



THE INDONESIAN JOURNAL OF CANCER CONTROL

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Jakarta, September – December 2025

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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.

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Keratoses Immunotherapy for Breast Cancer: How Far Have We Come?

Breast cancer remains the most prevalent cancer in Indonesia and worldwide. It is one of the oldest documented diseases, as recorded in the ancient Egypt in The Edwin Smith Surgical Papyrus (3,000–2,500 B.C.). Centuries later, the modern era of breast cancer treatment began to take shape with William Halsted's introduction of radical mastectomy in the late nineteenth century. Systemic therapy such as Methotrexate and Fluorouracil were first used first in the 1950s to treat breast cancer.

Since then, our understanding of breast cancer has evolved dramatically. What was once regarded largely as a single disease defined by its anatomical origin is now recognized as a biologically and molecularly heterogeneous group of malignancies. This understanding has led to more precise therapeutic strategies, from endocrine therapy, HER2-targeted treatment, antibody-drug conjugates, to immunotherapy

Just like any other novel treatment, initially immunotherapy was studied for the treatment of metastatic, triple negative disease. After the evidence of benefit of immune checkpoint inhibitors (ICI) has been proven in the advanced disease settings, the use was expanded to adjuvant and neoadjuvant settings. Moreover, there are trials underway that explore the use of ICI in hormone receptor positive and/or HER2 positive diseases.

The landscape of immunotherapy encompasses a broad range of approaches, from ICIs combined with chemotherapy to emerging combinations with PARP inhibitors, anti-HER2 therapies, and antibody-drug conjugates. The evidence is growing and we are

waiting for the matured results of the study to be able to use them in daily practice. Other often-overlooked immunotherapeutic approaches for breast cancer include breast cancer vaccines and adoptive cell therapies. Neither has achieved the same degree of success like in other type of cancers. However, scientists are still working on developing these immunotherapies to treat breast cancer.

In conclusion, breast cancer is a very heterogeneous disease and humans have tried to develop many modalities to treat the debilitating disease. Current strategy with available evidence placed immunotherapy as one of the treatment regimens in advanced and early disease, especially triple negative breast cancer.

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Systemic inflammation response index as a predictor of distant metastasis in breast cancer patients

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Abstract

Introduction: The Systemic Inflammation Response Index (SIRI) reflects systemic inflammation and immune response. Elevated SIRI has been linked to poor cancer outcomes by promoting tumor progression and metastasis. This study evaluates the relationship between pre-treatment SIRI and distant metastasis in breast cancer patients.

Methods: This retrospective cross-sectional study analyzed medical records of breast cancer patients at Margono Soekarjo Country Hospital between 2022 and 2024, with 869 patients included for analysis. Pre-treatment SIRI was calculated from complete blood count parameters. Metastatic status was confirmed by imaging and/or histopathology. SIRI was defined as neutrophils and monocytes divided by lymphocytes. Statistical analyses included comparison of SIRI between metastatic and non-metastatic groups, ROC analysis, and multivariable logistic regression to evaluate the discriminative ability and independent association of SIRI with distant metastasis, adjusting for age, histopathological type, and molecular subtype.

Results: Pre-treatment SIRI was significantly higher in the metastatic group than in the non-metastatic group (mean $\pm$ SD: 2.49 ± 2.68 vs. 0.41 ± 0.49 ; $p < 0.001$). ROC analysis identified an optimal SIRI cut-off of >0.60 , yielding 86% sensitivity, 85% specificity, and an AUC of 0.90, indicating excellent discriminatory performance. In multivariable logistic regression, higher SIRI independently predicted distant metastasis after adjustment of the confounding factors, with each one-unit increase associated with substantially increased odds (adjusted OR = 12.28; 95% CI: 8.22–18.33; $p < 0.001$).

Conclusion: Pre-treatment SIRI showed an association with distant metastasis in breast cancer, indicating its potential as a low-cost and non-invasive prognostic biomarker.

Keywords: Breast cancer, Distant Metastasis, Prognostic Biomarker, Systemic Inflammation Response Index (SIRI)

Abstrak

Pendahuluan: Systemic Inflammation Response Index (SIRI) mencerminkan inflamasi sistemik dan respons imun. Peningkatan SIRI telah dikaitkan dengan luaran kanker yang buruk melalui perannya dalam mendorong progresi tumor dan metastasis. Penelitian ini mengevaluasi hubungan antara SIRI sebelum terapi dan metastasis jauh pada pasien kanker payudara.

Metode: Penelitian potong lintang retrospektif ini menganalisis rekam medis pasien kanker payudara di RSUD Prof. Dr. Margono Soekarjo pada periode 2022–2024, dengan total 869 pasien yang diikutsertakan dalam analisis. SIRI sebelum terapi dihitung berdasarkan parameter pemeriksaan darah lengkap. Status metastasis dikonfirmasi melalui pemeriksaan pencitraan dan/atau histopatologi. SIRI didefinisikan sebagai jumlah neutrofil dikalikan monosit, kemudian dibagi limfosit. Analisis statistik meliputi perbandingan nilai SIRI antara kelompok metastasis dan nonmetastasis, analisis ROC, serta regresi logistik multivariat untuk mengevaluasi kemampuan diskriminatif dan hubungan independen SIRI dengan metastasis jauh, dengan penyesuaian terhadap usia, tipe histopatologi, dan subtype molekuler.

Hasil: Nilai SIRI sebelum terapi secara signifikan lebih tinggi pada kelompok metastasis dibandingkan kelompok nonmetastasis (rerata $\pm$ SD: $2,49 \pm 2,68$ vs. $0,41 \pm 0,49$; $p < 0,001$). Analisis ROC mengidentifikasi nilai cut-off SIRI optimal $>0,60$, dengan sensitivitas 86%, spesifisitas 85%, dan AUC 0,90, yang menunjukkan kemampuan diskriminatif yang sangat baik. Pada regresi logistik multivariat, SIRI yang lebih tinggi secara independen memprediksi metastasis jauh setelah dilakukan penyesuaian terhadap faktor-faktor perancu, dengan setiap peningkatan satu unit SIRI berhubungan dengan peningkatan odds yang substansial (adjusted OR = 12,28; 95% CI: 8,22–18,33; $p < 0,001$).

Kesimpulan: SIRI sebelum terapi menunjukkan hubungan dengan metastasis jauh pada kanker payudara, yang mengindikasikan potensinya sebagai biomarker prognostik yang murah dan noninvasif.

Kata kunci: Kanker payudara, metastasis jauh, biomarker prognostik, Systemic Inflammation Response Index (SIRI)

Background

Breast cancer is the most frequently diagnosed cancer among women worldwide, accounting for more than 10% of all newly diagnosed cancer cases annually. It is also the second leading cause of cancer-related morbidity and mortality.¹ According to the GLOBOCAN 2020 database, approximately 2,261,419 new cases of breast cancer and 684,996 breast cancer-related deaths were reported globally.² Breast cancer is a biologically heterogeneous disease that can be classified into four major molecular subtypes based on hormone receptor and human epidermal growth factor receptor 2 (HER2) status, namely luminal A, luminal B, HER2-overexpressing, and triple-negative breast cancer, each associated with distinct clinical behaviors and prognostic outcomes.³ Despite advances in diagnosis and treatment, distant metastasis remains the principal cause of breast cancer-related mortality, underscoring the need for reliable biomarkers to identify patients at high risk of metastatic progression.

Chronic inflammation has been increasingly recognized as a critical driver of cancer progression, contributing to tumor proliferation, invasion, immune evasion, and metastatic dissemination. Inflammation-based biomarkers derived from peripheral blood parameters have gained attention due to their accessibility and potential clinical utility. Recent studies have demonstrated that the systemic inflammation response index (SIRI), a blood-based inflammatory biomarker, has significant prognostic value in predicting clinical outcomes in various solid tumors.³ Since its introduction as a prognostic marker in pancreatic cancer in 2016, SIRI has demonstrated prognostic value across various solid malignancies.⁴ In breast cancer, however, existing studies evaluating SIRI have produced inconsistent results. Some studies have reported that elevated SIRI is significantly associated with poorer overall and disease-free survival. Wang et al. (2020) reported that breast cancer patients with a SIRI ≤ 0.65 had significantly better overall survival than those with a SIRI > 0.65 ($P < 0.001$).⁵ Similarly, Zhu et al. (2022) found that patients with low SIRI had longer disease-free survival (41.50 vs. 37.63 months) and overall survival (64.57 vs. 58.42 months) compared with those with high SIRI.⁶ The others have failed to demonstrate a significant prognostic. These discrepancies may be explained by heterogeneity in study populations, molecular subtypes, disease stages, treatment strategies, SIRI cut-off values, and selected clinical endpoints. Importantly, most previous investigations have focused primarily

on survival outcomes, whereas the predictive role of SIRI for distant metastasis remains insufficiently explored. To the best of our knowledge, this study is among the first to specifically evaluate the systemic inflammation response index as a predictor of distant metastasis in breast cancer patients. By focusing on metastatic outcomes rather than survival alone, this study aims to address an important gap in the literature and to clarify the clinical utility of SIRI as a simple and reliable biomarker for metastatic risk stratification.

Methods

This retrospective cross-sectional study was conducted using medical record data from breast cancer patients treated at Margono Soekarjo County Hospital between January 2022 and December 2024. A total of 4,432 breast cancer patients were identified; 869 were eligible, including 520 patients with distant metastasis and 349 patients with non-distant metastasis. Eligible patients had a histopathological confirmation and immunohistochemical examination of breast cancer, available complete blood count (CBC) data obtained prior to any treatment, and documented evaluation of metastasis. The presence of distant metastasis was confirmed through imaging modalities and/or histopathological examination. Patients with incomplete clinical data or missing pre-treatment laboratory results were excluded.

The systemic inflammation response index (SIRI) was calculated for each patient using pre-treatment CBC parameters. SIRI was defined as the product of neutrophil and monocyte counts divided by the lymphocyte count (neutrophils $\times$ monocytes / lymphocytes). All hematological parameters were obtained from routine laboratory examinations performed at the time of diagnosis, prior to the initiation of systemic or local cancer therapy.

Patients were categorized into metastatic and non-metastatic groups based on the presence of distant metastasis at diagnosis. Comparative analyses were performed to evaluate differences in SIRI values between the two groups. Receiver operating characteristic (ROC) curve analysis was used to assess the discriminative ability of SIRI in predicting distant metastasis and to determine the optimal cut-off value, based on the highest Youden index.

To identify whether SIRI was independently associated with distant metastasis, multivariable logistic regression analysis was conducted. Potential confounding variables included in the model were age, tumor

stage, and breast cancer receptor subtype. Results were reported as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). A p-value of <0.05 was considered statistically significant. Statistical analyses were performed using appropriate statistical software.

Results

Patients were categorized into metastatic and non-metastatic groups. The baseline characteristics of the study population are summarized in Table 1. Age did not differ significantly between the distant and non-distant metastasis groups (51 ± 11 vs. 52 ± 10 years; $p = 0.063$). Histopathological type showed a significant difference in distribution between groups ($p < 0.001$), with invasive ductal cancer being the most common histology in both groups (70% vs. 68%), followed by invasive lobular cancer, mixed histology, NST, and other types in smaller proportions. Molecular subtype distribution also differed significantly ($p < 0.001$); luminal A was the predominant subtype in the non-distant metastasis group (52% vs. 18%), whereas luminal B, HER2-positive, and triple-negative subtypes accounted for a larger proportion of cases in the distant metastasis group. Median pre-treatment SIRI was significantly higher in patients with distant metastasis than in those without (1.72 [IQR 2.04] vs. 0.27 [IQR 0.28]; $p < 0.001$).

Table 1. Characteristics of patients

Variable	Distant Metas n (%)	Non-Distant n (%)	p-value
Number of patients	520	349	
Age (mean $\pm$ SD)	51 ± 11	52 ± 10	
Age Group			0.063
<40 years	77(15)	33(9)	
40–50 years	171(33)	118(34)	
>50 years	272(52)	198(57)	
Histopathology type			<0.001
IDC	363(70)	239(68)	
ILC	56(11)	58(17)	
Mixed	28(5)	31(9)	
NST	53(10)	15(4)	
Others	20(4)	6(2)	
Molecular subtype			<0.001
Luminal A	93(18)	182(52)	
Luminal B	173(33)	95(27)	
HER2 Positive	105(20)	45(13)	
Triple Negative	149(29)	27(8)	
SIRI (Median, IQR)	1.72, 2.04	0.27, 0.28	<0.001

IDC : Invasive Ductal Carcinoma, ILC : Invasive Lobular Carcinoma, Mixed : IDC + ILC, NST : No Special Type, Others : tubular, medular, mucinous, cribriform, papillary, micropapillary, and Paget disease. (%) : percentage within each group

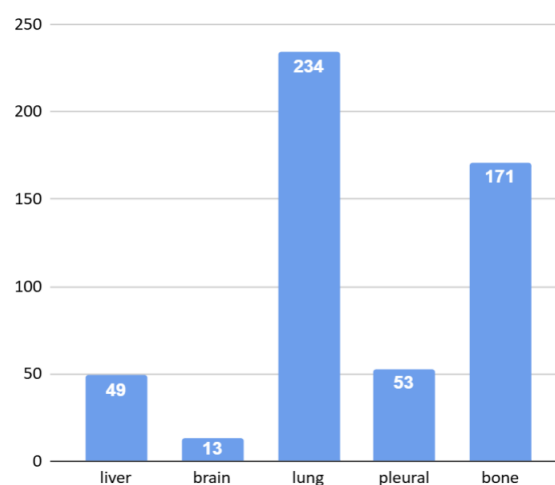


Figure 1. Distant metastasis distribution

The distribution of distant metastatic sites among breast cancer patients is illustrated in Figure 1. The lung was the most common site of distant metastasis, observed in 234 patients, followed by bone metastasis in 171 patients. Pleural involvement was identified in 53 patients, while liver metastasis was present in 49 patients. Brain metastasis was the least frequent, occurring in 13 patients. Overall, pulmonary and skeletal sites accounted for the majority of distant metastatic involvement in this study.

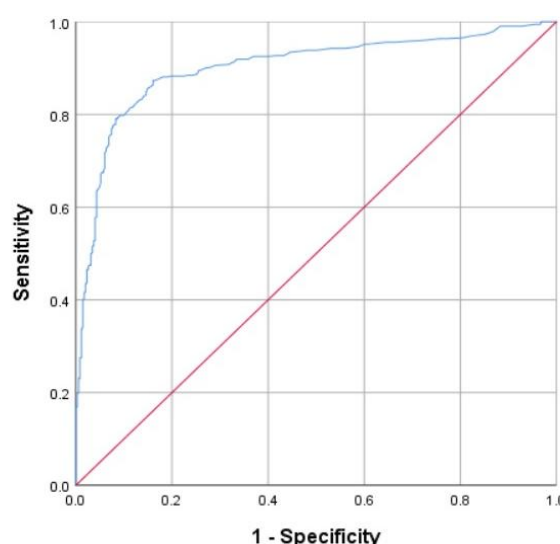


Figure 2. ROC Curve

Receiver operating characteristic (ROC) curve analysis demonstrated that the systemic inflammation response index (SIRI) had strong discriminatory ability for predicting the presence of distant metastasis in breast cancer patients. The optimal cut-off value was identified as $\text{SIRI} > 0.60$, which yielded a sensitivity of 86% and a specificity of 85%. The area under the ROC curve (AUC) was 0.90 (Figure 2), indicating very good diagnostic performance and clinically relevant discrimination between metastatic and non-metastatic disease.

Pre-treatment SIRI values were significantly higher in patients with distant metastasis compared with those without metastasis ($p < 0.001$). The distant metastatic group had a mean SIRI of 2.49 (SD = 2.68), whereas the non-distant metastatic group had a lower mean SIRI of 0.41 (SD = 0.49), indicating a markedly increased systemic inflammatory response among patients with metastatic disease.

Multivariable logistic regression analysis demonstrated that higher SIRI levels were independently associated with an increased likelihood of distant metastasis after adjustment for age, histological type, and molecular subtype. SIRI was analyzed as a continuous variable in the multivariable model. Each one-unit increase in SIRI was associated with a more than twelve-fold increase in the odds of distant metastasis (adjusted OR = 12.28; 95% CI: 8.22–18.33; $p < 0.001$). Age was inversely associated with distant metastasis (adjusted OR = 0.71; 95% CI: 0.54–0.93; $p = 0.014$), while histological type (adjusted OR = 1.23; 95% CI: 1.03–1.48; $p = 0.023$) and molecular subtype (adjusted OR = 2.01; 95% CI: 1.66–2.42; $p < 0.001$) were also identified as independent predictors of distant metastasis. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the discriminatory performance of SIRI. However, ROC-derived SIRI cut-off values were used for exploratory purposes only and were not applied to define categorical variables in the primary multivariable analysis.

