

Review Article

Lymph Node Metastasis: Scavenger Receptor Mechanisms and Chemotherapy Resistance in Para-Aortic Sanctuary-Like Sites

Metastização Ganglionar: Mecanismos dos Recetores de Eliminação e a Resistência à Quimioterapia Promovida por Áreas Tipo Santuário nos Gânglios Para-Aórticos

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ABSTRACT

Lymph-node metastasis is a major determinant of cancer staging, prognosis and therapeutic decision-making. Rather than functioning as passive filters, tumor-draining lymph nodes are biologically active compartments that undergo vascular, stromal, and immune remodeling before and during metastatic colonization. Tumor-derived soluble mediators, extracellular vesicles, and non-coding

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RNAs can reach regional lymph nodes through afferent lymphatics and contribute to pre-metastatic niche formation, while stromal and myeloid populations further shape the nodal microenvironment. Within lymph-node sinuses, specialized scavenger and lectin-like receptors expressed by endothelial cells and macrophages constitute a molecular interface that may be involved in tumor-cell adhesion, retention, and immune regulation. Stabilin-1/Clever-1, Stabilin-2, LYVE-1, and MARCO are among the most relevant candidates, although the nature and strength of the supporting evidence differ between receptors. Following metastatic colonization, progressive tumor-stroma interactions may generate vascular dysfunction, increased intranodal pressure, extracellular matrix remodeling, hypoxia, immunosuppression, tumor-cell-intrinsic resistance, and dormancy, all of which may contribute to therapeutic persistence. These mechanisms are particularly relevant to para-aortic lymph-node metastases, which have been discussed as potential sanctuary sites. However, direct human evidence demonstrating systematically reduced therapeutic exposure within para-aortic metastases remains limited. This review integrates pre-metastatic nodal conditioning, scavenger receptor biology, and mechanisms of treatment resistance within a temporal model of lymph node metastatic progression and critically examines whether para-aortic nodal disease may acquire sanctuary-like behavior.

Keywords: Drug Resistance; Neoplasm; Extracellular Vesicles; Lymph Nodes; Lymphatic Metastasis; Receptors; Scavenger

RESUMO

A metastização ganglionar constitui um importante determinante do estadiamento, do prognóstico e da decisão terapêutica em oncologia. Em vez de funcionarem como filtros passivos, os gânglios linfáticos de drenagem tumoral constituem compartimentos biologicamente ativos, sujeitos a remodelação vascular, estromal e imunitária antes e durante a colonização metastática. Mediadores solúveis, vesículas extracelulares e RNAs não codificantes derivados do tumor podem alcançar os gânglios regionais através dos vasos linfáticos aferentes e contribuir para a formação do nicho pré-metastático, enquanto populações estromais e mielóides modulam, adicionalmente, o microambiente ganglionar. Nos sinusoides, recetores *scavenger* e do tipo lectina expressos por células endoteliais e macrófagos constituem uma interface molecular potencialmente envolvida na adesão, retenção e regulação imunitária das células tumorais. Stabilin-1/Clever-1, Stabilin-2, LYVE-1 e MARCO apresentam particular relevância, embora a natureza e a robustez da evidência disponível sejam heterogêneas. Após a colonização metastática, a interação progressiva entre tumor e estroma pode originar disfunção vascular, aumento da pressão intraganglionar, remodelação da matriz extracelular, hipóxia, imunossupressão, mecanismos intrínsecos de resistência e dormência tumoral, o que pode contribuir para a persistência terapêutica. Estes mecanismos assumem interesse adicional nas metástases ganglionares para-aórticas, frequentemente discutidas como potenciais áreas de santuário. Contudo, a evidência humana direta de uma exposição terapêutica sistematicamente reduzida nestas localizações permanece limitada. Esta revisão integra o condicionamento ganglionar pré-metastático, a biologia dos recetores *scavenger* e os mecanismos de resistência terapêutica num modelo temporal da progressão metastática ganglionar, avaliando criticamente se a doença ganglionar para-aórtica pode adquirir um comportamento semelhante a um santuário.

Palavras-chave: Gânglios Linfáticos; Metástase Linfática; Recetores Depuradores; Resistência a Fármacos Antineoplásicos; Vesículas Extracelulares

INTRODUCTION

Lymph node (LN) involvement is one of the most clinically informative manifestations of cancer dissemination and remains a major determinant of pathological staging, prognosis, and therapeutic decision-making across multiple solid malignancies.¹ Historically, regional LNs were regarded primarily as passive filters in which tumor cells transported through afferent lymphatic vessels became mechanically trapped. This concept has progressively been replaced by a more dynamic model in which tumor-draining lymph nodes (TDLNs) constitute biologically active microenvironments

that can be remodeled by the primary tumor before, during, and after metastatic seeding.^{1,2}

The anatomical organization of the lymph node is particularly suited to this role. Afferent lymph continuously delivers soluble antigens, cytokines, growth factors, metabolites, extracellular vesicles (EVs), immune cells, and, ultimately, disseminated tumor cells to the subcapsular sinus.³ Lymphatic endothelial cells (LECs), sinus macrophages, fibroblastic stromal cells, and neighboring immune populations therefore constitute an early interface between the primary tumor and the regional

lymphatic environment.⁴ Tumor-induced alterations in these compartments may precede histologically detectable metastatic colonization and include lymphangiogenesis, stromal remodeling, altered antigen handling, and progressive immune dysregulation. These observations underpin the concept of the lymph-node pre-metastatic niche.^{4,5}

Nodal dissemination is not, however, an obligatory intermediate step towards systemic metastasis. Phylogenetic analyses of human colorectal cancer have shown that nodal and distant metastases may arise independently from different primary-tumor subclones.⁶ Conversely, experimental lineage-tracing studies have demonstrated that tumor cells established within metastatic LNs can invade nodal blood vessels, enter the systemic circulation, and subsequently seed distant organs.^{7,8} The biological significance of nodal metastasis is therefore context-dependent: it may reflect metastatic competence, provide a site for tumor evolution, or, in some settings, contribute directly to further dissemination.

