

Peri-Ureteral Urothelial Carcinoma Confined to the Adventitia with Spared Mucosal Integrity: An Extensive Comprehensive Review of a Clinically Occult Entity Within the Spectrum of Non-Muscle-Invasive Upper Tract Disease, Diagnostic Pitfalls, And Divergent Prognostic Implications

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ABSTRACT

Background: Upper tract urothelial carcinoma (UTUC) presenting as an exclusive peri-ureteral mass with infiltration of the adventitial soft tissue whilst maintaining absolute denudation of the overlying ureteric mucosa and lamina propria represents an extraordinarily rare and diagnostically treacherous pathological phenomenon. Unlike conventional invasive UTUC wherein transmural progression follows a sequential centripetal pattern, this non-mucosa-invasive yet peri-ureteral variant violates conventional staging paradigms, creating substantial nosological ambiguity. Current American Joint Committee on Cancer (AJCC) criteria lack explicit designation for neoplasms demonstrating extra-ureteral extension without concomitant subepithelial connective tissue or muscularis propria involvement, engendering a tangible risk for both under-staging and inappropriate therapeutic stratification. **Objective:** This comprehensive review aims to synthesize the extant, albeit fragmentary, literature concerning peri-ureteral urothelial carcinoma without mucosal involvement, elucidate its putative histogenetic mechanisms—including the prevailing hypothesis of origin within peri-ureteral or von Brunn's nest remnants—delineate the immunohistochemical challenges in distinguishing this entity from primary peri-ureteral adenocarcinoma or metastatic disease, and critically evaluate the oncological outcomes extrapolated from analogous pT3 subclassification data. **Methods:** A meticulous narrative synthesis of the literature was conducted, with focused interrogation of multicenter UTUC cohorts, contemporary genomic profiling studies, and institutional case reports to aggregate histomorphological descriptors, immunophenotypic profiles, and survival metrics. **Results:** Evidence suggests that extra-ureteral tumor extension without mucosal invasion, when stratified within pT3b disease, portends significantly inferior recurrence-free and cancer-specific survival compared to renal parenchymal invasion alone, with five-year cancer-specific survival approximating 54.3% in the largest available series. Furthermore, emerging data implicate distinct clonal evolutionary trajectories and chromatin regulatory gene alterations—particularly involving KMT2C and EP300—which may underpin the paradoxical phenotype of extra-ureteral dissemination without antecedent high-grade intraurothelial carcinoma. **Conclusions:** Peri-ureteral urothelial carcinoma with spared mucosa constitutes a distinct clinicopathologic entity that defies conventional staging logic and warrants formal recognition within future tumor-nodes-metastasis (TNM) frameworks. A heightened index of suspicion is mandated for ureteric tumors demonstrating eccentric adventitial thickening on cross-sectional imaging in the absence of an

ARTICLE DETAILS

Published On:
24 April 2026

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intraluminal component. Multidisciplinary collaboration between urologists, radiologists, and genitourinary pathologists is imperative to avert diagnostic oversight and facilitate the administration of risk-adapted perioperative therapeutic strategies.

KEYWORDS: Upper tract urothelial carcinoma; peri-ureteral invasion; non-mucosa-invasive urothelial carcinoma; pT3b subclassification; ureteral adventitia; extra-ureteral extension; von Brunn's nests; inverted growth pattern; diagnostic pitfall; AJCC staging discrepancy; chromatin regulatory genes; KMT2C; EP300; immunohistochemistry; GATA3; radical nephroureterectomy; adjuvant radiotherapy; cancer-specific survival.

Available on:

<https://ijmscrs.com>

INTRODUCTION

Urothelial carcinomas of the upper urinary tract represent a comparatively infrequent yet highly lethal constellation of malignancies, accounting for approximately five to ten percent of all renal tumors and merely a fraction of the overall urothelial neoplasms encountered in clinical practice, with an age-standardized incidence rate in Western populations favoring males at a ratio of approximately three to one and a median age at presentation surpassing the seventh decade of life. The biological behavior and prognostic stratification of these tumors are fundamentally predicated upon the depth of parietal invasion, a principle enshrined within the TNM staging schema wherein confinement to the subepithelial connective tissue denotes pTa or pT1 disease, involvement of the muscularis propria defines pT2, and infiltration beyond the muscularis into the peri-pelvic fat or peri-ureteral adventitia constitutes pT3 disease. This paradigm implicitly assumes a contiguous, radially progressive vector of tumor propagation; the neoplasm is anticipated to breach the urothelial surface, invade the lamina propria, transgress the muscularis mucosae and muscularis propria in sequence, and ultimately emerge within the peri-ureteral soft tissues. Consequently, the archetypal pT3 UTUC is visualized both endoscopically and histopathologically as an exophytic, endoluminal lesion with demonstrable transmural penetration.^{1,2,3,4}

However, this linear conceptualization is fundamentally challenged by the existence of an exceedingly uncommon variant wherein urothelial carcinoma is identified within the peri-ureteral adipose tissue or adventitial lymphovascular spaces in the conspicuous absence of any neoplastic involvement of the overlying ureteric mucosa, muscularis propria, or subepithelial connective tissue. This phenomenon, which may be operationally designated as peri-ureteral urothelial carcinoma with spared mucosal integrity, presents a profound ontogenetic and taxonomic conundrum. The neoplasm effectively achieves extra-organic dissemination without fulfilling the requisite histological criteria for intramural invasion. Such a presentation defies the orthodox understanding of tumor progression and invites critical interrogation regarding its cellular provenance, its route of egress from the ureteric wall, and its appropriate placement

within the hierarchical framework of prognostic staging systems.^{5,6,7,8}

The existing medical literature, while voluminous concerning conventional UTUC, remains remarkably reticent regarding this specific entity. The preponderance of evidence is derived not from prospectively designed trials or dedicated registries, but from fortuitous observations embedded within larger surgical series, isolated case reports detailing diagnostic dilemmas encountered during transurethral or ureteroscopic interventions, and extrapolative analyses of pT3 subclassification cohorts. Within the latter context, a seminal multicenter investigation by Yamada and colleagues has provided pivotal granularity by dichotomizing pT3 UTUC according to the anatomical substrate of invasion: pT3a, denoting infiltration confined to the renal parenchyma, and pT3b, encompassing those tumors exhibiting peripelvic or periureteral fat invasion. The relevance of this distinction to the current discourse is manifest, as a substantive proportion of pT3b tumors may, upon rigorous histopathological re-evaluation, demonstrate peri-ureteral extension in the relative absence of deep mural invasion. The survival differential elucidated by this study was stark; patients harboring pT3b disease exhibited a five-year cancer-specific survival of merely 54.3% compared to 80.0% for their pT3a counterparts, with concomitantly elevated hazards for locoregional recurrence and distant metastatic dissemination. This disparity underscores the aggressive biological potential of tumors capable of accessing peri-ureteral tissues, irrespective of the specific mechanism by which such access is attained.^{9,10,11,12}

Further complicating the diagnostic landscape is the subtlety of the histomorphological presentation. Unlike conventional high-grade invasive urothelial carcinoma, which typically elicits a robust desmoplastic stromal reaction and is characterized by overt cytological anaplasia and disordered architectural effacement, peri-ureteral deposits of non-mucosa-invasive disease may manifest as deceptively well-circumscribed, nested proliferations that closely simulate benign epithelial inclusions, endosalpingiosis, or mesothelial hyperplasia. The phenomenon of large nested variant urothelial carcinoma is particularly salient in this context; despite its ostensibly indolent low-grade cytomorphology, this

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variant possesses the capacity for extensive extra-ureteral dissemination and may be erroneously dismissed as a non-invasive inverted papilloma-like process if biopsy sampling is superficial or if the pathologist is not alerted to the discrepancy between the endoscopic findings and the imaging characteristics. Guo and colleagues have previously emphasized that the distinction between non-invasive inverted neoplasms and invasive large nested urothelial carcinoma is contingent not solely upon cytological features, but upon the topographic relationship of the cellular nests to the muscularis propria and adventitial compartments, a determination that may be unequivocally resolvable only upon complete excisional sampling.^{13,14,15,16,17}

Several competing histogenetic hypotheses have been advanced to reconcile the pathological paradox of extra-ureteral tumor without mucosal breach. The most widely accepted postulate implicates the malignant transformation of displaced urothelial cell rests, specifically the so-called von Brunn's nests which, under physiologic conditions, represent invaginations of surface urothelium into the lamina propria but may, on occasion, extend ectopically into the adventitial plane or even beyond the ureteric adventitia. Neoplastic transformation occurring within these deep-seated epithelial inclusions would engender an expansile mass centered within the peri-ureteral soft tissue, with secondary compression or encasement of the native ureter but without the development of a mucosal-based precursor lesion. This mechanism is conceptually analogous to the pathogenesis of inverted urothelial neoplasms and, in the context of the prostatic urethra, the phenomenon of intraepithelial extension of urothelial carcinoma within periurethral prostatic ducts without stromal invasion. The SEER Summary Staging Manual explicitly acknowledges this possibility, codifying non-invasive carcinoma involving the periurethral or prostatic ducts without stromal invasion as *in situ* disease, a precedent that lends credence to the recognition of analogous ureteric lesions as a discrete biological entity rather than an artifactual misclassification.^{18,19,20,21}

Alternative mechanistic explanations include the possibility of occult lymphovascular permeation with retrograde extravasation into the peri-ureteral connective tissue, or the phenomenon of tumor implantation within the adventitial sheath following prior ureteroscopic manipulation, although the latter hypothesis fails to account for cases diagnosed *de novo* without antecedent endoscopic instrumentation. Contemporary genomic interrogation of UTUC has furnished additional layers of complexity to this discourse. Meireles and colleagues, in their comparative biomarker profiling of UTUC with and without synchronous bladder involvement, demonstrated that distinct molecular subtypes and mutational signatures may influence the pattern and timing of disease dissemination. Moreover, Wang and associates have recently identified a high frequency of deleterious alterations in

chromatin regulatory genes—including KMT2C, ARID1A, and EP300—in UTUC cohorts, with particular enrichment of these mutations in tumors exhibiting specific single-base substitution signatures (SBS2 and SBS22) associated with APOBEC-mediated mutagenesis and aristolochic acid exposure, respectively. It is tempting to speculate that such genomic aberrations may confer upon a subset of UTUCs an unconventional phenotype characterized by adventitial tropism and independence from the conventional sequence of stepwise parietal invasion.^{22,23,24,25}

The diagnostic ramifications of failing to recognize this entity are substantial. A peri-ureteral mass identified on computed tomography urography in a patient with microscopic hematuria but unremarkable ureteroscopic visualization of the urothelial surface may be presumptively ascribed to a non-urothelial etiology, such as primary retroperitoneal fibrosis, inflammatory pseudotumor, metastatic lymphadenopathy, or a mesenchymal neoplasm. Consequently, the opportunity for curative-intent surgical extirpation may be delayed or entirely foreclosed. Conversely, the fortuitous detection of peri-ureteral urothelial carcinoma within a nephroureterectomy specimen performed for what was preoperatively characterized as non-muscle-invasive disease may precipitate a significant upward revision of the pathological stage, with attendant implications for adjuvant therapy and prognostic counseling. The work by Kim and colleagues, examining adjuvant treatment efficacy specifically within the pT3bN0-x subpopulation, revealed that while conventional adjuvant chemotherapy failed to confer a statistically significant improvement in local recurrence-free, distant metastasis-free, or cancer-specific survival, adjuvant radiation therapy was associated with substantial reductions in all three oncological endpoints. This observation underscores the imperative for accurate identification of peri-ureteral tumor involvement, as the therapeutic calculus for adjuvant radiation may be distinctly different for patients with microscopic adventitial deposits compared to those with conventional pT2 or pT3a disease.²⁶

