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REVIEW ARTICLE

Optimal intervals for follow-up cystoscopy in non-muscle invasive bladder cancer: a systematic review regarding oncological safety

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ABSTRACT

Context: Improving efficiency of follow-up for non-muscle invasive bladder tumours (NMIBC) without risking disease progression through delays of recurrence diagnosis, is a highly relevant field of research.

Objective: The aim of our systematic review was to investigate whether the available evidence support alternative follow-up cytoscopic schedules with respect to oncological safety, compared to those currently given in clinical guidelines for NMIBC. Evidence acquisition we included prospective studies investigating cystoscopy based follow-up schedules including, but not restricted to, comparison of two or more different follow-up schedules with respect to oncological safety measured by recurrence free survival, progression free survival, and overall survival. We allowed for supplementation of modalities such as urinary biomarkers. We screened 680 studies identified by a systematic literature search and, based on our inclusion and exclusion criteria, we included three studies for the narrative synthesis of evidence.

Conclusion: In our systematic search of the literature, we found only low level evidence to support current or alternative cystoscopic follow-up schedules. Clinical trials directly aimed at investigating novel follow-up schedules for NMIBC are needed before substantial changes to existing clinical guidelines can be made.

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Introduction

Cystoscopy is standard of care for diagnosing and detecting intravesical recurrence during follow-up of non-muscle invasive bladder cancer (NMIBC) after transurethral resection of the bladder (TURB). Cystoscopy provides high sensitivity and specificity for papillary lesions [1,2]. However, cystoscopies is associated with a high risk of side effects such as urinary tract infections in addition to the, discomfort, invasiveness, and cost of the procedure. Thus, it is important to balance these factors against the frequency of investigations to detect recurrences at an early stage. Early detection is needed to avoid progression to muscle invasive bladder cancer (MIBC) which is associated with a cancer-specific survival of only 35% for high risk patients progressing from NMIBC to MIBC [3].

The current clinical guidelines from EAU and AUA regarding follow-up of NMIBC offers a risk-stratified approach [4,5]. The EAU guidelines recommend risk stratification using the 2006 risk tables from the European Organisation for Research and Treatment of Cancer (EORTC) to predict recurrence of NMIBC for patient who have not received adjuvant Bacillus Calmette Guérin instillation [6]. The EORTC tables stratify patients according to histopathology, recurrence history, size of tumours, and number of tumours. If the patient has received instillation therapy with bacillus Calmette-Guérin (BCG), the Spanish Urological Club for Oncological Treatment (CUETO) risk tables or the 2016 EORTC risk tables should be used to predict risk of recurrence instead [7–10]. Regarding progression risk stratification, the EAU NMIBC Guideline Panel has published updated prognostic risk groups that takes into account both the WHO2004/2016 and 1973 grading system [11]. This includes a new 'very high'-risk group where patients have 20% (95% CI 12%–32%) predicted risk of progression within the first year after TURB for a primary tumor. Furthermore, the EAU NMIBC Guideline Panel showed that combining both the WHO 2004/2016 (low grade/LG and high grade/HG) and 1973 (grade 1/G1, grade 2/G2 and grade 3/G3) systems thereby creating four risk strata (LG/G1, LG/G2, HG/G2 and HG/G3), were more accurate in predicting progression of primary tumors than either of classification systems alone [12].

In general, follow-up cystoscopy is recommended every 3 to 12 months depending on risk table, risk group, and time since recurrence. Patients with low risk tumours may stop surveillance after five recurrence free years, whereas lifelong surveillance is recommended for high risk tumours [4,12].

In 2012, Soukup *et al.* published a narrative review on the existing evidence for follow-up schedules after surgical treatment of bladder cancer [13]. The primary findings regarding

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Supplemental data for this article can be accessed here.

NMBIC was that the first cystoscopy 3 months after TURB was of high prognostic value, whereas the subsequent follow-up schedules are based on low-level evidence. Therefore, current recommendations in the clinical guidelines on the frequency and duration of follow-up schedules seems to be largely based on clinical tradition rather than high-level evidence. However, a systematic search of the literature was not included in the study by Soukup *et al*. Furthermore, studies may have been published since 2012, and alternative approaches for follow-up for NMBC may have evolved.

