Optimizing the diagnostic process of urinary bladder cancer

On standardized care pathway, computed tomography, artificial intelligence, and a newly developed urine-based cancer marker

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To Racha, Sidra and Sandra

…the loves of my life

"Width of life is more important than the length of life."

Ibn Sina (Avicenna)

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ABSTRACT

The thesis contains of five articles in three different subprojects. The overall aim of this thesis is to investigate the development of the investigation of macroscopic hematuria over time, the effects of this development on urinary bladder cancer (UBC) characteristics and possible improvements to the investigation process using auxiliary tools such as computed tomography urography (CTU), artificial intelligence (AI) interpretation of CTU and urine-based cancer marker tests.

We have therefore studied the impact of early detection of UBC on its characteristics in the first two articles (I and II) which were retrospective, observational, cohort studies (2010-2019). We could show that, following the implementation of the standardized clinical pathway (SCP) in Sweden for patients with macroscopic hematuria, the median time to diagnosis for UBC decreased nationally from 37 to 27 days and in NU Hospital Group from 29 to 12 days. The percentage of cT2-4 tumors decreased in the NU Hospital Group from 26% to 20% ($p=0.035$) during SCP. To enhance the diagnostic process, we propose stricter adherence to SCP and extending the 13-day window for transurethral resection of bladder tumors (TURBT), particularly in less urgent cases, to prioritize severe cases with treatable diseases for prompt assessment.

We also evaluated the potential of CTU as a single investigation method as well as AI interpretation of CTU to improve the investigation of patients with suspected UBC in articles III and IV. Article III is a retrospective diagnostic accuracy study (2016-2019), and article IV is an observational case-control study (2016-2022). We showed that CTU has a high accuracy in detection of UBC with a false negative rate of 0.07 (95% CI 0.04-0.12), and a negative predictive value (NPV) of 0.99 (95% CI 0.92-1.0). As a result, our studies demonstrate that CTU can effectively rule out UBC, suggesting that forgoing cystoscopy may be a reasonable approach in 57% of patients. Our newly developed AI-based model has a sensitivity of 0.83 (95% CI, 0.76-0.89), and NPV of 0.97 (95% CI 0.95-0.98). This AI-based image analysis model may assist radiologists in the initial assessment of CTUs for patients with macroscopic hematuria.

Finally, we have evaluated a new urine test with an mRNA panel (GeneXpert BC) to detect or exclude UBC in article V which was a multicenter nested case-control diagnostic study (2020-2022). In this study, involving 273 subjects (case group, n=151, and control group, n=122), the sensitivity of GeneXpert BC was 0.94 (95% CI 0.89-0.97), and NPV was 0.99 (95% CI 0.97-1.00). Consequently, GeneXpert BC was shown as a reliable triage test in ruling out UBC, suggesting that 44% of our patients might have been exempted from routine primary investigation of macroscopic hematuria which might potentially save healthcare resources and spare patients the discomfort of unnecessary examinations.

Keywords: *Artificial intelligence, bladder cancer, convolutional neural networks, deep learning, diagnostic accuracy, GeneXpert, health services organization, hematuria, mRNA, population-based, standardized care pathways, trends, computed tomography urography, Xpert.*

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1. Sammanfattning på svenska

Urinblåsecancer (UBC) är en vanlig form av cancer och står för ca 3% av alla globala maligniteter, med makroskopisk hematuri (synlig blod i urinen) som det främsta symptomet. En försening i diagnosen av UBC är kopplad till sämre prognos. Det är därför av stor vikt att upptäcka UBC så tidigt som möjligt. År 2016 infördes i Sverige ett snabbt nationellt utredningsspår kallat standardiserat vårdförlopp (SVF) för flera cancerdiagnoser, inklusive UBC. Målet var bland annat att minska väntetiderna för utredning och behandling av patienter med denna tumörsjukdom. Trots detta är de nuvarande utredningsmetoderna, cystoskopi och datortomografi urografi (DTU), kostsamma, tidskonsumerande och resurskrävande, har kända komplikationer och endast omkring 10-15% av patienterna som undersöks har faktiskt en underliggande cancer i urinorgan.

Det övergripande syftet med denna avhandling är att undersöka utvecklingen av utredningen av makroskopisk hematuri över tid, effekterna av denna utveckling och möjliga förbättringar av utrednings-processen. Vi har därför studerat hur tidig upptäckt av UBC kan påverka tumöregenskaper. Vi har även utvärderat potentialen av DTU som enskild utredningsmetod samt artificiell intelligens (AI)-tolkning av DTU för att förbättra utredningen av patienter med misstänkt UBC. Slutligen har vi utvärderat ett nytt urintest med en mRNA-panel (GeneXpert BC) för att påvisa eller utesluta UBC med hög diagnostisk säkerhet.

Vi kunde observera en minskning av mediantiden till diagnosen efter implementeringen av SVF 2016, även om den inte nådde de rekommenderade nivåerna. Det fanns dock skillnader mellan regioner och olika sjukhus beroende på hur SVF-rekommendationerna tillämpades. Vår forskning indikerar att SVF-implementering i NU-sjukvården associerade med färre upptäckta aggressiva tumörer, men detta observerades inte nationellt. Vi föreslår att mer arbete behöver göras för att kategorisera patienter med olika prioriteringar inför utredningen och att prioritera de med misstänkt allvarligare tumörer för en snabbare utredning vilket kräver ytterligare forskning. Vi rekommenderar även att implementera strategier för att förbättra tillämpning av SVF-rekommendationer i hela landet.

Våra studier visade att DTU effektivt kan utesluta UBC, vilket antyder att avstå från cystoskopi kan vara ett rimligt tillvägagångssätt för 57% av patienterna som kommer med makroskopisk hematuri. Dessutom har vi utvecklat och utvärderat en ny AI-baserad bildanalysmodell för att underlätta radiologers initiala bedömning av DTU för patienter med makroskopisk hematuri och därmed förkorta utredningstiden. Det finns potential för ytterligare studier för att förbättra DTU-tekniken och integrera AI inom diagnostiken av UBC.

Vi har även utvärderat ett nytt urintest (GeneXpert BC), som testades i samband med utredning av makroskopisk hematuri. Resultaten visar att detta test är nästan lika effektivt som cystoskopi för att utesluta UBC. Med detta test kan upp till 44% av patienterna med makroskopisk hematuri undvika cystoskopi och DTU. Slutligen, utarbetade vi ett nytt diagnostiskt schema för att undersöka patienter med makroskopisk hematuri med syftet att reducera vårdkostnader, minimera obehag för patienterna och minska eventuella komplikationer kopplade till de befintliga undersökningarna (DTU och cystoskopi). Detta kräver naturligtvis ytterligare forskning i större studier i framtiden för att validera detta schema samt våra resultat.

2. LIST OF PAPERS

This thesis, comprising three distinct subprojects, is based on the following studies which are referred to in the text by their Roman numerals:

2.1. Subproject I (The impact of SCP on diagnosis and management of UBC)

I. *Abuhasanein S, Jahnson S, Aljabery F, Gårdmark T, Jerlström T, Liedberg F, et al. Standardized care pathways for patients with suspected urinary bladder cancer: the Swedish experience. Scand J Urol. 2022;56(3):227-32.*

II. *Abuhasanein S, Jahnson S, Kjölhede H. Shortened time to diagnosis for patients suspected of urinary bladder cancer managed in a standardized care pathway was associated with an improvement in tumour characteristics. BJUI Compass. 2023.*

2.2. Subproject II (The role of CTU and AI in diagnosis of UBC)

III. *Abuhasanein S, Hansen C, Vojinovic D, Jahnson S, Leonhardt H, Kjölhede H. Computed tomography urography with corticomedullary phase can exclude urinary bladder cancer with high accuracy. BMC Urol. 2022;22(1).*

IV. *Abuhasanein S, Edenbrandt L, Enqvist O, Jahnson S, Leonhardt E, Trägårdh E, et al. A novel model of artificial intelligence (AI) based automated image analysis of CT urography to identify bladder cancer in patients investigated for macroscopic hematuria.*

2.3. Subproject III (Urine-based cancer marker - GeneXpert BC)

V. *Abuhasanein S, Radmann J, Jahnson S, Kjölhede H. Diagnostic performance of GeneXpert BC as a triage test for patients presenting with macroscopic hematuria suspected of urinary bladder cancer. A multicenter nested case-control study.*

3. Content

4. Abbreviations

AI	Artificial intelligence
ALA	Aminoluevenic acid
CI	Confidence interval
Cis	Carcinoma in situ
CLAIM	Checklist for Artificial Intelligence in Medical Imaging
CMP	Corticomedullary phase
CNN	Convolutional neural networks
CTU	Computed tomography urography
DL	Deep learning
EP	Excretory phase
FNR	False negative rate
FPR	False positive rate
IDR	Inter-decile range (10-90%)
IQR	inter-quartile range (25-75%)
ISUP	International Society of Urological Pathology
IVIT	Intravesical instillation therapy
LDA	linear discriminant analysis
LG	Low grade
LMP	Low malignant potential
MDTC	Multidisciplinary team conference
MIBC	Muscle invasive bladder cancer
NAC	Neoadjuvant chemotherapy
NBI	Narrow band imaging
NMIBC	Non-muscle invasive bladder cancer
NP	Nephrographic phase
NPV	Negative predictive value
OS	Overall survival
PDD	Photodynamic diagnosis
PPV	Positive predictive value
RT	Radiation therapy
SCP	Standardized care pathway
SD	Standard deviation

SLR	Second-look resection
SNRUBC	Swedish National Register of Urinary Bladder Cancer
TNM	Tumor, node, metastasis
TURBT	Transurethral resection of bladder tumor
UBC	Urinary bladder cancer
UP	Unenhanced phase
UTUC	Urothelial cancer in urinary tracts
WHO	World Health Organization

5. Definitions

SCP (standardized care pathway) is a nationwide healthcare initiative from 2016 and onwards in Sweden aiming to ensure that individuals with suspected cancer encounter a highly organized and expertly managed system for cancer care that minimize unnecessary delays in treatment, in accordance with national and international guidelines.

SNRUBC (The Swedish National Bladder Cancer Register), is a comprehensive and nationwide database specifically created to gather and manage data related to the diagnosis and management of urinary bladder cancer. This register includes patients and tumor characteristics, primary treatment, and result of follow-up after five years from 1997 and is assembled in a database available for quality control and research.

6. Background

6.1. Historical view

Over time, our understanding of cancer, specifically urinary bladder cancer (UBC), has undergone profound transformations, resulting in enhanced diagnostic and therapeutic approaches for UBC. Ongoing research and the progress of medical technologies, histopathology, anesthesia, and antibiotics provided optimism for improved outcomes. To grasp this journey, we must embark on a historical exploration, starting at the very origins, long before the emergence of humans. The existence of cancer actually predates humanity itself, as archaeological discoveries of tumors in animals bear witness to its presence [1].

The first documentation of human cancer is traceable to the Edwin Smith Papyrus (an ancient Egyptian medical text, 3000 BC), which depicted a case of breast cancer [2]. Additional historical evidence includes ancient Egyptian records that portrayed cancer as a severe and untreatable disease, often linking it to ”the curse of the gods” [1, 3]. The most ancient example of cancerous growths in humans has been identified in well-preserved Egyptian and Peruvian mummies, dating as far back as 1500 BC. Furthermore, among the earliest scientifically documented cases of widespread cancer was that of a Scythian king resided in the Southern Siberian, approximately 2,700 years ago [4].

In the ancient Greece, Hippocrates (460-370 BC) postulated a connection between "cancer" and "an overabundance of black bile, along with an imbalance in the four bodily humors (blood, phlegm, yellow bile, and black bile)". Hippocrates coined the term "carcinoma", likening the disease to a crab that clings to its surroundings with its pincers [5]. The Roman physician Celsus (25 BC-50 AD) subsequently translated this term into "cancer", adopting the Latin word for crab. Galen, (a Greek physician in the Roman Empire, 129-200 AD) described these growths using the Greek term "oncos", meaning swelling [1]. Many centuries elapsed before the 16th century when Paracelsus conducted his research on tumors afflicting mine workers. He proposed an alternative theory, suggesting that the cancers in these workers were a result of deposits of sulfur and arsenic

salts in their blood, rather than an excess of black bile as previously believed [1].

Already in 1686, it was documented that the presence of blood in urine might be indicative of UBC. This observation was made by Dutch surgeon Fredericus Ruysch (1638-1731). In his book "Observationum", we find the earliest known illustration of papillary tumors of the urinary bladder (Figure 1). Nevertheless, UBC was once regarded as an accidental discovery during lithotomy procedures for stone removal. Fabricus Hildanus (1560-1624), a lithotomist, documented the inadvertent removal of a superficial UBC while performing lithotomy. The initial description of low- and high-grade UBC was provided by the French surgeon Francois Chopart (1743–1795) [6]. It was not until 1874, when the Austrian surgeon Theodor Billroth (1829-1894) performed a suprapubic removal of UBC that couldn't be extracted through a lateral lithotomy incision [7].

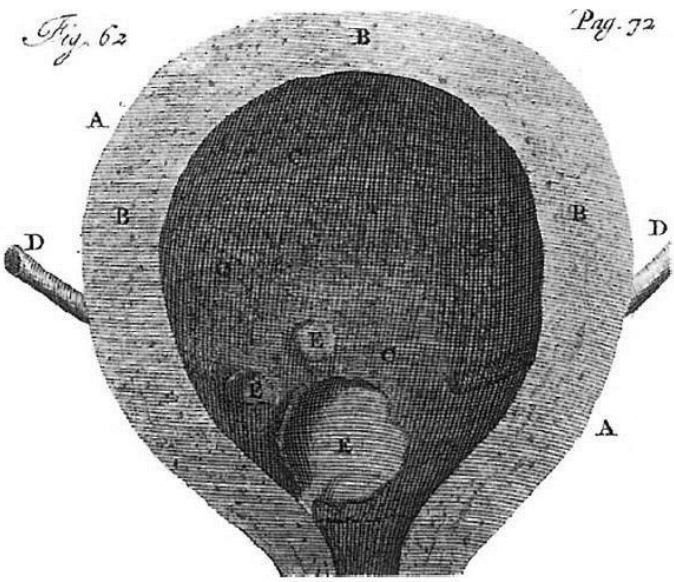


Figure 1. The first illustration of urinary bladder cancer made by Fredericus Ruysch (1638-1731) in his book "Observationum"

A long journey to gain direct visualization into the urinary bladder culminated in the groundbreaking discovery by Maximilian Nitze (a German urologist and nestor of modern urology) in 1877. He pioneered the predecessor to the contemporary cystoscope, marking a significant advancement in the field and enabling the availability of transurethral resection of bladder tumors (TURBT) [8]. The first documented cystectomy dates back to the late 19th century. It was performed by the British surgeon Sir William Thornley Stoker in 1887 [9]. Further progress was made in enhancing our understanding of epidemiology of UBC when a correlation was supposed between UBC and environmental carcinogens, specifically through occupational exposure to aniline dye, in the year 1895 [10].

Another milestone was achieved by the Greek-American pathologist George Nicholas Papanicolaou who described urine cytology for the first time in 1945 [11]. The correlation between infiltration depths into the bladder wall and the prognosis of UBC was not investigated until 1946 when the American urologist Hugh J. Jewett (1904–1990) conducted his research [6]. The first staging classification, as proposed by Jewett, was later refined by another urologist, Victor F. Marshall (1913–2001). In 1952, this collaborative effort resulted in the introduction of the Jewett-Strong-Marshall Staging system. Starting from 1967, Hugh J. Jewett and his colleagues collaborated under the American Joint Committee System (AJCC) to establish the tumor-nodes-metastasis (TNM) classification, which remains in use to this day, even for UBC [6].