It is against this backdrop of diagnostic ambiguity, nosological uncertainty, and emerging therapeutic nuance that the present comprehensive review is undertaken. We endeavor to collate and critically appraise the disparate threads of evidence pertaining to peri-ureteral urothelial carcinoma without mucosal invasion, spanning the domains of histopathology, molecular oncology, clinical radiology, and surgical therapeutics. In so doing, we aspire not only to furnish the practicing urologist and genitourinary pathologist with a pragmatic framework for the recognition and management of this elusive entity, but also to advocate for its formal acknowledgment within future iterations of the TNM classification, thereby rectifying a long-standing lacuna in the staging canon. The imperative for such recognition is not merely semantic; it is a prerequisite for the accurate

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documentation of incidence rates, the delineation of prognostic correlates, and the design of clinical trials directed at this unique patient subset. In an era of precision oncology, wherein therapeutic decision-making is increasingly predicated upon nuanced pathological and molecular determinants, the invisibility of this entity within the formal staging nosology represents an untenable anachronism. The following sections will systematically address the histopathological differential diagnosis, the extant evidence base for therapeutic intervention, and the frontiers of translational research that may ultimately illuminate the enigmatic pathogenesis of this perplexing manifestation of upper tract urothelial carcinoma.²⁷

BACKGROUND

The diagnostic and therapeutic landscape of upper tract urothelial carcinoma has undergone substantial evolution over the past two decades, yet the medical literature remains remarkably deficient in its characterization of a singularly perplexing pathological phenotype: peri-ureteral urothelial carcinoma that achieves extra-ureteral extension whilst preserving the absolute histological integrity of the overlying ureteric mucosa and muscularis propria. This entity, which we shall henceforth operationalize under the descriptive rubric of non-mucosa-invasive peri-ureteral urothelial carcinoma, represents not merely an academic curiosity but a formidable clinical conundrum that lays bare the fundamental inadequacies of contemporary staging nosology and compels a radical reconsideration of the conventional ontogenetic narrative ascribed to tumors of the upper urinary tract epithelium.²⁸

Urothelial carcinoma of the upper urinary tract constitutes a relatively uncommon yet disproportionately lethal neoplasm, accounting for approximately five to seven percent of all renal malignancies and merely one-tenth of the overall burden of urothelial tumors encountered in genitourinary oncology practice, with an estimated age-standardized incidence in Western populations ranging from 1.2 to 2.1 cases per one hundred thousand person-years and a well-documented male preponderance approximating a three-to-one ratio. The median age at clinical presentation typically surpasses the seventh decade of life, and established risk factors include aristolochic acid nephropathy, Balkan endemic nephropathy, Lynch syndrome associated with germline mutations in DNA mismatch repair genes, and prolonged exposure to occupational carcinogens such as aromatic amines and cyclophosphamide. The prognostic stratification of these neoplasms, as codified within the tumor-nodes-metastasis staging framework promulgated by the American Joint Committee on Cancer and the Union for International Cancer Control, rests fundamentally upon the precise anatomical depth of parietal invasion, with infiltration beyond the muscularis propria into the peri-pelvic adipose tissue or peri-

ureteral adventitia constituting pT3 disease and involvement of adjacent viscera or through the renal parenchyma into the perinephric fat defining pT4 disease.²⁹

This staging paradigm, however, operates upon an implicit and heretofore largely unchallenged assumption regarding the spatial and temporal trajectory of tumor propagation. The conventional model posits that urothelial carcinogenesis originates within the surface epithelium, progresses through sequential stages of flat dysplasia and carcinoma in situ, subsequently manifests as an exophytic or endoluminal papillary proliferation, and thereafter invades the underlying subepithelial connective tissue, penetrates the muscularis mucosae and muscularis propria in a contiguous radial fashion, and ultimately emerges within the peri-ureteral soft tissues only after traversing the full thickness of the ureteric wall. Within this conceptual framework, the identification of extra-ureteral tumor extension serves as a reliable histological surrogate for antecedent deep mural invasion, and the diagnosis of pT3 disease is rendered with the implicit understanding that transmural penetration has occurred. The corollary of this assumption is that the ureteric mucosa and lamina propria, in cases of peri-ureteral tumor involvement, will invariably demonstrate either overt invasive carcinoma or, at minimum, antecedent flat urothelial dysplasia or carcinoma in situ contiguous with the site of parietal penetration.³⁰

It is precisely this foundational assumption that the entity under discussion fundamentally and irreconcilably contravenes. The extant literature, although fragmentary and derived predominantly from fortuitous observations embedded within larger surgical series, contains incontrovertible documentation of urothelial carcinoma identified within the peri-ureteral adventitia and adjacent fibroadipose tissue in specimens wherein exhaustive histopathological examination of the overlying ureteric mucosa, lamina propria, and muscularis propria has revealed no evidence of neoplastic involvement whatsoever. These cases defy the conventional staging algorithm at every turn. They are, by definition, non-muscle-invasive by virtue of the absolute absence of tumor within the muscularis propria, yet they simultaneously fulfill the anatomical criterion for pT3 disease by virtue of the presence of tumor within peri-ureteral soft tissue. The neoplasm has, in essence, achieved extra-organic dissemination without ever having formally invaded the organ of origin. This ontological paradox engenders profound consternation for the practicing pathologist, for whom the assignment of a pT category under such circumstances is an exercise in attempting to reconcile irreconcilable staging criteria, and for the treating urologist, who must formulate adjuvant therapeutic recommendations based upon a disease designation that simultaneously signifies both non-muscle-invasive and extra-ureteral disease.³¹

The concept of subclassifying pT3 upper tract urothelial carcinoma according to the anatomical substrate of invasion

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has emerged in recent years as a compelling framework for resolving, or at least mitigating, the prognostic heterogeneity that has long been recognized within this population. The seminal multicenter investigation conducted by Yamada and colleagues, encompassing 323 patients who underwent radical nephroureterectomy for pT3 disease across eleven Japanese institutions, provided pivotal granularity by dichotomizing this cohort according to whether the invasive tumor was confined to the renal parenchyma, designated pT3a, or had extended into the peripelvic or periureteral adipose tissue, designated pT3b. The survival differential elucidated through this subclassification was stark and clinically meaningful. Patients harboring pT3b disease exhibited a five-year recurrence-free survival of merely 42.4 percent, a five-year cancer-specific survival of 54.3 percent, and a five-year overall survival of 47.8 percent, whereas their pT3a counterparts demonstrated substantially more favorable outcomes, with corresponding survival estimates of 70.1 percent, 80.0 percent, and 76.8 percent, respectively. These disparities achieved statistical significance at stringent thresholds and persisted across multiple sensitivity analyses. The corroborative investigation by Suhara and colleagues, published contemporaneously and derived from an independent multicenter cohort of 308 patients, similarly demonstrated that pT3b status constituted an independent risk factor for both recurrence and cancer-specific mortality, with adjusted hazard ratios of 2.04 and 2.31, respectively, following multivariable adjustment for established prognostic covariates including nodal involvement and lymphovascular invasion.³²

The relevance of this pT3 subclassification schema to the specific entity of non-mucosa-invasive peri-ureteral urothelial carcinoma is both direct and profound. Within any large cohort of tumors classified as pT3b, a subset will inevitably, upon rigorous histopathological re-evaluation, demonstrate peri-ureteral fat invasion in the conspicuous absence of antecedent or concomitant mucosal involvement. These cases, although ostensibly aggregated within the pT3b category, may represent a biologically distinct phenomenon rather than merely an anatomical variant of conventional transmural disease. The survival outcomes documented for pT3b UTUC as a whole, which are unequivocally inferior to those observed for pT3a disease and, in some series, indistinguishable from those of pT4 disease, may therefore reflect the prognostic contribution of this peculiar subset. Whether non-mucosa-invasive peri-ureteral tumors carry the same adverse prognosis as conventional pT3b tumors with overt mucosal and mural invasion remains, at present, an unanswered question of substantial clinical importance, as the answer carries direct implications for the intensity of postoperative surveillance and the threshold for administering adjuvant therapeutic interventions.³²

The therapeutic implications of this diagnostic entity have been further illuminated through the work of Kim and

colleagues, whose multicenter analysis of adjuvant treatment efficacy specifically within the pT3bN0-x subpopulation yielded findings that challenge conventional practice patterns and underscore the imperative for accurate pathological characterization. In this investigation encompassing 222 patients with pT3b disease treated with radical nephroureterectomy, adjuvant platinum-based chemotherapy, administered to approximately one-third of the cohort, failed to confer any detectable improvement in local recurrence-free survival, distant metastasis-free survival, or cancer-specific survival following rigorous adjustment for confounding variables through propensity score methodology. Adjuvant radiation therapy, in contradistinction, was associated with substantial and statistically significant reductions in all three oncological endpoints, with five-year local recurrence-free survival improving from 54.2 percent to 83.9 percent, distant metastasis-free survival improving from 48.1 percent to 72.1 percent, and cancer-specific survival improving from 55.5 percent to 76.4 percent. These observations, although derived from retrospective data and requiring prospective confirmation, suggest that the therapeutic calculus for patients with peri-ureteral tumor extension may differ meaningfully from that applied to patients with conventional pT2 or pT3a disease. They further imply that accurate identification of peri-ureteral involvement, including those cases occurring in the absence of detectable mucosal disease, is not merely an academic exercise but a prerequisite for risk-appropriate postoperative management.³²

The histogenetic mechanisms underlying this paradoxical phenomenon have been the subject of considerable speculation but limited empirical investigation. The prevailing hypothesis, articulated in various forms across several published case reports and small series, invokes the malignant transformation of displaced urothelial cell rests situated ectopically within the peri-ureteral adventitia. The ureter, embryologically derived from the mesonephric duct, develops through a complex process of elongation and canalization that may occasionally sequester epithelial inclusions within the peri-ureteral soft tissues. Von Brunn's nests, which under physiological conditions represent invaginations of the surface urothelium into the lamina propria and are encountered with increasing frequency with advancing age, have been documented on rare occasions to extend beyond the confines of the muscularis propria and into the adventitial plane. Neoplastic transformation occurring within such deep-seated epithelial inclusions would engender an expansile mass centered within the peri-ureteral soft tissue, with secondary encasement or compression of the native ureter but without the development of a mucosal-based precursor lesion. This mechanistic model is conceptually analogous to the pathogenesis of inverted urothelial neoplasms, wherein endophytic proliferation arises from the basal layers of the urothelium and extends downward into the subepithelial connective tissue while maintaining an

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intact overlying mucosal surface, and to the phenomenon of intraepithelial extension of urothelial carcinoma within periurethral prostatic ducts without stromal invasion, a scenario explicitly codified within the SEER Summary Staging Manual as *in situ* disease. The nested variant of urothelial carcinoma, originally characterized by Badoual and colleagues and subsequently elaborated in larger clinicopathological series, is particularly germane to this discussion, as this variant is notorious for its deceptively benign cytomorphology and its propensity for extensive invasion despite low-grade architectural features. The nested variant typically manifests as confluent aggregates of cytologically bland urothelial cells arranged in irregular nests and cords that infiltrate the lamina propria and muscularis propria while eliciting minimal desmoplastic stromal reaction. When such nests arise from, or extend into, ectopic urothelial inclusions within the adventitia, they may produce a peri-ureteral tumoral deposit that is histologically indistinguishable from metastatic carcinoma or primary adenocarcinoma of peri-ureteral glandular elements.³²

Alternative mechanistic explanations warrant careful consideration. The possibility of occult lymphovascular invasion with retrograde extravasation of tumor cells into the peri-ureteral connective tissue has been advanced, although this hypothesis fails to account for cases wherein exhaustive examination reveals no intravascular tumor component. The phenomenon of peri-ureteral tumor implantation following ureteroscopic manipulation represents another plausible mechanism, particularly given the well-documented risk of tumor seeding along percutaneous nephrostomy tracts and ureteroscopic biopsy sites, yet this explanation cannot be invoked for the subset of cases diagnosed *de novo* without antecedent endoscopic instrumentation. The hematogenous dissemination of metastatic deposits to the ureteral adventitia, a well-characterized pattern of secondary ureteral involvement classically associated with carcinomas of the breast, lung, prostate, and colon, must also be considered in the differential diagnosis. Marincek and colleagues, in their comprehensive review of metastatic disease of the ureter, delineated four distinct radiographic patterns of tumoral spread, including hematogenous adventitial metastases spreading along periureteral vessels and scirrhous metastatic spread along periureteral lymphatic channels. The distinction between primary peri-ureteral urothelial carcinoma arising from ectopic epithelial rests and metastatic urothelial carcinoma from an occult synchronous primary tumor elsewhere in the urinary tract, although conceptually straightforward, may prove practically impossible in the absence of definitive molecular clonality testing.³²

The emerging discipline of urothelial cancer genomics has furnished additional layers of complexity to this discourse and may ultimately provide the explanatory framework required to reconcile these seemingly incompatible observations.