A particularly relevant component of the nodal interface is the expression of scavenger receptors (SRs) and related lectin-like receptors by sinusoidal endothelial cells and macrophages. SRs comprise structurally diverse proteins involved in ligand recognition, internalization, adhesion, clearance, and immune regulation.^{9,10} A characteristic scavenger/lectin-receptor signature has been identified in human LN sinuses, raising the possibility that receptor-ligand interactions contribute to the retention and subsequent fate of lymph-borne malignant cells.¹¹

For the surgeon, these concepts extend beyond mechanistic interest. Nodal involvement influences disease staging, the extent of lymphadenectomy, indications for adjuvant treatment, and radiation-field design. In selected anatomical settings, particularly para-aortic lymph-node disease, decisions regarding systemic therapy, locoregional treatment, and surgical resection remain challenging because the biological significance and therapeutic behavior of nodal metastases vary substantially between tumor types.^{12,13}

Tumor-derived EVs are considered an active component of early nodal conditioning, capable of modifying the lymphatic endothelial, stromal, and immune compartments before tumor-cell arrival.¹⁴ These changes may establish a microenvironment more permissive to subsequent metastatic seeding and may alter the cellular context in which the specialized scavenger/lectin-receptor repertoire of lymph-node sinuses operates.^{14,15} Once tumor cells reach the node, scavenger-receptor-mediated adhesion, ligand recognition,

and immune regulation may contribute to their retention and successful colonization. Progressive metastatic growth can subsequently lead to vascular dysfunction, extracellular matrix (ECM) remodeling, hypoxia, immunosuppression, tumor cell dormancy, and other mechanisms capable of reducing therapeutic efficacy.^{10,14}

Within this framework, sanctuary-like behavior is viewed as a potential late property of an established and progressively remodeled nodal metastasis.¹⁶ A direct causal sequence linking EV-mediated conditioning to scavenger receptor induction, tumor cell capture, and chemotherapy resistance has not yet been demonstrated. Nevertheless, integrating these temporally related processes provides a biologically testable model for understanding how a tumor-draining lymph node may evolve from an immune-organizing compartment into a metastasis-supporting and treatment-resistant niche.^{17,18} Para-aortic lymph-node metastases provide a clinically relevant setting in which to examine whether this evolution can, in selected circumstances, generate true pharmacological sanctuary behavior.¹⁹

Accordingly, this review integrates scavenger-receptor biology with pre-metastatic niche formation, EV-mediated intercellular communication, and the vascular, stromal, metabolic, and immune determinants of treatment resistance, with particular emphasis on para-aortic nodal disease.

THE METASTATIC CASCADE TO LYMPH NODES

LYMPHATIC INVASION AND DISSEMINATION

Lymphatic metastasis requires coordinated changes in tumor-cell phenotype, ECM organization, lymphatic vessel biology, and host responses. Although epithelial-to-mesenchymal transition has traditionally been presented as a discrete event, current evidence supports the broader concept of epithelial-mesenchymal plasticity (EMP), in which malignant cells occupy dynamic epithelial, mesenchymal, and hybrid states.^{20,21} Such plasticity can enhance motility, invasive capacity, and adaptation while preserving epithelial features compatible with collective migration and subsequent proliferation (Fig. 1).²²

Local invasion also requires restructuring of basement membranes and interstitial ECM. Tumor cells interact with fibroblasts, macrophages, and other stromal populations that provide proteolytic, chemotactic, and survival signals, facilitating progression towards lymphatic vessels.^{23,24} The VEGF-C/VEGFR-3 axis is one of the best-established regulators of tumor-associated lymphangiogenesis. Preclinical