Eugene Bricker (1917-1972), another American surgeon known for his pioneering work in urology and the development of the "Bricker procedure", had introduced the ileal conduit in 1950 [7]. The identification of tobacco smoking as a significant risk factor for UBC dates back to the mid-20th century [12]. Epidemiological studies conducted in the 1960s provided convincing evidence linking cigarette smoking to an increased risk of developing UBC [13, 14]. In 1976, the Mexican urologist Juan J. Morales made a significant clinical breakthrough by reporting the first clinical application of intravesical Bacillus Calmette-Guérin (BCG) for the treatment of superficial UBC [7]. BCG began to be used in Sweden in clinical studies from the mid-1980s. The adoption of intravesical

chemotherapy commenced in the early 1900s [15]. Triethylenethiophosphoramide (Thiotepa) is one of the oldest intravesical chemotherapeutic agents [16]. Additional intravesical chemotherapy agents comprising Valrubicin, Doxorubicin (Adriamycin), Epirubicin, and Mitomycin C were used [15, 17].

The progress in imaging modalities, notably computed tomography urography (CTU), has enhanced the detection, staging and surveillance of UBC [7]. The journey toward developing a non-invasive urine-based cancer marker began with urinary cytology in the 1940s. It progressed through the introduction of the UroVysion Fluorescence In Situ Hybridization (FISH) test in 2001 [18], and advanced with the introduction of the GeneXpert BC, a novel mRNA (messenger ribonucleic acid) test, in 2017 [19]. The journey has been long, marked by crucial and noteworthy accomplishments, yet many achievements still await realization.

6.2. Anatomical, embryonical and histological aspects

The urinary bladder is a vital organ with a unique anatomy and histology, designed to store and release urine from the body. It is a muscular, hollow sac-like structure located in the abdomen beneath the pelvic cavity, situated behind the pubic bone, and enveloped by the prepelvic fat. In males, the bladder is adjacent to the prostate at its base, while in females, it is positioned adjacent to the vagina and the uterus. The rectum is located posteriorly to the bladder [20-22] (Figure 2)

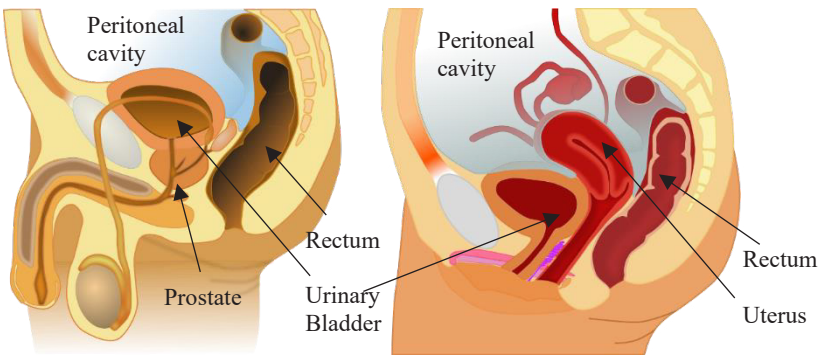


Figure 2. The relationship of the bladder and adjacent organs in men (left) and women (right). Wikimedia Commons, accessed January 13, 2024, https://commons.wikimedia.org/wiki/File:Male_and_female_anatomy.svg

The urinary bladder development initiates during the fourth week of embryonic period when the urogenital septum partitions the cloaca into two distinct parts: the posterior part forming the rectum, and the anterior part evolving into the urogenital sinus. The urogenital sinus undergoes continued growth to give rise to the bladder. A portion of the mesonephric duct combines with the cloaca and is integrated into the posterior wall of the bladder. As the kidneys ascend within the developing embryo, the ureters lengthen and eventually establish superior openings into the bladder. Simultaneously, the roots of the mesonephric ducts descend and merge to form the trigone region of the bladder [23].

The wall of the urinary bladder comprises four distinct layers. The innermost layer is the mucosa, which is lined with transitional epithelium. Histologically, the urothelium presents itself as multiple layers of cells, including basal cells, intermediate cells, and umbrella cells. This specific epithelium is designed to accommodate stretching without compromising the bladder lining's integrity. It is well-suited to withstand the mechanical stresses associated with stretching and the potentially harmful effects of urine exposure. The most prevalent type of UBC, known as urothelial carcinoma (previously referred to as transitional cell carcinoma, TCC), originates in this layer [20, 21] (Figure 3).

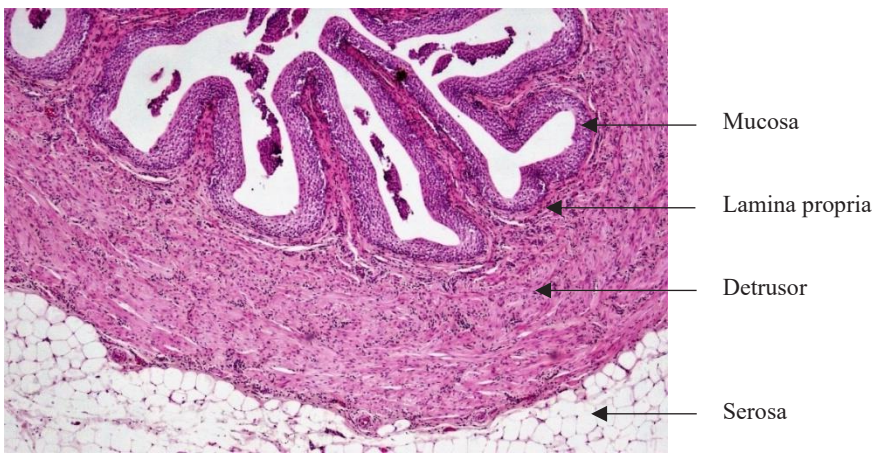


Figure 3. Histology of urinary bladder wall. Flickr, accessed January 13, 2024. https://www.flickr.com/photos/146824358@N03/27025223777/in/photostream/

The second layer is submucosa (lamina propria), connective tissue which contains blood vessels and a submucosal plexus. Muscularis, the third layer, is composed of smooth muscle fibers forming three sublayers: inner longitudinal, middle circular, and outer longitudinal. These muscles aid in bladder contraction and expulsion of urine. The last and outermost layer is serosa (adventitia) which provides structural support. Over time, if UBC left untreated, it can invade these deeper layers of the bladder wall and potentially spread to other organs [20, 21].

The urinary bladder is well-supplied with blood through a network of vessels originating from the superior and inferior vesical arteries arising from the anterior branch of the internal iliac artery, reinforced by contributions from the obturator and inferior gluteal arteries. In females, additional branches originate from the uterine and vaginal arteries. The bladder is drained by a complex network of veins located on its lower lateral surfaces, emptying into the internal iliac veins. Lymphatic vessels responsible for draining the bladder begin in various plexuses, including the mucosal, intermuscular, and serosal plexuses ending in the external, internal, or common iliac lymph node groups. The bladder is innervated by nerves originating from the pelvic plexuses including both sympathetic and parasympathetic nerves, playing essential roles in regulating bladder tone and the micturition reflex [20, 21].

6.3. Epidemiology of urinary bladder cancer

UBC is an important global health issue, characterized by a diverse landscape in terms of epidemiology, investigation, treatment, and surveillance. It is acknowledged as the cancer entailing the highest lifetime treatment costs per patient [24]. UBC is a prevalent form of cancer, accounting for 3% of global cancer diagnoses [25], with an estimated 573 000 new cases occurring worldwide in 2020 [26, 27]. The number of new global UBC cases projected to rise from 573 000 in 2020 to 991 000 in 2040, assuming that the global incidence rates observed in 2020 remain unchanged. Furthermore, UBC ranks as the tenth most frequently diagnosed cancer and the thirteenth leading cause of cancer-related deaths on a global scale [28, 29].

The incidence of UBC varies across countries, with the highest incidence rates observed in Europe, the United States, and Egypt, while the lowest rates are found in sub-Saharan Africa, South America, and Asia [28-30]. In 2020, approximately 213 000 individuals globally died due to UBC [28]. Mortality rates exhibit variations, with the highest rates observed in certain regions of Europe and northern Africa. These incidence and mortality patterns could be attributed to disparities in factors such as the extent of the tobacco epidemic, alterations in coding practices, the prevalence of schistosomiasis (particularly in Africa), and variations in occupational exposures [31] (Figure 4).

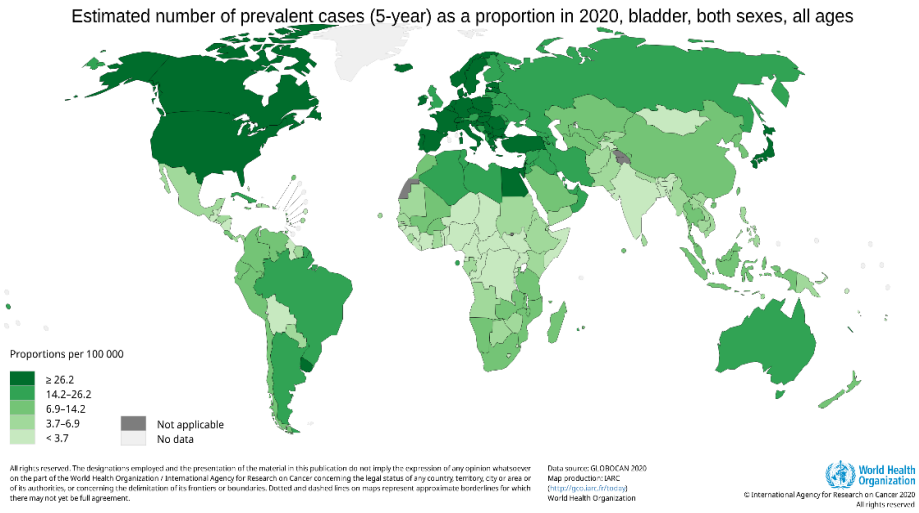


Figure 4. Estimated 5 years prevalence of patients with UBC worldwide. https://gco.iarc.fr/today/online-analysis-table

In Sweden, UBC was ranked as the 4th most common cancer among men and the 8th among women in 2021. During 2021, Sweden reported 3 554 newly diagnosed cases of UBC, and there were 30 296 people living with UBC. Furthermore, there were 734 documented UBC-related deaths. Notably, between 1997 and 2016, the incidence of UBC in Sweden increased by 38% among men and 39% among women. However, there was a slight decline in mortality rates during this time, possibly due to improved detection methods of smaller and less aggressive tumors. The

relative 10 year survival rates for patients with UBC in Sweden stand at 66% and 70% for women and men respectively [32-34] (Figure 5).

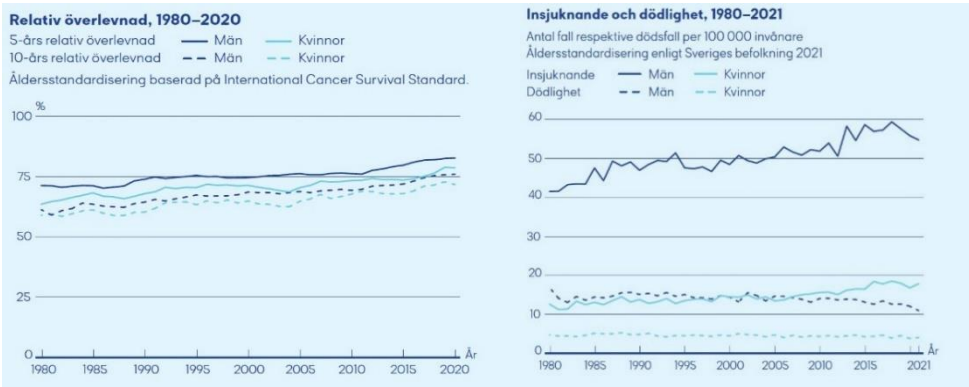


Figure 5. Incidence, mortality (1980-2021) (right) and 5- and 10-years relative survival (1980-2020) (left) of UBC in Sweden. (CANCER I SIFFROR. Populärvetenskapliga fakta om cancer 2023. Socialstyrelsen). Access January 21, 2024. https://www.socialstyrelsen.se/statistik-och-data/statistik/alla-statistikamnen /cancer/

In Sweden, gender distribution man: woman is 3:1, and the typical age of onset is around 75 years in both genders [28, 35]. Additionally, the cumulative risk of being diagnosed with, and dying from UBC before the age of 75, is one in 53 for men and one in 112 for women [28]. Previous research has indicated that women tend to present with UBC at more advanced stages, experience lower overall survival (OS), have reduced cancer-specific survival (CSS), and face higher risks of disease recurrence, progression, and mortality compared to their male counterparts [36-38]. Nevertheless, caution should be warranted when interpreting studies addressing gender disparities.

Detecting UBC at an early stage enhances the likelihood of full recovery and improved survival. This is due to the fact that the earlier the stage, the more favorable the prognosis. Cancer-specific survival rates in UBC patients vary, ranging from 98% for less aggressive Ta tumors to 85% for T1 tumors and 7-45% for more aggressive muscle-invasive tumors (T2-4). Older age, presence of histopathologies other than urothelial tumors, and higher stages were associated with poorer survival outcomes [25, 39].

6.4. Etiology

Early detection and lifestyle modifications, such as smoking cessation, might play a crucial role in improving outcomes for UBC patients [40]. UBC risk increases with age, with the majority of cases occurring in people over 55 years old [25]. Several well-established risk factors contribute to the development of UBC such as tobacco smoking, accounting for about half of all UBC cases and 37% of its deaths [41-43]. Tobacco is a significant source of well-recognized carcinogenic substances, including aromatic amines and N-nitroso compounds leading to DNA damage and cancer formation [44]. In a comprehensive meta-analysis of 83 studies, the pooled relative risk (RR) for current smokers compared to individuals who have never smoked was 3.47 (95% confidence interval (CI) 3.07–3.91), and for former smokers, the RR was 2.04 (95% CI 1.85–2.25) [45].

The second known risk factor for UBC is the occupational exposure to carcinogenic chemicals, such as aromatic amines, polycyclic aromatic hydrocarbons, chlorinated hydrocarbons, and petroleum products, with approximately 10% of all UBC cases might be attributed to occupational exposure [46]. The protozoan infection known as schistosomiasis affecting approximately 240 million people globally has an elevated risk of UBC [47]. The use of radiotherapy (RT) for treating cancers affecting the urinary bladder area has been linked to an increased risk of developing UBC [44]. Additional risk factors for UBC such as chronic irritation resulting from chronic catheterization, the presence of bladder stones, recurrent urinary tract infections, dietary factors, and certain medications were reported, however, no strong conclusive association had been established [44].

6.5. Symptomatology

The primary symptom associated with UBC is visible blood in the urine, known as macroscopic hematuria [48], which stands out as the single alarming symptom with the highest positive predictive value (PPV) for cancer, detecting malignancies in 5-34% of cases [49]. A concentration of 1 ml of blood in one liter of urine is enough to color urine red [50].

Prevalence of macroscopic hematuri in some studies is about 2.5 % in the population [51]. In Sweden, its reported that around 220 out of 100 000 inhabitants were annually referred to a urologist for investigation of macroscopic hematuria [52].

Compared to microscopic hematuria, macroscopic hematuria has been linked to higher stages of UBC, however, the clinical significance of microscopic hematuria is more contentious, with varying diagnostic yield [53]. A Cochrane analysis of whether screening for microscopic hematuria could decrease morbidity and mortality showed that the quality of the reported studies was insufficient to provide any definitive recommendations [54]. Consequently, the Swedish guidelines advised against a urological investigation of patients presenting with microscopic hematuria [55]. This stringent Swedish policy was not observed to have a negative impact on the survival rates of patients with UBC in Sweden [56]. Nevertheless, others continue to recommend testing and even suggest repeat testing if the initial assessment is normal [57]. However, the guidelines from the European Association of Urology (EAU) do not offer specific recommendations for the investigation of hematuria [55, 58]. Lower urinary tract symptoms (LUTS) e.g., urgency, frequency etc. are the sole presenting symptom in approximately 4 % of newly diagnosed UBC patients [59]. However, non-specific, persistent fatigue or weakness can be a possible symptom, especially in advanced cases of UBC [60].

