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Exploring the enigma of not macroscopically detectable urothelial carcinoma: A scoping review on the definition, prevalence, diagnosis, and management of positive urinary cytology with absent macroscopic disease

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Introduction There is a significant gap in the literature for cases of positive urinary cytology in the absence of macroscopically detectable disease for urothelial carcinoma. This condition, which we might define as not macroscopically detectable urothelial carcinoma (NMDUC), may be relatively rare but presents significant challenges in management and patient information. This review aims to search the literature for information useful for managing this condition.

Material and methods We structured the review as a scoping review given the desire to have a qualitative definition of NMDUC, without restrictions on study design or demographic characteristics.
The review was structured around 5 domains: definition, diagnostic criteria, population, management, and time of disease progression. The review was conducted following the PRISMA for Scoping Reviews (PRISMA-ScR) guidelines.

Results We found a total of 411 studies and selected 16 for inclusion in the review. Notably, no studies adequately addressed the definition of NMDUC directly. Our findings highlight the diagnostic challenges posed by NMDUC, especially the reliability of positive urinary cytology.
The literature indicates a significant gap in the standardisation of diagnostic criteria and management for NMDUC.

Conclusions NMDUC represents a critical area of urological research requiring further investigation and clearer diagnostic guidelines. We propose the initiation of an international registry to better understand the prevalence, impact, and progression of NMDUC, aiming to standardise the definition and enhance management strategies. This work lays the groundwork for future research that could lead to significant improvements in the diagnosis and treatment of this challenging condition.

Key Words: urothelial carcinoma ‹› scoping review ‹› urinary cytology ‹› not macroscopically detectable urothelial carcinoma ‹› upper urinary tract

INTRODUCTION

Urothelial carcinoma (UC), in its most frequent location in the bladder and rarer location in the upper urinary tract (UT), represents the seventh most common carcinoma in the male population and the tenth when considering both sexes [1]. The diagnosis of UC involves the use of endoscopic examinations (cystoscopy or upper tract endoscopy), imaging tests, and urinary cytology [2].
The significance of positive urinary cytology lies in its potential to detect UC with high sensitivity

in high-grade (HG) tumours (84.0%) and carcinoma *in situ* (CIS) (28.0–100.0%), but low sensitivity in low-grade (LG) tumours (16.0%) [3]. Positive voided urinary cytology can indicate an UC anywhere in the urinary tract; negative cytology, however, does not exclude its presence. It is also important to consider that the interpretation of cytological examination is operator-dependent, with the potential for both false positives and false negatives. In this perspective, the prospect of using artificial intelligence in sample interpretation is very interesting [4].

Early detection is crucial for effective treatment and improved patient outcomes. However, there is a subset of cases characterised by positive urinary cytology despite the absence of detectable tumours through conventional imaging or endoscopic techniques. This condition (often improperly defined as occult urothelial carcinoma – OUC) [5] underscores the limitations of current diagnostic modalities and raises concerns regarding optimal management strategies.

The literature, however, seems to lack studies that present the definition, diagnostic criteria, and prevalence of not macroscopically detectable urothelial carcinoma (NMDUC) of the UT. Furthermore, the criteria for diagnosing the absence of macroscopically detectable disease (MDD) remain inconsistent, contributing to challenges in the standardisation of care.

Therefore, this scoping review aims to systematically explore and synthesise the current literature on NMDUC, with a focus on cases presenting with positive urinary cytology in the absence of MDD in the upper urinary tract. Specifically, we seek to determine the prevalence and incidence of this condition, clarify the definition and diagnostic criteria, examine the criteria for the absence of MDD, evaluate existing management strategies, and understand the timing of disease progression. Through this review, we intend to provide a foundation for future research directions and contribute to the optimisation of diagnostic and management protocols for patients with NMDUC.