Comprehensive genomic profiling studies have demonstrated that upper tract urothelial carcinomas harbor distinct mutational signatures compared to their urothelial bladder carcinoma counterparts, with higher frequencies of alterations in chromatin regulatory genes and DNA damage repair pathways. Wang and colleagues, in their comparative analysis of 34 UTUC and 49 urothelial bladder carcinoma specimens, identified frequent deleterious mutations in KMT2C, ARID1A, EP300, and SMARCA4 across both anatomical sites, but observed that rapid relapse and progression of non-muscle-invasive disease were specifically correlated with alterations in KMT2C and EP300. Hoffmann and colleagues, in their comprehensive review of chromatin regulator alterations in urothelial carcinogenesis, proposed a model wherein disruption of histone-modifying enzymes and components of the SWI/SNF chromatin remodeling complex promotes cellular plasticity, disrupts normal differentiation programs, and facilitates clonal expansion through epigenetic dysregulation. It is biologically plausible that specific constellations of chromatin regulatory gene mutations may confer upon a subset of UTUCs an unconventional phenotype characterized by adventitial tropism, independence from the conventional sequence of stepwise parietal invasion, and the capacity for extra-ureteral dissemination at an apparently early stage of neoplastic progression. The enrichment of such mutations in UTUC patients exhibiting single-base substitution signatures SBS22 and SBS2, associated respectively with aristolochic acid exposure and APOBEC-mediated mutagenesis, suggests that environmental and host factors may interact with genomic vulnerability to produce this peculiar biological behavior.^{32,33}

DIAGNOSIS

The diagnostic odyssey of peri-ureteral urothelial carcinoma without mucosal invasion represents one of the most formidable challenges in contemporary genitourinary pathology and uro-oncology, a conundrum wherein the very tools conventionally employed to establish the presence and characterize the nature of upper tract malignancies are rendered paradoxically inadequate by the peculiar anatomical distribution and growth pattern of the neoplasm itself. The diagnostic armamentarium available to the clinician confronting a patient with suspected upper tract urothelial carcinoma encompasses urinary cytology, cross-sectional imaging modalities including computed tomography urography and magnetic resonance urography, direct endoscopic visualization through ureteroscopy with or without narrow-band imaging or photodynamic diagnosis, and tissue acquisition via ureteroscopic biopsy or percutaneous needle sampling under image guidance. Each of these diagnostic modalities, when deployed in isolation or in combination, carries distinct performance characteristics, inherent limitations, and specific vulnerabilities when applied

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to the diagnostic scenario wherein the neoplastic process is situated predominantly or exclusively within the peri-ureteral adventitial compartment with absolute sparing of the overlying urothelial surface. The systematic deconstruction of these diagnostic challenges, the explication of the interpretative pitfalls that attend each modality, and the formulation of an integrated diagnostic algorithm that acknowledges the unique biological behavior of this entity constitute essential prerequisites for the timely recognition and appropriate management of this elusive pathological phenomenon.³³

The diagnostic odyssey frequently commences, as in the seminal case report by Gholami and colleagues published in late 2025 which represents the first formally documented instance of this entity in the peer-reviewed literature, with the incidental detection of otherwise unexplained hydronephrosis on surveillance imaging performed in a patient with remote history of non-muscle-invasive bladder cancer managed with intravesical bacillus Calmette-Guérin immunotherapy. This index case, a seventy-five-year-old male who had remained recurrence-free for a decade following his initial bladder cancer diagnosis before developing a low-grade bladder recurrence after ten years and subsequently demonstrating left hydronephrosis and peri-ureteric thickening on surveillance computed tomography, illustrates with painful clarity the fundamental diagnostic paradox that defines this entity. The patient underwent what would conventionally be considered the definitive diagnostic evaluation for suspected upper tract urothelial carcinoma, including direct ureteroscopic visualization of the entire ureteric lumen and selective urinary cytology sampling, both of which returned entirely within normal limits. The ureteroscopic appearance of the urothelium was unremarkable, demonstrating no evidence of erythema, mucosal irregularity, papillary excrescence, or plaque-like thickening; the ureteric orifice effluxed clear urine without particulate matter or visible debris; and the selectively obtained urinary cytology revealed only benign urothelial cells without any cytomorphologic features suggestive of dysplasia or malignancy. It was only through the performance of computed tomography-guided percutaneous biopsy of the peri-ureteral soft tissue thickening, a procedure rarely indicated in the standard diagnostic algorithm for suspected urothelial carcinoma and one that carries attendant risks of bleeding, infection, and theoretical tumor seeding along the needle tract, that the diagnosis of low-grade papillary urothelial carcinoma external to the ureter was ultimately established.³³

This index case crystallizes the central diagnostic dilemma with extraordinary precision. Conventional white light ureteroscopy, which affords the urologist the ability to inspect the ureteric mucosa with remarkable spatial resolution and has historically been regarded as the reference standard for the detection of upper tract urothelial neoplasms, is rendered

diagnostically inert when confronted with a neoplasm that does not involve the mucosal surface. The ureteroscopic appearance of the ureter in such cases is, by definition, within normal limits; there is simply no mucosal abnormality to visualize. The application of enhanced endoscopic techniques including narrow-band imaging and photodynamic diagnosis with 5-aminolevulinic acid, which exploit differential light absorption characteristics and porphyrin accumulation respectively to accentuate the contrast between dysplastic or neoplastic urothelium and normal surrounding mucosa, would similarly be expected to yield negative results in the absence of mucosal involvement. Ricciardi and colleagues, in their comprehensive 2025 review of epigenetic and other biomarkers for UTUC diagnosis and surveillance, have emphasized that while optical enhancement technologies have demonstrably improved the sensitivity of endoscopic detection for flat urothelial lesions including carcinoma in situ and have reduced the false-negative rate of white light ureteroscopy for conventional exophytic tumors, these technologies remain fundamentally dependent upon the presence of an intraurothelial or superficial neoplastic component accessible to optical interrogation. They are, by their very physical and pharmacological principles, incapable of detecting a neoplasm sequestered entirely within the adventitial compartment and separated from the optical field by an intact, optically unremarkable mucosal surface and muscularis propria.³³

The diagnostic performance of urinary cytology in this specific clinical scenario is similarly constrained by fundamental biological and anatomical considerations. Urinary cytology, whether performed on voided specimens or on urine selectively aspirated from the upper tract at the time of retrograde pyelography or ureteroscopy, operates on the premise that neoplastic urothelial cells will exfoliate from the tumor surface and become suspended in the urinary stream, where they can be recovered through centrifugation and identified through characteristic cytomorphologic features including increased nuclear-to-cytoplasmic ratio, nuclear membrane irregularity, hyperchromasia, and coarsely clumped chromatin pattern. The sensitivity of urinary cytology for the detection of upper tract urothelial carcinoma is notoriously variable across published series, with estimates ranging from as low as twenty percent to as high as seventy-five percent depending upon tumor grade, tumor stage, and the technical expertise of the interpreting cytopathologist, but even the most optimistic assessments acknowledge that cytology is least sensitive for low-grade lesions and for tumors that do not exhibit a substantial exophytic or superficially invasive component. In the specific context of peri-ureteral urothelial carcinoma without mucosal invasion, the neoplasm is by definition separated from the urinary stream by an intact and non-neoplastic urothelial barrier, and there exists no biological mechanism by which neoplastic

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cells could gain access to the urinary space. The selective upper tract cytology in such cases would be anticipated to be universally negative, and a negative cytology result, far from providing reassurance regarding the absence of malignancy, merely reflects the anatomical inaccessibility of the neoplastic cells to the urinary compartment.³⁴

The diagnostic imaging characteristics of this entity, while more promising than either ureteroscopy or cytology in suggesting the presence of an underlying neoplastic process, are nonetheless fraught with their own distinctive interpretative challenges and differential diagnostic considerations. Computed tomography urography, which combines non-contrast and nephrographic-phase imaging with excretory-phase opacification of the urinary collecting system and has supplanted intravenous pyelography as the imaging modality of choice for the evaluation of suspected upper tract pathology, is exquisitely sensitive for the detection of intraluminal filling defects, mural thickening, and peri-ureteral soft tissue abnormalities. The imaging findings that should prompt consideration of peri-ureteral urothelial carcinoma without mucosal invasion include eccentric adventitial thickening, soft tissue stranding within the peri-ureteral fat that extends contiguously from the ureteric adventitia into the surrounding retroperitoneum, and discrete peri-ureteral mass lesions that encase or compress the adjacent ureter without demonstrable intraluminal component or mural invasion. These radiographic findings, however, are by no means specific for urothelial carcinoma and must be meticulously distinguished from a broad and heterogeneous array of alternative diagnostic possibilities that encompass both benign and malignant entities of diverse histogenetic derivation.³⁵

The differential diagnosis of a peri-ureteral soft tissue abnormality identified on cross-sectional imaging is extraordinarily extensive and includes non-neoplastic inflammatory conditions such as retroperitoneal fibrosis, which may be idiopathic or secondary to medications including methysergide and certain beta-adrenergic antagonists, immunoglobulin G4-related disease with peri-ureteral involvement, Erdheim-Chester disease, inflammatory pseudotumor, and xanthogranulomatous pyelonephritis with peri-ureteral extension. Infectious etiologies including tuberculosis, fungal infections, and parasitic infestations may produce peri-ureteral inflammatory masses that closely simulate malignancy on imaging. Benign neoplastic processes that may arise in or secondarily involve the peri-ureteral soft tissues include schwannomas, neurofibromas, leiomyomas, and solitary fibrous tumors. Malignant neoplasms of non-urothelial origin that must be considered in the differential diagnosis include primary retroperitoneal sarcomas, lymphomas with peri-ureteral lymphadenopathy, metastatic disease to the peri-ureteral lymphatics from diverse primary sites including breast, lung,

prostate, and colon, and direct extension of primary tumors arising from adjacent organs including the colon, uterine cervix, and ovary. The radiographic appearance of peri-ureteral thickening or mass, even when accompanied by hydronephrosis and when occurring in a patient with established risk factors for urothelial carcinoma, does not in isolation permit the confident diagnosis of primary peri-ureteral urothelial carcinoma, and tissue confirmation is uniformly required before the initiation of definitive surgical or systemic therapy.³⁶

The critical contribution of Arienzo and colleagues, published in 2024 and describing a truly extraordinary case of metastatic upper tract urothelial carcinoma with nest-like features presenting initially as malignant pleural effusion in an oldest-old male patient with situs inversus totalis, provides invaluable insights into the imaging-pathologic correlation that may ultimately permit the ante-mortem recognition of this elusive entity. In this remarkable case, total body computed tomography performed during the diagnostic workup of a massive left pleural effusion containing epithelioid neoplastic cells arranged in short cords, clusters, and nest-like structures revealed no evidence of a primary tumor within the urinary bladder or elsewhere in the genitourinary tract, but did demonstrate a concentric parietal thickening of the proximal left ureter that was sufficiently subtle as to have been initially overlooked. This case underscores the imperative for meticulous, systematic evaluation of the entire upper tract collecting system in patients presenting with metastatic urothelial carcinoma of unknown primary, with particular attention directed toward the detection of mural or adventitial abnormalities that may be radiographically inconspicuous yet histopathologically significant. The concentric parietal thickening described by Arienzo and colleagues, which correlated at the cytopathologic level with a nested variant urothelial carcinoma characterized by GATA3 positivity, p63 expression, and uroplakin II immunoreactivity, may represent a distinctive imaging signature of peri-ureteral urothelial carcinoma without mucosal invasion, particularly when the nested variant histology is present. The nested variant of urothelial carcinoma, originally characterized by Badoual and colleagues in the French pathology literature and subsequently elaborated in larger clinicopathologic series, is notorious among genitourinary pathologists for its deceptively benign cytomorphology, its bland low-grade appearance that belies its aggressive metastatic potential, and its distinctive architectural pattern of confluent nests and cords that infiltrate deeply through the ureteric wall while eliciting minimal desmoplastic stromal reaction. The concentric, relatively well-circumscribed pattern of ureteric involvement observed in the case reported by Arienzo and colleagues, which produced circumferential adventitial thickening rather than an irregular, infiltrative, spiculated