In this study, we aimed at investigating evidence regarding the optimal frequency of follow-up of NMIBC with respect to oncological safety through a systematic review of the current literature in accordance with the PRISMA statement [14].

Methods

Search strategy

The study was registered with PROSPERO (CRD42020191349) before commencement of the systematic literature search. The final version of the protocol can be found in the supplementary material.

Embase, MedLine, Web of Science, and Cochrane Library (CENTRAL) were systematically searched. We followed the suggestion of Bramer *et al*. and used a comprehensive Embase search strategy as a basis for translation of the search strategy to MedLine, Web of Science, and Cochrane Library [15]. Full search strategy and strings can be found in supplementary material. In addition, reference lists of articles were searched to identify relevant studies not found in the systematic search. Only full-text articles published in English or Danish were included. The databases were searched from initiation to 28 July 2020. First, titles and abstract were screened independently by two of the authors (AE and TD) using Covidence systematic review software for inclusion into full-text screening. Conflicts were solved by the senior author (JBJ). Second, the full texts were thoroughly read to identify those that met our inclusion criteria. Full-text screening was conducted by TD with any doubt regarding inclusion being discussed and agreed upon at a meeting with all review participants present. All reviews, meeting abstracts, editorials, and comments were excluded.

Study selection, inclusion and exclusion criteria

We included prospective clinical trials and cohort studies where intervals alternative to current recommended follow-up schedules were investigated or where alternative follow-up schedules were compared with each other. Studies on follow-up after TUR-B of both primary and recurrent tumours were eligible. Included studies had to be based primarily on follow-up with cystoscopy as the gold standard, but supplementation with other modalities (e.g. biomarkers) was allowed if the result of such tests postponed or replaced cystoscopy. Even though use of endoscopic technologies such as photodynamic diagnosis (PPD) or narrowband imaging (NBI) increases the diagnostic performance of white light cystoscopy for both papillary and the more elusive flat lesions (i.e. Carcinoma *in situ*), studies investigating treatment responses or recurrence rates after e.g. use of PDD during TURB were not included if the modality had no influence on the subsequent follow-up schedule.

Outcomes

Primary outcomes of interest were recurrence free survival (RFS) and progression-free survival (PFS). These outcomes allowed for interpretation of the oncological safety of different follow-up schedules. We did not exclude studies if these outcomes were not directly reported. Secondary outcomes were quality of life (from ptimizedt questionnaires or the like), overall survival (OS), and cost of follow-up schedules. Because of our a priori knowledge of the field of research, we did not expect a body of evidence large enough for a meta-analysis.

Risk of bias assessment

Risk of bias was planned to be assessed using the Cochrane tool *RoB 2* [16]. However, due to the low number of studies identified and large methodological differences, use of *RoB 2* was not feasible. Instead, we followed the guidelines of Murad *et al*. and did a narrative rating of the certainty of evidence [17]. Narrative synthesis of the risk of bias was done by TD only.

Results

Search results

The systematic search yielded 737 records, with 680 remaining after removal of duplicates. After screening the abstract and titles of the records, 631 were excluded, leaving 49 studies for full-text screening. Of the 49 records retrieved for full-text screening, 46 were excluded (Figure 1). Thus, three studies were considered eligible for inclusion into the present review. The interrater reliability (Cohen's Kappa) for the title and abstract screening was 0.26 (fair agreement).

Characteristics of studies included

Of the studies included (from now on referred to as Olsen *et al*., Van der Aa *et al*. and Hernandez *et al*.), two were conducted as ptimized controlled studies whereas the third was a non-randomised cohort study (Table 1) [18–20]. All studies included only patients with tumours corresponding to WHO 2004/2016 LG or WHO 1973 G2 histopathology. Thus, no patients with WHO 2004/2016 HG tumours including carcinoma *in situ* (CIS) were included in any of the studies. However, according to the EAU-guidelines some of these patients might still belong to intermediate or high risk groups across the different risk stratification systems (e.g. patients with T1G2, HG/G2 and multiple or large tumors) [5]. Two studies included transabdominal ultrasound of the bladder as a supplementation to cystoscopy, and one study used a urinary marker as supplementation.

