Younger Men With Prostate Cancer Have Lower Risk of Upgrading While on Active Surveillance: A Meta-analysis and Systematic Review of the Literature

Amr Mahran[1], Andrew Turk[1], Christina Buzzy, Michael Wang, Julia Yang, Mandy Neudecker, Irina Jaeger, and Lee E. Ponsky

Active surveillance has become a popular option for patients with low risk prostate cancer. Our objective was to examine the correlation between age and the risk of Gleason upgrading and biopsy progression. A systematic search was conducted. Eight studies met our eligibility criteria including 6522 patients with a median age of 65.8 (41-86) years. Per decade decrease in age, the pooled odds ratio and hazard ratio (CI 95%) for Gleason upgrading were 0.83 (0.73-0.94) and 0.87 (0.82-0.92), and for biopsy progression were 0.80 (0.74-0.86) and 0.88 (0.79-0.99), respectively. Overall, younger patients have a lower risk of GS upgrading and biopsy progression. UROLOGY 121: 11–18, 2018. © 2018 Elsevier Inc.

In the 1990s, active surveillance (AS) was introduced as a strategy to defer definitive treatment until tumor progression or reclassification.[1,2] Most low-risk prostate cancers are indolent and unlikely to significantly impact patients' quality of life or life expectancy. In these patients, AS performs as well as definitive treatment modalities.[2] The American Urological Association (AUA) provides Grade A and B recommendations for AS in patients with very-low and low-risk prostate cancer, respectively. In addition, AS may be offered selectively to patients with favorable intermediate-risk cancer (Grade C recommendation), however, it can be associated with a higher risk of metastasis compared to definitive treatments.[3] The NCCN also strongly considers AS for very-low-risk and low-risk prostate cancer and as an acceptable option for patients with favorable intermediate-risk prostate cancer.[4] Regular PSA checks (no more often than 6 months), digital rectal examinations (DRE) and repeat biopsy (no more often than 12 months) are components of AS unless otherwise indicated. In case of persistently rising PSA with negative biopsy or suspected anterior lesions, MRI may be considered for detection of potential upstaging.[4]

It is important to consider the often indolent and less-aggressive nature of prostate cancer in younger patients. At diagnosis, older patients are more likely to have high-risk prostate cancer than younger patients.[5,6] In addition, older age at the time of prostate cancer diagnosis serves as a significant predictor of cancer-specific mortality.[7]

AS may lead to avoidance of potential bothersome side effects associated with definitive treatments (e.g. erectile dysfunction and urinary incontinence), which could negatively impact patients' quality of life, especially in the younger population.[8,9] Klotz et al. have shown in a large prospective study that up to 50%-60% of AS patients remain free from intervention for over 15 years.[2] However, even with strict inclusion criteria, histological upgrading can occur in up to 28% of patients.[10,11] The role of age when considering placement of patients on AS is not well-reported in the literature.[12]

In this systematic review, our aim is to investigate the correlation between the risk of Gleason upgrading and biopsy progression and age in patients on AS in the current literature.

MATERIALS AND METHODS

This study follows the MOOSE Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies[13] and has been registered on the international prospective register of systematic reviews (PROSPERO #CRD42018082145). The study used the GRADE system to generate and evaluate the evidence.[14]

[1] *These authors contributed equally to this work.*

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From the Division of Urologic Oncology, Urology Institute, University Hospitals Cleveland Medical Center, Cleveland, OH; the Case Western Reserve University School of Medicine, Cleveland, OH; the Department of Urology, Assiut University, Egypt; and the Core Library, University Hospitals Cleveland Medical Center, Cleveland, OH

Address correspondence to: Lee E. Ponsky, M.D., Division of Urologic Oncology, Urology Institute, University Hospitals Cleveland Medical Center, 11100 Euclid Avenue, Cleveland, OH 44106. E-mail: Lee.ponsky@uhhospitals.org

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Literature Search

A systematic search of publications on the association of age of patients on AS and biopsy outcomes was conducted using online databases (MEDLINE, EMBASE, Cochrane [with online Ovid interface], and Web of Science). The search was performed in collaboration with an expert reference librarian (MN) who aided in formulating the search strategy. The search was limited to the English language on articles published between 1980 and April 2017. Search terms included MeSH and EMBASE terms, in addition to keywords, including prostate cancer, prostate neoplasm, AS, and conservative management. Two researchers (AT and AM) reviewed the search details independently to identify eligible articles. A relevant paper published in June 2017 was included.[10] The full search strategies are available in the appendix.