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mass, may reflect this distinctive nested variant growth pattern and should alert the interpreting radiologist to the possibility of this specific histologic subtype.^{36,37,38}

The histopathological diagnosis of peri-ureteral urothelial carcinoma without mucosal invasion, when tissue is ultimately obtained either through image-guided percutaneous biopsy or through definitive surgical extirpation with radical nephroureterectomy, rests upon the demonstration of malignant urothelial cells within the peri-ureteral adventitia or adjacent fibroadipose tissue in the absence of neoplastic involvement of the overlying ureteric mucosa, lamina propria, and muscularis propria. This diagnostic determination requires that the surgical pathology specimen be processed and examined according to a rigorous protocol that ensures comprehensive sampling of the entire ureteric segment, with particular attention directed toward the region of the ureter corresponding anatomically to the peri-ureteral tumor deposit identified on preoperative imaging or intraoperative inspection. The current iteration of the World Health Organization classification of urinary and male genital tumors, as articulated by Comp  rat and colleagues in their 2022 summary of the fifth edition modifications, provides detailed histomorphologic criteria for the diagnosis of conventional urothelial carcinoma and its numerous histologic variants but offers no explicit guidance for the classification of tumors exhibiting this peculiar topographic distribution. The diagnostic report in such cases must therefore provide a comprehensive and transparent description of the pathologic findings, including detailed documentation of the absence of tumor within each of the ureteric mural layers, the precise anatomical location and dimensions of the peri-ureteral tumor deposit, the histologic grade according to the 2022 World Health Organization grading system, the presence or absence of lymphovascular invasion, and the status of the ureteric and peri-ureteric surgical margins. The assignment of a pT category under these circumstances is inherently problematic, as the tumor does not conform to any of the discrete pT designations codified within the American Joint Committee on Cancer staging manual. Some authorities have advocated for the assignment of pT3 designation based upon the anatomical location of the tumor deposits within the peri-ureteral adipose tissue, accompanied by a descriptive comment explaining the absence of demonstrable intramural invasion; others have proposed that such tumors be designated as pTis or pTa with peri-ureteral extension, although this approach conflates fundamentally distinct biological phenomena and risks underestimating the metastatic potential of these lesions.^{38,39}

The immunohistochemical armamentarium available to the pathologist confronting a peri-ureteral tumor of uncertain histogenesis is both extensive and diagnostically powerful when deployed judiciously and interpreted within the

appropriate clinical and morphologic context. The demonstration of diffuse, strong nuclear immunoreactivity for GATA3, a zinc-finger transcription factor involved in the differentiation of urothelial and breast epithelial tissues, represents the single most valuable immunohistochemical marker for the confirmation of urothelial lineage in a poorly differentiated or anatomically ambiguous neoplasm. GATA3 expression is retained in the vast majority of urothelial carcinomas regardless of tumor grade or histologic variant, with reported sensitivity estimates exceeding ninety percent in most published series, and its specificity for urothelial carcinoma is high when considered in the appropriate anatomic context. Complementary markers including p63, a member of the p53 family of transcription factors that is consistently expressed in the basal and intermediate layers of normal urothelium and in the majority of urothelial carcinomas, and high-molecular-weight cytokeratins including cytokeratin 5 and cytokeratin 5/6, which are preferentially expressed in basal-type urothelial carcinomas and in the nested variant, provide additional confirmatory evidence of urothelial differentiation. Cytokeratin 7 is nearly uniformly expressed in urothelial carcinoma, although its utility as a lineage-specific marker is limited by its expression in a broad range of epithelial malignancies including carcinomas of the lung, breast, ovary, and pancreas. Cytokeratin 20 demonstrates a more restricted expression pattern, with approximately one-third to one-half of urothelial carcinomas exhibiting positive immunoreactivity, and the combined assessment of cytokeratin 7 and cytokeratin 20 expression patterns may provide valuable discriminatory information in the distinction of urothelial carcinoma from colorectal adenocarcinoma, which typically exhibits a cytokeratin 7-negative, cytokeratin 20-positive immunophenotype.³⁹

The landmark transcriptomic profiling study conducted by Fontugne and colleagues, published in *Modern Pathology* in late 2023, has fundamentally advanced our understanding of the molecular heterogeneity of upper tract urothelial carcinoma and has provided critical insights into the immunohistochemical correlates of distinct molecular subtypes that may prove invaluable in the diagnostic evaluation of histologically ambiguous cases. These investigators performed comprehensive immunohistochemical characterization of a cohort of sixty-six patients with surgically treated muscle-invasive or at least pT1 upper tract urothelial carcinoma, employing a multiplex immunohistochemistry panel encompassing GATA3, cytokeratin 5, and TUBB2B, complemented by additional immunostains for cytokeratin 20, p16, Ki67, mismatch repair system proteins, and programmed death-ligand 1. Through this rigorous immunohistochemical approach and correlation with three-prime RNA sequencing data, Fontugne and colleagues demonstrated that the consensus molecular

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classification originally developed for muscle-invasive bladder cancer robustly stratifies upper tract tumors into discrete subtypes with distinct biological characteristics and clinical implications. All pT1 tumors examined in their series were classified as luminal papillary subtype, characterized immunohistochemically by GATA3 positivity, cytokeratin 20 expression, and relative absence of basal marker expression. Among tumors with pT2 or higher stage, luminal papillary tumors remained the predominant molecular subtype, constituting 57.2 percent of cases, a proportion significantly higher than that observed in muscle-invasive bladder cancer cohorts. The luminal papillary subtype was significantly associated with fibroblast growth factor receptor 3 mutations, which were identified in forty percent of the overall cohort, and was characterized by low immune cell infiltration and low programmed death-ligand 1 expression, findings with potential therapeutic implications for patients with advanced disease.³⁹

The independent investigation by Sikic and colleagues, published in PLOS ONE in 2017 and representing one of the largest immunohistochemical profiling studies of upper tract urothelial carcinoma conducted to date, provides complementary and directly actionable guidance for the diagnostic pathologist. These investigators examined the expression of seven basal and luminal immunohistochemical markers, including cytokeratin 5, epidermal growth factor receptor, CD44, cytokeratin 20, p63, GATA3, and FOXA1, in tumor samples from 222 patients with upper tract urothelial carcinoma treated with radical nephroureterectomy. Through hierarchical clustering analysis, Sikic and colleagues identified a basal-like subtype characterized by enrichment of cytokeratin 5, epidermal growth factor receptor, and CD44 expression in 23.9 percent of cases, and a luminal-like subtype characterized by enrichment of cytokeratin 20, GATA3, p63, and FOXA1 expression in 13.1 percent of cases. The majority of tumors, constituting 60.8 percent of the cohort, expressed little to no immunohistochemical markers of either subtype, and a small fraction of 2.2 percent demonstrated co-expression of markers from both subtypes. Recognizing the practical constraints of clinical pathology practice, wherein the routine application of multi-marker immunohistochemical panels may be neither feasible nor cost-effective, Sikic and colleagues developed a simplified classification algorithm employing only cytokeratin 5 and cytokeratin 20 as surrogate markers for basal and luminal subtypes respectively. Using receiver-operator characteristic analysis to establish optimal cut-off values, with immunoreactive scores greater than one for cytokeratin 5 and greater than six for cytokeratin 20 defined as positive, they stratified upper tract tumors into four discrete categories. The cytokeratin 20-positive, cytokeratin 5-negative immunophenotype, which corresponds to the luminal papillary molecular subtype, was identified as an independent

negative prognostic marker conferring a 3.83-fold increased risk of cancer-specific death compared to the other three immunophenotypic categories.⁴⁰

The diagnostic relevance of these molecular and immunohistochemical subclassification schemes to the specific entity of peri-ureteral urothelial carcinoma without mucosal invasion lies in their capacity to provide lineage-specific diagnostic confirmation in cases where the histomorphologic features are ambiguous, the anatomic distribution is aberrant, and the differential diagnosis encompasses a broad array of benign and malignant mimics. The nested variant of urothelial carcinoma, which as previously discussed may be overrepresented among tumors exhibiting peri-ureteral adventitial growth with mucosal sparing, is notoriously difficult to distinguish from benign proliferative conditions including florid von Brunn's nest hyperplasia, cystitis cystica and cystitis glandularis, and inverted papilloma on the basis of histomorphology alone. The immunohistochemical profile of nested variant urothelial carcinoma, which typically demonstrates diffuse cytokeratin 7 positivity, variable cytokeratin 20 expression, retained GATA3 and p63 nuclear immunoreactivity, and a low Ki-67 proliferative index that may paradoxically suggest benignity, must be meticulously correlated with the architectural features of the lesion, the topographic relationship of the neoplastic nests to the muscularis propria and adventitial compartments, and the presence or absence of frankly invasive foci with associated desmoplastic stromal reaction. The 1984 autoradiographic investigation by Blume and colleagues, although now four decades old and focused exclusively upon von Brunn's nests within the urinary bladder rather than the ureter, established the fundamental principle that benign von Brunn's nests exhibit the same proliferative behavior as the overlying normal urothelium and do not represent precancerous precursor lesions. The StatPearls review of cystitis cystica by Abdel Magied and colleagues, most recently updated in 2024, reiterates that cystitis cystica and cystitis glandularis represent reactive inflammatory changes rather than neoplastic proliferations, although they acknowledge that the intestinal type of cystitis glandularis may uncommonly progress to vesical adenocarcinoma. The distinction between benign reactive epithelial inclusions and nested variant urothelial carcinoma, however subtle and challenging, carries profound therapeutic implications and must be adjudicated with the full complement of clinical, radiographic, immunohistochemical, and molecular data available to the diagnostic pathologist.⁴⁰ The diagnostic challenge is further compounded by the well-documented phenomenon of biopsy under-grading and under-staging in upper tract urothelial carcinoma, a limitation that is magnified exponentially when the neoplasm is situated predominantly within the peri-ureteral adventitia and is therefore inherently inaccessible to conventional

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ureteroscopic biopsy techniques. Katayama and colleagues, in their 2023 multicenter investigation encompassing 371 patients who underwent ureteroscopic biopsy followed by radical nephroureterectomy across thirteen institutions, demonstrated that biopsy grade is not merely a technical artifact but rather a biologically and prognostically significant variable. Patients whose ureteroscopic biopsies demonstrated high-grade urothelial carcinoma were significantly more likely to harbor unfavorable pathologic features in the subsequent nephroureterectomy specimen, including lymphovascular invasion and lymph node metastases, and exhibited significantly worse overall survival, cancer-specific survival, and recurrence-free survival on multivariable analysis adjusting for established prognostic factors. Furthermore, high-grade biopsy in patients with clinically non-muscle-invasive disease significantly predicted upstaging to pathologically advanced disease at final resection compared to patients with low-grade biopsy. These findings suggest that tumor-specific biological factors, including intrinsic genomic instability and aggressive growth potential, contribute to both the histologic grade appreciable at biopsy and the final pathologic stage determined at nephroureterectomy. In the specific context of peri-ureteral urothelial carcinoma without mucosal invasion, wherein the endoscopic visualization of the ureteric mucosa is normal and the selective cytology is negative, the performance of conventional ureteroscopic biopsy targeting the visibly unremarkable urothelium would be expected to yield benign or nondiagnostic tissue and would provide no insight into the underlying peri-ureteral neoplasm. The decision to proceed directly to image-guided percutaneous biopsy of the peri-ureteral soft tissue abnormality, bypassing ureteroscopy entirely, requires that the clinician maintain a high index of suspicion for this entity and recognize that the conventional diagnostic algorithm is fundamentally ill-suited to its detection.⁴¹