Discussion

The systemic inflammation response index (SIRI), which integrates neutrophil and monocyte counts relative to lymphocytes, reflects the balance between tumor-promoting inflammation and anti-tumor immune surveillance. In the present study, an elevated SIRI was associated with adverse clinic-pathological features and poorer outcomes, supporting its role as a prognostic biomarker. Our findings

highlight the relevance of systemic inflammation in the metastatic process of breast cancer. Based on the distribution illustrated in Figure 1, metastatic involvement was grouped into lung, pleural, liver, brain, and bone sites. Patients with distant metastasis exhibited significantly higher SIRI values compared with non-metastatic patients (median 1.72 vs 0.27, $p < 0.001$), suggesting that a heightened inflammatory state may facilitate tumor dissemination. High SIRI indicates pro-tumorigenic inflammation, in which neutrophils promote invasion and metastasis while monocytes differentiate into tumor-associated macrophages (TAMs) that foster progression; lymphocytes provide anti-tumor immunity. Neutrophils promote invasion, angiogenesis, and metastatic niche formation, while circulating monocytes can differentiate into TAMs that support tumor progression and immune evasion. Conversely, lymphocytes play a central role in antitumor immunity, and reduced lymphocyte counts reflect impaired immune surveillance. Together, these mechanisms provide a biological rationale for the observed association between elevated SIRI and distant metastasis.⁷

Our study reported that SIRI and distant metastases were related with the p -value of < 0.001 . Further multivariable analysis was performed to adjust for potential confounders. Higher SIRI was independently associated with a more than twelve-fold increase in the odds of distant metastasis for each one-unit increase in SIRI (adjusted OR 12.28; 95% CI 8.22–18.33; $p < 0.001$). As shown in Figure 2, the ROC curve demonstrates strong discriminative performance. The sensitivity reached 86% and the specificity 85%. The area under the ROC curve (AUC) was 0.90, indicating that the model has good-to-excellent accuracy in distinguishing between outcome groups.

Previous studies have explored the prognostic value of SIRI in breast cancer, particularly in relation to treatment response and survival outcomes. Pre-treatment SIRI was a more crucial and integral prognostic index for patients with breast malignant tumors receiving neoadjuvant chemotherapy (NACT).⁸ It may assist clinicians in predicting patient prognosis and in evaluating treatment response. In this context, a SIRI threshold of 0.72 demonstrated significant predictive value for response to NACT, particularly in relation to pathological complete response (pCR).^{8,9} Conversely, higher SIRI levels were associated with poorer survival outcomes as well as more advanced tumor and nodal stages. In a

2025 study of 348 breast cancer patients (185 non-metastatic, 163 distant metastatic), Boruta and LASSO analyses identified SIRI as one of five key biomarkers (with ALI, MLR, AGR, GNRI) for distant metastasis risk. Elevated SIRI independently increased metastasis odds (OR 1.38 per standardized unit, 95% CI: 1.05–1.81), with median SIRI higher in metastatic cases (0.98 vs. 0.80). ROC analysis showed moderate predictive accuracy (AUC 0.608, cutoff 0.974). These findings are consistent with previous studies in breast cancer cohorts, which have reported SIRI cutoff values ranging from 0.65 to 0.80, further underscoring the relevance of SIRI as an inflammation-based prognostic indicator.¹⁰

The median age of the patients was 52 years. Participants were stratified by age into reproductive stage: <40 years (predominantly reproductive age), 40–50 years (perimenopausal transition), and >50 years (predominantly postmenopausal). The relationship between age and SIRI may be influenced by multiple sources of bias, including comorbid conditions, chronic low-grade inflammation associated with aging, hormonal status, and non-cancer-related inflammatory processes. Importantly, to date, no studies have reported a strong, direct positive or negative correlation between SIRI and age specifically within distant metastatic breast cancer populations, highlighting a relevant research gap and underscoring the need for further focused investigation.³ This study reported that histological type emerged as an independent predictor of distant metastasis after multivariable adjustment (adjusted OR = 1.23; 95% CI 1.03–1.48; $p = 0.023$). Although the magnitude of association was modest compared with SIRI and molecular subtype, this finding suggests that tumor histology contributes independently to metastatic potential. No study related to SIRI and histopathological subtype. Variations in tumor architecture, stromal interaction, and patterns of local invasion across histological subtypes may underlie these differences in metastatic behavior.

Invasive ductal carcinoma (IDC) constituted the majority of cases, consistent with prior epidemiological reports, while invasive lobular carcinoma (ILC) and mixed histologies accounted for smaller proportions. Previous studies have shown that ILC, despite often presenting with favorable receptor profiles, may exhibit distinct metastatic patterns and delayed dissemination, which could partially explain its independent association with distant metastasis. The relatively weaker effect size observed in this study suggests that histological type is a contributory

factor rather than a dominant determinant of metastatic risk, particularly when systemic inflammatory burden and molecular characteristics are taken into account.¹¹

Molecular subtype demonstrated a strong and statistically significant association with distant metastasis (adjusted OR = 2.01; 95% CI 1.66–2.42; $p < 0.001$), underscoring its central role in breast cancer progression. This finding aligns with established evidence that intrinsic tumor biology, reflected by hormone receptor and HER2 status, critically influences metastatic behavior and clinical outcomes. Previous findings showed that patients with ER/PR-negative status had a higher proportion of high SIRI (25.0% and 23.0%, respectively) compared with those with ER/PR-positive status (11.6% and 10.4%; $P = 0.005$ and $P = 0.006$, respectively).¹² As in this study, the analyses were performed based on molecular subtypes rather than individual biomarkers (ER, PR, HER2, and Ki-67), because molecular subtyping represents an integrated biological classification that reflects tumor hormone dependency, proliferative activity, and oncogenic signaling pathways.

More aggressive subtypes, particularly HER2-positive and triple-negative breast cancers, are known to exhibit higher proliferative activity, genomic instability, and early metastatic spread, which is consistent with the elevated odds observed in this study. In contrast, luminal subtypes, especially luminal A, generally demonstrate more indolent disease courses and lower metastatic potential. The robust independent effect of molecular subtype in our multivariable model highlights that biological aggressiveness remains a key driver of distant metastasis, even after adjusting for histology and systemic inflammatory markers such as SIRI.^{11, 13, 14}

Meta-analyses show elevated SIRI links to larger tumors (T3-T4 OR=1.73), advanced stages, and poor OS across breast cancer, with subtype-specific prognostic roles (e.g., stronger in HER2+).³ Direct SIRI-histopathological type correlations remain unreported in metastatic breast cancer, focusing instead on prognostic independence. Increased neutrophil and monocyte counts may promote tumor progression by secreting pro-inflammatory cytokines, angiogenic factors, and immunosuppressive mediators, while reduced lymphocyte levels reflect impaired antitumor immunity. This inflammatory milieu may contribute to chemotherapy resistance and aggressive tumor behavior, explaining the observed association between high SIRI and unfavorable treatment

response and prognosis. As SIRI is derived from routine complete blood count parameters, it represents a low-cost, readily available, and non-invasive biomarker that can be easily implemented in daily clinical practice. Elevated SIRI at diagnosis may help identify patients who require more intensive metastatic workup, closer surveillance, or earlier systemic treatment strategies, particularly in resource-limited settings.

Nevertheless, several limitations should be acknowledged. The retrospective nature of the study precludes definitive conclusions regarding causality. Differences in study populations, endpoints, and analytical methods across existing studies limit direct generalizability and highlight the need for standardized cutoff calibration. Furthermore, non-cancer-related inflammatory conditions, including infections and concomitant medications such as corticosteroids, as well as the timing of blood sample collection, may influence SIRI values and introduce potential confounding. In addition, molecular subtypes were analyzed as composite categories rather than being stratified by individual biomarkers (ER, PR, HER2, and Ki-67), which may have obscured the independent contribution of each biomarker and introduced residual bias. Further research is needed to validate SIRI as a robust prognostic predictor through prospective, multicenter studies with standardized cutoff calibration. Longitudinal assessment of SIRI during treatment may provide additional prognostic value by capturing dynamic changes in systemic inflammation and immune status. Moreover, integrating SIRI with established clinicopathological factors, molecular subtypes, and genomic biomarkers could enhance prognostic stratification and support more individualized treatment decision-making.

Conclusion

Pre-treatment SIRI was associated with the presence of distant metastasis in breast cancer, supporting its potential as a practical, low-cost, and non-invasive prognostic biomarker. SIRI may be considered as an adjunct parameter in initial clinical assessment to support risk stratification. Further prospective multi-center studies are warranted to validate its clinical utility and determine an optimal cut-off before broader implementation.

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Conflict of Interests

The authors declare no conflicts of interest. The authors had full access to all study data and took responsibility for the integrity and accuracy of the analysis.

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Treatment options after PD-1/PDL-1 inhibitors in dMMR/MSI-H colorectal cancer: A systematic review

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Abstract

Background: Colorectal cancer (CRC) remains a leading cause of cancer-related mortality. Approximately 13% of CRCs are microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR), resulting in high tumor mutational burden and immunogenicity. These tumors are particularly responsive to programmed cell death protein 1 (PD-1) or programmed death-ligand 1 inhibitors (PD-L1). However, despite the durable responses, up to one-third experience progression due to primary or acquired resistance. The optimal management strategy following progression on PD-1/PD-L1 inhibitors remains undefined.

Results: A total of 504 studies were identified, one retrospective cohort study and eight case reports met inclusion criteria, comprising 38 patients with metastatic MSI-H/dMMR CRC. All studies demonstrated a low risk of bias. The cohort study reported limited efficacy of chemotherapy (ORR 13%, median PFS 2.9

Objective: This systematic review summarizes current and emerging treatment options in this setting.

Methods: A systematic search was performed. Eligible studies included case reports and observational studies of MSI-H/dMMR CRC patients who progressed on PD-1/PD-L1 blockade and received subsequent chemotherapy, targeted therapy, or combination immunotherapy. Risk of bias was assessed using the Joanna Briggs Institute checklist for case reports and the Newcastle–Ottawa Scale for cohort studies.

months, OS 7.4 months), whereas combination regimens especially PD-1 with bevacizumab or CTLA-4 blockade yielded durable responses up to 12–36 months. Most adverse events were manageable.

Conclusion: Following progression on PD-1/PD-L1 inhibitors, conventional chemotherapy offers modest benefit, whereas combination strategies integrating immunotherapy or anti-angiogenic agents show greater and durable efficacy.

Keywords: MSI-H/dMMR colorectal cancer, PD-1/PD-L1 inhibitor, post-PD-1 progression, treatment options

Abstrak

Latar Belakang: Kanker kolorektal (*colorectal cancer*/CRC) masih menjadi salah satu penyebab utama kematian terkait kanker. Sekitar 13% kasus CRC memiliki *microsatellite instability-high* (MSI-H) atau *mismatch repair-deficient* (dMMR), yang menyebabkan tingginya beban mutasi tumor dan imunogenisitas. Tumor ini sangat responsif terhadap inhibitor *programmed cell death protein 1* (PD-1) atau *programmed death-ligand 1* (PD-L1). Meskipun respons yang dihasilkan dapat bertahan lama, hingga sepertiga pasien mengalami progresi akibat resistensi primer maupun didapat. Strategi tata laksana optimal setelah progresi dengan inhibitor PD-1/PD-L1 masih belum ditetapkan.

Tujuan: Tinjauan sistematis ini merangkum pilihan terapi terkini dan terapi yang sedang berkembang pada kondisi tersebut.

Metode: Penelusuran sistematis dilakukan untuk mengidentifikasi penelitian yang relevan. Studi yang memenuhi kriteria meliputi laporan kasus dan studi observasional pada pasien CRC MSI-H/dMMR yang mengalami progresi setelah terapi penghambatan PD-1/PD-L1 dan selanjutnya mendapatkan kemoterapi, terapi target, atau imunoterapi kombinasi. Risiko bias dinilai menggunakan Joanna Briggs Institute checklist untuk laporan kasus dan Newcastle–Ottawa Scale untuk studi kohort.

Hasil: Sebanyak 504 studi teridentifikasi, dan satu studi kohort retrospektif serta delapan laporan kasus memenuhi kriteria inklusi, dengan total 38 pasien CRC metastatik MSI-H/dMMR. Seluruh studi menunjukkan risiko bias yang rendah. Studi kohort melaporkan efektivitas kemoterapi yang terbatas (ORR 13%, median PFS 2,9 bulan, OS 7,4 bulan), sedangkan regimen kombinasi, terutama PD-1 dengan bevacizumab atau penghambatan CTLA-4, menghasilkan respons yang bertahan lama hingga 12–36 bulan. Sebagian besar efek samping dapat ditangani.

Kesimpulan: Setelah terjadi progresi dengan inhibitor PD-1/PD-L1, kemoterapi konvensional memberikan manfaat yang terbatas, sedangkan strategi kombinasi yang mengintegrasikan imunoterapi atau agen antiangiogenik menunjukkan efektivitas yang lebih baik dan respons yang lebih bertahan lama.

Kata kunci: inhibitor PD-1/PD-L1, kanker kolorektal MSI-H/dMMR, pilihan terapi, progresi pasca-PD-1

Background

Colorectal cancer (CRC) is one of the most common malignancies worldwide, ranking third in incidence and a leading cause of cancer-related mortality.¹ Approximately 13% of CRCs exhibit microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR), resulting from inactivation of mismatch repair genes such as *MLH1*, *MSH2*, *MSH6*, and *PMS2*.² These defects lead to an accumulation of DNA replication errors and a hypermutated phenotype, which generates a high neoantigen load and increases tumor immunogenicity.³ As a result, MSI-H/dMMR tumors are particularly responsive to immune checkpoint blockade targeting the PD-1/PD-L1 pathway.

Pembrolizumab, an immunotherapy targeting PD-1, became the first-line standard of care (SOC) for patients with unresectable or metastatic MSI-H/dMMR CRC following the results of the phase III KEYNOTE-177 trial. In this study, pembrolizumab demonstrated a median progression-free survival (PFS) of 16.5 months compared to 8.2 months with chemotherapy (HR 0.60, 95% CI: 0.45–0.80; $p = 0.0004$), and durable overall survival (OS) benefits with more than five years of follow-up. Importantly, median OS was over twice as long for patients treated with pembrolizumab, despite a 62% cross-over rate from chemotherapy. Pembrolizumab also showed a favorable safety profile, with fewer grade 3–4 adverse events compared to standard chemotherapy regimens.^{4,5}

Despite the remarkable efficacy of pembrolizumab in patients with dMMR/MSI-H metastatic colorectal cancer, a subset of patients still experiences disease progression, suggesting that intrinsic or acquired resistance mechanisms may occur even in this highly immunogenic tumor subtype. In the phase III KEYNOTE-177 trial, approximately 29% of patients experienced primary disease progression, highlighting that not all dMMR/MSI-H CRCs respond to PD-1 blockade and that a proportion may harbor resistance to anti-PD-1 monotherapy.⁵ The CheckMate 142 study investigated combination immunotherapy with nivolumab and ipilimumab and demonstrated improved outcomes compared with PD-1 inhibition alone. In the first-line treatment cohort, only 13% of patients experienced direct progression on the combination, while in previously treated cohorts, the rate of progression was 12% with nivolumab plus ipilimumab compared to 26% with nivolumab monotherapy. These results suggest that dual

checkpoint blockade may help overcome some mechanisms of resistance seen with single-agent PD-1 therapy.⁶ However, these studies largely included immunotherapy-naïve patients, limiting their applicability to those progressing after pembrolizumab.

Currently, no established treatment guidelines exist for patients who progress following pembrolizumab or other PD-1/PD-L1 inhibitors. Ongoing clinical trials such as NIPIRESCUE (NCT05310643), and those evaluating novel bispecific antibodies like cadonilimab are investigating new strategies to overcome resistance and improve outcomes in this challenging clinical setting. Therefore, this systematic review aims to summarize current and emerging treatment options for patients with dMMR/MSI-H CRC after progression on pembrolizumab, focusing on efficacy, safety, and reported adverse events to guide future therapeutic directions.

Materials and Methods

This systematic review was registered in the PROSPERO database (registration number: [CRD420251-175508](#)) and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive literature search was performed between September and October 2025 with no restriction on publication date.