Eligibility Criteria and Study Selection

Our primary interest was to catalogue studies that included age as a predictor for pathological outcomes of prostate cancer patients on AS. We conducted a primary search for AS articles within the references given by the reference librarian, following which, we refined our search to specifically include articles that used age as a variable as described in the abstracts.

Quality Evaluation of the Included Studies

We evaluated the included studies using the NewCastle—Ottawa Quality Assessment Scale for cohort studies and the Cochrane risk of bias tool for randomized control trials (Table 1).[15,16] Further evaluation using the quality assessment tool from the National Heart, Lung and Blood institute was conducted *(Supplementary table 1)*.[17]

Data Abstraction, Synthesis and Analysis

Data abstraction was performed using a standardized form, which included study characteristics such as author, year, type of study, and number of patients. In two studies by Wong et al.[18] and Mergel et al.,[19] we roughly calculated the pooled median age using the median of the medians for age in each study's subgroups (Tukey's Ninther),[20] and then we identified the lower and upper ranges within these subgroups and reported them as the interquartile range (IQR) for each study. We used the same method to roughly estimate the median age and IQR of the population included in the current study.

For all the included studies, except that by Leapman et al.,[12] the odds ratios were calculated as the reciprocal of the odds ratio (1/OR) to express GS upgrading and biopsy progression as a per year decrease in age instead of a per year increase as originally reported. Subsequently, OR, hazard ratios (HR), and confidence intervals (CI) for age as a predictor were expressed as a per decade decrease in age rather than per year (by exponentiation to the tenth power).[21] Standard errors (SE) were calculated using the equation: log [upper CI]−log [lower CI], divided by (2 × 1.96).

To undermine the heterogeneity among studies, a random-effects model was used to derive the ORs and HRs.[22] Heterogeneity among the studies was assessed by statistical testing of I^2.[23] Review Manager 5.3 software was used to generate forest plots and to assess the risk of bias. (RevMan 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration).

RESULTS

Out of 6,091 studies, eight were included for formal synthesis and final analysis (Fig. 1). Six studies were prospective[12,24-27] including a randomized, double blinded study,[19] while two were retrospective studies.[18,28] Four studies were performed in the US,[12,26-28] two in Canada,[18,25] and one from multiple countries.[24] Evaluation of the quality of included studies was performed using the Ottawa NewCastle system for observational studies and the Cochrane risk of bias tool for randomized control trials, and overall, the quality of the included studies was good (Table 1).

Overall, 6,522 patients constituted the study population. Ages ranged from a median of 61-68 years with a roughly estimated median of 65.8 (41-86) years. Patients were monitored for varying periods of time ranging between 1.6 and 6.5 years (Table 1).

Because of the studies' varying outcomes, we performed subgroup analyses using GS upgrading independently and biopsy progression (GS upgrading and/or increased tumor volume) as study outcomes. Simply, Gleason upgrading refers to the increase of Gleason score during follow-up, while biopsy progression indicates either Gleason upgrading, tumor volume increase or both (for study-specific definitions, please refer to Table 1). Some studies utilized logistic regression and reported odds ratios, while other studies performed Cox regression and reported hazard ratios. Within each of the two outcomes, subgroup analyses were performed according to the regression method used.

Subgroup Analysis of Studies with GS Upgrading as an Outcome

Five studies (4,525 patients) were analyzed for this outcome with two studies reporting ORs and three studies reporting HRs (Table 1). Pooled analysis for this outcome showed that younger patients were associated with a lower risk of GS upgrading—OR (per decade decrease in age) 0.83, 95% CI 0.73-0.94, Z = 2.86, P = .004 (Fig. 2A), and HR 0.87, 95% CI 0.82-0.92, Z = 5.16, P < .0001 (Fig. 2B). Heterogeneity might not be important in both analyses (I^2 = 0%).