The integration of emerging epigenetic biomarkers into the diagnostic algorithm for suspected upper tract urothelial carcinoma offers a non-invasive adjunctive strategy that may prove particularly valuable in scenarios where conventional diagnostic modalities are nondiagnostic or contradictory, as is uniformly the case in peri-ureteral urothelial carcinoma without mucosal invasion. Ricciardi and colleagues, in their comprehensive 2025 review, have provided a detailed analysis of the performance characteristics of DNA methylation-based urinary assays for the detection of upper tract urothelial carcinoma, with particular emphasis upon the Bladder EpiCheck platform. This assay, which interrogates a predefined panel of fifteen methylation-sensitive genomic loci and generates a quantitative methylation score ranging from zero to one hundred, has demonstrated extraordinary diagnostic accuracy in published validation studies, with reported sensitivity estimates reaching 97.4 percent and

specificity estimates approaching 100 percent for the detection of high-grade upper tract tumors. The biological rationale for the application of such assays to the diagnosis of peri-ureteral urothelial carcinoma without mucosal invasion is that neoplastic cells, even when sequestered entirely within the adventitial compartment and separated from the urinary stream by an intact non-neoplastic urothelium, may nonetheless release tumor-derived DNA into the urine through mechanisms including transurothelial migration of intact cells, passive diffusion of cell-free nucleic acids across the ureteric wall, or exosomal transport of epigenetic material. The sensitivity of DNA methylation-based urinary assays for tumors confined to the peri-ureteral soft tissues without mucosal involvement has not been systematically evaluated and represents a critical knowledge gap requiring urgent investigation. Nonetheless, the non-invasive nature, excellent patient tolerability, and superior diagnostic performance characteristics of these epigenetic biomarkers render them an attractive adjunctive diagnostic strategy in cases of unexplained peri-ureteral thickening or peri-ureteral mass lesions, particularly when the performance of percutaneous needle biopsy is contraindicated or technically infeasible.⁴¹ The ultimate diagnostic resolution of peri-ureteral urothelial carcinoma without mucosal invasion, in the vast majority of reported cases including the index case documented by Gholami and colleagues, is achieved not through preoperative biopsy but through definitive surgical extirpation with radical nephroureterectomy performed for suspected but unconfirmed upper tract malignancy or for presumptive benign conditions such as refractory ureteropelvic junction obstruction or non-functioning hydronephrotic kidney. The nephroureterectomy specimen, which encompasses the entire kidney, the full length of the ureter, and a cuff of peri-ureteral adventitial tissue, must be processed according to a rigorous pathologic protocol that ensures comprehensive sampling of the ureter at closely spaced intervals, with particular attention directed toward the segment of the ureter corresponding to the peri-ureteral abnormality identified on preoperative imaging. The pathologist must meticulously document the presence or absence of tumor within each of the ureteric mural layers at each sampled level, the precise anatomical relationship of any peri-ureteral tumor deposits to the ureteric adventitia and muscularis propria, the histologic grade and variant histology of any identifiable neoplastic component, the presence or absence of lymphovascular invasion, and the status of the ureteric and peri-ureteric soft tissue margins. The diagnostic report must acknowledge, explicitly and transparently, the fundamental incongruity between the anatomical stage of the tumor as determined by the presence of peri-ureteral adipose tissue involvement and the pathological stage as defined by the American Joint Committee on Cancer criteria, which presume transmural invasion as a prerequisite for extra-ureteral extension. The

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reporting pathologist may elect to designate such tumors as pT3 with a descriptive comment explaining the absence of demonstrable intramural invasion, or may assign a pT category based upon the deepest level of unequivocal mural invasion identified, which in these cases is by definition pT0 or pTis, with a separate notation indicating the presence of peri-ureteral tumor deposits of uncertain biological significance. Neither approach is entirely satisfactory, and both risk miscommunicating essential prognostic information to the treating urologist and medical oncologist. The resolution of this nosological dilemma requires formal acknowledgment of this entity within future iterations of the tumor-nodes-metastasis staging classification, accompanied by explicit guidance regarding the appropriate categorization of such tumors for purposes of cancer registration, prognostic stratification, and therapeutic decision-making.⁴¹

The diagnostic approach to peri-ureteral urothelial carcinoma without mucosal invasion thus demands a fundamental reconceptualization of the conventional diagnostic algorithm for suspected upper tract malignancy, one that acknowledges the inherent limitations of ureteroscopic visualization and selective urinary cytology in the detection of neoplasms confined to the adventitial compartment, recognizes the distinctive but non-specific imaging characteristics of such lesions on computed tomography urography, maintains a high index of suspicion for this entity in patients presenting with unexplained peri-ureteral soft tissue abnormalities even in the face of negative endoscopic evaluation, and embraces the judicious application of image-guided percutaneous biopsy and emerging epigenetic urinary biomarkers as complementary diagnostic strategies. The diagnostic odyssey is fraught with potential for delay, misdiagnosis, and inappropriate therapeutic intervention; the interval between initial imaging abnormality and definitive histopathologic diagnosis in published case reports has ranged from several months to several years, during which time patients may undergo repeated endoscopic procedures, empiric anti-inflammatory therapy for presumptive retroperitoneal fibrosis, or prolonged radiographic surveillance for presumed benign peri-ureteral inflammatory conditions. The imperative for diagnostic vigilance is underscored by the aggressive biological behavior of these tumors, which despite their peculiar growth pattern and absence of conventional intramural invasion, have demonstrated capacity for lymph node metastasis, distant dissemination, and cancer-specific mortality comparable to that of conventional pT3 upper tract urothelial carcinoma with overt transmural invasion. The path forward requires not merely incremental improvements in existing diagnostic technologies, but a paradigmatic shift in the conceptual framework through which we approach the diagnosis of upper tract malignancy, one that decouples the detection of urothelial neoplasia from the visualization of mucosal abnormality and embraces the possibility that

urothelial carcinoma may arise, progress, and disseminate through pathways that operate entirely independently of the conventional sequence of stepwise parietal invasion.^{40,41}

TREATMENT

The therapeutic approach to peri-ureteral urothelial carcinoma without mucosal invasion presents an extraordinary conundrum that defies facile extrapolation from the established management algorithms for conventional upper tract urothelial carcinoma and demands a nuanced, multidimensional consideration of the unique biological characteristics, anatomical distribution, and prognostic implications inherent to this peculiar pathological entity. The absence of explicit recognition within contemporary staging nosology, the extreme rarity of the condition which precludes the conduct of prospective clinical trials targeting this specific population, and the fundamental incongruity between the anatomical stage of the tumor as determined by the presence of peri-ureteral adipose tissue involvement and the pathological stage as defined by the American Joint Committee on Cancer criteria collectively conspire to render therapeutic decision-making an exercise in extrapolation, inference, and multidisciplinary consensus rather than the application of evidence-based guidelines derived from high-quality randomized controlled trials. The treatment landscape for this entity is thus necessarily constructed from three principal evidentiary pillars: the extrapolation of outcomes from patients with conventional pT3b upper tract urothelial carcinoma exhibiting overt transmural invasion, the cautious application of emerging data regarding perioperative systemic therapy in UTUC populations with variant histology or adverse genomic features, and the meticulous individualization of therapeutic intensity based upon a comprehensive assessment of each patient's unique clinicopathologic profile, competing comorbidities, renal functional reserve, and personal preferences following exhaustive shared decision-making discourse.⁴²

The foundational therapeutic intervention for peri-ureteral urothelial carcinoma without mucosal invasion, as for all non-metastatic upper tract urothelial malignancies irrespective of stage or histologic variant, remains radical nephroureterectomy with excision of an ipsilateral bladder cuff. This procedure, which accomplishes en bloc extirpation of the renal unit, the entire length of the ureter, and a circumferential cuff of peri-ureteral adventitial tissue together with the intramural ureter and surrounding vesical musculature, represents the only therapeutic modality capable of achieving complete oncologic resection with negative surgical margins in patients presenting with this peculiar anatomical distribution of disease. The imperative for complete surgical extirpation is magnified in the context of peri-ureteral urothelial carcinoma without mucosal invasion,

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wherein the neoplasm is situated predominantly or exclusively within the adventitial compartment and is therefore inherently inaccessible to endoscopic ablation techniques, impervious to intraluminal instillation therapies, and biologically predisposed toward locoregional dissemination through peri-ureteral lymphatic channels and venous plexuses. The performance of radical nephroureterectomy in this clinical scenario accomplishes not only the therapeutic objective of complete tumor extirpation but also the diagnostic objective of comprehensive histopathological characterization, permitting definitive confirmation of the diagnosis, accurate assessment of the precise anatomical distribution and extent of peri-ureteral tumor deposits, identification of variant histology elements including nested, micropapillary, or sarcomatoid components, evaluation of lymphovascular invasion status, and determination of surgical margin adequacy.⁴²

The conduct of radical nephroureterectomy for suspected or confirmed peri-ureteral urothelial carcinoma without mucosal invasion must be approached with meticulous attention to surgical technique and oncologic principles that extend beyond those conventionally applied to the management of intraluminal upper tract tumors. The ureter, which in this entity is typically encased or compressed by an eccentric or concentric adventitial tumoral mass but exhibits an intact and grossly unremarkable mucosal surface, must be dissected with wide circumferential clearance of peri-ureteral soft tissues to ensure complete resection of the neoplastic adventitial deposits and minimize the risk of positive soft tissue margins. The performance of ipsilateral regional lymphadenectomy, although its therapeutic benefit in upper tract urothelial carcinoma remains a subject of ongoing investigation and debate, assumes particular importance in the management of peri-ureteral tumors given the high propensity of these lesions for occult lymphatic dissemination and the critical prognostic and therapeutic implications of accurate nodal staging. The template of lymph node dissection should be tailored to the anatomical location of the primary tumor, with hilar and retroperitoneal nodal packets addressed for renal pelvic and proximal ureteral lesions, and ipsilateral pelvic lymphadenectomy performed for distal ureteral tumors. The bladder cuff excision must be executed with uncompromising completeness to eliminate the possibility of residual intramural ureteral disease or peri-ureteral tumor extending to the ureterovesical junction, a consideration of particular relevance given the tendency of peri-ureteral urothelial carcinoma to track along the adventitial sheath to the level of the bladder insertion.⁴²

The postoperative management of patients with resected peri-ureteral urothelial carcinoma without mucosal invasion is fundamentally contingent upon the accurate histopathological characterization of the surgical specimen and the assignment of an appropriate pathological stage, a determination that is, as previously discussed, fraught with nosological ambiguity and

interpretative subjectivity. The weight of available evidence, derived predominantly from the seminal multicenter investigation conducted by Kim and colleagues and published in the International Journal of Radiation Oncology, Biology, Physics, suggests that patients with pT3b upper tract urothelial carcinoma, defined by the presence of tumor infiltration into the peripelvic or peri-ureteral adipose tissue, derive substantial and statistically significant oncologic benefit from the administration of adjuvant radiation therapy directed to the renal fossa, ureteral bed, and regional lymphatic basins. In this landmark study, which analyzed the multicenter data of 222 patients with pT3bN0-x disease treated with radical nephroureterectomy across five tertiary referral centers, the administration of adjuvant radiation therapy to 39 patients representing 17.6 percent of the analytic cohort was associated, after rigorous adjustment for potential confounding variables through propensity score matching methodology, with dramatic improvements in all three principal oncologic endpoints. The five-year local recurrence-free survival was 83.9 percent among patients receiving adjuvant radiation therapy compared to merely 54.2 percent among those undergoing surgery alone, representing an absolute improvement of 29.7 percent and a relative risk reduction of extraordinary magnitude. The five-year distant metastasis-free survival was similarly enhanced, with estimates of 72.1 percent versus 48.1 percent favoring the adjuvant radiation therapy cohort, and the five-year cancer-specific survival demonstrated commensurate improvement at 76.4 percent compared to 55.5 percent. These survival advantages achieved statistical significance at stringent thresholds, with P-values of 0.001, 0.032, and 0.038 respectively, and persisted across multiple sensitivity analyses examining the robustness of the findings to alternative analytic assumptions and model specifications.^{41,42}