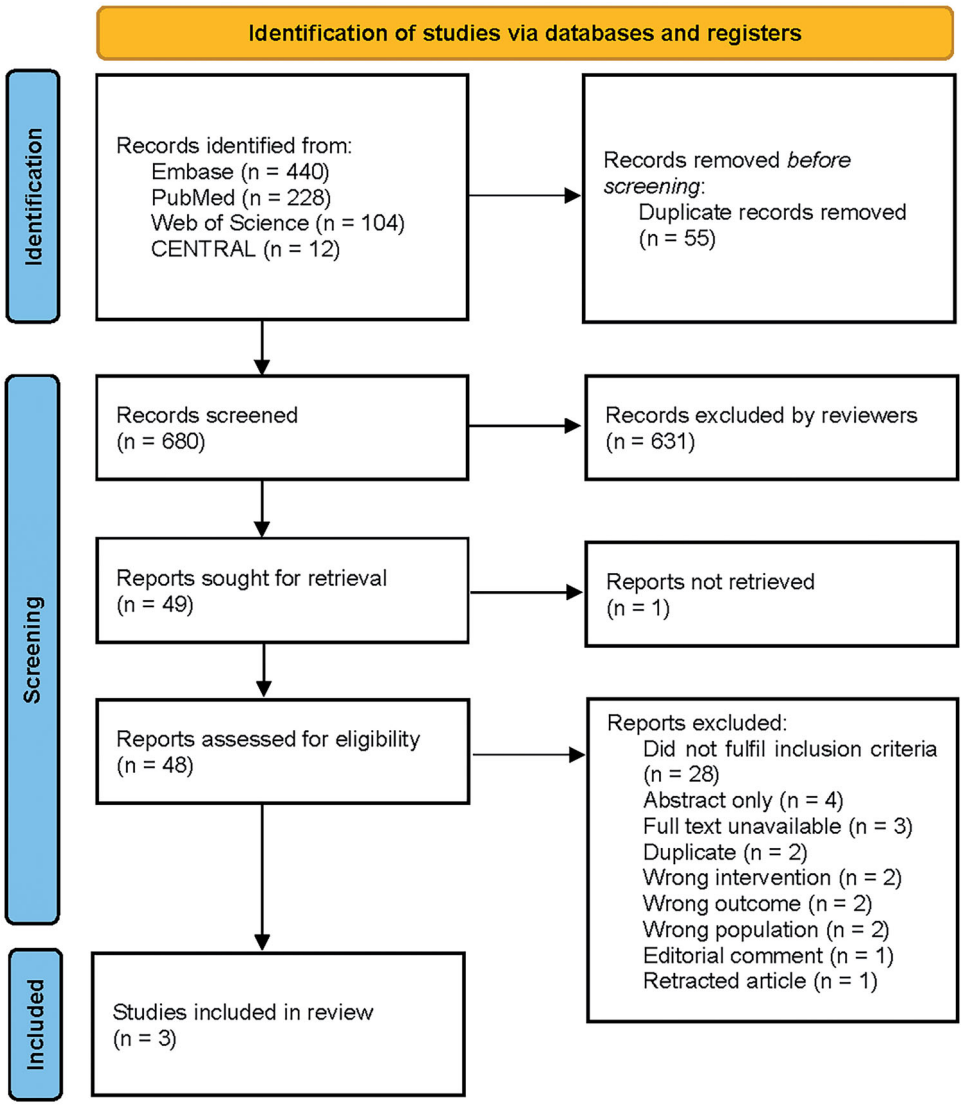

Figure 1. PRISMA flow diagram. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Table 1. Characteristics of included trials.

Author (year, country of publication)	Study design	Population	Intervention	Control	Primary outcome measures
Olsen *et al.* (1994, Denmark)	RCT	$n = 102$ pTa Bergkvist grade 1 & 2	Regimen I: Alternating TUS and cystoscopy every 6 months for 2 years, then cystoscopy yearly	Regimen II: TUS every 3 months for 2 years including yearly cystoscopy	Progression Tumour-related death
Van der Aa *et al.* (2010, Netherlands)	RCT	$n = 448$ pTa, pT1 WHO 1973 Grade 1 & 2	Cystoscopy at 3, 12, and 24 months after TURB. MA of urine every 3 months Cystoscopy if positive MA	Cystoscopy every 3 months	Time to recurrence
Hernandez *et al.* (2016, Spain)	Case series	$n = 252$* pTa, pT1 WHO 1973 Grade 1 & 2 Size < 1 cm Less than 5 tumours	AS of recurrences of NMIBC	Cystoscopy every 3–4 months for 2 years and biyearly thereafter	Long term safety Progression in grade and stage

*186 patients - some patients participate twice due to recurrence(s).
Abbreviations: RCT: randomised controlled trial; MA: microsatellite analysis; TUS: transabdominal ultrasound; NMIBC: non-muscle invasive bladder cancer; AS: active surveillance.