The Lymph-Node Metastatic Cascade: From Priming to Sanctuary

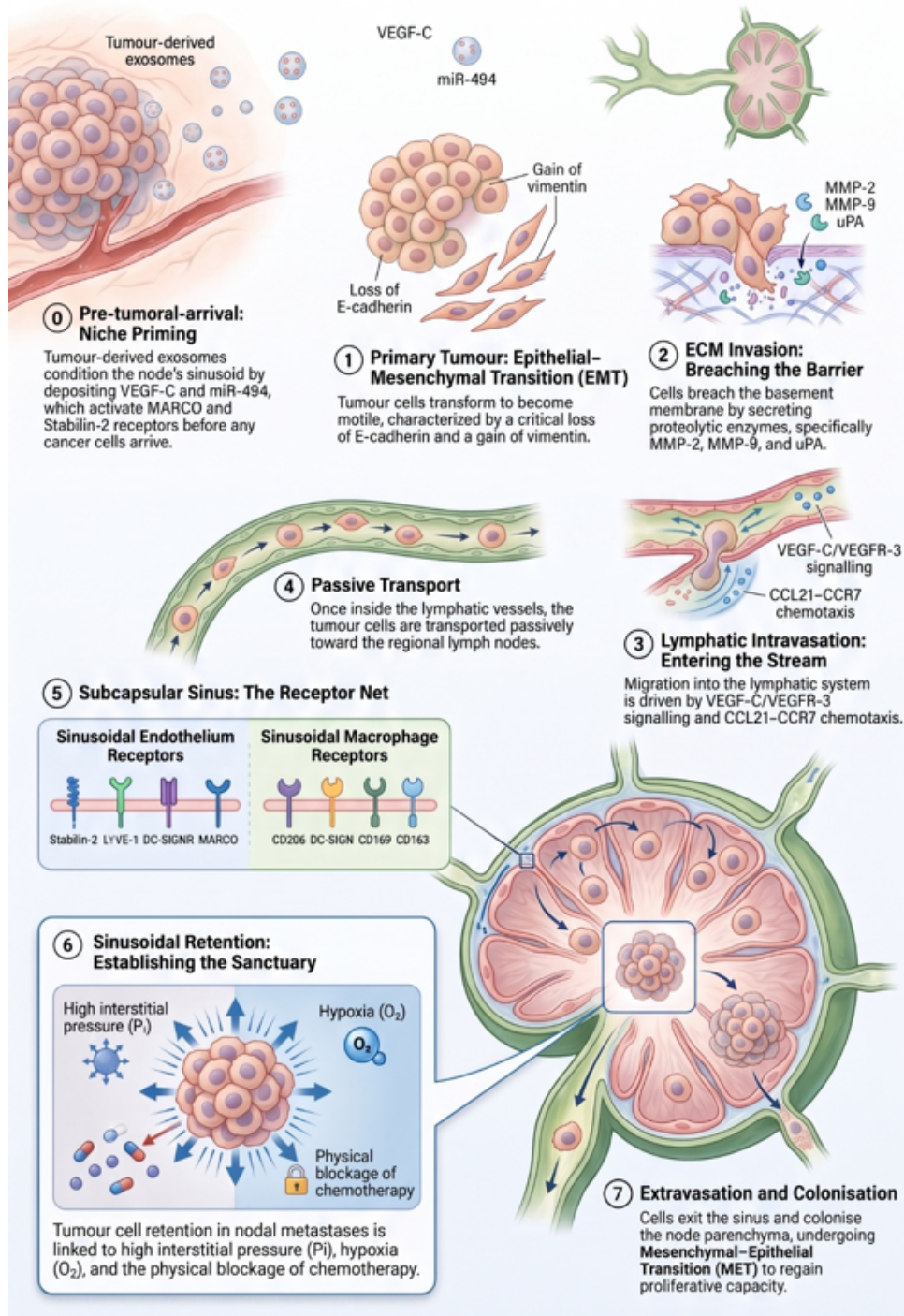


Figure 1. Lymph node metastatic cascade with scavenger receptors. (0) Pre-tumoral-arrival phase: tumour-derived exosomes condition the sinusoid, depositing VEGF-C and miR-494 and activating MARCO and Stabilin-2 before any tumour cell arrives; (1) primary tumour with cells undergoing EMT (loss of E-cadherin, gain of vimentin); (2) extracellular-matrix invasion with MMP-2/MMP-9 and uPA degrading the basement membrane; (3) lymphatic intravasation with VEGF-C/VEGFR-3 signalling and CCL21-CCR7 chemotaxis; (4) passive transport in lymphatic vessels to the sentinel node; (5) capture in the subcapsular sinus by compartmentalised scavenger receptors — on the sinusoidal endothelium (Stabilin-2, LYVE-1, DC-SIGNR, MARCO) and sinusoidal macrophages (CD206, DC-SIGN, CD169, CD163), with CD36 and Stabilin-1 completing the repertoire; (6) sinusoidal retention through receptor-ligand interactions that, by generating a microenvironment of high interstitial pressure and low oxygenation, physically and chemically block chemotherapy — the 'sanctuary-site' consequence; (7) extravasation and colonisation of the node parenchyma with mesenchymal-epithelial transition (MET), restoring proliferative capacity.

studies show that VEGF-C can expand lymphatic networks within draining nodes before apparent metastasis.²⁵ Tumor cells may also exploit physiological trafficking pathways such as CCL21-CCR7 to migrate towards lymphatic vessels.²⁶ Once tumor cells enter afferent lymphatic vessels, they are carried to the draining lymph node, where they first encounter the subcapsular sinus. Reaching the node, however, does not necessarily result in metastatic growth. Tumor cells must evade local immune control, interact with sinus-resident macrophages and lymphatic endothelial cells, and gain access to the nodal parenchyma. Those that persist must then adapt to the local microenvironment and exploit stromal, metabolic, and vascular support to establish a growing metastatic deposit.^{19,27}

PRE-METASTATIC NICHE FORMATION

The concept of a pre-metastatic niche describes molecular and cellular alterations occurring within a future metastatic site before the arrival of detectable malignant cells. Within TDLNs, these changes can involve lymphatic expansion, endothelial activation, stromal reorganization, and progressive modification of immune function.²⁸ Tumor-derived soluble mediators, EVs, and other molecular signals transported through afferent lymph provide a direct route for communication between the primary tumor and the regional node.²⁹

Importantly, pre-metastatic conditioning is not driven by a single pathway or cell type. Tumor-derived factors act together with lymphatic endothelial, stromal, and immune cells to reshape the draining lymph node.^{4,30} At the same time, the TDLN remains a major site of tumor-antigen presentation and T-cell priming. Its role is therefore not simply pro- or anti-tumor: immune surveillance and the development of a metastasis-permissive environment can coexist, and their relative contributions may change during tumor progression and across cancer types.³¹

STROMAL CELLS AND EXTRACELLULAR-MATRIX REMODELING

Fibroblastic populations contribute to metastatic progression at several stages. Within the primary tumor, cancer-associated fibroblasts (CAFs) can promote ECM remodeling, tumor-cell invasion, and lymphatic dissemination through matrix deposition, protease production, growth factors, and chemokines.²³ CAF-derived signals can also influence lymphatic endothelial cells and immune cell recruitment, thereby linking stromal remodeling to lymphatic progression.³²

The stromal landscape of the lymph node differs substantially from that of the primary tumor. Fibroblastic reticular

cells (FRCs) form a specialized network that supports lymph node organization and helps regulate immune cell trafficking, chemokine distribution, and antigen presentation. Importantly, these stromal cells can respond to tumor-derived signals before metastatic cells arrive, allowing the primary tumor to reshape both the architecture and immune function of the draining lymph node in advance of colonization.^{5,30}

After the arrival of metastatic cells, fibroblastic populations within nodal lesions may acquire phenotypic and functional states distinct from those of normal LN stroma. Such populations are sometimes described as metastasis-associated fibroblasts (MAFs) and may contribute to ECM deposition, tumor-cell survival, angiogenic signaling, and immune suppression.²³ Whether these states derive predominantly from resident nodal fibroblasts, recruitment of progenitor populations, or migration of tumor-associated fibroblasts is likely to depend on tumor type and remains incompletely defined in human LNs.