Search Strategy

Electronic databases including PubMed, ProQuest, ScienceDirect, and ClinicalTrials.gov were systematically searched. The search strategy combined Medical Subject Headings (MeSH) and free-text terms related to microsatellite instability-high or mismatch repair-deficient colorectal cancer and treatment resistance after pembrolizumab. The main search keywords were: ("MSI-H COLORECTAL CANCER" OR "dMMR COLORECTAL CANCER") AND ("pembrolizumab") AND ("progression" OR "resistance" OR "refractory") AND ("nivolumab" OR "pembrolizumab" OR "PD-1/PDL-1 Inhibitors" OR "chemotherapy" OR "treatment options" OR "clinical trial" OR "FOLFIRI" OR "FOLFOX" OR "CAPEOX" OR "irinotecan" OR "Trifluridine/tipiracil" OR "Targeted Therapy" OR "Encorafenib" OR "Trastuzumab" OR "pertuzumab" OR "Sotorasib" OR "Larotrectinib" OR "lenvatinib"). Additional searches were performed using the following terms to ensure comprehensive coverage: ("MSI-H COLORECTAL CANCER" OR

"dMMR COLORECTAL CANCER") AND ("pembrolizumab") AND ("progression") AND ("IMMUNOTHERAPY" OR "chemotherapy" OR "treatment options" OR "clinical trial" OR "SECOND LINE").

Inclusion and Exclusion Criteria

Studies were included if they involved patients with dMMR or MSI-H CRC who had previously received pembrolizumab or another PD-1/PD-L1 inhibitor or Ipilimumab or another Anti-CTLA-4 and reported outcomes, safety, or adverse events of subsequent systemic therapies such as chemotherapy, immunotherapy, or targeted therapy. Eligible study designs included randomized controlled trials (RCTs), retrospective cohorts, case series, case reports, and conference abstracts published in English. Studies were excluded if they specifically excluded patients with prior PD-1 or PD-L1 blockade, were preclinical or non-human studies, or did not provide original data such as reviews or commentaries.

Study Selection and Data Extraction

Three independent authors performed data extraction from all the included studies into a pre-piloted data extraction form in Microsoft Excel. The following was extracted from each study:

- General study information: author and year of publication, study design, and country or study location.
- Participant characteristics: patient age, sex, comorbidities, family history or hereditary cancer syndrome, and primary tumor location.
- Disease characteristics: stage at diagnosis, sites of metastasis, and molecular profiles including *BRAF*, *KRAS/NRAS* mutations, HER2 status, PD-L1 expression, and tumor mutational burden (TMB).
- Treatment history: prior lines of therapy (e.g., FOLFOX, FOLFIRI, CAPEOX, PD-1/PDL-1 inhibitors), treatment response to previous regimens, and time to progression on PD-1/PDL-1 inhibitors.
- Subsequent therapy and outcomes: type and duration of subsequent therapy, response to subsequent therapy, time to response, progression-free survival (PFS), overall survival (OS), and disease status at last follow-up.
- Safety outcomes: occurrence, grade, and management of adverse events.

Results

A total of 504 records were retrieved across databases (PubMed: 14; ProQuest: 293; ScienceDirect: 185; ClinicalTrials.gov: 12). After removing duplicates and screening titles and abstracts, studies that did not include patients with prior PD-1/PD-L1 exposure were excluded. Ultimately, 9 studies met the eligibility criteria and were included in the final analysis. The included studies consisted of eight case reports and one retrospective cohort study, representing approximately 38 patients with dMMR/MSI-H metastatic colorectal cancer (mCRC) who progressed after PD-1/PD-L1 inhibitor therapy. (Figure 1)

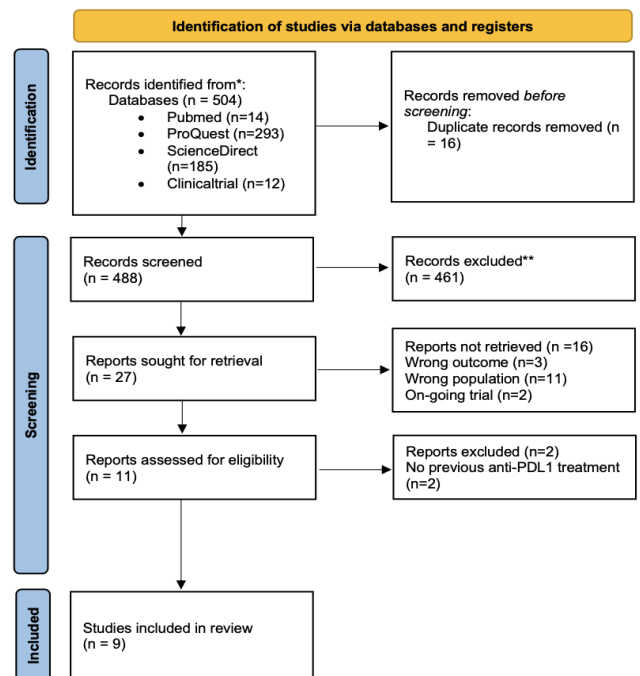


Figure 1: PRISMA flowchart outlining study search

Study Characteristics

Most of the studies included in this review were individual case reports, with one retrospective cohort study, highlighting the limited yet detailed clinical evidence available for MSI-H/dMMR colorectal cancer (CRC). The reported patient ages ranged from 39 to 84 years. The majority of cases presented with advanced-stage disease, most commonly Stage IV, and tumors were predominantly located in the right-sided or sigmoid colon, consistent with the proximal predilection typically observed in MSI-

H/dMMR CRC. Several cases demonstrated underlying hereditary cancer syndromes, particularly Lynch syndrome, or carried germline alterations in mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*), reinforcing the established link between MMR gene dysfunction and microsatellite instability.

Across the included studies, molecular analyses revealed that BRAF V600E and RAS mutations were among the most frequently reported alterations. Additional mutations, including *PTEN*, *TP53*, *CDH1*, and *BRCA1*, were also identified, reflecting the genetic heterogeneity of this subgroup (Table 1).⁷⁻¹⁵

Synthesis of Result

The majority of included studies described patients who had previously received PD-1 or PD-L1 inhibitors, either as monotherapy or in combination with CTLA-4 blockade, typically following first-line fluoropyrimidine-based chemotherapy. The time to progression after initial immune checkpoint inhibition (ICI) varied considerably, ranging from 1.5 to 24 months. Subsequent treatment approaches included chemotherapy rechallenge (FOLFIRI, FOLFOX, or trifluridine/tipiracil-based regimens), targeted agents such as encorafenib or trastuzumab-based combinations, and dual immune checkpoint blockade in select cases.

Chemotherapy remained the most frequently adopted approach after ICI progression. In the largest cohort by Bui et al. (2021), standard regimens such as FOLFOX, FOLFIRI, or trifluridine–tipiracil, often combined with bevacizumab or cetuximab, yielded modest efficacy outcomes (ORR 13%, DCR 45%, median PFS 2.9 months, and OS 7.4 months). Nevertheless, a small proportion of patients (13%) achieved durable disease control beyond 16 months, suggesting possible residual chemosensitivity or immune-mediated enhancement of response. Similarly, Hamre et al. (2021) described temporary disease stabilization with FOLFIRI plus bevacizumab before transitioning to dual ICI, indicating that cytotoxic therapy may still provide transient benefit in this context.¹²

Rechallenge with immunotherapy represented a notable strategy in several reports. Das et al. (2020), Chow et al. (2023), and Hamre et al. (2021) observed renewed tumour control following nivolumab and ipilimumab after PD-1/PDL-1 inhibitor failure, achieving partial or durable responses lasting 9 to 20 months.^{11,12,14} In Geusens et al. (2024), pembrolizumab rechallenge after resolution of immune-related haemophagocytic lymphohistiocytosis (HLH) demonstrated feasibility and transient benefit without recurrence of severe toxicity.⁹ These findings support the rationale for ICI rechallenge or combination blockade in selected patients with manageable prior immune toxicity and preserved performance status.

Encouraging results were also reported with immunotherapy–anti-angiogenic combinations, suggesting potential synergy. Huang et al. (2025) documented a complete and sustained response exceeding three years with camrelizumab plus bevacizumab, while Maggadottir et al. (2024) reported radiological necrosis and disease stabilization with Radium-223 TCR T-cell therapy, underscoring the promise of cellular immunotherapy in post-ICI settings.^{7,10} Overall, treatment responses across studies were heterogeneous but tended to be durable in-patient receiving combination or dual-ICI regimens. Adverse events, including arthralgia, pneumonitis, and HLH, were reported but were generally manageable with corticosteroids or treatment interruption, and no fatal toxicities occurred upon rechallenge. These collective findings highlight the need for prospective evaluation of optimal sequencing and combination strategies in MSI-H/dMMR CRC following ICI progression.

Risk of Bias

All included studies demonstrated a low risk of bias. However, four case reports provided insufficient details on immune-related adverse events (irAEs), merely stating that treatment was well tolerated without clear documentation of monitoring or adverse-event grading. Table 1 and 2 summarize the overall risk of bias of all included studies. (Table 3 & Table 4)

Table 1. Patient Characteristics

First Author	Study Design	Age	Family History/ Hereditary Syndrome	Primary Tumor Location	Stage at Diagnosis	Mutations
Huang 2025 ⁷	Case Report	40	MLH-1 and PMS-2 deficient	Sigmoid colon	Stage IV	KRAS mutation
Li. 2025 ⁸	Case Report	84	MLH1 (-), PMS2 (-), MSH2 (+), and MSH6 (+)	Right side colon	Stage IV	mutations in PTEN, TP53, and CDH1
Geusens 2024 ⁹	Case Report	48	MSI-H / dMMR (loss of MSH6)	Sigmoid colon	Stage IV	RAS/BRAF wild type
Maggadottir 2024 ¹⁰	Case Report	42	Lynch Syndrome	Colon	Stage IV	N/A
Chow 2023 ¹¹	Case Report	45	MLH1(-) and PMS2 expression	Ascending colon right side	Stage IIIB	N/A
Hamre 2021 ¹²	Case Report	53	N/A	Colon	Stage IV	BRAF V600E mutation
Schuler 2021 ¹³	Case Report	N/A	MLH1 (-)& PMS2 (-)	Right sided colon	Stage IIIC	BRAF V600E mutation
Das 2020 ¹⁴	Case Report	39	MSI-H with loss of MSH2 and MSH6	Colon	Stage IV	BRCA1 mutation reported
Bui 2021 ¹⁵	Cohort Retrospective	Median 56	Lynch syndrome 39%, Sporadic 29%	colon and rectum	Stage IV	RAS-mutated = 8 (26%) BRAF-mutated = 8 (26%) RAS&BRAF = 1 (3%) RAS/BRAF wild-type = 14 (45%).

Table 2. Treatment after PD-1/PDL-1 Progression

First Author	Prior Lines of Therapy	Time to Progression After PD-1/PDL-1 Inhibitors	Subsequent treatment	Response to subsequent treatment	Results	Adverse Events
Huang 2025 ⁷	Chemotherapy (Oxaliplatin/ capecitabine), Immunotherapy (PD-1 inhibitor)	1.5 months	Immunotherapy (PD-1 Inhibitor) + Anti-VEGF antibody	6 months to PR	PFS 3 years and ongoing OS: Alive at last report	N/A
Li. 2025 ⁸	Chemotherapy (Capecitabine), Anti-VEGF antibody, immunotherapy (PD-1 Inhibitor)	Immediately	Palliative	N/A	OS: 9 months.	N/A
Geusens 2024 ⁹	Immunotherapy (PD-1 Inhibitor)	9 months	Chemotherapy (FOLFOX, FOLFIRI) + Anti-EGFR antibody	PR initially after pembrolizumab rechallenge	PFS : 9 months from pembrolizumab initiation OS: Alive at last report	Grade 4 (life-threatening immune-related event)
Maggadottir 2024 ¹⁰	Chemotherapy (capecitabine/FOLFOX/ FOLFIRI), , Immunotherapy (PD-1 inhibitor)	24 months	Radium-1 TCR T-cell therapy	10 weeks post-treatment completion (radiologic evidence of necrosis)	Stable disease for 4 months post-treatment OS: 6 months (190 days) after completion of T-cell therapy	Grade 1 Low-grade fever and chills post-infusion; mild transient cholestasis and pruritus due to tumor compression
Chow 2023 ¹¹	Chemotherapy (FOLFOX/FOLFIRI), Anti-VEGF antibody, Immunotherapy (PD-1 inhibitor)	2 months	Immunotherapy Combination (PD-1 + CTLA-4 inhibitor)	2 months	PFS: ≥20 months OS: Alive at last report	N/A
Hamre 2021 ¹²	Chemotherapy (capecitabine/FOLFOX/ FOLFIRI)Immunotherapy (PD-1 inhibitor)	15 months	Chemotherapy (FOLFIRI) + Anti-VEGF antibody + Immunotherapy combination (PD-1 and CTLA-4 inhibitor)	Approximately 2 months (early symptomatic and biochemical improvement)	PFS: ≥18 months (ongoing) OS: ≥52 months since initial diagnosis; alive at last follow-up	Grade 1 (rash), Grade 2–3 (pneumonitis)
Schuler 2021 ¹³	Chemotherapy (Oxaliplatin/ capecitabine), Immunotherapy (PD-1 inhibitor)	After 3 doses of pembrolizumab	Chemotherapy (FOLFIRI)	After 2 courses SD	PFS: Ongoing complete remission as of last reported OS: Alive at last report	N/A
Das 2020 ¹⁴	Chemotherapy (capecitabine/FOLFOX/ FOLFIRI), , Immunotherapy (PD-1 inhibitor)	9,5 months	Immunotherapy combination (PD-1 and CTLA-4 inhibitor)	First radiologic improvement (20% reduction) at first post-combo scan (3 months after starting combo) and confirmed PR by 5 months	At least ≥5 months (time from start of combo to last reported follow-up with PR) and exact PFS not matured in report. OS: Alive at last report	Grade 2 (arthralgias on pembrolizumab).
Bui 2021 ¹⁵	Chemotherapy (capecitabine/FOLFOX/ FOLFIRI), Anti-VEGF antibody, Anti-EGFR antibody, Immunotherapy (PD1/PDL1 inhibitors)	Median duration: 5.6 months	Chemotherapy (FOLFOX, FOLFIRI 29 %, Trifluridine–tipiracil 16 %) + Anti-VEGF antibody 39 % + Anti-EGFR antibody 19 %	NR (within first 2–3 months for PD)	PFS: Median 2.9 months OS: Median 7.4 months	N/A

Table 3. Risk of Bias Assessment using Joanna Briggs Institute Critical Appraisal for Case Reports

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Risk of Bias
Huang 2025	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Li. 2025	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Low
Geusens 2024	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Maggadottir 2024	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Low
Chow 2023	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Low
Hamre 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Schuler 2021	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Low
Das 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low

Table 4. Risk of Bias Assessment using Newcastle-Ottawa Scale for Cohort Studies

Study	Selection				Comparability	Outcome			Risk of Bias
	#1	#2	#3	#4	#5	#6	#7	#8	
Bui 2021	**	N/A	**	**	*	**	**	**	Low

Discussion

The advent of immune checkpoint inhibitors (ICIs) targeting PD-1 and PD-L1 has substantially altered the therapeutic landscape of MSI-H or dMMR CRC. Despite the remarkable and durable responses observed in a subset of patients, a proportion eventually experiences disease progression, either due to primary resistance or acquired immune escape. The optimal management strategy following progression on pembrolizumab or other PD-1/PD-L1 inhibitors remains poorly defined. Several pieces of evidence will highlight the diversity of post-immunotherapy treatment approaches and their associated outcomes.

Standard Chemotherapy

Among the identified studies, the most frequently employed treatment strategies after progression on PD-1 blockade included cytotoxic chemotherapy, immune-based combination regimens, and targeted or experimental therapies. Chemotherapy may enhance the effects of prior immunotherapy by

increasing tumor antigen presentation, upregulating co-stimulatory molecules (e.g., B7-1), downregulating inhibitory checkpoints (e.g., PD-L1, B7-H4), and rendering tumor cells more susceptible to T-cell-mediated cytotoxicity. Prior exposure to anti-PD-1 therapy could therefore prime T cells and transiently improve responsiveness to subsequent chemotherapy, although this effect remains inconsistent in real-world settings.¹⁶ In a retrospective cohort by Bui et al. (2021), patients treated with standard regimens such as FOLFOX, FOLFIRI, or trifluridine–tipiracil achieved a disease control rate (DCR) of 45%, with median progression-free survival (PFS) and overall survival (OS) of 2.9 and 7.4 months, respectively. Similarly, another study reported a DCR of 58%, median PFS of 3.8 months, and OS of 8 months following chemotherapy post-ICI exposure.¹⁷ Collectively, these findings suggest that while chemotherapy retains modest antitumor activity after immune-therapy failure, its clinical benefits are generally limited and short-lived in this molecular setting.

