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Role of Androgen Receptor Expression in Non-Muscle-Invasive Bladder Cancer: a Systematic Review and Meta-analysis.

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Summary. In order to evaluate the potential prognostic/predictive role of androgen receptor (AR) expression in non-muscle-invasive bladder cancer (NMIBC), and whether it may represent a therapeutic target, we conducted a systematic search of the literature using 'androgen receptor or AR', 'testosterone', 'bladder cancer' and 'non-muscle invasive bladder cancer or NMIBC' as keywords. Eleven studies met the inclusion/exclusion criteria. No significant association was found between AR status and patients' gender (p=0.232), tumor size (p=0.975), tumor stage (p=0.237), tumor grade (p=0.444), tumor multicentricity (p=0.397), concomitant CIS (p=0.316) and progression of disease (p=0.397). On the other hand, relative lack of AR expression was significantly correlated to recurrent disease (p=0.001). Evidence for a direct correlation between AR expression and recurrence-free survival of patients with NMIBC indicate ARs as potential markers of BC behavior; moreover, the finding of a role of androgen blockade therapy in improving survival highlights the potential clinical application of this pathway, which deserves to be further explored.

Introduction

Bladder cancer (BC) is the second genitourinary malignancy and has a worldwide incidence of 550.000 new cases per year [GLOBOCAN 2018 [https://gco.iarc.fr/] accessed on 9th May, 2019]. Almost 75% of new cases present as non-muscle-invasive bladder cancer (NMIBC), while the remaining 25% present as muscle invasive bladder cancer (MIBC) at initial diagnosis. NMIBC carries a significant lifelong risk of disease recurrence as well as a risk of progression to MIBC, with obvious high lifetime costs per patient, especially in high-risk cases (Sievert et al., 2009; Norm et al., 2016). Following transurethral resection of the bladder tumor (TURBT), prevention of recurrence and progression of NMIBC continues to rely on intravesical instillation of mitomycin-C or Bacillus Calmette-Guérin (BCG) based on disease risk category and such a strategy has not significantly changed over the last decades. Current European Association of Urology (EAU) guidelines on NMIBC (Babjuk et al., 2017) acknowledge that "more research is needed to determine the role of molecular markers in improving the predictive accuracy of currently existing risk tables". Indeed, the identification of molecules/pathways or clinical features (such as bladder wall thickness) predicting the clinical outcomes or the response to available treatments as well as novel treatment targets, appear to be particularly attractive to improve therapeutic chances and to limit the costs (Cantile et al., 2003; Li et al., 2017; Cicione et al., 2018).

In this respect, it is worth mentioning that there is a gender-specific difference in BC incidence worldwide (Scosyrev et al., 2009; Zaitsu et al., 2015), with men tending to be diagnosed about three to four times more often than women, even when adjusting for lifestyle and environmental factors such as smoking and exposure to chemicals (Hartge et al., 1990; Hemelt et al., 2009; Chavan et al., 2014). This is in line with findings of animal studies showing that the incidence of both spontaneous and chemically induced BC is significantly higher in male than in female rats (Reid et al., 1984; Imada S. et al, 1997; Miyamoto et al., 2007).