MATERIAL AND METHODS

In conducting this scoping review, we aimed to explore the extent of the literature addressing the phenomenon of positive urinary cytology in NMDUC. Our review protocol was structured around 5 key domains: 1) the definition, 2) the diagnostic criteria, 3) the population (prevalence and incidence of the condition), 4) management strategies for patients, and 5) the timing and patterns of disease progression. To capture a comprehensive body of literature, we employed a systematic search strategy across multiple electronic databases (PubMed, Embase, Web of Science, and Cochrane Library) on 8 December 2023. The search was designed to include a range of terms and synonyms across our key domains, such as “positive urinary cytology”, “upper tract urothelial carcinoma”, and “absence of visible tumour”, among others. Boolean operators (AND, OR) were used to combine search terms within and across these domains to ensure a broad yet specific capture of relevant literature. The search strategy was tailored to each database to leverage specific indexing systems, such as Medical Subject Headings (MeSH) in PubMed, ensuring a thorough retrieval process.

Eligibility criteria were predefined to include studies that specifically discussed positive urinary cytology in the context of absent macroscopically visible disease, across any age, sex, or ethnicity, and without restrictions on the study design, to encompass a wide range of evidence. Case reports were excluded. The screening process was conducted in 2 phases: an initial title and abstract screening followed by full-text review, with discrepancies resolved through consensus or third-party adjudication. This methodological approach was designed to minimise bias and ensure the reliability and validity of the scoping review’s findings.

Non-English language publications were excluded from consideration, reflecting our language proficiency constraints and focusing on literature readily accessible for further analysis. To carry out this research, we employed Arksey and O'Malley's rigorous methodological framework for systematic scoping reviews, enhanced with verified additions such as evaluating the quality of the research [6–9].

RESULTS

Following the systematic application of our search strategy across the predetermined electronic databases, the initial retrieval process yielded a diverse set of studies across our 5 defined domains. Specifically, for the domain concerning the definition prevalence and incidence of positive urinary cytology in the absence of MDD, we identified 84 papers, of which 10 met our inclusion criteria for detailed analysis. In exploring the diagnostic criteria of the condition, our search resulted in 59 papers, of which only 3 were included. The investigation into the population yielded 60 papers, of which none was included. For management strategies applicable to this condition, we found 100 papers, narrowing down to 2 that provided insightful and relevant information. Lastly, the domain addressing the timing of disease progression was the most

fruitful, with 108 papers found and one selected for its direct relevance and contribution to understanding disease dynamics over time.

The studies that we ultimately included in the review amounted to 16, as shown in Table 1. Table 2 lists the studies with a summary of the extracted information are listed.

Despite the studies found and selected, none of them provided a definition of NMDUC, diagnostic criteria, the population of interest, the timing of disease presentation and progression from the detection of cytological positivity, or its management. This condition is addressed more as a problem of diagnostic sensitivity rather than as a distinct nosological entity. However, our definition lies precisely in this grey area between the diagnostic limitations of currently available methods and the evidence of positive urinary cytology in the upper urinary tract.

All the selected articles emphasise the need for rapid recognition of urothelial disease. The urinary cytology that should be used to investigate UTUC is selective ureteral cytology using the barbotage technique, which, according to Malm et al. [10], has a 91% efficacy in diagnosing high-grade UC, similar to that of a biopsy; however, in cases where UTUC is already suspected from CT, it does not add sensitivity or significant information and therefore has no real clinical utility [11].

It should also be considered that although selective ureteral cytology is strongly indicative of UTUC in the absence of macroscopically detectable lesions,

Table 1. *Summary of the articles found, analysed, and included*

Category	Papers Found	Full analysis	Selected
Definition	84	26	10
Diagnostic criteria	59	15	3
Population	60	18	0
Management	100	22	2
Timing	108	14	1