Rechallenge of Immunotherapy

The findings in this study suggest that dual immune checkpoint blockade may reinduce antitumor immunity in selected patients. Several case reports and retrospective analyses have highlighted the potential benefit of combining or sequencing immunotherapeutic agents after resistance to ICI. Rechallenge strategies may involve single-agent or combination approaches, though no dedicated clinical trials have yet evaluated this in CRC. Evidence from other malignancies, such as melanoma and non-small cell lung cancer (NSCLC), shows mixed outcomes with immunotherapy rechallenge. Reuse of the same anti-CTLA-4 or anti-PD-1/PD-L1 agents yields modest efficacy (ORR 11–53%, DCR 47–83%), while switching between PD-1/PD-L1 inhibitors produces inconsistent results, likely due to small cohorts. Cross-class rechallenge appears more favorable, as patients previously treated with anti-CTLA-4 therapy achieved higher response rates (22–36%) to subsequent anti-PD-1/PD-L1 therapy than the reverse sequence ($\leq 22\%$), suggesting that overcoming tumor microenvironmental immunosuppression is key. Combination rechallenge using anti-PD-1 plus anti-CTLA-4 has shown improved responses and survival in some settings, though results remain heterogeneous.¹⁸ Another study found that single-agent rechallenge achieved comparable ORR and DCR to initial therapy but yielded longer PFS and OS than in patients who permanently discontinued ICIs across NSCLC, melanoma, and renal cell carcinoma.¹⁹

Several case reports further support these findings. Re-challenge with dual checkpoint blockade (e.g., nivolumab plus ipilimumab) or switching between anti-PD-1 agents was associated with disease stabilization or partial responses in selected cases.¹⁴ Another case report reported in which the combination of camrelizumab and bevacizumab resulted in a complete and durable response exceeding three years.⁷ These outcomes suggest that modulation of the tumor microenvironment through anti-angiogenic agents may restore or enhance immune responsiveness in dMMR/MSI-H tumors previously resistant to PD-1 blockade.

Similarly, the case described by Hamre et al. (2021) demonstrated that subsequent chemotherapy with FOLFIRI and bevacizumab achieved prolonged disease stability exceeding 18 months, potentially reflecting immune priming or “chemosensitization” induced by

prior immunotherapy exposure. Collectively, these observations indicate that the integration of ICIs with agents targeting angiogenesis or cytotoxic mechanisms warrants further investigation in this setting.

Targeted therapy

Targeted therapies used in CRC include anti-VEGF agents, anti-EGFR agent, BRAF and MEK pathway inhibitor, and Her2-targeted therapy. This review showed a combination of immunotherapy with anti-angiogenic therapy reported a complete and sustained response exceeding three years with camrelizumab plus bevacizumab. Anti-VEGF agents help restore normal tumor vasculature, improve oxygen delivery, facilitate immune-cell entry, and convert the immunosuppressive tumor milieu into one more favorable for immunotherapy.²⁰ Studies that investigate this combination have been shown to be favorable in other types of cancer, including lung cancer, hepatocellular carcinoma, gastric cancer, and cervical cancer.²¹

EGFR-TKIs indirectly strengthen anti-tumor immune responses and counteract immunosuppression in the tumor microenvironment, creating a rationale for combining targeted agents with immunotherapies. However, the combination of anti-EGFR and immunotherapy in CRC is yet to be explored. This combination has also been explored in NSCLC, which showed favorable results, though associated with serious adverse events and lack of definitive studies.²²

BRAF and MEK inhibitors exert potent antitumor effects by suppressing tumor cell proliferation and inducing apoptosis while enhancing tumor immunogenicity, providing a biological rationale for their combination with immunotherapy. However, no clinical evidence currently supports this strategy in colorectal cancer.²³ Preliminary studies in melanoma suggest that combining BRAF/MEK inhibitors with ICIs may yield durable responses in anti-PD-1–refractory cases, although outcomes appear comparable to those achieved with dual ICI therapy as subsequent therapy.^{24,25}

Combining HER2-targeted therapy with PD-1/PD-L1 inhibitors leverages HER2 blockade–induced immune activation and prevents PD-L1–mediated adaptive resistance, resulting in a more sustained and potent anti-tumor immune response.²⁶ This combination has been shown in the KEYNOTE-811 study, which showed improved ORR in gastric cancer.²⁷

Cellular Immunotherapy

Beyond conventional therapies, adoptive cellular immunotherapy has emerged as a promising modality for patients with ICI-refractory MSI-H/dMMR CRC. Maggadottir et al. (2024) reported temporary disease stabilization following treatment with TCR-engineered T-cell therapy, highlighting the potential of personalized T-cell-based strategies to overcome immune escape. Although such therapies remain investigational, they underscore the growing emphasis on individualized and mechanistically guided immunotherapeutic interventions for this subset.

Beyond conventional therapies, adoptive cellular immunotherapy has emerged as a promising modality for patients with ICI-refractory MSI-H/dMMR colorectal cancer. Genetically engineered T-cell receptor (TCR)-T therapies leverage patient-derived T cells re-programmed to recognize neo-antigen peptides presented on MHC, offering the potential to overcome immune-escape mechanisms inherent in these high-mutation-burden tumours. Early clinical experience in MSI-H CRC demonstrates feasibility and safety of TCR-T approaches, albeit with limited durability of response. Reviews of engineered T cells in colorectal cancer highlight the mechanistic rationale and key challenges (e.g., antigen heterogeneity, tumour microenvironment suppression) of translating this modality into meaningful outcomes in solid tumours.²⁸

Although still investigational, TCR-T therapy underscores the growing emphasis on individualized and mechanistically guided immunotherapeutic interventions for this subset of CRC. Continued development of neoantigen-specific TCRs, improved T-cell persistence, and combination strategies to optimize the tumour environment may help unlock its full potential in the post-PD-1/PD-L1 inhibitor setting.

Clinical and Safety Outcomes

Clinical outcomes following post-ICI treatment were heterogeneous across studies. Objective response rates ranged from 13% in the larger retrospective series to complete and durable responses in isolated cases. PFS varied widely, from approximately three months to several years, reflecting the diversity of interventions and patient populations. Notably, durable responses were more frequently observed in those receiving immune-based or anti-angiogenic combinations rather than cytotoxic chemotherapy alone.

Treatment-related adverse events were generally mild to moderate (Grade 1–2) and manageable with supportive measures and corticosteroids. Immune-related toxicities, including rash, arthralgia, and pneumonitis, were infrequent and did not preclude continued therapy in most cases, supporting the feasibility of combination or sequential approaches following prior ICI exposure.

Clinical Implication

The limited and variable activity of chemotherapy following PD-1 blockade raises the possibility that the immunologic landscape of dMMR/MSI-H CRC changes after ICI resistance. Mechanisms such as antigenic loss, mutations in interferon signaling pathways, or T-cell exclusion may contribute to therapeutic failure. Consequently, strategies aiming to reverse immune resistance through reactivation of exhausted T cells, modulation of the tumor vasculature, or recruitment of innate immunity represent a rational next step in the evolution of treatment paradigms for this population.

Limitations

The current body of evidence remains constrained by small sample sizes, retrospective designs, and the predominance of anecdotal reports. The heterogeneity in treatment regimens and reporting standards further limits the comparability of outcomes. Nevertheless, the collective findings emphasize that chemotherapy retains modest activity, while immunotherapy-based combinations and emerging cellular approaches hold promise for achieving durable control after PD-1 inhibitor failure.

Future prospective studies should aim to stratify patients by molecular mechanisms of resistance, incorporate translational endpoints, and evaluate rational combinations of immunotherapy, targeted agents, and cytotoxic chemotherapy. Such efforts will be essential to optimize post-ICI therapeutic sequencing and to extend survival for patients with dMMR/MSI-H metastatic CRC.

Conclusion

This systematic review highlights the paucity of evidence and absence of standardized treatment strategies for patients with MSI-H/dMMR colorectal cancer who progress following PD-1/PD-L1 inhibitor therapy. Across available studies, chemotherapy provides only modest and short-lived benefits,

whereas combination strategies integrating checkpoint blockade, anti-angiogenic agents, or targeted therapies yield more durable responses in selected cases. Rechallenge with immunotherapy particularly dual checkpoint inhibition appears feasible and may restore anti-tumour activity in a subset of patients, although robust predictive markers remain undefined. Emerging evidence also supports the potential of adoptive cellular immunotherapies, such as TCR-engineered T-cell therapy, as novel approaches to overcome immune resistance in this setting. However, their clinical application remains experimental and confined to early-phase studies. Collectively, these findings underscore the need for prospective, biomarker-driven trials to elucidate mechanisms of ICI resistance and to establish optimized therapeutic sequencing following PD-1/PD-L1 inhibitor failure in MSI-H/dMMR colorectal cancer.

Author Contributions

MT, ALS, FP contributed to the study design, data collection, data extraction, and analysis. MT, ALS, FP wrote the first draft of the manuscript and edited the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Infiltrative basal cell carcinoma of the scalp: Five-month post-excision follow-up with z-plasty reconstruction

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Abstract

Introduction: Basal cell carcinoma (BCC) is the most common non-melanoma skin cancer, accounting for 75–80% of cases. Although typically slow-growing and rarely metastatic, certain histological variants, such as infiltrative BCC, can exhibit aggressive local behaviour and high recurrence risk. Commonly associated with prolonged ultraviolet exposure, BCC may also arise from non-traditional risk factors such as chronic trauma.

Case Illustration: We report a case of infiltrative BCC on the scalp of a 48-year-old male physician with a history of chronic trauma. The lesion evolved over three years from a 0.5 cm pruritic, erythematous papule into a 2.2 cm ulcerated nodule. The patient underwent wide local excision and Z-plasty reconstruction. Histopathology revealed basaloid cell nests infiltrating the dermis with fibrotic stroma, consistent with the infiltrative subtype. At five-month follow-up, the surgical site had healed, but a new erythematous papule was noted, raising concern for recurrence. The patient denied systemic symptoms but reported mild pruritus.

Discussion: This case highlights an unusual presentation of BCC in a non-sun-exposed region, possibly triggered by chronic mechanical irritation. Infiltrative BCC is characterized by its subclinical extension and higher recurrence rates. Subtle changes at post-operative sites may indicate early recurrence, necessitating vigilant long-term follow-up. Clinical examination, dermoscopy, and histopathological confirmation are essential for early detection and intervention.

Conclusion: Infiltrative BCC can present in atypical locations and behave aggressively despite initial treatment. Early recognition and multidisciplinary follow-up are key to optimizing outcomes and preventing recurrence.

Keywords: basal cell carcinoma, chronic trauma, recurrence, scalp, skin neoplasms

Abstrak

Pendahuluan: Karsinoma sel basal (KSB) merupakan kanker kulit non-melanoma yang paling sering dijumpai, mencakup sekitar 75–80% dari seluruh kasus. Meskipun umumnya tumbuh lambat dan jarang bermetastasis, beberapa varian histologis tertentu, seperti KSB tipe infiltratif, dapat menunjukkan perilaku lokal yang agresif serta risiko kekambuhan yang tinggi. KSB umumnya berhubungan dengan paparan sinar ultraviolet jangka panjang, namun dapat pula muncul akibat faktor risiko non-tradisional, seperti trauma kronis.

Ilustrasi Kasus: Kami melaporkan suatu kasus KSB infiltratif pada kulit kepala seorang laki-laki berusia 48 tahun dengan riwayat trauma kronis. Lesi berkembang selama tiga tahun, bermula dari papul eritematosa pruritik berukuran 0,5 cm menjadi nodul ulseratif berdiameter 2,2 cm. Pasien menjalani eksisi lokal luas diikuti dengan rekonstruksi Z-plasti. Pemeriksaan histopatologi menunjukkan sarang sel basaloid yang menginfiltrasi dermis dengan stroma fibrotik, sesuai dengan sub tipe infiltratif. Pada evaluasi lima bulan pasca-operasi, area pembedahan telah sembuh, namun ditemukan papul eritematosa baru yang menimbulkan kecurigaan terhadap kekambuhan. Pasien tidak mengeluhkan gejala sistemik, tetapi melaporkan pruritus ringan.

Diskusi: Kasus ini menyoroti presentasi KSB yang tidak lazim pada area yang tidak terpapar sinar matahari, yang kemungkinan dipicu oleh iritasi mekanik kronis. KSB infiltratif ditandai oleh perluasan subklinis dan angka kekambuhan yang lebih tinggi. Perubahan klinis yang samar pada area pasca-operasi dapat menjadi tanda awal kekambuhan, sehingga diperlukan pemantauan jangka panjang yang ketat. Pemeriksaan klinis, dermoskopi, serta konfirmasi histopatologis merupakan komponen penting dalam deteksi dini dan penatalaksanaan yang tepat.

Kesimpulan: KSB infiltratif dapat muncul pada lokasi atipikal dan menunjukkan perilaku agresif meskipun telah dilakukan terapi awal. Pengenalan dini serta tindak lanjut multidisiplin berperan penting dalam mengoptimalkan luaran klinis dan mencegah kekambuhan.

Kata kunci: karsinoma sel basal, neoplasma kulit, rekurensi, skalp, trauma kronik

Introductions

Basal cell carcinoma (BCC) is a low-grade, slow-growing cutaneous neoplasm that arises from the basal layer of the epidermis and invades surrounding tissue.¹ It accounts for approximately 75–80% of non-melanoma skin cancers (NMSC). The incidence of BCC has risen significantly over the past three decades, with reports suggesting a 20–80% increase. Men are more frequently affected than women, and individuals with fair skin are at higher risk than those with darker skin tones.²

Clinically, BCC typically appears as a shiny, pink papule or nodule with surface telangiectasia. While metastasis is rare, BCC can be highly destructive and disfiguring if not treated adequately.³ Pathogenesis commonly involves mutations in the Hedgehog signaling pathway, particularly in the patched 1 (PTCH1) gene, which encodes a receptor for the sonic hedgehog ligand. Dysregulation of this pathway contributes significantly to carcinogenesis in BCC.⁴

Primary risk factors for BCC include prolonged ultraviolet (UV) exposure, genetic predisposition, arsenic ingestion, ionizing radiation, and chronic trauma. Treatment selection depends on histologic subtype, anatomical location, patient comorbidities, and recurrence risk. Surgical excision with clear margins remains the gold standard, especially for high-risk tumors. Mohs micrographic surgery is preferred in cosmetically sensitive or high-recurrence areas due to superior tissue preservation and cure rates. Other treatment options include topical agents for superficial BCC, radiation therapy for inoperable tumors, and Hedgehog pathway inhibitors such as vismodegib or sonidegib for advanced cases.^{5,6} This case highlights an unusual anatomical and etiological presentation of infiltrative BCC in a non-sun-exposed scalp region, while also reinforcing the importance of early recognition of potential recurrence and the critical role of multidisciplinary follow-up.

Case Illustration

A 48-year-old male physician presented with a lesion on the scalp, initially noticed three years prior as 0.5 cm shiny, erythematous papule that was intensely pruritic, leading to repeated scratching. Over time, the lesion ulcerated, bled intermittently, and progressively enlarged. The patient denied significant sun exposure due to routine helmet use while commuting and denied any family history of malignancy. He reported

no systemic symptoms such as weight loss, fever, or lymphadenopathy.

Clinical examination revealed a 2.2 cm translucent nodular lesion with central ulceration and telangiectasia (Figure 1). There were no palpable lymph nodes. The patient underwent wide local excision with 4 mm margins, followed by rotational Z-plasty flap closure. Histological analysis revealed nests and cords of basaloid cells infiltrating the dermis, with peripheral palisading, peritumoral clefting, and surrounding fibrotic stroma. Mitoses were present, consistent with infiltrative BCC (Figure 4). Sutures were removed one month post-operatively, with no signs of infection or dehiscence (Figure 2).



Figure 1. Pre-operative lesion on occipital region



Figure 2. One-month post-operative appearance

At the five-month follow-up, the patient reported occasional mild pruritus and discomfort at the scar site. He denied the appearance of new lesions. But physical examination showed a well-healed Z-shaped scar with a new erythematous papule at the surgical site (Figure 3). The patient had been self-medicating with an herbal supplement and declined

topical scar treatments. He was advised to continue routine dermatological follow-up, avoid scratching the lesion site, and use protective equipment during his work.



