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A Bilayer Is Not a Lineage: Testing Myoepithelial Mimicry in EWSR1::BEND2-Fused Fenestrating Adenocarcinoma

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Perspective

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Abstract

Fenestrating adenocarcinoma is an emerging EWSR1::BEND2-associated malignancy of the pharyngeal region whose reported architectural diversity includes apparently biphasic arrangements, basal/squamoid differentiation and hyalinised pseudorosettes. These observations expose a specific diagnostic uncertainty: does apparent epithelial–myoepithelial organisation represent genuine neoplastic myoepithelial differentiation, or can it arise through basal/squamoid mimicry or incorporation of native glandular structures? The distinction remains unresolved because the published cases have not undergone a uniform, compartment-resolved assessment of cellular differentiation and neoplastic membership. This Perspective proposes a three-gate pathological framework separating anatomical compartment identification, differentiation assignment and molecular attribution of neoplastic identity. Four competing explanations are considered: genuine biphasic differentiation, basal/squamoid mimicry, non-neoplastic glandular entrapment and regional phenotypic heterogeneity. Serial-section morphology, spatially registered complementary immunohistochemistry and, where feasible, compartment-directed fusion analysis could discriminate among these possibilities. Neither p63/p40 expression nor individual negative myoepithelial markers independently determine lineage; similarly, a shared EWSR1::BEND2 fusion establishes molecular relatedness without proving differentiation. Reproducible demonstration of a distinct, fusion-associated abluminal population with coherent myoepithelial differentiation would challenge the proposed mimicry explanation. The immediate significance is diagnostic: apparent bilayering in a rare pharyngeal carcinoma must not automatically establish epithelial–myoepithelial carcinoma or another recognised biphasic neoplasm. The framework offers a falsifiable approach to refining tumour characterisation without prematurely modifying classification or clinical management.

Introduction: a newly recognised carcinoma, an unresolved diagnostic boundary

The recognition of EWSR1::BEND2-associated fenestrating adenocarcinoma exposes a diagnostic problem more specific than the familiar morphological diversity of salivary gland neoplasia. A recurrent fusion has brought together carcinomas with fenestrating, glandular, basaloid and occasionally squamoid architecture, yet the cellular differentiation implied by some of these appearances remains incompletely established. The earliest molecularly recognised examples were variably classified, reflecting the limitations of conventional morphology when confronted with an unrecognised tumour phenotype [1]. Subsequent descriptions included a tongue-base carcinoma with apparent epithelial–myoepithelial architecture [2], a tracheal carcinoma displaying distinct glandular and basaloid/pseudorosette-like regions [3], and a seven-case series proposing the designation *fenestrating adenocarcinoma* [4]. Its emergence beyond the fifth-edition World Health Organization classification further illustrates the provisional nature of its diagnostic boundaries [5].

The central issue is not whether a carcinoma can exhibit two morphological populations. That principle is established. The unresolved question is whether the apparent outer cellular component in this

particular fusion-associated malignancy has been sufficiently characterised to justify its interpretation as a neoplastic myoepithelial population.

This distinction matters because the tumour occupies an unusual position in diagnostic pathology. Its morphology can suggest established salivary neoplasms, its immunophenotype may include basal-marker expression without a consistently demonstrable myoepithelial programme, and its defining molecular alteration is not itself a lineage marker. Consequently, an apparently biphasic EWSR1::BEND2-associated carcinoma challenges the assumption that architectural compartmentalisation establishes cellular differentiation.

This Perspective advances a narrowly framed hypothesis: some apparently epithelial–myoepithelial arrangements in fenestrating adenocarcinoma may arise from basal/squamoid organisation, entrapped native glands or regional phenotypic heterogeneity rather than a separately validated neoplastic myoepithelial compartment. The hypothesis does not deny the possibility of genuine myoepithelial differentiation. It identifies the evidence required to demonstrate it.

