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Active surveillance for non-muscle invasive bladder cancer: A systematic review and pooled-analysis

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ABSTRACT

Introduction: One of the Non-Muscle Invasive Bladder Cancer (NMIBC) treatment options recently recommended by International Guidelines is represented by Active Surveillance (AS),. Herein we carried out a systematic review and pooled-analysis of currently available evidences in order to provide recommendations for daily urological practice.

Material and Methods: The PubMed, EMBASE, and Coch rane Library databases were searched with the terms "Non-Muscle Invasive" or "pTa/pT1" and "Bladder Cancer" or "Bladder Tumor". A meta-analysis was conducted to estimate the pooled upstage rate (from pTa to pT1/T2), the pooled upgrade (from G1–2 to G3), the proportion of pts still in AS and the pooled AS failure rate across all studies. A random-effects model was used to derive the pooled effect sizes and the 95% confidence intervals (CIs).

Results: 7 studies were included, accounting for 558 patients (pts). AS failure rate was 67% (95%CI 44–84%) and 32% of pts were still on AS (14–56%) during a median AS time of 15,6 months. Progression to worst grade or stage was observed in 19% of pts (95%CI 11–30%). Upgrade to G3 and upstage to pT1 were observed in 44% (95%CI 13.6–79.8%) and 8% (95%CI 3.9–15.9%) respectively.

Conclusions: AS for Low Grade NMIBC can be considered safe and feasible, even if only in clinical trial context. We encourage multicenters to perform randomized clinical trials to obtain data about the quality of life of pts on AS, which are scarce, and to rapidly make AS an integral part of daily urological practice as soon as possible.

Introduction

Non-muscle invasive urothelial cell carcinoma (NMIBC) of bladder cancer (BC) represents one of the most expensive malignancies to treat and follow-up, due to its high recurrence rate and cancer-specific mortality rate of <1% [1, 2, 3]. International Guidelines have recently recommended Active surveillance (AS) as one of the therapeutic options for Low-Grade (LG) Non-Muscle Invasive Bladder Cancer (NMIBC) [4–6].

AS was reported for the first time in 2003 by Soloway and Coll, who reported a minimal risk of progression and impact on cancer-specific survival comparing to transurethral resection of bladder tumor (TURBT). AS would finally lead to a reduction in the number of surgeries throughout the patient lifetime, without compromising the possibility of intervention in case of progression [7].

Furthermore, the same Authors pointed out the costs related to hospital stays and management of patients (pts), especially in old and co-morbid ones, and the risks related to repeated TURBT.

Thus, subsequent articles evidenced the importance of specific competence for urologists, both during the first cystoscopy with the ability of identifying small lesions with a LG Ta appearance at a high degree of accuracy at the pathological examination, and during FU-cystoscopy, with the capacity of predicting the stage and the grade of recurrence [8, 9, 10].

In the light of the paucity of data on appropriate pts selection for AS, we carried out a systematic review and poo pooled-analysis of currently