Subgroup Analysis of Studies with Biopsy Progression as an Outcome

Five studies (3,716 patients) defined pathological biopsy (Bx) progression as an outcome- three studies reported odds ratios (OR), and 2 studies reported HR (Table 1). Pooled analysis for this outcome showed that younger patients had a lower risk of pathological Bx progression—OR (per decade decrease in age) 0.80, 95% CI 0.74-0.86, Z = 5.84, P = < .0001 (Fig. 2C) and HR 0.88, 95% CI 0.79-0.99, Z = 2.06, P = .04 (Fig. 2D). Heterogeneity might not be important regarding the odds ratio analysis (I^2 = 0%), while there was moderate heterogeneity in the hazard ratio analysis (I^2 = 52%).

DISCUSSION

The primary finding of our study is that younger patients (per decade decrease in age) on AS are associated with an average of 13%-17% (6%-8% up to 18%-27%) lower risk of GS upgrading and 12%-20% (1%-14% up to 21%-26%) lower risk of pathological biopsy progression. For example, a 50-year-old patient is expected to have an average of 13%-17% lower risk of GS upgrading and an

Table 1. Description and quality assessment of the included articles

First Author (Year)	Type of Study (Country)	Total (n)	GSU: n (%)	Biopsy Progression n (%)	Median Age (IQR)	Follow-Up Period (Years)	Definition of GSU (OR and/or HR [95% CI] or Coefficient, SE)	Definition of Biopsy Progression (OR and/or HR [95% CI])	*NEWCASTLE-Ottawa Scale for Cohort Studies*		
									Selection (4 Stars)	*Comparability (2 Stars)*	*Outcome (3 Stars)*
Anderson C. B. (2015)[28]	Retrospective (USA)	646	58 (9)	NR	66 (61-72)	2 *(limit)*	GS ≥ 7 on confirmatory biopsy [OR 1.05 (1.01-1.09), *P* = .009]	NR	★★★	★	★★★
Bul M. (2013)[24]	Prospective (The Netherlands, Italy, Finland, Japan, Germany, France, Canada, Sweden, Spain, Australia, Norway, Czech Republic, Austria, Switzerland, Turkey, Belgium and New Zealand)	1480	NR	415 (28%)	65.6 (61-70.4)	1.6 *(median)*	NR	≥3 positive biopsy cores and/or GS > 6 [OR 1.02 (1.00-1.04), *P* = .02]	★★★	★	★★★
Jain S. (2015)[25]	Prospective (Canada)	862	186 (21.3)	NR	68 (41-86)	6.5 *(median)*	Any increase in primary or secondary Gleason grade on repeat biopsy [Coefficient 0.34, SE 0.01, *P* = .0044]	NR	★★★	★	★★★
Leapman M. (2017)[12]	Prospective (USA)	1433	NR	NR	63 (57-68)	4.1 *(median)*	Any increase in GS to 3+4 or higher [HR 0.969 (0.956-0.983), *P* < .01]*	GS upgrade ≥ 7 or tumor volume to > 33% positive cores (HR 0.981 [0.970-0.993]), *P* < .01*	★★★	★★	★★★
Tosoian J. (2015)[26]	Prospective (USA)	1298	233 (18)	467 (36)	66 (62-69)	*5 (median)*	Grade reclassification to GS 3+4 and 4+3 or greater [HR 1.03 (1.01-1.06), *P* < .05]	NR	★★★	★	★★★

Continued

Table 1. Continued

First Author (Year)	Type of Study (Country)	Total (n)	GSU: n (%)	Biopsy Progression n (%)	Median Age (IQR)	Follow-Up Period (Years)	Definition of GSU (OR and/or HR [95% CI] or Coefficient, SE)	Definition of Biopsy Progression (OR and/or HR [95% CI])	*NEWCASTLE-Ottawa Scale for Cohort Studies*		
									Selection (4 Stars)	*Comparability (2 Stars)*	*Outcome (3 Stars)*
Whitson J. (2011)[27]	Prospective (USA)	241	-	55 (23)	61 (54-68)	NR	NR	(GS increase ≥ 7) or volume increase (to > 33% of cores positive or > 50% of the maximum core positive) [OR 1.8 (1.7-1.9), *P* = .02]†	★★★	★	★★★
Wong L. (2013)[18]	Retrospective (Canada)	286	58 (20)	116 (40.5)	63.4 (57.8-70.1)	*3.4 (median)*	Increase to GS ≥ 7 [HR 1.05 (1-1.10), *P*= .04]	Increase in GS ≥ 7 (grade-related progression) and/or volume-related progression (core > 3 or single core maximum involvement >50%) [HR 1.05 (1.01-1.09), *P* = 0.01]	★★★	★	★★★
Margel D. (2013)[19]	Randomized double-blind Study (Canada and/or USA)	276	NR	94 (34.1)	65.75 (48-81)	*3 (limit)*	NR	≥4 cores positive for cancer or a single core involvement of (≥ 50%) or grade progression (GS ≥ 7) (OR 1.05 [1.01-1.08], *P* = .009)			

