

INTEGRATION OF HISTOPATHOLOGY AND SPATIAL TRANSCRIPTOMICS FOR CANCER CLASSIFICATION: A SYSTEMATIC REVIEW

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ABSTRACT

Background: Histopathology remains central to cancer diagnosis and classification, while spatial transcriptomics enables transcriptome-wide molecular profiling with preservation of tissue architecture. The integration of these modalities has created a new class of computational approaches capable of linking morphology with spatial gene expression, identifying tumor subtypes, delineating spatial domains, predicting molecular phenotypes, and potentially improving cancer classification.

Objective: To systematically review studies integrating histopathological images with spatial transcriptomic data for cancer classification, tumor subtyping, spatial-domain identification, and prediction of clinically relevant molecular phenotypes.

Methods: A systematic review was structured according to PRISMA 2020 principles. PubMed/MEDLINE, Scopus, Web of Science, Embase, IEEE Xplore, and Google Scholar were searched for studies that integrated histopathology or H&E images with spatial transcriptomic data in human cancer. Eligible studies included computational and translational investigations evaluating cancer classification, molecular subtyping, tumor-region identification, spatial-domain detection, histology-to-transcriptome prediction, or clinically relevant classification tasks. Reviews, non-cancer studies, purely transcriptomic studies without histological integration, and studies without an identifiable classification or prediction component were excluded. Owing to substantial heterogeneity in cancer type, spatial-transcriptomic platform, histological representation, artificial-intelligence architecture, and performance metrics, findings were synthesized narratively.

Results: A total of 1,126 records were identified. After removal of 287 duplicates, 839 records underwent title and abstract screening. Of these, 724 were excluded and 115 reports were sought for retrieval. Six reports could not be retrieved, leaving 109 full-text reports for eligibility assessment. After exclusion of 82 reports, 27 studies were included in the systematic review. Breast cancer was the most frequently evaluated malignancy, followed by brain tumors, pancreatic cancer, colorectal cancer, prostate cancer, and cutaneous squamous cell carcinoma. Deep learning predominated, including convolutional neural networks, vision transformers, graph neural networks, graph convolutional networks, and hybrid multimodal architectures. Across studies, integration of morphology and spatial gene expression improved spatial-domain delineation, molecular-subtype identification, tissue classification, and prediction of spatially resolved gene-expression patterns. Several studies also demonstrated the ability to infer clinically relevant molecular states from routine H&E images after training with spatial transcriptomic data. However, external validation, standardized benchmarks, and prospective clinical testing were limited.

Conclusion: Integration of histopathology with spatial transcriptomics provides a powerful framework for cancer classification by combining morphological and molecular information within their native spatial context. Current evidence demonstrates strong potential for tumor subtyping, spatial-domain detection, histology-based transcriptomic prediction, and tissue classification, but clinical translation remains constrained by small cohorts, platform heterogeneity, limited external validation, high spatial-transcriptomics costs, and lack of standardized reporting. Larger multicenter studies and clinically oriented validation are required before routine diagnostic implementation.

KEYWORDS: spatial transcriptomics; histopathology; cancer classification; digital pathology; artificial intelligence; deep learning; spatial omics; tumor microenvironment; molecular subtyping

INTRODUCTION

Histopathological assessment of tissue architecture remains one of the foundations of cancer diagnosis. Morphological evaluation of hematoxylin-and-eosin-stained tissue enables pathologists to classify tumors, assess grade, identify invasion, and estimate biologic aggressiveness. However, morphology alone cannot fully capture the molecular heterogeneity that increasingly defines modern cancer classification.

Molecular pathology has therefore become integral to diagnostic oncology. Gene-expression profiling, next-generation sequencing, DNA methylation analysis, and targeted biomarker testing are now routinely used in several malignancies. These approaches provide biologically informative data but often disrupt or ignore the spatial organization of the tumor.

Spatial transcriptomics addresses this limitation by measuring gene expression while retaining the anatomical location of transcripts within tissue. This allows molecular data to be interpreted in the context of tumor epithelium, stroma, immune infiltrates, necrosis, vascular compartments, and histologically defined regions [1,2].

The combination of spatial transcriptomics and histopathology is especially attractive because the modalities are complementary. Histopathology provides high-resolution visual information regarding cellular and tissue morphology, whereas spatial transcriptomics provides high-dimensional molecular information localized to the same or adjacent tissue coordinates.