The implications of these observations for the management of peri-ureteral urothelial carcinoma without mucosal invasion are profound and directly actionable. Although the Kim investigation did not specifically stratify the pT3b cohort according to the presence or absence of concomitant mucosal invasion, and although the study population undoubtedly consisted predominantly of patients with conventional transmural disease, there exists no plausible biological rationale to suggest that the therapeutic efficacy of adjuvant radiation therapy would be attenuated in the subset of patients whose peri-ureteral tumor deposits occur in the absence of demonstrable intramural invasion. The mechanism of action of therapeutic ionizing radiation, which exerts its cytotoxic and cytostatic effects through the induction of deoxyribonucleic acid damage, particularly double-strand breaks, and the activation of apoptotic cascades in rapidly proliferating neoplastic cells, is independent of the precise histogenetic pathway by which those cells arrived in the peri-ureteral adventitial compartment. The locoregional recurrence risk

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following radical nephroureterectomy for peri-ureteral tumors, which is attributable to microscopic residual disease in the tumor bed, occult deposits in peri-ureteral lymphatic channels, and viable tumor cells seeded along surgical dissection planes, would be anticipated to be at least as high in the setting of non-mucosa-invasive disease as in conventional pT3b tumors, and the capacity of adjuvant radiation therapy to eradicate such microscopic residual disease and thereby reduce the hazard of both local failure and subsequent distant dissemination should be preserved irrespective of the presence or absence of an intramural tumor component. The weight of current evidence therefore supports the strong consideration of adjuvant radiation therapy in medically fit patients with completely resected peri-ureteral urothelial carcinoma without mucosal invasion, particularly in the presence of additional adverse pathologic features including high tumor grade, lymphovascular invasion, positive or uncertain surgical margins, and extensive or multifocal peri-ureteral tumor deposits.⁴²

The appropriate radiation treatment volume, fractionation schedule, and total dose for adjuvant therapy in this clinical context have not been definitively established through prospective randomized trials and must be individualized based upon the specific anatomical distribution of the primary tumor, the extent and location of peri-ureteral tumor deposits as documented in the surgical pathology report, the status of the surgical margins, and the results of any lymph node dissection performed at the time of nephroureterectomy. The Kim investigation and the institutional protocols reflected therein employed conventionally fractionated external beam radiation therapy administered to a median total dose of 50.4 Gray in 1.8 Gray daily fractions, with treatment volumes encompassing the ipsilateral renal fossa, the entire anatomic course of the resected ureter, and the regional lymph node basins at risk for occult metastatic involvement including the para-aortic, paracaval, and ipsilateral common iliac nodal stations depending upon the primary tumor location. Contemporary radiation oncology practice has witnessed the emergence of intensity-modulated radiation therapy and volumetric modulated arc therapy as preferred delivery techniques that afford superior target volume conformality, enhanced dose homogeneity, and more favorable normal tissue sparing compared to conventional three-dimensional conformal approaches, thereby reducing the risk of treatment-related toxicities including radiation enteritis, nephritis in the contralateral renal unit, and myelosuppression. The integration of modern image-guided radiation therapy strategies, including daily cone-beam computed tomography and orthogonal kilovoltage imaging, ensures precise and reproducible patient positioning and target localization throughout the treatment course, further optimizing the therapeutic ratio of adjuvant radiation therapy in this high-risk population.⁴²

The role of adjuvant systemic chemotherapy in the management of peri-ureteral urothelial carcinoma without mucosal invasion is considerably more controversial and less clearly defined than that of adjuvant radiation therapy, with the available evidentiary base yielding apparently contradictory conclusions depending upon the specific population under investigation, the particular chemotherapeutic regimens employed, and the methodological approaches applied to confounding control. The Kim multicenter investigation, which provides the most directly relevant evidence for the pT3b subpopulation of interest, failed to demonstrate any detectable oncologic benefit associated with the administration of adjuvant chemotherapy in patients with peripelvic or peri-ureteral fat-infiltrating disease. Among the 74 patients comprising 33.3 percent of the analytic cohort who received adjuvant platinum-based chemotherapy following radical nephroureterectomy, the five-year local recurrence-free survival, distant metastasis-free survival, and cancer-specific survival were statistically indistinguishable from those observed in patients undergoing surgery alone, with P-values of 0.786, 0.436, and 0.458 respectively. The absence of any discernible signal of efficacy persisted across multiple analytic approaches including propensity score-matched comparisons and multivariable regression modeling with comprehensive adjustment for potential confounding variables, and the survival estimates in the adjuvant chemotherapy and surgery-alone groups were virtually superimposable at 67.9 percent for both cohorts at five years.⁴²

These null findings stand in apparent contradistinction to the broader body of evidence supporting the efficacy of adjuvant platinum-based chemotherapy in appropriately selected patients with high-risk upper tract urothelial carcinoma following radical nephroureterectomy. The comprehensive systematic review and network meta-analysis conducted by Liu and colleagues, encompassing 43 studies with 13,132 patients and published in *Urologic Oncology: Seminars and Original Investigations* in 2025, demonstrated that adjuvant chemotherapy significantly improved overall survival with a pooled hazard ratio of 0.74, cancer-specific survival with a pooled hazard ratio of 0.74, and disease-free survival with a pooled hazard ratio of 0.61. The POUT trial, a landmark phase III randomized controlled investigation that has fundamentally shaped contemporary practice patterns and guideline recommendations, definitively established the efficacy of adjuvant platinum-based chemotherapy in patients with locally advanced, node-positive, or margin-positive upper tract urothelial carcinoma following nephroureterectomy, demonstrating significant improvements in disease-free survival and emerging evidence of overall survival benefit with extended follow-up. The apparent discordance between these positive meta-analytic and trial findings and the null results reported by Kim and colleagues specifically within the

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pT3b subpopulation merits careful consideration and may reflect several non-mutually-exclusive explanatory hypotheses. It is plausible that peri-ureteral fat-infiltrating tumors, whether arising through conventional transmural invasion or through the unconventional pathway of adventitial origin without mucosal involvement, represent a biologically distinct subset of UTUC characterized by relative chemoresistance, unique genomic alterations including enrichment of chromatin regulatory gene mutations, or distinct patterns of clonal evolution that attenuate the efficacy of conventional platinum-based regimens. Alternatively, the null findings may reflect the relatively modest sample size of the pT3b subpopulation, the retrospective non-randomized study design with attendant susceptibility to unmeasured confounding and selection bias, or the heterogeneous chemotherapeutic regimens and variable cisplatin eligibility criteria applied across the contributing institutions and over the extended study accrual period.^{42,43}

The management of peri-ureteral urothelial carcinoma without mucosal invasion is further complicated by the imperative to distinguish this entity from its most formidable histopathologic mimic: the mechanical implantation of benign or low-grade malignant urothelial tissue into the peri-ureteral soft tissues occurring as a consequence of antecedent ureteroscopic instrumentation with biopsy or stent placement. The seminal case series reported by Wobker and colleagues and published in the American Journal of Surgical Pathology documented four patients in whom small nests of cytologically bland urothelium were identified within the peri-ureteral or peripelvic adipose tissue of nephroureterectomy specimens following preoperative ureteroscopic biopsy, creating a histologic picture that superficially simulated pT3 disease and could easily be misconstrued as invasive urothelial carcinoma extending beyond the ureteric wall. The distinction between true peri-ureteral urothelial carcinoma, which carries an adverse prognosis and may warrant consideration of adjuvant radiation therapy or systemic chemotherapy, and iatrogenic mechanical implantation, which represents a benign histologic artifact devoid of metastatic potential and requiring no adjuvant therapy whatsoever, rests upon a constellation of histomorphologic features including the presence of associated linear fibrosis, hemosiderin deposition, foreign body giant cell reaction, and hemosiderin-laden macrophages in the peri-ureteral soft tissues, the absolute cytologic blandness of the implanted urothelial nests which lack the nuclear atypia, mitotic activity, and architectural disarray characteristic of true malignancy, and the concordance between the low-grade or benign histology of the antecedent endoscopic biopsy and the cytologically bland appearance of the peri-ureteral deposits. The misdiagnosis of mechanical implantation as bona fide peri-ureteral invasive carcinoma exposes the patient to the substantial morbidity, potential mortality, and considerable financial cost of unwarranted

adjuvant therapy, while the converse error of dismissing true peri-ureteral urothelial carcinoma as benign implantation artifact denies the patient access to potentially life-prolonging postoperative treatment. The resolution of this diagnostic dilemma demands meticulous histopathologic examination of the nephroureterectomy specimen by an experienced genitourinary pathologist, comprehensive correlation with the findings of the antecedent ureteroscopic biopsy, and multidisciplinary discussion among the treating urologist, radiologist, and pathologist to ensure accurate classification and appropriate therapeutic decision-making.⁴³

The emergence of adjuvant immune checkpoint inhibition as a therapeutic strategy in urothelial carcinoma has introduced both new opportunities and new uncertainties into the management landscape for patients with high-risk upper tract tumors following radical nephroureterectomy. The CheckMate 274 trial, a phase III randomized controlled investigation of adjuvant nivolumab versus placebo in patients with high-risk muscle-invasive urothelial carcinoma following radical surgical resection, included a prespecified subgroup of patients with upper tract primary tumors and demonstrated significant improvements in disease-free survival with adjuvant immunotherapy that were consistent with the benefits observed in the overall trial population. The AMBASSADOR trial, evaluating adjuvant pembrolizumab in an analogous patient population, has similarly reported positive findings that support the efficacy of adjuvant programmed cell death protein 1 blockade in reducing recurrence risk following definitive surgical management of high-risk urothelial carcinoma. However, the extrapolation of these trial findings to the specific subpopulation of patients with peri-ureteral urothelial carcinoma without mucosal invasion is rendered problematic by several considerations. The systematic review and meta-analysis conducted by Liu and colleagues, which included pooled analysis of three randomized controlled trials comprising 384 patients with upper tract urothelial carcinoma, failed to demonstrate a statistically significant improvement in either disease-free survival with a hazard ratio of 1.19 and confidence intervals crossing unity, or overall survival with a hazard ratio of 1.28, for adjuvant immunotherapy compared to observation or placebo. These null findings raise the possibility that upper tract urothelial carcinoma may exhibit differential responsiveness to immune checkpoint inhibition compared to urothelial bladder carcinoma, potentially reflecting distinct tumor mutational burden, programmed death-ligand 1 expression patterns, or composition of the tumor immune microenvironment. The network meta-analysis conducted by Liu and colleagues further suggested that combining adjuvant chemotherapy with adjuvant immunotherapy might offer superior disease-free survival compared to adjuvant chemotherapy alone, and that adjuvant chemotherapy alone outperformed adjuvant immunotherapy alone in ranking analyses, although these findings are derived

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from indirect comparisons and should be considered hypothesis-generating rather than practice-defining.⁴²

The optimal timing of perioperative systemic chemotherapy relative to radical nephroureterectomy represents another domain of active investigation and evolving practice standards with direct relevance to the management of patients with suspected or confirmed peri-ureteral urothelial carcinoma without mucosal invasion. The systematic review and meta-analysis conducted by Naushad and colleagues and published in *Urologia* in late 2025 provides the most contemporary and comprehensive comparative analysis of neoadjuvant versus adjuvant chemotherapy in upper tract urothelial carcinoma, synthesizing data from five studies comprising 1,938 patients. This investigation demonstrated that neoadjuvant chemotherapy, administered prior to radical nephroureterectomy, achieved significantly higher rates of pathological downstaging at final surgical pathology with an odds ratio of 2.13 and a lower risk of positive surgical margins with an odds ratio of 0.59 compared to adjuvant chemotherapy administered postoperatively. The rates of lymph node metastasis and overall survival were comparable between the neoadjuvant and adjuvant approaches, indicating that the therapeutic efficacy of perioperative platinum-based chemotherapy is preserved irrespective of sequencing when patients are able to receive and complete their planned treatment course. Critically, Naushad and colleagues emphasized the well-documented risk of clinically significant renal function decline following radical nephroureterectomy, which renders a substantial proportion of patients ineligible to receive cisplatin-based chemotherapy in the adjuvant setting due to inadequate glomerular filtration rate. The neoadjuvant administration of chemotherapy prior to surgical extirpation circumvents this impediment by delivering treatment while the ipsilateral renal unit remains in situ and the contralateral kidney has not yet been subjected to compensatory hyperfiltration injury, thereby maximizing the proportion of patients who can receive and potentially benefit from guideline-recommended perioperative systemic therapy. These findings support the consideration of neoadjuvant platinum-based chemotherapy in patients presenting with peri-ureteral soft tissue abnormalities on preoperative cross-sectional imaging that are suspected to represent urothelial carcinoma, even in the absence of confirmatory tissue diagnosis, provided that the imaging characteristics are sufficiently compelling and the patient is deemed an appropriate candidate for systemic therapy following comprehensive multidisciplinary evaluation.^{42,43}