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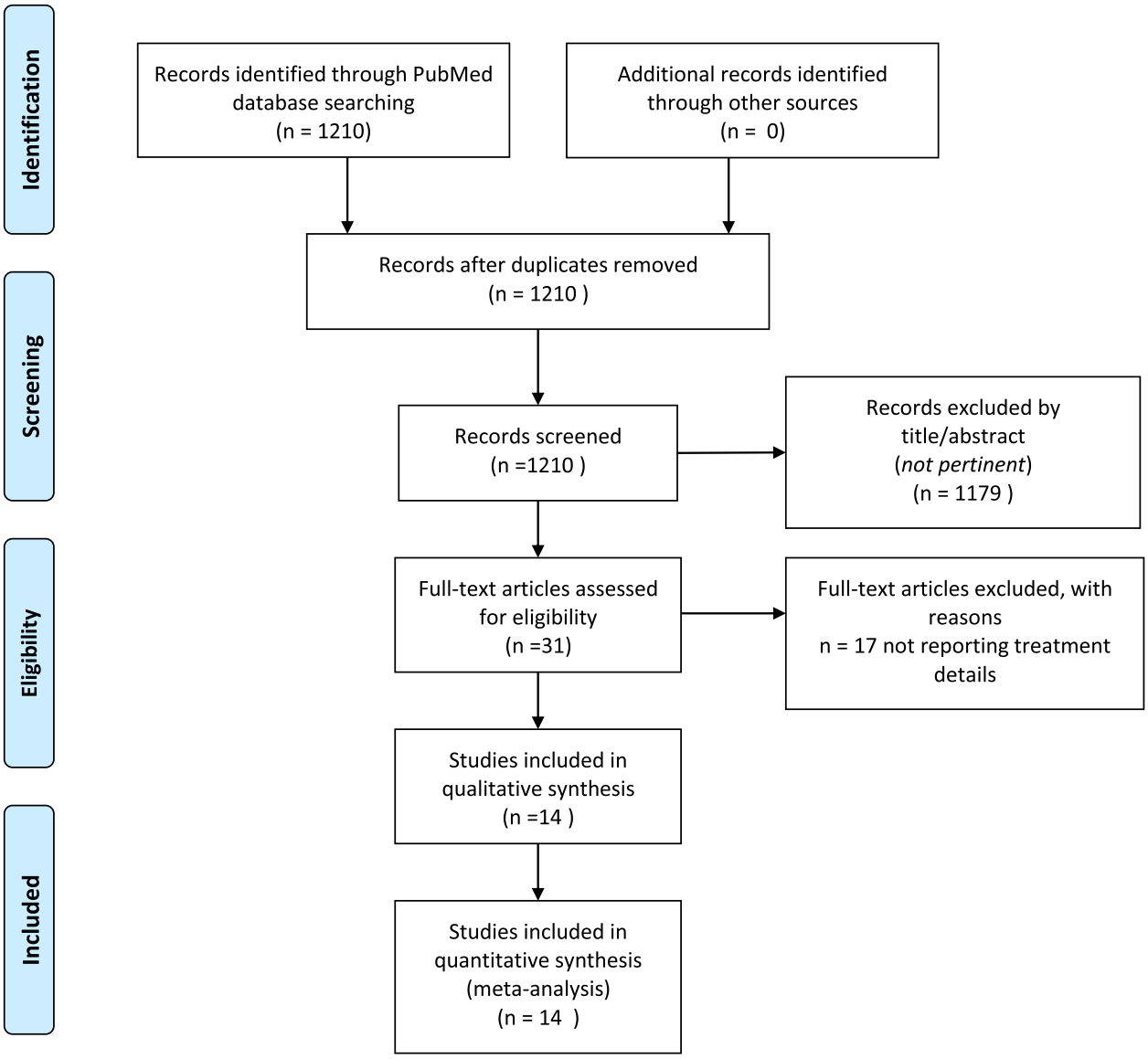

Fig. 1. PRISMA Flow Diagram of included studies.

available evidences, to evaluate the oncological outcome defined as failure rate, progression rate, upstage and upgrade.

Material and methods

Search strategy and inclusion criteria

The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) group guidelines. The PubMed, EMBASE, and Cochrane Library databases were searched with the terms "Non-Muscle Invasive" or "pTa/pT1" and "Bladder Cancer" or "Bladder Tumor". Eligible studies were defined as it follows: 1. Publication since inception up to May 1st, 2020; 2. English language; 3. Full text papers about prospective trials or retrospective case series of NMIBC treated with AS; 4. Clearly reported outcome measures: AS failure, upgrade to G3, upstage to pT1–2. The exclusion criteria regarded case reports and TURBT executed for pathological definition of metastatic BC.

Data extraction

Authors, study procedures, statistical design, outcomes, of each paper were recorded. Data regarding number of pts, gender, median time from first TURBT to AS failure, previous intra-vesical therapy, median F-U, median AS duration, baseline pathology, rates and type of failures were investigated. Two reviewers separately evaluated all articles for eligibility and quality and subsequently extracted data (RH and FP). Additionally, Nottingham-Ottawa-Scale was used for quality check of retrospective studies.

Statistical analysis

A meta-analysis was conducted to estimate the pooled upstage rate (from pTa to pT1/T2), the pooled upgrade (from G1–2 to G3), the proportion of pts still in AS and the pooled AS failure rate across all studies (the primary endpoint). A random-effects model was used to derive the pooled effect sizes and 95% confidence intervals (CIs). The Cochran Q test and I^2 statistic were used to assess heterogeneity. A funnel plot and Begg's and Egger's test were produced for the primary endpoint analysis.

Table 1
characteristics of included studies.