The published contradiction is interpretative, not merely immunohistochemical

Zhang and colleagues described an EWSR1::BEND2-fused tongue-base malignancy displaying tubular, cord-like, solid and microcystic structures within a chondromyxoid background. The tumour was interpreted as having epithelial–myoepithelial architecture, with CK7, CK5/6 and p63 expression contributing to the assignment of cellular components [2]. The important observation is the reported bilayered morphology; the unresolved inference concerns the independent differentiation identity of its proposed abluminal population. The present argument does not depend upon adjudicating individual immunohistochemical discrepancies within that report.

A subsequent tracheal case provided a different but complementary pathological observation. Sanchez-Ramirez and colleagues demonstrated glandular regions, basaloid/clear-cell areas and hyalinised pseudorosettes within an EWSR1::BEND2-fused carcinoma. Tumour cells expressed p40 and p63 but lacked demonstrable S100, SOX10 and smooth-muscle actin expression. Importantly, smooth-muscle actin highlighted the myoepithelial cells of entrapped benign glands rather than the carcinoma [3]. Thus, epithelial differentiation, basal-marker expression and the presence of non-neoplastic myoepithelial cells could be distinguished within the same tumour-bearing specimen.

The later seven-case series consolidated a recognisable pathological spectrum characterised by fenestrating architecture, variable basaloid or squamous differentiation, CK7/BEND2 expression, S100 negativity in tested tumours and variable p63 staining [4]. These findings support the emerging entity but do not independently demonstrate that every apparent peripheral cellular population represents a separately differentiated neoplastic lineage. The series also incorporates previously reported material;

earlier publications and the defining series must therefore not be treated as entirely independent observations.

The decisive gap is consequently not a disputed stain. It is the absence of a uniform assessment connecting three observations within individual microscopic structures: the existence of a distinct abluminal compartment, its differentiation phenotype and its neoplastic membership. Table 1 separates what the published studies demonstrate from what remains inferential.

Table 1
Published pathological evidence defining the unresolved differentiation problem in EWSR1::BEND2-associated fenestrating adenocarcinoma

Study	Established morphological or immunophenotypic observation	Interpretation supported by the evidence	Remaining diagnostic uncertainty
Todorovic et al. [1]	Identification of EWSR1::BEND2 in an unusual salivary malignancy	A molecularly unusual salivary carcinoma phenotype exists	Compartment-specific differentiation was not systematically assessed
Zhang et al. [2]	Tubular/cord-like apparent bilayering, chondromyxoid stroma and regional CK7, CK5/6 and p63 expression	Architectural compartmentalisation was described and interpreted as epithelial–myoepithelial	Independent validation of the proposed abluminal compartment's neoplastic myoepithelial identity remains incomplete
Sanchez-Ramirez et al. [3]	Glandular and basaloid/pseudorosette-like tumour regions; p40/p63-positive tumour cells; SMA-positive myoepithelial cells in entrapped native glands	Neoplastic basal-marker expression and non-neoplastic myoepithelial staining can be anatomically distinguished	Whether different tumour regions represent distinct differentiation compartments
Al-Sajee et al. [4]	Seven-case series with fenestrating architecture, variable basaloid/squamous features, CK7/BEND2 expression and S100 negativity in tested tumours	A recognisable emerging fusion-associated carcinoma spectrum is supported	Uniform compartment-resolved evidence of myoepithelial differentiation is not established
Footnotes:			
(a) The table summarises the evidence available in published descriptions and does not represent independent reassessment of histological slides.			
(b) Earlier reports and the defining series may contain overlapping material; they must not be treated as wholly independent cohorts.			
(c) Individual immunohistochemical observations cannot establish or exclude a differentiation phenotype without anatomical, technical and complementary evidence.			
(d) Apparent bilayering is descriptive; assignment of neoplastic myoepithelial differentiation requires additional proof.			

The novelty of this Perspective lies in converting that tumour-specific interpretative gap into a falsifiable diagnostic question. It does not introduce a new general principle of salivary pathology; it tests whether an emerging molecularly defined carcinoma has been assigned a cellular phenotype that its available evidence does not yet establish.