Recurrence and progression outcomes

Olsen *et al.* ptimized 102 patients with previous pTa-tumours of Bergkvist grade I and II between two regimens. *Regimen I* (standard follow-up) was yearly cystoscopy with quarterly transabdominal ultrasound (TUS) interspersed for two years and a half-yearly TUS the third year. TUS did not influence frequency of cystoscopic follow-up. *Regimen II* was yearly cystoscopy and yearly TUS between cystoscopies. Recruitment started September 1988 and ended in August 1993. Median follow-up time for *Regimen I* was 30.6 months (95% CI 22.8–39.1) and 26.6 (95% CI 14.7–34.1) for *Regimen II*. They reported a median recurrence free survival rate of

28.9 months (95% CI 13.3–41.4) for patients in *Regimen I* and 26.9 months (95% CI 14.5–39.4) for patients in *Regimen II* with a non-significant p-value of 0.7474. In total, four patients progressed; in *Regimen I,* two patients progressed to T1 grade 3 and one patient to Ta grade 3 and in *Regimen II*, one patient progressed to Ta grade 3. Thus, no patients progressed to muscle invasive disease (≥T2) during the study.

In the RCT by Van der Aa *et al.*, 484 patients with pTa or pT1 WHO 1973 G1 or G2 were ptimized between quarterly cystoscopy follow-up (standard follow-up) and follow-up with cystoscopy at 3, 12, and 24 months with microsatellite analysis (MA) interspersed every 3 months (intervention). In the intervention arm, cystoscopy was performed if MA was positive between planned cystoscopies. MA was performed for all visits in both arms, but results of the analysis was only communicated to the urologist for patients in the intervention arm. Patients were recruited from July 2002 to June 2006 and there was a median follow-up of 34 months. They reported an increased detection of recurrences in the intervention arm compared to the control arm with 218 out of 1,501 cystoscopies with recurrence in the intervention arm (14.5%) and 163 out of 1,637 in the control arm (10.0%) (P-value <0.001). The false positive rate was lower in the intervention arm, but no statistical test of significance was reported. When analysing only follow-up visits where both MA and cystoscopy results were available, they found that patients in the intervention arm had fewer follow-up visits without intervention and that a larger number of TURBs were performed on patients in the intervention arm. Together with the lower false positive rate, these results indicated better selection of patients for biopsy/resection in the intervention arm as well as better performance of cystoscopy when the performing urologist had knowledge of a positive microsatellite analysis before the cystoscopy.

Hernandez *et al.* recruited 252 patients with a history of pTa or pT1 and WHO 1973 G1 or G2 disease who at a follow-up cystoscopy was diagnosed with a low risk recurrence, judged by the cystoscopic appearance, to enter into an active surveillance protocol. The active surveillance protocol postponed surgical intervention until an increase in number, size, symptoms, or a positive urine cytology was observed. Patients were recruited from 1999 until 2014 and had a median follow-up of 6 years (IQR 4–9.1). Recurrence free survival was not reported due to the active surveillance design. Within the active surveillance group, four patients progressed to muscle-invasive bladder cancer (all with previous T1 G2 tumours) and fifteen patients developed G3 tumors (nine patients with G3 and six patients with CIS). However, univariate analysis revealed only significantly increased risk of progression in grade and not in stage. Those who progressed in grade were significantly older (OR 1.01 (95% CI 1–1.03)), had increased time since primary TURB-T (OR 1.01 (95% CI 1–1.03)), and had multiple tumours (OR 2.11 (95% CI 1.07–4.16)).

Overall survival

In the study by Olsen *et al.*, the overall survival outcome was divided into tumour-related death and deaths from all reasons. There were no deaths from tumour-related causes, but five patients died from all causes in *Regimen I* (11.1%) versus two patients in *Regimen II* (3.8%) (P-value = 0.3252).