Author/year	N° of pts	Type of study	Country	Inclusion criteria	Pathological finding before observation	Initial stage%	Previous IV therapy (%)	Median follow up (Months)	Median AS (Months)	AS failure rate	Grade progression n (%)	Stage progression n (%)	Progression to MIBC, n(%)	NOS score
Soloway 2003[7]	32/56	retrospective	USA	small, recurrent, papillary, endoscopically appearing low grade tumors. < 3–4 tumors	Ta/T1/G1/G3	80%IR 20%HR	53,12%	38	10,09	50%	3 (9.3%)	2 (6.2%)	0	7
Martinez Caceres 2005[11]	13/15	prospective	SPAIN	Not reported	Ta/T1/G1/G3	69% IR 32% HR	–	–	5,76	100%	2 (15.4%)	3 (23%)	0	5
Pruthi 2008 [12]	22/35	retrospective	USA	Small tumor no size reported; no tumors not reported	Ta/T1/G1/G3	88,57% IR 11,43% HR	–	25	17,18	32%	2 (9%)	1 (4.5%)	0	6
Hernandez 2009/2016 [13,14]	186/252	prospective	SPAIN	Small tumor < 10 mm, < 5 tumors. Negative cytology	Ta/T1/G1/G2	77,14% IR 22,86% HR	43%	72	13,4	80%	42 (22%)	28 (15%)	4 (2.1%)	8
Gofrit 2006/2008/2018 [15–17]	52/75	prospective	ISRAEL	<10 mm papillary tumor found on routine cystoscopy. Negative cytology.	Ta G1/G3	100% IR	64,28%	–	16,5	93%	0	1 (1.9%)	0	5
Lozano 2014/2019 [18,19]	91/NA	prospective	SPAIN	Not Reported	PUNLMP Ta/T1a/LG	19,78 LR 60,44 IR 19,78 HR	84,61%	95,35	28	71%	10 (17.6%)	19 (20.8%)	0	9
Hurle 2016/2018/2019 [20–23]	162/174	prospective	ITALY	Small tumor < 10 mm, < 5 tumors. Negative cytology	Ta/T1a/G1-G2	85,61% IR 15,39% HR	37,65%	11,9	18,8	31%	16 (9.8%)	11 (6.8%)	0	6

PTS: Patients; IV: intravesical; AS: active surveillance; MIBC: muscle invasive bladder cancer; LR: low risk; IR: intermediate risk; HR: high risk.

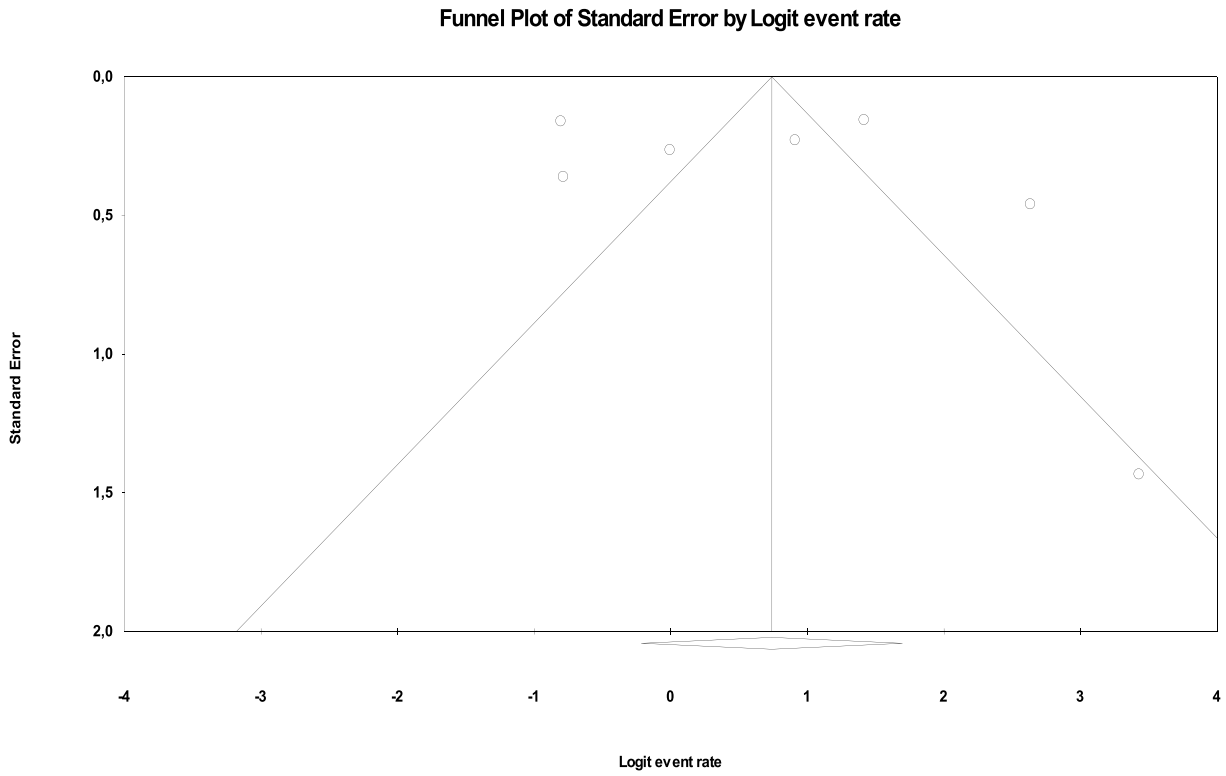

Fig. 2. Funnel plot of publication bias for active surveillance failure.

