015: Convergence of incidence rates between black and white women. CA Cancer J Clin. 2016;66(1):31-42
12. Adegbenro C, Ajala A, Ajayi O, et al. Awareness of breast cancer and practice of breast self-examination among rural women in Ife-North local government area, Osun state, South-West Nigeria. JCMPHC. 2014;26(1):76-87
13. Torre LA, Siegel RL, Ward EM, Jemal A. Global cancer incidence and mortality rates and trends—An update. CEBPE4. 2016;25(1):16-27. doi:https://doi.org/10.1158/1055-9965.EPI-15-0578
14. Elshami M, Qawasmi MA, Ghithan RJ, et al. Barriers to Timely Seeking of Breast Cancer Care Among Palestinian Women: A Cross-Sectional Study. JCO Glob Oncol. 2024;10:e2300373. doi:https://doi.org/10.1200/GO.23.00373
15. Elshami M, Naji SA, Dwikat MF, et al. Myths and common misbeliefs about colorectal cancer causation in Palestine: A national cross-sectional study. JCO Glob Oncol. 2024;10:e2300295. doi:https://doi.org/10.1200/GO.23.00295
16. Adejuyigbe FF, Balogun BR, Sekoni AO, Adegbola AA. Cervical cancer and human papilloma virus knowledge and acceptance of vaccination among medical students in Southwest Nigeria. Afr J Reprod Health. 2015;19(1):140-148
17. Olowookere S, Abioye-Kuteyi E, Airewele E, et al. Awareness and uptake of human papilloma virus vaccination and cervical cancer screening among

female undergraduate students in a tertiary institution in Nigeria. Niger J Fam Pract. 2012;3(1):27-32
18. Agbugui J, Obarisiagbon E, Nwajei C, Osaigbovo E, Okolo J, Akinyele A. Awareness and knowledge of prostate cancer among men in Benin City, Nigeria. J Biomed Res. 2013;12(2):42-47
19. Holt CL, Roth DL, Clark EM, Debnam K. Positive self-perceptions as a mediator of religious involvement and health behaviors in a national sample of African Americans. J Behav Med. 2014;37:102-112
20. Karunakaran U, Thekkandathil N, Joseph M, Kannankai S, Kumaran JA. Clinical breast cancer screening-A camp-based study among rural women in north Kerala. J Evid Based Med Healthc. 2017;4(54):3323-3328. DOI:10.18410/jebmh/2017/660
21. Padela AI, Peek M, Johnson-Agbakwu CE, Hosseinian Z, Curlin F. Associations between religion-related factors and cervical cancer screening among Muslims in greater Chicago. J Low Genit Tract Dis. 2014;18(4):326-332. doi:DOI: 10.1097/LGT.0000000000000026
22. Arozullah AM, Padela AI, Volkan Stodolsky M, Kholwadia MA. Causes and means of healing: An Islamic ontological perspective. J Relig Health. 2020;59(2):796-803
23. Islam N, Patel S, Brooks-Griffin Q, et al. Understanding barriers and facilitators to breast and cervical cancer screening among Muslim women in New York City: perspectives from key informants. J Community Med. 2017;3(1):1-14
24. Samat N, Ghazali S, Atang C. Cancer Awareness and knowledge: A community survey in Kedah and Perlis. Asian Soc Sci. 2014;10(21):10-18
25. Suhami N, Muhamad MB, Krauss SE. Why cancer patients seek Islamic healing. J Relig Health. 2016;55:1507-1518
26. Ahmad MM, Dardas LA, Ahmad H. Cancer prevention and care: A national sample from Jordan. J Cancer Educ. 2015;30:301-311
27. Ahmed SA, Sabitu K, Idris SH, Ahmed R. Knowledge, attitude and practice of cervical cancer screening among market women in Zaria, Nigeria. Niger J Med. 2013;54(5):316-319
28. Rezaei S, Peikanpour M, Zarei L, Mohammadnezhad G, Salamzadeh J. An adapted model of cost-related medication nonadherence among older adult patients with chronic diseases: an Iranian qualitative study. BMC Geriatr. 2023;23(1):208
29. Krauss NSMMSE. The Islamic Healing Approach to Cancer Treatment in Malaysia. Journal of Biology, Agriculture, and Health Care. 2014;4(6):106-107

InaJCC The Indonesian Journal of Cancer Control

Case Report

Rare delayed tracheal perforation after total thyroidectomy repaired with autologous pericardial patch

Ramadanus[1], Daan Khambri[2], Wirsma Arif Harahap[2], Rony Rustam[2], Yopi Triputra[2], Rahmat Taufik[2], Ari Oktavenra[2], Hendra Herizal[2]

e-ISSN 2797-457X
DOI: 10.52830/inajcc.v1i1.100

Received: October 24th, 2024
Accepted: February 15th, 2025

Authors' affiliations:
[1]Surgical Oncology Trainee, Medical Faculty of Andalas University/ Dr. M. Djamil General Hospital Padang, Indonesia
[2]Surgical Oncology Departement, Medical Faculty of Andalas University/Dr. M. Djamil General Hospital Padang, Indonesia

Corresponding author:
E-mail: *daankhambri567@gmail.com*

Abstract

Background: Thyroidectomy is a general surgical procedure that is very common with 3–5% complication rate. Tracheal perforation after thyroidectomy is rare at 0.06%, and is usually identified and repaired intraoperatively. Delayed tracheal perforation is even rarer, with only few cases reports with different management.
Case illustration: A 57-year-old female underwent total thyroidectomy for infiltrating bilateral thyroid cancer. Tumor infiltration to the trachea was shaved, followed by tracheostomy to secure the airway. Perforation symptoms appear on day 4 after the patient experienced choking in the form of progressive slem production. Perforation was found in the shaven area fused to the tracheostomy hole sized 2x3 cm. The patient was managed in stages, initially with debridement and antibiotics followed by surgical repair. Tracheal repair surgery performed an autologous pericardial patch combined with a PTFE vascular implant. The patient was extubated 1 week after repair and discharged alive. No further complications on follow-up.
Discussion: In this case, perforation happened due to mechanical force on the remaining thin shaved tracheal wall during choking. Autologous pericardial patch was used due to its several advantages combined with PTFE vascular implant as rigid stenting that prevent collapse when breathing.
Conclusion: Autologous pericardial patch combined with PTFE was sufficient to close delayed perforated trachea after thyroidectomy.

Keywords: *Autologous Pericardial Patch, Delayed tracheal perforation, Total thyroidectomy*

Abstrak

Latar Belakang: Tiroidektomi merupakan prosedur bedah umum yang cukup sering dilakukan, dengan tingkat komplikasi sekitar 3–5%. Perforasi trakea pasca-tiroidektomi merupakan komplikasi langka dengan insidensi sekitar 0,06% dan biasanya dapat diidentifikasi serta diperbaiki selama operasi berlangsung. Perforasi trakea yang muncul secara terlambat merupakan kondisi yang jauh lebih jarang, dengan hanya sedikit laporan kasus dan variasi dalam penatalaksanaannya.
Ilustrasi Kasus: Perempuan berusia 57 tahun menjalani tiroidektomi total akibat kanker tiroid bilateral dengan infiltrasi ke trakea. Dilakukan *shaving* pada infiltrasi tumor pada dinding trakea, kemudian dilakukan trakeostomi untuk menjaga jalan napas. Gejala perforasi muncul pada hari ke-4 pascaoperasi setelah pasien mengalami tersedak disertai peningkatan produksi sputum progresif. Perforasi ditemukan pada area *shaving* yang berfusi dengan lubang trakeostomi berukuran 2×3 cm. Pasien ditata laksana secara bertahap, dimulai dengan *debridement* dan pemberian antibiotik, kemudian dilanjutkan dengan pembedahan perbaikan. Rekonstruksi trakea dilakukan menggunakan *autologous pericardial patch* yang dikombinasikan dengan implan vaskular PTFE. Pasien berhasil diekstubasi satu minggu setelah operasi dan dipulangkan dalam kondisi baik tanpa komplikasi lanjutan pada tindak lanjut.
Diskusi: Pada kasus ini, perforasi terjadi akibat gaya mekanik pada dinding trakea yang menipis akibat *shaving* selama episode tersedak. Penggunaan *autologous pericardial patch* dipilih karena memiliki beberapa keunggulan biokompatibilitas, sedangkan implan vaskular PTFE digunakan sebagai penopang yang kaku untuk mencegah kolaps trakea selama respirasi.
Kesimpulan: Kombinasi *autologous pericardial patch* dan implan PTFE terbukti efektif untuk menutup perforasi trakea yang timbul terlambat pasca-tiroidektomi.

Kata Kunci: *Autologous pericardial patch, perforasi trakea tertunda, tiroidektomi total*

Background

Total thyroidectomy is frequently performed for various indications, including benign multinodular goiter and thyroid cancer. It is a safe procedure with 3–5% complication rate. Several common complications including hypoparathyroidism, recurrent laryngeal nerve injury, and, less commonly, tracheal injury.[1–3] Tracheal perforation after thyroidectomy is rare ranging at 0.06% - 0.5%, and is usually identified and repaired intraoperatively. It can lead to significant morbidity if not recognized and managed promptly.[4] Several factors contribute to the risk of delayed tracheal perforation. These include extensive surgical dissection, especially in cases involving large goiters or malignancies that may adhere to the trachea, and the use of diathermy, which can cause thermal injury to surrounding tissues. Additionally, patients with a history of neck radiotherapy may have increased susceptibility to tracheal injury due to fibrosis and altered tissue integrity.[5–7]

Delayed tracheal perforation following total thyroidectomy is even rarer but particularly concerning due to the potential for airway compromise and the need for urgent intervention critical complication.[8,9] While immediate tracheal injuries are more commonly recognized, delayed perforations can occur days to weeks postoperatively, often complicating the clinical picture of the patient.

Symptoms of delayed perforation can include subcutaneous emphysema, respiratory distress, and pneumomediastinum, which may manifest several days postoperatively.[9,10] The clinical presentation may be subtle initially, with patients experiencing mild symptoms that can progress to severe respiratory compromise if not addressed. Diagnosis typically involves imaging studies, such as CT scans, which can reveal air leakage or direct visualization of the perforation.[11]

Management strategies typically involve securing the airway, which may require intubation or tracheastomy, followed by surgical repair of the tracheal defect if feasible.[4,12] The timing of intervention is crucial; early recognition and management can significantly improve outcomes, while delays can lead to severe complications, including prolonged ventilation or the need for more extensive surgical repairs.[8,10]

To date there is only few publications presenting delayed tracheal perforation after total thyroidectomy with very limited option of surgical technique for repair.

Case Illustration

We report a case of a 57-year-old female complaining mass on the neck for 30 years. The lump grew progressively for 3 months. Patient also complained about hoarseness for 3 weeks. CT scans show inhomogeneous hypodense mass with intralesional calcification in both thyroid lobes, especially on the left. There was also enlargement on the bilateral neck lymph nodes.

The patient underwent surgery for total thyroidectomy. Intraoperatively tumor infiltrated the trachea in the second ring on the left side. We performed tumor shaving with scalpel leaving a thin and soft tracheal wall. Tracheostomy was performed to secure airway. The patient observed in the ICU without any problems and on the third day moved to the regular room.

Day 4 after the operation, there was a lot of slem seepage from tracheostomy wound after the patient experienced choking. Due to massive increased slem production, explorations were carried out. We found tracheal perforation on the shaven area fused to the tracheostomy hole sized 2x3 cm. Given dirty and contaminated wounds, we decided to perform only debridement, and the tracheostomy was replaced with an endotracheal tube. The patient was readmitted to the ICU and given broad spectrum antibiotic.

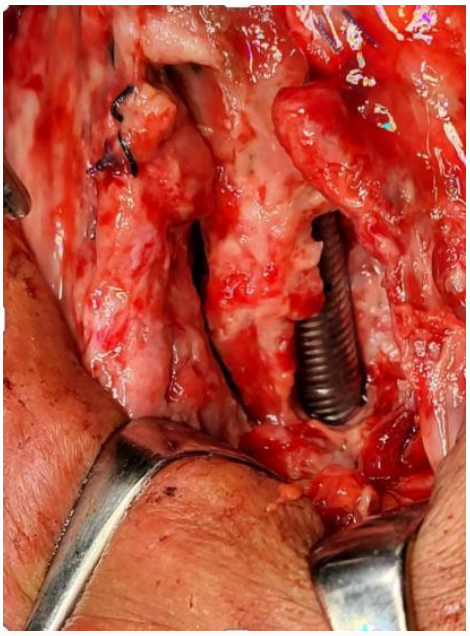

Figure 1. Perforated trachea on the shaven area fused to tracheostomy hole. Tracheostomy tube was removed and replaced with an endotracheal tube.

Day 7 patient underwent tracheal repair surgery using autologous pericardial patch combined with PTFE vascular implant. The patient was extubated 1 week after repair and discharged alive. There was no further complication on the follow-up visit. Patient can talk normally without any hoarseness. Postoperative histopathology examination showed a papillary thyroid carcinoma with anaplastic component.

Discussion

Thyroidectomy is commonly performed worldwide. It is a safe procedure with rate of complications less than 3%–5%.[13] With only few cases reported globally, delayed tracheal perforation without an intraoperative tracheal injury is an uncommon complication. It has been reported that 4–27 days after thyroidectomy, tracheal perforation still exists. The risk factors include female sex and toxic thyroid nodules, especially large nodules and compress the trachea for a long time, weakening the cartilaginous wall of trachea. Tracheal perforation risk factors also include prolonged high doses of steroids prior to surgery, prior radiation therapy, high pressure during the procedure, suction tube damage to the trachea, and disruption of blood flow during the coagulation process with an electrocautery device. Coughing repeatedly or getting infections due to blood clots can also become risk factors after surgery.[14,15]

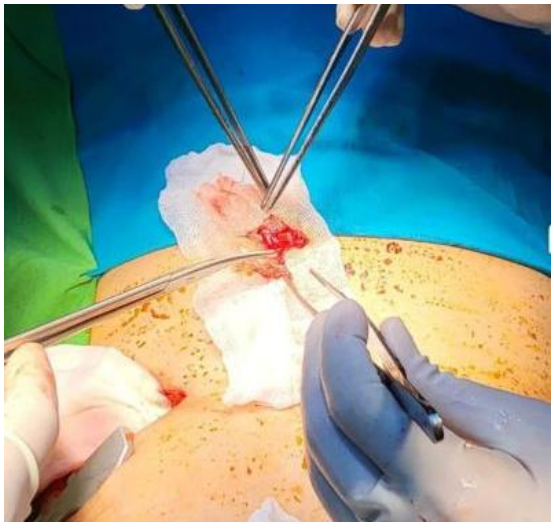

Figure 2. Autologous pericardial patch was harvested through “mini thoracotomy” procedure. An 8 cm incision was made on the anterior of left fifth intercostal.

In this particular case, the thyroid mass was large and already compress tracheal for about 30 years. The trachea was also infiltrated by the cancer that made the operation became more challenging. The incidence of coughing on the day 4 was suspected as a trigger of the perforation. Perforation occurs secondary to elevated subglottic pressure through a thin and weak portion of the trachea, following coughing where subglottic pressure is markedly elevated.[14]

The most common symptoms of delayed tracheal perforation are neck swelling and subcutaneous emphysema. In addition, there are also several cases of fever, coughing, hemoptysis, and respiratory distress reported.[15]

Our patient didn’t experience any neck swelling or emphysema. The main symptom was massive slem production instead. The tracheostomy tube and the gap in the tracheostomy wound prevented emphysema, as well as the symptoms of dyspnea or respiratory distress. But it made it easier for infections to occur.

Our decision not to perform immediate perforation repair was appropriate. Considered the high contamination of the patient's wound, performing an immediate repair will increase the risk of failure and potentially lead to greater morbidity. We removed the tracheostomy tube and replaced it with an endotracheal tube to secure the airway. By cleaning the contamination, closing the wound and treating the infection, we prepared the optimal wound conditions for repair.

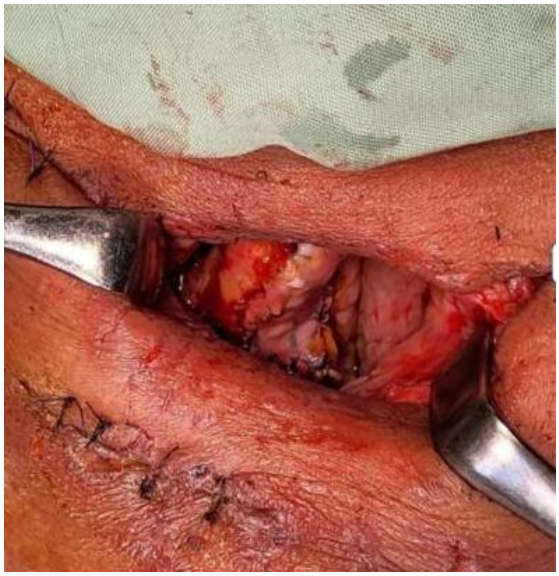

Figure 3. The trachea after repaired. Firstly, the defect repaired with autologous pericardial patch, the PTFE was placed over as a stent to support it from collapsing and prevent stenosis in the future. The PTFE is then covered again with the remaining pericard.

The degree of the patient's symptoms and the size of the tracheal defect determine how the defect is treated.[16]

Conservative measures like bed rest, low-dose steroid therapy, high-pressure oxygen supply, and antibiotics may be used in patients with minor defects and no or improving respiratory distress.[17] Primary suturing is adequate if the defect is small and the inflammation is not severe. Muscle flaps can be used to reinforce non-circumferential defects and localized severe inflammation; tracheal resection and reconstruction or anastomosis may be required for circumferential defects that extend beyond half of the trachea.[18,19]

The use of free autologous pericardial patches as tracheal substitutes has several benefits, including the ability to be used in surgical settings, ease of handling, flexibility, and customization to the specific needs of each case, lack of tissue rejection and foreign body reactions, and—above all—the ability to maintain an airtight seal of the reconstructed airway. Within months, mature granulation tissue replaces the free pericardial patches, which act as a scaffold for the reepithelialization of the respiratory mucosa to restore normal mucociliary flow to the larynx.[20,21]

Long-term outcomes of pericardial patch tracheaplasty have shown promise, with studies indicating successful epithelialization and integration of the patch within months post-surgery. Respiratory epithelium covers the mesenchymal tissue of the pericardium. According to the postmortem study, the pericardial patch has been well-integrated into the surrounding trachea and cannot be identified in its original form. Throughout the repaired trachea, a full epithelium lining was seen, along with the development of normal mucosal and submucosal structures, including glands and vessels. The pericardial patch becomes well incorporated as early as three months.[22]

The use of pericardial patch in tracheal reconstruction combined with stenting has been reported in several cases, which can be either internal or external stenting. This aims to prevent pericardial floating and stenosis.[21] In this case we use PTFE vascular implant as a external stenting. PTFE is a Synthetic polymer that has been used in many surgical applications, especially in reconstructive and vascular surgery. Polytetrafluoroethylene (PTFE) has emerged as a significant material in the field of tracheal reconstruction due to its mechanical strength and durability, making it a suitable candidate for reinforcing tracheal repairs.