It is also worth mentioning that women are more likely to have more aggressive tumors carrying a worse outcome, and that postmenopausal women have an increased risk of developing BC than premenopausal women (McGrath et al., 2006; Scosyrev et al., 2009; Bray et al., 2011; Burge et al., 2016), thus underlying the estrogen protective role in BC (Ye et al., 2019). Taking all these data together, and considering that the urinary bladder shares the same origin from the urogenital sinus as seminal vesicles, prostate, and bulbourethral glands (Boorjian et al., 2004), BC has been regarded as a putative endocrine-related malignancy, prompting research on the role of hormones and their receptors in its development (Hartge et al., 1990; Dobruch et al., 2016; Ide et al., 2017). Gender-specific discrepancies in BC incidence and prognosis, and the evidence of androgen receptor (AR) expression in the urethral and bladder epithelium (Rosenzweig et al., 1995) have led several authors to investigate the role of AR in BC development and progression (Imada et al., 1997; Miyamoto et al., 2007; Hsu et al., 2013; Lin et al., 2013; Lombard and Mudryj, 2015; McBeth et al., 2015; Kawahara et al., 2016; Li et al., 2017; Sikic et al., 2017). The presence of AR has been demonstrated in several tissues in the lower urinary tract and may affect growth, differentiation and maintenance of urinary bladder tissue (Rahmani et al., 2013; Shortliffe et al., 2014; Lombard and Mudryj, 2015). Preclinical studies on animals and human urothelial cell lines have shown an association between AR expression and the development of BC (Imada et al., 1997; Miyamoto et al., 2007; Zheng et al., 2011; Hsu et al., 2013; Lin et al., 2013; Li et al., 2017). Testosterone (but not its converting form, 5α-dihydrotestosterone) has been found to increase the risk of developing both bladder calculi and BC in female rats, whereas estrogen as well as antiandrogen molecules (i.e. flutamide) inhibit BC incidence in male rats (Okajima et al., 1975; Terada et al., 1992; Imada et al., 1997). Clinical studies found an association between androgen-deprivation therapy (ADT) for prostate cancer and a decreased incidence, recurrence and progression of BC (Izumi et al., 2014; Shiota et al., 2015, 2017; Morales et al., 2016). Other studies however failed to demonstrate

gender-specific differences in AR expression in BC, and yielded conflicting results regarding AR association with BC progression (Mir et al., 2011; Tuygun et al., 2011; Miyamoto et al., 2012; Mashhadi et al., 2014; Nam et al., 2014). According to a recent meta-analysis, AR expression at protein level in BC overall ranges from 12.9% to 53.4% (Li et al., 2017).
The present study focused on AR expression in NMIBC, in order to explore its potential prognostic/predictive value as well its putative therapeutic implications.

Materials and methods

Search strategy
The research protocol was established *a-priori* and approved by all the coauthors prior to conducting the systematic review. The review protocol consisted of four different parts: 1) literature search, 2) study identification and selection, 3) data extraction, 4) statistical analysis.
In May 2019 a computerized systematic literature search of papers published up to 15th May 2019 was performed by using two electronic databases (PubMed (MEDLINE) and Google Scholar). The literature search strategy was adapted according to the different research engine. The combined terms: 'androgen receptor or AR', 'testosterone', 'bladder cancer' and 'non-muscle invasive bladder cancer or NMIBC' were used as the search keywords. Additional records on this topic were identified from references cited in the selected manuscripts or within previous systematic reviews of the literature.

Inclusion and exclusion criteria
The identification and selection of the studies were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria and the Population, Intervention, Comparator, Outcomes (PICO) methodology (Moher et al., 2010; Ouzzani et al., 2016) (www.prisma-statement.org).
The inclusion criteria were: (1) only studies published in English in peer-reviewed journals, including abstracts of the potentially relevant international congresses of the last 5 years; (2) AR expression was measured by immunohistochemistry or PCR-based methods in BC tissue specimens obtained by transurethral resection or cystectomy for review purposes, although only immunohistochemistry-based studies were included in the meta-analysis for the purpose of uniformity; (3) the correlation between AR and clinical, pathological and prognostic parameters was evaluated; specifically, these studies compared the positivity of AR to patients' gender and tumor size, stage, grade, multicentricity, presence of concomitant CIS, and assessed prognostic significance of their expression, e.g. recurrence-free survival (RFS) or progression-free survival (PFS) in patients with NMIBC; (4) sufficient published data was used to estimate an odds ratio (OR) with a 95% confidence interval (CI). Studies were excluded if: (1) they were case reports, letters, abstracts for meetings and reviews without original data, or were animal or laboratory studies; (2) data were overlapping or insufficient; namely, the outcomes of interest were not reported and it was impossible to calculate outcomes from the originally published data.