Figure 3. Five-month post-operative appearance

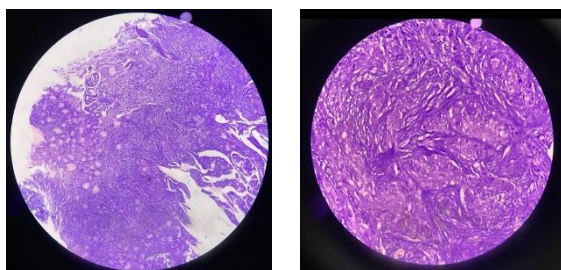


Figure 4. Histopathological appearance under 10x and 40x magnification

Discussion

Infiltrative BCC is a histologically aggressive variant characterized by deeply penetrating cords of tumor cells, often with indistinct clinical margins. Compared to nodular or superficial subtypes, infiltrative BCC has a higher rate of subclinical spread and recurrence.⁷ This case highlights the importance of long-term surveillance following surgical excision of high-risk BCC, particularly in patients with aggressive histological features (infiltrative subtypes) and lesions exceeding 2 cm in diameter.⁸ At five months post-operatively, the patient presented with intermittent pruritus and pain at the surgical site. Physical examination revealed a new erythematous papule within the post-operative scar, raising clinical concern for possible recurrence or post-surgical reactive changes.

The recurrence rate of BCC varies based on multiple factors including tumor subtype, location, size, treatment modality, and margin status. Lesions on high-risk sites (nose, periorbital region, ears), positive surgical margins, immunosuppression, and prior incomplete treatment increase recurrence likelihood. Infiltrative BCCs excised with inadequate margins can recur in up to 40–50% of cases.⁹

Although the patient exhibited no systemic symptoms or palpable lymphadenopathy, any new lesion arising within or adjacent to a surgical scar warrants thorough evaluation. Subtle findings—such as: (1) New papule, nodule, or plaque at the surgical site, (2) Hypertrophic or keloid-like scar changes, (3) Telangiectasia, erythema, or shiny "waxy" appearance, (4) Pruritus, tenderness, or ulceration, (5) Scar thickening, margin irregularity or rolled edges—may represent early signs of recurrence. While residual or recurrent BCC typically presents within the first three years post-treatment, high-risk histologic subtypes like infiltrative BCC tend to recur earlier and more insidiously than nodular or superficial variants. The infiltrative subtype, characterized by irregular tumor margins and deeper dermal invasion, often evades clear excision margins and is associated with increased local recurrence rates, particularly if histologic clearance is not achieved.¹⁰

Close dermatologic follow-up, including dermoscopic examination and possible re-biopsy of suspicious lesions, is essential to confirm or exclude recurrence.¹¹ Imaging modalities such as high-frequency ultrasound or reflectance confocal microscopy may be considered in ambiguous cases, particularly in cosmetically sensitive or surgically altered areas.¹² In this case, the patient was referred back to a dermatologist for further evaluation of the erythematous papule to ensure timely detection and intervention.

Beyond clinical monitoring, patient education plays a pivotal role in recurrence prevention and early detection. Primary risk factor likely contributed to BCC development in this case is chronic mechanical trauma from repeated scratching. The underlying pathomechanism of trauma-induced BCC remains unclear.¹³ Experimental studies by Wong et al. and Kasper et al. have demonstrated that wound healing environments can facilitate tumorigenesis in genetically predisposed cells. PTCH1 and SMO mutations are commonly implicated in sporadic BCC, leading to unchecked Hedgehog pathway

activation.^{14,15} Thus, the patient was counseled to avoid scratching the surgical site and to monitor for any new or evolving skin changes. Lastly, diagnosis of recurrence is based on a combination of clinical evaluation, dermoscopy, and, when indicated, histopathology or imaging.

Conclusion

Infiltrative BCC can arise in atypical, non-sun-exposed locations and may be associated with less common risk factor such as chronic trauma. This case underscores the aggressive nature of infiltrative BCC and the need for wide excision, individualized surgical planning, and vigilant long-term follow-up. Even in the absence of systemic symptoms, subtle changes at the surgical site (such as a new papule) may signal early recurrence. Clinicians should maintain a high index of suspicion and educate patients on scar surveillance to optimize outcomes and prevent delay in re-intervention.

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Conflict of Interests

The authors declare no conflict of interest.

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Cutaneous squamous cell carcinoma on infraauricular region: A case report at Dr. Sardjito Hospital, Yogyakarta

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Abstract

Introduction: Cutaneous squamous cell carcinoma (cSCC) is a type of skin cancer commonly found in sun-exposed areas with a high risk of tissue invasion and metastasis. Managing cSCC in the head and neck requires both surgical and non-surgical approaches, especially in aggressive cases involving sensitive areas like the ears and neck.

Case Illustration: A 39-year-old woman had a wound below her left ear that progressed into a lump over the past two months. After undergoing a biopsy, she was referred to Dr. Sardjito General Hospital in Yogyakarta. The patient only complained of decreased appetite due to a discomfort in her left jaw. Physical examination revealed a hyperpigmented mass with an ulcer on its surface in the left infraauricular region, measuring 7 x 5 cm, along with left-sided level IIb cervical lymphadenopathy. Histopathological examination confirmed the presence of Keratinizing Squamous Cell Carcinoma (SCC), pT3N1M0. The patient underwent surgery with wide excision accompanied by radical neck dissection (RND), followed by wound reconstruction using a rotational skin flap.

Discussion: cSCC is a form of skin cancer with a relatively high prevalence. cSCC remains invasive and prone to recurrence, especially in high-risk cases. Diagnosis of cSCC is made through histopathological examination and imaging, while primary management involves surgery, such as wide excision or Mohs Micrographic Surgery (MMS). In high-risk cSCC cases, additional procedures like Radical Neck Dissection (RND) are often required to reduce the risk of regional recurrence, non-surgical therapies may be considered as adjuvant treatments to improve overall survival.

Conclusion: The presence of lymph node and other organ involvement is a special consideration in patients with cSCC of the head and neck region who will undergo surgical procedures in the form of wide excision and RND.

Keywords: cutaneous squamous cell carcinoma, head and neck cancer, metastasis, wide excision

Abstrak

Pendahuluan: Cutaneous Squamous Cell Carcinoma (cSCC) adalah kanker kulit agresif yang sering muncul pada area terpapar matahari seperti kepala-leher, dengan risiko tinggi invasi jaringan dan metastasis. Penanganannya memerlukan pendekatan multidisiplin bedah maupun non-bedah, terutama pada kasus risiko tinggi di area sensitif.

Laporan Kasus: Seorang wanita berusia 39 tahun dirujuk ke RSUP Dr. Sardjito dengan keluhan benjolan di bawah telinga kiri dalam dua bulan terakhir yang mengganggu nafsu makan akibat rasa mengganjal di rahang. Pemeriksaan fisik menunjukkan massa hiperpigmentasi berukuran 7 x 5 cm dengan ulkus di regio infraaurikula sinistra dan limfadenopati colli sinistra level IIb. Pemeriksaan pencitraan menunjukkan keterlibatan nodal regional tanpa metastasis jauh, sementara histopatologi mengonfirmasi Keratinizing Squamous Cell Carcinoma stadium pT3N1M0. Pasien menjalani eksisi luas disertai Radical Neck Dissection (RND), dilanjutkan rekonstruksi menggunakan kulit flap.

Diskusi: cSCC memiliki prevalensi tinggi pada area yang kronis terpapar sinar ultraviolet. Faktor risiko utama mencakup status immunocompromised dan lesi prekursor. Meski tidak seagresif melanoma, cSCC risiko tinggi bersifat invasif dan rentan rekurensi. Diagnosis ditegakkan melalui histopatologi dan pencitraan. Tatalaksana utamanya adalah pembedahan seperti eksisi luas atau Mohs Micrographic Surgery. Pada kasus dengan keterlibatan nodal, prosedur tambahan RND sangat krusial untuk mengontrol penyebaran lokoregional, sedangkan terapi ajuvan seperti radioterapi atau kemoterapi dapat dipertimbangkan guna meningkatkan kesintasan pasien.

Kesimpulan: Keterlibatan limfonodi regional menjadi pertimbangan khusus yang krusial pada pasien cSCC kepala-leher yang menjalani eksisi luas dan RND demi mengoptimalkan kontrol lokoregional.

Kata kunci: eksisi luas, kanker kepala dan leher, karsinoma sel skuamosa kutan, metastasis

Background

Masses in the head and neck region are commonly encountered in both pediatric and adult populations. In children, infection is the most frequent underlying etiology. Conversely, in the adult population, head and neck masses are primarily driven by malignancy. Consequently, the presence of a head and neck mass in an adult patient must be presumed malignant until proven otherwise.¹

Although most head and neck cancers (HNC) originate from primary head and neck organs—such as the oropharynx, nasopharynx, thyroid, or presenting as lymphoma—some cases arise from other tissues, with the skin being a notable example.² Cutaneous Squamous Cell Carcinoma (cSCC) is the second most common non-melanoma skin cancer after Basal Cell Carcinoma (BCC). It accounts for approximately 20% of all skin malignancies and is responsible for 75% of all skin cancer-related mortalities. The incidence of cSCC has been steadily rising each year, driven by an aging population and increased exposure to risk factors such as ultraviolet radiation, smoking, human papillomavirus (HPV) infection, and immunosuppressive states.³

The predilection sites for cSCC typically involve chronically sun-exposed areas, including the scalp, ears, cheeks, forehead, temples, nose, and mouth. However, cases occurring in other parts of the body are also frequently documented.⁴ Generally, cSCC presents as a slow-growing, wart-like skin lesion that may or may not be painful. In Bowen's disease or bowenoid papulosis, the lesions usually manifest as hyperpigmented papules, whereas epidermodysplasia verruciformis typically presents as flat skin lesions. A highly aggressive variant of cSCC is the Marjolin's ulcer, which develops from chronic wounds or scars. Aggressive cSCC is characterized by a diameter > 2 cm, depth > 5 mm, high recurrence rates, perineural invasion, and locoregional metastasis.⁵

Given the high mortality rate associated with cSCC, prompt diagnosis and appropriate treatment are mandatory to prevent progression and recurrence. The primary management for head and neck cSCC typically involves wide local excision (extirpation), with adjuvant radiotherapy indicated for cases exhibiting high-risk histopathological features or nodal involvement.⁴⁻⁶

Surgical management and subsequent reconstruction of head and neck cSCC, particularly in the infra-

auricular and external ear regions, pose unique challenges. This is due to the aggressive nature of the lesion, which can invade underlying tissues up to the cranium, infiltrate the facial nerve (CN VII) leading to facial palsy, and metastasize to the cervical lymph nodes and parotid gland. Considering these challenges, we present a case report highlighting the successful excision of an infra-auricular cSCC combined with a Radical Neck Dissection (RND) in an adult patient.

Case Illustration

A 39-year-old woman presented with a chief complaint of a lump below her left ear that had developed over the past two months. Initially, the lesion appeared as a small erosion measuring 0.5 × 0.5 cm, which then widened by approximately one fingerbreadth within a week. Over the last month, the lesion became increasingly prominent. The complaint was not accompanied by pain or fever. For the past 1.5 months, the patient had been receiving treatment at Pura Raharja Hospital, where she underwent a biopsy procedure and was prescribed analgesics. She was subsequently referred to Dr. Sardjito General Hospital, Yogyakarta, for further management.



Figure 1. Clinical appearance of the mass

Currently, the patient complained of a decreased appetite due to a foreign body sensation in her left jaw. Upon admission, she was conscious (*compos mentis*) with vital signs within normal limits. Localized examination of the head and neck region revealed a hyperpigmented mass in the left infraauricular region, measuring 7 × 5 cm. The mass featured an ulcerated surface, a firm consistency, distinct borders, and was fixed to the underlying tissue. No palpable cervical

lymphadenopathy was detected during the initial physical examination. Other physical findings were within normal limits. Laboratory evaluations only demonstrated leukocytosis.

Radiological evaluations, including plain cervical and chest X-rays, were within normal limits. However, contrast-enhanced Multi-slice Computed Tomography (MSCT) of the head revealed a left auricular mass suggestive of malignancy, along with left-sided level IIb cervical lymphadenopathy. Histopathological and immunohistochemical profiles from the biopsy specimen confirmed a well-differentiated Keratinizing

Squamous Cell Carcinoma, with a tumor diameter of 5.8 cm and an invasion depth of 11 mm. Based on the American Joint Committee on Cancer Staging Manual (AJCC 8th edition), the cSCC was classified as stage pT3N1M0.

The patient underwent aggressive surgical management consisting of a wide local excision combined with a Radical Neck Dissection (RND). Following the extirpation of the tumor and the evacuation of the regional cervical lymph nodes, defect reconstruction was performed using a local skin flap, and a surgical drain was placed for postoperative wound drainage.

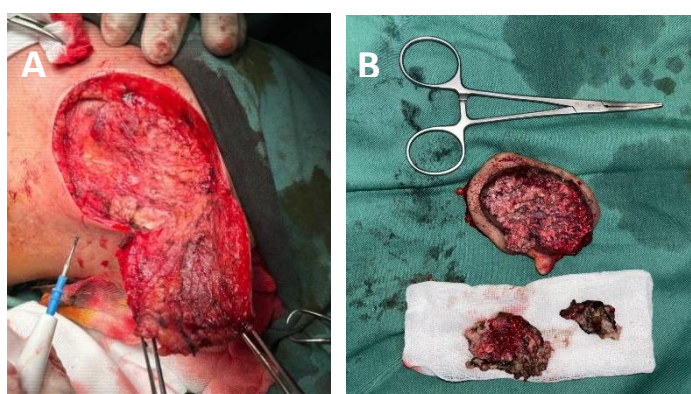


Figure 2. During the operation (A) The tumour of the infraauricular region (B)

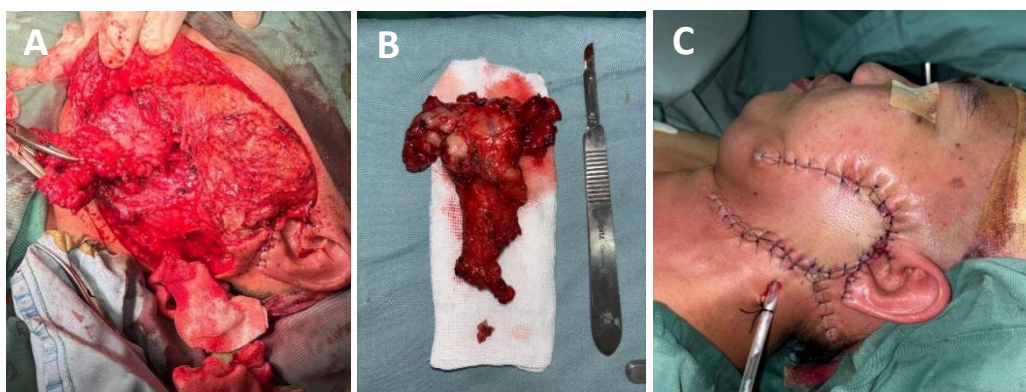


Figure 3. During the operation (A) The sample of RND (B) After defect closure (C)

Discussion

Cutaneous Squamous Cell Carcinoma (cSCC) is a highly prevalent non-melanoma skin cancer originating from keratinocytes in the epidermal layer, specifically the stratum spinosum. In the Caucasian population, cSCC, alongside basal cell carcinoma (BCC), constitutes the most frequently diagnosed

skin malignancy compared to melanoma.⁷ cSCC accounts for approximately 20% of all skin cancer cases and is responsible for 75% of mortalities associated with skin malignancies. Comprehensive national incidence data for cSCC in Indonesia remain unavailable. However, according to the 2020 Global Cancer Observatory (GLOBOCAN) report,

skin cancer cases in Indonesia reached approximately 18,000, with an estimated 3,000 deaths.⁸

The pathogenesis of cSCC involves an interplay of multiple environmental and intrinsic host risk factors. Ultraviolet (UV) radiation is the most significant environmental factor driving cSCC oncogenesis. Consequently, cSCC predominantly affects chronically sun-exposed areas with approximately 80% of cases localized to the head and neck region, including the scalp, ears, cheeks, forehead, temples, nose, and mouth. Nevertheless, cSCC lesions in other anatomical sites are also widely documented. Other environmental carcinogens include exposure to arsenic, nitrosamines, and polycyclic aromatic hydrocarbons. Intrinsic risk factors include advanced age, male sex, and Caucasian race. Furthermore, an immunocompromised status secondary to HIV infection, immunosuppressive medications, or leukemia significantly upgrades the risk. Precursor skin lesions, such as Marjolin's ulcers (chronic wounds), human papillomavirus (HPV)-induced lesions, and actinic keratosis, also serve as high-risk predisposing factors.⁹

Based on keratinocyte differentiation observed via histopathological examination, cSCC is classified into well-differentiated, moderately differentiated, and poorly differentiated types, which correlate directly with tumor biological activity, recurrence rates, and mortality prognosis.¹⁰ Accurate tumor staging is equally paramount to guide therapeutic modalities. Staging criteria defined by the American Joint Committee on Cancer Staging Manual (AJCC 8th edition) and the Brigham and Women's Hospital (BWH) system are widely adopted in clinical practice.¹¹ Although cSCC is generally less aggressive than melanoma, it remains locally invasive and prone to recurrence. High-risk cSCC is characterized by a tumor diameter ≥ 2 cm, invasion depth ≥ 2 mm, high recurrence rates, perineural invasion, locoregional metastasis, or a classification of stage T2b/T3 under the BWH system or T3 under the AJCC-8 guidelines.^{5,11}

To date, the gold standard for diagnosing cSCC is histopathological evaluation via skin biopsy, which accurately identifies tumor staging and differentiation. Complementary imaging modalities, including plain head/cervical radiographs, contrast-enhanced Computed Tomography (CT), and Magnetic Resonance Imaging (MRI), are essential to detect distant metastasis, regional lymph node involvement, and perineural invasion. Therefore,

radiologic staging is critical for comprehensive patient evaluation.