6.6. Tumor classification

Urothelial carcinoma is the most common histological type of UBC, constituting approximately 90% of all cases [61], followed by squamous cell carcinoma (5%) and adenocarcinoma (3%). In general, these types of UBC and other histological variants of urothelial carcinoma tend to have a more aggressive clinical progression compared to conventional urothelial carcinoma [62].

To stage UBC, the generally accepted TNM system is used. This classification system is regularly updated to correspond to the latest research regarding tumor pathology and immunology with the 8th edition from 2017 being the latest version [63, 64]. According to the TNM staging

system, Ta tumors are defined as those that remain confined beneath the basal membrane, while T1 tumors are distinguished by their penetration through the lamina propria. Other UBC stages include those that invade the bladder muscle (T2), extend to perivesical tissue (T3), or affect adjacent organs such as the prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, or abdominal wall (T4). Another form of UBC, specifically flat, high-grade tumors that are restricted to the mucosal layer, is categorized as carcinoma in situ (Cis or Tis), which sometimes go unnoticed during routine cystoscopy [65] (Figure 6).

T - Primary Tumor	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma *in situ*: "flat tumor"
T1	Tumor invades subepithelial connective tissue
T2a	Tumor invades superficial muscle (inner half)
T2b	Tumor invades deep muscle (outer half)
T3a	Tumor invades perivesical tissue microscopically
T3b	Tumor invades perivesical tissue macroscopically
T4a	Tumor invades prostate stroma, seminal vesicles, uterus, or vagina
T4b	Tumor invades pelvic wall or abdominal wall
N - Regional Lymph Nodes	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node in the true pelvis
N2	Metastasis in multiple regional lymph nodes in the true pelvis
N3	Metastasis in a common iliac lymph node(s)
M - Distant Metastasis	
M0	No distant metastasis
M1a	Non-regional lymph nodes
M1b	Other distant metastasis

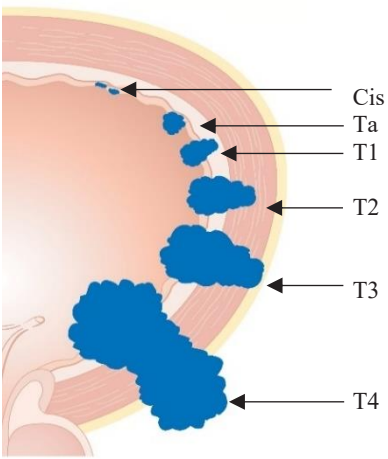


Figure 6. The 8th edition of TNM Classification of urinary bladder cancer (2017)

UBC can be broadly divided into two principal categories. The first is non-muscle-invasive bladder cancer (NMIBC), which is limited to the innermost layers of the bladder lining and constitutes 70-80% of all cases including Ta, Cis, and T1 stages. This category generally has a more favorable prognosis, especially when diagnosed and treated at an early stage. The second category is muscle-invasive bladder cancer (MIBC), characterized by the cancer's penetration into the muscle layer of the bladder wall and the potential extension into nearby tissues or organs. MIBC makes up the remaining 20-30% of all cases including stages T2, T3, and T4. MIBC is more aggressive and carries a higher risk of progression and metastasis if not treated promptly [58, 63, 64, 66].

The histopathological classification of UBC, as stipulated by the World Health Organization (WHO), has undergone a transformation over the years to align with our deepening understanding of the disease. The WHO's initial 1973 system introduced a grading method for UBC that became widely adopted [67]. It involved the categorization of tumors into three grades (G1, G2, and G3) based on the extent of cellular and architectural atypia, ranging from minimal atypia (G1) to pronounced atypia (G3). The WHO 1973 system has been a robust grading system; however, a notable limitation was the ambiguity surrounding the G2 category [68]. In 1999, the WHO, in conjunction with the International Society of Urological Pathology (ISUP), refined the WHO 1973 system by introducing the concept of papillary urothelial neoplasm of low malignant potential (PUNLMP) and presented better and more detailed definition of the different grades G1-3. This updated system, known as WHO1999, encompassed three refined categories -in addition to PUNLMP-, Grade 1, Grade 2 and Grade 3 [69]. *The WHO 1999 system is employed within this thesis with PUNLMP considered as G1 tumors.*

In 2004, the WHO, based on the results from the group of pathologists having created the WHO1999, introduced another classification system, which was further refined in 2016 and later in 2022 [70], known as WHO2004/2016 [68, 69] This system simplified the classification into just two categories: low grade (LG), which incorporated WHO 1973/1999 G1 and some G2, denoting well to moderately differentiated tumors, and high grade (HG), corresponding to WHO 1973/1999 G3 and some G2 cases, signifying poorly differentiated and more aggressive tumors. This system also included PUNLMP as a distinct group [68, 69].

7. Diagnostic evaluation

The diagnosis of UBC relies on various diagnostic methods including cystoscopy, computed tomography urography (CTU), as well as non-invasive tests like urine cytology and urine-based cancer markers [58, 71]. TURBT serves as the primary treatment for NMIBC, and as the standard diagnostic evaluation method for almost all cases of UBC [72]. Prior to and following TURBT, it is advisable to perform bimanual palpation for more accurate clinical staging [58]. In some cases of NMIBC as T1, it is recommended to perform a second-look resection (SLR) within 2 to 6 weeks due to the fact that the rate of residual disease after the initial resection can be as high as 53 %, and the possibility of upstaging to MIBC may be 5 % [73].

7.1 Cystoscopy

Cystoscopy is the established method for direct visualization of the bladder mucosa and detecting pathological lesions in the bladder. The process involves inserting a cystoscope, either rigid or flexible (approximately 6 mm or greater in diameter) via the urethral meatus. The cystoscope is then advanced into the bladder, and the entire mucosal surface is inspected (Figure 7). Small lesions may be examined by biopsy or cauterized under local anesthetic in the office. However, depth of invasion or histological diagnosis of malignant tumors can be reliably determined by pathological examination of the specimen after TURBT.

Flexible cystoscopy is a minimally invasive procedure that is generally associated with low morbidity. However, it is important to note that it results in significant healthcare costs and can lead to patient discomfort. Furthermore, patients may experience symptoms post cystoscopy such as dysuria (50%), increased urinary frequency (37%), macroscopic hematuria (19%), and urinary tract infection (3%) [74-79]. Furthermore, cystoscopy might overlook approximately 5-10% of tumors, particularly Cis [80, 81]. Additionally, it has also been noted that around 20-30% of presumed recurrent UBCs assessed via cystoscopy were in fact benign lesions [82].

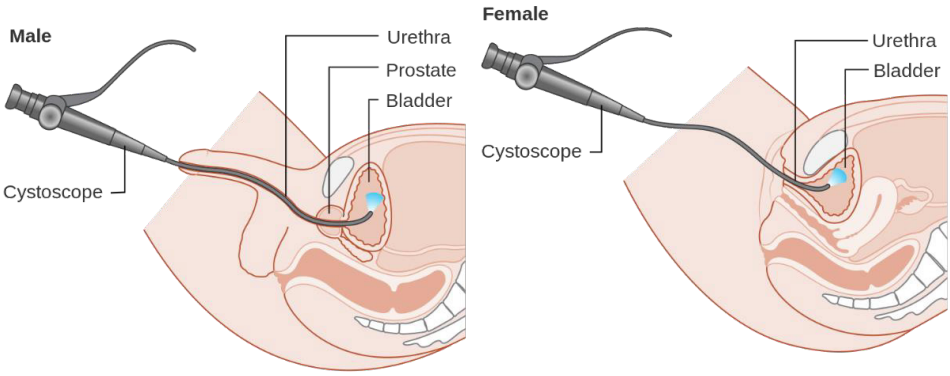


Figure 7. Flexible cystoscope in men (left) and women (right). Wikimedia, January 13, 2024. https://commons.wikimedia.org/wiki/File:Diagram_showing_a_cystoscopy_for_a_man_and_a_woman_CRUK_064_ru.svg#/media/File:Diagram_showing_a_cystoscopy_for_a_man_and_a_woman_CRUK_064.svg

While conventional white light cystoscopy is frequently performed and considered sufficient for identifying bladder abnormalities [22] (Figure 8), there is growing interest in the potential benefits of fluorescent cystoscopy called as photodynamic diagnosis (PDD). In this approach, a fluorescent dye, called aminoluevenic acid (ALA) is instilled into the bladder, accumulates predominantly in malignant tissue, and contributes to better visualization of tumors. The bladder is then examined under violet or blue light. This illumination highlights suspicious areas and enables more targeted biopsies demonstrating promising results with a reduced risk of recurrence and improved detection rates [83, 84].

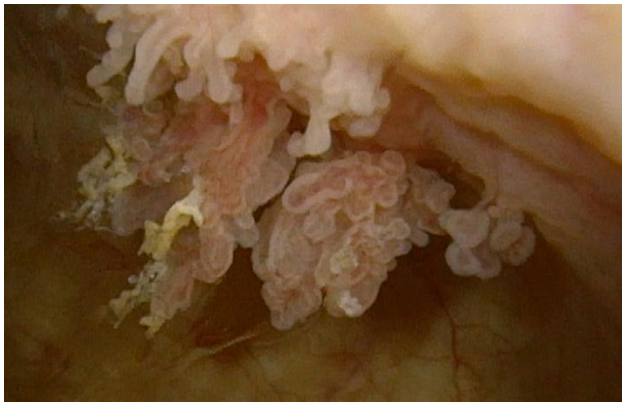


Figure 8. Classic exophytic urothelial tumor in the urinary bladder using white cystoscopy

Narrow band imaging (NBI) is another optical image enhancement technology utilized the penetration of light into superficial bladder tissues, with strong absorption by hemoglobin. Consequently, it significantly enhances the visibility of capillaries and delicate surface structures of tissues in the bladder. This enhancement of contrast allows for improved visualization of tumors with a cell nucleus compared to inflammatory conditions, such as a catheter lesion lacking a cell nucleus [85]. In many cases, a combination of these techniques might be employed, where initial inspection is done using white light followed by targeted evaluation using NBI or PDD for suspicious areas.

7.1. Computed tomography urography (CTU)

CTU is a multiphase CT scan specifically designed for visualizing the kidneys, ureters, and bladder. Various protocols exist for contrast administration, image acquisition, and timing, each with its own advantages and limitations. The introduction of new reconstruction algorithms, such as iterative and deep-learning-based methods, has enhanced image quality [86-88].

In summary, the preparation for the CTU involves the patient consuming 1000 mL of water and refraining from urinating approximately 90 minutes before the procedure. During CTU, the patient is positioned in a supine posture, and the examination comprises four distinct phases: an unenhanced phase (UP), a corticomedullary phase (CMP), a nephrographic phase (NP), and an excretory phase (EP) [71, 89, 90] (Figure 9). However, other methods are utilized to acquire different CT phases. The capability of detecting UBC using CTU with CMP has been described as comparable with flexible cystoscopy. Therefore, its advocated to employ CTU as the initial examination to evaluate bladder in patients with macroscopic hematuria [91, 92].

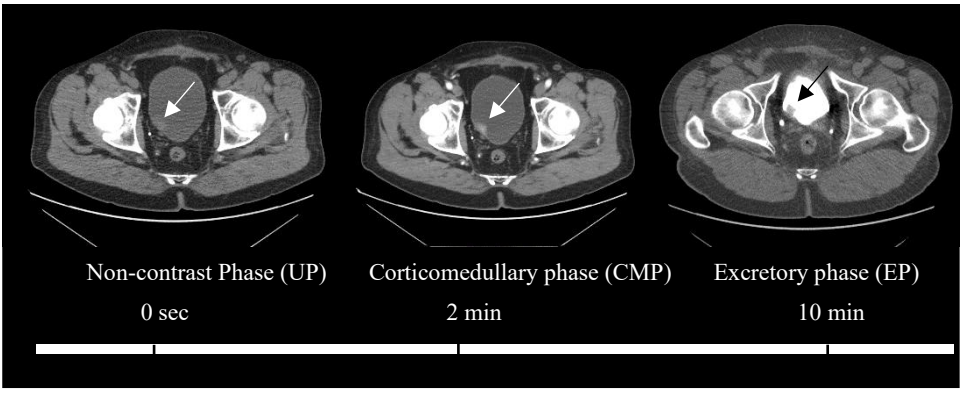


Figure 9. Different phases of CTU. (The arrow indicates a UBC lesion)

CTU with these phases has demonstrated a good specificity in identifying UBC, allowing individuals with positive results to proceed directly to TURBT without requiring a preceding cystoscopy [71]. Furthermore, CTU exhibits a good sensitivity in diagnosing UBC, particularly when using CMP (the phase with the most comprehensive diagnostic information in this regard) [91]. The diagnostic accuracy of CTU has a sensitivity of 96% and a negative predictive value (NPV) of 93%, with CMP as the phase with highest diagnostic accuracy, successfully identifying 93% of all UBC lesions [93]. However, it is important to highlight that this study [93] involved a relatively small number of patients with heterogenous population, included not only individuals with macroscopic hematuria, but also those with microscopic hematuria, flank/abdominal colic pain, and patients with previous urothelial cancers. Therefore, there is a need for additional studies to validate these findings, particularly for patients presenting primarily with macroscopic hematuria.

However, interpreting CTU results may have challenges and relies on expertise, resulting in varying sensitivity rates ranging from 59% to 92% [94]. Additionally, the process of interpreting CTU can be time-intensive, particularly when dealing with numerous CTU slices, and there is a possibility of overlooking significant pathology [95]. Finally, the financial burden on healthcare facilities with unnecessary cystoscopies and CTUs should not be underestimated [96]. Nevertheless, numerous

patients experiencing macroscopic hematuria or other urinary tract symptoms may have compromised kidney function, preventing the use of contrast medium due to the risk of acute renal insufficiency. In such cases, imaging of the urinary tract using ultrasound or magnetic resonance imaging (MRI) is used, but of limited value [97-99].

7.2. Transurethral resection of bladder tumor (TURBT)

TURBT is a common surgical procedure used in the diagnosing of lesions in the bladder and treating early-stage UBC. It involves the removal of abnormal or cancerous tissue while preserving the majority of the healthy parts of bladder, making it a treatment of choice for patients with NMIBC [21, 72]. Before the procedure, the patient is usually given general or spinal anesthesia and a resectoscope with a thin tube with a light and camera, is inserted through the urethra and into the bladder. Using specialized instruments passed through the cystoscope, the surgeon resects the abnormal tissue or tumor from the bladder lining. To enhance the quality of resection while adhering to the principles of cancer surgery, the concept of performing a one-piece resection, known as en bloc TURBT has been proposed as an option for selected tumors [100]. Resection in one piece allows for the retrieval of a higher-quality specimen, and potentially reduce the risk of disease recurrence and minimize the chance of tumor spillage [101].

After the tumor has been excised, the surgeon might cleanse the bladder with a sterile solution, such as normal saline. This procedure has shown enhancements when compared to the control group, specifically in terms of the reduced recurrence rate during follow-up and the extended period to the first recurrence [102]. Furthermore, adhering to EAU guidelines, it is recommended to administer a single dose of chemotherapy postoperative into the bladder. This is important for eliminating circulating tumor cells post-TURB, exerting a possible ablative effect on residual tumor cells at the resection site [58]. Various drugs like Mitomycin C, Epirubicin or Gemcitabine have been employed, resulting in varying outcomes [58, 103]. Administering continuous bladder irrigation with sterile water following TURBT could potentially be as effective as a single

dose of intravesical chemotherapy (Mitomycin C) in preventing of tumor recurrence [104].