All statistical analyses were conducted at the 5% significance level with Comprehensive Meta-Analysis software (version 3.3.070, November 20, 2014).

Outcomes of interest

Definition of AS failure, median AS time, progression rate, upgrade and upstage primary

Results

Characteristics of included studies

Prisma flowchart summarized the search and extraction (Fig. 1)

A total of 1210 papers was identified; among these, 14 (12 prospective and 2 retrospective) were included. Statistical analyses were performed excluding studies reporting data from the same series. Only the most recent ones were taken in consideration, and for this reason the final number of included studies is 7. All studies enrolled patients with a history of LG NMIBC.

Inclusion criteria for AS entrance are summarized for each study in Table 1.

Failure criteria were fairly homogeneous among the studies: increasing in the number of tumor, increasing in the tumor size, presence of hematuria and, only in 3 studies, the presence of positive cytology. In all the studies, patients had the possibility of withdrawn the AS and undergo surgery.

Overall 558 pts (698 AS events) were included in AS protocol, the number of events was higher than the number of patients, because a patients could enter/exit in AS more than once during follow up for NMIBC.

Main results

Of 698 AS events, 124 (17.7%) pts had a BC deemed to be of high risk (Table 1; Suppl. file 1).

AS failure rate was 67% (95%CI 44–84%; Fig.2) and 32% of pts were still on AS (14–56%) during a median AS time of 15,6 months. Progression to worst grade or stage was observed in 19% of pts (95%CI 11–30%). Upgrade to G3 and upstage to pT1 were observed in 44% (95%CI 13.6–79.8%) and 8% (95%CI 3.9–15.9%) respectively. Muscle invasive BC was found in 1.3% (0.6–2.7%).

Publication bias

Analysis of funnel plot shows no evidence of publication bias (Fig.2). Both Begg's and Egger's test were not significant confirming the absence of publication bias ($P = 0.5$ and $=0.03$ respectively).

Discussion

Literature data about AS are scarce and published by the same groups; we found 12 full papers and 2 congress abstract (see table 1). Recently Marcq et al. [24] published a review on 6 articles published before August 2018. This metanalysis is performed also on the recent update of the series of Hurle and Gofrit and on the new series of AS patients reported by Lozano.

The inclusion and exclusion criteria were similar in all groups, particularly regarding stage (pTa and pT1a), grade (low/G1-G2), size (< 10 mm), number of lesions (range 1–5), absence of hematuria, negative urine cytology. Hurle has recently proposed two possible amendments of AS protocol during pandemic, regarding the increase of dimensions and number of lesions up to a maximum of seven [25].

No contraindications were reported to enter in AS; obviously the compliance and the motivation of the patients to the strict in-office follow up is of crucial importance.

Considering the end-points, the only two statistically relevant included the AS failure rate, related to previous intra-vesical therapies ($p = 0.03$) (AS results more feasible in pts without a history of repeated intra-vesical instillations) and, for pts still in AS, the intermediate risk as baseline; in these cases, it is intuitive that these pts could perform AS for

longer time compared to the low number of high risk pts (e.g. pT1a and High Grade Ta).

Furthermore, none of the included articles reported oncological outcomes stratified by group risk. It would be of main interest to understand if risk group is a risk factor for AS failure, thus we encourage new studies to identify patients characteristics that could help urologist to predict the probability of failure of those who are enrolled in AS program.

Moreover, the safety of AS is supported by a sufficient F-U period (median: 38 months, range 9–95 months).

Surprisingly, our group have recently reported the histological outcome of patients who failed AS because of positive in office cystoscopy with the presence of lesions described as "typical neoplastic appearance", approximately 30% of patients deemed to have AS failure did not harbor any neoplastic lesion. [22].

According to reported data, AS appears to be feasible and safe in a selected subset of patients with previous diagnosis of LG-NMIBC. The analyzed studies enrolled low, intermediate and high risk patients, nevertheless no sub analysis with stratification have been reported.

However, AS if feasible only in clinical trial context at the moment. We encourage multicenter, randomized clinical trials to make AS an integral part of daily urological practice as soon as possible.

Additionally, there were no data about the quality of life of pts in AS. In our center, no one has dropped out of the protocol, appreciating the opportunity of being monitored with flexible cystoscopies in an outpatient setting instead of being operated [25].

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Declaration of Competing Interest

Nothing to declare

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ctarc.2021.100369.

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