Data extraction
After reviewing the titles and the abstracts, two independent reviewers (FS and LC) ascertained whether they met inclusion criteria. Then, full-text articles were read exhaustively. Articles that reported data about at least one of the outcomes of interest were included in our analysis. Only studies with original or primary data were included. Duplicate or repeated cohorts were excluded. When more than one paper referred to the same cohort only the most recent was considered. A

third author (GC) resolved eventual discrepancies. The following data were collected from each study: first author's name, journal, publication date, study method, total number of patients analyzed and number of patients with positive/negative AR status, and data on AR expression according to patients' gender (male vs. female), tumor size (low/<3 cm vs. high/≥3 cm), tumor stage (pTa-is vs. pT1), tumor grade (low vs. high), tumor multicentricity (single vs. multiple), concomitant CIS (present vs. absent), and recurrence/progression of disease (present vs. absent). We did not define a minimum number of patients for inclusion in our meta-analysis. The cut-off score of the AR positive group varied among the different immunohistochemical studies, and has been reported in Table 1. AR positive cases were defined according to the original articles.

Statistical analysis

Odd ratios with their 95% CIs were calculated to assess the correlation between AR with clinical and pathological parameters. Heterogeneity was assessed by an I^2 test; therefore, the OR estimate or RD for each study was calculated using the fixed-effects model. Otherwise, the random-effects model was used. The significance of the pooled OR or RD was determined by the Z-test and a $P \leq 0.05$ was considered to be statistically significant. An estimate of potential publication bias was performed using the funnel plot with a Begg's test, and the funnel plot asymmetry on the natural logarithm scale of the OR or RD was measured using a linear regression approach. All statistical tests were performed with MedCalc version 14.8.1.

Results

Based on inclusion and exclusion criteria, 11 studies published between 2004 and 2018 were eligible for analysis (Fig. 1). They involved a total of 778 patients (median sample size 97, range 27-169). According to single cut-off levels, AR expression was positive in 289 out of 778 cases overall (37.15%) (Table 1).

No significant association was found between AR status and patients' gender (p=0.232), tumor size (p=0.975), tumor stage (p=0.237), tumor grade (p=0,444), tumor multicentricity (p=0.397), concomitant CIS (p=0.316) and progression of disease (p=0,397). Relative lack of AR expression was significantly correlated to recurrent disease (p=0.001) on the basis of 3 studies involving 281 patients (Table 2). No significant heterogeneity of association between AR status and the clinical and pathological parameters was identified in any case, so fixed-effects models were used in the analysis. Forest plots of OR for patients' gender, tumor stage, grade and multicentricity and disease recurrence/progression are available in Fig. 2 (a through f).

Discussion

Mechanism of signaling by AR

AR is a nuclear steroid hormone receptor, member of the steroid hormone nuclear receptor superfamily, whose gene is located on the X chromosome (q11-12). The molecule is a ligand-inducible transcription factor composed of four distinct domains, namely the N-terminal transactivation domain, the DNA binding domain, a hinge region and the C-terminal ligand-binding domain (LBD); the latter associates with heat shock proteins (HSPs) in the cytoplasm (Heinlein et al., 2004). As testosterone enters the target cell, it binds to AR either directly or after conversion to 5alpha-dihydrotestosterone (DHT) by 5alpha-reductase (Heinlein et al., 2004; Li et al., 2017). Subsequently, the dimerized androgen-AR complex induces a conformational change in the AR.

HSPs are released and the complex translocates into the nucleus whereby the activated AR binds to the tissue-specific androgen-response element and recruits further proteins (i.e. general transcription factors and RNA polymerase II), leading to specific transcriptional activation or repression of androgen-regulated genes, emergence of oncogenic fusion genes by promoting DNA breaks and chromosomal rearrangements (Heinlein et al., 2004; Lin et al., 2009; Davey and Grossmann, 2016; Li et al., 2017). A number of co-regulatory proteins (coactivators and corepressors) usually mediate such receptor transactivation by facilitating DNA occupancy, chromatin remodeling, and by ensuring AR protein stability and proper AR subcellular distribution (Heinlein et al., 2004; Li et al., 2017). Alternatively, ligand-independent activation of the AR pathway may occur by non-androgenic proteins such as epidermal growth factor (EGF) and cytokines, mostly in prostate cancer cells (Lamont and Tindall, 2011; Li et al., 2017).