7.3. Non-invasive urine-based cancer markers

Urine-based cancer markers for UBC play a vital role in the early detection, diagnosis, and surveillance of this disease, offering non-invasive and potentially earlier detection compared to traditional methods [81]. Numerous urine-based cancer markers have been developed to improve the detection of UBC, yet none of these tests are currently integrated into the established routine practices on a large scale [58]. Nevertheless, there are specific situations where diagnostic markers for UBC may have a potential utility including screening, particularly in high-risk groups, evaluating individuals with voiding symptoms, assessing those with hematuria, and monitoring patients with UBC or upper tract urothelial carcinoma (UTUC) [81, 105, 106].

Non-invasive urine-based cancer markers come with a set of benefits and drawbacks. Foremost, they may reduce the need for invasive procedures, such as tissue biopsies, making them more patient-friendly due to the ease of urine sample collection and the reduced risk of complications. Additionally, these tests can be conducted more frequently, allowing for ongoing monitoring of cancer progression and potential recurrences. However, there are limitations to consider. Many urine-based markers may not offer the same level of sensitivity or specificity as alternative tests like tissue biopsies. This can result in the risk of both false negatives, particularly in the case of early-stage cancer detection, and false positives, which may necessitate further unnecessary invasive procedures. Furthermore, the reliability of test results may be influenced by numerous factors, including the quality of the urine sample, the timing of collection, and individual variations. It's important to note that these tests are often tailored to specific types of cancer and may not be suitable for detecting other bladder pathologies, such as those detected through cystoscopy [107-114].

Urine-based cancer markers can be categorized into several subtypes with the most well-established examples highlighted within each subtype, as presented below:

1. Exfoliated cells-based, urine-based cancer markers: Exfoliated cells-based urine markers refer to substances detected in urine samples that are derived from cells that have naturally shed or exfoliated from the urinary tract as urine cytology, ImmunoCyt/uCyt+, and UroVysion.

Urine cytology: As a diagnostic procedure used to examine cells shed into the urine to detect abnormalities, urine cytology is a traditional method for diagnosing UBC. Urine cytology was initially introduced into practice in 1945 by Papanicolaou and Marshall and continues to be considered the gold standard among urine-based tests for detecting UBC, typically in conjunction with cystoscopy [11]. Urine cytology has low sensitivity of 0.37 (95% CI 0.35–0.39) and high specificity of 0.95 (95% CI 0.94–0.95) [115]. This test offers benefits due to its ease of use and high specificity. Furthermore, biochemical variations, hematuria, inflammation, and other variables that might otherwise lead to false positive results do not commonly influence urine cytology [116]. Nevertheless, urine cytology has drawbacks, including variable interpretations among cytopathologists [117]. Due to its relatively low sensitivity, especially for low-grade (LG) UBC tumors, urine cytology is generally not suitable as a stand-alone diagnostic or follow-up test for UBC [111, 118].

2. Protein Biomarkers: These are proteins that can be detected in the urine of patients with UBC such as NMP22.

NMP22 (Nuclear Matrix Protein 22): NMP22 is a protein located within the nucleus of human cells, whose elevated levels can be detected in the urine of individuals with UBC. When compared to urine cytology, NMP-22 has higher sensitivity (0.68 vs. 0.44) [119], however lower specificity 0.70 (95% CI: 0.55–0.81) [120].

3. mRNA biomarkers: mRNA markers refer to specific messenger RNA molecules that can be detected in the cells in urine related to UBC as CxBladder and GeneXpert BC.

GeneXpert BC: In October 2016, GeneXpert BC was introduced, employing reverse transcription polymerase chain reaction (RT-PCR) to investigate five markers that exhibit increased expression in the urine of patients with UBC [121]. These markers are ABL1, UPK1B, IGF2, CRH, and ANXA10. ABL1 (ABL Proto-oncogene 1) is employed as a reference to confirm the presence of human cells and human RNA in the urine sample [19]. The other targets are linked to specific aspects: IGF2 (Insulin-like growth factor 2) is associated with cell proliferation, CRH (Corticotropin-releasing hormone) is related to neuroendocrine stress response and inflammation, ANXA10 (Annexin 10) is involved in cell growth and signal transduction, and UPK1B (Uroplakin 1B) is associated with epigenetic dysregulation in UBC [106].

GeneXpert BC provides rapid results, typically within 90 minutes, making it advantageous for timely diagnosis and treatment planning [19]. GeneXpert BC is an automated testing platform, ensuring consistency and standardization of results across different laboratories [108, 109]. This reduces the likelihood of variability in testing outcomes and enhances the reliability of the diagnostic process. *Our multicenter nested case-control study (article V) is about this assay.*

4. MicroRNA biomarkers: MicroRNAs (miRNAs) are compact RNA molecules consisting of 20–22 nucleotides, regulating gene expression at the post-transcriptional level [122]. Altered miRNA profiles detected in urine might have a significant role in the onset and progress of diverse diseases, including UBC. The diagnostic accuracy of miRNAs has undergone extensive assessment, with emerging evidence showing promising results. However, the potential application and validity of miRNAs in UBC diagnosis remain to be determined [123].

5. Genetic/epigenetic detection markers. Molecular alterations specific to tumors, encompassing both genetic and epigenetic abnormalities, have been identified as pivotal factors in the development of UBC [124]. For instance, fibroblast growth factor 3 (FGFR3) mutations

have been identified as valuable markers for recurrence in NMIBC, with a sensitivity of 0.78 and specificity of 1.00 [125]. The combination of DNA hypermethylation with a positive FGFR3 mutation enhances the diagnostic accuracy for recurrence, when compared to using the FGFR3 mutation assay alone [126]. Another marker is Bladder EpiCheck (BE), which is a urine test that employs 15 unique DNA methylation biomarkers to detect UBC with a sensitivity of 0.68 and a specificity of 0.88 [127].

6. Metabolomic Biomarkers: These biomarkers entail the analysis of metabolites found in urine offering a window into metabolic alterations linked to cancer. Elevated levels of specific metabolites may serve as potential indicators of UBC [128].

7.4. Diagnostic delay

Despite the widespread recognition of macroscopic hematuria as a worrisome alarm sign, and evidence demonstrating the harmful effects of delayed UBC diagnosis and treatment, significant delays persist in the management of patients with UBC. While the median time from the initial occurrence of hematuria to surgical intervention averages about 70 days, it has been estimated that approximately two-thirds of patients experiencing macroscopic hematuria are affected by these delays. These delays can be attributed to factors associated with the healthcare system or/and factors associated with the patients themselves [129-131].

The total delay from the initial symptom to treatment in UBC patients is longest compared to other types of cancer [132]. These delays have been associated with decreased disease-specific survival (DSS) and overall survival (OS) [133]. Particularly as patients with MIBC, who receive a late diagnosis, become unsuitable for curative treatment, often due to delays in referral from primary care units [132-134]. In a large meta-analysis involving 17 532 patients which showed that a longer delay between UBC diagnosis and radical cystectomy (RC) results in a higher risk of overall death (hazard ratio (HR) 1.34, 95% CI 1.18–1.53). Although there might not be an absolute safe period of delay, evidence suggests that significantly worse prognosis is observed when patients experience delays to the definitive treatment longer than three months [135, 136].

The reasons behind delays are multifaceted and include a lack of general awareness about the seriousness of symptoms, scheduling issues for surgery, limited hospital resources, seeking multiple medical opinions, social factors, misdiagnosis, reluctance to treat, and patients' comorbidities [137-140]. Centralization of healthcare may have also contributed to delays, as patients may need to be transferred to centers better equipped to manage their care, which requires additional time for medical optimization. Additionally, residing in high-poverty neighborhoods or rural areas has been associated with increased delays in receiving RC [139, 141].

Looking at it from a healthcare standpoint, efficient management of patients experiencing macroscopic hematuria has shown to be linked with decreased costs and a decrease in the number of patient visits [142]. From the patient's standpoint, the benefits revolve around an enhanced chance of a cure and a diminished psychological toll resulting from diagnostic delays. Furthermore, when viewed from the disease perspective, it is established that delays in cancer diagnosis may have a negative impact on the prognosis [132].

Based on what is mentioned above, the delay in UBC patients may be divided into the following five categories (Figure 10):

1. **Patient delay**, from onset of complaints (macroscopic hematuria) to the first contact with general practitioner (GP).
2. **General practitioner (GP) delay**, from the first GP contact with the patient to the GP referral.
3. **Hospital delay**, from the GP referral to the first hospital visit.
4. **The diagnostic delay**, from the first hospital visit to TURBT.

5. **The treatment delay,** from TURBT to subsequent treatment steps which varies depending on the type of UBC. In the case of MIBC, this delay encompasses the time between TURBT and RC (preceded by NAC or not) or RT. For metastatic disease, the delay refers to the time to initiate oncological therapy. High grade NMIBC entails a delay to adjuvant therapy with BCG or Mitomycin. However, for patients with LG NMIBC, such delay is nonexistent.

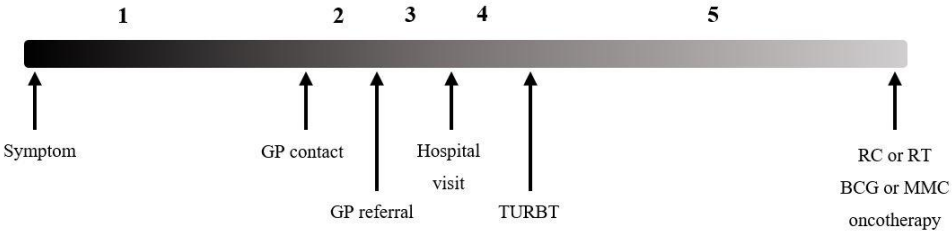


Figure 10. Different delays in the process of diagnosing and treatment of UBC patients

7.5. Standardized care pathway for UBC patients in Sweden

Alarmingly, a significant number of patients with hematuria do not receive appropriate and timely GP referrals for evaluation by urologists [143]. The referral rates for patients with macroscopic hematuria were found to be about 69-77%. The relatively low rates of referral for patients can be attributed, at least in part, to the fact that hematuria is a symptom commonly associated with other non-life-threatening urologic conditions, such as urinary tract infections (UTI), benign prostatic hyperplasia (BPH), urolithiasis and other benign urological conditions [117, 143, 144].

In Swedish healthcare, among various factors, the prevalence of extended waiting time and the inadequacy of timely cancer treatment led to the initiation of a nationwide healthcare initiative. From 2016, Sweden implemented a standardized care pathway (SCP) for patients suspected for UBC with primary objective to establish an organized and expertly managed system that minimized unnecessary delays in treatment, as well as by adhering to a consistent approach in accordance with national and

international guidelines [55]. This entails that every eligible patient presenting with suspicion of UBC in any unit of the health care system should be referred to a urologist within 24 hours. Suspicion of UBC could be radiological imaging or any symptom indicative of UBC. The lower age limit was changed from 40 to 50 years in 2018 due to the paucity of UBC cases below 50 years age [49, 142].

The diagnostic process includes CTU and cystoscopy, which should be completed within 7 days from the time of referral. Furthermore, TURBT should be performed within 13 days from the date of referral, serving both as a diagnostic and therapeutic procedure. Additionally, the recommended maximum time limits from the date of referral were as follows: 19 days for the pathological report of the TURBT specimen, 26 days for the Multidisciplinary Team Conference (MDTC) for patients with cT1-cT4 tumors, 37 days for RC if neoadjuvant chemotherapy (NAC) is not administered, 39 days for start of NAC if planned, and 43 days for radiotherapy (RT) [49, 55, 142].

7.6. Artificial intelligence and UBC

Artificial intelligence (AI) pertains to the computational capacity of machines to imitate and perform human cognitive functions, including reasoning, learning, and problem-solving [145, 146]. It is instigating a profound transformation in healthcare and decision-making for clinicians making it increasingly integral to the healthcare system [147]. In the realm of healthcare, there are several relevant subfields within AI, including Machine Learning (ML), Deep Learning (DL), and neural networks like Convolutional Neural Networks (CNNs). ML empowers computer systems to acquire knowledge, discern data patterns, and formulate adaptive algorithms to identify intricate patterns within datasets [148]. Among the neural network architectures, CNNs are prominently tailored for automatically learning spatial hierarchies of features [149]. The integration of AI technology into UBC diagnostics and prognostics holds the potential to enhance patients' quality of life by reducing unnecessary procedures [150, 151].

AI offers various applications in the care of UBC. Although cystoscopy remains the foremost diagnostic approach for individuals with suspected UBC, it is noteworthy that reported diagnostic errors range from 10% to 40% [80, 152]. Recently, a CNN-based model designed for automated UBC detection during cystoscopy has shown promising results achieving per-frame sensitivity and specificity values of 0.91 and 0.99, respectively [153]. In another study [154], a CNN model was utilized on a dataset of cystoscopic images, demonstrated successful UBC diagnosis with a sensitivity of 0.90 and specificity of 0.94.

Many research investigations have employed ML to identify genes with the capacity to forecast disease recurrence or progression. Additionally, some studies have focused on evaluating the efficacy of NAC and identifying patients who may not be responsive to this treatment, which enables the timely discontinuation of chemotherapy to avoid adverse effects [155]. While AI may have its potential in the context of UBC, particularly in the areas of diagnosis and treatment monitoring, there is currently a lack of an integrated AI system for interpreting CTU images within the context of primary evaluation of macroscopic hematuria.

8. Rationale and knowledge gaps

Several areas in the context of the UBC diagnosis process warrant further investigation. These include the need to delve deeper into early UBC detection in SCP context and its impact on patient outcomes. Additionally, there is a necessity to enhance the diagnostic capabilities of CTU for individuals with macroscopic hematuria and evaluate the implications of integrating AI technology into the interpretation process. The investigation of novel urine-based cancer markers for potential utilization as a triage test in patients with macroscopic hematuria also represents a key area for further exploration.

Early detection of UBC is important for timely treatment, because that early-stage UBC may be more manageable and associated with better outcomes [58]. In order to enhance the early detection of cancer, a range of strategies have been put into action including initiatives aimed at increasing public awareness regarding the significance of seeking medical care when experiencing alarm symptoms. Additionally, efforts have been made to educate GPs on the accurate evaluation of patients with macroscopic hematuria in accordance with guidelines [156]. Hence, in Sweden, SCP for individuals with suspected UBC was implemented in 2016 [91, 157, 158].

Reducing the time needed for diagnosis is important to ensure timely access to appropriate care. Therefore, there is a need to investigate whether the reduction in diagnostic delay under the SCP era has an impact on tumor characteristics, specifically whether it results in the identification of less aggressive tumors and a greater proportion of patients being treated in accordance with guidelines. Another challenge with SCP is its high resource demand, as both cystoscopy and CTU need to be completed within a limited time frame. While being effective, cystoscopy, the gold standard for diagnosis and follow-up of UBC, is an invasive procedure that may lead to patient discomfort and carries the risk of bleeding and infection in approximately 5% of cases [114, 159, 160].

CTU in turn plays a significant role in the early diagnosis and staging of UBC allowing for the visualization of tumors, assessment of

their size and location, and evaluation of potential invasion into surrounding tissues, lymph nodes and metastasis [91]. Nonetheless, CTU has drawbacks, e.g. exposes patients to radiation, elevating the risk of developing secondary cancers and contrast nephropathy [97, 161] and other drawbacks mentioned before. Therefore, there is a need to optimize this diagnosis process and develop a non-invasive test that can effectively identify patients for whom cystoscopy and/or CTU may be omitted. This approach would enable urologists to allocate resources efficiently by concentrating on patients who genuinely necessitate prompt examinations. Moreover, it would be possible to reduce the cost and shorten the time for diagnosis and treatment.