The management of peri-ureteral urothelial carcinoma without mucosal invasion is further nuanced by the substantial biological and therapeutic heterogeneity introduced by the presence of variant histology elements, which are overrepresented in upper tract primary tumors compared to urothelial bladder carcinoma and may exert profound effects

on both the natural history of disease and the responsiveness to conventional systemic therapies. The investigation conducted by Park and colleagues and published in *Clinical Genitourinary Cancer* in 2024 provides the most detailed analysis to date of adjuvant chemotherapy efficacy specifically in patients with variant histology upper tract urothelial carcinoma following radical nephroureterectomy. Among 131 patients with non-metastatic variant histology UTUC identified from a single tertiary referral center experience, the administration of adjuvant platinum-based chemotherapy was associated with a significant prolongation of time to recurrence following rigorous adjustment for confounding variables through stabilized inverse probability of treatment weighting methodology. The beneficial effect of adjuvant chemotherapy on recurrence risk was not, however, uniform across all variant histology subtypes; significant improvements in time to recurrence were observed in patients with squamous differentiation, glandular differentiation, and micropapillary components, whereas patients with sarcomatoid variant histology derived no detectable benefit from adjuvant systemic therapy and continued to experience high rates of disease progression and cancer-specific mortality irrespective of postoperative treatment allocation. These observations carry direct and immediate implications for the management of peri-ureteral urothelial carcinoma without mucosal invasion, as the nested variant of urothelial carcinoma, which is disproportionately represented among tumors exhibiting adventitial growth with mucosal sparing, was not specifically analyzed in the Park investigation and its chemosensitivity profile remains poorly characterized. The identification of any variant histology component in the peri-ureteral tumor deposits or in the antecedent endoscopic biopsy specimen, when available, should prompt multidisciplinary discussion regarding the potential utility of adjuvant chemotherapy, with careful consideration of the specific variant subtype identified and the existing evidence base, such as it is, regarding its therapeutic responsiveness.^{43,44,45}

The surveillance strategy following definitive surgical management and completion of any administered adjuvant therapy must be tailored to the substantial residual risk of disease recurrence that characterizes peri-ureteral urothelial carcinoma without mucosal invasion, a risk that approximates that of conventional pT3b UTUC and substantially exceeds that of organ-confined disease. The pattern of recurrence following radical nephroureterectomy for peri-ureteral tumors is predominantly locoregional, involving the ipsilateral renal fossa, the ureteral bed, and the regional retroperitoneal and pelvic lymph node basins, with a substantial minority of patients experiencing distant metastatic dissemination to the lungs, liver, bone, and non-regional nodal stations. The surveillance regimen should therefore incorporate regular cross-sectional imaging of the chest, abdomen, and pelvis with computed tomography or magnetic resonance imaging at

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intervals of three to six months for the first two to three years following surgery, with gradual extension of imaging intervals thereafter in patients who remain disease-free. Cystoscopic surveillance of the urinary bladder is mandatory at regular intervals given the substantial risk of metachronous urothelial bladder carcinoma development in patients with a history of upper tract disease, although the optimal frequency of cystoscopic examination in this specific subpopulation has not been established through prospective investigation. The emerging role of circulating tumor DNA as a sensitive and specific biomarker for molecular residual disease and early recurrence detection in urothelial carcinoma holds particular promise for patients with peri-ureteral tumors, in whom radiographic surveillance may be confounded by post-surgical inflammatory changes in the renal fossa and ureteral bed and in whom the early identification of treatment-responsive oligometastatic disease may expand therapeutic options and improve outcomes. The incorporation of serial circulating tumor DNA testing into routine surveillance protocols for high-risk UTUC patients, including those with peri-ureteral disease, is an area of active investigation and rapid clinical adoption, although formal practice guidelines have not yet been updated to reflect this evolving evidence base.^{45,46}

The management of metastatic disease arising from peri-ureteral urothelial carcinoma without mucosal invasion follows the same principles as the management of metastatic conventional urothelial carcinoma of the upper tract or urinary bladder, with platinum-based combination chemotherapy serving as the foundational first-line treatment for cisplatin-eligible patients and programmed death ligand-1 checkpoint inhibitors, enfortumab vedotin, and erdafitinib representing important therapeutic options in the platinum-refractory setting and in patients with specific genomic alterations including fibroblast growth factor receptor aberrations. The distinctive biological characteristics of upper tract urothelial carcinoma, including the higher prevalence of deleterious mutations in chromatin regulatory genes and DNA damage repair pathways and the distinct mutational signatures associated with aristolochic acid exposure and APOBEC-mediated mutagenesis, may influence the responsiveness of metastatic disease to specific systemic therapies and warrant consideration in treatment selection, although the evidentiary basis for biomarker-driven therapeutic decision-making specifically in the upper tract population remains less developed than in urothelial bladder carcinoma. The enrollment of patients with metastatic peri-ureteral urothelial carcinoma in clinical trials investigating novel therapeutic agents and combination strategies should be strongly encouraged to accelerate progress and expand treatment options for this underserved patient population.^{47,48}

The therapeutic landscape for peri-ureteral urothelial carcinoma without mucosal invasion is thus characterized by

profound evidentiary gaps, substantial nosological ambiguity, and the imperative for highly individualized treatment decision-making that integrates the best available extrapolated evidence with meticulous assessment of each patient's unique clinicopathologic profile, competing comorbidities, and personal preferences. The foundational intervention of radical nephroureterectomy with wide peri-ureteral soft tissue clearance and ipsilateral regional lymphadenectomy must be executed with uncompromising surgical precision to maximize the probability of complete resection and minimize the risk of locoregional failure. The strong consideration of adjuvant radiation therapy is supported by high-quality multicenter comparative effectiveness research demonstrating substantial and statistically significant improvements in local control, distant metastasis-free survival, and cancer-specific survival in the analogous pT3b population, and the absence of any plausible biological rationale to suggest attenuation of this benefit in patients whose peri-ureteral tumor deposits occur without concomitant mucosal invasion. The role of adjuvant systemic chemotherapy is more controversial and less clearly defined, with available evidence suggesting that the null findings observed specifically within the pT3b subpopulation must be weighed against the positive meta-analytic and randomized trial evidence supporting adjuvant platinum-based chemotherapy in high-risk UTUC more broadly, and that decisions regarding adjuvant chemotherapy administration must be individualized based upon the presence or absence of variant histology elements, nodal involvement, and other adverse prognostic features. The neoadjuvant administration of platinum-based chemotherapy prior to nephroureterectomy should be considered in patients presenting with convincing peri-ureteral soft tissue abnormalities on preoperative imaging, as this approach maximizes the likelihood of completing guideline-recommended perioperative systemic therapy by circumventing the post-nephrectomy renal function decline that frequently precludes cisplatin administration in the adjuvant setting. The rigorous histopathologic distinction between true peri-ureteral urothelial carcinoma and iatrogenic mechanical implantation of benign or low-grade malignant urothelium secondary to antecedent ureteroscopic instrumentation is of paramount importance, as these two entities carry diametrically opposed prognostic and therapeutic implications and their conflation exposes patients to substantial risk of either overtreatment with toxic and ineffective adjuvant therapy or undertreatment with denial of potentially life-prolonging postoperative intervention. The conduct of prospective clinical trials specifically designed to address the therapeutic questions that uniquely pertain to patients with peri-ureteral UTUC, including those with the non-mucosa-invasive variant, represents the single most important unmet need in the evidence base and must be

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prioritized by funding agencies, cooperative oncology groups, and the academic urologic oncology community. In the absence of such trials, the management of this elusive and biologically aggressive entity will remain an exercise in extrapolation, inference, and the art of medicine, dependent upon the wisdom and experience of multidisciplinary teams caring for these challenging patients and the rigorous application of evidence-based principles to the unique circumstances of each individual case.^{48,49,50}

CONCLUSION

The odyssey through the diagnostic, histopathological, and therapeutic landscapes of peri-ureteral urothelial carcinoma without mucosal invasion culminates not in the comfortable certitude of definitive practice guidelines or algorithmically derived management protocols, but rather in a sobering recognition of the profound epistemological and nosological challenges that this perplexing entity lays bare at the very foundations of contemporary uro-oncologic practice. This comprehensive review has endeavored to assemble the fragmentary and widely dispersed evidentiary threads pertaining to this extraordinary pathological phenomenon, to subject those threads to rigorous critical scrutiny, and to weave from them a coherent conceptual fabric that may serve both as a practical guide for the practicing clinician confronting such a case and as a provocative stimulus for the investigative community whose collective efforts will be required to resolve the many outstanding questions that remain. The entity that we have operationally designated as peri-ureteral urothelial carcinoma without mucosal invasion, far from representing a mere academic curiosity or an esoteric footnote in the voluminous literature on upper tract malignancies, emerges from this synthesis as a phenomenon of substantial biological significance, considerable clinical importance, and profound theoretical implications that extend well beyond the narrow confines of this specific diagnostic scenario to challenge foundational assumptions regarding the ontogeny, progression, and staging of urothelial neoplasia itself.

The cardinal insight that crystallizes from this comprehensive analysis is that the conventional conceptual framework through which we apprehend upper tract urothelial carcinoma, a framework predicated upon the assumption of contiguous radial tumor propagation from the mucosal surface through the lamina propria and muscularis propria to the adventitial soft tissues, is fundamentally inadequate to accommodate the full spectrum of biological behaviors exhibited by neoplasms arising from or involving the urothelium of the renal pelvis and ureter. The existence of peri-ureteral urothelial carcinoma without demonstrable involvement of the overlying ureteric mucosa, lamina propria, or muscularis propria represents an incontrovertible refutation of the universality of this sequential progression

model and compels a fundamental reconsideration of the pathways through which urothelial malignancies may arise, disseminate, and produce clinically significant morbidity and mortality. The prevailing hypothesis of malignant transformation within ectopic urothelial cell rests situated within the peri-ureteral adventitia, although supported by circumstantial evidence and conceptual analogy to well-characterized phenomena elsewhere in the genitourinary tract, remains unproven and may ultimately prove to be an oversimplification of a more complex and heterogeneous reality wherein multiple distinct pathogenetic mechanisms converge upon a common phenotypic endpoint. The nested variant of urothelial carcinoma, with its deceptively bland cytomorphology and its notorious propensity for extensive infiltration in the absence of conspicuous cytologic anaplasia, may be disproportionately represented among tumors exhibiting this peculiar growth pattern, and the distinctive biological characteristics of this variant including its relative chemoresistance and its association with specific genomic alterations may illuminate the mechanistic basis for the apparent independence from conventional stepwise parietal invasion. The emerging molecular taxonomy of upper tract urothelial carcinoma, with its delineation of distinct transcriptomic subtypes and its identification of recurrent genomic alterations including mutations in chromatin regulatory genes such as KMT2C, ARID1A, and EP300 that are enriched in UTUC compared to urothelial bladder carcinoma, offers a powerful explanatory framework for reconciling the phenotypic heterogeneity of these tumors with their underlying biological diversity and may ultimately enable the identification of patients at risk for unconventional patterns of disease dissemination through molecular biomarker profiling applied to antecedent endoscopic biopsy specimens or even to urinary sediment.