Conclusion

The combination of pericardial patches and polytetrafluoroethylene (PTFE) in tracheal repair represents a promising approach to addressing tracheal defects particularly as a complication after thyroidectomy.

References

1. Vassiliou I, Tympa A, Arkadopoulos N, Nikolakopoulos F, Petropoulou T, Smyrniotis V. Total thyroidectomy as the single surgical option for benign and malignant thyroid disease: A surgical challenge. Arch Med Sci. 2013;9(1):74–8.
2. Padur AA, Kumar N, Guru A, Badagabettu SN, Shanthakumar SR, Virupakshamurthy MB, et al. Safety and Effectiveness of Total Thyroidectomy and Its Comparison with Subtotal Thyroidectomy and Other Thyroid Surgeries: A Systematic Review. J Thyroid Res. 2016;2016.
3. Cannizzaro MA, Lo Bianco S, Picardo MC, Provenzano D, Buffone A. How to avoid and to manage post-operative complications in thyroid surgery. Updates Surg. 2017;69(2):211–5.
4. Alqahtani SM, Almussallam B, Alatawi AS, Alsuhaimi NA, Albalawi A, Albalawi NS, et al. Post-Thyroidectomy Complications and Risk Factors in Tabuk, Saudi Arabia: A Retrospective Cohort Study. Cureus. 2020;12(10).
5. Seenarain V, Trivedi A, Flukes S, Tjhin WE. Diagnosis and surgical repair of delayed tracheal perforation post thyroidectomy in context of previous craniospinal radiotherapy – A case report. Int J Surg Case Rep [Internet]. 2022;91(December 2021):106761. Available from: https://doi.org/10.1016/j.ijscr.2022.106761
6. López-Morales P, Candel-Arenas MF, Martínez-Sanz N, Medina-Manuel E, Giménez-Francés C, Albarracín-Marín-Blázquez A. Delayed tracheal perforation after thyroid surgery in patient with neck radiotherapy. Cir y Cir (English Ed. 2023;91(1):113–6.
7. Testini M, Logoluso F, Lissidini G, Gurrado A, Campobasso G, Cortese R, et al. Emergency total thyroidectomy due to non traumatic disease. Experience of a surgical unit and literature review. World J Emerg Surg [Internet]. 2012;7(1):9. Available from: http://www.wjes.org/content/7/1/9
8. Stevens MN, Bolduan A, Gelbard A. Delayed Tracheal Perforation Following Total Thyroidectomy. Laryngoscope. 2022;132(1):17–9.
9. Han YS, Lee DW, Lee HS. A Case of Tracheal Perforation and Pneumomediastinum after Thyroidectomy Young. J Clin Otolaryngol. 2021;32:312–6.
10. Shew M, Boyd C, Kraft S. Delayed Multifocal Tracheal Injury Following Thyroidectomy: A Case Report and Review of the Literature. Cureus. 2020;12(5).
11. Nguyen H, Le Trinh H, Nguyen H, Nguyen H Van, Le Q Van. Surgical Treatment of Advanced Thyroid Cancer with Tracheal Invasion. Case Rep Endocrinol. 2021;
12. Koeppen M, Scott B, Morabito J, Fiegel M, Eckle T. Pneumomediastinum and Bilateral Pneumothoraces Causing Respiratory Failure after Thyroid Surgery. Case Rep Anesthesiol. 2017;2017(Figure 1):1–5.

13. Tartaglia N, Iadarola R, Di Lascia A, Cianci P, Fersini A, Ambrosi A. What is the treatment of tracheal lesions associated with traditional thyroidectomy? Case report and systematic review. World J Emerg Surg. 2018;13(1):1–6.
14. Azar SS, Patel E, Evans LK, Blood TC, Su-velez BM, Chhetri DK. Delayed Tracheal Perforation After Partial Thyroidectomy : A Case Report and Review of the Literature. Ear, Nose Throat J. 2023;102(8):NP410–2.
15. Heo DB, Son HO, Wool H, Sung J, Koo BS. Delayed Tracheal Perforation After Thyroidectomy : A Case Report and Literature Review. Ear, Nose Throat J. 2023;0(0):1–6.
16. Geum SY, Park JW, Kim JK, Lee DW. A Case of Tracheal Perforation Occurring 1 Month after Thyroidectomy. J Clin Otolaryngol. 2021;32:317–21.
17. Colás RE, Quintáns RA, Linacero MS, Celi AE, Martin PL. Quistes coloides subcutáneos posquirúrgicos. Cir Esp. 2016;94(1):49–50.
18. Jacqmin S, Lentschener C, Demirev M, Gueroult S, Herman P, Ozier Y. cervical trachea following thyroidectomy. 2005;19:347–8.
19. Han X, Mu Q, Liu C, Lu X, Yin D, Ren K, et al. Covered Stent Implantation in the Treatment of Tracheal Rupture after Thyroidectomy. J Vasc Interv Radiol [Internet]. 2016;27(11):1758–61. Available from: http://dx.doi.org/10.1016/j.jvir.2016.04.017
20. Foroulis C, Karapanagiotidis G, Papakonstantinou C. Pericardial Patch Tracheoplasty for the Repair of a Long, Multisegmental Postintubation Tracheal Damage. Artif Organs. 2012;36(9):835–9.
21. Wang B, Zhang Z, Guo Y, Yu F. Trachea repair using an autologous pericardial patch combined with a 3D carbon fiber strent: A case report. Front Surg. 2023;(January):1–5.
22. Fanous N, Husain SA, Ruzmetov M, Rodefeld MD, Turrentine MW, Brown JW. Anterior pericardial tracheoplasty for long-segment tracheal stenosis : Long-term outcomes. J Thorac Cardiovasc Surg [Internet]. 2010;139(1):18–25. Available from: http://dx.doi.org/10.1016/j.jtcvs.2009.09.040.

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Case Report

Misdiagnosis of lung adenocarcinoma mimicking of pulmonary tuberculosis: a case report

Tria Meirissa[1,2], Andreas Infianto[1,2], R. Dicky Wirawan L[1,2], Sukarti[1,3], Tetra Arya Saputra[1,3], Deschairul[2]

e-ISSN 2797-457X
DOI: 10.52830/inajcc.v1i1.114

Received: November 5th, 2024
Accepted: February 21st, 2025

Authors' affiliations:
[1]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Lampung University, Indonesia
[2]Ahmad Yani Hospital, Metro, Lampung, Indonesia
[3]Abdul Moeloek Hospital, Bandar Lampung, Lampung, Indonesia

Corresponding author:
E-mail: meirissatria@gmail.com

Abstract

Background: Pulmonary abnormalities caused by lung cancer can be clinically and radiologically similar to pulmonary tuberculosis (TB). Pulmonary symptom of TB and lung cancer overlap each other such as chronical dyspnea, coughing, hemoptysis, chronic pain and weight loss. Radiologically such as cavities, infiltrates, nodules and miliary. These similarities make it challenging for clinicians and causes misdiagnosis with incidence between 0,03% and 30,4% worldwide.
Case Presentation: A 65-year-old male with chief complaint of shortness of breath and chronic cough for three months, accompanied by symptoms of atypical chest pain, weight loss and indigestion. Chest physical examination found dullness of percussion and decrease breath sound on left side hemithorax. Chest X-ray showed cavity in the left lung. The bronchoscopy result showed mass in the left bronchial and left upper lobe. Biopsy results were obtained adenocarcinoma.
Discussion: Pulmonary tuberculosis and lung cancer often mimic each other on imaging, sharing features such as irregular consolidations and thick-walled cavities. This similarity frequently leads to diagnostic confusion and potential misclassification, especially in regions with high tuberculosis prevalence. Accurate distinction requires thorough pathological and microbiological confirmation to ensure proper management.
Conclusions: Diagnosing pulmonary tuberculosis and lung adenocarcinoma is challenging especially based on similarity of clinical and radiological findings, resulting in significant misdiagnosis. Further examinations and clinician expertise are essential to differentiate.

Keywords: *Lung Adenocarcinoma, Pulmonary Tuberculosis, Misdiagnosis*

Abstrak

Latar Belakang: Kelainan paru akibat kanker paru dapat menyerupai tuberkulosis (TB) paru baik secara klinis maupun radiologis. Gejala klinis TB dan kanker paru sering tumpang tindih, seperti sesak napas kronis, batuk, hemoptisis, nyeri dada kronis, dan penurunan berat badan. Gambaran radiologis yang mirip meliputi kavitas, infiltrat, nodul, dan pola milier. Kesamaan ini menjadi tantangan bagi klinisi dan sering menyebabkan salah diagnosis, dengan insidensi berkisar antara 0,03% hingga 30,4% di seluruh dunia.
Ilustrasi Kasus: Seorang laki-laki berusia 65 tahun datang dengan keluhan utama sesak napas dan batuk kronis selama tiga bulan, disertai nyeri dada atipikal, penurunan berat badan, dan gangguan pencernaan. Pemeriksaan fisik toraks menunjukkan pekak pada perkusi serta penurunan suara napas pada hemitoraks kiri. Foto toraks menunjukkan kavitas di paru kiri. Hasil bronkoskopi memperlihatkan massa pada bronkus kiri dan lobus atas kiri. Hasil biopsi menegakkan diagnosis adenokarsinoma paru.
Diskusi: Tuberkulosis paru dan kanker paru sering menunjukkan kemiripan pada pencitraan, dengan temuan seperti konsolidasi tidak teratur dan kavitas berdinding tebal. Kesamaan ini sering menimbulkan kebingungan diagnostik dan salah klasifikasi, terutama di wilayah dengan prevalensi TB yang tinggi. Pembedaan yang akurat memerlukan konfirmasi patologis dan mikrobiologis yang menyeluruh untuk memastikan penatalaksanaan yang tepat.
Kesimpulan: Diagnosis tuberkulosis paru dan adenokarsinoma paru merupakan tantangan tersendiri karena kesamaan temuan klinis dan radiologis yang dapat menyebabkan salah diagnosis. Pemeriksaan lanjutan dan keahlian klinisi sangat penting untuk membedakannya.

Kata Kunci: Adenokarsinoma paru, tuberkulosis paru, salah diagnosis

Background

Lung cancer and pulmonary tuberculosis (TB) are global health problems. Lung cancer is the leading cause of cancer deaths in the world. The World Health Organization (WHO) states that lung cancer was ranked 8th as a cause of death in 2004 and will increase to 6th in 2030.[1] Pulmonary tuberculosis is a major global health problem, especially in developing countries, WHO estimates 9.6 million new cases of pulmonary TB in 2014.[2] Indonesia is the country with the 4th largest number of pulmonary TB patients in the world with 5.7% of the total number of pulmonary TB patients in the world.[3] Pulmonary abnormalities causes by lung cancer can be clinically and radiologically similar to pulmonary TB. Pulmonary symptom of TB and lung cancer overlap each other such as chronical dyspnoe, coughing, hemoptysis, chronic pain and weight loss. Radiologically such as cavities, infiltrates, nodules and miliary.[4] The early symptoms of lung cancer are almost the same as pulmonary TB, so for countries with a high prevalence of pulmonary TB such as Indonesia, this needs to be a concern. Delays in the diagnosis of lung cancer can be caused by misdiagnosis in countries where pulmonary TB is endemic.4 These similarities make it challenging for clinicians and causes misdiagnosis with incidence between 0,03% and 30,4% worldwide.[5]

Case Illustration

A 65-year-old man with a chief complaint of shortness of breath for three months, shortness of breath that worsens especially when the patient coughs. The patient also complained of a cough with phlegm for three months, but the phlegm was difficult to remove. The patient's complaint was also accompanied by intermittent left chest pain that did not spread. The patient experienced a decrease in appetite followed by a weight loss of five kg in three months. The patient's occupation is a farmer who is often exposed to smoke from burning. History of smoking six cigarettes for 50 years with a moderate Brinkman Index. Physical examination of the chest found asymmetric inspection, palpation of stem fremitus decreased in the medial left lung, dull percussion in the medial left lung and decreased vesicular auscultation in the medial left lung.

Chest X-ray showed a cavity in the medial left lung. The results of the contrast chest CT scan showed a cavity mass with pneumonic reaction, clear boundaries, regular edges, non-calcification measuring 6.1cm x 6.1cm x 5.9cm in the superior segment of the inferior lobe of the left lung. There was enlargement of the left para-tracheal, sub carina and left peribronchial lymph nodes. The results of the Epidermal Growth Factor Receptor (EGFR) mutation status examination were wild type

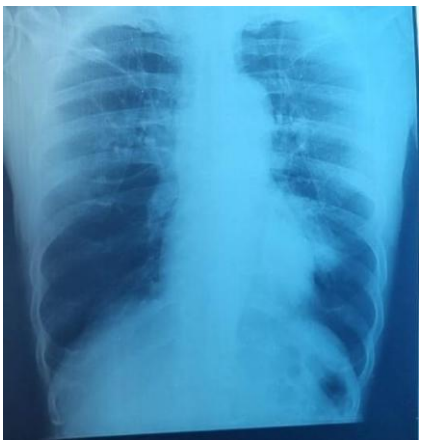

Figure 1. Chest X-ray: A cavity in the medial left lung

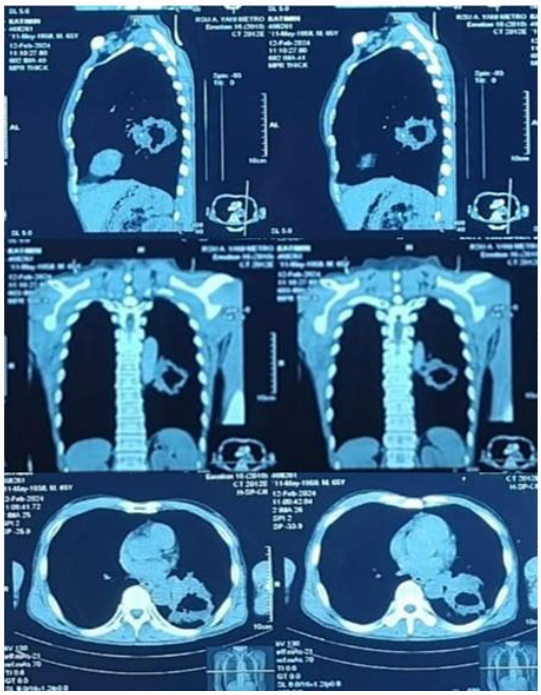

Figure 2. Contrast chest CT scan: A Cavity in the inferior lobe of the left lung

The patient underwent bronchoscopy and showed stenosing infiltration, hyperemia and easy bleeding in the left main bronchus and left upper lobe. The conclusion of the patient's bronchoscopy was suggestive of malignancy. The histopathology results of the bronchial brushing were malignant epithelial tumor with a non-small cell tumor favor adenocarcinoma.

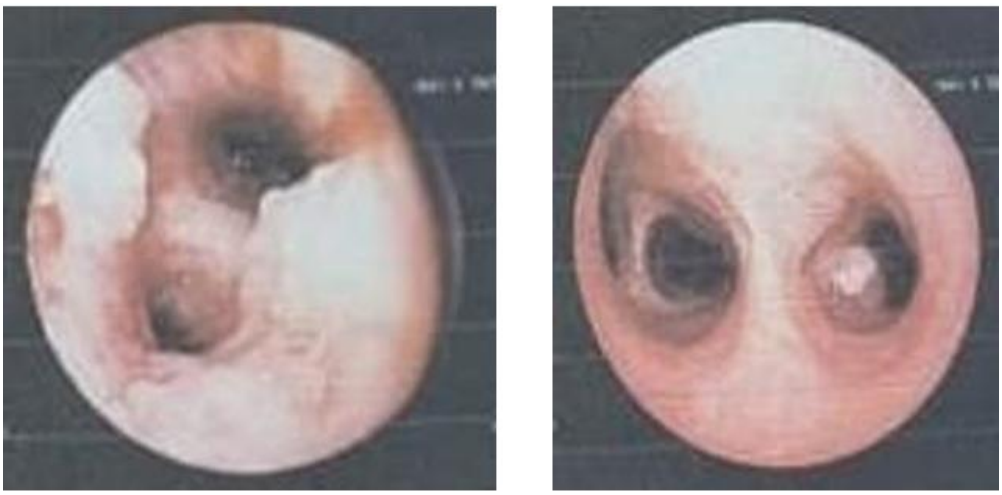

Figure 3. Bronchoscopy: Mass in the left main bronchus and left upper lobe

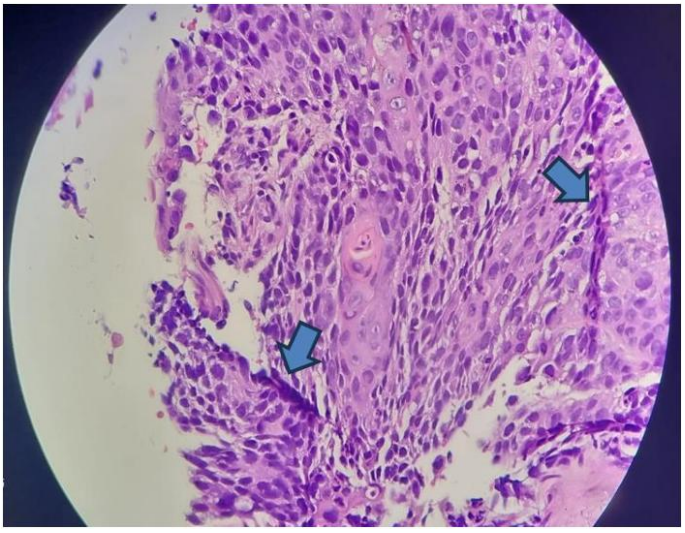

Figure 4. Histopathology of bronchial brushing from bronchoscopy: acinar pattern

Discussion

Tuberculosis and lung cancer have been confused and misdiagnosed for centuries. There is especially in countries with low TB incidence diagnostic challenges with risk of diagnosis getting missed. Radiological features suggestive of lung cancer, like consolidations with irregular margins and thick-walled cavities, showing high metabolic activity on the 18-FDG-PET and CT-imaging are also typical for lung tuberculosis. Differentiation according to the radiological findings cannot be provided. The diagnosis must be confirmed by pathological and microbiological tests. Prytz et al. reported about 91 patients with presumptive diagnosis of lung cancer, who underwent thoracotomy, but proved to have pulmonary TB.[6]

At chest X-ray, tuberculosis may manifest as five main entities: Parenchymal disease, lymphadenopathy, miliary disease (evenly distributed diffuse small 2–3-mm nodules, with slight lower lobe predominance), pleural effusion and cavitation. Parenchymal lesions are characterized by dense, homogeneous, or non-homogenous parenchymal consolidation in any lobe (mostly upper lobe predilection) and fibrotic changes. Mass with or without collapse is the commonest radiological finding in lung cancer.[7] Malignant lesions have irregular margins with radiating strands. Lung cancer may also reveal as hilar prominence (in case of central tumors), pulmonary nodule (in case of peripheral tumors), widening of the mediastinum (suggestive of spread to lymph nodes), total or partial

atelectasis of a segment, lobe or lung (mechanical effect causing obstructive collapse), unresolving consolidation (pneumonia), cavitation (eccentric, irregular margin with nodularity), elevated diaphragm (caused by phrenic nerve palsy) or pleural effusion (25.1%). A normal chest x-ray is found in 0.4% of cases of lung cancer.[7]

A chest CT scan is frequently the second step either to follow up on an abnormal chest X ray finding or to evaluate troublesome symptoms in those with a normal chest x-ray. Centrilobular densities in and around the small airways and "tree-in-bud" appearances were the most characteristic CT features of pulmonary tuberculosis. It is best non-invasive method for lung cancer. Lung mass is not visible on conventional X-rays unless they are larger than 5-6 mm in diameter. In the CT images, however, modern CT machines can detect lesions up to 1-2 mm in diameter, hence CT is more sensitive than chest radiography and it can accurately tell tumor site, size and invasion to adjoining structures such as mediastinum, chest wall etc.[7]

Cavities are gas-filled lesions that appear in the mass zone in the lung and occur in approximately one of six cases of bronchial carcinoma. These lesions form due to damage of the alveolar wall caused by the expulsion of necrotic tissue through the bronchial tree[8,9] and tumor infiltration containing proteases and mucins.[10] The appearance of mass like cavities like pulmonary TB can lead to misdiagnosis based on radiological findings. Misdiagnosis cases in U.S. in the last 10 years reached 26 (0.03%), while a three-year study found 37 patients (1.3%) were misdiagnosed. Similar case in India reached 14 out of 70 (20%) and Indonesia 30,4% misdiagnosed.[6,11] This indicates that the presence of cavities can lead to misdiagnosis, but with the further examination and clinician expertise, an accurate diagnosis can be established.