Table 2. *The analysed studies and summary of the information*

Author	Year	Main result
Malm et al. [10]	2017	Barbotage technique in 91.0% of cases have a similar effectiveness to biopsy
Zhang et al. [11]	2020	The barbotage cytology of upper urinary tract has a sensitivity between 55.0% and 92.0% for UTUC, the performance is better when considering HG alone
Rouprêt et al. [12]	2012	The presence of positive cytology for HG in the absence of macroscopically detectable lesion of the bladder is strongly indicative of UTUC. In case of bladder visible lesion, the selective barbotage cytology is less reliable
Mishriki et al. [13]	2012	Cytology can be useful in the diagnosis of haematuria only when CT and cystoscopy are negative. The number of patients with UC with only positive cytology was extremely low (2 out 2,778)
Piaton et al. [14]	2013	Despite of the high sensitivity of p16/NK4a and p16/Ki-67, there was no significant difference with traditional urinary cytology
Kata et al. [15]	2016	Describe the specificity and negative predictive value of positive cytology for CIS and HG (91.9% and 93.4%) especially in the brushing of the upper tract. Unfortunately, such positivity is not sufficient to locate the disease. FISH is more sensitive for LG than HG or CIS 6/10 patient with CIS in a biopsy from white light ureteroscopy do not have CIS in the final nephroureterectomy exam NBI, PDD, CLE and OCT can slightly increase the diagnostic power Cytology remains the more accurate methods in CIS and flat lesions
Iinuma et al. [16]	2020	CIS or HG can be found in normal appearing mucosa when cytology is positive
Bus et al. [17]	2016	OCT is a ureteroscope probe to get high resolution imaging to decide whether to perform a biopsy with a sensitivity of 86.7%
Fukuhara et al. [18]	2019	ALA-PDD has a sensitivity of 95.8% in the diagnosis of UC but with 19.4% of false positive
Geavlete et al. [19]	2012	NBI vs WLC allows for superior detection rate in CIS, Ta, and T1 tumours (95.5% vs 61.9%/93.9% vs 85.2%/94.8% vs 83.9%)
Iordache et al. [20]	2018	NBI enhanced the diagnosis of UTUC by improving the choice of the biopsy site with a detection rate of 98.4% (vs 91.8% in WL) but with more false positive biopsies
Sudah et al. [21]	2016	Sensitive of 3.0 T MRU compared to CTU: detection rate would highlight lesions up to 3–4 mm
Nonomura et al. [22]	2000	Evaluated diagnostic criteria for "occult" BC recidive after BCG instillation to define recurrence with positive urinary cytology: negative random biopsies, negative radiological imaging, and positive urinary cytology
Schwalb et al. [23]	1994	Absence of clear guidelines in case of positive CTM in the absence of macroscopically visible tumour; the appearance of positive CMT in the absence of macroscopically detectable disease as a high-risk condition

ALA-PDD – 5-aminolevulinic acid (ALA)-mediated photodynamic diagnosis; BC – Bacillus Calmette; BCG – Bacillus Calmette-Guérin; CIS – carcinoma *in situ*; CLE – confocal laser endomicroscopy; CT – computed tomography; CTM – computed tomography-myelography; CTU – CT urography; FISH – fluorescent *in situ* hybridisation; HG – high-grade; LG – low-grade; MRU – magnetic resonance urography; NBI – narrow-band imaging; OCT – optical coherence tomography; PDD – photodynamic diagnosis; UC – urothelial carcinoma; UTUC – urinary tract urothelial carcinoma; WLC – white light cystoscopy

this could be unreliable if bladder disease is also present [12]. Considering this efficacy, it is unthinkable to overlook positive cytology from barbotage and consider it simply as a false positive.

An important aspect is that urinary cytologies performed during the diagnostic phase in suspected UC can lead to a significant increase in healthcare costs. If we consider that the average cost of spontaneous voiding cytology in Europe is about $40 and that patients who present only with this positivity in the absence of MDD on cystoscopy or CT must undergo second-level tests such as ureteroscopy with biopsy, the cost of diagnosis could increase to an average of $12,000. Careful analysis was conducted by Mishriki et al. [13], who estimated a 10.5% false positive rate in positive high-grade spontaneous voiding cytology, and in their case series only 2 out of 2,778 patients actually had UTUC in the absence of MDD (CT and ureteroscopies). The authors conclude by suggesting the removal of urinary cytology from UC diagnostic guidelines because it would expose a larger number of patients to unnecessary diagnostic tests, increasing risks and costs, while being useful for diagnosing an extremely small number of patients with UTUC [13]. This study perfectly captures the problem we are analysing, but from an opposing perspective: in the absence of more accurate diagnostic methods, is it ethically correct to overlook the diagnosis of UTUC even in such a small number of patients?

Therefore, we need diagnostic methods that allow us to overcome the limitations of cytology in terms of location accuracy (where the UC is located) and diagnostic sensitivity. Markers such as p16/Ki-67 dual labelling have shown high sensitivity, but not significantly higher than cytology [14]. Even FISH has its limitations, having greater sensitivity for low-grade UC or CIS but less sensitivity in high-grade UC or CIS [15].