Role of AR in bladder carcinogenesis

Preclinical studies showed that both male and female AR-knockout mice (ARKO) did not develop BBN-induced BC, though absence or low levels of androgens could restore AR signaling and androgens could induce bladder carcinogenesis independently of AR (Miyamoto et al., 2007; Lombard and Mudryj, 2015; Inoue et al., 2018). Another study showed that mice had lower incidence of carcinogen-induced BC and a higher survival rate than wild-type mice when AR was ablated in the urothelium; moreover, a human normal urothelial cell line was more prone to carcinogenesis upon AR overexpression (Hsu et al., 2013).

On the other hand, clinical studies failed to confirm an unequivocal association between AR expression and BC development and progression (Okajima et al., 1975; Imada et al., 1997; Miyamoto et al., 2007; Hsu et al., 2013). Putative reasons for the conflicting results reported so far include: (1) AR expression, and thus the role of AR might change paralleling the functional and phenotypical changes of BC cells during tumor progression (Miyamoto et al., 2012); (2) different AR subtypes (AR 1 and AR2) have different roles in BC carcinogenesis (Sikic et al., 2017). Indeed, AR activation may modulate multiple independent pathways in BC cells, through activating/inhibiting different molecules such as EGFR/HER2, Wnt/β-catenin, p53, GATA3, Slug (Zheng et al., 2011; Hsu et al., 2013; Li et al., 2013, 2014; Jing et al., 2014). Finally, AR expression in BC has been found in 42 to 78% of tumor specimens (Zhuang et al., 1997; Boorjian et al., 2004, 2009; Kauffman et al., 2011), thus suggesting great heterogeneity.

AR expression in NMIBC

The present meta-analysis pointed out a significant direct association between AR expression in NMIBC and recurrence-free survival. This is in keeping with the results of a previous meta-analysis by Ide et al. (2017), as well as of previous single studies using IHC (Miyamoto et al., 2012; Nam et al. 2014; Izumi et al., 2016; Yonekura et al., 2018) and quantitative real-time PCR (Sikic et al., 2017; Yasui et al., 2019) to assess AR status and demonstrating that higher AR expression at both mRNA and protein levels was correlated with favorable outcome in NMIBC. Interestingly, in the study by Yonekura et al. (2018), AR positivity was an independent predictor of both first and multiple recurrences by a multivariate model. Indeed, loss of AR expression has been found to be strongly associated with higher grade and more invasive tumors (Miyamoto et al., 2012). This might suggest that AR positivity could play a role in the natural history of BC. Other studies, however, failed to confirm the prognostic role of AR expression (Zheng et al., 2011; Kauffman et al., 2011; Mir et al., 2011; Tuygun et al., 2011; Kawahara et al., 2015).

Although AR positive tumors showed a tendency to higher progression-free survival in two of the nine examined studies (Nam et al., 2014; Kim et al., 2015), the present meta-analysis failed to demonstrate a statistically significant correlation between AR status and NMIBC progression.

Likewise, Boorjian et al. detected AR positivity in 75% of NMI- as opposed to 21.4% MI-BCs, indicating that lower AR status was associated with tumor progression (Boorjian et al., 2004). Since then, an association between AR downregulation and increased tumor grade and stage of urothelial cancer has been reported by several authors (Boorjian et al., 2009; Rau et al., 2011; Tuygun et al., 2011; Miyamoto et al., 2012; Shyr et al., 2013; Ide et al., 2015; Williams et al., 2015; Godoy et al., 2016), though others failed to confirm it (Mir et al., 2011; Mashhadi et al., 2014; Elzamy et al., 2018). On the basis of a comprehensive meta-analysis of these data, the authors of a recent review proposed low AR expression having a role in BC development (Chen et al., 2017). This is somewhat contrary to the tumor promoting effect of AR signaling in BC (Li et al., 2017), as well as to the well-known role of AR in prostate cancer progression (Boorjian et al., 2009). Potential reasons could be: (1) AR signaling and other pathways complementarily stimulate BC development (Izumi et al., 2016); (2) the role of AR may change during the progression of BC (Sikic et al., 2017).