Metastatic dissemination is therefore not exclusively tumor-cell autonomous. Platelets, neutrophils, macrophages, and stromal cells can provide survival or immune-protective signals during dissemination and colonization.^{20,23} However, the contributions of these multicellular interactions vary across experimental models, and there is currently insufficient evidence for a general mechanism whereby fibroblasts physically accompany tumor cells through the lymphatic circulation to establish nodal metastases.

NON-CODING RNAs IN METASTATIC CONDITIONING

Non-coding RNAs (ncRNAs) constitute an additional layer of regulation of metastatic behavior. microRNAs (miRNAs/miRs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs) can influence gene-expression processes involved in EMP, cell survival, stem-like properties, lymphangiogenesis, immune regulation, and stromal activation.^{24,33}

Several ncRNAs identified in the literature are relevant to these processes. miR-21 and miR-155 have been implicated in tumor progression and immune regulation across multiple malignancies, whereas members of the miR-200 and miR-34 families are important regulators of epithelial-mesenchymal plasticity.^{21,34} Among lncRNAs, MALAT1 has been associated with tumor-cell plasticity, proliferation, and metastatic behavior, whereas GAS5 more commonly exerts tumor-suppressive functions by regulating proliferation, apoptosis, and treatment response.^{35,36} Importantly, the biological effects of individual ncRNAs are highly context-dependent

and may vary according to cellular origin, molecular targets, and disease stage.³⁷

Evidence linking specific ncRNAs directly to human LN pre-metastatic niche formation remains more limited than that supporting their broader roles in cancer progression. Their relevance to nodal conditioning becomes particularly important when ncRNAs are incorporated into EVs, which can protect RNA cargo from extracellular degradation and permit transfer to endothelial, stromal, and immune cells.¹⁴

EXTRACELLULAR VESICLES AND NODAL CONDITIONING

EVs are a heterogeneous population of membrane-delimited particles released by virtually all cell types and capable of transferring biologically active molecules between cells. Their cargo may include proteins, lipids, metabolites and different classes of nucleic acids and can reflect both the cellular origin and the physiological or pathological state of the releasing cell. EVs can therefore act as mediators of intercellular communication by modifying the phenotype and function of recipient cells.³⁸

The lymphatic system provides a particularly relevant route for the dissemination of tumor-derived EVs. Interstitial fluid from the primary tumor drains into the initial lymphatic vessels and is transported directly towards the regional TDLNs. Tumor-derived EVs can therefore expose LECs, sinus macrophages, FRCs, and other nodal populations to tumor-associated information before metastatic cells arrive.^{16-18,39}

One of the best-supported consequences is lymphatic endothelial remodeling. Hood *et al*⁴⁰ demonstrated that melanoma-derived EVs accumulate in sentinel LNs and induce molecular and structural changes preceding metastatic colonization. García-Silva *et al*¹⁶ subsequently showed that melanoma-derived small EVs enriched in NGFR/p75NTR are transported through lymphatic vessels and internalized by LECs, activating ERK and NF- κ B signaling, increasing ICAM-1 expression and promoting lymphangiogenesis and tumor-cell adhesion; disruption of EV-associated NGFR reduced nodal metastasis in preclinical models.

Evidence from other malignancies supports the existence of functionally specialized EV subpopulations. In bladder cancer, ITGA6-positive EVs targeted lymphatic vessels via an ITGA6-CD151 interaction and transferred circRNA-LIPAR to LECs, thereby inducing an E-selectin-associated lymphatic remodeling pathway; experimental disruption of this pathway reduced LN metastasis.⁴¹ In head and neck

cancer, tumor-derived EVs modified FRCs via an IFNGR1/JAK1/STAT1-associated pathway, thereby increasing PD-L1 expression and impairing CD8⁺ T-cell activity.⁴²

EV-mediated conditioning also affects immune regulation. Leary *et al*¹⁸ demonstrated rapid transport of melanoma-derived EVs to draining nodes, with uptake by LECs and medullary sinus macrophages. EV-associated tumor antigens could be presented through MHC class I by LECs and promoted the deletion of tumor-antigen-specific CD8⁺ T cells.

Collectively, these findings support a model of multicompartmental nodal conditioning in which tumor-derived EVs can modify lymphatic vessel phenotype, endothelial adhesion pathways, stromal organization, antigen handling, and immune responses. However, a direct mechanistic relationship between EV-mediated nodal conditioning and regulation of the sinusoidal scavenger-receptor repertoire has not yet been demonstrated.

SCAVENGER RECEPTORS IN LYMPH-NODE METASTASIS THE SINUSOIDAL SCAVENGER/LECTIN-RECEPTOR SIGNATURE

Once lymph-borne tumor cells reach the conditioned node, the sinusoidal compartment becomes a critical interface between disseminated cells and the host microenvironment.⁴³ Scavenger receptors comprise a structurally heterogeneous family of cell-surface receptors with broad ligand-recognition and clearance functions. Individual members additionally participate in adhesion, endocytosis, lipid metabolism, antigen handling, leukocyte trafficking, and immune regulation.^{10,44}

Martens *et al*¹¹ provided the principal basis for considering this receptor repertoire in LN metastasis. Comparative gene-expression profiling of human LNs and tonsillar tissue identified a 13-gene scavenger/lectin-receptor signature preferentially associated with LN sinuses. Importantly, Martens *et al* did not assess tumour-cell binding or metastatic colonisation. The reported signature comprised CD36, CD68, CD163, CD206 (MRC1), CD209 (DC-SIGN), CLEC4M (L-SIGN/DC-SIGNR), LYVE-1, MARCO, MSR1, STAB1 (Stabilin-1/Clever-1), STAB2 (Stabilin-2), SIGLEC1 (CD169/sialoadhesin), and THBD (thrombomodulin) as the thirteenth gene. In the original study, nine of these 13 markers were validated by immunohistochemistry: Stabilin-2, LYVE-1, DC-SIGNR, MARCO, Stabilin-1, the mannose receptor/MMR (MRC1/CD206), DC-SIGN, sialoadhesin (SIGLEC1/CD169), and CD163. The remaining signature genes were not validated as sinusoidal proteins by IHC in that study. We have

therefore removed any implication that the Martens study itself established tumour-cell adhesion and now distinguish its expression findings from subsequent receptor-specific functional studies. These findings support the possibility that retention of lymph-borne malignant cells involves active molecular interactions, but expression alone does not establish a causal metastatic role for every receptor.