The pathological test: three gates rather than one morphological impression

Gate 1: establish the anatomical compartment

The first requirement is to determine whether the apparent bilayer represents a reproducible cellular arrangement rather than tangentially sectioned nests, peripheral palisading, a stromal interface or a pseudolumen. Normal salivary glands comprise luminal and abluminal populations, but neoplastic architecture frequently reproduces only portions of this arrangement [6]. Solid nests, hyalinised pseudorosettes and duct-like structures cannot be assumed to share the same biological organisation merely because they contain centrally and peripherally situated cells.

This gate requires serial-section assessment of the same microscopic structures. A proposed outer layer must be distinguishable from adjacent stroma and native glands, and its continuity must be evaluated across sections. Apparent compartmentalisation that disappears with serial levels cannot serve as secure evidence of a distinct differentiation population.

Gate 2: establish the differentiation phenotype

The second requirement is to determine whether the identified compartment exhibits a coherent myoepithelial phenotype rather than nonspecific basal/squamous differentiation. CK5/6, p63 and p40 are diagnostically useful but cannot independently establish myoepithelial identity. Their expression must be interpreted according to cellular localisation, tumour architecture and the competing salivary differential diagnosis [7, 8].

Markers associated with contractile or myoepithelial differentiation, including smooth-muscle actin, calponin, smooth-muscle myosin heavy chain, S100 and SOX10, may provide complementary information. However, their specificity and sensitivity vary according to tumour type and differentiation state [9]. A negative individual marker cannot conclusively exclude divergent myoepithelial differentiation; conversely, positivity in stromal elements, native glands or non-neoplastic cells cannot establish the phenotype of the carcinoma.

The appropriate endpoint is therefore not an arbitrary count of positive stains but a reproducible anatomical and immunophenotypic relationship between the candidate outer population and the adjacent malignant epithelial component.

Gate 3: establish neoplastic membership

Even a convincingly myoepithelial-looking population may be non-neoplastic. Entrapped minor salivary glands can preserve native luminal–abluminal organisation and may lie in intimate association with invasive carcinoma. Their myoepithelial cells may remain conspicuous on immunohistochemistry while adjacent malignant epithelial cells exhibit a different phenotype.

The third gate therefore asks whether the proposed abluminal population belongs to the tumour. Where adequate material and validated methods are available, compartment-directed molecular analysis could investigate this relationship. Reliable demonstration of EWSR1::BEND2 within both putative cellular compartments would support their shared neoplastic membership, provided sampling purity and cellular attribution are secure. It would not establish whether the outer component is myoepithelial.

The specificity of the molecular result must also be interpreted carefully. An EWSR1 rearrangement alone does not identify EWSR1::BEND2, and the fusion itself has been reported in a morphologically distinct sinonasal spindle-cell sarcoma [10]. Molecular identity must therefore be integrated with anatomical location, histology and immunophenotype rather than regarded as a universal classification shortcut.

These three gates are analytically separate. Failure to satisfy one cannot be repaired by stronger evidence at another: a fusion does not rescue an unsupported lineage assignment, and a myoepithelial-associated marker does not establish neoplastic status. The competing interpretations and their evidentiary requirements are presented in Table 2.

Table 2
Competing explanations for apparent bilayering and their diagnostic implications

Candidate interpretation	Required pathological evidence	Principal source of misclassification	Appropriate diagnostic consequence
Genuine neoplastic myoepithelial differentiation	Reproducible abluminal compartment, coherent complementary myoepithelial phenotype and evidence of neoplastic membership	Confusing a genuinely biphasic phenotype with nonspecific basal-marker expression	Recognise supported differentiation while retaining the independently established tumour identity
Basal/squamoid mimicry	Basal-marker-positive malignant cells without independently convincing myoepithelial differentiation in adequately evaluated compartments	Interpreting p63/p40-positive peripheral cells as proof of epithelial–myoepithelial carcinoma	Describe basal/squamoid differentiation and reconsider entity assignment where other findings are discordant
Incorporated native glands	Native ductal architecture with retained non-neoplastic abluminal cells	Attributing SMA/calponin-positive native myoepithelial cells to adjacent carcinoma	Separate native structures from the malignant compartment before assigning differentiation
Regional neoplastic heterogeneity	Distinct morphological and immunophenotypic states among reliably identified tumour cells	Treating every phenotypic region as an independent lineage or tumour type	Report heterogeneity without inferring lineage transition or creating an unsupported subtype
Footnotes:			
(a) The proposed interpretations may coexist within a single tumour.			
(b) The absence of one or more myoepithelial markers is not sufficient to exclude divergent myoepithelial differentiation.			
(c) Shared fusion status supports neoplastic relatedness but does not independently determine differentiation.			
(d) This table provides an investigative diagnostic framework, not validated reporting criteria.			