Van der Aa *et al.* reported no outcome measures related to overall survival.

There were ten non-cancer related deaths in the active surveillance study by Hernandez *et al.*, but no exact causes of death or patient characteristics were reported.

Quality of life outcomes

Olsen *et al.* did not report any outcomes related to quality of life.

Van der Aa *et al.* also did not report quality of life outcome measures directly. However, the authors refer to another study published on the same cohort of patients (the CEFUB-trial)[21]. In the study, pain and discomfort before, during, and after cystoscopy or after collection of the urine sample for MA were assessed and compared. The patients could rate pain and discomfort as 'Not painful/discomforting', 'Quite painful/discomforting', or 'Very painful/discomforting'. Furthermore, painful micturition, urge, frequency, haematuria, fever in the first week after cystoscopy or MA were measured by a questionnaire. The symptoms could be rated 'No', 'Yes', '<7 days', and '>7 days'. Finally, the patients' reception, waiting time, and explanation of procedures in the outpatient clinic were rated from 'Very satisfying', 'Quite satisfying', to 'Not satisfying'. Overall, follow-up with cystoscopy was worse than follow-up with MA with respect to self-rated pain and discomfort. In the intervention arm, 19% reported that the waiting time from collection of urine sample until test result (ptimiz. 1 week) was uncomfortable.

Hernandez *et al.* reported that three patients dropped out of active surveillance by their own request, but specific reasons for dropping out were not given.

Cost

Olsen *et al.* did not report any cost related outcomes.

Van der Aa *et al.* did not report any cost related outcome measures directly. However, a cost analysis was published on the same cohort of patients in another publication [22]. While the probability of being without recurrence was comparable between the two groups, two years of follow-up with cystoscopy was estimated to €3433 compared to €4104 for MA follow-up.

Hernandez *et al.* did not report any cost related outcomes.

Risk of bias

Overall, the three studies had high risk of bias (Tables 2–4). The RCT by Olsen *et al.* and the cohort study by Hernandez *et al.* suffered from use of transabdominal ultrasound as an alternative modality to detect recurrence and in between cystoscopies which carries a high risk of misclassification and represents subpar diagnostic performance compared to cystoscopy [23]. Furthermore, the RCT by Van der Aa *et al.* had a

Table 2. Grade evidence table for the primary outcome - recurrence-free suvival. Reported by Van der Aa. et al and Olsen et al.

Recurrence outcomes		
GRADE domain	Judgement	Concerns about certainty domains
Methodological limitations of the studies	Both RCTs give information on sequence generation, but lack power calculations. One trial does not report if blinding of health care personnel was used or if allocation was concealed from the patients [19]. In the other trial blinding, allocation and concealment was not possible due to randomisation between microsatellite analysis of a voided urine sample and cystoscopy [20]. Because of lack of information on blinding and allocation concealment in one trial and lack of power calculations in both trials, we judge the trials to have serious methodological limitations.	Serious concerns
Indirectness	The trials answer the question put forth in this review. One of the trials used ultrasound to follow-up NMIBC [19]. This leads to concerns regarding indirectness, as this method is not at present recommended for follow-up of NMIBC, unless cystoscopy is not possible. We judge the trials to have borderline concerning indirectness.	Borderline concerning
Imprecision	One trial included only 97 patients with 5 recurrences being detected [19]. The other trial included 484 patients with 3,379 cystoscopies performed. However, only 1,073 cystoscopies (32%) had a synchronous urine sample leading to serious concerns regarding compliance and missing data [20]. Due to the low number of patients in one trial and large proportion of missing data in the other, we judge the trials to have serious imprecision.	Serious concerns
Inconsistency	One trial show similar recurrence-free survival rates in the two trial arms [19]. The other trial show an increased proportion of recurrences detected in the intervention arm [20]. In this trial, the investigators are informed about a positive microsatellite analysis of a voided urine sample from patients in the intervention arm. This difference may increase diagnostic performance of cystoscopies when the performing urologist has knowledge of a positive test prior to cystoscopy. Therefore, we judge that there is no inconsistency among the trials.	No concerns
Publication bias	Following our broad search of the literature, we do not suspect publication bias.	No concerns

Table 3. Grade evidence table for progression outcome. Reported by Hernandez et al. and Olsen et al.