Mapping in white light (WLC) is advisable in patients with positive cytology, to assess the concurrent finding of CIS in areas of abnormal mucosa (reddish or mossy) at the time of TUR, noting that CIS or HG disease can also be found in areas of normal mucosa when there is a positive cytology [16]. For this reason, developments in endoscopic techniques also seek to find solutions for diagnosing lesions in the absence of MDD.

Optical coherence tomography (OCT) [17], narrow band imaging (NBI), photodynamic diagnosis (PDD) [18], and confocal laser endomicroscopy (CLE) seem to increase diagnostic power by only 20% compared to white-light endoscopy (WL), so selective cytology with barbotage remains more accurate in diagnosing CIS and flat lesions, even though it cannot localise the disease [15]. For example, compared to WL cystoscopy, NBI shows a higher detection rate for CIS (95.2% vs 61.9%), TaHg (93.9% vs 85.2%), and T1Hg (94.8% vs 83.9%) [19]. In studies on the upper tract, however, NBI increases the detection rate compared to WL (98.4% vs 91.89%, respectively), improving the accuracy of biopsy site selection in ureteroscopy, but also resulting in an increase in false positives on histological examination (17.5% vs 10.1%) [20].

Considering imaging techniques, the sensitivity of CT urography (CUT) is similar to that of magnetic resonance urography (detection rate of 96.0% vs 93.6%), with the ability to detect lesions as small as 3–4 mm [21].

Although no diagnostic criteria for NMDUC have emerged, some authors have attempted to classify similar conditions. Nonomura et al. [22], in a study on the safety and efficacy of BCG instillations for upper tract CIS, selected 4 criteria to classify recurrence: 1) cytology positivity, 2) multiple negative bladder biopsies (including the prostatic urethra), 3) negative URO-CT (CUT), and 4) positivity of selective ureteral cytology on the same side as the first detection of the disease.

Schwalb et al. [23] also highlighted the absence of clear guidelines in the case of positive cytology but in the absence of macroscopically visible tumours. In their study, they evaluated a population of non-muscular invasive bladder cancer (NMIBC) patients treated with BCG, defining the absence of visible tumours and/or negative bladder biopsies, negative urinary cytology (from spontaneous voiding or catheterisation), or flow cytometry for one year as a complete response. The authors considered the appearance of positive cytology in the absence of MDD as a high-risk condition even in the case of an initial complete response [23]. These are attempts to categorise a high-risk condition to perhaps perform early radicalisation and improve the patient's prognosis. However, the 2 studies attempt to categorise a recurrence by considering a region that had already been affected by UC and which, after initial conservative treatment, might require additional treatment. The condition we are trying to categorise in this work, on the other hand, concerns all cases without MDD but with persistently positive barbotage cytology. As we have already emphasised, positive cytology strongly indicates the presence of UC but does not define its location. So, how should we proceed?

DISCUSSION

None of the articles found in our review provided information on NMDUC, which appears to be

an uncategorised nosological entity situated in a limbo between the sensitivity of diagnostic methods and the false positivity of urinary cytology. In our opinion, this scoping review highlights a gap in the literature that we will attempt to define.

Ragonese et al. [5] define occult urothelial tumour as cytological positivity without clinical or endoscopic evidence of UC in any part of the urinary tract; given the high specificity of cytology for HG and CIS, close to 90%, and the impact that diagnostic delay has on the patient's prognosis, this risk cannot be ignored. In their work, they accurately described the available diagnostic methods, in which our review did not reveal significant improvements or advancements [5].

Although this work is valuable, it presents an incorrect definition of occult urothelial tumour. Occult carcinoma is a relatively rare entity (0.3–1.0% of all newly diagnosed breast carcinomas, for example) and is clinically defined as a malignant neoplasm in which the primary lesion is difficult to identify. This tumour, which appears metastatic, is diagnosed clinically and through histological analysis. For some patients, the micro primary carcinoma can be detected when a patient is being evaluated for autopsy. Occult tumours are most often associated with breast, thyroid, and gynaecological carcinomas [24]. Cases of UC presenting as occult tumour in the literature are sporadic and are described as mediastinal masses or multi-organ metastases with an extremely poor prognosis [25, 26]. Occult urothelial tumour therefore represents the extreme progression of NMDUC: our diagnostic capabilities have failed, and a non-macroscopically detectable disease has progressed to systemic metastatic disease.