Conclusion

Diagnosing pulmonary tuberculosis and lung adenocarcinoma is challenging especially based on similarity of clinical and radiological findings, resulting in significant misdiagnosis. Further examinations and clinician expertise are essential to differentiate. The high cost and inaccessibility of diagnostic investigations such as chest CT scan and bronchoscopy may contribute to their inadequate utilization early enough. In tertiary centers, waiting period for these investigations is often unacceptably long, further adding to the delay. Attempts are needed to minimize this lag period by maintaining a high index of suspicion, low threshold for referral and aggressive as well as appropriate investigative work up and prompt initiation of treatment. This is of major concern as early diagnosis of lung cancer can increase the chance of tumor resectable and timely chemo-radiotherapy may provide better quality of life.

Acknowledgements

Only written if present. People who are contributed to the study but does not meet the criteria for authorship must be acknowledged and listed. The source of funding, financial grants, and conflict of interest must be acknowledged and listed.

Conflict of Interests

This part should declare authors' conflicts of interest, including sources of support for the work and authors' authority to access the study data.

References

1. World Health Organization. World health statistics. Geneva: WHO Press; 2008. p. 10-31
2. World Health Organization. Global tuberculosis report 2015. 20th ed. Geneva: WHO Press; 2015. P. 1-28
3. Kementerian Kesehatan Republik Indonesia. Pedoman nasional pengendalian tuberculosis. Jakarta: Kementerian Kesehatan RI; 2016. p. 1-210
4. Wulandari L, Mega Juwita P. Disseminated Tuberculosis Mimicking Lung Cancer with Multiple Bone Metastasis: A Case Report. 8(3). https://e-journal.unair.ac.id/IJTID/
5. Singh VK, Chandra S, Kumar S, Pangtey G, Mohan A, Guleria R. A common medical error: Lung cancer misdiagnosed as sputum negative tuberculosis. Asian Pacific J Cancer Prev. 2009;10:335–8.
6. Hammen I. Tuberculosis mimicking lung cancer. Respir Med Case Rep. 2015;16:45-47. doi:10.1016/j.rmcr.2015. 06.007
7. Bhatt M, Kant S, Bhaskar R. Pulmonary tuberculosis as differential diagnosis of lung cancer. South Asian J Cancer 2012;1:36-42.
8. McKay MJ. What's in a (tumor) cavity? Transl Lung Cancer Res. 2020;9(1):8-9. doi:10.21037/tlcr.2019. 10.01
9. Tannous T, Mak A, Keating M. Small-Cell Lung Cancer Cavities: Primary or Secondary? Cureus. Published online March 4, 2021. doi:10.7759/cureus.13691
10. Sakai T, Azuma Y, Koezuka S, et al. Adenocarcinoma in situ detected on a thin-walled lung cavity: a case report. Surg Case Rep. 2022;8(1). doi:10.1186/ s40792-022-01413-w
11. Aviani J, Maulana S, Haryatie I, Raharjo F, Sutanto YS, Setijadi AR. Annisa Dian Harlivasari: Keterlambatan Diagnosis Kanker Paru Karena Kesalahan Diagnosis Sebagai Tuberkulosis. Vol 37.; 2017

InaJCC The Indonesian Journal of Cancer Control

Review Article

Mechanisms of target therapy resistance in non-small cell lung cancer

Nadia Amalia Haq, Andika Chandra Putra, Fariz Nurwidya, Jamal Zaini, Elisna Syahruddin

e-ISSN 2797-457X
DOI: 10.52830/inajcc.v1i1.115

Received: November 23rd, 2024
Accepted: March 3rd, 2025

Authors' affiliations:
Department Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Indonesia - Persahabatan Hospital National Respiratory Center, Jakarta, Indonesia

Corresponding author:
E-mail: amaliahaq@gmail.com

Abstract

In the past two decades, research on driver mutations has revolutionized lung cancer treatment with the emergence of targeted therapies as a new therapeutic strategy that significantly improves the prognosis of lung cancer. Targeted therapies are designed to recognize and disrupt specific proteins or pathways involved in the growth, spread and survival of cancer cells with high effectiveness. The use of targeted therapies has been shown to provide better progression-free survival and overall survival compared to traditional chemotherapy in NSCLC patients with targeted mutations. However, most patients eventually develop resistance regardless of the type and line of targeted therapy used. Resistance can occur in patients who initially respond targeted therapy. This is due to adaptive changes in tumor cells and the tumor microenvironment during drug exposure, through genetic and epigenetic processes forming secondary resistance. Understanding targeted therapies and their resistance mechanisms is essential to manage effective treatment for patients.

Keywords: *mutation, resistance, targeted therapy*

Abstrak

Dalam dua dekade terakhir, penelitian mengenai mutasi penggerak telah merevolusi pengobatan kanker paru dengan munculnya terapi target sebagai strategi terapeutik baru yang secara bermakna meningkatkan prognosis kanker paru. Terapi target dirancang untuk mengenali dan mengganggu protein atau jalur spesifik yang berperan dalam pertumbuhan, penyebaran dan kesintasan sel kanker dengan efektivitas yang tinggi. Penggunaan terapi target terbukti telah memberikan kesintasan bebas progresivitas dan kesintasan keseluruhan lebih baik dibandingkan kemoterapi tradisional pada pasien KPKBSK yang memiliki target mutasi. Namun, sebagian besar pasien akhirnya menunjukkan resistansi terlepas dari jenis dan lini pengobatan terapi target yang digunakan. Resistansi terjadi pada pasien yang awalnya merespons terapi target. Hal ini disebabkan oleh perubahan adaptif pada sel tumor dan lingkungan mikro tumor selama pajanan melalui proses genetik maupun epigenetik membentuk resistansi sekunder. Pengetahuan mengenai terapi target dan mekanisme resistansinya penting dipahami untuk dapat mengelola terapi efektif pada pasien.

Kata kunci: *mutasi, resistansi, terapi target*

Background

Cancer is the second leading cause of death in the United States and an unsolved global public health problem. In the United States, it is estimated that there will be 1,918,030 new cases of cancer and 609,360 cancer deaths by 2022 with lung cancer accounting for approximately 350 deaths each day and being the leading cause of cancer deaths. Statistically, lung cancer results in higher mortality than breast, prostate, colorectal and leukemia cancers combined. Lung cancer is one of the most life-threatening cancers worldwide with a five-year survival rate of only 19%, second only to pancreatic cancer.[1]

In general, lung cancer diagnoses are divided into two main groups: small cell carcinoma lung cancer (SCLC = KPKSK) and non-small cell carcinoma lung cancer (NSCLC= KPKBSK)). About 13% of cases are SCLC which is the more aggressive type with a lower five-year relative survival rate. others are NSCLC which accounts for 85% of all lung cancer diagnoses. NSCLC lung cancer can be further classified into adenocarcinoma with a five-year relative survival rate of 17%, large cell carcinoma has a five-year relative survival rate of 9% and squamous cell carcinoma a five-year relative survival rate of 14%.[2]

Current treatment options for lung cancer include surgical resection, chemotherapy, radiotherapy, targeted therapy and immunotherapy. In the last two decades, research into driver mutations has revolutionized the treatment of lung cancer with the emergence of targeted therapy as a new therapeutic strategy significantly improving the prognosis of lung cancer. In contrast to traditional chemotherapy that attacks rapidly dividing cells in general, targeted therapies are designed to recognize and disrupt specific proteins or pathways that play a role in cancer cell growth, spread and survival.[3,4]

In the last two decades, the identification of genetic alterations that regulate tumor growth and survival has significantly changed the therapeutic pathway of JPBSK based on its molecular characteristics. These genetic alterations become therapeutic targets. This is because tumor dependence on one or more oncogenic proteins or signaling pathways that result in tumor cell proliferation is usually regulated by driver mutations. Inhibition of these specific oncogenes can interfere with tumor growth so that the tumor stops growing or even shrinks and disappears. Drugs targeting these pathways have been developed and some of them have been clinically approved for NSCLC patients due to their high response rate and better specificity compared to standard chemotherapy.[5]

Targeted therapy first emerged with the discovery and development of tyrosine kinase inhibitors (TKIs) that target mutations in the epidermal growth factor receptor (EGFR). Successful therapy using first-generation TKIs, such as gefitinib and erlotinib as well as second-generation (afatinib, dacomitinib) has consistently shown high efficacy in the treatment of JPBSK with EGFR mutations. Furthermore, the identification of genetic rearrangements, such as anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1) has enabled the development of more specific and effective targeted therapies, such as crizotinib and alectinib.[6]

Despite extensive research, the prognosis of lung cancer remains disappointing with a five-year survival of around 15%. This is partly due to the development of drug resistance in the cancer tissue. Understanding the mechanisms of drug resistance provides an opportunity to develop more effective therapeutic strategies, including drug combinations, next-generation development and personalized approaches by adjusting the genetic profile of individual patients. Therefore, continuous research and multidisciplinary collaboration are necessary to translate scientific findings into effective interventions.[6,7]

Targeted Therapy Type

Targeted therapy is a treatment approach designed to target specific molecules or biological pathways involved in cancer growth and development. This approach is based on understanding the role of specific genetic mutations or molecular changes to be the main driver of tumor growth in contrast to chemotherapy which works by attacking all rapidly dividing cells including normal cells. Drugs are specifically designed to interfere with or inhibit the activity of such target molecules thereby stopping or slowing the growth of cancer cells with high effectiveness using targeted therapy.[3]

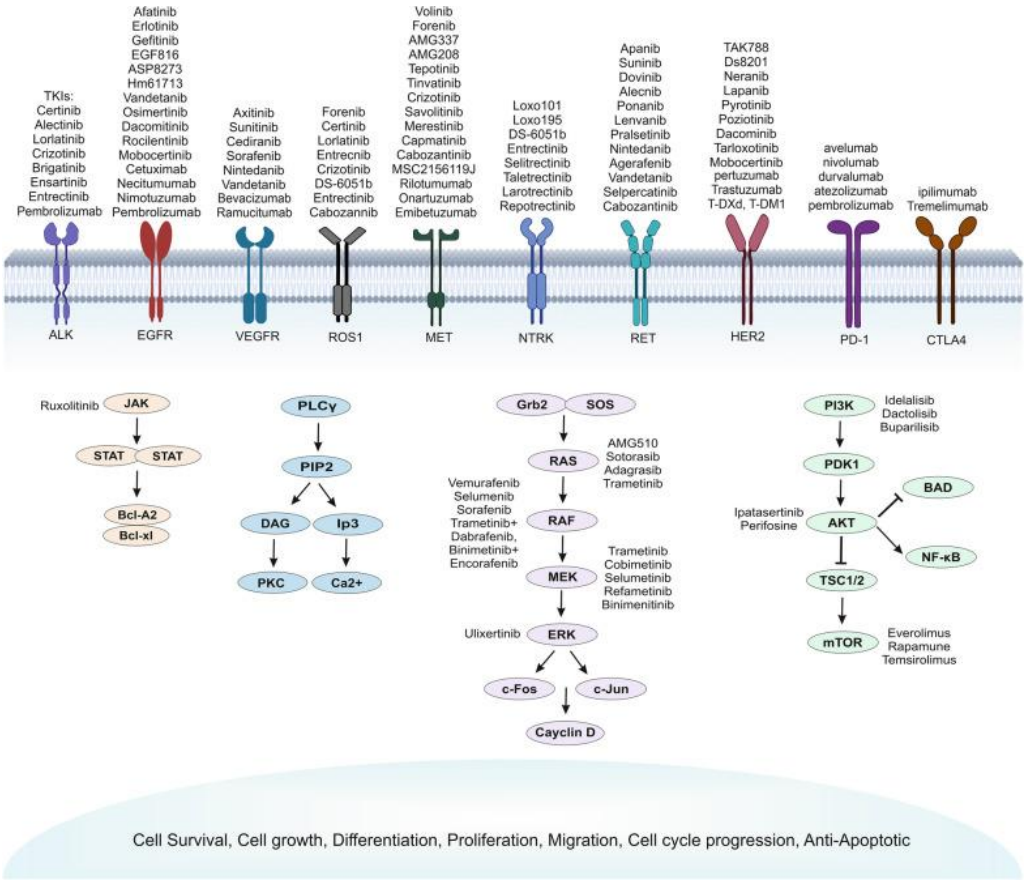

Figure 1. Target therapy[6]
Source: Araghi M, Mannani R, Heidarnejad maleki A, Hamidi A, Rostami S, Safa SH, et al. Recent advances in non-small cell lung cancer targeted therapy: an update review. Vol. 23, Cancer Cell International. BioMed Central Ltd; 2023.

By understanding and identifying specific genetic and molecular changes in cancer cells, these therapies can directly target pathways that are important for cancer growth or survival. This not only improves the effectiveness of treatment, but also reduces damage to normal cells, reduces side effects and improves the quality of life for patients. Targeted therapies have brought about revolutionary changes in the clinical management of lung cancer by providing more targeted treatment options and improving patient life expectancy. Some examples of targeted therapies in lung cancer include inhibition of EGFR, ALK, ROS1 and v-Raf murine sarcoma viral oncogene homolog B1 (BRAF).[3]

EGFR Inhibitors

EGFR mutation is the most common driver mutation in NSCLC. This mutation occurs in about 16% of adenocarcinoma patients. Currently, the use of targeted therapy in the form of TKIs has been widely used with a response of 50%-80%. The efficacy of TKIs varies based on the driver mutation. Mutations in exons 19 and 21 account for 85%-90% of all EGFR mutations and are considered to have a good response to TKIs. In contrast, patients with exon 20 mutations that occur in about 4% of EGFR mutations do not respond to TKIs.[8]

First-generation EGFR-TKI therapies work reversibly and compete with ATP for binding to the EGFR tyrosine kinase domain. In 2015, first-generation EGFR-TKIs, namely gefitinib, erlotinib and icotinib have been used as the first line of NSCLC therapy with EGFR mutations. The 2009 Iressa Pan-Asia study comparing gefitinib with chemotherapy using carboplatin and pacliataxel conducted in East Asia concluded that first-generation TKIs provide better progression-free survival (PFS) than chemotherapy.[9] Similar results were also obtained from the 2012 European Tarceva versus Chemotheraphy study conducted in Europe. In this study erlotinib was proven superior compared to platinum-based chemo-therapy.[10]

Second-generation EGFR TKIs, afatinib and dacomitinib, were then developed to combat first-generation resistance. Afatinib is an irreversible dual-specificity EGFR inhibitor designed to bind covalently to both EGFR and human epidermal growth factor receptor (HER2), while dacomitinib is an irreversible pan-HER inhibitor. The broad spectrum of activity allows second-generation EGFR-TKIs to improve tumor growth inhibition compared to first-generation EGFR-TKIs.[1]

In the 2017 ARCHER study, dacomitinib, a first-generation EGFR inhibitor, significantly prolonged PFS and overall survival time compared to gefitinib in CKD patients with EGFR activating mutations.11 However, afatinib and dacomitinib showed low maximum tolerated doses so that the second generation was reported to cause more frequent and severe side effects including skin and gastrointestinal toxicity. After receiving first- and second-generation EGFR-TKI therapy for 9-13 months, most patients develop resistance. The T790M mutation in exon 20 is the most common mechanism of resistance, accounting for 50%-60% of patients treated with first- and second-generation TKIs.[1,11,12]

A third-generation EGFR-TKI therapy was then developed to counter the previous generation of resistance, Osimertinib, which has good efficacy against secondary resistance. Osimertinib selectively targets the T790M mutation by covalently binding to residue C797 at the adenosine triphosphate (ATP) binding site on the EGFR receptor. The ATP molecule cannot bind and becomes inactive because it is irreversible. Besides being used for the T790M mutation, Osimertinib is also used for the L868R mutation. Osimertinib shows good tolerability with lower toxicity reports compared to previous generations. Osimertinib also shows about 200 times greater potency against EGFR L858R or T790M mutations compared to wild-type EGFR.[1]