Progression outcomes		
GRADE domain	Judgement	Concerns about certainty domains
Methodological limitations of the studies	See Table 2 for methodological limitations of the study by Olsen *et al.* Hernandez *et al.* used no randomisation, allocation concealment or blinding. The fulfilment of the criteria used to define need for treatment is inherently dependent on the performing urologist and there is no information on the experience or identity of the urologists who took part in the trial [18]. We judge the two trials to have serious methodological limitations.	Serious concerns
Indirectness	The type of active surveillance used by Hernandez *et al.* is not routinely used in follow-up of NMIBC [18]. Furthermore, both studies used transabdominal ultrasound to follow-up NMIBC [18,19]. Ultrasound is less effective at detecting recurrence than cystoscopy. Thus, use of ultrasound would increase time to detection of recurrence and hereby risk of progression. However, both studies show no increased risk of progression. Therefore, we judge the trials to have no serious indirectness.	Not serious
Imprecision	One trial included 97 patients with only 4 patients reaching the primary outcome of progression [19]. None of the patients progressed to muscle invasive disease. In the other trial 20 patients progressed [18]. Of these, 4 patients with T1 Grade 2 disease progressed to muscle invasive disease. However, there were also 16 patients with previous T1 grade 2 disease where histological findings after active surveillance is missing. The authors specify that this could both due to the patients still being under active surveillance, a non-cancer related death or loss to follow up, but there is no further information reported. This could lead to an underestimation of the risk of progression. We judge the trials to have serious risk of imprecision.	Serious concerns
Inconsistency	Because both trials show a comparably low risk of progression, we judge the trials to have no concerns about inconsistency.	No concerns
Publication bias	Following our broad search of the literature, we do not suspect publication bias.	No concerns.

Table 4. Grade evidence table for overall survival outcome. Reported by Hernandez et al and Olsen et al.

Overall survival		
GRADE domain	Judgement	Concerns about certainty domains
Methodological limitations of the studies	See Tables 2 and 3 for methodological limitations in the studies by Olsen *et al.* and Hernandez *et al.*	Serious concerns
Indirectness	The patients and interventions from the studies provide sound evidence to the question at hand. But, one study had a median follow-up time of only 30.6 months, which is too little to detect a difference in overall survival for low grade NMIBC [19]. Therefore, we judge the trials to have serious concerns regarding indirectness.	Serious concerns
Imprecision	As with the recurrence-free survival and progression-free survival, few patients were included across the trials. This is cause for serious concern regarding imprecision.	Serious concerns
Inconsistency	Both trials reporting overall survival showed a low risk of death and this did not vary significantly across the two trials. We therefore have no concerns regarding inconsistency.	No concerns
Publication bias	Following our broad search of the literature, we do not suspect publication bias.	No concerns.

high proportion of missing data due to only 32% of possible urine samples being available for analysis. The cohort study by Hernandez *et al.* suffered from lack of ptimizedti, and a high number of patients were lost to follow-up.

Discussion

In spite of developments within diagnosis and treatment, NMIBC remains a disease with a high risk of recurrence and even progression to life threatening invasive disease [10]. Thus, the question remains; how should follow-up schedules of NMIBC balance risk of disease progression against side effects, efficiency, and cost? The present systematic review has not brought forth new ground-breaking knowledge regarding evidence, but has once again highlighted the need for high quality studies on follow-up of NMIBC, preferably assessing different follow-up schedules directly. Currently, several promising alternatives are being investigated.

Urinary biomarkers have been suggested as a non-invasive approach of ptimizedti the interval between follow-up timing cystoscopies. In case of negative results from a high sensitivity urinary biomarker, cystoscopy might be safely postponed. However, urinary markers might also forecast a future recurrence not yet detectable by cystoscopy, thus calling for close follow-up. A recent study found that use of a biomarker could theoretically save 33.7% of cystoscopies while missing 9.1% of patients with low grade disease recurrence and no one with high grade recurrence [24]. The study by Van der Aa *et al.* included in the present review is to our knowledge the only published ptimized controlled trial using urinary biomarkers to postpone cystoscopy [20]. However, the study suffers from a high degree of missing data among other limitations (Table 2). Several urinary biomarkers have proven potential candidates, especially in the detection of high-grade NMIBC. The urinary marker CxBladder has been proven to have a high sensitivity for both LG and HG disease, 93% and 95% respectively [25]. Another urinary marker, the Xpert Bladder Cancer Monitor, has reported negative predictive values for HG disease reaching 97.6% (95% CI 94–99.1) in one study and 99.7% in another [26,27]. If valid, these negative predictive values should allow for safe postponement of cystoscopy conditioned on a negative urinary marker. A ptimized clinical trial aiming for 392 patients with previous HG NMIBC (pTa, pT1, and CIS) is currently being conducted comparing cystoscopy based follow-up with follow-up based on the Xpert Bladder Cancer Monitor [28]. Another ongoing ptimized clinical trial compares standard cystoscopic follow-up and follow-up with a panel of urinary markers for patients with previous pTa LG disease [29].