Going a step further would be to train an AI model to identify UBC automatically. AI algorithms have the potential to analyze CTU images with speed and precision, and hopefully reduction in the likelihood of false negatives or false positives. AI-driven interpretation of CTU images can aid in the identification of tumors at an earlier, more treatable stage, potentially improving survival rates. However, developing AI algorithms specifically tailored for UBC detection in CTU remains a challenge. Research is needed to refine and customize these algorithms to ensure their reliability.

There is still a necessity to delve into the advancement of the diagnostic process, specifically focusing on the utilization of non-invasive urine tests for UBC detection. Traditionally, urine cytology has been utilized as part of the diagnostic and follow-up procedures to examine the existence of malignant cells in urine, yet it displays a limited sensitivity and low NPV, despite its high specificity [11, 162]. Furthermore, the evaluation of urinary cytology can be complicated by the existence of minimal blood in the urine, chronic urinary tract infections, or bladder stones [114]. It is also a time-consuming procedure that is not often conducted on the same day as the clinical visit. Additionally, its assessment relies on the expertise of a skilled cytopathologist, introducing subjectivity, variations across laboratories, and interpretations dependent on pathological factors [105, 107]. Therefore, there is a necessity to identify other sensitive biomarkers for early, treatable UBC detection.

9. Thesis aims

The primary objective of this thesis is to investigate the impact of early UBC detection on tumor characteristics and the potential for utilizing CTU, AI interpretation of CTU, and a newly developed urine-based tumor marker to enhance the evaluation of patients with suspected UBC, particularly those with macroscopic hematuria. The thesis comprises three distinct subprojects, each with its unique aims, as outlined below:

9.1. Subproject I (The impact of SCP on diagnosis and management of UBC)

The objectives of this subproject were two-fold, focusing on both the national and local levels. On a national scale, our aim was to assess variations in time intervals related to diagnosis and treatment, tumor characteristics (including stage, grade, and size), and the treatment strategies used in UBC patients before and after the implementation of the SCP in Sweden. At the local level, our goal was to assess whether the implementation of the SCP within an institution where SCP was consistently employed led to any modifications in tumor characteristics, and if there were any shifts in the criteria employed to prioritize patients for immediate evaluation when there was suspicion of UBC.

9.2. Subproject II (The role of CTU and AI in diagnosis of UBC)

The goals of this subproject had a dual focus also. Firstly, it aimed to assess the diagnostic precision of CTU with specifically CMP, in excluding UBC and whether this could potentially eliminate the need for cystoscopy. The other objective was to evaluate whether AI-based automated image analysis could be employed to assess CTU images for the presence of UBC in patients experiencing macroscopic hematuria.

9.3. Subproject III (Urine-based cancer marker - GeneXpert BC)

The objective of this subproject was to evaluate the diagnostic accuracy of GeneXpert BC as a novel urine-based mRNA cancer marker as a triage test for individuals with macroscopic hematuria. This evaluation aimed to primarily rule out UBC, potentially reducing the need for additional investigations involving cystoscopy or CTU in the cohort of macroscopic hematuria.

10. Methodology

10.1. Patients, studies design, and data acquisition

10.1.1 The impact of SCP on diagnosis and management of UBC

In article I, a retrospective, observational, and register-based cohort study was conducted, utilizing national population-based data obtained from SNRUBC. This study included all patients in Sweden diagnosed with UBC between 2010 and 2019, categorizing them mainly into two periods (before and after SCP implementation). Patient and tumor characteristics, primary treatment, and OS were analyzed in relation to the time taken to perform TURBT. Various time intervals were examined.

Article II is retrospective observational study including all patients diagnosed with UBC in 2010-2019 at the NU-Hospital Group (serves a population of 310 000 inhabitants in the western region of Sweden). To assess the impact of SCP, UBC patients were divided into two diagnostic time periods: before (2010-2015) and during (2016-2019) SCP. Data were collected from medical records and analyzed, including patients', tumor characteristics and treatment related to the time periods before and after the implementation of SCP.

10.1.2. The role of CTU and AI in diagnosis of UBC

A retrospective diagnostic accuracy study (article III)was conducted including all individuals who underwent assessment for macroscopic hematuria with CTU and cystoscopy at NU-Hospital Group 2016-2019. The study cohort was divided into a study group and control group. The study group consisted of all patients with UBC, while a control group comprising 113 patients was randomly selected from the entire cohort who were negative for UBC. Two radiologists independently evaluated the CTUs, with blinding to all clinical information. The study assessed diagnostic accuracy of CTU regarding UBC and determined the proportion of potentially avoidable cystoscopies.

Article IV was an observational case-control study conducted in accordance with the CLAIM (Checklist for Artificial Intelligence in Medical Imaging) guidelines [163]. This study encompassed all individuals who had undergone an assessment for macroscopic hematuria within the NU-Hospital Group. A training cohort was established spanning from 2016 to 2019, while a validation cohort was formed covering the years 2020 to 2022. All CTUs were anonymized and transferred to a dedicated research database (Recomia.org). Detailed data on patient and tumor characteristics were recorded. To assess the performance of the AI model, sensitivity, specificity, NPV, and PPV metrics were calculated. The reference standard for comparison was the histopathological verification of findings obtained through cystoscopy or TURBT.

10.1.3. Urine-based cancer marker - GeneXpert BC

This study is a multicenter nested case-control diagnostic study, reporting according to CONSORT (Consolidated Standards of Reporting Trials) 2010 statement [164]. Moreover, the study protocol was registered in the ISRCTN registry (International Standard Randomised Controlled Trial Number) under the identifier ISRCTN17940603 before the study's commencement. We prospectively enrolled a series of patients undergoing assessment for macroscopic hematuria 2020-2022. Prior to cystoscopy, participants provided a voided urine sample and completed a symptom questionnaire. These patients were categorized into two arms: a case arm, comprising all patients with suspected UBC based on cystoscopic or radiological findings, and a control arm, primarily consisting of a random sample of patients whose evaluations did not reveal UBC/UTUC.

Within 30 minutes of urine collection, 4.5 ml was mixed with the GeneXpert BC preservative. The urine sample can be stored at room temperature and analyzed within 7 days. The assay determined the cycle threshold (ct) results of five mRNA targets, which were combined into a linear discriminant analysis (LDA) total score. A test was reported as positive when the total LDA score was ≥ 0.22. The study assessed the count of patients for whom cystoscopies and CTUs could be omitted.

Two thresholds were utilized. The primary threshold (LDA ≥ 0.22) was chosen based on a previous study [165] and unpublished results (Cepheid, personal communication, June 2020), indicating an estimated sensitivity between 0.90-0.95 and a specificity of approximately 0.50. This choice aimed to minimize false negatives while optimizing the potential reduction in unnecessary cystoscopies and CTUs. Subsequently, a secondary threshold was retrospectively calculated as the highest LDA ensuring 100% sensitivity for any high-grade UBC (cTaG3, Tis, T1+).

10.2. Statistical considerations

In each article, we employed diverse statistical methods, tailored to the specific research questions and datasets at hand. Continuous variables were characterized using different measures in different studies. In article I, the median and inter-decile range (IDR) were used to reduce the impact of outliers, while in other studies, we utilized the median and interquartile interval (IQR), or mean and standard deviation (SD) were deemed suitable. Inter-rater variability in the interpretation of CTUs in article III was assessed using Cohen's kappa, a statistic for measuring the level of agreement between two observers categorizing items, with a value above 0.80 indicating good agreement.

In articles III, IV, and V, we conducted a power calculation to determine the appropriate sample size. This approach offers several advantages as helping to establish the minimum sample size necessary to detect a meaningful effect ensuring that resources (time, money, and effort) were used efficiently. Moreover, power calculations prevent researchers from collecting a sample that is excessively large reducing the risk of Type I errors (false positives). A large sample could lead to statistically significant results even for non-meaningful effects. Furthermore, by specifying the minimum effect size of interest, power calculations increase the study's likelihood of detecting a genuine effect, if it exists which minimize the risk of Type II errors (false negatives) that may occur due to a small sample size.

To assess differences between groups and subgroups, we employed various statistical tests depending on the nature of the data and the research

question being addressed. The Chi-squared (Chi2) test was utilized to determine if there is a significant association between two categorical data. The Wilcoxon signed-rank test, a non-parametric statistical hypothesis test, was used to compare the means of two related groups and examine the distributions of these groups. The Mann-Whitney U test, another non-parametric statistical test, was employed to compare the distributions of two independent groups, particularly in data of ordinal or continuous scale.

Kaplan-Meier curve, a statistical method used for estimating the survival probability of a group of individuals over time to analyze and visualize time-to-event data to assess OS concerning other variables (I). Additionally, sensitivity, specificity, NPV, and PPV metrics were calculated when deemed necessary and appropriate. In article V, symptom questionnaires were used to identify additional factors that could influence the outcome, with the goal of improving the sensitivity and specificity of the assay (GeneXpert BC).

Logistic regression analysis was utilized in article II to predict the likelihood of an event happening, specifically to decide which patients were given priority for evaluation within 13 days, encompassing all patients before and during SCP. Receiver operating characteristic (ROC) analysis was conducted in articles III, IV, and V, and the area under the curve (AUC) was also calculated. ROC analysis served to evaluate the diagnostic accuracy of a test (CTU or GeneXpert BC) or a model (AI-based image analysis) assessing the ability of a modality to distinguish between two categories, typically cancer-positive and cancer-negative cases. P-values<0.05 were considered statistically significant in all studies. Statistical analyses were performed using SPSS versions 27, 28 and 29 (IBM Corp., Armonk, NY, USA).

10.3. Ethical reflections and approvals

Each of the research subprojects adhered to the principles outlined in the Declaration of Helsinki. The project involved the utilization of sensitive patient information from various datasets, which, when amalgamated, could potentially compromise privacy by revealing personally identifiable information. Such an occurrence could result in a

breach of patient confidentiality and privacy. It is important to note, however, that all the data underwent pseudonymization through the assignment of a unique study code and can solely be accessed by the authorized researchers. Furthermore, for retrospective articles, the Swedish Ethical Review Authority granted a waiver for informed consents, as reviewing patients' medical records would not impact the care they had already received.

The implementation of AI in healthcare and using cancer markers in comparison to traditional diagnostic methods gives rise to some ethical issues, encompassing patient confidentiality, data protection, and the transparency of AI decision-making. For a moment, let us consider a hypothetical scenario where the issues linked to the generalizability and interpretability of AI models have been effectively resolved, and clinical trials have substantiated the effectiveness and safety of these models. Under these assumptions, there would be an inevitable surge in the detection of subtle cases of cancer, such as small tumors that seldom manifest symptoms or metastasize during a patient's lifetime. This widely recognized phenomenon, often termed over-diagnosis, can lead to substantial physical and psychological consequences, like the adverse effects of unnecessary treatment, and cancer-related anxiety among patients. Hence, as AI models begin to find their way into healthcare, it is of utmost importance for physicians to actively engage in their development to ensure that their use aligns with the fundamental medical principle of *primum non nocere,* “first, do no harm.”.

Similarly, and in the context of using cancer markers in comparison to traditional diagnostic methods, some ethical concerns arise. When cancer markers are employed, there is a possibility of detecting extremely small or slowly developing tumors that may never pose a threat to a patient's well-being throughout their lifetime causing overdiagnosis and overtreatment, subjecting patients to unnecessary procedures, treatments, and the associated risks. Additionally, cancer markers may occasionally produce false-positive results resulting in unwarranted stress, anxiety, and the need for further testing or treatment, causing psychological distress for patients.

In article V, prior informed consent was obtained from participants. The patient's participation is entirely voluntary, and they had the option to withdraw at any time without needing to provide a reason, with no consequences for their future care or treatment. Moreover, they were informed that they could request the deletion of their information or restrict the processing of their personal data. Participants were also informed that the project would collect and record information about them, storing examination results in a coded database to ensure unauthorized access is prevented. In accordance with the EU General Data Protection Regulation (GDPR), patients have the right to access their information managed in the study, and this service is provided free of charge. In CTU studies (III, IV), there were no additional radiation risks for the participants since patients had already undergone imaging as part of the routine examination for macroscopic hematuria and no extra imaging was conducted. Thesis articles were approved by the Swedish Ethical Review Authority as followed:

Approval (No. 2020-02397) for articles I and II.

Approval (No. 2020-01127) for article III.

Approval (No.2020-01127) for article IV with an approved amendment (No. 2022-05590-02) for adding more participants.

Approval (No. 2019-05582) for article V with an approved amendment (2021-01786) for adding more participating centers and the written informed consent was obtained from all patients included in this study.

11. Results and comments

11.1. The impact of SCP for diagnosis and management of UBC

In Article I, at a national basis (with a population of 10 million inhabitants), out of a total of 26 795 included patients, the median time from referral to TURBT decreased from 37 days to 27 days ($p<0.001$) following the implementation of the SCP. There was a slight decrease in the proportion of patients with cT2-T4 tumors (from 22% to 21%, $p=0.01$), but this change was not consistent over time (Figure 11). In the subgroup of patients with cT1+ tumors, there was an increase in the percentage of patients discussed at the MDTC after the SCP implementation. However, for patients with cT2-4, no significant differences were observed in terms of curative treatment (RC or RT, 48% vs 49%, $p=0.25$) or the use of NAC (14% in both time periods, $p=0.25$) between before and after SCP.

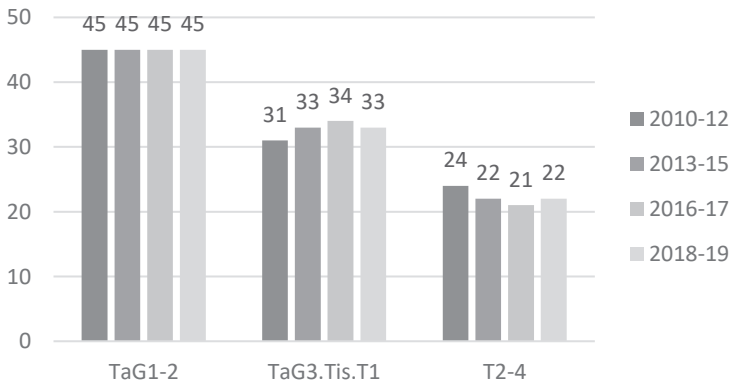
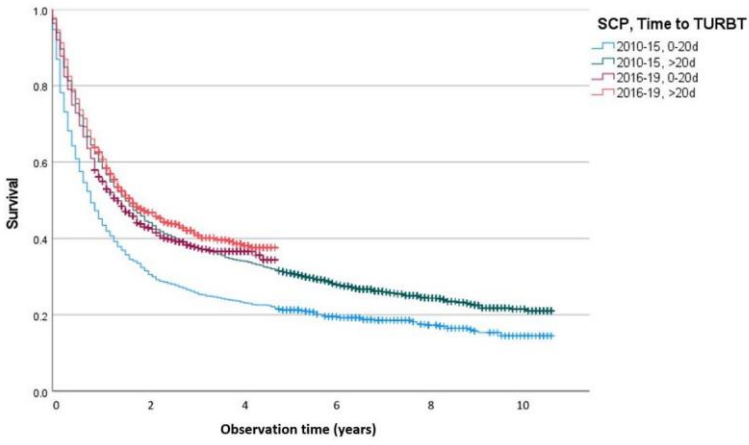


Figure 11. TNM distribution of patients with UBC over time 2010-2019 in Sweden

After SCP, patients who underwent TURBT within 20 days and had cT1+ tumors were generally younger and were more likely to receive treatment following established guidelines. Conversely, no such differences were observed in the group where the time to TURBT exceeded 20 days. Among patients with cT2-4 tumors who underwent TURBT within 20 days, Kaplan-Meier analysis demonstrated improved OS after the SCP implementation (difference between the groups within 20 days before and after SCP - Log rank Chi2 35.55, $p<0.001$). However,

this improvement was not observed in the group where TURBT occurred after 20 days (difference between the groups >20 days before and after SCP - Log rank Chi2 4.02, p=0.045) (Figure 12).