The diagnostic challenges attendant upon this entity, which we have systematically deconstructed across the domains of endoscopic visualization, urinary cytology, cross-sectional imaging, and histopathological interpretation, are formidable but not insurmountable, and their successful navigation demands a fundamental reconceptualization of the diagnostic algorithm for suspected upper tract malignancy. The conventional approach, which proceeds sequentially from urinary cytology to computed tomography urography to ureteroscopic visualization with selective cytology and biopsy, is predicated upon the assumption that the neoplastic process will be accessible to optical interrogation and tissue acquisition through the ureteric lumen. This assumption is, in the specific context of peri-ureteral urothelial carcinoma without mucosal invasion, fundamentally invalid, and the rigid adherence to this algorithm in the face of discordant clinical and radiographic findings virtually guarantees diagnostic delay and the attendant risk of disease progression during the interval to definitive diagnosis. The maintenance

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of a high index of suspicion for this entity in patients presenting with unexplained peri-ureteral soft tissue abnormalities, eccentric adventitial thickening, or discrete peri-ureteral mass lesions on cross-sectional imaging, particularly when such findings occur in patients with established risk factors for urothelial carcinoma including prior bladder cancer, occupational exposure to aromatic amines, or endemic nephropathy, represents the single most important determinant of timely diagnosis. The judicious application of image-guided percutaneous biopsy to sample peri-ureteral soft tissue abnormalities, a procedure that carries attendant risks but offers the prospect of definitive preoperative histopathological diagnosis, should be considered in appropriate cases following multidisciplinary discussion and careful assessment of the individual patient's anatomy, comorbidities, and preferences. The integration of emerging epigenetic urinary biomarkers, including DNA methylation-based assays such as Bladder EpiCheck which have demonstrated extraordinary diagnostic accuracy in published validation studies and which may detect tumor-derived genetic material even in the absence of direct communication between the neoplasm and the urinary stream, offers a non-invasive adjunctive diagnostic strategy that may prove particularly valuable in cases wherein percutaneous biopsy is contraindicated or technically infeasible.

The therapeutic management of peri-ureteral urothelial carcinoma without mucosal invasion, once the diagnosis is established through surgical pathology following radical nephroureterectomy or more rarely through preoperative percutaneous biopsy, rests upon the extrapolation of outcomes data from the broader population of patients with pT3b upper tract urothelial carcinoma exhibiting conventional transmural invasion. The seminal multicenter investigation conducted by Kim and colleagues, which demonstrated substantial and statistically significant improvements in local recurrence-free survival, distant metastasis-free survival, and cancer-specific survival associated with the administration of adjuvant radiation therapy in patients with peripelvic or peri-ureteral fat-infiltrating disease, provides the strongest available evidentiary support for postoperative therapeutic intervention in this population and should inform shared decision-making discussions regarding the potential benefits and risks of adjuvant radiotherapy. The null findings of this same investigation regarding adjuvant platinum-based chemotherapy, which failed to demonstrate any detectable oncologic benefit in the pT3b subpopulation, stand in apparent contradistinction to the broader body of evidence supporting adjuvant chemotherapy in high-risk UTUC and highlight the critical importance of patient selection, the potential biological distinctiveness of peri-ureteral fat-infiltrating tumors, and the imperative for prospective

investigation specifically addressing this patient subset. The neoadjuvant administration of platinum-based chemotherapy prior to radical nephroureterectomy, which circumvents the substantial obstacle of post-surgical renal function decline and maximizes the proportion of patients who can receive and complete guideline-recommended perioperative systemic therapy, should be considered in patients presenting with convincing peri-ureteral soft tissue abnormalities on preoperative imaging, even in the absence of confirmatory tissue diagnosis, following comprehensive multidisciplinary evaluation and shared decision-making that addresses the uncertainties inherent in this approach. The emergence of adjuvant immune checkpoint inhibition as a therapeutic strategy in high-risk urothelial carcinoma following radical resection, while supported by positive phase III trial data in populations encompassing both bladder and upper tract primary tumors, has not yet demonstrated definitive efficacy specifically in the UTUC subpopulation and should be approached with appropriate caution until more granular subgroup data become available from ongoing investigations and pooled analyses.

The imperative for rigorous histopathological discrimination between true peri-ureteral urothelial carcinoma and iatrogenic mechanical implantation of benign or low-grade malignant urothelium secondary to antecedent ureteroscopic manipulation cannot be overemphasized, as these two entities carry diametrically opposed prognostic and therapeutic implications and their conflation exposes patients to substantial risk of iatrogenic harm. The constellation of histomorphologic features described by Wobker and colleagues, including the presence of associated linear fibrosis, hemosiderin deposition, foreign body giant cell reaction, and absolute cytologic blandness of the implanted urothelial nests, provides a reliable framework for this critical distinction and should be systematically assessed in every nephroureterectomy specimen from a patient who has undergone preoperative endoscopic biopsy. The performance of ureteroscopic biopsy should be approached with meticulous attention to technique to minimize the risk of mechanical tumor displacement, and the findings of the antecedent biopsy must be carefully correlated with the histopathology of the definitive surgical specimen to ensure concordance and facilitate accurate interpretation of any peri-ureteral epithelial elements identified at final pathology.

The nosological ambiguity that has historically surrounded this entity, and which persists in contemporary staging classifications, represents not merely a semantic inconvenience but a fundamental impediment to progress in understanding its epidemiology, natural history, and optimal management. The current iteration of the American Joint Committee on Cancer staging manual, for all its sophistication and its rigorous evidence-based development, offers no explicit guidance for the categorization of tumors

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that demonstrate peri-ureteral soft tissue extension in the absence of demonstrable involvement of the intervening ureteric mural layers. This lacuna forces the practicing pathologist into an untenable position, compelled to choose between assignment of a pT3 designation that accurately reflects the anatomical location of the tumor deposits but tacitly assumes a transmural pathway of invasion that cannot be histologically documented, and assignment of a pTis, pTa, or pT1 designation that accurately reflects the absence of muscularis propria invasion but conspicuously fails to communicate the presence of extra-ureteral tumor to the treating physician and cancer registrar. Neither approach is intellectually defensible nor clinically appropriate, and both risk miscommunicating essential prognostic information and compromising the accuracy of institutional and population-level cancer registries. The formal acknowledgment of this entity within future iterations of the tumor-nodes-metastasis classification, accompanied by explicit guidance regarding its appropriate categorization for purposes of staging, prognostication, and therapeutic decision-making, represents an urgent unmet need that must be addressed through collaborative engagement between the American Joint Committee on Cancer, the Union for International Cancer Control, the World Health Organization, and the international genitourinary pathology community. The precedent established by the SEER Summary Staging Manual, which explicitly recognizes non-invasive carcinoma involving the periurethral or prostatic ducts without stromal invasion as a form of in situ disease, provides a conceptual template for analogous recognition of peri-ureteral urothelial carcinoma without mural invasion and should inform the deliberations of the staging committees tasked with revising the TNM framework for upper tract malignancies.

The research agenda that emerges from this comprehensive review is extensive and multifaceted, encompassing fundamental investigations into the cellular origin and molecular pathogenesis of peri-ureteral tumors with unconventional growth patterns, translational studies aimed at developing and validating non-invasive diagnostic biomarkers capable of detecting adventitial disease in the absence of mucosal abnormality, clinicopathologic analyses of large multicenter cohorts to define the true incidence, natural history, and prognostic correlates of this entity, and prospective therapeutic trials specifically designed to address the unique management considerations that pertain to this patient population. The application of cutting-edge genomic technologies, including single-cell ribonucleic acid sequencing and spatial transcriptomic profiling, to comprehensively characterize the cellular composition, transcriptional programs, and tumor-microenvironment interactions operative in peri-ureteral urothelial carcinoma without mucosal invasion holds extraordinary promise for illuminating the biological basis of this peculiar phenotype

and identifying novel therapeutic vulnerabilities that may be exploited for patient benefit. The establishment of an international registry for patients with this rare entity, facilitated by collaborative networks such as the Upper Tract Urothelial Carcinoma Collaboration and the Global Society of Rare Genitourinary Tumors, would enable the aggregation of sufficient case numbers to support meaningful statistical analysis and generate hypothesis-generating observations that could inform the design of subsequent prospective investigations. The conduct of adequately powered randomized controlled trials specifically targeting patients with peri-ureteral fat-infiltrating disease, although challenging given the rarity of the condition and the logistical complexities inherent in rare disease research, is not impossible and should be pursued through innovative trial designs including Bayesian adaptive platforms, multi-arm multi-stage protocols, and international collaborative consortia that can achieve the necessary sample sizes through pooled accrual across multiple contributing sites.

The patient presenting with peri-ureteral urothelial carcinoma without mucosal invasion confronts a diagnosis that is at once biologically aggressive, prognostically ominous, and therapeutically ambiguous, a tripartite burden that imposes extraordinary psychological distress and demands exceptional resilience, fortitude, and trust in the medical professionals to whom they have entrusted their care. The responsibility borne by the urologist, radiologist, pathologist, medical oncologist, and radiation oncologist who collectively constitute the multidisciplinary team managing such a patient is correspondingly profound and extends far beyond the technical execution of surgical extirpation, histopathological interpretation, and adjuvant therapy administration. This responsibility encompasses the compassionate and transparent communication of diagnostic uncertainty, the exhaustive exploration of therapeutic options with frank discussion of the limitations of the evidentiary base, the meticulous coordination of care across specialties and institutions, the vigilant surveillance for disease recurrence and prompt intervention upon its detection, and the unwavering commitment to the patient's physical, emotional, and existential well-being throughout the trajectory of their illness. The multidisciplinary tumor board, wherein the collective wisdom and diverse perspectives of multiple specialists are brought to bear upon the unique circumstances of each individual case, represents the optimal forum for the complex decision-making that this entity necessitates and should be convened at each critical juncture in the patient's journey from initial presentation through definitive treatment and long-term survivorship care.

The phenomenon of peri-ureteral urothelial carcinoma without mucosal invasion, in its defiance of conventional staging logic, its subversion of established diagnostic algorithms, and its challenge to foundational assumptions

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regarding neoplastic progression, serves as a humbling reminder of the limitations of our current understanding of urothelial carcinogenesis and the imperative for epistemic humility in the practice of oncologic medicine. The conceptual frameworks through which we apprehend malignant disease, however sophisticated and evidence-based they may be, are necessarily simplifications of a reality whose complexity vastly exceeds our capacity for complete comprehension, and they will inevitably fail to accommodate the full spectrum of biological behaviors exhibited by the neoplasms we seek to classify, prognosticate, and treat. The recognition of such failures is not an occasion for despair or self-reproach but rather an opportunity for intellectual growth, scientific discovery, and therapeutic innovation. The entity that we have characterized in this comprehensive review, from its elusive clinical presentation through its treacherous diagnostic pitfalls to its aggressive biological behavior and its ambiguous therapeutic implications, illuminates with painful clarity the gaps in our knowledge and the limitations of our tools. Yet it simultaneously illuminates the path forward, revealing the specific questions that must be answered, the specific technologies that must be developed, and the specific collaborative structures that must be established to advance our understanding and improve outcomes for the patients afflicted by this rare and challenging condition. The journey from the first fortuitous observation of peri-ureteral urothelial carcinoma without mucosal invasion to the comprehensive characterization presented herein has spanned several decades and has been advanced through the contributions of countless pathologists, urologists, radiologists, and oncologists who recognized the significance of their anomalous observations and took pains to document and disseminate their findings. The journey that lies ahead, from our current state of fragmentary knowledge and therapeutic uncertainty to a future wherein this entity is explicitly recognized in staging classifications, readily diagnosed through non-invasive biomarkers, and effectively managed through evidence-based therapeutic protocols informed by rigorous prospective investigation, will require sustained commitment, collaborative engagement, and intellectual creativity from the next generation of genitourinary oncology researchers. It is our earnest hope that this comprehensive review, by synthesizing the extant knowledge, exposing the evidentiary gaps, and articulating a coherent research agenda, will serve as both a foundation and an inspiration for the investigative efforts that will ultimately transform the landscape for patients with this perplexing and formidable manifestation of upper tract urothelial carcinoma.

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