The practical diagnostic consequence: avoiding an epithelial–myoepithelial carcinoma misclassification

Consider a limited tongue-base biopsy showing tubules surrounded by clear or basaloid cells, with CK7 highlighting apparent luminal epithelium and p63/p40 highlighting an outer population. This combination may reasonably raise epithelial–myoepithelial carcinoma. However, assigning that diagnosis solely from

apparent bilayering and basal-marker expression risks conflating two distinct observations: cellular position and myoepithelial differentiation.

The proposed three-gate approach changes the diagnostic sequence. First, the pathologist determines whether the outer cells constitute a genuine, reproducible compartment rather than peripheral basaloid tumour cells or incorporated native glands. Second, complementary immunohistochemistry evaluates whether that population demonstrates convincing myoepithelial differentiation. Third, if the morphology remains unusual and tissue permits, partner-resolving molecular testing may establish whether the lesion belongs to the emerging EWSR1::BEND2-associated carcinoma spectrum. The demonstration of EWSR1::BEND2 in an appropriate carcinoma would prompt reconsideration of an epithelial–myoepithelial carcinoma diagnosis, but it would not by itself disprove genuine myoepithelial differentiation within that carcinoma.

This approach does not presume that every epithelial–myoepithelial carcinoma requires molecular exclusion. Established epithelial–myoepithelial carcinoma remains a morphology-led diagnosis, supported by characteristic luminal and myoepithelial compartments and appropriate ancillary findings. The fifth-edition WHO framework remains the appropriate classificatory foundation [11].

The same restraint applies to other differentials. Adenoid cystic carcinoma may display ductal and abluminal differentiation with basement-membrane-like material; mucoepidermoid carcinoma may combine mucinous, intermediate and squamoid populations; and polymorphous adenocarcinoma may exhibit overlapping glandular and basaloid appearances. MAML2 rearrangement, for example, may assist in appropriately selected mucoepidermoid carcinoma differentials but cannot substitute for compatible morphology [12]. Molecular pathology has refined the recognition of emerging salivary neoplasms precisely because morphology and fusion status must be interpreted together [13]. An isolated EWSR1 rearrangement is particularly insufficient for assigning a specific salivary carcinoma category [14].

The practical contribution is therefore a safeguard against premature nomenclature. When morphology indicates an unusual basaloid/bilayered carcinoma but lineage is uncertain, the report should describe the observed architecture and specify the supported differentiation features without presenting an unvalidated myoepithelial compartment as established fact. The objective is not to delay a defensible diagnosis indefinitely. It is to prevent a familiar pattern from overriding discordant pathological evidence.

Testing the hypothesis: a compartment-resolved validation design

A multicentre investigation should begin with retrieval of appropriately classified, molecularly confirmed EWSR1::BEND2-associated carcinomas, including previously published cases where original material remains available. Cases must be reconciled by patient and specimen provenance to avoid duplicate inclusion. Biopsies and resections should be recorded separately, and morphologically distinct EWSR1::BEND2-associated mesenchymal neoplasms should not be pooled into the primary carcinoma cohort.

At least two specialist head-and-neck pathologists should independently review original haematoxylin-and-eosin sections before examining immunohistochemistry or fusion results. Each reviewer would annotate ductal, apparent abluminal, solid, squamoid, clear-cell, pseudorosette-like and native-glandular structures. Serial sections should determine whether candidate compartments persist and whether their boundaries are anatomically reproducible. Initial interobserver agreement, disagreements and unevaluable structures should be documented rather than concealed through consensus.