Table 1. Target Therapy of EGFR TKIs in NSCLC

Class	Medicine	EGFR Sensitization Mutation	EGFR Binding
First Generation	Gefitinib	Deletion 19/L858R	Competitive Reversible
	Erlotinib	Deletion 19/L858R	
	Icotinib	Deletion 19/L858R	
Second Generation	Afatinib	Delesi 19/L858R/T790M	Covalent Irreversible
	Dacomitinib	Delesi 19/L858R/T790M	
Third Generation	Lazertinib	Delesi 19/L858R/T790M	Covalent Irreversible
	WZ4002		
	Rociletinib		
	Osimertinib		
	Olmutinib		
	Avitinib		
	Nazartinib		
	Maverletinib	Delesi 19/L858R/T790M	
	Naquotinib	Delesi 19/L858R/T790M	
	Almonertinib	Delesi 19/L858R/G719X/L861Q/T790M	
	Alflutinib	Delesi 19/L858R/G719X/L861Q/T790M	
Fourth Generation	EAI1001	L858R/T790M/C797S	Allosteric Reversible
	EAI1045	L858R/T790M/C797S JBJ-09-063	
	JBJ-09-063	L858R/T790M/C797S	
	BLU945	L858R/T790M/C797S	Unknown
	BBT176	L858R/T790M/C797S	

Source: Chhouri H, Alexandre D, Grumolato L. Mechanisms of acquired resistance and tolerance to EGFR targeted therapy in non-small cell lung cancer. Cancers. 2023;15:2- 18

In patients who progressed on first-generation EGFR-TKI treatment and harbor the T790M mutation, osimertinib significantly improved PFS and OS compared with chemotherapy. Osimetinib has shown better efficacy than gefitinib or erlotinib in NSCLC who have not received EGFR-TKIs. AZD9291 (Osimertinib) versus platinum-based doublet-chemotherapy in locally advanced or metastatic non-small cell lung cancer research (AURA3) compared the efficacy of osimertinib in patients receiving osimertinib. Patients given osimetinib had a lower incidence of serious adverse events than those treated with first- or second-generation EGFR- TKIs.[13] However, patients with EGFR activating mutations who were given

osimertinib as first-line treatment also eventually developed resistance. [1,13,14]

Despite the favorable outcomes of targeted therapies compared to conventional chemotherapy, their effectiveness is often limited by the emergence of secondary resistance. One of the most common mechanisms of resistance is the emergence of the T790M mutation in EGFR. This mutation occurs in approximately 50%-60% of patients who initially respond to first and second generation TKI therapy. The T790M mutation occurs when the amino acid threonine at position 790 in the EGFR tyrosine kinase domain changes to methionine. This mutation causes resistance to first- and second-generation EGFR by reducing the drug's affinity for EGFR.[8]

ALK Inhibitors

One of the molecular receptors targeted by targeted therapy is alteration of the anaplastic lymphoma kinase (ALK) gene encoding the fusion-driving oncoprotein. Mutations and rearrangements in the ALK gene that result in abnormal fusion proteins have been identified as the main driver in about 5% of NSCLC cases. ALK inhibitors were then developed to target and inhibit the abnormal activity of the ALK fusion protein. Crizotinib, a first generation ALK inhibitor showed good efficacy in inhibiting the proliferation of ALK positive tumor cells and improving FS compared to chemotherapy. However, resistance to crizotinib is often found through secondary mutation mechanisms in the ALK kinase domain or activation of alternative signaling pathways. To overcome this, second- and third-generation ALKs such as ceritinib, alectinib and lorlatinib were developed and are now widely used.[15,16]

There are currently five ALK tyrosine kinase inhibitors that have been widely used to treat ALK-positive NSCLC. These drugs include the first generation ALK-TKI crizotinib, the second generation ceritinib, alectinib and brigatinib and the third generation lorlatinib. Although the latest generation ALK-TKIs have better kinase selectivity and higher ability to overcome drug resistance, resistance is inevitable. Most of the resistance mechanisms to ALK-TKIs are dependent on ALK protein kinases. ALK-dependent resistance mechanisms including gene amplification and secondary mutations in ALK kinases account for half the incidence of resistance to crizotinib, including mutations in the L1196M, L1152R and G1202R genes. These mutations alter the ALK protein to become active without the need for stimulation, increasing binding affinity with ATP and leading to drug resistance.[3]

Table 2. Target Therapy of ALK TKI in NSCLC

Generation	Medicine	*Objective Response Rate* (ORR)	Median PFS (Months)
First	Crizotinib	74%	10.9
Second	Ceritinib	73%	16.6
Second	Alectinib	83%	25.7
Second	Brigatinib	74%	24
Third	Lorlatinib	76%	NR
Third	Ensartinib	75%	25.8

Source: Wu J, Lin Z. Non-small cell lung cancer targeted therapy: Drugs and mechanisms of drug resistance. Int J Mol Sci. 2022;23:1-18.

Secondary mutations in the ALK kinase domain are more common in patients with secondary resistance to newer generation ALK inhibitors, accounting for approximately 50%-70% of resistant cases compared to primary ALK resistance. One of the secondary mutations that often occurs after administration of first-generation ALK-TKIs is mutations in the G1202R gene. G1202R gene mutations account for about 42% of brigatinib-resistant cases, 21% of ceritinib-resistant cases and 29% of resistant cases in patients taking alectinib.

These mutations result in alterations in the adenosine triphosphate (ATP) binding domain of the ALK receptor, which reduces the affinity of the TKI to the target, thereby reducing the effectiveness of the drug.[1,17]

The third generation ALK inhibitor lorlatinib is a small macrocyclic molecule with good brain permeability. Lorlatinib can inhibit most of the first and second generation ALK inhibitor-resistant mutations especially the G1202R mutation. Clinical data showed lorlatinib produced an objective response of 45% including in ALK-positive patients who already had secondary resistance. Lorlatinib was approved by the Food and Drug Administration in 2018 as second-line therapy for ALK-positive NSCLC. However, lorlatinib drug resistance is also inevitable. Studies show that about 35% of the resistance mechanisms to lorlatinib are combined mutations of two or three gene sites, such as I1171N + L1198F, G1202R+ L1204V+ G1269A.[18]

C-ros Oncogene 1 (ROS1) Inhibitor

The ROS1 gene is a gene encoding one of the receptor tyrosine kinases located at 6q22 on the long arm of chromosome six. This gene belongs to the insulin receptor family that plays a role in cell growth

and proliferation. In NSCLC mutation or rearrangement of the ROS1 gene leads to constitutive activation of signaling pathways that promote cancer cell growth and survival. This mutation or rearrangement is in the form of a gene fusion, where the ROS1 gene joins with other genes produce a constitutively active fusion protein. One example of a gene fusion that often occurs is CD74-ROS1, which is a merger between the CD74 gene and ROS1.[19]

Expression of the ROS1 fusion gene results in autophosphorylation of the tyrosine kinase ROS-1 which initiates a signal cascade through the Mitogen-Activated Protein Kinase (MAPK) pathway and phosphorylation of RAS. Phosphorylation is the addition of phosphate groups into the structure of a protein. As a result, the receptor tyrosine kinase is constitutively active which means the protein will transmit a signal pathway for the cell to proliferate without the need for external ligands. Activated signaling pathways include Mitogen-Activated Protein Kinase/Extracellular signal- Regulated Kinase (MAPK/ERK) which is important for the regulation of cell growth, differentiation and cell survival. Phosphorylation of ERK proteins in this pathway promotes transcription of genes that support proliferation and inhibit apoptosis.[19-21]

There is also activation of the phosphoinositide 3-Kinase/ Protein kinase B (PI3K/AKT) signaling pathway. The PI3K/AKT pathway is dysregulated due to mutation or amplification of the gene encoding the receptor protein. As a result, the signal is continuously activated without a trigger. Activation of this pathway will result in rapid, uncontrolled cancer cell division and cancer cells are more resistant to apoptosis. Cancer cells will create metabolic conditions favoring cancer cell growth and survival and will also increase the ability of cancer cells to spread to other tissues.[19,21-23]

A similar mechanism is also obtained with the activation of the Janus Kinase/Signal Transducer and Activator of Transcription (JAK/STAT) signaling pathway, a biochemical reaction that starts with the activation of cytokine receptors on the cell surface and culminates in the activation of STAT transcription factors in the nucleus. This pathway plays an important role in regulating the expression of genes involved in various cellular processes. Proliferation of cancer cells will be increased, apoptosis inhibited and increase the ability of cancer cells to metastasize. The JAK/STAT pathway has a significant role in various processes of cancer development, so it can be an important target in the development of cancer therapy. JAK inhibitors are currently being developed and to inhibit this pathway and reduce cancer progression.[19-22]

ROS 1 inhibitors are targeted therapies designed to inhibit ROS1 protein kinase activity. ROS1 inhibitors work by binding to the kinase domain of the rearranged ROS1 protein, inhibiting its catalytic activity and preventing autophosphorylation. With the ROS1 receptor inhibited, ERK activation can be prevented thereby stopping the signal cascade of the MAPK/ERK signaling pathway so that the proliferation ability of cancer cells is reduced. addition, the PI3K/AKT pathway will also be disrupted due to the failure of the autophosphorylation results in binding sites for adaptor proteins, such as Growth Factor Receptor-Bound Protein 2 (GRB2) or GRB2-Associated Binding Protein 2 (GAB2) becoming inactive so that the mechanism of and proliferation of cancer cells is inhibited and cancer cells are more easily apoptotic.[19,21]

There are several approved tyrosine kinase inhibitors that inhibit both ROS1 and ALK, including crizotinib, ceritinib and lorlatinib. There is also entrectinib which inhibits both ROS and neurotrophic tyrosine receptor kinase (NRTK). Crizotinib was the first drug used in patients with ROS1 mutations. Duration of Response (DOR) was 72% (95% CI, 58%-84%) with a median duration of response of 17.6 months and median PFS of 19.2 months. Despite the high initial response rate, most crizotinib- treated patients eventually experienced disease progression due to inadequate central nervous system (CNS) penetration or the development of ROS1 resistance mutations.[1,19]
Another drug that has also been widely used is ceritinib, a second-generation TKI given to TKI-naive and crizotinib-resistant ALK-positive NSCLC patients. Ceritinib selectively inhibits ROS1 with 20 times more potency than crizotinib in preclinical studies. Clinical trials showed response in crizotinib-naive patients ORR 67% (95% CI, 48-81%) DOR for 21 months (95% CI, 17-25 months) and PFS 19.3 months (95% CI, 1-37 months). There was also lorlatinib with strong CNS penetration. The response of lorlatinib was significantly higher in TKI-naive patients with an ORR of 62% (95% CI, 38%-82%) PFS of 21 months (95% CI, 4.2-31.9) compared to those with crizotinib ORR of 35% (95% CI, 21%-52%) and PFS of 8.5 months (95% CI, 4.7-15.2). In patients with intracranial metastases, intracranial responses were achieved in 64% of naïve patients and 50% of patients who had received crizotinib.[19]

Resistance Mechanism

Targeted therapy has been shown to provide better PFS and OS in patients with CKD. However, most patients eventually show resistance regardless of the type and line of treatment used. The spatiotemporal heterogeneity of tumors facilitates the complexity and diversity of molecular resistance mechanisms. Resistance to targeted therapy is divided into two groups, namely innate or primary resistance and secondary resistance resulting from the adaptive capacity of the body and cancer cells to target therapy exposure. Each consists of tumor intrinsic and extrinsic mechanisms.[23,24]

Primary Resistance

Primary resistance is the innate resistance possessed by the tumor as well as by the individual. The development of resistance occurs before the tumor is exposed to the targeted therapy. Primary resistance is caused by mutations of both driver and passenger genes. This results in decreased treatment potency. Intrinsic primary resistance is where the tumor does not respond to the target therapy from the start of treatment. Primary resistance is mostly related to the lack of sensitive target receptor sites, or the cancer has the ability to activate alternative signaling pathways that can replace the function of the inhibited target protein. For example, EGFR exon 20 or KRAS mutations can provide enough signal to support tumor growth even though the EGFR receptor is inhibited with EGFR-TKIs.[25]

In primary resistance, tumor extrinsic factors may also play a role. Extrinsic factors refer to mechanisms originating from the tumor microenvironment or external factors that affect the effectiveness of the target therapy. Extrinsic factors include ineffective antigen presentation, T cell priming, activation, transport and migration or the presence of suppressive immune cells in the tumor microenvironment that are not targeted by immunotherapeutic agents. Tumor extrinsic mechanisms of primary resistance include mutations in genes that harbor immune regulatory function resulting in reduced neoantigen presentation and impaired antitumor immune responses.[25,26]

Secondary Resistance

Acquired resistance occurs when patients who initially respond to targeted therapy later relapse and develop resistance. This can be caused by adaptive changes in tumor cells and the tumor microenvironment during treatment exposure through epigenetic or translational events that establish secondary resistance. Secondary resistance may result from clonal evolution of tumor cells that acquire specific genetic changes that interfere with the antitumor immune response. Response rates and tumor control rates to EGFR-TKIs effectively do not reach 100% but range from 75%-80% regardless of drug generation; some patients respond only for a very short initial duration (<3 months). A special situation of secondary resistance is pharmacokinetic therapy failure.[28]

The main mechanisms of tumor cell intrinsic activity that led to secondary resistance to targeted therapy are resistance, activation of alternative pathways and tissue transformation. Target resistance and alternative pathway activation are acquired through genetic alterations. Both mechanisms depend on the core signaling pathways of the driving oncogene. Examples are secondary kinase mutations and amplification of driver genes. Tissue transformation or phenotypic change mechanisms are forms of phenotypic plasticity that involve cellular reprogramming. These mechanisms cover a wide spectrum, ranging from transient phenotypic changes to full transition into a new histologic subtype, such as the change of NSCLC to SCLC. [4,27]

Molecular Resistance Mechanism

One of the best known and genomically simplest mechanisms of resistance to targeted therapies is genetic alterations in driver oncogenes that allow the continuation of tumor cell signaling pathways despite exposure. This condition is often also described as therapeutic resistance. The two most common manifestations of secondary resistance in JPBSK are T790M kinase domain mutations and overexpression of target oncogenes in tumor cells. Resistance mechanisms in the form of genetic alterations are seen in response to almost every targeted therapy in NSCLC starting from first generation inhibitors.[4]

T790M Mutation

The T790M mutation is the main secondary resistance mechanism that occurs in patients with EGFR-TKIs. In cancers with EGFR mutations, the kinase domain of EGFR undergoes structural changes that result in the tumor being more active in sending signals for cancer cell growth and proliferation. Targeted therapy TKIs bind to the EGFR kinase domain at the ATP binding site, preventing ATP from binding and activating the signaling pathway. Without ATP, EGFR cannot transfer phosphate to intracellular proteins that transmit signals, thus inhibiting cancer cell growth. The T790M mutation replaces the amino acid threonine (T) with methionine (M) at position 790 in the EGFR kinase domain which is located close to the ATP receptor site.[27]

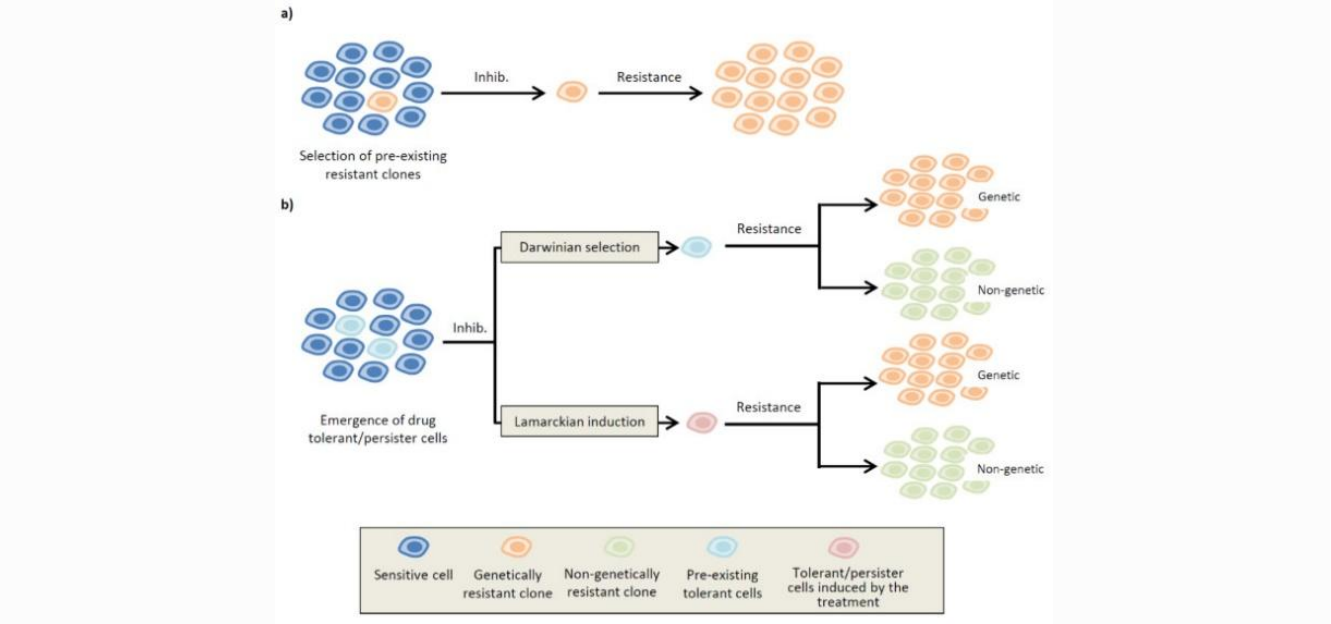

Figure 2. Clonal Selection Results in Resistance[28]
Source: Swayden M, Chhouri H, Anouar Y, Grumolato L. Tolerant/sister cancer cells and the path to resistance to targeted therapy. Cells. 2020;9:1-13

The T790M mutation causes structural changes around the ATP receptor site so that the affinity of EGFR for ATP increases. Although TKIs try to bind to the kinase domain, ATP competes more easily and binds to the receptor due to its higher affinity. As a result, EGFR remains active in sending growth signals leading therapy resistance. Tumor cells with the T790M mutation start because they are able to survive and continue to grow despite continued targeted therapy. The number of resistant cells increases and the tumor size increases again or stops shrinking.[27]

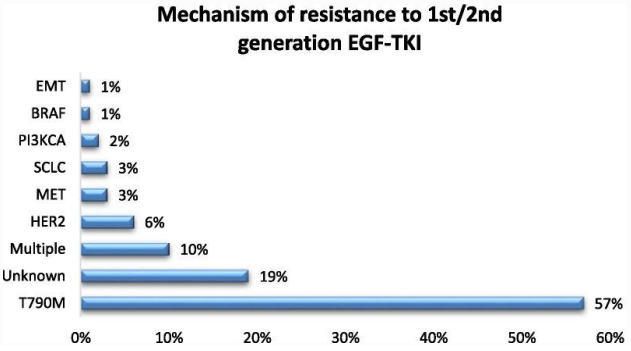

Figure 3. Secondary Resistance Caused By 1st and 2nd Generation EGFR-TKIs[21]
Source: Majeed U, Manochakian R, Zhao Y, Lou Y. Targeted therapy in advanced non-small cell lung cancer: Current advances and future trends. J Hematol Oncol. 2021;14:1-20