Surgical intervention represents the cornerstone of management for nearly all cSCC cases. Electrodesiccation and curettage (ED&C) can be utilized in selected low-risk lesions, yielding success rates up to 97%.¹¹ Conventional wide local excision (WLE) with a 4–6 mm margin for low-risk cSCC extending up to the mid-subcutaneous adipose layer achieves an oncologic clearance rate of approximately 95%.^{12,13} However, because cSCC cells frequently infiltrate subclinically beyond the clinically apparent margins, Mohs Micrographic Surgery (MMS) is strongly recommended for high-risk cSCC, tumors in immunocompromised individuals, and lesions in anatomically critical areas where tissue conservation is paramount, such as the head and neck.^{11,14} The clinical algorithm presented in Figure 4 represents an adaptation of the cSCC management guidelines from the European Association of Dermato-Oncology (EADO) and the National Comprehensive Cancer Network (NCCN).¹⁵

Additional surgical interventions beyond primary tumor extirpation are frequently required. In high-risk cSCC, metastasis to regional lymph nodes is a common occurrence due to the complex lymphatic drainage patterns of the head and neck region. Concomitant involvement of surrounding structures, such as the parotid gland and other salivary glands, is also frequently documented. A cohort study conducted in a United States hospital revealed that metastatic head and neck cSCC predominantly infiltrates the parotid gland as well as level II and III cervical lymph nodes⁶. Not infrequently, patients may also require temporal bone resection and the sacrifice of the facial nerve (CN VII) to achieve complete oncological clearance. Because nodal metastasis significantly worsens the patient's prognosis, patients with clinically positive cervical lymph nodes typically undergo Radical Neck Dissection (RND). In cases involving invasion into the parotid gland or other salivary tissues, RND is often combined with a parotidectomy or excision of the affected gland. However, contemporary guidelines increasingly advocate for selective neck dissection (SND) in specific scenarios. This shift is supported by recent studies demonstrating that patients undergoing selective neck dissection achieve regional control and overall survival rates of 85–100%, which are comparable to those undergoing conventional RND.¹⁵

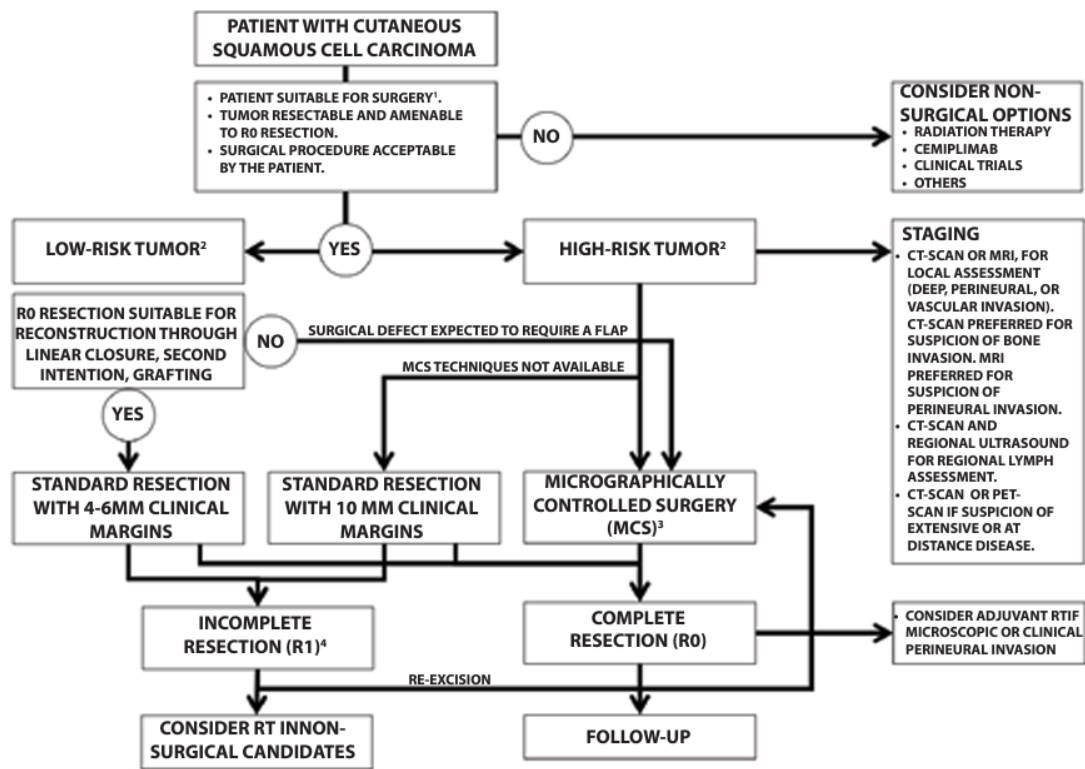


Figure 4. Algorithm of cSCC management based on EADO dan NCCN¹⁵

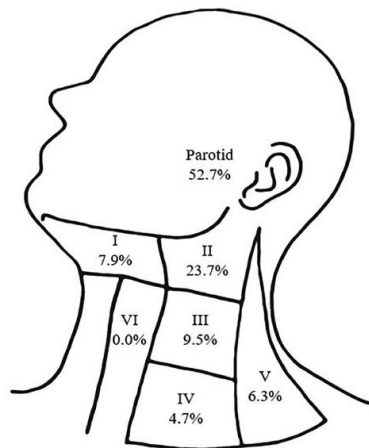


Figure 5. Locoregional metastatic predilection of SCC in head-neck.⁶

In addition to surgical interventions, non-surgical modalities represent important therapeutic options in the management of cSCC. For low-risk cSCC and cSCC *in situ*, photodynamic therapy (PDT) serves as an alternative tissue-conserving approach to optimize

cosmetic outcomes, although literature indicates it is associated with higher recurrence rates.¹⁶ Other ablative techniques, including laser therapy (carbon dioxide or erbium), electrocoagulation, and cryosurgery, may also be considered, particularly in patients who are ineligible for surgery or present with strict surgical contraindications. However, these ablative modalities carry a significantly higher risk of cSCC recurrence compared to standard surgical interventions.¹⁴

For high-risk cSCC, non-surgical approaches are primarily utilized as adjuvant therapies to eradicate residual microscopic tumor cells following surgical resection. Adjuvant modalities include radiotherapy, chemotherapy regimens utilizing capecitabine, epidermal growth factor receptor (EGFR) inhibitors (such as cetuximab and panitumumab), or immune checkpoint inhibitors targeting programmed death-1 (PD-1), such as cemiplimab. Current literature demonstrates that incorporating adjuvant non-surgical therapies yields a significantly higher overall survival rate compared to surgical management alone.^{11,14}

In the present case, the patient was classified as having stage T3 cSCC according to the AJCC-8 system, which categorizes it as a high-risk cSCC. While both wide local excision (WLE) and Mohs Micrographic Surgery (MMS) are viable options for high-risk lesions, clinical evidence indicates that MMS offers superior cure rates and significantly lower recurrence rates compared to standard excision.^{17,18} During cSCC surgery, achieving clear clinical and microscopic tumor margins is paramount. When relying solely on clinical margins for high-risk tumors, the excision margin must be at least 6 mm; if additional high-risk features are identified, the margin should be extended up to 9 mm. Nevertheless, tailoring the excision margin based on an individualized clinical assessment of each tumor remains the highly recommended approach.^{11,15}

In the present case, a Radical Neck Dissection (RND) was performed due to the confirmed involvement of level IIb cervical lymph nodes. In a standard RND procedure, in addition to the resection of cervical lymph node levels I–V, the operation involves the removal of a portion of the parotid gland, the sterno-cleidomastoid muscle, the internal jugular vein, and the spinal accessory nerve. While this aggressive approach is widely utilized to achieve complete oncological clearance in affected areas and significantly reduce regional recurrence rates, it is associated with substantial postoperative morbidity, most notably shoulder movement dysfunction^{19,20}. Consequently, to minimize these complications, contemporary guidelines increasingly advocate for selective neck dissection, which has been shown to offer regional recurrence and overall survival rates comparable to those of conventional RND¹⁵.



Figure 6. Wide excision procedure of cSCC in left infraauricular region



Figure 7. RND procedure

A non-surgical approach may also be considered for this patient, given the high-risk nature of the cSCC. Evidence from several studies indicates that patients with high-risk cSCC who receive systemic therapy following surgical resection experience lower 5-year locoregional recurrence rates compared to those managed with surgery alone.¹¹ Consequently, a multidisciplinary team approach is highly recommended for the long-term postoperative management of this patient.

Conclusion

Surgical intervention, via either wide local excision (WLE) or Mohs Micrographic Surgery (MMS), remains the cornerstone of management for both low-risk and high-risk cSCC. In cSCC localized to the head and neck region, critical factors such as cervical lymph node metastasis, salivary gland invasion, facial nerve (CN VII) involvement, and cosmetic tissue conservation must be carefully evaluated during tumor

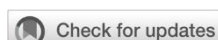
extirpation. Furthermore, the administration of adjuvant non-surgical therapies can significantly improve overall survival rates and minimize recurrence in high-risk cSCC cases.

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Pharmacologic Strategies to Prevent Anthracycline-Related Cardiotoxicity

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Abstract

Anthracycline-induced cardiotoxicity is a major complication of cancer therapy and a growing concern as long-term survival improves. Increasing cancer incidence, aging populations, and prevalent comorbidities further heighten vulnerability to cardiovascular injury. Standardized terminology such as cancer therapy-related cardiovascular toxicity and cancer therapy-related cardiac dysfunction, has been introduced to support clinical assessment. This narrative review aims to synthesize current evidence on pharmacologic strategies used to prevent anthracycline-related cardiotoxicity. Foundational therapies, including ACE inhibitors, angiotensin receptor blockers, β -blockers, and mineralocorticoid receptor antagonists, have shown variable cardioprotective effects, with heterogeneous outcomes across clinical trials. Emerging approaches such as angiotensin-neprilysin inhibition, statins, and SGLT2 inhibitors demonstrate promising early results but remain limited by short follow-up periods and inconsistent findings. Additional options, including biologically active compounds and cardiometabolic-targeted therapies, currently lack sufficient clinical support. Dexrazoxane remains the only FDA-approved agent for anthracycline cardiotoxicity prevention. Overall, pharmacologic prevention plays a central role in mitigating anthracycline-induced cardiovascular injury, underscoring the need for further research to refine targeted strategies and improve long-term cardiovascular outcomes in cancer survivors.

Keywords: *anthracycline cardiotoxicity, cardio-oncology, pharmacologic prevention*

Abstrak

Kardiotoksitas akibat antrasiklin merupakan salah satu komplikasi utama terapi kanker dan menjadi perhatian yang semakin besar seiring meningkatnya angka kesintasan jangka panjang. Peningkatan insidensi kanker, populasi yang menua, serta tingginya prevalensi komorbiditas semakin meningkatkan kerentanan terhadap cedera kardiovaskular. Terminologi yang terstandarisasi, seperti *cancer therapy-related cardiovascular toxicity* dan *cancer therapy-related cardiac dysfunction*, telah diperkenalkan untuk mendukung penilaian klinis. Tinjauan naratif ini bertujuan untuk merangkum bukti terkini mengenai strategi farmakologis yang digunakan untuk mencegah kardiotoksitas terkait antrasiklin. Terapi dasar, termasuk ACE inhibitor, angiotensin receptor blocker, β -blocker, dan antagonis reseptor mineralokortikoid, telah menunjukkan efek kardioprotektif yang bervariasi, dengan hasil yang heterogen pada berbagai uji klinis. Pendekatan yang lebih baru, seperti inhibisi angiotensin-neprilisin, statin, dan inhibitor SGLT2, menunjukkan hasil awal yang menjanjikan, tetapi bukti yang tersedia masih terbatas oleh masa tindak lanjut yang singkat dan temuan yang tidak konsisten. Pilihan lain, termasuk senyawa aktif biologis dan terapi yang menargetkan aspek kardiometabolik, saat ini masih belum memiliki dukungan klinis yang memadai. Dexrazoxane tetap menjadi satu-satunya agen yang disetujui FDA untuk pencegahan kardiotoksitas akibat antrasiklin. Secara keseluruhan, pencegahan farmakologis memiliki peran penting dalam mengurangi cedera kardiovaskular akibat antrasiklin, sekaligus menegaskan perlunya penelitian lebih lanjut untuk menyempurnakan strategi yang lebih terarah dan meningkatkan luaran kardiovaskular jangka panjang pada penyintas kanker.

Kata kunci: *kardio-onkologi, kardiotoksitas antrasiklin, pencegahan farmakologis.*

Background

Major advances in oncology have markedly improved long-term survival, shifting clinical priorities toward preventing the cardiovascular consequences of cancer therapy.¹ Many anticancer agents, especially anthracyclines, are associated with substantial cardiotoxic potential, and in cancers such as early-stage breast cancer, survival now surpasses that of heart failure populations, underscoring the need for cardiovascular preservation during treatment.^{2,3}

Because cancer and cardiovascular disease share multiple risk determinants, assessment of cardiovascular status before therapy initiation is increasingly emphasized in contemporary oncology practice.⁴ This need is reinforced by rising cancer incidence, aging populations, and the high prevalence of comorbid conditions such as hypertension and diabetes, all of which elevate vulnerability to treatment-related injury.⁵

Real-world data further highlight the magnitude of this problem. In the CARDIOTOX-2020 registry, more than one-third of patients developed cardiotoxic manifestations during therapy.⁶ Such injury may be acute, chronic, or delayed, ranging from subclinical biomarker elevation to overt dysfunction.⁷ To standardize terminology and guide clinical decision-making, the 2022 European cardio-oncology consensus introduced the concepts of cancer therapy–related cardiovascular toxicity (CTR-CVT) and cancer therapy–related cardiac dysfunction (CTR-CD).⁸

Given the increasing prevalence of CTR-CVT/CD and the limited effectiveness of post-injury treatment, preventive pharmacologic strategies have become central to modern cardio-oncology. This review synthesizes current evidence on cardiovascular-protective therapies, with particular emphasis on preventing anthracycline-induced toxicity.