Patients at risk						
2010-15, 0-20 days	934	302	221	148	80	26
2010-15, >20 days	2240	1027	772	516	246	74
2016-19, 0-20 days	790	259	69			
2016-19, >20 days	1364	439	100			

Figure 12. Kaplan-Meier curves for patients with stage cT2-4 (n=5872) in Sweden

In Article II regarding patients at the NU Hospital Group, the median time from referral to TURBT decreased from 29 to 12 days after implementation of SCP (p<0.001). This noticeable change began in 2016 (when implementation of SCP was occurred). Additionally, there was a reduction in the proportion of cT2-4 tumors after implementation of SCP, dropping from 26% to 20% (p=0.035) (Figure 13). Furthermore, tumors identified after implementation of SCP tended to be smaller in size (p=0.023).

After implementation of SCP in NU Hospital group, there were no statistically significant distinctions between the groups of patients who underwent TURBT within 13 days and those who had TURBT after 13 days. In contrast, before the implementation of the SCP, the majority of patients treated within 13 days had advanced tumors and were typically admitted from the emergency department.

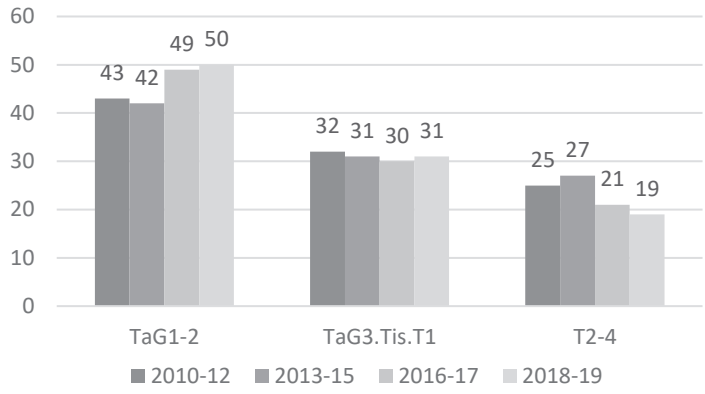


Figure 13. TNM distribution of patients with UBC 2010–2019 in NU Hospital Group

The logistic regression analysis of patients diagnosed during SCP found no statistically significant factors differentiating between groups undergoing TURBT within or after 13 days, except for emergency admission, which emerged as a statistically significant independent predictor ($p<0.001$) (Table 1).

Variable name	Before SCP, 2010-2015		During SCP, 2016-2019	
	HR Multivariate (95 %CI)	p-value	HR Multivariate (95 %CI)	p-value
Admission modality	1		1	
Emergency	0.04 (0.02-0.10)	<0.001	0.52 (0.23-1.14)	0.102
Age groups	1		1	
≥ 75 years	1.81 (0.90-3.63)	0.097	1.49 (0.92-2.40)	0.103
Tumor size	1		1	
> 30 mm	0.75 (0.34-1.63)	0.464	0.88 (0.47-1.45)	0.507
Number of tumors, single	1		1	
Multiple	0.85 (0.41-1.70)	0.621	1.21 (0.75-1.97)	0.439
TNM				
cTaG1-2	1		1	
cTaG3, Tis, T1	1.64 (0.70-3.86)	0.254	0.74 (0.43-1.30)	0.291
cT2-4	1.01 (0.40-2.52)	0.985	1.11 (0.54-2.27)	0.744

Table 1. Logistic regression analyses before and after the implementation of SCP in the patients from NU Hospital Group using the dichotomized time to TURBT (≤13 days or >13 days) as the dependent variable

11.2. The role of improved CTU and AI in diagnosis of UBC

In Article III, the study involved a cohort of 2 195 patients, with a final evaluation conducted on 297 of them (207 in the UBC group and ninety in the control group). A high-quality CTU image is distinguished by adequate bladder filling, the absence of nonspecific bladder wall thickening, the lack of an indwelling catheter, the absence of bladder stones, and minimal image distortions. Limited-quality CTU image is characterized by the occurrence of one or more of the aforementioned factors. The re-evaluation of CTUs resulted in the classification of 174 patients as positive (POS: indicating the presence of UBC – regardless quality of CTU), forty-six patients as indeterminate, (IND: no UBC in CTU with limited image quality). Lastly, seventy-seven patients were classified as negative (NEG: no UBC in CTU with high images quality) (Figure 14).

Out of the fifteen patients with negative CTUs, only three individuals (constituting 1.4% of all tumors) presented with high-risk UBC, specifically two with cT1 tumors and one with cT2. Upon closer examination, it became evident that in two of these cases, a discernible thickening of the bladder wall in the tumor location was observable. In the solitary case with cT2, the initial radiological report accurately identified the presence of UBC.

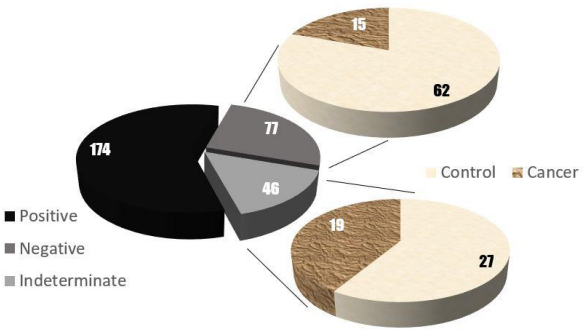


Figure 14. Results of re-evaluation of CTUs

The inter-rater reliability among the assessors was notably strong, with a measurement of κ 0.84. The study revealed a false negative rate of 0.07 (95% CI 0.04-0.12) and NPV of 0.99 (95% CI 0.92-1.0). The AUC was determined to be 0.93 (95% CI 0.90-0.96) (Figure 15). Notably, only 2.9% (3 out of 102) of patients with HG UBC experienced false negative CTU results. This suggests that cystoscopy could have potentially been avoided in 57% of cases. As a result, we have to perform 357 cystoscopies to identify one patient with false-negative CTU in the HG UBC group.

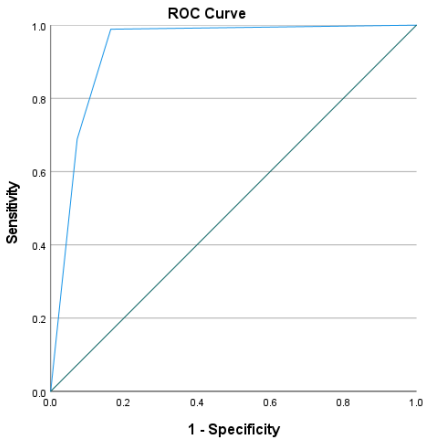


Figure 15. Receiver operating characteristic (ROC) for CTU in detecting UBC

In Article IV, the initial training cohort to develop our AI model comprised a total of 530 subjects (2016-2019). Following an optimization process, we applied our AI model to the validation cohort comprising a new set of four hundred subjects (2020-2021). After applying exclusion criteria in the validation cohort, a total of 248 eligible subjects were retained (UBC group=142 (57%) and a control group=106 (43%), all of whom had undergone assessable CTU before cystoscopy. The AI model performance resulted in a sensitivity of 0.83 (95% CI 0.76-0.89), specificity of 0.76 (95% CI 0.67-0.84), and NPV of 0.97 (95% CI 0.95-0.98). Among the patients in the false-negative group (n=24), the majority had solitary and small tumors with cTaG1-2 in 71% of cases (Table 2).

Variable		Patients
TNM and grade	cTaG1-2	17 (71)
	cTaG3, Tis, T1	5 (21)
	cT2-4	2 (8)
	N+	0
	M1	0
Number of tumors	Solitary	16 (67)
Size of tumor	≤ 10 mm	12 (50)

Table 2. Characteristics of patients with histopathologically proven UBC and false negative results in AI image analysis (n=24)

11.3. Urine-based cancer marker - GeneXpert BC

In Article V, the study involved 1 505 individuals who presented with macroscopic hematuria between September 2020 and December 2022 at the three participating centers. Following exclusion criteria, the final analysis included 273 subjects, divided into a case group (n=151, all had UBC), and a control group (n=122, all did not have UBC) (Figure 16). Using the predefined threshold of LDA ≥ 0.22, the sensitivity was 0.94 (95% CI 0.89-0.97), and NPV was 0.99 (95% CI 0.98-1.00). For cases of high-grade disease, the sensitivity was 1.0 (95% CI 0.94-1.00).

Among all UBC and UTUC cases, a small fraction (6% of all UBCs, n=9) exhibited false-negative results with the GeneXpert BC assay, and these cases were exclusively associated with LG UBC (cTaG1-2). These patients had solitary (78%) and small (median of 7.5 mm) tumors. The percentage of patients with negative test results using the primary threshold (LDA≥ 0.22) was 44% of the final cohort, eliminating the need for further investigation with cystoscopy or CTU. For those with a false-negative GeneXpert BC assay, seventy-one cystoscopies are required to identify one patient with a TaG1-2 tumor.

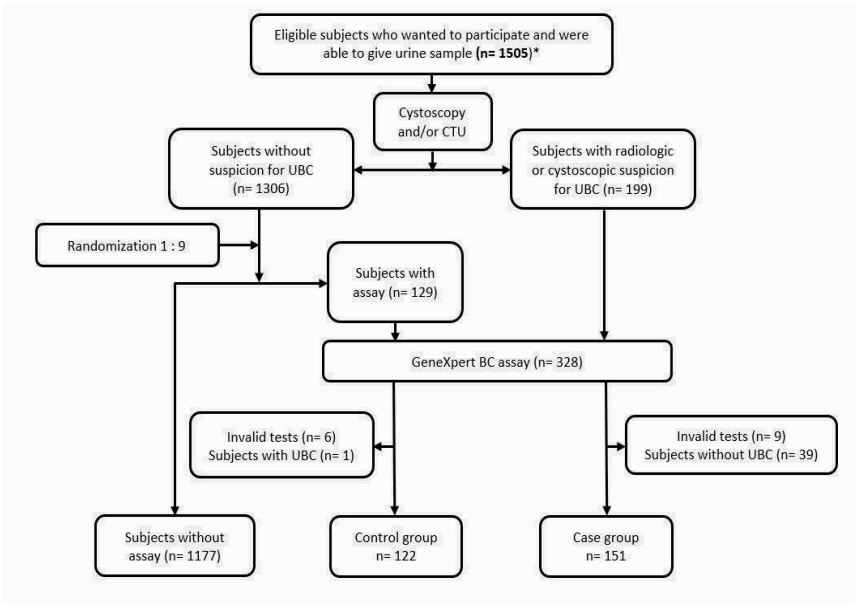


Figure 16. Flow diagram showing inclusion of patients in the study of GeneXpert BC

The GeneXpert BC test achieved the highest sensitivity, not missing any cases of HG UBC, with an LDA score of ≥ 0.33. In this scenario, the sensitivity was 0.88 (95% CI 0.82-0.93), with an NPV of 0.98 (95% CI 0.97-0.99). The proportion of patients with a negative test result using the secondary threshold (LDA ≥ 0.33) after generalizing the control group to the entire control arm and considering invalid results was 63%. Our research introduced a novel diagnostic approach (chapter 15) that tries to integrate GeneXpert BC as a triage test in routine practice for ruling out UBC/UTUC in patients with macroscopic hematuria.

12. General Discussion

12.1. The impact of SCP on diagnosis and management of UBC

In our first studies (I and II), we found a reduced time from referral to TURBT after the implementation of SCP. However, despite this enhancement, time from referral to TURBT did not attain the recommended guideline levels, and there was a noticeable trend of time reduction even before the implementation of the SCP. Theoretically, a delay in conducting a TURBT could potentially permit the UBC to advance, becoming more invasive or spreading to other areas of the body, which is associated with poorer outcome [133]. More advanced stages of the disease often require more aggressive treatments, such as RC, chemotherapy, or RT, which are associated with greater side effects [133].

Generally, the delay in the diagnosis and treatment of UBC can be broken down into several distinct parts, each with its own contributing factors. This division is based on insights from the medical literature and a consideration of what is clinically relevant [166]. Here, we will discuss the supposed different delays involved in UBC:

1. Patient Delay (symptom to first GP visit).

This represents the time it takes for a patient to seek medical care after experiencing symptoms suggestive of UBC (macroscopic hematuria). Patient delay can vary greatly depending on factors such as awareness of symptoms, fear of diagnosis, individual health-seeking behavior, and socioeconomic and demographic factors, such as low income and minority status [132-134, 167]. The reduction of patient delay often involves public awareness campaigns and education regarding the significance of promptly seeking medical evaluation for symptoms related to UBC. In study II, the observed improvement in clinical stage during the SCP may not solely be attributed to post-referral management. The time from symptoms to GP visit, given the noticed increased attention surrounding the SCP's introduction, could also be a significant factor. Unfortunately, our studies lacked data in this regard.

2. GP Delay (the first contact with GP to GP referral).

After a patient's initial visit to their GP, there may be a delay in the GP's recognition of potential UBC symptoms and in referring the patient for further urological diagnostic tests. In a Canadian study 2015, median overall referral delay was 30 days (in women, 56 days, and in men 23 days, $p < 0.0001$) [168]. GP delay can arise from a variety of factors, such as competing medical priorities, limited access to diagnostic resources, or misinterpreting an alarming symptom like macroscopic hematuria as a secondary indicator for BPH or UTI. Communication barriers between patients and GPs also contribute to this delay. Patients may not fully express their symptoms or concerns during the initial consultation, either due to fear, embarrassment, or a lack of awareness regarding the severity of their symptoms. Another key factor may be the limited time available for GP consultations.

To mitigate this delay, initiatives such as awareness campaigns for healthcare providers, and the general public can be implemented. Additionally, it is important to enhance GPs training and provide support in promptly addressing UBC symptoms [156]. Optimizing the referral pathway from primary care units to urological units is another factor that needs attention to streamline this process.

3. Hospital Delay (GP Referral to cystoscopy).

Once a patient has been referred to a specialized medical facility, there may be a delay in securing an appointment or admission for further evaluation. Hospital delay can be influenced by factors such as scheduling availability, resource constraints, and the complexity of the healthcare system. Streamlining the referral process and ensuring timely access to hospital services is crucial to reducing this delay. The delay between symptom and referral (combining delays 1 and 2) might have a more substantial impact on prognosis than the time from referral to TURBT (delays 3 and 4) [166]. However, in the Swedish SCP, patients are expected to be referred within 24 hours from primary care units to a urological unit and being investigated with cystoscopy within one week.

4. Diagnostic Delay (cystoscopy to TURBT).

This phase represents the time it takes from the first hospital visit to diagnosis, namely, the actual diagnostic procedure (TURBT). Diagnostic delay can occur due to several factors, including the need for extensive pre-operative assessments, waiting for specialized equipment, and administrative factors. Efficient scheduling, appropriate use of diagnostic tests, and effective communication between healthcare providers can help minimize diagnostic delay.

Some studies have consolidated these four types of delay, and the median duration from the onset of symptoms to TURBT has been documented as falling within the range of 70 to 110 days [129, 166]. As our study focused on delays 3 and 4, we have limited information regarding delays 1 and 2. However, it is worth noting that time from referral to TURBT in Sweden was not as long as mentioned in literature, before SCP (37 days nationally, 29 days in NU Hospital Group) compared to after SCP (27 and 12 days respectively). For patients with LG NMIBC this is the last delay they might be affected by.

5. Treatment Delay (TURBT to RC, RT, definitive oncotherapy, or BCG/MMC).

For patients with NMIBC and intermediate or high risk for progression, a treatment delay is the delay between TURBT and administration of BCG or MMC. Delayed administration may compromise the therapy's efficacy as the optimal window for immune activation may be missed. A delay may allow residual cancer cells to persist or proliferate, increasing the risk of tumor recurrence. Moreover, delayed BCG therapy may contribute to the progression of the disease to a more advanced, muscle-invasive stage, posing a greater challenge in terms of treatment and prognosis.