MET Amplification

MET amplification mechanism is one of the secondary resistance responses in EGFR- TKI administration. MET amplification is an important mechanism in resistance to targeted therapy in lung cancer. MET protein is a receptor tyrosine kinase involved in various biological processes including cell growth, differentiation and proliferation. Activation of MET by its ligand, hepatocyte growth factor (HGF) leads to the activation of intracellular signaling pathways that are important for the regulation of various cellular functions. Amplification of the MET gene leads to an increase in the number of MET receptors expressed on the cell surface which in turn can result in excessive signal activation. MET amplification occurs in approximately 10%-15% of patients with lung cancer who have received erlotinib, gefitinib or afatinib. MET amplification remains a major resistance mechanism in approximately 15% of patients with failure of first-line osimertinib therapy.[29]

MET amplification may occur as a mechanism of resistance to EGFR inhibitors, such as gefitinib or erlotinib. MET activation through gene amplification can trigger downstream signaling pathways independent of the EGFR pathway. MET amplification causes resistance by continuously activating signaling pathways, such as those regulated by MAPK, STAT and PI3K/AKT independent of EGFR activation or

signaling. These signals are relayed through the two adaptors HER3/ERBB3 when MET is triggered by genomic amplification or growth factor receptor associated binding protein 1 (GAB1) when MET is activated by HGF. Consequently, MET can trigger resistance by activating signaling pathways independent of EGFR through interactions with specific adaptors depending on its activation mechanism.[29]

The AURA3 study showed that MET amplification was the most common mechanism of resistance (19%), often co-occurring with the EGFR C797S mutation and possibly associated with CDK6 and BRAF amplification.[13] MET amplification can also occur as a mechanism of resistance to third-generation TKIs, either with or without loss of the T790M mutation. Osimertinib, although effective against the T790M mutation, is not designed to address MET amplifycation. Therefore, detection of MET amplification in patients who experience disease progression during therapy with osimertinib or other EGFR-TKIs is crucial.[13,29]

Activation Of Alternative Pathways

Activation of alternative signaling pathways refers to the condition that tumor cells develop mechanisms to avoid the inhibitory effects of targeted therapies by activating other cellular signaling pathways. This activation may occur as a mechanism of acquired resistance to EGFR-TKIs, ALK-TKIs, ROS1 inhibitors and other targeted therapies. When tumor cells are administered targeted therapies that target signaling pathways, cancer cells can adapt by activating other pathways that promote cell survival and proliferation independently. One common example is the activation of the MET signaling pathway known as hepatocyte growth factor receptor, which can compensate for the inhibited EGFR pathway and support tumor growth.[25]

Alternative pathway activation caused by ALK-TKI administration includes mutations in the G1269A, C1156Y, I1171T/N/S, S1206C, E1210K, L1152P/R, V11180L, G1128A, F1174V and L1196M genes. Patients with EGFR-TKI resistance, ROS-1 inhibitors and ALK-TKIs show similarities in that there can be recurrent mutations in RTK-KRAS (EGFR, KRAS, BRAF), TP53 and other genes in TKI- independent pathways. These genes will function as downstream mediators or alternative signaling pathways so that cancer cells can still metabolize, avoid apoptosis and proliferate even though the main pathway is inhibited by targeted therapy.[1]

Phenotypic Changes

One of the resistance mechanisms that can occur is phenotypic changes, especially through epithelial to mesenchimal transition (EMT) and transformation.

This change in phenotype allows cancer cells to avoid the inhibitory effects of targeted therapies and still proliferate and metastasize. The mechanism of EMT is the biological process of epithelial cells losing their epithelial characteristics, such as strong cell-cell adhesion and cell polarity and acquiring mesenchymal properties, including increased migration, invasion power, resistance to apoptosis as well as the ability to differentiate into various other cell types. These properties make EMT play a key role in tumor progression and metastasis.[28]

In the EMT mechanism, there are changes in the expression of genes that regulate cell properties, there is a decrease in the expression of epithelial cell proteins including E- cadherin which forms a complex with beta-catenin and other proteins to mediate the adhesion of epithelial cells. E-cadherin proteins also maintain epithelial cell polarity which is important for structural defense and cellular communication. The EMT process is also accompanied by increased expression of N-cadherin proteins. N- cadherin protein is a mesenchymal cell protein that functions for mesenchymal cell adhesion. The resulting bonds from N-cadherin proteins are looser so that cells can detach from the tissue and migrate in the extracellular matrix. The decreased intercellular density caused by the loss of E-cadherin which is replaced by N-cadherin allows the cells to become invasive and more therapy-resistant.[6]

There is one other protein that contributes to the EMT process, and that is vimentin. Vimetin is an intermediate filament protein that is a key marker of mesenchymal cells. Vimentin plays an important role in cell mobility, supporting cell shape changes necessary for migration and invasion. This protein interacts with the cytoskeleton and modifies the cytoskeleton so that cells have the structural flexibility needed for migration. Vimentin concentrations are very low early in tumor development, but increase as the tumor spreads, so elevated vimetin levels are also associated with poor prognosis in malignancies.[30,31]

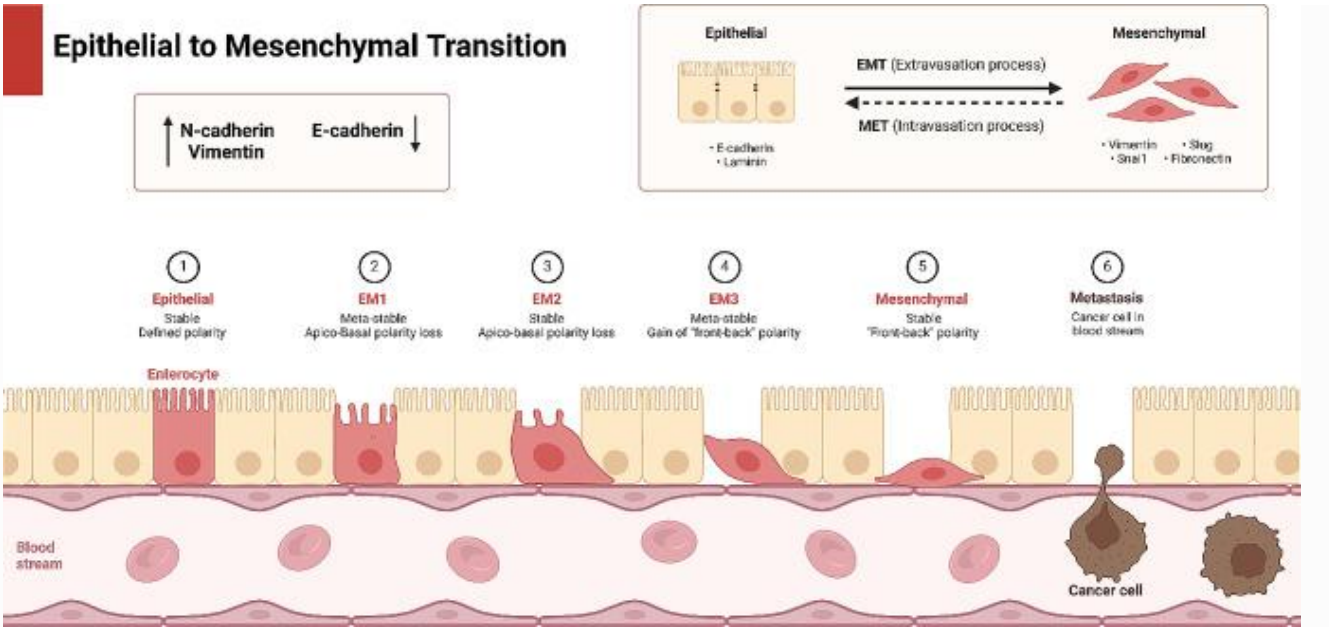

Figure 4. Epithelial to Mesenchymal Transition[32]
Source: Ashrafizadeh M, Dai J, Torabian P, Nabavi N, Aref AR, Aljabali AAA, et al. Circular RNAs in EMT-driven metastasis regulation: Modulation of cancer cell plasticity, tumorigenesis and therapy resistance. Cell Mol Life Sci. 2024;81:1-25.

In addition to EMT, cancer cells also have the ability to change into other histologic types, also known as histologic transformation, for example the transformation of NSCLC into SCLC. Histologic transformation into SCLC was first reported in America in 2006 in a woman diagnosed with adenocarcinoma. The patient was given erlotinib with partial response. At month 18, tumor progression occurred in the form of tumor metastasis in the brain. The second biopsy showed SCLC with positive synaptomycin. At autopsy, it was found that the SCLC had metastasized to several organs without any adeconarcinoma tissue.[33]

Histological changes caused by continuous exposure to the targeted therapy led to clonal selection. Cells that do not have the target therapy receptor will tend to survive and replicate to become dominant in the tumor cell population. Among these surviving cells are often cells with mutations of the tumor protein p53 (TP53) and retinoblastoma 1 (RB1) genes, which are part of the tumor suppressor gene family. The TP53 gene acts as a guardian of the genome by controlling DNA repair and apoptosis. Mutation or loss of TP53 function causes cancer cells to avoid apoptosis resulting in uncontrolled proliferation. RB1 gene expression functions as an inhibitor of cell proliferation by regulating G1 phase to S phase in the cell cycle by binding to and inhibiting transcription factors.[31]

There is also a role for the transcription factor Achaete-Scute Complex-Like 1 (ASCL1) in regulating the expression of genes involved in the differentiation of neuroendocrine cells. ASCL1 factor is highly expressed in neuroendocrine tumors, including SCLC. This process is driven by signaling pathways such as TGF- β/SMAD. Signals from TGF-β induce phosphorylation of Sma and Mad-related protein 2 (SMAD2) which then forms a complex with SMAD4. This complex moves to the nucleus and binds to the promoter of the ASCL1 gene thereby increasing its transcription. Increased ASCL1 expression leads to a change in phenotype from epithelial NSCLC cells to a neuroendocrine phenotype that is characteristic of NSCLC. These transformed cells exhibit more aggressive properties and are resistant to targeted therapies, such as EGFR-TKIs.[31,34]

Epigenetic Changes

Cancer has traditionally been viewed as a genetic disease, but recent studies have shown epigenetic changes play an important role in cancer development. Epigenetic changes are a major contributor to transcriptional heterogeneity, causing changes in the expression of key oncogenes and tumor suppressor genes, affecting various signaling pathways. Epigenetic changes are a major contributor to transcriptional heterogeneity, causing changes in the expression of

key oncogenes and tumor suppressor genes thereby affecting various signaling pathways. Major epigenetic regulation mechanisms include DNA methylation, histone modification, regulation by non-coding RNA and chromatin remodeling.[35]

DNA Methylation

DNA methylation involves the addition of methyl groups to cytosine residues in nucleotides that cause suppression of gene expression. In NSCLC, methylation of tumor suppressor gene promoters can result in loss of expression of the gene, allowing cancer cells to evade normal growth control. DNA methylation mainly occurs at CpG dinucleotides (concentrated in dense regions called CpG islands) that inhibit RNase binding to the gene strand thus leading to the deactivation of the corresponding gene. DNA methylation is a normal condition that occurs with age. However, DNA methylation is controlled by DNA methyltransferase (DNMT) and DNA demethylase (TET).[35]

In the mechanism of cancer progressivity, there is also a decrease in DNMT expression. Reduced expression of DNMT1 inhibits lung cancer cell growth in vitro and in vivo, while low expression of DNMT3A is associated with poor prognosis. The relationship between overall DNA methylation changes and EGFR-TKI response was illustrated in a study involving 79 patient subjects with adenocarcinoma before and after EGFR-TKI administration conducted by Fang Su et al in China in 2021. The researchers identified 216 CpG sites whose methylation differed in EGFR-TKI responding and non-responding patients. Most of the probes (203/216) showed higher DNA methylation in non-responders compared to responders. The findings suggest that DNA hypermethylation correlates with poor EGFR-TKI response.[35-37]

Histone Modification

Histone modifications are chemical changes that occur in histone tails, including acetylation, methylation and phosphorylation. These modifications affect chromatin structure and the regulation of gene expression, playing an important role in cancer development and resistance to therapy. Acetylation is the addition of an acetyl group (CH_3CO) to the lysine in the tail of a histone. Acetylation will reduce the positive charge on the histone resulting in a weakening of the histone's bond to negatively charged DNA. As a result, DNA is more accessible to transcription factors and gene expression increases, including oncogenes that play a role in tumor growth and resistance to targeted therapies.[35]

There is also the process of histone methylation, which is the addition of one or more methyl groups (CH_3) on lysine or arginine residues in the histone tail. This modification can change the architecture of the nucleosome, which consists of DNA wrapped around a histone. These modifications will affect how tightly or loosely the DNA is bound to the histone thus regulating the accessibility of those genes for transcription. Methylation occurs on lysine residues such as H3K4, H3K9, H3K27, H3K36 and H4K20, but also on arginine residues, such as H3R2, H3R8 and H4R3. These changes contribute to the complexity of genetic regulation and may influence the development of therapeutic resistance in cancer.[38]

In addition, histone modification in the form of phosphorylation also affects the replicative ability and resistance of cancer cells. Histone phosphorylation is a post- translational modification that involves the addition of phosphate groups to specific residues in histone proteins. Phosphorylation is carried out by protein kinases that add phosphate groups (PO_4^{3-}) on serine, threonine or tyrosine residues in the tail of histones. Phosphorylation often occurs on histone H3 at residues Ser10 and Ser28 and on H2AX at residue Ser139 known as γH2AX. These modifications can change the chromatin structure to be more open, allowing accessibility of transcription factors to the DNA and increasing transcription of genes especially progenitors.[38]

Non-coding RNA

Non-coding RNA (ncRNA) chains are RNAs that are not translated into proteins but have important functions in gene regulation including microRNA (miRNA), long non-coding RNA (lncRNA) and circular RNA (circRNA). Despite its very small size of about 22 nucleotides, miRNA can regulate the expression of oncogenes and tumor suppressor genes. MiRNAs can bind to messenger RNA (mRNA) that will be translated. MiRNAs that have bound to mRNA will be recognized by a protein complex called RNA- induced silencing complex (RISC). The recognized complex will then be cut by RICS so that there is no translation of gene. Some miRNAs, such as miR-21, miR-200c and miR-20a have been identified to suppress tumor suppressor genes and induce EMT.[39]

In addition to NSCLC, miR-214 upregulation in various tumor types, including ovarian cancer and esophageal squamous cell carcinoma promotes tumor progression and drug resistance. The miR-214

molecule may act as a biological courier that propagates resistance capabilities. Transfer of exosomal miR-214 from gefitinib- resistant cells to gefitinib-sensitive cells may confer a resistance phenotype that ultimately leads to resistance to gefitinib. However, the signaling pathway through which exosomal miR-214 confers resistance to gefitinib remains unidentified. Further research is needed to decipher the mechanism by which exosomal miR-214 mediates resistance to gefitinib.[39,40]

In addition to miRNAs, lncRNAs are also known to have longer nucleotides, namely 200-220 nucleotides, which have an important role in tumor development and resistance. Exosomes can carry lncRNAs in the exchange of information between cells, including in NSCLC patients. LncRNAs in exosomes in tumor patients can provide a picture of tumor progression and may be involved in changes in the tumor microenvironment. Studies show the expression of lncRNA in increased in osimertinib-resistant NSCLC patients compared to osimertinib-sensitive patients so lncRNA may be related to osimertinib resistance.[41]

One of the mechanisms of lncRNAs is by regulating the wingless untegration 1 (Wnt) signaling pathway that mediates the interaction between DNA, mRNA, miRNA and protein and thus directly plays a role in the initiation of tumor growth and its resistance to targeted therapies. In an in vitro study by, deletion of lncRNA urothelial carcinoma-associated 1 (UCA1) can reduce the likelihood of gefitinib resistance by inhibiting the signal transducer and activator of transcription 3 (STAT 3) signaling pathway in NSCLC. In addition, lncRNA UCA1 also interacts with the TGF-β signaling pathway which plays an important role in cancer cell migration and invasion. However, the mechanism of how Whether lncRNAs in exosomes contribute to target therapy resistance is not fully understood.[41]

Tumor Microenvironment

The tumor microenvironment is a complex environment around the tumor that consists of different cellular components, including tumor cells, T cells, B cells, dentritic cells, myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), carcinoma-associated fibroblasts, tumor blood vessels, lymphatic tissue, fat cells, extracellular components, microvesicles, cytokines and chemokines. Under physiological conditions, these components are responsible for maintaining immunological homeostasis but can also trigger inflammation that leads to the formation of precancerous lung lesions and carcinogenesis. During the progression of SCI, changes occur in the TME that support inflammation and angiogenesis, modulation of the immune system which overall contributes to the progress of SCI, spread of metastasis and determination of prognosis.[42-44]

Under physiological conditions, the innate and adaptive immune systems function to detect and eliminate cancer cells. However, cancer cells can adapt and develop resistance to antitumor effects by disrupting the relationship between antagonistic effectors (CD8 cytotoxic) and regulatory T cells (CD4 Tregs). The resulting TME imbalance can aid cancer cell survival. In addition, tumor cells can excrete cytokines such as IL-4, IL-10, IL-13 and TGF-b resulting in TAM polarization. TAM polarization will encourage macrophages to become M2 which has anti-inflammatory and pro-tumor properties compared to M1 which has pro-inflammatory properties.[44]

M1 macrophages respond to infection and tissue damage. M1 macrophages produce proinflammatory cytokines such as TNF-α, IL-1β and IL-6 as well as reactive oxygen and nitrogen species (ROS and RNS) to eliminate pathogens and tumor cells. These cytokines stimulate the activity of T cells and natural killer (NK) cells that can attack and destroy tumor cells.