STABILIN-1/CLEVER-1

Stabilin-1, also known as Clever-1, is expressed by selected endothelial and macrophage populations and participates in scavenging, leukocyte trafficking, and immune regulation.⁴⁵ Karikoski *et al*⁴⁶ demonstrated that loss or inhibition of Clever-1 reduced tumor progression and metastatic burden in *in vivo* models.

These findings support a functional role for Clever-1 in tumor progression and lymphatic dissemination. More recent work has increasingly highlighted its immunoregulatory function, particularly in maintaining suppressive macrophage states.⁴⁷ However, evidence that Stabilin-1 acts as a major physical anchor for metastatic tumor cells within human lymph-node sinuses remains limited.

STABILIN-2 AND LYVE-1

Stabilin-2 is expressed by specialized sinusoidal endothelial populations and possesses ligand-binding and adhesive properties compatible with a role in tumor-cell retention. In tongue carcinoma, homotypic Stabilin-2 interactions were reported to facilitate tumor-cell adhesion and were associated with LN metastasis.⁴⁸ This provides receptor-specific functional evidence, although its relevance across other malignancies has not been established.

LYVE-1 is a hyaluronan-binding receptor expressed by LECs and selected macrophage populations. Experimental studies have demonstrated hyaluronan-dependent interactions between tumor cells and LYVE-1-expressing cells.^{49,50} Its real contribution to human nodal metastatic colonization remains uncertain.

MARCO

MARCO is a class A SR expressed predominantly by macrophages. Its strongest evidence in cancer concerns the modulation of tumor-associated macrophage phenotype rather than direct tumor-cell adhesion.⁵¹ Georgoudaki *et al*⁵² demonstrated that antibody targeting of MARCO reprogrammed tumor-associated macrophages, inhibited tumor progression and metastasis, and enhanced the efficacy of immune-checkpoint blockade in preclinical models.

Eisinger *et al*⁵³ subsequently showed that MARCO targeting enhanced natural-killer-cell-mediated tumor killing. MARCO may therefore contribute to metastatic permissiveness predominantly by regulating the myeloid immune environment.⁵¹ Its expression in nodal sinus macrophages provides a plausible interface between lymph-borne tumor material and local immune responses, but direct MARCO-dependent capture of human metastatic cells within LN sinuses remains unproven.

SINUS MACROPHAGES AND CONTEXT-DEPENDENT METASTATIC CONTROL

Sinus macrophages should not be viewed as uniformly prometastatic. CD169-positive macrophages capture lymph-borne particles and antigens and can contribute to local antitumor immunity. In mouse models of breast cancer, Tacconi *et al*⁵⁴ found that CD169-positive macrophages were the predominant macrophage population in naïve lymph nodes and expanded markedly in tumor-draining nodes in response to tumor-derived signals. Depletion of these populations increased metastatic burden, with subcapsular sinus macrophage depletion particularly favoring distant lung metastasis. Notably, this protective effect was linked to B-cell responses in the draining node, as B-cell depletion abolished the loss-associated difference in metastasis associated with CD169-positive macrophages. These findings illustrate that sinus macrophages can actively restrain, rather than simply facilitate, metastatic progression.

Conversely, subcapsular sinus macrophages can also support metastatic progression. In melanoma models, Virgilio *et al*⁵⁵ showed that these cells promoted sentinel lymph-node metastasis through an IL-1 α -STAT3-dependent pathway. Their effects are therefore highly context-dependent, varying with anatomical location, activation state, tumor type, and the surrounding signaling environment. Rather than being intrinsically pro- or antimetastatic, the scavenger- and lectin-receptor-rich sinusoidal compartment may be better viewed as a specialized tumor-host interface, where tumor-cell retention and processing intersect with local immune regulation.

FROM NODAL COLONISATION TO CHEMOTHERAPY RESISTANCE

Following successful tumor-cell retention and metastatic establishment, progressive expansion of the nodal lesion remodels normal LN architecture and generates new selective pressures.^{31,56} At this stage, therapeutic persistence may emerge through interacting vascular, stromal, metabolic, immunological and tumor-cell-intrinsic mechanisms. Importantly,

Table 1. Relevant scavenger receptors to lymph node metastasis.

Receptor	Main relevant populations	Proposed role	Current evidence
Stabilin-1/ Clever-1	Macrophages/ endothelial cells	Scavenging, trafficking and immune regulation	Functional preclinical evidence; clinically druggable pathway ^{46,47}
Stabilin-2	Sinusoidal endothelial cells	Adhesion and tumour-cell retention	Direct experimental evidence in selected tumour models ⁴⁸
LYVE-1	LECs; selected macrophages	Hyaluronan-dependent interactions	Experimental adhesion evidence ^{49,50}
MARCO	Macrophages	Myeloid immune regulation and metastatic permissiveness	Strong preclinical immunological evidence ⁵¹⁻⁵³
CD169/Siglec-1	Sinus macrophages	Particle/antigen capture and immune regulation	Context-dependent, including tumour-restrictive effects ^{54,55}

the mechanisms responsible for initial tumor-cell retention should be distinguished from those responsible for resistance within an established metastasis.³¹ Current evidence does not demonstrate that SR-mediated tumor-cell adhesion directly causes the stromal and vascular abnormalities that later impair treatment efficacy.

STROMAL AND VASCULAR BARRIERS

Systemically administered anticancer agents reach LNs predominantly through their blood vasculature, although physicochemical characteristics and lymphatic transport also influence tissue exposure. It has been demonstrated that experimentally increasing nodal vascular permeability did not necessarily increase the accumulation of systemically administered chemotherapy, illustrating that permeability alone does not determine effective drug delivery.⁵⁷

Progressive metastatic growth can alter nodal architecture, vascular compression and tissue mechanics. Experimental studies indicate that solid stress and altered vessel function can impair perfusion and therapeutic delivery in desmoplastic tumours, while studies of metastatic LNs suggest that intranodal pressure can influence the response to lymphatic drug delivery.⁵⁸ However, these findings do not show that elevated interstitial fluid pressure generally limits small-molecule cytotoxic chemotherapy. For bulky nodal metastases, any analogous effect remains an inference requiring site-specific validation. The distinction is important because small-molecule cytotoxics reach tissues predominantly through diffusion and vascular delivery, whereas interstitial-pressure effects are particularly relevant to macromolecules and nanoparticles.