For patients with MIBC, there may be a delay in initiating definitive treatment, such as NAC and/or RC, RT or other oncotherapies for MIBC or metastasized disease. This time of surgical delay has been previously examined, revealing that a delay exceeding 3 months in patients

with MIBC can adversely affect survival [169]. Treatment delay can arise due to various factors, including the necessity for additional diagnostic tests, treatment planning, the need to transfer patients to better-equipped hospitals, surgical scheduling, and patient-related factors. Notably, patients with MIBC who underwent care transitions were at a higher risk of experiencing treatment delays of three months or more [170]. To mitigate such delays, an effective coordination between specialists and patients, along with optimized treatment protocols, is required.

These latter three delays (3, 4 and 5) were consolidated into what is referred to as "System delay", which constitutes an important portion of the overall delay experienced by UBC patients [132]. In our studies, data on delays 1 and 2 were not available, but delays (3, 4, and 5) were investigated separately, with data for different periods (Figure 17). The time from referral to treatment (delay 4 and 5) before the implementation of SCP differs between the national and local levels, but this time is almost the same after implementation of SCP.

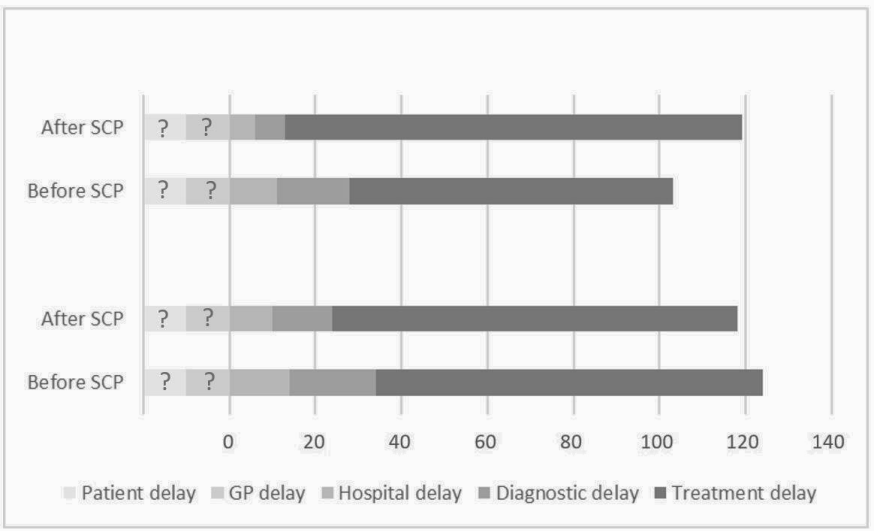


Figure 17. Different delays (in days) in UBC diagnosis and treatment process for patients in Sweden (below) and NU Hospital Group (above). The mentioned treatment delay is only referred to the time between TURBT and radical cystectomy, regardless of NAC

Interestingly, while hospital delay (3) and diagnostic delay (4) became shorter after SCP in the NU Hospital Group, the time to definitive treatment (5) is longer, resulting in the actual system delay (combined 3, 4, and 5) being slightly longer after SCP compared to before. Understanding the reasons for this complexity is challenging, as it involves factors such as the requirement for supplementary diagnostic tests, more usage of NAC after SCP, the necessity to transfer patients to university hospitals following centralized care plan, and various patient-related factors. A collaborative effort involving healthcare providers, patients, and the healthcare system is important in minimizing all UBC delays and ensuring that patients with UBC receive timely and effective care.

It's important to highlight that a shorter duration from referral to TURBT does not necessarily translate into a shorter timeframe for definitive treatment, such as RC [49, 171]. This underscores the significance of considering the entire process from symptom onset to definitive treatment. Our findings, aligned with the results of Nilbert et al. and Blick et al. [49, 171], who emphasized the importance of taking the entire process from symptom to definitive treatment into account. This indicates that the enhancement of the management of patients with alarm symptoms is a multifaceted and complex undertaking, as reflected in the outcomes post-SCP showing a shorter time to TURBT but not to subsequent treatment [49, 135, 166, 171]. Nevertheless, from a patient's viewpoint, receiving timely information about a potential benign or malign cause of macroscopic hematuria is also significant.

In Article I, we did not observe a consistent shift in the distribution of TNM stages nationally over time. In contrast, in Article II, we documented a reduction in the percentage of cT2-4 tumors, decreasing from 26% to 20%. Concurrently, there was an increase in the proportion of cTaG1-2 tumors, increasing from 42% to 49%. Furthermore, we identified a decline in the percentage of larger tumors (>3 cm), decreasing from 41% to 33%. In essence, these findings indicate more favorable tumor characteristics during SCP. These variations in results between our national (I) and local (II) studies may likely be attributed to a higher adherence to SCP guidelines at the NU-Hospital group, resulting in more favorable results. Nevertheless, this result should be approached with

caution as a pure register study and a more classical retrospective study at our institution might give different result.

The process of selecting patients with advanced UBC for earlier investigation generally follows a clinical decision-making approach encompassing several mechanisms. Patients exhibiting serious symptoms such as macroscopic hematuria, or other signs of advanced UBC, having a history of smoking, occupational exposure to carcinogens, may prompt early investigation. However, we observed that patients with cT1+ tumors who underwent TURBT within 20 days had a higher proportion of cN+ disease before SCP. This suggested a selection of patients with advanced tumors for early TURBT before SCP, aligning with the findings of Wallace et al [166]. Such selection disappeared after the implementation of SCP, as all patients with macroscopic hematuria were required to undergo the same investigation pathway. The question of whether the even distribution after SCP is advantageous for patients or if prioritizing those with advanced tumors and curable disease would be more beneficial is a matter for discussion. However, considering the prompt prioritization of patients with advanced UBC for a specific pathway within SCP is a worthwhile consideration for modifying this approach.

Before the implementation of SCP (II), more than half of the patients treated within 13 days were emergency cases. These patients may have presented with more advanced tumors, which could account for the higher percentage of larger and cT2-4 tumors in the group treated within 13 days compared to those treated after 13 days. Notably, this observation is supported by the fact that only 32% of patients with cT2-4 tumors before SCP and within 13 days underwent cystectomy, in contrast to 56% during SCP. However, similar disparities related to emergency admissions were not observed during SCP. During SCP, a higher percentage of cT2-4 patients underwent cystectomy in the group that had TURBT within 13 days compared to those who had the procedure after 13 days (56% versus 35%). Similar trends were observed for the cT1 group treated with SLR and intravesical instillation therapy (IVIT). These observations appear to suggest a certain level of prioritization for further treatment after SCP, although a more systematic prioritization of groups of patients might optimize management.

We did not observe any disparity in tumor aggressiveness between the groups who underwent TURBT within or after 13 days. While emergency admission was the sole statistically significant independent predictor for patients undergoing TURBT within 13 days, logistic regression analysis revealed no differences when comparing age, tumor size, number, and stage between patients before and during SCP. Based on these observations, it is reasonable that, rather than imposing a strict time constraint for all UBC patients, prioritizing timely definitive treatment is particularly critical for patients with advanced tumors beyond TaG1-2. This necessitates a significant and careful modification of SCP selection process for the management of this specific subgroup [166, 171].

Kaplan-Meier curves indicated differences in survival before and after SCP, especially in groups with a shorter time to TURBT. These differences reflect variations in patient and tumor characteristics, as well as management decisions, which may be influenced by numerous factors beyond the implementation of SCP. Due to potential selection bias and disparities in observation periods between groups before and after SCP, conducting detailed statistical methods based on overall survival, such as Cox analysis, did not appear to yield meaningful results.

Various countries have different approaches regarding the investigation of patients with asymptomatic microscopic hematuria ranging from no investigation to full investigation plans to detect malignancies. However, in Sweden, patients with asymptomatic microscopic hematuria are not subjected to any investigation, due to the low diagnostic yield, which stands at 1.85% [55, 77, 172]. Consequently, the current Swedish SCP focuses solely on investigating patients with macroscopic hematuria, and individuals younger than 50 years undergo evaluation outside the SCP. Such strategy poses a risk of diminishing public awareness [173, 174], and may need further public information.

Our findings were subjected to criticism from other colleagues [175] who argued that "the reduction from 37 to 27 days to UBC resection is of marginal clinical significance". It has been shown that diagnostic delays exceeding two weeks have been associated with a slightly worsened overall survival for UBC patients in other studies (HR 1.19 (1.0-1.4))

[166], suggesting that reducing the median time from referral to TURBT by around ten days might be advantageous.

12.2. The role of improved CTU and AI in diagnosis of UBC

In cases of macroscopic hematuria, the standard approach conducted in Sweden after SCP involves a combination of CTU and cystoscopy. We found (III) that CTU exhibited a high sensitivity (0.93), potentially obviating the need for cystoscopy in a majority of patients presenting with macroscopic hematuria. This was consistent with the findings by Helenius et al., [91] where sensitivity and specificity were reported as 0.87 and 0.99, respectively. It is noteworthy that Helenius et al. study, although yielding high accuracy, included a relatively small number of UBCs (55) compared to our study (207). In another study [92] involving 395 consecutive patients with macroscopic hematuria, CTU missed no MIBC. In our research, among 207 patients, only fifteen (7%) had tumors overlooked by a negative CTU with high image quality, which revealed no additional bladder abnormalities. Among these fifteen patients, only three had HG UBC, representing 1.4% of all patients with UBC. The high inter-observer agreement in our study adds credibility to these results, indicative of the findings' relevance in a clinical setting.

This implies that CTU might be applicable for assessing UBC, not limited to UTUC, and that, given a high-quality CTU, cystoscopy might be dispensable in the initial evaluation of macroscopic hematuria in 57% of all patients. Such a shift could have several benefits, including a reduction in diagnosis delay for UBC patients, the avoidance of patient discomfort and potential complications in non-cancer cases, and a potential decrease in healthcare costs [176]. However, individuals with a negative CTU and persistent macroscopic hematuria may still require cystoscopy. The extent of these missed tumors and the impact of such a diagnostic approach will necessitate further larger studies.

This estimate (57%), however, is conservative, considering that it accounts for the 21% of patients who did not undergo CTU as per the protocol. The protocol itself may be improved by emphasizing of the

importance of bladder examination. Furthermore, the 22% of inconclusive CTUs could potentially see improvement with greater proficiency in conducting and interpreting these CTU examinations, along with potential adjustments to the CTU protocol, especially emphasizing proper urinary bladder filling before the examination.

There are various suggestions for optimizing CTU. One approach could involve better patient mobilization before contrast injection, which might yield a more uniform contrast mixture in the bladder, making contrast defects easier to detect. Increasing diuresis using medications like furosemide to improve bladder filling might also enhance CTU quality. It may be worthwhile to consider whether the use of a higher radiation dose in CMP could have detected some of the smaller tumors, especially while balancing radiation exposure. These optimizations could contribute to the refinement of CTU as an effective diagnostic tool in UBC detection.

AI has gained a place in diagnostics and monitoring of treatment of UBC. Many studies showed that AI may be used to improve cystoscopic diagnosis of UBC using cystoscopic pictures [154, 177, 178]. Our findings align with those of Ikeda et al. [154] who trained a CNN based AI model using 2102 cystoscopic pictures and achieved sensitivity of 0.90 underscoring the promising role of AI in improving the diagnostic accuracy of UBC. While other studies focused on identifying response of UBC to NAC by AI based CT-based decision-support system [179], or assessment of UBC stage by a CNN model [180], no such studies were conducted in the context of AI based assessment of CTU in order to primarily detect UBC. This was even confirmed by a review of Borhani et al. [88] about AI usage in UBC detection and outcome prediction, revealed a scarcity of studies focused on assessing of AI usage within the realm of CTU for UBC detection purposes.

We (IV) developed a novel model of AI based automatic image analysis using CNN for the detection of UBC in patients with macroscopic hematuria. For all patients conducted in the study, we had a sensitivity of 0.83 (95% CI, 0.76-0.89) and a high NPV of 0.97 (95% CI 0.95-0.98) indicating that this AI model is reliable in identifying patients with UBC in CTU. In particular subgroups, such as female subjects or patients with

HG UBC, our model achieved higher NPV of 0.99. In the future, this could enable the development of distinct assessment algorithms tailored to specific subject subgroups by categorizing CTU scans accordingly. Nevertheless, the lower specificity, standing at 0.76, implies that there will be a number of patients receiving false positive results, necessitating further examination with cystoscopy. This represents an advancement of the findings reported by Gordon et al. [181] who developed a computerized segmentation tool for both the inner and outer bladder walls as part of an image analysis for CTU. While they had shown that the DL-CNN-assisted tool is accurate in segmentation of both the inner and outer bladder walls, we could identify urinary bladder and detect UBC in about 83% of UBC cases.

Generally, the accuracy of AI models was validated by a large meta-analysis that demonstrated a diagnostic accuracy of AI to be equivalent to that of healthcare professionals in detecting diseases from medical imaging [182]. CTU has demonstrated promise as a non-invasive method for accurately identifying UBC, and AI-assisted detection and diagnostic tools are in their way to be sufficiently precise in evaluating CTU scans. This, in turn, could complement the work of radiologists, reducing the time needed in CTU evaluation and enhancing the quality of care for patients presenting with macroscopic hematuria and potentially conserving healthcare resources.

However, using AI in medical applications, especially in radiology, presents several challenges and concerns: Integrating AI systems into existing healthcare infrastructure and ensuring compatibility with various medical devices and systems can be complex. In our study, the AI analysis failed to detect twenty-four cases of UBC. These tumors exhibited common features, being small in size (all <3 cm) and solitary, with 85% falling into the cTaG1-2 category. This highlights the need for refining the current diagnostic process and emphasizes the importance of a thorough investigation, including cystoscopy in certain cases.

In two cases where the AI model produced false negative results, patients presented with cT2-4 tumors. However, the evaluation of their CTUs posed specific challenges. In one case, a female patient had a small

flat tumor located apically within a poorly distended urinary bladder, adjacent to the small intestine, rendering the assessment more intricate. The other case involved a male patient with a CTU marked by complexities such as the tumor's small size situated in the bladder neck and the mixed attenuation of the prostate (Figure 18). Notably, both patients exhibited significant squamous cell differentiation in the UBC, raising an intriguing question that merits further exploration—whether tumors with squamous cell differentiation present distinct or different visual characteristics in CTU or not. These observations indicate that our AI model for detection of UBC by CTU needs further refinement before introduction in clinical practice.

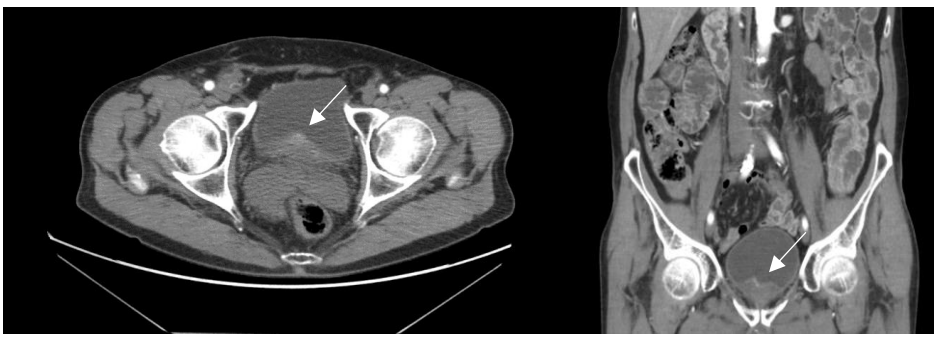


Figure 18. False negative case (a small 1 cm T2G3 tumor with squamous cell differentiation in the neck of urinary bladder) is shown in coronal and axial reconstruction in the corticomedullary phase of CTU.