In addition, M1 macrophages have strong phagocytic ability and promote adaptive immune responses by enhancing antigen presentation to T cells. This ability makes patients with M1 polarization tend to have a better prognosis.[42,46,47]

M2 macrophages under physiological conditions play a role in wound healing, tissue regeneration and suppressing excessive immune responses. These macrophages secrete anti-inflammatory cytokines such as IL-10 and TGF-β as well as growth factors that support angiogenesis and tissue remodeling. TGF-β cytokines produced by M2 promote EMT making cancer cells resistant to targeted therapies with a high propensity for metastasis. In addition, M2 macrophages produce matrix metalloproteinases (MMPs) that remodel the extracellular matrix (ECM), allowing cancer cells to spread and increasing resistance to therapy. [42,46,47]

Polarization of TAMs to the M2 macrophage phenotype supports resistance to targeted therapies, tumor growth and metastasis by creating an immune-suppressive environment, supporting angiogenesis and reducing effector T cell activity so that TME becomes beneficial to cancer cells. Several studies have showed that a high number of TAMs and

polarization to the M2 phenotype were associated with poor prognosis and resistance to EGFR mutation in CKD patients. In addition to modulating TAMs, cancer cells can also modify ECM components and fibroblasts to provide favorable structural support for tumor cell growth. [42,46,47]

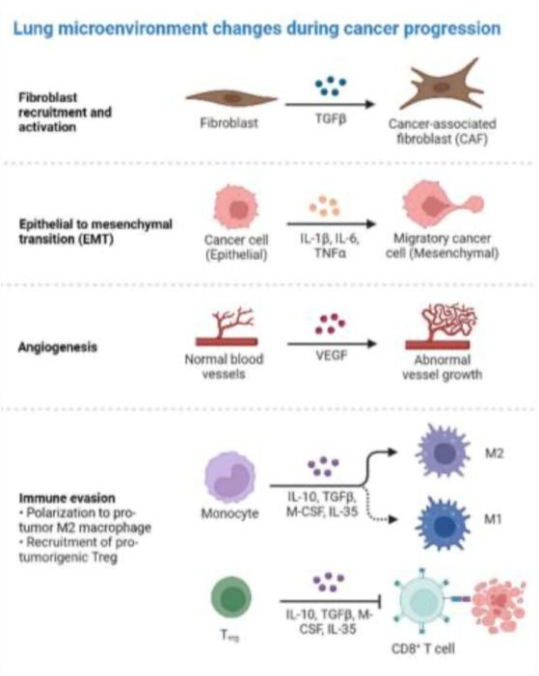

Figure 5. Changes in Tumor Microenvironment[42]
Source: Madeddu C, Donisi C, Liscia N, Lai E, Scartozzi M, Macciò A. EGFR-mutated non-small cell lung cancer and resistance to immunotherapy: Role of the tumor microenvironment. Int J Mol Sci. 2022;23:1-16.

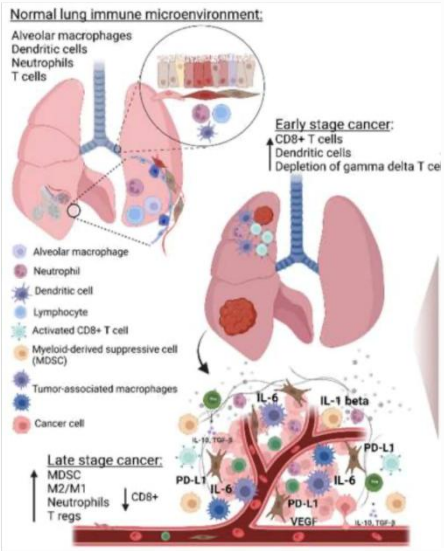

Figure 6. Changes in Tumor Microenvironment[42]
Source: Madeddu C, Donisi C, Liscia N, Lai E, Scartozzi M, Macciò A. EGFR-mutated non-small cell lung cancer and resistance to immunotherapy: Role of the tumor microenvironment. Int J Mol Sci. 2022;23:1-16.

Drug Efflux and Metabolism

Drug release mechanism is one of the important processes in the development of resistance to targeted therapy in patients with CKD. Drug expulsion is the mechanism by which cancer cells pump drugs out of cells, reducing the intracellular concentration of drugs and reducing the effectiveness of therapy. Previous studies have increasingly shown that multi drug resistant (MDR) genes in cancer mediate increased chemotherapy drug expenditure that reduces drug uptake by cancer cells. Increased drug release is accomplished by increases the regulation of protein transporters located in the cell membrane and regulates transporter expression so that the number of transporters increases.[22]

In cancer stem cells, there is an upregulation of four MDR family genes. The MDR1 gene, also called ATP Binding Cassette Subfamily B Member 1 (ABCB1) encodes the glycopotein-P (P-gp) protein, a Ca2+-dependent efflux pump. Due to the increase of P-gp, the target therapy that has entered the cell will be released back out of the cell quickly, thus reducing the intracellular accumulation of the drug and the desired effect of therapy cannot be achieved. This regulation does not only occur in targeted therapy, but also in alkaloid, paklitaxel and antibiotic chemotherapy. Up-regulation of MDR genes is usually followed by resistance to many types of drugs. Furthermore, using cRNA, MDR genes are transferred to other cells that are still sensitive to the target therapy.[22]

Target Therapy Resistance Implications

Evaluation of Treatment

Advances in targeted therapy have brought new hope for lung cancer patients, especially those with specific mutations that can be effectively intervened. Targeted therapies offer a more targeted approach in inhibiting the growth and spread of cancer cells. However, as these therapies advance, it is important to understand that patient response to therapy may vary. addition, cancer cells can develop resistance which must be monitored for cancer management navigation. Regular check-ups are crucial in the management of patients receiving targeted therapy.[24]

Periodic detection of resistance is required as one of the strategies to deliver targeted therapy. One of them is the examination of DNA strands released by tumor cells into the bloodstream identified as circulating tumor DNA (ctDNA). The ctDNA chain can provide

ctDNA analysis provides specific molecular information about tumor cell-derived DNA and the mutations that take place. ctDNA analysis from blood overcomes some of the obstacles faced by invasive tumor biopsies, allowing for easier, cheaper and periodic sampling of tumor DNA. Quantitative and qualitative analysis of ctDNA provides an immediate evaluation useful for diagnosis and prognosis. Therefore, ctDNA is a potential biomarker for detecting targetable mutations, monitoring therapy response and identifycation of novel drug resistance mechanisms in JPBSK.[45]

Another use of ctDNA analysis after administration of therapy is for quantitative assessment of drug effects by measuring ctDNA sequentially during treatment. A correlation between ctDNA changes and treatment effects has been demonstrated in several NSCLC studies. In addition, some studies have shown that ctDNA analysis can identify the emergence of drug resistance mutations several months before conventional radiographic imaging, providing a potential opportunity to improve or change therapy before clinical deterioration to achieve better clinical outcomes. However, to date there is no recommendation on what time interval molecular identification should be performed to detect resistance and the effectiveness of therapy.[45]

Strategy Against Resistance

The evolution of targeted therapies does not stop at the development of new drugs. Treatment approaches are now more focused on personalization by mapping the molecular profile of individual tumors to determine the most effective therapy. One of the resistance-fighting strategies being developed includes combining two or more targeted drugs that inhibit different signaling pathways to prevent cancer cells from developing resistance to a single pathway. Combination of targeted therapy with immunotherapy, combination of targeted therapy with chemotherapy and combination of targeted therapy with other targeted therapies are currently being vigorously conducted in clinical trials. [18,24,50]

Combination of EGFR TKI with Pyruvate Dehydrogenase Kinase

Glycolysis is the main way that cancers obtain energy from glucose, a process that greatly influences progression. Targeting one of the enzymes involved in the process, pyruvate dehydrogenase kinase (PDK) is one way to fight resistance that is currently being developed either given alone or in combination with other systemic therapies. The PDA inhibitor, dichloroacetate (DCA) has been developed to reduce cancer progressivity. Recent studies have shown that the combination of erlotinib and gefitinib with DCA provides a synergistic effect in the therapy of EGFR mutation- positive JPBSK.[47]

Combination of EGFR TKIs with Bcl-2 inhibitors

Overexpression of the antiapoptotic gene family Bcl-2 (consisting of Bcl-s, Bcl-XL and Mcl-1) accompanied by dysregulation of the proapoptotic gene family (including Bad, Bom, Bac and Bak) has been investigated to be one of the mechanisms of chemotherapy and radiotherapy resistance in lung cancer. This shows that Bcl-2 has the potential to be a therapeutic target. The Bcl-2 gene has four homologous domains, namely BH1, BH2, BH3 and BH4. Administration of BH3 mimic agents binds to the hydrophobic arm of Bcl-2 or Bcl-XL to be a competitive inhibitor. Gossypol (AT- 101) showed a pan-Bcl-2 inhibitor in in vitro and in vivo studies increasing gefitinib sensitivity in NSCLC with EGFR T790M mutation and increasing apoptosis in tumors.[47]

Immunotherapy

Immune checkpoint inhibitors are a class of drugs that inhibit immune control points (checkpoints) typically used by cancer cells to avoid detection and elimination by the immune system. The two most targeted checkpoints are programmed death 1 (PD- 1)/ Programmed death-ligand 1 (PD-L1) and Cytotoxic T-Lymphocyte Antigen (CTLA-4). In NSCLC this strategy has shown success in overcoming resistance to targeted therapies, such as EGFR- TKIs. Immunotherapy can currently be administered if a positive PD-1 or PD-L1 result is obtained on immunohistochemical examination. The combination of EGFR- TKIs with PD-1/PD-L1 inhibitors can improve treatment effectiveness by activating T cells to attack EGFR-TKI-resistant cancer cells and improve anti-tumor response by suppressing M2 TAMs activity. Studies show that the combination of pembrolizumab with osimertinib results in increased antitumor activity.[46]

Combination of EGFR TKIs and Chemotherapy

Combination of EGFR-TKIs with chemotherapy is one way to delay resistance. In the phase II NEJ005 trial, the combination of gefitinib with carboplatin and pemetreksed showed an overall improvement in PFS and OS in patients with EGFR mutations, especially with concurrent combination regimens with a median OS of 42 months.50 The phase III NEJ009 trial compared carboplatin and pemetreksed chemotherapy plus gefitinib with gefitinib alone. The combination group had

a significantly longer PFS of 20.9 months compared with 11.9 months for gefitinib alone. [47,48]

Combination of EGFR-TKIs with Specific Small Molecule Inhibitors

The combination of EGFR-TKIs with specific inhibitors selected based on the underlying secondary resistance mechanism has shown good improvement in therapeutic outcomes. EGFR-TKI resistance mechanisms involving activation of alternative signaling pathways are overcome through alternative pathway inhibition. The combination of EGFR-TKIs with specific small molecule inhibitors allows the targeting of multiple signaling pathways at once that support cancer cell proliferation and survival. Studies show that the addition of PI3K inhibitors to EGFR-TKIs can overcome resistance and the combination of PI3K inhibitors with EGFR-TKIs can reduce the risk of cancer cell proliferation and survival.

MEK and PI3K inhibitors have also been shown to be an effective therapeutic strategy to control JPBSK with secondary EGFR-TKI resistance. ROS1 rearrangements caused by EGFR-TKIs can be overcome by combining crizotinib.[47]

Developing A New Generation of inhibitors

The development of new drugs not only aims to obtain drugs with higher efficacy but also aims to overcome resistance caused by the previous generation. Currently, fourth-generation EGFR-TKI inhibitors are in the clinical trial phase with a primary focus on targeting the T790M/C797S drug-resistant mutation. The fourth-generation inhibitor EAI045 is the first selective small molecule variant inhibitor in studies to have shown efficacy in a mouse model of JPBSK when used together with cetuximab. Another targeted therapy, JBJ-04-125-02 has shown good ability in slowing down C797S resistance both as monotherapy and in combination with other agents. Another fourth-generation EGFR-TKI inhibitor under development, tQB3804 can overcome resistance due to secondary mutations and is currently in phase one clinical trials.[24]

Next-generation ROS1 inhibitors are also under development. PF-06463922 is currently undergoing clinical evaluation in NSCLC with positive ALK fusions and ROS1 mutations. This drug is a new generation small molecule ROS1/ALK inhibitor that has shown potent inhibition against various oncogenic ROS1 fusion variants and selective activity against various kinases. Repotrectinib (TPX-0005) shows effectiveness against secondary mutations occurring in the ROS1, NTRK1-3 and ALK genes. Repotrectinib is designed to have higher affinity and better brain penetration compared to first- and second-generation inhibitors. Repotrectinib binds simultaneously to the kinase domains of ROS1, ALK and NTRK preventing autophosphorylation and activation of downstream signaling pathways that support cancer cell growth and survival.[51-52]

Conclusion

1. Targeted therapy improves PFS and OS in patients with NSCLC who have target mutations better than chemotherapy.
2. Resistance to targeted therapy is classified into primary resistance, which is a mutation already present before exposure to targeted therapy, and secondary resistance acquired after targeted therapy administration.
3. The development of secondary resistance occurs due to phenotypic and genotypic changes that result in target immunity, activation of alternative pathways and tissue transformation.
4. Periodic evaluations are required in patients on targeted therapy to monitor resistance patterns developing in cancer cells and guide therapy delivery.
5. To combat resistance several strategies are used including the development of new drug generations and the combination of targeted therapy with targeted therapy, chemotherapy or immunotherapy.

Acknowledgements

No funding was received for this research.

Conflict of Interests

The authors declare no conflict of interest..

References

1. Wu J, Lin Z. Non-Small Cell Lung Cancer Targeted Therapy: Drugs And Mechanisms Of Drug Resistance. Int J Mol Sci. 2022;23:1-18.
2. Zalaquett Z, Hachem CR, Kassis Y, Hachem S, Eid R, Kourie HR, et al. Acquired Resistance Mechanisms To Osimertinib: The Constant Battle. Cancer Treat Rev. 2023;116:1- 11.
3. Lin JJ, Shaw AT. Resisting Resistance: Targeted Therapies In Lung Cancer. Trends Cancer.2016;235064.
4. Meador CB, Hata AN. Acquired Resistance To Targeted Therapies in NSCLC: Updates And Evolving Insights. Pharmacol Ther. 2020;210:1-27.

5. Chhouri H, Alexandre D, Grumolato L. Mechanisms Of Acquired Resistance And Tolerance To EGFR Targeted Therapy In Non-Small Cell Lung Cancer. Cancers. 2023;15:2- 18
6. Araghi M, Mannani R, Heidarnejad MA, Hamidi A, Rostami S, Safa SH, et al. Recent Advances In Non-Small Cell Lung Cancer Targeted Therapy; An Update Review. Cancer Cell Int. 2023;23:2-26
7. Swayden M, Chhouri H, Anouar Y, Grumolato L. Tolerant/Sister Cancer Cells And The Path To Resistance To Targeted Therapy. Cells. 2020;9:2601
8. Rotow J, Bivona TG. Understanding And Targeting Resistance Mechanisms in NSCLC. Nat Rev Cancer. 2017;17:637-58
9. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, et al. Gefitinib Or Carboplatin-Paclitaxel In Pulmonary Adenocarcinoma. N Engl J Med. 2009;361:947- 57
10. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, et al. Erlotinib Versus Standard Chemotherapy As First-Line Treatment For European Patients With Advanced EGFR Mutation-Positive Non-Small-Cell Lung Cancer (EURTAC): A Multicentre, Open-Label, Randomized Phase 3 Trial. Lancet Oncol. 2012;13:239-46
11. Wu YL, Cheng Y, Zhou X, et al. Dacomitinib Versus Gefitinib As First-Line Treatment For Patients With EGFR-Mutation-Positive Non-Small-Cell Lung Cancer (ARCHER 1050): A randomized, open-label, phase 3 trial. Lancet Oncol. 2017;18:1454-66.
12. Paz-Ares L, Tan EH, O'Byrne K, Zhang L, Hirsh V, Boyer M, et al. Afatinib Versus Gefitinib In Patients With EGFR Mutation-Positive Advanced Non-Small-Cell Lung Cancer: Overall Survival Data From The Phase Iib LUX-Lung 7 Trial. Ann Oncol. 2017;28:270-7
13. Mok TS, Wu YL, Ahn MJ, Garassino MC, Kim HR, Ramalingam SS, et al. Osimertinib or Platinum-Pemetrexed In EGFR T790M-Positive Lung Cancer. N Engl J Med. 2017;376:629-40
14. Du X, Shao Y, Qin HF, Tai YH, Gao HJ. ALK-Rearrangement In Non-Small-Cell Lung Cancer (NSCLC): ALK Rearrangement In Lung Cancer. Thorac Cancer. 2018;9:423-30
15. Rothenstein JM, Chooback N. ALK Inhibitors, Resistance Development, Clinical Trials. Curr Oncol. 2018;59-67
16. Cooper AJ, Sequist LV, Lin JJ. Third-Generation EGFR And ALK Inhibitors: Mechanisms Of Resistance And Management. Nat Rev Clin Oncol. 2022;19:499-514.
17. Desai A, Lovly CM. Strategies To Overcome Resistance To ALK Inhibitors In Non-Small Cell Lung Cancer: A Narrative Review. Transl Lung Cancer Res.2023;12:615-628.
18. Song X, Zhong H, Qu X, Yang L, Jiang B. Two Novel Strategies To Overcome The Resistance To ALK Tyrosine Kinase Inhibitor Drugs: Macrocyclic Inhibitors And Proteolysis-Targeting Chimeras. MedComm. 2021;2:341-50.
19. Azelby CM, Sakamoto MR, Bowles DW. ROS1 Targeted Therapies: Current Status. Curr Oncol Rep. 2021;23:1-9.
20. Tang Z, Zhang J, Lu X, Wang W, Chen H, Robinson MK, et al. Coexistent Genetic Alterations Involving ALK, RET, ROS1 Or MET In 15 Cases Lung Adenocarcinoma. Sci Rep. 2017;31:307-12.
21. Majeed U, Manochakian R, Zhao Y, Lou Y. Targeted Therapy In Advanced Non-Small Cell Lung Cancer: Current Advances And Future Trends. J Hematol Oncol. 2021;14:1-20
22. Emran TB, Shahriar A, Mahmud AR, Rahman T, Abir MH, Siddiquee MFR, et al. Multidrug Resistance In Cancer: Understanding Molecular Mechanisms, Immunoprevention And Therapeutic Approaches. Front Oncol. 2022;12:1-58.
23. Khan SU, Fatima K, Aisha S, Malik F. Unveiling the Mechanisms And Challenges Of Cancer Drug Resistance. Cell Commun Signal. 2024;22:1-26.
24. Fu K, Xie F, Wang F, Fu L. Therapeutic Strategies For EGFR-Mutated Non-Small Cell Lung Cancer Patients With Osimertinib Resistance. J Hematol Oncol. 2022;15:1-23.
25. Reita D, Pabst L, Pencreach E, Guérin E, Dano L, Rimelen V, et al. Molecular Mechanism Of EGFR-TKI Resistance In EGFR-Mutated Non-Small Cell Lung Cancer: Application To Biological Diagnostics And Monitoring. Cancers. 2021;13:1-43.
26. Passaro A, Brahmer J, Antonia S, Mok T, Peters S. Managing Resistance To Immune Checkpoint Inhibitors In Lung Cancer: Treatments And Novel Strategies. J Clin Oncol. 2022;40:598-610
27. Leonetti A, Sharma S, Minari R, Perego P, Giovannetti E, Tiseo M. Resistance Mechanisms To Osimertinib In EGFR-Mutated Non-Small Cell Lung Cancer. Br J Cancer. 2019;121:725-337.
28. Swayden M, Chhouri H, Anouar Y, Grumolato L. Tolerant/Sister Cancer Cells And The Path To Resistance To Targeted Therapy. Cells. 2020;9:1-13.
29. Coleman N, Hong L, Zhang J, Heymach J, Hong D, Le X. Beyond Epidermal Growth Factor Receptor: MET Amplification As A General Resistance Driver To Targeted Therapy In Oncogene-Driven Non-Small-Cell Lung Cancer. ESMO Open. 2021;:1-9.
30. Usman S, Waseem NH, Nguyen TKN, Mohsin S, Jamal A, Teh MT, et al. Vimentin is At The Heart Of Epithelial Mesenchymal Transition (EMT) Mediated Metastasis. Cancers. 2021;13: 2-29
31. Giaccone G, He Y. Current Knowledge Small Cell Lung Cancer Transformation From Non- Small Cell Lung Cancer. Semin Cancer Biol. 2023;94:1-10
32. Ashrafizadeh M, Dai J, Torabian P, Nabavi N, Aref AR, Aljabali AAA, et al. Circular RNAs in EMT-driven Metastasis Regulation: Modulation Of Cancer Cell Plasticity, Tumorigenesis And Therapy Resistance. Cell Mol Life Sci. 2024;81:1-25.
33. Zakowski MF, Ladanyi M, Kris MG. EGFR Mutations In Small-Cell Lung Cancers In Patients Who Have Never Smoked. N Engl J Med. 2006;355:213-5.
34. Ding X, Shi M, Liu D, Cao J, Zhang K, Zhang R, et al. Transformation to Small Cell Lung Cancer Is Irrespective Of EGFR And Accelerated By SMAD4-Mediated ASCL1 Transcription Independently Of RB1