General solid-tumor studies provide additional mechanistic context. Hyaluronan accumulation can compromise vascular function and therapeutic delivery, whereas stromal

modulation and decompression of tumor vessels can improve perfusion.^{59,60} Such findings demonstrate how ECM-rich tumor microenvironments can influence pharmacological access, but direct extrapolation to metastatic LNs requires site-specific evidence.

HYPOXIA, INTRINSIC RESISTANCE, AND DORMANCY

Hypoxia is another potential contributor to chemotherapy resistance. Direct measurements have demonstrated marked hypoxic regions in human LN metastases.⁶¹ Reduced oxygenation can activate HIF-dependent signaling, alter cellular metabolism, promote plasticity, and reduce responsiveness to therapies whose efficacy depends directly or indirectly on oxygen availability.⁶²

Tumor-associated acidosis and nutrient limitation may further modify drug uptake and cellular sensitivity.⁶³ These phenomena occur broadly across solid tumors and should therefore be interpreted as properties that metastatic LNs may acquire rather than unique characteristics of the nodal compartment.

DRUG-EFFLUX PUMPS AND CELL-INTRINSIC RESISTANCE

ATP-binding cassette (ABC) transporters and related cellular mechanisms can reduce intracellular concentrations of anticancer agents and contribute to multidrug resistance. Alterations in DNA-damage responses, apoptosis, metabolism, and cell state may further determine treatment sensitivity.^{63,64} Evidence is currently insufficient to conclude that para-aortic lymph node (PALN) metastases systematically overexpress specific transporters such as ABCB1 or ABCC1, or particular drug-metabolizing enzymes, relative to metastases at other anatomical sites. Demonstrating such a mechanism would require paired molecular and pharmacological studies.

TUMOR DORMANCY

Tumor-cell dormancy provides a mechanism of therapeutic persistence that is conceptually distinct from inadequate drug exposure. Disseminated tumor cells may enter reversible quiescent or slowly proliferative states and subsequently contribute to delayed relapse.^{65,66} Primary experimental work has implicated ERK/p38 signalling in the balance between proliferative and dormant states,⁶⁷ while the broader dormancy literature supports roles for the microenvironment, immune surveillance and tissue-specific niches.^{65,66} Evidence that surgery itself reliably “awakens” dormant nodal disease remains context-dependent and should not be presented as an established clinical mechanism. Therapies preferentially targeting proliferating cells may therefore show reduced efficacy against dormant populations. Dormancy is also influenced by ECM interactions, vascular niches, immune surveillance, and tissue-specific signals.⁶⁶ Therefore, the persistence of viable malignant cells after chemotherapy does not, by itself, demonstrate a pharmacological sanctuary. Residual disease may instead reflect quiescence, intrinsic resistance, or microenvironmental protection.

IMMUNE-MEDIATED TREATMENT RESISTANCE

The immune microenvironment can also shape therapeutic response within metastatic LNs. Lamorte *et al*⁶⁸ showed that medullary sinus macrophages can engulf therapy-damaged tumor cells and, in doing so, induce IL-33 production and regulatory T-cell activation, ultimately limiting CD8⁺ T-cell responses. At the same time, tumor-draining LNs remain an important source of tumor-reactive CD8⁺ T cells, including stem-like populations capable of sustaining antitumor immunity.⁶⁹ Studies in human samples further show that regional LNs can support dynamic T-cell responses during immune-checkpoint blockade, whereas these responses may become impaired once metastatic involvement creates a more immunosuppressive nodal environment.⁷⁰ Metastatic LNs should therefore be viewed as treatment-modulating ecosystems in which drug exposure, tumor-cell state, and local immune function converge to influence therapeutic outcome.

PARA-AORTIC LYMPH NODES AS SANCTUARY SITES

A pharmacological sanctuary site is an anatomical or biological compartment in which effective therapeutic exposure is consistently reduced by barriers to drug penetration, distribution, or activity.⁷¹ In the present context, no second, PALN-specific pharmacological barrier has been demonstrated in humans; proposed vascular, stromal or physical barriers should therefore be regarded as mechanisms

that may modify treatment response rather than as proven causes of reduced drug exposure.

PALN metastases provide a relevant setting for investigating sanctuary-like resistance. Established lesions may develop vascular dysfunction, altered tissue mechanics, hypoxia, stromal remodeling, immune suppression, and intrinsic drug resistance.^{57,72} However, these features do not by themselves establish a pharmacological sanctuary, because they may affect treatment response without producing a reproducible reduction in drug concentration or target engagement. What remains uncertain is whether the para-aortic location itself creates a reproducible pharmacological disadvantage compared with other metastatic sites.

Direct human studies comparing drug concentrations or pharmacodynamic target engagement in PALN metastases with matched primary tumors or metastases at other sites are lacking or very limited.⁷³ Accordingly, the term “sanctuary” should be used here as a hypothesis or sanctuary-like phenotype rather than as an established pharmacological property. Poor outcomes associated with PALN involvement may also reflect occult systemic dissemination or adverse tumour biology, rather than reduced drug exposure at the para-aortic site itself. The clinical evidence should therefore be interpreted separately for different malignancies.

COLORECTAL CANCER

PALN metastases are uncommon in colorectal cancer and are generally classified as distant metastatic disease. Evidence regarding surgical management derives predominantly from retrospective series.

A systematic review and meta-analysis reported an association between para-aortic lymphadenectomy and improved long-term survival in selected patients, particularly after complete resection and in the presence of limited nodal burden.⁷⁴ These findings are highly susceptible to selection bias and do not establish a causal survival benefit from surgery.