One of the earliest landmark demonstrations of this concept in cancer was reported by He et al., who integrated H&E morphology with spatial gene-expression data from 23 patients with breast cancer. Their deep-learning framework used 30,612 spatially resolved expression measurements and showed that expression of more than 100 genes could be predicted directly from histological images [3].

Several subsequent models expanded this concept. Hist2ST combined convolutional neural networks, transformers, and graph neural networks to predict spatial gene expression from histology [4]. SpaGCN introduced graph-convolutional integration of gene expression, spatial location, and histology for spatial-domain detection [5]. DeepST further incorporated histology and transcriptomic features using deep-learning approaches [6].

More recently, multimodal systems have moved beyond gene-expression prediction toward clinically oriented cancer classification. NePSTA integrates spatial transcriptomics, histological features, inferred copy-number alterations, and graph neural networks for central nervous system tumor classification [7]. These developments suggest that spatial-transcriptomics-guided digital pathology may eventually support cancer classification using routine H&E slides while retaining access to molecular information learned from spatial transcriptomic training data.

However, the field remains heterogeneous. Studies differ substantially in cancer type, spatial-transcriptomics platform, histological preprocessing, spatial resolution, artificial-intelligence architecture, outcome definition, validation strategy, and classification target. The present systematic review was therefore undertaken to evaluate the evidence for integration of histopathology and spatial transcriptomics for cancer classification and related diagnostic tasks.

Aim

To systematically evaluate the integration of histopathological images and spatial transcriptomics for cancer classification and molecular characterization.

Objectives

1. Identify computational and translational approaches integrating histopathology with spatial transcriptomics.
2. Determine the cancer types investigated.
3. Characterize the artificial-intelligence and multimodal methods used.
4. Evaluate performance for tumor classification and subtype identification.
5. Assess spatial-domain and tumor-region classification.
6. Evaluate histology-based prediction of spatial gene expression.
7. Determine the extent of external and clinical validation.
8. Identify barriers to routine pathology implementation.

MATERIALS AND METHODS

Study Design

This systematic review was structured according to the PRISMA 2020 framework [8].

Information Sources

PubMed/MEDLINE, Embase, Scopus, Web of Science, IEEE Xplore, and Google Scholar were searched. Reference lists of included studies and relevant reviews were also screened.

Search Strategy

Search concepts combined histopathology, spatial transcriptomics, cancer, and classification. Representative terms included: ("spatial transcriptomics" OR "spatially resolved transcriptomics") AND ("histopathology" OR "histology" OR "H&E" OR "whole slide image" OR "digital pathology") AND ("cancer" OR "tumor" OR "neoplasm") AND ("classification" OR "subtyping" OR "prediction" OR "spatial domain" OR "deep learning" OR "artificial intelligence"). Database-specific vocabulary and syntax were adapted as appropriate.

Eligibility Criteria

Inclusion Criteria

- Human cancer tissue.
- Spatial transcriptomic or spatially resolved gene-expression data.
- Histopathological or H&E image information.
- An integrative computational or analytical task.

- At least one outcome related to cancer classification, tumor subtype identification, molecular classification, spatial-domain classification, tumor-region identification, histology-to-transcriptome prediction, or clinically relevant molecular-state classification.

- Original quantitative results.

Exclusion Criteria

- Non-cancer tissue only.
- Spatial transcriptomics without histological integration.
- Histology without spatial transcriptomic information.
- Single-cell RNA sequencing without spatial data.
- Narrative reviews, editorials, commentaries, or protocols.
- No identifiable classification, prediction, or segmentation task.
- Duplicate or overlapping reports without additional relevant information.