Technical issues in assessing AR expression

The prevalence of AR expression in the entire cohort of our meta-analysis was as high as 37.15%, ranging from 8.7% to 75%. However, in the study by Miyamoto et al. (2007) on animal models and human BC cell lines, the AR gene was detected in all 33 NMIBC specimens examined. Likewise, Yasui et al. (2019) retrieved AR mRNA by RT-qPCR in 81.1% of their pTa/T1 BC samples. These findings altogether suggest that measurement of AR expression at the molecular level by PCR-based techniques may overcome the technical limitations of immunohistochemistry, thus yielding more reliable results. The use of immunohistochemistry in almost all studies assessing AR status is due to its many advantages, including being simple and allowing to locate the protein, whether it is nuclear or cytoplasmic. Putative disadvantages are its semi-quantitative nature, interobserver variability, lack of standardized cut-offs, and differences in antibody epitopes, antigen retrieval methods, reagents and procedures in different laboratories (Mir et al., 2011), which may all be the cause of discrepant results. Interestingly, in one of the largest studies so far by Mir et al. (2011), three different monoclonal antibodies (namely, F39.4, NCL-AR-318 and AR441) targeting different epitopes have been used to assess AR expression in a cohort of 472 BCs from two institutional centers, with double-check blind validation and a further random sample analysis carried out in a third center, yielding overall similar results. In our analysis, the three most used antibodies (clones NCL-AR-318, 2F12 and AR441) all address the N-terminus of the human AR protein by targeting a prokaryotic recombinant protein of 321 amino acids (the first two) and the aminoacid sequence 299-315 (the latter one), respectively.

Still, immunohistochemistry remains the gold standard in assessing prognostic parameters in several tumors, such as breast cancer, where there is general consensus on standardized methods and assessment scores. Moreover, ongoing technical improvements and the increasing use of quality controls move on toward standardization of immunohistochemical methods and results.

Aside from the technical issues in AR assessment, our meta-analysis has other limitations, namely the small number and retrospective nature of the included studies

To our knowledge, this study was the first meta-analysis to clarify the prognostic value of AR expression in NMIBC. In consideration of the above limitations, studies on large selected cohorts should be designed to further validate this topic.

Therapeutic implications of AR expression in NMIBC

AR assessment may also have therapeutic implications in NMIBC. The interaction between intravesical BCG, the current standard treatment for high-risk NMIBC, and AR has been suggested by preclinical and clinical studies. Specifically, AR pathway inhibitors like antiandrogens have been

reported to improve the efficacy of BCG treatment (Chen et al., 2003; Shang et al., 2015) by reversing the DHT-dependent down-regulation of BCG-induced IL-6 expression, or by promoting BCG attachment to BC cells via recruitment of monocytes and macrophages following AR degradation. These findings have been supported by a recent clinical study reporting a significant decrease of recurrences in NMIBC patients under androgen deprivation treatment (ADT) or 5alpha-reductase inhibitors treatment (Shiota et al., 2017), and by ongoing clinical trials (Kang and Ku, 2017; Schweizer et al., 2017). Finally, ADT itself proved to be an independent prognosticator of BC recurrence in one retrospective analysis comparing prostate cancer patients with concurrent NMIBC who received or did not receive ADT (Izumi et al., 2014).

Conclusion

Available data suggest a direct correlation between AR expression and recurrence-free survival of patients with NMIBC, as well as the possibility to further improve this survival by androgen blockade. Turning findings into clinical practice, patients expressing AR seem to be at lower risk thus more suitable for conservative treatments, whereas those lacking AR expression seem to be at higher risk of disease, therefore they could benefit from immediate aggressive treatments. Further studies are however needed to confirm the potential value of this pathway in the decision-making process of patients with NMIBC.

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Figure legends

Figure 1. Flow chart of literature search and selection process of the studies included in the present meta-analysis.