The clinical uncertainty is reflected in contrasting contemporary viewpoints. Glynne-Jones and Harrison⁷⁵ argued that routine PALN resection should not be recommended because para-aortic disease may represent occult systemic dissemination and prospective evidence is lacking. Peacock,⁷⁶ in contrast, argued that radical local treatment may be justified in carefully selected patients with isolated or limited oligometastatic disease. Available evidence therefore supports biological heterogeneity rather than a uniform pharmacologically protected para-aortic compartment.

GASTRIC CANCER

Gastric cancer provides important evidence against universal chemotherapy inaccessibility of PALN disease. In the phase II JCOG0405 study, patients with bulky regional and/or para-aortic nodal metastases received neoadjuvant S-1 plus cisplatin followed by D2 gastrectomy with para-aortic LN dissection. The R0 resection rate was 82%, while the 3- and 5-year overall survival rates were approximately 59% and 53%, respectively.⁷⁷ The study did not establish an independent survival benefit from para-aortic dissection because it lacked a randomised control group. It nevertheless demonstrated clinically meaningful systemic treatment responsiveness in extensive nodal disease.

A 2026 integrated analysis of three JCOG phase II studies further evaluated the therapeutic value of para-aortic dissection in gastric cancer with extensive nodal metastases.⁷⁸ These studies emphasise systemic-treatment response and patient selection rather than intrinsic pharmacological isolation of para-aortic disease.

CERVICAL CANCER

In cervical cancer, PALN involvement is an important prognostic and treatment-planning determinant. Para-aortic irradiation has an established role in appropriately selected patients,⁷⁹ and contemporary ESGO/ESTRO/ESP recommendations incorporate nodal distribution into definitive chemoradiotherapy planning, including extended-field treatment and nodal dose escalation when indicated.⁸⁰ The ability to achieve

disease control using multimodal treatment further indicates that the adverse prognosis associated with PALN involvement does not itself demonstrate sanctuary pharmacology.

PHARMACOLOGICAL SANCTUARY OR TREATMENT-RESISTANT NICHE?

The available evidence supports a continuum rather than a binary distinction between ordinary nodal metastasis and pharmacological sanctuary. A metastatic node may progressively acquire features associated with treatment resistance, including vascular dysfunction, stromal remodelling, hypoxia, immune suppression and tumor-cell quiescence.^{81,82} Whether these changes reduce effective therapeutic exposure sufficiently to constitute a true sanctuary remains an empirical question.

The clinical meaning of PALN involvement differs across tumor types: it may represent systemic or selected oligo-metastatic disease in colorectal cancer,⁸³ extensive but chemotherapy-responsive nodal disease in gastric cancer,⁸⁴ and a radiotherapy-planning determinant in cervical cancer.⁸⁵ Anatomical depth alone would not be expected to reduce exposure to an intravenously administered drug. Demonstration of true sanctuary behavior ultimately requires direct pharmacokinetic or pharmacodynamic evidence.

THERAPEUTIC IMPLICATIONS

Understanding the biological organisation of the nodal metastatic niche identifies several potential therapeutic opportunities.

Table 2. Clinical evidence and management of para-aortic lymph node (PALN) metastasis by tumor type

Tumor type	Clinical significance of PALN involvement	Key evidence on treatment/management	Practical implication for surgeons
Colorectal cancer	Uncommon; generally classified as distant metastatic disease	Retrospective series only; meta-analysis suggests a survival association with PALN lymphadenectomy after complete resection and limited nodal burden, but at high risk of selection bias ⁷⁴ ; contrasting expert positions on routine resection. ^{75,76}	Individualize: radical resection may be considered only in carefully selected, oligometastatic patients; not a standard approach.
Gastric cancer	Extensive regional/PALN disease historically associated with poor prognosis	JCOG0405 (neoadjuvant S-1+cisplatin, D2 gastrectomy with PALN dissection): R0 82%; 3-/5-year OS ~59%/53% ⁷⁷ ; 2026 integrated analysis of three JCOG phase II trials. ⁷⁸	Extensive PALN disease is not synonymous with unresectability; systemic response and patient selection, not anatomical location alone, should guide the decision.
Cervical cancer	Important prognostic and radiotherapy-planning determinant	Para-aortic irradiation established in selected patients ⁷⁹ ; ESGO/ESTRO/ESP recommendations incorporate nodal distribution into definitive chemoradiotherapy planning. ⁸⁰	PALN status should inform radiation-field design (extended-field treatment, nodal dose escalation), not be treated as a uniformly resistant compartment.

Among SR-directed approaches, Stabilin-1/Clever-1 currently has the greatest clinical maturity. Bexmarilimab is a humanised antibody targeting Clever-1-positive immunosuppressive macrophages. In the phase I/II MATINS study of refractory solid tumors, treatment was associated with macrophage activation, increased immune signalling and disease control in subsets of patients.⁸⁶ These findings establish Clever-1 as a clinically druggable immunoregulatory pathway but do not demonstrate prevention of nodal tumor-cell capture.

Further evidence for pharmacological targeting of Clever-1 has emerged from BEXMAB, in which bexmarilimab combined with azacitidine showed clinical activity in high-risk myelodysplastic syndrome and relapsed or refractory acute myeloid leukaemia.⁸⁷ Although these findings do not directly concern nodal metastasis, they strengthen evidence that Clever-1-associated macrophage states are therapeutically modifiable. Macrophage-reprogramming therapies constitute a broader and increasingly active field of cancer immunotherapy.⁸⁸

MARCO-directed therapy remains predominantly preclinical. Antibody-mediated targeting can modify macrophage phenotype, enhance NK-cell activity and improve checkpoint-blockade efficacy in experimental models.^{52,53}

Pre-metastatic EV pathways provide another potential intervention point. The NGFR-dependent melanoma pathway and ITGA6-dependent bladder-cancer pathway demonstrate that defined EV-associated molecules can participate functionally in nodal conditioning.^{16,41} Selective targeting of such pathways may be more biologically feasible than global inhibition of EV secretion, which would interfere with physiological intercellular communication.

ncRNA-directed strategies, including antisense oligonucleotides and miRNA-based approaches, remain largely preclinical.⁸⁹ Their translation to nodal disease will depend on molecular specificity and effective delivery to lymphatic tissues.