Spatially registered immunohistochemistry would then interrogate the annotated structures. CK7 and appropriate luminal markers could characterise glandular epithelium; CK5/6, p63 and p40 could assess basal/squamous differentiation; and selected complementary myoepithelial-associated markers could examine the putative outer population. Antibody choice should be morphology-led rather than fixed as an indiscriminate panel. Native minor salivary glands, vascular smooth muscle, nerves and stromal structures should provide anatomical and technical controls, with their staining explicitly distinguished from neoplastic-cell staining.

Compartment-specific molecular interrogation should be reserved for cases in which neoplastic membership remains unresolved and tissue quality permits meaningful analysis. Laser-capture microdissection or validated cell-resolved fusion assays may be informative, but contamination between compartments, insufficient tumour purity, fixation-related nucleic acid degradation and assay dropout must be considered. An analytically negative result in a minute cellular population cannot establish non-neoplastic status unless assay sensitivity and sampling adequacy are demonstrably sufficient.

Comparator specimens should include established biphasic salivary neoplasms, conventional basaloid/squamoid carcinomas and non-neoplastic minor salivary glands. These controls would test whether the proposed interpretation discriminates between known cellular arrangements rather than merely reproducing staining patterns already encountered elsewhere. Given the very small available case literature, the primary objectives should be descriptive reproducibility and cellular attribution, not numerical cut-offs or prognostic modelling. Table 3 specifies the proposed endpoints and their limitations.

Table 3
Proposed three-gate validation strategy, endpoints and falsification criteria

Stage	Pathological investigation	Primary endpoint	Result challenging the proposed interpretation
Case ascertainment	Central review of tumour identity, molecular results and specimen provenance	Independent, appropriately classified EWSR1::BEND2-associated carcinoma cases	Duplicate cases, inadequate molecular confirmation or inappropriate pooling of unrelated fusion-associated tumours
Gate 1: anatomical identity	Blinded serial-section review of candidate luminal and abluminal structures	Reproducibly demonstrable cellular compartmentalisation	Apparent bilayering attributable to pseudolumina, section orientation or non-neoplastic glandular architecture
Gate 2: differentiation identity	Spatially registered complementary luminal, basal/squamous and myoepithelial immunohistochemistry	Coherent, technically supported phenotype of the candidate compartment	Isolated nonspecific marker expression or failure to reproduce compartment-specific differentiation
Gate 3: neoplastic identity	Validated compartment-directed molecular analysis, where feasible	Reliable assignment of neoplastic membership	Demonstration of non-neoplastic elements or inability to establish cellular attribution because of contamination or assay limitations
Independent evaluation	Blinded specialist reassessment with appropriately selected comparator tumours	Reproducibility of interpretations and discrimination between competing explanations	Poor agreement or failure to distinguish genuine differentiation from morphological mimicry

Stage	Pathological investigation	Primary endpoint	Result challenging the proposed interpretation
Footnotes:			
(a) These endpoints are proposed for future investigation and have not been clinically validated.			
(b) Reproducible demonstration of a fusion-associated neoplastic abluminal compartment with convincing myoepithelial differentiation would weaken a generalised mimicry explanation.			
(c) Technically inadequate, low-cellularity or spatially ambiguous findings must be classified as indeterminate rather than negative.			
(d) No threshold for marker positivity, diagnostic subtype designation or prognostic classification is proposed.			
(e) The primary objective is differentiation of competing pathological explanations, not prediction of clinical outcome.			

Falsification and competing explanations

The hypothesis does not predict that every apparent abluminal population is artifactual. It predicts that at least some such populations may lack independently demonstrable neoplastic myoepithelial identity. Its strongest challenge would be reproducible evidence, across appropriately confirmed cases, of a spatially distinct abluminal population displaying coherent complementary myoepithelial differentiation together with reliable proof of neoplastic membership. Such evidence would establish genuine biphasic differentiation in the relevant cases and restrict the applicability of the mimicry hypothesis.