12.3. The dilemma with urine-based cancer markers in UBC

The use of urine-based cancer markers in the context of UBC detection presents a complex dilemma in the field of oncourology. The early detection of UBC is a key for effective treatment and improved patient outcome. Cystoscopy and CTU, as previously discussed, are prevalent diagnostic methods employed for patients with macroscopic hematuria. While these methods are beneficial, they do present certain drawbacks and limitations, as highlighted in various sections of this text [75, 91, 183, 184]. While infrequent, there exists a slight risk of injury to the urethra, or bladder during cystoscopy, which could potentially result

in unnecessary complications. It is important to note that cystoscopy primarily examines the interior of the bladder and urethra but does not offer a comprehensive view of the entire urinary tract. It is not infallible, with reported overall sensitivity ranging from 0.87 to 1.00, and NPV ranging between 0.98 and 1.00 [185]. Furthermore, it was revealed that patients were willing to opt for alternatives to cystoscopy if the sensitivity of the replacement biomarker was in the range of 0.90-0.95 [186].

In order to improve the selection of patients for diagnostic cystoscopy and reduce costs, potential complications, and unnecessary testing, there is an obvious clinical need for new non-invasive cancer markers. While various Urine-based cancer markers have been developed, none of them are presently employed as a preliminary test for patients who present with macroscopic hematuria as part of routine clinical practice [107].

Numerous studies have delved into the applicability of GeneXpert BC for monitoring patients with previously identified UBC, and their findings have shown promise [19, 108, 121, 187-189]. Nevertheless, only few reports have focused on GeneXpert BC as a preliminary diagnostic test for a group of patients with macroscopic hematuria [109, 165, 190]. Pichler et al. [19] have reported that GeneXpert BC exhibits effectiveness in monitoring patients with UBC, even in cases of LG UBC, with high sensitivity. GeneXpert BC outperformed urine cytology (with respective sensitivities of 0.33 vs. 0.76, $p < 0.001$) and its diagnostic performance in detecting recurrence during the follow-up of NMIBC showed sensitivity and NPV of 0.72 and 0.92, respectively [191].

In our study (V), we have demonstrated the effectiveness of GeneXpert BC as a reliable initial triage test for patients with macroscopic hematuria, achieving a sensitivity of 0.94 and NPV of 0.99. These findings align with the results reported in other studies [165, 190, 192]. In a study by Kavcic et al. involving 156 patients with both micro- and macroscopic hematuria, the sensitivity and NPV of GeneXpert BC were 1.00 [192]. However, it is noteworthy that our study included larger number of participants and focused specifically on individuals with macroscopic hematuria. This cohort is known to be at higher risk for UBC and other

urological malignancies compared to those with only microscopic hematuria [193]. In our study, ROC curve yielded an AUC of 0.89 (95% CI 0.85-0.93, p<0.001). This AUC value closely resembled the ROC curve reported by Kavcic et al. [192] (AUC = 0.86, 95% CI 0.80–0.90; p<0.001), underscoring the performance of GeneXpert BC in ruling out UBC.

Elsawy et al. [190] conducted a study involving 181 patients with hematuria and reported that the GeneXpert BC assay displayed a high level of accuracy, with a sensitivity of 0.74 (95% CI: 0.67-0.79) and NPV of 0.92 (95% CI: 0.89–0.96). Notably, for high-grade UBC, GeneXpert BC exhibited an NPV of 1.00, which aligns with the findings in our study. The somewhat lower sensitivity observed in their study could be attributed to the inclusion of patients experiencing both macroscopic and microscopic hematuria, which may influence the test's performance. Similarly, in a multicenter study, Wallace et al. [165] reported that, at a threshold LDA of 0.40, they achieved a sensitivity of 0.73 and a specificity of 0.90 in a cohort of 93 patients with macroscopic hematuria. In contrast, our study employed a lower threshold value, resulting in a higher sensitivity and a lower specificity. The lower LDA threshold was chosen as our primary objective was to establish a method for excluding UBC, which holds greater clinical relevance as a triage test.

We have demonstrated that 44% of cystoscopies can be omitted in the primary setting of macroscopic hematuria evaluation, which was close to the results (33%) by Hurle et al. [187]. Nonetheless, it is important to note that we applied a lower threshold value of 0.22, whereas Hurle's study utilized a threshold value of 0.40. Additionally, their study was focused on assessing GeneXpert BC for monitoring patients under active surveillance for recurrent UBC, rather than considering its application as a triage test in a healthy population with macroscopic hematuria. Likewise, D'Elia et al. [194] conducted a study involving eighty-two patients undergoing ureterorenoscopy due to suspected UTUC. They demonstrated that even with a relatively high threshold LDA of 0.45, GeneXpert BC exhibited high sensitivity and NPV, both reaching 1.00 in the regard of UTUC detection. This performance eliminated the need for unnecessary ureterorenoscopy, thereby reducing invasiveness and the associated risks of endoscopy complications. Collectively, these observations suggest that

the GeneXpert BC assay could potentially serve as a valuable tool in the future for assessing patients experiencing macroscopic hematuria, considering the substantial workload that such patients pose in urology.

Many urological guidelines recommend cystoscopy and a radiological investigation (e.g., CTU) for nearly all individuals with macroscopic hematuria [195]. A substantial percentage (approximately 85%) of patients presenting with macroscopic hematuria do not have UBC, UTUC or renal cell carcinoma. Consequently, following the traditional approach of conducting both cystoscopies and CTUs in all such cases leads to a high number of unnecessary procedures and healthcare costs [196]. The highest sensitivity of the GeneXpert BC test, which did not miss any cases of HG UBC, was achieved with an LDA score of ≥ 0.33. In this scenario, the sensitivity was 0.88 (95% CI 0.82-0.93), with an NPV of 0.98 (95% CI 0.97-0.99). We introduced a diagnostic approach (chapter 15) that incorporates GeneXpert BC as an integrated part of a rational system for diagnosing UBC in patients presenting with macroscopic hematuria.

Urine-based markers, despite their potential, come with inherent limitations and hurdles. One such obstacle involves the risk of false negatives, which can result in delayed diagnosis and treatment. Similarly, false positives can lead to unnecessary invasive procedures and instill anxiety in patients. Another challenge arises in cases where cancer markers identify UBC/UTUC before visual detection is possible [197, 198]. Additionally, factors such as cost-effectiveness and accessibility pose significant limitations. While non-invasive testing holds advantages, it may not always be feasible or affordable, particularly in healthcare settings with constrained resources. Effectively addressing these challenges requires continuous research, the advancement of diagnostic tools, and a patient-centered approach that carefully balances invasiveness with accuracy in UBC diagnosis.

13. Thesis conclusions

Our research demonstrates that while the implementation of SCP on a national level resulted in a reduction in the time from referral to TURBT, these improvements fell short of meeting the recommended guidelines, indicating an insufficient adherence to SCP recommendations. At NU Hospital Group, where SCP adherence was rigorous, the implementation of SCP was linked to improvement in tumor characteristics. However, such improvement was not evident at the national level. Interestingly, during the SCP period, there were no significant differences in patient or tumor characteristics between those who underwent TURBT within 13 days (as recommended in SCP guidelines) and those who did so later. This suggests the possibility of extending the 13-day window for TURBT, particularly in less urgent cases, to prioritize more severe cases with treatable diseases.

Our studies showed that CTU with CMP can effectively rule out UBC. Hence, in cases where CTU results are negative, the option of omitting cystoscopy could be deemed a sensible course of action. Our findings indicate that, in 57% of patients being evaluated for macroscopic hematuria, primary cystoscopy could potentially have been avoided. We have also developed a new AI-based automatic image analysis model utilizing CNN to aid radiologists in the initial assessment of CTUs for patients with macroscopic hematuria. This model effectively identifies and excludes UBC. Although 10% false negative results may indicate a possibility of improving the model, providing valuable assistance to radiologists during the initial assessment of CTU in the future.

Regarding urine-based cancer markers, our study highlights that GeneXpert BC can serve as a precise triage test in the diagnostic evaluation of individuals presenting with macroscopic hematuria. This has the potential to reduce the need for cystoscopy and CTU in nearly half of the patients in macroscopic hematuria cohort. Furthermore, we propose a novel diagnostic strategy (chapter 15) that integrates GeneXpert BC as a triage test for diagnosing UBC in patients with macroscopic hematuria.

14. Future perspectives

Our thesis, founded on the findings from our five studies, underscores the intricate and challenging nature of the UBC diagnosis process. The future perspectives in UBC research are vital for advancing early detection methods, enhancing patient outcomes, and alleviating the burden of this disease. Future investigations should aim to determine the ideal sequence of diagnostic tests (such as cystoscopy, CTU, and urine-based cancer markers) to maximize both efficiency and accuracy in the process of diagnosis of the disease.

Developing strategies to enhance the criteria of the SCP and finding a compromise to ensure that distinct patient groups follow tailored paths within the SCP is important to get timely diagnosis of aggressive tumors. When assessing patients with macroscopic hematuria, we recommend extending the time interval beyond 13 days between referral and TURBT. This adjustment would prioritize those requiring prompt evaluation and prevent a displacement effect which should be investigated in future studies. Furthermore, it is necessary to conduct additional research to investigate the impact of several types of diagnostic delays on tumor characteristics and outcomes.

Although CTU is valuable, there is still scope for enhancing its sensitivity and specificity, particularly in detecting small or early-stage tumors. In cases where CTU results are negative and the image quality is excellent, it might be a reasonable consideration to forgo cystoscopy. Large-scale prospective studies in the future should be conducted to validate these findings. Moreover, it is necessary to explore the implications of overlooking HG tumors through CTU, and these effects could potentially be alleviated through enhancements in CTU protocols or the future incorporation of urine-based cancer markers in the initial investigation setting.

We have developed a novel AI-based automatic image analysis model to assist radiologists in the initial assessment of CTUs for patients with macroscopic hematuria. However, the clinical effectiveness of this technology capable of influencing diagnostic decision-making should be

verified through prospective randomized clinical trials. Furthermore, AI models might have the potential to optimize CTU protocols and interpretation, thereby improving the results of CTU examination.

Finally, GeneXpert BC test demonstrates the potential to serve as a dependable triage test in the diagnostic evaluation of individuals presenting with macroscopic hematuria. This could potentially reduce the need for cystoscopy and CTU. We have put forth a novel diagnostic strategy (chapter 15) that integrates GeneXpert BC as a triage test for diagnosing UBC in patients with macroscopic hematuria. Therefore, we strongly recommend that future research to evaluate our findings and our novel algorithm in prospective large-scale studies.

15. Suggested novel approach for investigation of patients with macroscopic hematuria

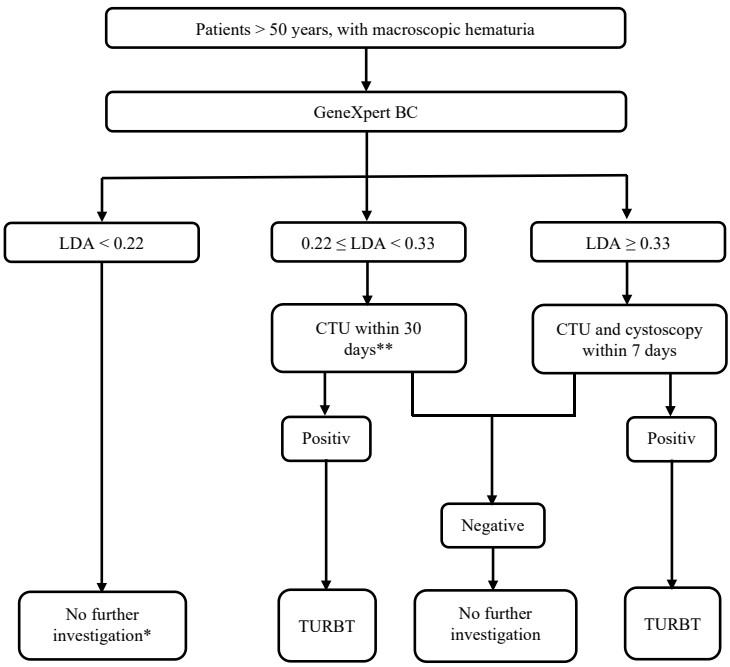
Below, we outline a novel method for managing patients with macroscopic hematuria based on our findings of this thesis. Patients experiencing macroscopic hematuria will be initially tested with GeneXpert BC. Patients who receive inconclusive/invalid GeneXpert BC results may be requested to undergo another urine test. If the results remain inconclusive, they should proceed with conventional diagnostic method (CTU or/and cystoscopy). Based on the test results, patients will be managed according to the protocol outlined below:

1. If LDA < 0.22, the malignancy risk is considered low, and suspicion of cancer is dismissed, and no further investigations are required. However, patients needing investigation for other possible reasons other than cancer (recurrent UTIs, LUTS, BPH, etc.) should proceed according to the local routine.
2. If $0.22 \leq$ LDA < 0.33, CTU will be scheduled within the next 30 days. In the case that the CTU yields high-quality results meeting all quality criteria and does not indicate cancer, suspicions of cancer are ruled out. It is crucial to emphasize that in cases where the CTU results are inconclusive or if there are contraindications for CTU, cystoscopy must be considered.
3. If LDA $\geq$ 0.33, the patient will be scheduled for a CTU and cystoscopy within 7 days. If these CTU and cystoscopy do not indicate cancer, no further investigations are required. A later cystoscopy or CTU may be reasonable as well (need further discussion).

With this setup, we anticipate that approximately 44% of patients (those with LDA < 0.22) will forego further examinations, providing relief to the healthcare system. Approximately 18% will undergo CTU ($0.22 \leq$ LDA < 0.33) without cystoscopy, as our findings indicate that CTU can identify almost all high grade tumors. The remaining 38% will undergo CTU and cystoscopy.

With this study, we try to comprehensively address all aspects of this thesis. We conduct a rapid test that potentially shortens the overall

time until an investigation for macroscopic hematuria. With a quick test time of 90 minutes, we believe that the time to subsequent CTU and cystoscopy, if indicated, will not be significantly prolonged. Additionally, with a reduced number of primary cystoscopies (62%) and CTUs (44%), it will be possible for faster cystoscopies and CTUs. The subsequent flowchart outlines the study progression in various arms along with each corresponding outcome (Figure 19).



* Any recurrent, heavy, or persistent macroscopic hematuria should warrant full urological investigation with both cystoscopy and CTU.

** If contraindications such as impaired kidney function or claustrophobia exist for CTU, or if the CTU yields poor quality images with inconclusive results, cystoscopy should be considered.

Figure 19. The proposed diagnostic approach utilizing GeneXpert BC as a triage test for the diagnosis of bladder cancer in patients presenting with macroscopic hematuria

Based on the pricing information we have today, where cystoscopy costs 4500 Swedish crowns (SEK), CTU is priced at 4000 SEK, and GeneXpert BC is priced at 2000 SEK, we can use this algorithm to estimate potential healthcare savings. According to previous research,

approximately 22 000 patients annually seek healthcare for macroscopic hematuria. Our research suggests that approximately 44% of these patients could avoid further investigation but still require GeneXpert BC. Implementing this approach could potentially save around 62.9 million SEK annually.

For patients with $0.22 \leq LDA < 0.33$, it is recommended to undergo CTU only. This strategy could annually result in savings of approximately 9.9 million SEK. For those with LDA≥ 0,33, it will be extra costs of 16,7 million SEK (GeneXpert BC costs). This leads to an annual savings of approximately 56.1 million SEK. This estimate errs on the side of caution because it does not include the expenses incurred by individuals who have undergone CTU or cystoscopy, and because minor findings that require additional investigation with added costs are not factored in. One significant benefit of implementing such strategy is that it could open up opportunities to address other non-malignant urological conditions that were given lower priority during the era of SCP.

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