In Non-Small Cell Lung Cancer. Cell Commun Signal. 2024;22:1-16.
35. Shi J, Chen Y, Peng C, Kuang L, Zhang Z, Li Y, et al. Advances in Targeted Therapy Against Driver Mutations And Epigenetic Alterations In Non-Small Cell Lung Cancer. Oncologie. 2022;24:613-48.
36. Wajapeyee N, Gupta R. Epigenetic Alterations And Mechanisms That Drive Resistance To Targeted Cancer Therapies. Cancer Res. 2021;81:5589-95
37. Su SF, Liu CH, Cheng CL, et al. Genome-wide Epigenetic Landscape Of Lung Adenocarcinoma Links HOXB9 DNA Methylation To Intrinsic EGFR-TKI Resistance And Heterogeneous Responses. JCO Precis Oncol. 2021;5:418-31.
38. Shi J, Chen Y, Peng C, Kuang L, Zhang Z, Li Y, et al. Advances in Targeted Therapy Against Driver Mutations And Epigenetic Alterations In Non-Small Cell Lung Cancer. Oncologie. 2022;24:613-48.
39. Cheng D, Wang B, Wu L, Chen R, Zhao W, Fang C, et al. Exosomal Non-Coding Rnas- Mediated EGFR-Tkis Resistance In NSCLC With EGFR Mutation. Med Oncol. 2023;40:23-32.
40. Zhang Y, Li M, Hu C. Exosomal Transfer Of mir-214 Mediates Gefitinib Resistance In Non-Small Cell Lung Cancer. Biochem Biophys Res Commun. 2018;507:457-64.
41. Chen X, Wang Z, Tong F, Dong X, Wu G, Zhang R. lncRNA UCA1 Promotes Gefitinib Resistance As A ceRNA to Target FOSL2 by Sponging miR-143 in Non-small Cell Lung Cancer. Mol Ther Nucleic Acids. 2020;19:643-53.
42. Madeddu C, Donisi C, Liscia N, Lai E, Scartozzi M, Macciò A. EGFR-Mutated Non- Small Cell Lung Cancer And Resistance To Immunotherapy: Role Of The Tumor Microenvironment. Int J Mol Sci. 2022;23:1-16.
43. Chen S, Tang J, Liu F, Li W, Yan T, Shangguan D, et al. Changes of Tumor Microenvironment In Non-Small Cell Lung Cancer After TKI Treatments. Front Immunol. 2023;14:1-14.
44. Cheng D, Ge K, Yao X, Wang B, Chen R, Zhao W, et al. Tumor-Associated Macrophages Mediate Resistance Of EGFR-Tkis In Non-Small Cell Lung Cancer: Mechanisms And Prospects. Front Immunol. 2023;14:1-12.
45. Nanjo S, Bivona TG. Circulating Tumor DNA Analysis In Patients With EGFR Mutant Lung Cancer. J Thorac Dis. 2018;4061-4.
46. Xiang Y, Liu X, Wang Y, Zheng D, Meng Q, Jiang L, et al. Mechanisms of Resistance To Targeted Therapy And Immunotherapy In Non-Small Cell Lung Cancer: Promising Strategies To Overcome Challenges. Front Immunol. 2024;15:1-29.
47. Zhang K, Yuan Q. Current Mechanism Of Acquired Resistance To Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitors And Updated Therapy Strategies In Human Nonsmall Cell Lung Cancer. J Cancer Res Ther. 2016;2;12-7.
48. Hosomi Y, Morita S, Sugawara S, Kato T, Fukuhara T, Gemma A, et al. Gefitinib Alone Versus Gefitinib Plus Chemotherapy For Non-Small-Cell Lung Cancer With Mutated Epidermal Growth Factor Receptor: NEJ009 Study. J Clin Oncol. 2020;38:115-23.
49. Sugawara S, Oizumi S, Minato K, Harada T, Inoue A, Fujita Y, et al. Randomized Phase II Study Of Concurrent Versus Sequential Alternating Gefitinib And Chemotherapy In Previously Untreated Non-Small Cell Lung Cancer With Sensitive EGFR Mutations: NEJ005/TCOG0902. Ann Oncol. 2015;26:888-94.
50. Oizumi S, Sugawara S, Minato K, Harada T, Inoue A, Fujita Y, et al. Updated survival Outcomes Of NEJ005/TCOG0902: A Randomized Phase II Study Of Concurrent Versus Sequential Alternating Gefitinib And Chemotherapy In Previously Untreated Non-Small Cell Lung Cancer With Sensitive EGFR Mutations. ESMO Open. 2018 Feb 23;3:1-100.
51. Shaw AT, Ou SHI, Bang YJ, Camidge DR, Solomon BJ, Salgia R, et al. Crizotinib in ROS1 Rearranged Non-Small-Cell Lung Cancer. N Engl J Med. 2014;371:1963-71.
52. Shaw AT, Riely GJ, Bang YJ, Kim DW, Camidge DR, Solomon BJ, et al. Crizotinib in ROS1-Rearranged Advanced Non-Small-Cell Lung Cancer (NSCLC): Updated Results, Including Overall Survival, From PROFILE 1001. Ann Oncol. 2019;30:1121-6.

InaJCC The Indonesian Journal of Cancer Control

Special Article

Bridging the complexity of triple negative breast cancer care through multidisciplinary team approach

Ibnu Purwanto

e-ISSN 2797-457X
DOI: 10.52830/inajcc.v1i1.116

Received: November 28rd, 2024
Accepted: April 7th, 2025

Authors' affiliations:
Internal Medicine, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada/Dr Sardjito Hospital, Jl. Farmako, Sekip Utara, Daerah Istimewa Yogyakarta Yogyakarta, 55281, Indonesia

Corresponding author:
E-mail: *ibnupurwanto@ugm.ac.id*

Abstract

Triple-negative breast cancer (TNBC) is still associated with a grave prognosis, especially compared to other breast cancer subtypes. TNBC carries a high risk of recurrence and distant metastasis, resulting in lower survival rates. Additionally, TNBC exhibits significant heterogeneity at the histopathological and multiomics levels, further complicating the development of effective treatments. While some TNBC subtypes may initially respond to chemotherapy, resistance frequently develops, increasing the risk of aggressive recurrence. The approach to TNBC management has undergone significant transformations in recent years, recognizing it as a heterogeneous disease with diverse biology and behavior. Chemotherapy remains the cornerstone of treatment for most TNBC cases, with the incorporation of PD-L1 CPS or immune cell (IC) scores and BRCA status being crucial for optimizing patient management. Besides the advancement of TNBC treatment, the multidisciplinary team also plays a key role in TNBC management, enabling improved diagnosis, treatment outcomes, disease monitoring, and management of adverse events.

Keywords: *Breast cancer, multidisciplinary team, treatment, triple-negative breast cancer*

Abstrak

Kanker payudara *triple-negative* (TNBC) dikaitkan dengan prognosis yang buruk, terutama bila dibandingkan dengan subtipe kanker payudara lainnya. TNBC memiliki risiko tinggi terhadap kekambuhan dan metastasis jauh, yang berujung pada angka ketahanan hidup yang lebih rendah. Selain itu, TNBC menunjukkan heterogenitas yang signifikan pada tingkat histopatologis maupun multiomik, sehingga semakin mempersulit pengembangan terapi yang efektif. Meskipun beberapa subtipe TNBC dapat memberikan respons awal terhadap kemoterapi, resistensi sering kali muncul kemudian dan meningkatkan risiko kekambuhan agresif. Pendekatan terhadap penatalaksanaan TNBC telah mengalami perubahan besar dalam beberapa tahun terakhir, dengan pengakuan bahwa penyakit ini bersifat heterogen dengan biologi dan perilaku yang beragam. Kemoterapi tetap menjadi pilar utama pengobatan bagi sebagian besar kasus TNBC, dengan penilaian skor PD-L1 CPS atau sel imun (IC) serta status BRCA yang penting untuk mengoptimalkan penatalaksanaan pasien. Selain kemajuan dalam terapi TNBC, peran tim multidisiplin juga sangat krusial dalam meningkatkan diagnosis, hasil pengobatan, pemantauan penyakit, serta penanganan efek samping terapi.

Kata Kunci: *kanker payudara, tim multidisiplin, terapi, kanker payudara triple-negatif*

Introduction

Breast cancer is the most diagnosed type of cancer worldwide, with an incidence of 2.3 million cases and causing 685,000 deaths annually.[1] In Indonesia, breast cancer is also the cancer with the highest incidence and is the leading cause of cancer-related deaths.[2]

Breast cancer is a heterogeneous disease, classified based on the expression of estrogen receptors, progesterone receptors, and human epidermal growth factor receptor 2 (HER2). Breast cancer cells that express hormone receptors are referred to as hormone receptor-positive breast cancer, cells that express HER2 are referred to as HER2-positive breast cancer, while cells that express none of the three are classified as triple-negative breast cancer (TNBC).[3,4] The molecular classification of breast cancer consists of the luminal A and B subtypes, which overlap with ER+ breast cancer; the HER2-enriched subtype, which overlaps with HER2+ breast cancer and can be TP53-mutated or wild type; and basal-like breast cancer, which overlaps with TNBC, and the claudin-low breast cancer subtype.[5] Shortly the definition of TNBC is the absence of immunostaning for estrogen and progesterone receptors and lack of overexpression or amplification of human epidermal growth factor receptor 2.[6]

Hormone receptor-positive breast cancer accounts for about 70–80% of all breast cancer cases, the HER2-positive subtype makes up around 15–20%, and triple-negative accounts for about 10–15%. Each breast cancer subtype has a different carcinogenesis pathway, resulting in differences in treatment selection and patient prognosis.[7,8] According to data from The Surveillance, Epidemiology, and End Results (SEER), patients with hormone receptor-positive breast cancer have a 5-year survival rate of around 90%, HER2-positive around 80–85%, while triple-negative breast cancer (TNBC) has the lowest survival rate, around 60–70%, highlighting the many treatment challenges that still remain unsolved.[9]

TNBC Classification

Based on genetic expression, TNBC can be classified into various subtypes with distinct clinical characteristics and prognoses, each requiring different therapeutic modalities. Two major classifications of TNBC are the Vanderbilt and Baylor classifications. The Vanderbilt classification divides TNBC into six subtypes: basal-like 1 (BL1), basal-like 2 (BL2), immune-modulatory (IM), mesenchymal (M), mesenchymal stem–like (MSL), and luminal androgen receptor (LAR).[10] However, further observation revealed that most of the IM and MSL subtype markers originate from tumor microenvironment gene expression; thus, they were removed in the revised classification known as TNBCtype-4.[11,12] The BL1 subtype is characterized by increased expression of genes involved in cell replication and DNA damage repair, while BL2 is marked by myoepithelial and cell growth gene markers. The mesenchymal subtype shows increased expression of genes involved in epithelial-to-mesenchymal transition, motility, and cell growth. The LAR subtype is characterized by luminal gene expression derived from androgen receptors.[13] The Vanderbilt classify-cation is the most extensively studied by researchers, both in terms of patient characteristics and therapeutic responses.

The BL1 subtype is associated with younger age at diagnosis, higher Ki-67 index, and more frequent lymph node involvement. BL1 and BL2 subtypes are highly sensitive to platinum-based chemotherapy (pathological complete response [pCR]: 65.4% and 47.7%, respectively). The mesenchymal subtype tends to metastasize to the lungs and shows a poorer response to platinum-based chemotherapy (pCR: 36.4%). The LAR subtype is more commonly diagnosed at an older age, is associated with larger tumor size, more frequent lymph node involvement, and bone metastases, and shows the poorest response to platinum-based chemotherapy (pCR: 21.4%).[14] Unlike the mesenchymal subtype, survival in LAR patients can be improved with the use of androgen receptor antagonists (bicalutamide, abiraterone acetate, and enzalutamide), achieving a clinical benefit rate (CBR) of up to 33%.[15]

The Baylor classification divides TNBC into basal-like immune-suppressed (BLIS), basal-like immune-activated (BLIA), luminal-AR (LAR), and mesenchymal (MES) subtypes.[16] Although not identical, the Baylor and Vanderbilt classifications share similarities in terms of basal, luminal androgen, and mesenchymal features. The BLIS subtype has the best prognosis. It is characterized by decreased expression of B cells, T cells, and natural killer cells. Compared to the Vanderbilt classification, this subtype resembles the BL1 subtype. In contrast to BLIS, the BLIA subtype has the poorest prognosis. It is marked by increased expression of B cells, T cells, and natural killer cells. Compared to the Vanderbilt

classification, this subtype is similar to the immune-modulatory subtype. The LAR and mesenchymal subtypes in the Baylor classification are equivalent to those in the Vanderbilt classification.[17] Unlike the Vanderbilt classification, the Baylor classification has not yet been extensively studied in terms of patient characteristics or treatment response.

Some authors have divided TNBC into AR-positive and AR-negative TNBC based on the expression of the androgen receptor (AR). AR-negative TNBC is also known as quadruple-negative breast cancer (QNBC). There exist differences regarding the tumor biology and molecular profiles between QNBC and TNBC. For instance, expression of epidermal growth factor (EGF) and genes involved in immune response, which results in higher proliferative and immunogenic properties when compared to TNBC, leading to a worse prognosis. For this reason, a distinct subtype classification for QNBC, independent of TNBC, is recommended.[18]

Genetic and Epigenetic in TNBC

Genetically, triple-negative breast cancer (TNBC) is frequently characterized by mutations in key tumor suppressor genes, including TP53, BRCA1/2, PIK3CA, RB1, PTEN, and MYC. These alterations contribute to cell cycle dysregulation, impaired DNA repair, and tumor progression.[19] Many of these mutations have been extensively studied as potential therapeutic targets. For instance, mutations in BRCA1 and BRCA2, which encode essential proteins in the homologous recombination (HR) DNA repair pathway, render cancer cells particularly vulnerable to Poly (ADP-ribose) polymerase (PARP) inhibitors, such as Olaparib.[20] PARP enzymes play a critical role in repairing single-strand DNA breaks via the base excision repair pathway. Inhibition of PARP leads to the accumulation of single-strand breaks, which are eventually converted into double-strand breaks during DNA replication.[21] In cells with functional HR, these lesions can be repaired. However, in BRCA-mutated cells with homologous recombination deficiency (HRD), the inability to repair double-strand breaks results in cell death—a therapeutic mechanism known as synthetic lethality.[22]

Epigenetic dysregulation also plays a significant role in TNBC pathogenesis. Aberrant DNA methylation patterns, such as promoter hypermethylation of tumor suppressor genes such as *BRCA1* and *CDKN2A*, result in gene silencing. Histone modifications and deregulated non-coding RNAs, including microRNAs.[23] MicroRNAs (miR) are small non-coding RNA molecules that regulate gene expression by inhibiting translation or inducing degradation of target mRNAs. In the context of TNBC, miRNAs can function either as oncogenes or tumor suppressors, depending on the genes they regulate. Several miRNAs, such as miR-21 and miR-155, have been identified as oncogenic, promoting cancer cell proliferation, angiogenesis, and metastasis. In contrast, other miRNAs, such as miR-34a and miR-200c, act as tumor suppressors by inhibiting tumor growth and spread.[24,25] Notably, several of these deregulated microRNAs also contribute to the regulation of epithelial-to-mesenchymal transition (EMT), a key process in TNBC progression that facilitates tumor invasion, metastasis, and treatment resistance. In TNBC, EMT is associated with enhanced cellular invasion and migration, as well as resistance to systemic chemotherapy, including platinum-based agents.[26] The main regulators of EMT are believed to include the TGF-β, Notch, and Wnt signaling pathways, and the process is also influenced by tumor microenvironmental factors such as hypoxia and the expression of miR (such as miR- 200c, miR-21 and miR-34a). These combined mechanisms lead to increased expression of transcription factors such as SNAI1, SNAI2 (Slug), Twist, and Zeb1/Zeb2, which drive the mesenchymal transition.[27]

Approved Treatment

The ideal treatment for TNBC includes complete tumor resection and systemic chemotherapy. The commonly used chemotherapy regimen is a combination of anthracyclines and taxanes (AC-T), namely doxorubicin, cyclophosphamide, followed by paclitaxel or docetaxel. Platinum-based chemotherapy is often used in TNBC, particularly in patients with BRCA gene mutations, involving carboplatin or cisplatin followed by paclitaxel or docetaxel.[28] Chemotherapy can be administered either pre-operatively (neoadjuvant) or post-operatively (adjuvant).

Since TNBC lack the expression of ER and PR and have amplification or over expression of HER2, hormonal therapies designed to inhibit ER and PR and anti-HER2 treatment are not effective. Moreover, the high heterogeneity of TNBC tumors makes it very difficult to find a universally useful targeted therapy. Indeed, there is no available biologically effective targeted therapy for TNBC yet.[29]

The management approach to TNBC has undergone significant transformations in recent years, recognizing

it as a heterogeneous disease with diverse biology and behavior.[30-32] Chemotherapy remains the cornerstone of treatment for most TNBC cases, with the incorporation of PD-L1 CPS or immune cell (IC) scores and BRCA status crucial for optimizing patient management.[33]

In patients without targetable molecular expression, determining the intrinsic subtype of breast cancer can help guide the selection of the most optimal systemic chemotherapy regimen.[10-14,16,34-36] Patients with the basal-like subtype (based on EGFR and CK 5/6 expression) tend to respond better to platinum-based chemotherapy, whereas patients with the mesenchymal subtype (based on vimentin expression) may benefit more from non-platinum-based chemotherapy, such as anthracyclines.