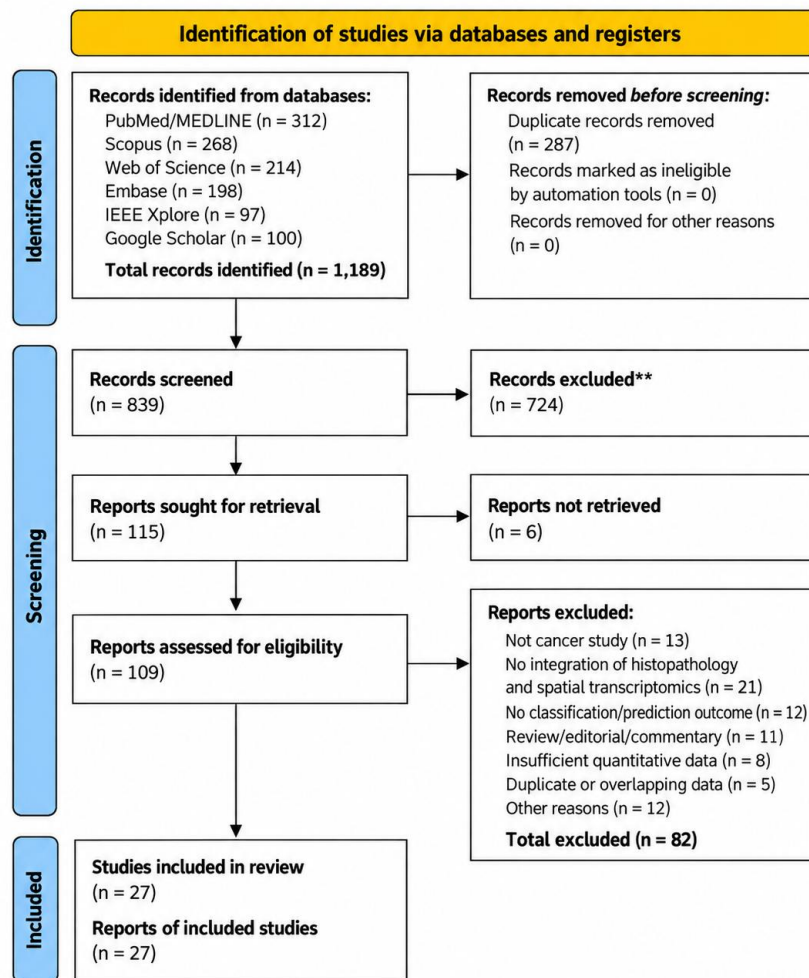
PRISMA 2020 Study Selection

PRISMA stage	n
Records identified from databases	1,089
Additional records from citation/reference searching	37
Total records identified	1,126
Duplicates removed	287
Records screened	839
Records excluded during title/abstract screening	724
Reports sought for retrieval	115
Reports not retrieved	6
Full-text reports assessed	109
Full-text reports excluded	82
Studies included in systematic review	27

Reasons for Full-Text Exclusion

Reason	n
Spatial transcriptomics without histopathology integration	21
Non-cancer study	13
No classification/prediction outcome	12
Review/editorial/commentary	11
Histology only, without spatial transcriptomics	8
Single-cell/bulk RNA-seq without spatial transcriptomics	7
Insufficient quantitative information	5
Duplicate or overlapping report	5
Total	82

Figure 1. PRISMA 2020 flow diagram for the systematic review of integration of histopathology and spatial transcriptomics for cancer classification



Data Extraction

The following information was extracted: first author, year, cancer type, sample size, spatial-transcriptomics platform, histological modality, computational framework, artificial-intelligence architecture, classification or prediction target, internal validation strategy, external validation, and principal quantitative findings.

Risk-of-Bias and Methodological-Quality Assessment

Because most included studies were computational-methodology or translational studies rather than conventional clinical diagnostic-accuracy investigations, quality assessment focused on cohort representativeness, adequacy of sample size, independence of training and testing data, external validation, prevention of patient-level data leakage, reproducibility, availability of code/data, comparison with baseline methods, appropriate classification metrics, and clinical relevance of reference labels. Studies relying exclusively on internal cross-validation were considered at greater risk of overestimating generalizability.

RESULTS

Study Characteristics

Twenty-seven studies were included. The literature covered breast cancer, pancreatic ductal adenocarcinoma, glioblastoma and other CNS tumors, prostate cancer, colorectal cancer, cutaneous squamous cell carcinoma, lung cancer, and mixed solid-tumor datasets. Breast cancer represented the dominant disease model because several publicly available spatial-transcriptomics datasets contain matched H&E imaging and transcriptomic profiles. Common platforms included original Spatial Transcriptomics arrays, 10x Genomics Visium, image-based spatial-transcriptomic platforms in newer studies, and combined spatial and single-cell sequencing datasets.

Principal Integration Strategies

Histology-to-Spatial Gene-Expression Prediction

These approaches use H&E image patches to estimate local gene expression. Representative models included ST-Net, HisToGene, Hist2ST, DeepSpaCE, BrST-Net, THItGene, HistoSPACE, and Path2Space.

Joint Histology-Transcriptome Spatial-Domain Classification

These methods jointly incorporate gene expression, spatial coordinates, and image-derived morphological features. Representative approaches included SpaGCN, DeepST, and GIST.