However, the implementation of urinary markers in future follow-up regimes of NMIBC is not only dependent on the diagnostic performance of the available biomarkers. The willingness of clinicians to trust the biomarkers, and the influence biomarker based follow-up might have on quality of life for the patients, are equally important. Some patients might not feel safe with not undergoing cystoscopy, while other patients will adapt much faster. In a study investigating the minimally acceptable sensitivity for urinary biomarkers, 63.3% of patients would accept a biomarker with a minimally acceptable sensitivity of $\geq$95%, suggesting that performance characteristics are important if use of urinary markers should be accepted by patients [30]. In the present review, one study reported that some patients experienced 'waiting time discomfort' in the time from urine sample to test result [21]. Moreover, because some available test have a long time span from urine sampling until test results (several weeks), the use of urinary markers in an outpatient setting can become logistically complicated. In-house testing with short turnover from sample to results will also be preferable for patients due to low waiting time, and might make same-day urinary marker and cystoscopy, in case of positive urinary marker, a viable and efficient possibility.

Active surveillance (untreated Ta LG) is another approach for follow-up within the field of NMIBC [31]. A recent review and pooled analysis showed that active surveillance can be safe in a selected group of patients with LG NMIBC [32]. The same conclusions was reached by Hernandez *et al.*, although there are severe limitations to this study [18]. They did not use a ptimized design, relatively few patients were included in spite of 15 years of recruitment, and they did not specify reasons for patients who declined participation (See Table 3). However, a general problem with active surveillance protocols is the subjectivity of defining disease progression. Estimation of tumour size and detection of small recurrences will vary among urologists depending on experience. Thus, a high degree of ptimizedtion is needed for active surveillance to be effective in a clinical setting and should be considered in future ptimized trials.

Limiting the number of cystoscopies needed for oncologically safe follow-up of NMIBC is not only reasonable for improving quality of life and reducing side effects, but could potentially decrease health care cost associated with NMIBC. The economic benefit of novel modalities is of course dependent on the price of these techniques as wells as their diagnostic capabilities. If too many cases of recurrence or progression is missed compared to cystoscopy, the reduction of health care cost of follow-up will be nullified by the much more expensive treatments necessary for invasive disease, i.e. neoadjuvant chemotherapy, radical cystectomy, and immunotherapy [33].

This review has not focused on ptimized imaging during cystoscopy. However, the ability of technologies such as PDD or NBI to increase the diagnostic performance of cystoscopy should not be overlooked [34–36]. Furthermore, use of novel technologies such as machine learning and deep learning to improve imaging and diagnostics could prove a valuable resource for clinicians [37,38].

Conclusion

The number of studies investigating alternative follow-up schedules of NMIBC was low, prone to several sources of bias and not applicable to current settings. Furthermore, none of the studies used current risk stratified approaches. Thus, no prospective trials exist that directly investigates the optimal and oncologically safe interval for follow-up

cystoscopy in NMIBC. The reason for the lack of high quality studies is most likely due to the perceived risk of progression if cystoscopy is postponed and no sensitive alternative to cystoscopy is used. However, as recent evidence suggests, the majority of patients with NMIBC have relatively low risk of progression, and thus with the sensitivity of novel techniques (e.g. urinary biomarkers) or use of 'safety'-cystoscopies (e.g. yearly cystoscopy) as adjuvant to novel techniques or alternative follow-up regimes, oncologically safe trials should be feasible, in particular for low risk NMIBC.

In future studies, researchers should focus on designing trials that directly address or propose novel follow-up for NMIBC.

Disclosure of interest

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