Improving nodal drug delivery represents a complementary strategy. Engineered delivery systems can exploit particle size, surface chemistry and targeting ligands to alter lymphatic trafficking.⁹⁰ In experimental metastatic-LN models, lymphatic administration of cisplatin increased target-node exposure and reduced metastatic growth relative to systemic delivery.⁹¹ Translation to deep PALN disease requires further investigation.

Therapeutic manipulation of TDLNs must also account for their immune function. Tumor-free or partially preserved draining nodes contain progenitor tumor-reactive T-cell populations capable of contributing to systemic antitumor responses.⁹² In experimental metastatic models, delaying TDLN irradiation rather than administering it concomitantly with primary-tumor irradiation preserved the efficacy of combined radiotherapy and immune-checkpoint blockade.⁹³

The translational priority is therefore not simply to identify additional mechanisms, but to determine which mechanisms dominate in individual nodal lesions and how they can be measured clinically. Future studies should combine tissue-based spatial and molecular profiling with circulating biomarkers and direct pharmacological assessment of metastatic nodes. Such an approach could distinguish lesions in which treatment failure primarily reflects impaired drug delivery from those dominated by tumor-cell-intrinsic resistance, dormancy or an immunosuppressive microenvironment. In parallel, therapeutic strategies may target distinct stages of nodal progression: interference with EV-mediated conditioning before metastatic establishment, modulation of scavenger-receptor-associated macrophage states, improvement of nodal drug delivery, and preservation or restoration of tumor-draining LN immune function. Ultimately, paired analysis of primary tumors, metastatic nodes and distant lesions will be required to define biologically meaningful nodal phenotypes and identify which patients are most likely to benefit from systemic, locoregional or node-directed interventions.

LIMITATIONS AND FUTURE DIRECTIONS

Several limitations prevent a unified mechanistic model linking nodal conditioning, SR-mediated interactions and chemotherapy resistance.

Much of the mechanistic evidence derives from *in vitro* or *in vivo* preclinical studies.^{5,16,18,46,54,55} Human LN architecture, stromal composition and macrophage biology may differ substantially from those of experimental models.

The sinusoidal scavenger/lectin-receptor signature demonstrates specialised receptor expression but does not establish that each component participates directly in metastatic adhesion.^{11,48,54,55} Functional studies using human nodal tissue are required to determine which receptors are necessary or sufficient for tumor-cell retention.

The relationship between pre-metastatic EV signalling and SR biology remains particularly important.^{11-16,40-42} Longitudinal

studies should determine whether physiologically released tumor EVs alter the abundance, localisation or activity of sinusoidal receptors before metastatic-cell arrival and whether these changes influence subsequent seeding.

Stromal evolution also requires greater temporal resolution.^{5,30,31,56} Comparative analysis of tumor-free TDLNs, micrometastatic lesions and established nodal metastases could determine whether particular fibroblast states precede tumor-cell arrival or arise predominantly as a consequence of metastatic growth.

Similarly, many ncRNA observations remain associative.^{14,34,37} Functional studies should establish whether candidate miRNAs, lncRNAs, and circRNAs reach specific nodal cell populations at biologically relevant concentrations and are required for metastatic niche formation.

Persistent nodal disease following chemotherapy must also be separated mechanistically into inadequate drug exposure, tumor-cell-intrinsic resistance, dormancy and microenvironmental protection.^{57,63,65,68,71} These mechanisms have distinct therapeutic implications and cannot be inferred from treatment failure alone.

Most importantly, the sanctuary-site hypothesis requires direct human pharmacological evidence.^{57,71,73} Studies comparing anticancer-drug concentrations, target engagement, perfusion, oxygenation and stromal characteristics across matched primary tumors, nodal metastases and distant lesions are required to determine whether PALNs or other nodal compartments genuinely experience reduced effective therapeutic exposure.

Single-cell sequencing, spatial transcriptomics, multiplex imaging and spatial proteomics may help resolve the endothelial, fibroblastic, myeloid and lymphoid states accompanying progression from tumor-free TDLN to established metastatic disease.^{5,94}

Circulating biomarkers may complement tissue-based analysis. EV-associated molecules, ncRNAs and circulating tumor DNA (ctDNA) could contribute to detection of molecular residual disease or metastatic progression.^{95,96} Longitudinal ctDNA analysis in TRACERx demonstrated that molecular residual-disease approaches can anticipate metastatic relapse in lung cancer, although their capacity to identify nodal dissemination specifically remains to be established.⁹⁷

CONCLUSION

Lymph-node metastasis should be viewed as a dynamic and evolving process rather than as the passive accumulation of disseminated tumor cells. The evidence reviewed here supports a temporal model in which early tumor-driven nodal conditioning and interactions at the sinusoidal interface may facilitate metastatic establishment, while subsequent remodeling of the nodal microenvironment creates distinct selective pressures that can influence therapeutic response. Importantly, the mechanisms governing tumor-cell retention and colonization should be distinguished from those responsible for treatment persistence, and current evidence does not support a single causal pathway linking scavenger-receptor-mediated interactions to later therapeutic resistance.

This distinction is particularly relevant to para-aortic lymph-node metastases. Their clinical behavior varies across tumor types, and although established lesions may acquire features consistent with a treatment-resistant niche, the para-aortic location itself cannot currently be considered a pharmacological sanctuary. Demonstrating true sanctuary behavior will require direct evidence of reduced effective therapeutic exposure or target engagement within metastatic nodes. Viewing nodal metastasis as an evolving tumor-host ecosystem may therefore provide a more useful framework for identifying when and how nodal disease becomes therapeutically resistant and for defining the vulnerabilities that could be targeted clinically.

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All authors contributed to the design, analysis, and writing of the manuscript, contributed to the final manuscript, and approved the final version.

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