Conceptual Framework for Cardiovascular Prevention in Cardio-Oncology

The primary objective of cardio-oncology is to optimize cancer outcomes while minimizing cardiovascular injury and preventing exacerbation of pre-existing disease. Multidisciplinary involvement is essential, as coordinated care facilitates personalized prevention strategies throughout the cancer trajectory.⁹ A foundational concept in this field is permissive cardiotoxicity, which supports continuing effective

cancer therapy while implementing protective interventions rather than prematurely discontinuing treatment.¹⁰ Even in patients with known cardiovascular disease, appropriate monitoring and individualized prevention can enable safe therapy continuation without precipitating major events.¹¹

Baseline cardiovascular risk assessment is essential prior to anthracycline exposure and typically includes validated scoring systems such as HFA-ICOS, echocardiographic evaluation, and biomarker measurement.¹² Because anthracycline cardiotoxicity affects diverse myocardial and vascular cell types, risk cannot be estimated solely by cumulative dose. Thus, comprehensive prevention and early detection strategies have become integral components of cardio-oncology practice.¹³

Multiple professional societies recommend foundational cardiovascular-protective pharmacotherapies such as ACE inhibitors, β -blockers, angiotensin receptor blockers (ARB), and mineralocorticoid receptor antagonists (MRA) as part of preventive pathways.⁸ A meta-analysis of randomized trials highlights their potential, showing that spironolactone reduced LVEF decline and troponin release, enalapril significantly lowered BNP, and statins showed the greatest improvement in LVEF among the evaluated classes.¹⁴

Foundational Cardioprotective Therapies: RAAS Inhibition and β -Blockers

ACE inhibitors have long been used because of their antifibrotic and remodeling-preventive effects. However, evidence is mixed. For instance, the PROACT trial found that starting enalapril shortly before anthracycline therapy did not significantly reduce troponin elevation or prevent deterioration in LVEF or GLS, suggesting that monotherapy may be insufficient for robust prevention.¹⁵ In the PRADA trial, candesartan preserved LVEF during anthracycline-based therapy, whereas metoprolol did not exhibit similar benefit.¹⁶

Combined RAAS inhibition and β -blockade has demonstrated more consistent cardioprotection in certain settings, likely because the two mechanisms act synergistically to mitigate remodeling, oxidative stress, and neurohormonal activation. For instance, the combination of enalapril and carvedilol prevented LVEF decline in patients undergoing therapy for hematologic malignancies.⁷ Carvedilol may offer additional benefit through antioxidant effects and

modulation of β -arrestin signaling, thereby reducing mitochondrial injury and apoptotic pathways.^{17,18}

Clinical trials, however, remain heterogeneous. The CECCY trial reported stabilization of diastolic function and lower troponin release with carvedilol but did not demonstrate significant prevention of early LVEF reduction.¹⁹ Similarly, the PREVENT-HF study found that long-term carvedilol was safe in childhood cancer survivors but did not significantly improve structural cardiac parameters.²⁰

Emerging Pharmacologic Strategies

Angiotensin-Neprilysin Inhibition

Interest in sacubitril/valsartan has increased due to its dual neurohormonal effects and the capacity to enhance endogenous natriuretic peptide signaling.²¹ The SARAH trial provided early evidence supporting its cardioprotective potential, showing smaller declines in GLS and LVEF compared with placebo over six months in patients receiving anthracyclines. Nevertheless, short follow-up duration and the absence of hard outcomes such as survival limit broad implementation. Mild hypotension and electrolyte disturbances were more frequent in the treatment group.²²

Mineralocorticoid Receptor Antagonists

MRAs theoretically reduce fibrosis and oxidative stress, central pathways in anthracycline toxicity.²³ Small RCTs support these protective properties. One study showed that spironolactone attenuated LVEF decline and preserved diastolic function compared with placebo.²⁴ However, the ELEVATE trial found no significant benefit of eplerenone over six months.²⁵ Larger trials are needed before MRAs can be routinely recommended for prevention.

Statins

Statins exert pleiotropic anti-inflammatory and antioxidant effects that may counteract anthracycline and trastuzumab-associated injury.^{26,27} Evidence remains inconsistent across studies. A result study demonstrated meaningful reduction in LVEF decline among lymphoma patients treated with atorvastatin, whereas other studies did not observe similar benefits in more heterogeneous cancer populations.²⁸⁻³⁰ Concerns regarding myalgia effect also affect real-world use.³¹

Biologically Active Compounds

Natural compounds such as resveratrol, melatonin, curcumin, and spirulina demonstrate cardioprotective effects in preclinical models.³²⁻³⁵ However,

clinical evidence remains sparse, inconsistent, and rarely designed to assess oncologic safety. These agents cannot be recommended outside research settings due to uncertainty in efficacy and possible interactions with cancer therapies.³⁶

Cardiometabolic Pathways as Therapeutic Targets

Decades of research have identified oxidative stress and ferroptosis as dominant pathways in anthracycline-induced injury, yet clinical translation remains challenging.³⁷ Dexrazoxane continues to be the only FDA-approved agent for preventing anthracycline cardiotoxicity, but concerns persist regarding its use in patients with reduced LVEF and its compatibility with modern chemotherapy regimens.³⁸ Increasing recognition of the roles of inflammation, metabolic dysfunction, endothelial injury, and impaired energetics has driven interest in therapies targeting cardiometabolic pathways.³⁹

SGLT2 Inhibitors

SGLT2 inhibitors have emerged as promising agents due to broad cardiovascular benefits across heart failure phenotypes.⁴⁰ Preclinical studies show that dapagliflozin and empagliflozin mitigate anthracycline-induced oxidative stress, inflammation, endothelial dysfunction, and structural injury, leading to improved strain parameters, biomarkers, and histopathologic profiles.^{41,42} A large recent meta-analysis demonstrated significant reductions in heart failure hospitalization and incident heart failure among cancer patients receiving SGLT2 inhibitors, particularly those treated with anthracyclines.⁴³

Conclusions

Pharmacologic prevention of cancer therapy-related cardiovascular toxicity is essential in contemporary oncology, given the increasing number of long-term cancer survivors at risk for treatment-induced injury. Foundational therapies such as ACE inhibitors, angiotensin receptor blockers, and β -blockers provide partial cardioprotection but leave substantial residual risk. Emerging agents including angiotensin-neprilysin inhibitors, mineralocorticoid receptor antagonists, statins, cardiometabolic modulators, and SGLT2 inhibitors, offer promising additional benefit, although the evidence remains heterogeneous and often preliminary. These preventive strategies are particularly relevant for mitigating anthracycline-induced cardiotoxicity, which remains the most clinically significant and extensively studied form of chemotherapy-

related cardiovascular injury. Future work should prioritize mechanistically targeted therapies, standardized definitions of cardiotoxicity, and integrated cardio-oncology pathways to enable personalized prevention and improve long-term cardiovascular outcomes in cancer survivors.

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Conflict of Interests

The authors declare no conflict of interest in this review.

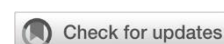
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Cutaneous Angiosarcoma

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Abstract

Cutaneous angiosarcoma (cAS) is a rare but highly aggressive malignant vascular neoplasm originating from endothelial cells and accounting for approximately 1–2% of all soft tissue sarcomas. The disease predominantly affects elderly individuals and most commonly involves the skin of the head and neck region. Cutaneous angiosarcoma may occur sporadically (Wilson–Jones type) or in association with chronic lymphedema (Stewart–Treves syndrome) and previous radiation exposure. Early diagnosis remains challenging because its clinical manifestations are highly variable and often mimic benign inflammatory, vascular, or traumatic conditions, leading to delayed recognition and treatment. This review summarizes the current understanding of cutaneous angiosarcoma, including its epidemiology, risk factors, pathogenesis, clinical manifestations, diagnostic evaluation, management, prognosis, and follow-up. Diagnostic approaches rely on a combination of clinical assessment, dermoscopy, histopathological examination, immunohistochemistry, and imaging studies to establish the diagnosis and determine disease extent. Surgical resection remains the mainstay of treatment and is frequently combined with radiotherapy and systemic therapies for advanced disease. Novel therapeutic modalities, including targeted therapy, immunotherapy, and electrochemotherapy, have emerged as promising options for selected patients. Despite advances in treatment, the prognosis of cutaneous angiosarcoma remains poor because of its aggressive behavior, high recurrence rate, and metastatic potential. Increased awareness and early recognition are essential to facilitate timely diagnosis and optimize patient outcomes.

Keywords: *angiosarcoma, cutaneous angiosarcoma, soft tissue sarcoma*

Abstrak

Angiosarkoma kutaneus (*cutaneous angiosarcoma/cAS*) merupakan neoplasma vaskular ganas yang jarang tetapi sangat agresif, berasal dari sel endotel, dan mencakup sekitar 1–2% dari seluruh sarkoma jaringan lunak. Penyakit ini terutama terjadi pada individu lanjut usia dan paling sering mengenai kulit di daerah kepala dan leher. Angiosarkoma kutaneus dapat terjadi secara sporadik (tipe Wilson–Jones) atau berhubungan dengan limfedema kronis (sindrom Stewart–Treves) maupun riwayat paparan radiasi sebelumnya. Diagnosis dini masih menjadi tantangan karena manifestasi klinisnya sangat bervariasi dan sering menyerupai kondisi inflamasi, vaskular, atau traumatik yang jinak, sehingga dapat menyebabkan keterlambatan dalam pengenalan dan penatalaksanaan. Tinjauan ini merangkum pemahaman terkini mengenai angiosarkoma kutaneus, termasuk epidemiologi, faktor risiko, patogenesis, manifestasi klinis, evaluasi diagnostik, tata laksana, prognosis, dan tindak lanjut. Pendekatan diagnostik mengandalkan kombinasi penilaian klinis, dermoskopi, pemeriksaan histopatologi, imunohistokimia, dan pemeriksaan pencitraan untuk menegaskan diagnosis serta menentukan luas penyakit. Reseksi bedah tetap menjadi terapi utama dan sering dikombinasikan dengan radioterapi serta terapi sistemik pada penyakit lanjut. Modalitas terapi baru, termasuk terapi target, imunoterapi, dan elektrokemoterapi, telah berkembang sebagai pilihan yang menjanjikan pada pasien terpilih. Meskipun terdapat kemajuan dalam terapi, prognosis angiosarkoma kutaneus tetap buruk karena sifatnya yang agresif, angka kekambuhan yang tinggi, dan potensi metastasis. Peningkatan kewaspadaan serta pengenalan dini sangat penting untuk memfasilitasi diagnosis yang tepat waktu dan mengoptimalkan luaran pasien.

Kata kunci: *angiosarkoma, angiosarkoma kutaneus, sarkoma jaringan lunak*

Background

Angiosarcoma (AS) is a highly aggressive malignancy of vascular endothelial cells with a predilection for superficial soft tissue and skin.^{1,2} The clinical term for AS in the skin is called cutaneous angiosarcoma (cAS).¹⁻³ Tumors can originate from various other anatomical locations such as the scalp, breast, and extremities.⁴ The prevalence of AS ranges from 1-2% of all soft tissue sarcomas.² Diagnosis of cAS is a challenge, because the clinical manifestations are nonspecific.⁵ Surgical resection followed by adjuvant radiotherapy is the main treatment option, but there is a high risk of local recurrence and metastasis.^{2,6} Chemotherapy is given for advanced regional cAS or metastatic conditions.^{5,6} Various other modalities such as targeted therapy, immunotherapy, and electrochemotherapy are starting to be developed to improve clinical response and short-term outcomes.¹⁻³

This literature review discusses the definition, epidemiology, risk factors, clinical features, diagnostics, management, prognosis, and follow-up of cAS, excluding AS that occurs in internal organ.

Definition

The term AS is an aggressive malignant tumor of vascular endothelial cells with a predilection primarily for the face and scalp, especially in the geriatric population (Wilson-Jones type AS) originating from the dermis and can progress to the subcutaneous.^{5,7,8} Tumor cells are susceptible to metastasis through blood vessels and the lymphatic system.⁷ In general, AS is grouped into primary AS and secondary AS. Secondary AS is usually associated with a history of radiotherapy and chronic lymphedema.⁹ Other divide AS as cAS, AS associated with lymphedema (Stewart-Treves syndrome), and radiation-associated AS (RAA).⁹

Epidemiology

The prevalence of soft tissue sarcoma in the head and neck ranges from less than 5%, which 10% are classified as AS.⁸ The predilection for cAS is 60% in the head and neck. The ratio between men and women is reported to be around 2:1, with a mean age at diagnosis of 65-70 years.^{1,9,10} As many as 93.5% of AS lesions in the head and neck manifest on the skin, while 6.5% are noncutaneous AS found in the nasopharynx, oropharynx, and peripheral nerves.⁹ The predilection of cAs in the head and neck is common in the male geriatric population, and accounts for 0.1% of all head and neck malignancies.^{1,3} The

latency period between radiation and the development of cAS is 2-30 years, with the periode of 5 years which is shorter than the development of other radiation-induced neoplasms.^{1,11} The development of AS in chronic lymphedema represents about 5% of all AS. The majority of reported cases have occurred in the upper extremities following radical mastectomy for locally advanced breast cancer with a latency period of 10-15 years.^{1,11}

Pathogenesis

Risk factors for AS include chronic lymphedema, radiation, and chronic sun exposure.^{1,10} Other factors include genetic syndromes, exposure to carcinogens such as thorium dioxide, arsenic, and vinyl chloride.^{12,13} Chronic lymphedema following breast cancer therapy, filariasis or Milroy's disease is associated with AS due to accumulation of protein-rich interstitial fluid that inter-feres with the immune response, resulting in stimulation of lymphangiogenesis and collateral blood vessel growth.^{1,11,13} This type of AS has also been reported in patients with congenital lymphedema, filariasis, and morbid obesity.¹⁰ Upregulation of the NTSR1, ANKRD1, and CDKN2C genes is associated with primary cAS while UNC5A, CTLA4, ISLR2, ICOS, RAB17, FLT4, and RASGRP3 have been identified in secondary cAS.¹

Radiotherapy is an independent risk factor for the development of cAS, contributing to almost a quarter of all cases. This is consistent with various types of cancer treated with radiation, such as cervical cancer, endometrial cancer, lymphoma, and breast cancer.¹³ The predilection for RAA is mainly found in the edge of the area exposed to radiation.¹² Breast cancer it occurs within 5 years after radiation, while in body locations other than the breast tend to occur within 10 years after the diagnosis of primary cancer.¹³ There is a genetic predisposition for the development of AS after radiotherapy, namely upregulation of genes such as MYC, KIT, FLT4, and RET and downregulation of CDKN2C have been reported in RAA.^{1,8}

Several familial syndromes associated with AS include neurofibromatosis type 1, Maffucci syndrome, bilateral retinoblastoma, hemochromatosis, and Klippel-Trenaunay syndrome. Although rare, several studies have documented that AS can develop in port wine stains, hemangiomas, and lymphangiomas.¹³ Mutations in the genes involved are TP53, KRAS, PTPRB, and PLCG1. Mutations in the TP53 gene, which is responsible for the synthesis of the

tumor suppressor protein p53. PTPRB and PLCG1 genes play an important role in activating angiogenesis. A novel fusion gene, NUP160-SCL43A3, was identified in 9 of 25 cases of AS, which plays a role in regulating other genes in angiogenesis.¹

The occurrence of cAS in post-renal transplant patients raises the suspicion that immunosuppression is a risk factor for the development of cAS.¹³ Also, xeroderma pigmentosum and HIV can also be found in cAS.¹ However, the exact pathogenesis is still unclear. Neoplasms developing in hemodialysis fistulas in immunocompetent patients have also been reported, indicating that vascular flow abnormalities may trigger neovas-culogenesis.^{1,13}

Clinical Features

The clinical presentation of cAS is highly variable.⁷ Initially, AS appears as a benign vascular tumor with a predilection for the face, scalp, and neck.^{2,8} The initial clinical presentation of cAS is nonspecific, presenting with erythema and hematoma on chronically sun-exposed skin (Figure 1). The presentation resembles rosacea, dermatitis, hemangioma, xanthelasma, cellulitis, and angioedema.¹ Some cases show a reddish-black border with bleeding into the skin, making it appear like "ink being soaked up by blotting paper."¹⁰



Figure 1. Angiosarcoma on the scalp of an elderly. (Archieve Skin Tumor and Surgery Division, Dermatology and Venereology Department, Cipto Mangunkusumo Hospital)

Lesions can develop into nodules, exophytic tumors, ulcerations, and hemorrhages, resembling epithelial neoplasms such as squamous cell carcinoma, kerato-acanthoma, basal cell carcinoma, atypical fibroxanthoma, and malignant melanoma.² cAS lesions are multifocal and extend beyond the clinically visible lesion boundaries, making it challenging to determine

the extent of cAS.¹ On physical examination, head tilt maneuver can increase blood supply, thus helping visualize the tumor.^{1,10}

In Stewart-Treves syndrome, there is dusky erythema in lymphedema.¹⁰ Systemic symptoms can occur in all cAS variants such as abdominal pain, nausea, vomiting, and changes in bowel motility. In cases of metastasis, there will be symptoms according to the organs involved.¹⁴

Diagnostics

Diagnostic evaluation of cAS cases includes dermoscopy, skin biopsy, immunohistochemistry (IHC). Imaging such as ultrasonography (USG) and magnetic resonance imaging (MRI) may determine the extent of the primary lesion before surgery. Computed tomography scan (CT scan) and positron emission tomography (PET) examinations to detect metastasis.^{8–10,13}

Multipel atypical vascular structure is one of the key dermoscopy features of cAS. The dermoscopic appearance that can be found in cAS is dark red and pulp structureless zone on a light red background, violet hue, thick white, perpendicular, and polygonal lines in all lesions. In the center of the lesion, there are dark red, purple dots, and clods dots around follicular openings, which look like white and yellow circles.¹⁵ In RAA, it shows a more homogeneous reddish white pattern.¹⁶



Figure 2. Multiple atypical vascular structure is one of dermoscopy key feature of cAS. (Archieve Skin Tumor and Surgery Division, Dermatology and Venereology Department, Cipto Mangunkusumo Hospital)

There are three ways to obtain histopathological specimens, namely 1) tumor resection and biopsy followed by surgery; 2) frozen section followed by wide resection; and 3) hollow needle puncture

performed before surgery.^{10,14} Image of irregular blood vessels in the dermis and atypical endothelial cells lining the blood vessel space will be the most common pathological appearance (Figure 3).