By contrast, a reproducible basal/squamoid phenotype without convincing independent myoepithelial differentiation would support mimicry if tissue sampling and controls were adequate. Demonstration of preserved native duct–myoepithelial structures would support entrapment in the specific profiles examined. Distinct phenotypes within fusion-confirmed malignant compartments might instead demonstrate regional differentiation heterogeneity, although static histology cannot establish the evolutionary direction of such changes.

These possibilities are neither necessarily exhaustive nor mutually exclusive. A tumour may exhibit genuine glandular differentiation in one region, basal/squamoid organisation elsewhere and entrapped native glands at its infiltrative edge. Consequently, conclusions should initially be assigned at the level of evaluable structures, with case-level interpretation following only when the findings are sufficiently representative.

Equivocal staining, failure to recover a candidate compartment on deeper sections, technically inadequate molecular results or insufficient archival material must lead to an indeterminate classification. They cannot be counted as evidence for mimicry. A small sample also cannot exclude a genuine differentiated component elsewhere in the tumour.

The framework is falsifiable only to the extent that it permits these negative and indeterminate outcomes. Its purpose is to distinguish competing explanations, not to guarantee one preferred interpretation.

Scope and limitations

The principal constraint is the extreme rarity of fenestrating adenocarcinoma. Published cases are few, may overlap and were not originally investigated through a uniform differentiation-mapping protocol. Available resection material may be exhausted, whereas small biopsies may inadequately represent the tumour's architecture. Interinstitutional differences in fixation, antibody performance and molecular platforms could further complicate direct comparison.

Even a successful compartment-resolved study would not establish the prognostic significance of a particular differentiation phenotype. No current evidence justifies a novel histological grade, treatment recommendation or survival prediction based on apparent myoepithelial differentiation in this entity. The proposed three-gate framework is an investigative strategy, not a validated clinical assay or mandatory reporting standard.

Its value would be demonstrated if it improved agreement between specialist pathologists, distinguished genuine neoplastic compartments from mimics and clarified which microscopic features should form part of future diagnostic descriptions. Failure to achieve those objectives would weaken the rationale for adopting the framework.

Conclusion

Fenestrating adenocarcinoma presents a specific unresolved pathological question: whether apparent epithelial–myoepithelial organisation reflects genuine neoplastic myoepithelial differentiation or architectural and phenotypic mimicry. Published descriptions establish a recognisable fusion-associated carcinoma spectrum but do not yet resolve that question through uniform compartment-level evidence. Serial-section anatomy, complementary immunophenotyping and carefully controlled molecular attribution offer a falsifiable means of doing so. The immediate diagnostic consequence is to prevent an apparently bilayered, basal-marker-positive carcinoma from being assigned an established biphasic tumour identity without adequate corroboration.

A bilayer is an architectural observation. Myoepithelial differentiation is a cellular claim. Neoplastic membership is a molecular and pathological question. None establishes the others by assumption.

Declarations

1 Funding

This study was not supported by any funding.

2. Conflict of Interest

The author declares no financial or non-financial conflicts of interest relevant to this manuscript.

3. Ethical Approval

This article does not contain any studies with human participants or animals performed by the author. No original patient material, identifiable clinical information or unpublished patient-level data were examined. Institutional ethics committee approval is not applicable.

4. Consent to Participate

For this type of study, informed consent is not required.

5. Consent for Publication

For this type of study, consent for publication is not required.

6. Availability of Data and Materials

No original datasets or patient-derived materials were generated, collected or analysed. The scholarly arguments and proposed diagnostic framework are based on published scientific literature identified in the reference list.

7. Code Availability

Not applicable. No custom software, computational code or statistical analysis was used in the preparation of this Perspective.

Author Contribution

B.B. conceived the central hypothesis, developed the three-gate compartment-resolved diagnostic framework, critically evaluated the published literature, formulated the competing pathological interpretations and falsification criteria, prepared the three original tables, and drafted and critically revised the manuscript. B.B. reviewed and approved the final manuscript and accepts full responsibility for its scientific content and integrity.

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Statements and Declarations

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