Therefore, in the presence of positive selective cytology without evidence of MDD (and thus also in the absence of distant metastases), we believe it is more appropriate to refer to NMDUC. Undoubtedly, urinary cytology continues to play an important role in the follow-up of UC, but it can also lead to invasive and costly exams if falsely positive. The studies we encountered agree on the importance of early diagnosis and the intention to seek greater diagnostic power for UC.

This problem is linked to the current diagnostic limitations that have not been overcome by advances in endoscopic techniques (NBI, PDD), more specific laboratory tests (FISH, Ki-67), or improved resolution of radiological methods. The presence or persistence of positive cytology for CIS or HG, whether ureteral or vesical, in the absence of MDD remains a significant problem for both the clinician and the patient. The patient undergoes multiple and invasive evaluations without obtaining a diagnosis but only the persistence of suspicion. For the physician, this condition brings the risk of over-studying the patient while simultaneously missing the chance for early diagnosis and treatment. In the absence of guidelines or data on incidence, prevalence, and progression time, any follow-up appears empirical and arbitrary.

There is a need to propose a broadly accepted definition of NMDUC to build an international registry and estimate the impact, costs, prognosis, and management of this condition. The definition we propose includes the following (Figure 1):

- persistence of positive selective barbotage cytology for HG or CIS in a specific area (at least 2 different collections at intervals of no less than 30 days);
- negative results in white-light endoscopic evaluation;
- negative results from bladder and prostatic urethra biopsies;
- no urothelial suspicions lesions detectable on thin-slice URO-CT.

Starting from this definition, we hope to attract the interest of other centres in a prospective study. A clinical trial would pose significant ethical and clinical challenges because some patients could be treated with surgical radicalisation (of the area where cytological positivity persists) based only on cytology, while others would need to be placed under surveillance.

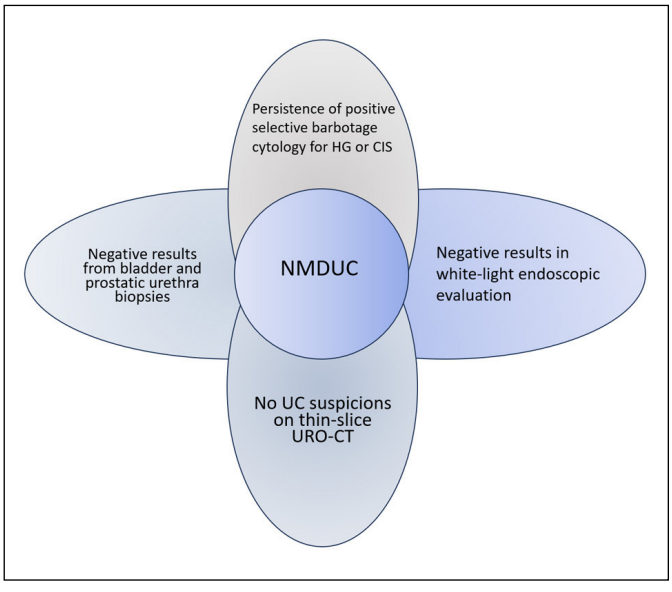

Figure 1. *Diagnostic criteria for not macroscopically detectable urothelial carcinoma (NMDUC).*

HG – high-grade; CIS – carcinoma *in situ*; UC – urothelial carcinoma; URO-CT – computed tomography urography

CONCLUSIONS

Our scoping review did not provide answers to any of the objectives we had set due to the almost complete lack of literature on this topic. Whether NMDUC is accepted as a nosological entity or as persistent false-positive cytology, guidelines are still needed to provide the patient with a clinical response.

Reusing an interesting definition by Malm et al., UTUC is like a jigsaw puzzle where each piece must be considered for the diagnosis: imaging, endoscopy, and cytology. In this puzzle, however, the outcome could be either early treatment or poor prognosis, depending on how the individual pieces are arranged.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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ETHICS APPROVAL STATEMENT

The ethical approval was not required.

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