In well-differentiated AS, the functional and morphological properties of the vascular endothelium are normal, there are many irregular blood vessels lined by endothelial cells.¹ In poorly differentiated AS, the tumor consists of cells with hyperchromatic pleomorphic nuclei, and variety of shapes, including round, epithelioid, polygonal, spindle-shaped primitive cells, along with high mitotic activity. These cells form vascular gaps that invade the connective tissue and subcutaneous tissue.^{1,10,17,18}

The histopathological finding of epithelioid cAS is dominated by round or polygonal cells with eosinophilic cytoplasm, vesicular nuclei, with nodular, micro-nodular, syncytial, and diffuse growth patterns and necrosis zones.^{1,18} Hypertrophic and papillomatous cAS are described as verrucous cAS.¹ Another rare case is pseudolymphomatous AS with severe inflammatory infiltrate and variable germinal center formation.¹

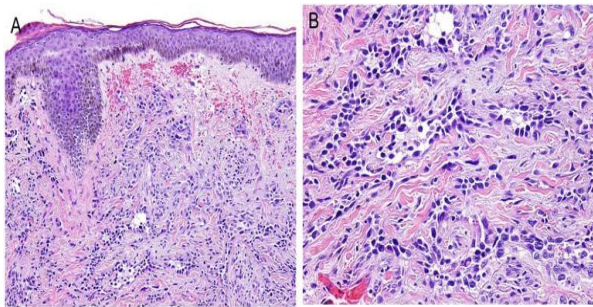


Figure 3. Histopathological examination of well-differentiated cutaneous angiosarcoma.¹

- A. Irregular blood vessels in the dermis (H&E, 10×).
- B. Atypical endothelial cells lining the vascular space

The most commonly used IHC markers for the diagnosis of cAS are CD31 and CD34.^{1,10} The CD31 marker (positivity rate 80%) has high sensitivity and specificity, with a diffuse, intense staining reaction and accentuation of the cytoplasmic membrane, but CD31 is also expressed in macrophages, histiocytes, and plasma cells. The markers CD34 (positivity rate 63%) and factor VII (positivity rate 83%) are also expressed in cAS, but are absent in poorly differentiated tumors, but CD34 can also be expressed in hematopoietic and fibrohistiocytic cells.^{1,2,10,17}

Nuclear IHC markers, such as ERG which is a homolog

of the Avian v-ets erythroblastosis virus E26 oncogene and FLI1 are highly sensitive for cAS, but FLI1 can also be found in leiomyosarcoma, squamous cell carcinoma, melanoma, and atypical fibroxanthoma.^{1,9} Claudin-5, a tight junction protein, is another sensitive vascular marker if additional confirmation of vascular origin is needed. This protein shows positive expression in most cases of cAS, but is not specific because it can be expressed by other vascular proliferations.¹ Lymphatic endothelial markers expressed in cAS are podoplanin D2-40, LYVE-1, c-MYC, PROX-1, and α -SMA. Strong ki67 positivity indicates a poor prognosis.⁹ Increased expression of the c-MYC oncogene through gene amplification is characteristic of RAA.¹⁰

Ultrasonography (USG) is primarily used to detect effusion and lesions in internal organs such as the liver, it can also serve as an initial imaging modality to assess superficial soft tissue involvement, including lymph nodes, in angiosarcoma.¹⁴ Meanwhile, MRI offers superior tissue characterization and differentiation between tumor mass and thrombus, making it useful for evaluating angiosarcoma not only in solid organs like the heart and liver, but also in lymphatic or subcutaneous tissues.¹⁴ Characteristic MRI findings include high-flow serpentine vessels within a dense, non-specific soft tissue mass, with contrast enhancement and non-enhancing areas indicating tumor necrosis.¹⁴ MRI is superior to CT scan in differentiating thrombus and tumor mass with tissue characterization.^{13,14} Diagnostic findings on MRI are high-flow serpentine vessels in a non-specific dense soft tissue mass with enhancement after intravenous contrast administration and non-enhancing areas that identify tumor necrosis.¹³

Regional spread or distant metastases are common in AS, occurring in 30% and 10% of cases, respectively.¹¹ Staging and grading of the primary tumor (T), regional lymph nodes (N), and distant metastases (M), and tumor grade (G) are used to classify soft tissue sarcomas according to the 8th edition of the revised American Joint Committee on Cancer (AJCC) cancer staging guidelines (Appendix, Table 1) adopting the grading system published by the French Federation of Cancer Centers Sarcoma Group (FNCLCC). Tumor grading is based on cell differentiation, mitotic rate, and extent of necrosis (Appendix, Table 2).^{10,19} The AS staging system varies depending on location, whether in the head and neck area, or in the trunk and extremities.^{10,20}

Table 1. TNM classification of soft tissue sarcomas in the head and neck region according to The American Joint Committee on Cancer Staging Manual 8th edition.¹⁰

Primary Tumor (T)	
TX	Primary tumor cannot be measured
T1	Tumor ≤ 2 cm
T2	Tumor > 2 cm to ≤ 4 cm
T3	Tumor > 4 cm
T4	Tumor invading surrounding anatomical structures
T4a	Tumor invading the orbita, base of the skull/dura mater, central organs of the head, the facial skull, the pterygoid muscles
T4b	Tumor invading the CNS, with the carotid sheath, invading the paravertebral muscle, or invading the CNS via perineural spreading
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No nodal metastasis
N1	Regional lymph nodes metastasis
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Table 2. Histologic grading of soft tissue sarcoma according to the American Joint Committee on Cancer Staging Manual 8th edition.¹⁰

Tumor differentiation	Number of mitosis	Tumor necrosis
Sarcoma shows strong similarities to normal adult tissue (for example low-malignancy leiomyosarcoma) (1 point)	0–9 mitosis per 10 HPF (1 point)	No tumor necrosis (0 point)
Sarcoma with distinct histological typing (for example myxoid round cell liposarcoma) (2 points)	10-19 mitosis/10 HPF (2 points)	< 50% nekrosis tumor (1 point)
Embryonal and non-differentiated sarcoma, sarcomas of questionable type, synovial sarcomas, soft tissue osteosarcoma, Ewing sarcoma/soft tissue primitive neuroectodermal tumor (PNET) (3 points)	≥ 20 mitosis/10 HPF (3 points)	≥ 50% nekrosis tumor (2 point)
The score of these variables are added up, resulting in the following grades		
GX	Grade cannot be assessed	
G1	Total score 2-3	
G2	Total score 4-5	
G3	Total score 6 or higher	

HPF: high power field

Management

A. Local Therapy

Surgery

Radical surgical resection is the main therapy for primary and recurrent cAS.^{1,10,11} Although there are no clear guidelines regarding the specific width of surgical margins in cAS, it is recommended to achieve

a margin of at least 3 cm or more and a deep margin.^{1,21} Rapid tumor growth and disease extension cause surgical margins to remain positive after resection.^{10,14} In head and neck cAS, surgical resection is not recommended due to the complex anatomical structure and risk of metastasis. Local recurrence and distant metastasis can occur as much as 30% - 100% after radical surgical resection.¹⁴

Radiotherapy

Definitive radiotherapy is used for tumors that cannot be surgically treated such as cAS in the head and neck. Because there are few previous studies on definitive radiotherapy for AS, the optimal radiotherapy management remains unclear.¹⁴ Radiotherapy with an average dose of 70 Gy can achieve local tumor control in approximately 50% of cases.¹⁰ Radiotherapy can be given as an adjuvant to surgical therapy in localized AS. The dose of radiotherapy as an adjuvant therapy in cAS surgery is 60 Gy, divided into 20 sessions. In RAA, the dose given is lower, namely 45-50 Gy.²⁰ In recurrent tumors, debulking or repeat resection can be performed followed by normofractionated and hyper fractionated radiotherapy or local brachytherapy.¹⁰

B. Systemic Therapy

Neoadjuvant chemotherapy is considered for palliative care, especially to preserve organ function in cAS with a predilection for the eye.^{10,20} Chemotherapy is also widely used in metastatic cAS and unresectable lesions.¹ A trend towards improved survival from chemotherapy treatment has not been proven so far, but a good response to chemotherapy is seen in subgroups with excellent local tumor control.¹⁰

Chemotherapy

The most commonly used chemotherapy for cAS is docetaxel, paclitaxel, and liposomal doxorubicin, but the National Comprehensive Cancer Network (NCCN) guidelines also include the use of vinorelbine, sorafenib, sunitinib, and bevacizumab.¹¹ Doxorubicin-based regimens are the gold standard for the management of soft tissue sarcomas with a median progression-free survival (PFS) of 3 months, while taxanes (paclitaxel) have shown better efficacy with a median PFS of 4-5 months.¹

Tyrosine kinase inhibitors (pazopanib, sorafenib, axitinib) are used to treat a variety of soft tissue sarcomas, one of which is cAS.¹ Pazopanib is a targeted therapy that was recently approved as a second-line treatment for advanced sarcomas.¹⁰ Pazopanib is a vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor that approved based on improved PFS compared with placebo in patients with chemotherapy-refractory sarcoma (4.6 months vs. 1.6 months).^{10,22} Pazopanib inhibits the receptors VEGFR-1, VEGFR-2, VEGFR-3, platelet-derived growth factor (PDGFR)- α , PDGFR- β , fibroblast growth factor receptor (FGFR)-1, FGFR-3,

c-KIT proto-oncogene, as well as other kinases such as B-Rapidly accelerated fibrosarcoma (B-RAF) of the MAP kinase pathway. The dose used is generally 800 mg per day orally. Reported side effects include decreased appetite, headache, hypertension, diarrhea, vomiting, hair loss, and exanthema.¹⁰ The combination of pazopanib and paclitaxel has been used for the management of advanced AS with a mean PFS of 11.6 months, but definitive conclusions regarding its use are lacking.²³ Bevacizumab, a VEGFR inhibitor, has been reported to be an option for the treatment of AS with a PFS of 6.5 months. Other therapies include carotuximab, a monoclonal antibody against endoglin, and regorafenib, a VEGFR2-TIE2 tyrosine kinase inhibitor.¹

Another targeted therapy is trabectedin, which has anti-neoplastic and multitargeted properties by inducing apoptosis and cell cycle arrest through binding to the minor groove of DNA and affecting DNA-binding proteins; activating the immune microenvironment by inhibiting monocyte and macrophage differentiation and cytokine production.^{10,24} It has been approved for the treatment of advanced soft tissue sarcoma in adults after failure of other treatments with intravenous administration of 1.5 mg/m² over 24 hours every 3 weeks. Reported side effects include infection, febrile neutropenia, vomiting, and hyperbilirubinemia.¹⁰ The combination of trabectedin with radiotherapy is also an active therapeutic option in patients with soft tissue sarcoma.²⁵

Recombinant IL-2 (rIL2)

Intralesional recombinant IL-2 (rIL2) initiates and maintains differentiation of Th1 and Th2 cells, increases cytolytic activity of natural killer (NK) cells, increases differentiation of regulatory T cells, and anti-tumor activity mediated by cytotoxic T cells, while suppressing Th17 differentiation resulting in complete remission in some cases.¹⁰ The definitive role of rIL2 has not been fully studied, but data suggest a role for the immune response in tumor control.¹⁰

Immunotherapy

Immunotherapy against programmed death 1 (PD-1) and its receptors including ligand-1 (PD-L1) and ligand-2 (PD-L2) is also considered as an effective therapeutic target in malignant tumors.¹⁴ Significant levels of PD-1-expressing T cells infiltration have been found in tumors as well as PD-L1 expression in tumor cells. Although large-scale clinical trials are still lacking, there are several small clinical trials that

have shown the curative effect of anti-PD-1 antibodies for AS.^{10,14} CTLA-4 inhibitors (tremelimumab) can also be given in combination therapy for cAS, although their efficacy is still being proven in phase II trials.²¹

Electrochemotherapy

The efficacy of surgery, radiotherapy, and chemotherapy is still very limited in the management of cAS. In the 2000s, electrochemotherapy was proposed as a potential therapy for superficial malignant lesions. Electrochemotherapy is an effective local therapy based on systemic or local injection of bleomycin or cisplatin combined with electroporation.²⁶ In a retrospective study, electrochemotherapy in 19 cases of advanced AS showed an objective response rate of 63%. Pain and bleeding decreased in one third of patients.²⁷ The International Network for Sharing Practices in Electrochemotherapy (InspECT) study had comparable results, namely in 20 patients with advanced AS, objective tumor response was observed in 80%, half of these cases showed complete remission. Bleeding control was achieved in 13 of 14 patients.²⁸ Electrochemotherapy had a good response in the treated area but new tumors could develop outside the area in less than 2 months.²⁹

Prognosis

The clinical outcome of AS is poor because it is difficult to control the primary tumor with relatively high local recurrence.⁸ A 2015 retrospective study evaluated the outcomes of cAS of the face and scalp

treated with a combination of surgery, radiation therapy, and/or chemotherapy. Among 55 AS patients, approximately 73% received a combination of surgery, radiation therapy, and/or chemotherapy, 15% received surgery, 2% received radiation therapy, 9% received chemotherapy, and 2% were observed. The reported 5-year locoregional tumor control was 18%; the 5-year recurrence-free rate was 16%.⁵ A 2021 retrospective study found that cAS of the scalp had a high local recurrence rate and poor prognosis. Among 41 patients with AS of the scalp, 30 patients had localized lesions and 11 patients had distant metastases. Overall, the mean survival rate was 16.6 months and the 5-year survival rate was 22%.⁷

Psychosocial Rehabilitation And Care

Depression and anxiety are comorbidities in cancer patients, associated with a relatively poor prognosis of cAS.^{30,31} Complex psychological adaptations related to biological, individual, and societal factors contribute to the risk of poor outcomes. Therefore, physical rehabilitation and psychosocial support are important aspects in improving the quality of life in cAS.^{9,30,31}

Follow-Up

Information regarding the specific follow-up time for cAS is not yet available. In the majority of cases, the individual follow-up interval is 6 weeks to 3 months, because AS is very progressive and has a poor prognosis. Imaging procedures are performed for appropriate management, taking into account prognosis, TNM stage, and location of metastases (Table 3).¹⁰

Table 3. Follow-up examinations for cutaneous angiosarcoma.¹⁰

Risk group	Year 1-3	Year 4-5	Year 6-10
Mainly favorable prognostic features (single tumor <5cm, one region, location on the trunk, superficial growth, solid portions, inflammation)	Evaluation every 3 months: clinical examination, biopsy (if applicable), imaging (if applicable)	Evaluation every 6 months: clinical examination, biopsy (if applicable), imaging (if applicable)	Evaluation every 12 months: clinical examination, biopsy (if applicable), imaging (if applicable)
Mainly unfavorable prognostic features (multifocal, satellites, > 5 cm; several regions; advanced age; location head/neck, scalp; deep invasion, no solid portions, high Ki-67, necroses)	Evaluation every six weeks: clinical examination, biopsy (if applicable) In the first three years: additional ultrasound of the locoregional lymph nodes every 3 months and chest CT every 6 months	Evaluation every 3 months: clinical examination, biopsy (if applicable) Only in cases of clinical suspicion of progression beyond the primary location: Imaging (ultrasound, CT, MRI)	Evaluation every 6 months: clinical examination, biopsy (if applicable) Only in cases of clinical suspicion of progression beyond the primary location: Imaging (ultrasound, CT, MRI)

Conclusion

The prevalence of AS is very rare but aggressive and often metastasizes. One of the most common variants of AS is cAS on the face and scalp, especially in the male geriatric population. The most commonly associated risk factors for AS are radiotherapy and chronic lymphedema. The clinical picture of AS is nonspecific, requiring additional examinations such as dermoscopy, histopathology, immunohistochemistry, and radiology. Although surgical resection followed by adjuvant radiotherapy or chemotherapy is the mainstay of cAS management, multimodality approaches such as targeted therapy, electrochemotherapy, and immunotherapy are currently being developed to improve quality of life.

Conflict of interests

The authors have no financial conflict of interest.

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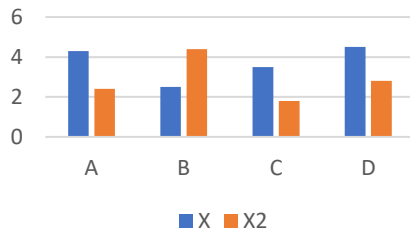
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