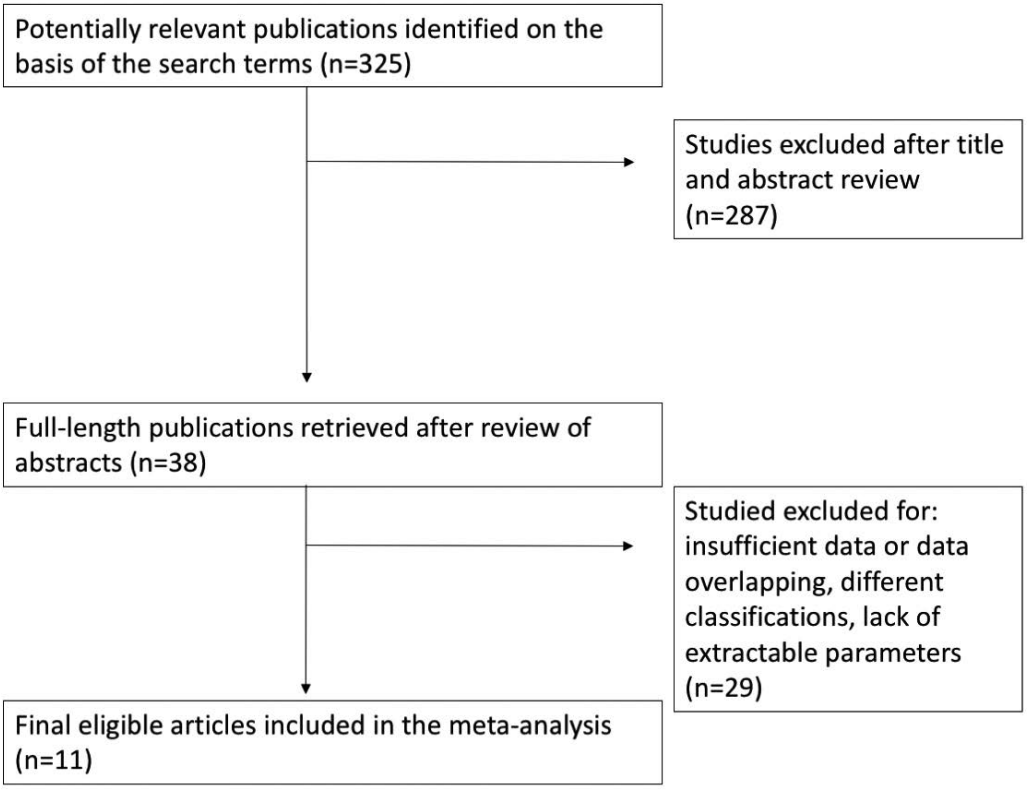
Figure 2. Forest plots of OR for patients' gender (a), tumor grade (b), tumor stage (c), tumor multicentricity (d), disease recurrence (e) and progression (f). Square indicates point estimate for each study into a horizontal line corresponding to 95% CI; size of square is a marker representing the effect size. Diamond is a possible representation of the pooled OR value, with its height standing for the estimated effect size and its width for the precision of the estimate.

REF	METHOD	STAGE	CLONE (IHC)	CUTOFF (IHC)	PREVALENCE n (%)	SIGNIFICANT ASSOCIATION	INDEPENDENT PREDICTOR
Boorjian, 2004	IHC	pTa,pTis,pT1	NCL-AR-318	NONE	21/28 (75,0)	NA	NA
Mir, 2011	IHC (TMA)		F39.4, NCL-AR-318, AR441	VARIABLE	11/126 (8,7)	NA	NA
Tuygun, 2011	IHC (TMA)	pTa,pT1	2F12	1%	64/106 (60,4)	AGE	NA
Miyamoto, 2012	IHC (TMA)	pTa,pT1	AR441	10%	49/97 (50,5)	NONE	NONE
Nam, 2014	IHC	pTa,pT1	2F12	10%	63/169 (37,2)	STAGE, MULTIPLICITY, RFS	RFS
Kim, 2015	IHC (TMA)	pTa,pT1	NA	30%	12/113 (10,6)	NONE	NONE
Izumi, 2016	IHC	pTa,pTis,pT1	N20	1-10%	44/72 (61,1)	RFS	RFS
Sikic, 2017	RT-qPCR	pT1	NA	NA	NA	RFS,PFS,CSS,KRT5, MULTIFOCALITY	RFS,CSS
Elzamy, 2018	IHC	pTa,pTis,pT1	AR441	10%	5/27 (18,5)	NA	NA
Yonekura, 2018	IHC	pTa,pTis,pT1	AR441	GIS 1.5	20/40 (50,0)	RFS,PFS	LOWER RISK OF FIRST RECURRENCE AND OF MULTIPLE RECURRENCES
Yasui, 2019	RT-qPCR	pTa,pT1	NA	NA	43/53 (81,1)	NONE	RFS