Immune checkpoint inhibitors (ICIs) are becoming increasingly relevant in the treatment of TNBC. PD-L1 expression, which serves as a negative prognostic factor in TNBC, has guided the implementation of anti-PD-L1 therapies, such as atezolizumab and pembrolizumab, which have been shown to significantly improve progression-free and overall survival in patients with PD-L1-positive metastatic TNBC.[37,38] However, in early-stage TNBC, the benefit of ICIs is independent of PD-L1 status as stated by ESMO guideline.[39]

The complexity of TNBC treatment is best illustrated by the management of metastatic TNBC. The treatment approach in this setting incorporates both biomarker-driven and pragmatic, region-sensitive strategies. First, PD-L1 testing should be performed to determine patient eligibility for ICIs. Additionally, germline BRCA1/2 mutation testing is recommended—particularly in younger patients and those with a family history of breast or ovarian cancer—to guide the use of PARP inhibitors. For first-line treatment, patients with PD-L1-positive tumors should receive ICIs in combination with chemotherapy. In contrast, for patients who are PD-L1-negative, or in settings where immunotherapy is not accessible, chemotherapy remains the standard of care as suggested by Pan-Asian adapted ESMO guideline. In subsequent lines of treatment, chemotherapy continues to play a central role. However, in patients with BRCA mutations, PARP inhibitors offer an effective targeted therapy option.[38] This level of complexity underscores the need for a multidisciplinary team approach to ensure optimal patient care.

Multidisciplinary Team

A multidisciplinary team (MDT) care policy was developed in the UK in 1995 to enhance the quality of care for cancer patients. MDT comprises a variety of professions, including medical, nursing, and allied workers, as well as diagnostic experts, who work together to identify the best treatment plan for each patient.[40-43] Previous research indicates that MDT care can aid in clinical decision-making. MDT treatment can prevent 98.8% of all drug mistakes and enhance overall care quality.[44] After the introduction of multidisciplinary care in the UK, breast cancer mortality in the intervention region was 18% lower than in the non intervention area.[45]

Various studies have demonstrated the benefits of multidisciplinary management of breast cancer, both in terms of patient outcomes and healthcare costs. A study by Kesson et al. in 2012 showed that breast cancer patients managed through a multidisciplinary approach had better disease-free survival and overall survival.[40] Similar findings were reported by Lu et al. in 2019, where breast cancer patients managed by a multidisciplinary team (MDT) had a 15.6% higher five-year survival rate.[46] Given these findings, it is no surprise that major global organizations such as ESMO, ASCO, and WHO consistently recommend MDT involvement in cancer patient management.[47] Freeman et al. (2015) showed that patients managed through an MDT approach incurred lower healthcare costs compared to those who were not managed through such a team.[48]

At Dr. Sardjito General Hospital in Yogyakarta, the MDT approach has actually been in place for nearly 20 years, initially focusing on the management of nasopharyngeal/head and neck cancers. This MDT program was a collaborative initiative between Dr. Sardjito Hospital, the Faculty of Medicine at Gadjah Mada University (UGM), VUMC Amsterdam, Antoni van Leeuwenhoek Hospital, and supported by the Dutch Cancer Society/Koningin Wilhelmina Fonds and ASIA-Link through the European Commission Programs on Capacity Building in Translational Research from Clinic to Basic Science. Nasopharyngeal cancer—the most common head and neck cancer—was chosen to pilot this effort in delivering adequate care for this specific tumor using internationally recognized protocols, known as the multidisciplinary approach.[49]

As expected, and as widely reported in international literature, patients managed through MDTs show a significantly lower risk of disease progression compared to those without MDT management (59 months vs. 12 months). Similarly, the mortality rate of nasopharyngeal cancer patients was significantly lower in the MDT group—just half that of the non-MDT group. The median overall survival in the non-MDT group was only 13 months, whereas more than half of the patients in the MDT group had not reached median survival at 5 years of follow-up. This study involved 178 nasopharyngeal cancer patients from January 1, 2016 to December 31, 2020.[50]

Various MDT implementations in nasopharyngeal, breast, colorectal, lung, and gastrointestinal tumors have shown improved patient outcomes.[40,51-54] The latest publication from Indonesia is a systematic review and meta-analysis by Pangarsa EA (2023), which included six studies from six countries (China, the UK, Taiwan, Australia, Africa, and France).[55] The review concluded that breast cancer patients who participated in well-organized MDT discussions had better survival outcomes compared to those who did not.

Although the benefits of MDTs have been widely recognized, the implementation of MDTs—particularly for triple-negative breast cancer—still faces many challenges. These include the unequal distribution of human resources in breast cancer management, the willingness of healthcare professionals who should be part of the MDT to engage in multidisciplinary care, the need for strong commitment to adhere to MDT decisions, and the necessity for appropriate regulatory support.

Conclusion

In conclusion, the complex and aggressive nature of TNBC demands a comprehensive and personalized treatment approach. Given its high heterogeneity and poor prognosis, TNBC management should not rely on a single therapeutic strategy. Instead, a multi-modality approach—integrating systemic chemotherapy, targeted therapies based on molecular profiling, and immunotherapy when appropriate—offers the best potential for improved outcomes. Equally important is the role of a MDT, which ensures that treatment planning is collaborative, evidence-based, and tailored to each patient's specific clinical and molecular characteristics. Strengthening MDT implementation, especially in resource-limited settings, is essential to bridging gaps in care and enhancing survival and quality of life for TNBC patients.

Acknowledgements

The author expresses gratitude to various Indonesian oncology multidisciplinary teams which have been providing excellent care for Indonesian cancer patients, including in Yogyakarta.

Conflict of Interests

The author declares no conflict of interest.

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;71(3):209-49.
2. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229-63.
3. Hammond ME, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer (unabridged version). Arch Pathol Lab Med. 2010;134(7):e48-72.
4. Wolff AC, Hammond ME, Hicks DG, Dowsett M, McShane LM, Allison KH, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol. 2013;31(31):3997-4013.
5. Perou CM, Sorlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, et al. Molecular portraits of human breast tumours. Nature. 2000;406(6797):747-52.
6. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin. 2024;74(1):12-49.
7. Bauer KR, Brown M, Cress RD, Parise CA, Caggiano V. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California cancer Registry. Cancer. 2007;109(9):1721-8.
8. Morris GJ, Naidu S, Topham AK, Guiles F, Xu Y, McCue P, et al. Differences in breast carcinoma characteristics in newly diagnosed African-American and Caucasian patients: a single-institution compilation compared with the National Cancer Institute's Surveillance, Epidemiology, and End Results database. Cancer. 2007;110(4):876-84.
9. Yang M, Hu X, Bao W, Zhang X, Lin Y, Stanton S, et al. Changing trends and disparities in 5-year overall survival of women with invasive breast cancer in the United States, 1975-2015. Am J Cancer Res. 2021;11(6):3201-11.

10. Lehmann BD, Bauer JA, Chen X, Sanders ME, Chakravarthy AB, Shyr Y, et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest. 2011;121(7):2750-67.
11. Lehmann BD, Jovanovic B, Chen X, Estrada MV, Johnson KN, Shyr Y, et al. Refinement of Triple-Negative Breast Cancer Molecular Subtypes: Implications for Neoadjuvant Chemotherapy Selection. PLoS One. 2016;11(6):e0157368.
12. Prat A, Cruz C, Hoadley KA, Diez O, Perou CM, Balmana J. Molecular features of the basal-like breast cancer subtype based on BRCA1 mutation status. Breast Cancer Res Treat. 2014;147(1):185-91.
13. Prat A, Cheang MC, Galvan P, Nuciforo P, Pare L, Adamo B, et al. Prognostic Value of Intrinsic Subtypes in Hormone Receptor-Positive Metastatic Breast Cancer Treated With Letrozole With or Without Lapatinib. JAMA Oncol. 2016;2(10):1287-94.
14. Echavarria I, Lopez-Tarruella S, Picornell A, Garcia-Saenz JA, Jerez Y, Hoadley K, et al. Pathological Response in a Triple-Negative Breast Cancer Cohort Treated with Neoadjuvant Carboplatin and Docetaxel According to Lehmann's Refined Classification. Clin Cancer Res. 2018;24(8):1845-52.
15. Traina TA, Miller K, Yardley DA, Eakle J, Schwartzberg LS, O'Shaughnessy J, et al. Enzalutamide for the Treatment of Androgen Receptor-Expressing Triple-Negative Breast Cancer. J Clin Oncol. 2018;36(9):884-90.
16. Burstein MD, Tsimelzon A, Poage GM, Covington KR, Contreras A, Fuqua SA, et al. Comprehensive genomic analysis identifies novel subtypes and targets of triple-negative breast cancer. Clin Cancer Res. 2015;21(7):1688-98.
17. Hubalek M, Czech T, Muller H. Biological Subtypes of Triple-Negative Breast Cancer. Breast Care (Basel). 2017;12(1):8-14.
18. Bhattarai S, Saini G, Gogineni K, Aneja R. Quadruple-negative breast cancer: novel implications for a new disease. Breast Cancer Res. 2020;22(1):127.
19. Derakhshan F, Reis-Filho JS. Pathogenesis of Triple-Negative Breast Cancer. Annu Rev Pathol. 2022;17:181-204.
20. Domagala P, Huzarski T, Lubinski J, Gugala K, Domagala W. PARP-1 expression in breast cancer including BRCA1-associated, triple negative and basal-like tumors: possible implications for PARP-1 inhibitor therapy. Breast Cancer Res Treat. 2011;127(3):861-9.
21. Tutt A, Ashworth A. The relationship between the roles of BRCA genes in DNA repair and cancer predisposition. Trends Mol Med. 2002;8(12):571-6.
22. McCabe N, Turner NC, Lord CJ, Kluzek K, Bialkowska A, Swift S, et al. Deficiency in the repair of DNA damage by homologous recombination and sensitivity to poly(ADP-ribose) polymerase inhibition. Cancer Res. 2006;66(16):8109-15.
23. Pont M, Marques M, Sorolla A. Latest Therapeutical Approaches for Triple-Negative Breast Cancer: From Preclinical to Clinical Research. Int J Mol Sci. 2024;25(24).
24. Santana T, de Oliveira Passamai L, de Miranda FS, Borin TF, Borges GF, Luiz WB, et al. The Role of miRNAs in the Prognosis of Triple-Negative Breast Cancer: A Systematic Review and Meta-Analysis. Diagnostics (Basel). 2022;13(1).
25. Singh S, Saini H, Sharma A, Gupta S, Huddar VG, Tripathi R. Breast cancer: miRNAs monitoring chemoresistance and systemic therapy. Front Oncol. 2023;13:1155254.
26. Hill DP, Harper A, Malcolm J, McAndrews MS, Mockus SM, Patterson SE, et al. Cisplatin-resistant triple-negative breast cancer subtypes: multiple mechanisms of resistance. BMC Cancer. 2019;19(1):1039.
27. Felipe Lima J, Nofech-Mozes S, Bayani J, Bartlett JM. EMT in Breast Carcinoma-A Review. J Clin Med. 2016;5(7).
28. Medina MA, Oza G, Sharma A, Arriaga LG, Hernandez Hernandez JM, Rotello VM, et al. Triple-Negative Breast Cancer: A Review of Conventional and Advanced Therapeutic Strategies. Int J Environ Res Public Health. 2020;17(6).
29. Purwanto I, I D, T A, S M. Treatment options for Indonesian triple negative breast cancer patients: a literature review of current state and potentials for future improvement. JMedSci. 2020;52:81-101.
30. Fusco N, Sajjadi E, Venetis K, Ivanova M, Andaloro S, Guerini-Rocco E, et al. Low-risk triple-negative breast cancers: Clinico-pathological and molecular features. Crit Rev Oncol Hematol. 2022;172:103643.
31. Venetis K, Sajjadi E, Peccatori FA, Guerini-Rocco E, Fusco N. Immune plasticity in pregnancy-associated breast cancer tumorigenesis. Eur J Cancer Prev. 2023;32(4):364-9.
32. Tsang JY, Tse GM. Update on triple-negative breast cancers - highlighting subtyping update and treatment implication. Histopathology. 2023;82(1):17-35.
33. Gennari A, Andre F, Barrios CH, Cortes J, de Azambuja E, DeMichele A, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Ann Oncol. 2021;32(12):1475-95.
34. Lehmann BD, Pietenpol JA. Identification and use of biomarkers in treatment strategies for triple-negative breast cancer subtypes. J Pathol. 2014;232(2):142-50.
35. Lehmann BD, Pietenpol JA, Tan AR. Triple-negative breast cancer: molecular subtypes and new targets for therapy. Am Soc Clin Oncol Educ Book. 2015:e31-9.
36. Prat A, Perou CM. Mammary development meets cancer genomics. Nat Med. 2009;15(8):842-4.
37. Purwanto I, Heriyanto DS, Ghozali A, Widodo I, Dwiprahasto I, Aryandono T, et al. Overexpression of Programmed Death-Ligand 1 Receptor mRNA as an Independent Negative Prognostic Factor for Triple Negative Breast Cancer. World J Oncol. 2020;11(5):216-22.
38. Im SA, Gennari A, Park YH, Kim JH, Jiang ZF, Gupta S, et al. Pan-Asian adapted ESMO Clinical Practice Guidelines for the diagnosis, staging and treatment of patients with metastatic breast cancer. ESMO Open. 2023;8(3):101541.
39. Loibl S, Andre F, Bachelot T, Barrios CH, Bergh J, Burstein HJ, et al. Early breast cancer: ESMO Clinical

Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2024;35(2):159-82.
40. Kesson EM, Allardice GM, George WD, Burns HJ, Morrison DS. Effects of multidisciplinary team working on breast cancer survival: retrospective, comparative, interventional cohort study of 13 722 women. BMJ. 2012;344:e2718.
41. Bellanger M, Zeinomar N, Tehranifar P, Terry MB. Are Global Breast Cancer Incidence and Mortality Patterns Related to Country-Specific Economic Development and Prevention Strategies? J Glob Oncol. 2018;4:1-16.
42. Kang JJ, Wong RJ, Sherman EJ, Rybkin A, McBride SM, Riaz N, et al. The 3 Bs of cancer care amid the COVID-19 pandemic crisis: "Be safe, be smart, be kind"-A multidisciplinary approach increasing the use of radiation and embracing telemedicine for head and neck cancer. Cancer. 2020;126(18):4092-104.
43. Scott JM, Thomas SM, Herndon JE, 2nd, Douglas PS, Yu AF, Rusch V, et al. Effects and tolerability of exercise therapy modality on cardiorespiratory fitness in lung cancer: a randomized controlled trial. J Cachexia Sarcopenia Muscle. 2021;12(6):1456-65.
44. Rogers MJ, Matheson L, Garrard B, Maher B, Cowdery S, Luo W, et al. Comparison of outcomes for cancer patients discussed and not discussed at a multidisciplinary meeting. Public Health. 2017;149:74-80.
45. Tsai CH, Hsieh HF, Lai TW, Kung PT, Kuo WY, Tsai WC. Effect of multidisciplinary team care on the risk of recurrence in breast cancer patients: A national matched cohort study. Breast. 2020;53:68-76.
46. Lu J, Jiang Y, Qian M, Lv L, Ying X. The Improved Effects of a Multidisciplinary Team on the Survival of Breast Cancer Patients: Experiences from China. Int J Environ Res Public Health. 2019;17(1).
47. Cufer T, Kosty MP, Curriculum Development Subgroup EAGCWG. ESMO/ASCO Recommendations for a Global Curriculum in Medical Oncology Edition 2023. JCO Glob Oncol. 2023;9:e2300277.
48. Freeman RK, Ascioti AJ, Dake M, Mahidhara RS. The Effects of a Multidisciplinary Care Conference on the Quality and Cost of Care for Lung Cancer Patients. Ann Thorac Surg. 2015;100(5):1834-8; discussion 8.
49. Tan I. Towards Globalization of Indonesian Multidisciplinary Head and Neck Surgery and Oncology. . UGM, Pidato Pengukuhan Jabatan Guru Besar pada Fakultas Kedokteran, Universitas Gadjah Mada. 2007.
50. Taroeno-Hariadi KW, Herdini C, Briliant AS, Husodoputro HK, Dhamiyati W, Indrasari SR, et al. Multidisciplinary Team Meeting in the Core of Nasopharyngeal Cancer Management Improved Quality of Care and Survival of Patients. Health Serv Insights. 2023;16:11786329231204757.
51. de Castro G, Jr., Souza FH, Lima J, Bernardi LP, Teixeira CHA, Prado GF, et al. Does Multidisciplinary Team Management Improve Clinical Outcomes in NSCLC? A Systematic Review With Meta-Analysis. JTO Clin Res Rep. 2023;4(12):100580.
52. Rizky D, Yunarvika V, Putra YR, Pangarsa EA, Kartiyani I, Panunggal DG, et al. Impact of independent multidisciplinary work on the survival rate of stage 3 and 4 nasopharyngeal cancer in Indonesia: a retrospective cohort study. Ann Med Surg (Lond). 2023;85(9):4248-55.
53. Taberna M, Gil Moncayo F, Jane-Salas E, Antonio M, Arribas L, Vilajosana E, et al. The Multidisciplinary Team (MDT) Approach and Quality of Care. Front Oncol. 2020;10:85.
54. Koco L, Weekenstroo HHA, Lambregts DMJ, Sedelaar JPM, Prokop M, Futterer JJ, et al. The Effects of Multidisciplinary Team Meetings on Clinical Practice for Colorectal, Lung, Prostate and Breast Cancer: A Systematic Review. Cancers (Basel). 2021;13(16).
55. Pangarsa EA, Rizky D, Tandarto K, Setiawan B, Santosa D, Hadiyanto JN, et al. The effect of multidisciplinary team on survival rates of women with breast cancer: a systematic review and meta-analysis. Ann Med Surg (Lond). 2023;85(6):2940-8.

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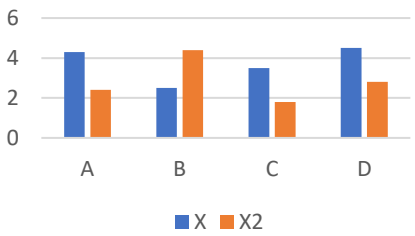

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