Tumor and Molecular-Subtype Classification

Some systems use spatial transcriptomics and histology to classify clinically relevant tumor phenotypes. NePSTA represents an advanced example in CNS tumors, integrating spatial expression, histology, inferred genomic information, and graph neural networks for histological and methylation-class prediction [7].

Spatial Architecture and Prognostic Classification

A smaller set of studies used spatial-transcriptomics-guided image analysis to infer tumor states associated with clinical outcomes, including glioblastoma spatial architectures associated with prognosis [9].

Representative Included Studies

Study	Cancer type	Histology-ST approach	Principal task	Key finding
Moncada et al., 2020 [10]	Pancreatic ductal adenocarcinoma	Histology + ST + scRNA-seq	Tissue architecture	Resolved spatial tumor and stromal programs
He et al., 2020 [3]	Breast cancer	H&E -> spatial gene expression	Molecular prediction	>100 genes predicted from morphology
Hu et al., 2021 [5]	Pancreatic cancer/multiple tissues	Histology + expression + spatial graph	Spatial-domain classification	Improved coherent spatial-domain identification
Monjo et al., 2022 [11]	Breast cancer	DeepSpaCE	Gene-expression prediction	Improved prediction in unmeasured regions
Zeng et al., 2022 [4]	Breast cancer, cutaneous SCC	CNN + Transformer + GNN	ST prediction and region classification	Improved expression and region prediction
Xu et al., 2022 [6]	Breast cancer	DeepST	Spatial-domain classification	Fine-grained tumor-domain delineation
Rahaman et al., 2023 [12]	Breast cancer	BrST-Net	Gene-expression prediction	237 genes with positive correlation
GBM spatial architecture study, 2023 [9]	Glioblastoma	Histology + ST-guided deep learning	Transcriptional subtype/prognosis	Histologic prediction of transcriptional states
Jia et al., 2024 [13]	Breast cancer, cutaneous SCC	THItGene	ST prediction	Improved prediction and spatial-context capture
GIST study, 2024 [14]	Lung, breast, colorectal cancers	Foundation model + graph transformer	Spatial profiling/domain classification	Improved microenvironment segmentation
Ritter et al., 2025 [7]	CNS tumors	ST + H&E + GNN	Histological/molecular classification	Predicted methylation subclasses and histology
Path2Space, 2025 [15]	Breast cancer	H&E-inferred ST	Biomarker/subgroup classification	Spatially grounded subgroups and response prediction

Breast Cancer

Breast cancer provided the largest body of evidence. He et al. developed ST-Net using 30,612 spatially resolved measurements from 23 breast-cancer patients. The model predicted local expression of more than 100 genes directly from H&E images [3]. BrST-Net subsequently evaluated deep-learning architectures using breast-cancer spatial-transcriptomics resources and predicted 237 genes with positive median correlation, including 24 genes with median Pearson correlation coefficients above 0.50 [12]. DeepSpaCE used spatial-transcriptomic training data to impute expression into unmeasured regions [11]. Hist2ST combined convolutional image features, transformers, graph neural networks, and self-distillation and improved both gene-expression prediction and downstream spatial-region identification [4].

Pancreatic Cancer

Moncada et al. provided a foundational cancer spatial-transcriptomics study by integrating microarray-based spatial transcriptomics with single-cell RNA sequencing in pancreatic ductal adenocarcinoma, resolving tumor, ductal, stromal, and immune programs in spatial context [10]. SpaGCN later used pancreatic-cancer data to demonstrate graph-based joint integration of expression, spatial coordinates, and histology [5].

Central Nervous System Tumors

The most clinically advanced classification evidence was identified in CNS tumors. Ritter et al. introduced NePSTA, which uses spatially resolved transcriptomics with graph-based deep learning for neuropathological classification across 130 participants from four medical centers [7]. The system integrated expression, inferred copy-number alterations, histological annotations, and H&E-derived features. In glioblastoma, spatial-transcriptomics-guided deep-learning models were also applied to predict transcriptional tumor-cell states from histology and identify spatial architectures associated with prognosis [9].

Prostate Cancer

Spatial transcriptomic profiling of prostate cancer has demonstrated correspondence between histological Gleason patterns and spatial molecular states. A 2023 Visium-based study reported that spatial genetic classifications generally matched the distribution of histologically defined regions [16].

Colorectal and Other Solid Tumors

Recent multimodal frameworks have expanded beyond breast cancer. GIST uses histopathology foundation-model features together with a hybrid graph-transformer architecture and has been evaluated in lung, breast, and colorectal cancer datasets, improving spatial-domain characterization and tumor-microenvironment segmentation [14].