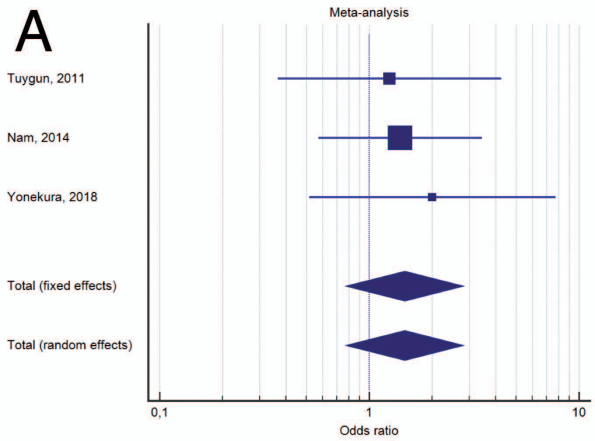
Table 1. Overview of the prognostic role of AR expression in NMIBC according to selected studies. CSS, cancer-specific survival; IHC, immunohistochemistry; KRT5, cytokeratin 5; PFS, progression-free survival; RFS, recurrence-free survival; RT-qPCR, quantitative real-time polymerase chain reaction; TMA, tissue microarra

Stratification	N° of studies	References	Pooled OR (95% CI)			Heterogeneity	
			Fixed effects	Random effects	P value	I^2 (%)	P value
Patients' gender (male vs. female)	3	(Tuygun, Nam, Yonekura)	1,475 (0,780-2,790)	1,474 (0,778-2,792)	0,232	0,00	0,8712
Tumor size (low <3 cm vs. high ≥3 cm)	2	(Izumi, Yonekura)	1,000 (0,265-3,768)	0,979 (0,261-3,677)	0,975	0,00	0,4897
Tumor stage (pTa-Tis vs. pT1)	8	(Boorjian, Mir, Tuygun, Miyamoto,Nam, Izumi, Elzamy, Yonekura)	1,256 (0,861-1,832)	1,178 (0,728-1,906)	0,237	21,35	0,2599
Tumor grade (low vs. high)	4	(Tuygun, Nam, Izumi, Yonekura)	1,200 (0,753-1,912)	1,170 (0,656-2,085)	0,444	27,80	0,2452
Tumor multicentricity (single vs. multiple)	4	(Tuygun, Nam, Izumi, Yonekura)	1,209 (0,779-1,876)	1,106 (0,598-2,044)	0,397	43,21	0,1522
Concomitant CIS (present vs. absent)	2	(Nam, Izumi)	1,428 (0,711-2,867)	1,416 (0,701-2,859)	0,316	0,00	0,6321
Recurrence (present vs. absent)	3	(Nam, Izumi, Yonekura)	0,411 (0,248-0,682)	0,412 (0,248-0,684)	**0,001**	0,00	0,8658
Progression (present vs. absent)	2	(Nam, Kim)	0,714 (0,327-1,558)	0,720 (0,331-1,566)	0,397	0,00	0,5187

Table 2. Meta-analysis between AR expression and clinicopathological and prognostic features of NMIBC (significant results are highlighted in bold).

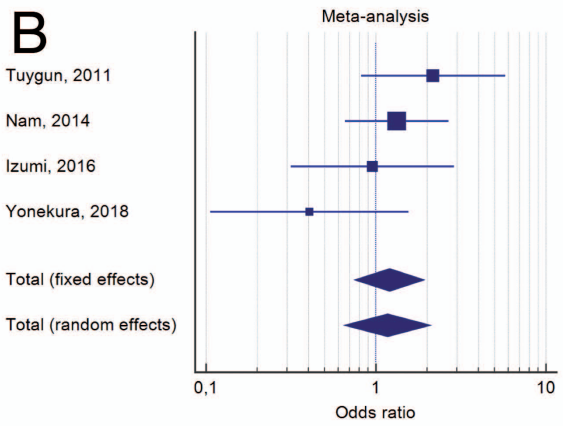

Potentially relevant publications identified on the basis of the search terms (n=325)
Studies excluded after title and abstract review (n=287)
Full-length publications retrieved after review of abstracts (n=38)
Studied excluded for: insufficient data or data overlapping, different classifications, lack of extractable parameters (n=29)
Final eligible articles included in the meta-analysis (n=11)