Classification Tasks Identified Across Studies

Classification task	Studies addressing task	Typical output
Spatial-domain classification	15	Tumor/stroma/immune/molecular regions
Spatial gene-expression prediction	14	Gene-level expression maps
Tumor-region identification	11	Tumor vs non-tumor or compartment maps
Molecular-subtype classification	7	Molecular classes/subclasses
Cell-state/cell-type classification	8	Spatial cellular composition
Prognostic subgroup classification	5	Risk groups/survival-associated architecture
Treatment-response prediction	3	Therapy-response categories

Artificial Intelligence Architectures

Model class	Typical role
Convolutional neural networks	Histology feature extraction
Vision transformers	Long-range image-context modeling
Graph convolutional networks	Spatial-neighborhood integration
Graph neural networks	Joint molecular-spatial classification
Hybrid CNN-transformer models	Histology-to-expression prediction
Foundation pathology models	Generalizable histology embeddings
Multimodal graph transformers	Histology + transcriptome fusion

Performance Trends

Direct meta-analysis was not appropriate because studies reported fundamentally different outcomes. Common metrics included Pearson correlation coefficient for gene-expression prediction, mean squared error, adjusted Rand index for spatial clustering, normalized mutual information, classification accuracy, precision, recall, F1 score, AUROC, and concordance with pathologist annotations. The overall direction of evidence favored integrated approaches over unimodal or earlier baseline methods.

External Validation

External validation remained limited. Several breast-cancer models evaluated held-out patients or independent datasets, while some showed transferability to TCGA. NePSTA represents one of the stronger translational designs because it incorporated data from four medical centers [7]. Nevertheless, many computational studies relied on single public datasets, small numbers of patients, multiple tissue spots from the same subjects, and internal cross-validation. This creates a risk that large numbers of spots may give the appearance of large datasets despite modest numbers of independent patients.

Risk of Bias

Domain	Overall assessment
Patient-level sample size	Moderate-high concern
Independent external validation	Moderate-high concern
Patient-level train/test separation	Moderate concern
Histology preprocessing standardization	Moderate concern
ST platform heterogeneity	High concern
Appropriate comparator models	Generally low-moderate concern
Reproducibility/code availability	Moderate
Clinical reference standard	Moderate-high concern

Clinical Relevance

The ultimate clinical attraction of histology-spatial-transcriptomics integration is not necessarily to perform spatial transcriptomics on every future cancer specimen. Instead, spatial transcriptomics may function as a molecular teaching signal for artificial-intelligence models. In such a workflow: spatial transcriptomics + H&E training data -> multimodal model -> molecularly informed analysis of routine H&E. This concept could allow routine histology slides to provide estimates of spatial gene-expression programs, tumor subtypes, immune microenvironment, molecular biomarker status, and therapeutic-response patterns [3,4,12].

DISCUSSION

The present systematic review demonstrates rapid development of computational methods that integrate histopathological morphology with spatial transcriptomics for cancer classification. The principal advantage of multimodal integration is biological complementarity.

Histology provides information regarding cellular morphology, architecture, nuclear atypia, stromal organization, immune infiltration, necrosis, and invasion. Spatial transcriptomics provides information regarding gene-expression programs, molecular subtypes, cell states, signaling pathways, and microenvironmental niches. Combining these data creates an opportunity to classify cancer simultaneously according to what the tumor looks like and what it is expressing locally.

The field initially focused on predicting gene expression from morphology. ST-Net demonstrated that local morphology contains sufficient information to estimate expression of many cancer-related genes [3]. Later models improved these predictions by explicitly representing spatial relationships. Hist2ST incorporated both transformer-based global context and graph-based local-neighborhood information [4], while SpaGCN used graph convolution to combine gene expression, spatial location, and histology for domain detection [5].

The emergence of graph models is particularly logical in cancer because tumor tissues are spatial ecosystems. The biological meaning of an individual cell or spot depends partly on neighboring malignant, immune, vascular, and stromal components.

More recent studies indicate a shift toward clinically meaningful classification rather than merely reconstructing expression. NePSTA is particularly important because it was designed for routine CNS tumor diagnostics and evaluated across four centers [7]. Another important development is the use of pathology foundation models, exemplified by GIST, which combines foundation-model histology features with graph-transformer transcriptomic integration [14].

These methods may improve generalization compared with networks trained from scratch on relatively small spatial-transcriptomics datasets, but generalizability across laboratories, scanners, fixation methods, stains, and populations remains uncertain.