A



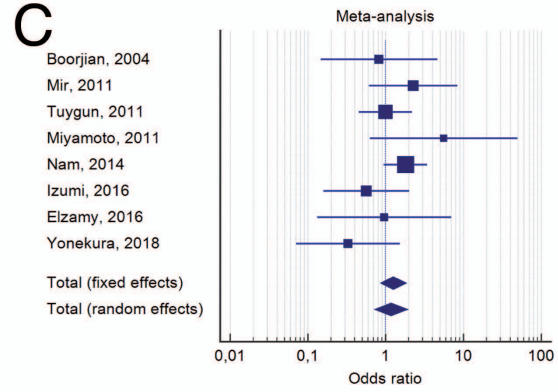
Pooled OR (95% CI)	
Fixed effects	Random effects
1,475 (0,780-2,790)	1,474 (0,778-2,792)

B



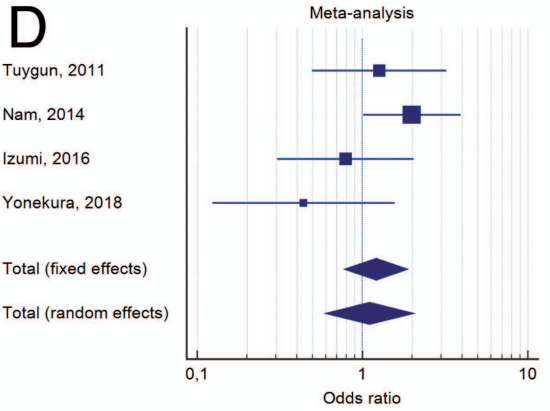
Pooled OR (95% CI)	
Fixed effects	Random effects
1,200 (0,753-1,912)	1,170 (0,656-2,085)

C



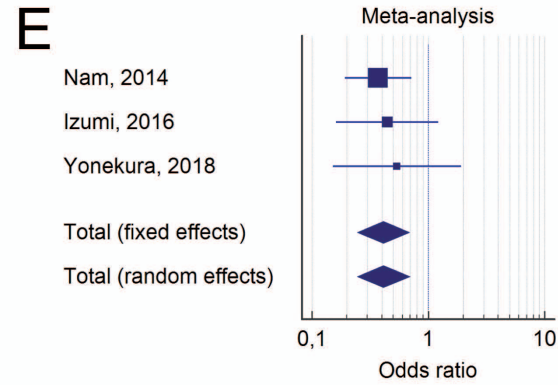
Pooled OR (95% CI)	
Fixed effects	Random effects
1,256 (0,861-1,832)	1,178 (0,728-1,906)

D



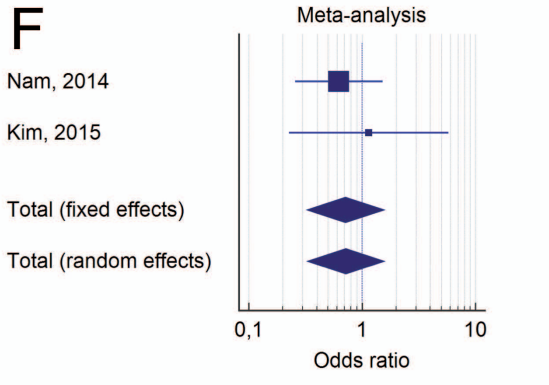
Pooled OR (95% CI)	
Fixed effects	Random effects
1,209 (0,779-1,876)	1,106 (0,598-2,044)

E



Pooled OR (95% CI)	
Fixed effects	Random effects
0,411 (0,248-0,682)	0,412 (0,248-0,684)

F



Pooled OR (95% CI)	
Fixed effects	Random effects
0,714 (0,327-1,558)	0,720 (0,331-1,566)