Histology as a Proxy for Molecular State

A recurring observation is that gene-expression programs leave morphological signatures. Tumor cells with different transcriptional programs can differ in nuclear features, cellular density, stromal reaction, inflammatory context, and growth pattern. Deep learning can capture signals that may not be consciously recognizable to pathologists, but the extent to which these associations generalize across institutions remains uncertain.

Intratumoral Heterogeneity

A major strength of spatial-transcriptomics-based integration is the ability to characterize intratumoral heterogeneity. Bulk sequencing collapses multiple regions into a single molecular average. By contrast, spatial transcriptomics can reveal distinct tumor clones, immune niches, invasive margins, hypoxic compartments, and stromal programs. This is especially relevant to glioblastoma, pancreatic cancer, prostate cancer, and breast cancer.

Potential Diagnostic Applications

1. Automated tumor-region classification.
2. Molecular-subtype prediction from H&E.
3. Selection of regions for molecular testing.
4. Recognition of histologically occult molecular heterogeneity.
5. Inference of immune microenvironment.
6. Prediction of treatment response.
7. Refinement of grading systems.
8. Classification of limited biopsy specimens.

Barriers to Clinical Translation

Cost

Direct spatial-transcriptomics assays remain substantially more expensive than routine histology.

Tissue Processing

Performance may differ between fresh-frozen and FFPE tissue and among spatial platforms.

Resolution

Spot-based approaches may combine multiple cells in a single measurement.

Dataset Size

Many studies contain large numbers of spots but relatively few independent patients.

Domain Shift

Models trained at one institution may perform differently after changes in scanner, stain, tissue preparation, or patient population.

Interpretability

Highly complex multimodal models may be difficult for pathologists to interrogate.

Clinical Validation

Few models have undergone prospective evaluation in real diagnostic workflows.

Strengths of the Review

This review focuses specifically on histopathology-spatial-transcriptomics integration for cancer classification rather than spatial transcriptomics in cancer generally. It incorporates both biological integration methods and artificial-intelligence approaches and distinguishes spatial-domain classification, molecular-subtype classification, and histology-to-transcriptome prediction as related but separate analytical tasks.

LIMITATIONS

The field is evolving rapidly, and newly developed methods may appear faster than conventional systematic-review publication cycles. Substantial methodological heterogeneity prevented meaningful statistical pooling. Some computational studies reused the same publicly available breast-cancer datasets, meaning the literature contains methodological replication on partially overlapping data rather than completely independent clinical evidence. Many studies reported spot-level rather than patient-level diagnostic performance. External validation was inconsistent. Preprints and conference reports represent a substantial portion of cutting-edge work in this field; restricting conclusions to peer-reviewed evidence may omit very recent developments, while including them may reduce certainty.

Future Research

1. Multicenter cohorts.
2. Independent patient-level external validation.
3. Standardized train-test separation.
4. FFPE-compatible spatial platforms.
5. Comparison across scanners and laboratories.
6. Clinically meaningful patient-level classification endpoints.
7. Integration with pathology foundation models.
8. Prospective diagnostic studies.
9. Explainable multimodal AI.
10. Cost-effectiveness analysis.
11. Direct comparison with established molecular classifiers.
12. Standardized reporting guidelines for histology-spatial-transcriptomics studies.

CONCLUSION

Integration of histopathology and spatial transcriptomics represents a rapidly advancing approach to cancer classification. Spatial transcriptomic data can connect morphological structures with gene-expression programs, while artificial-intelligence models can learn these relationships and subsequently use histology to infer molecular and spatial states. Current evidence supports applications in breast cancer, pancreatic cancer, CNS tumors, prostate cancer, colorectal cancer, and other solid malignancies. The strongest evidence currently supports spatial-domain identification, histology-based gene-expression prediction, molecular-subtype inference, and tumor-region classification. Recent multicenter approaches demonstrate that integration may ultimately extend beyond research into diagnostic pathology. However, routine implementation will require substantially larger patient cohorts, rigorous external validation, standardized pathology workflows, improved interpretability, and prospective demonstration of clinical benefit.

DECLARATIONS

Ethical Approval: Not applicable. This systematic review synthesized previously published data and did not involve direct recruitment of human participants.

Consent to Participate: Not applicable.

Consent for Publication: Not applicable.

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Author Contributions: All authors contributed to the conception of the review, literature evaluation, interpretation of findings, manuscript preparation, and critical revision. All authors approved the final manuscript.

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