Cochrane risk of bias tool					
Random sequence	***Allocation concealment***	***Performance bias***	***Detection bias***	***Attrition bias***	***Reporting bias***
Low risk	***Low risk***	***Low risk***	***Low risk***	***Low risk***	***Unclear risk***

Abbreviations: CI, confidence interval; GSU, Gleason score upgrading; HR, hazard ratio; n, number; NR, not reported; OR, odds ratio, SE, standard error.
ORs and HRs included in this table represent the original values before transformation for the purpose of the current study.
* Hazard ratios were reported per year decrease in age.
† Odds ratios were reported per decade increase in age.

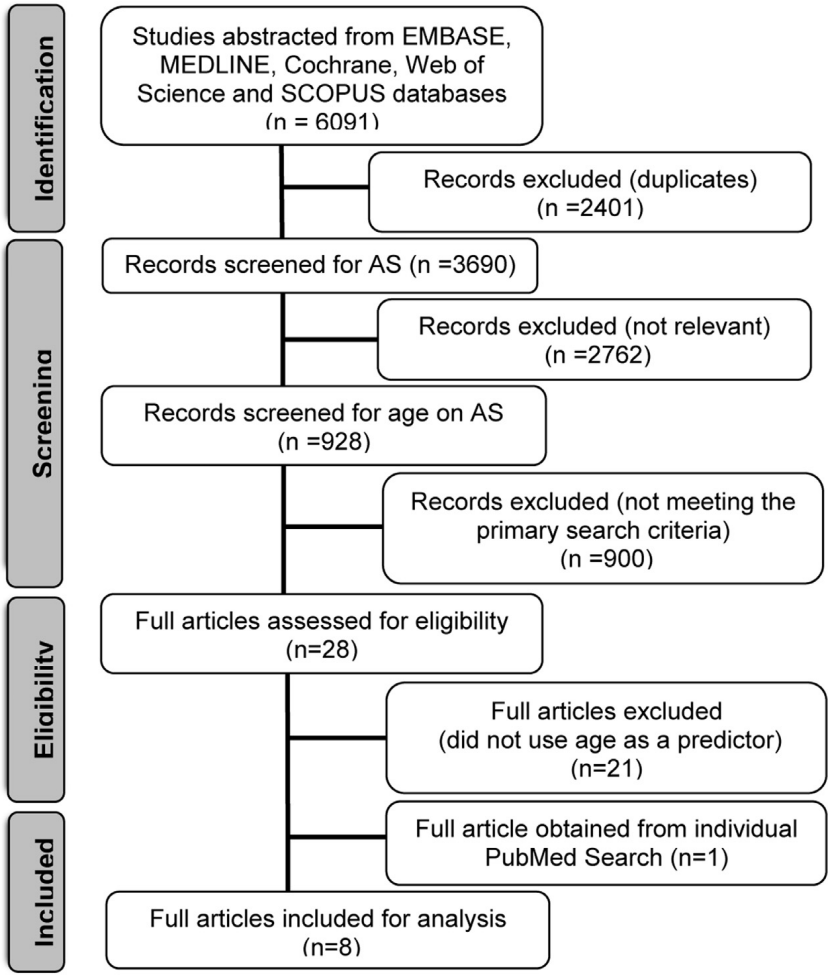

Figure 1. Flow chart of the study selection process.

average of 12%-20% lower risk of biopsy progression than a 60-year-old patient. Furthermore, a 50-year-old is expected to have an average of 26%-34% lower risk of GS upgrading and an average of 24%-40% lower risk of biopsy progression than a 70-year-old patient on AS for prostate cancer.

It has been reported that AS in eligible 65-year-old patients was associated with the highest quality-adjusted life years with low prostate cancer-specific mortality when compared to other definitive treatments.[29,30] Notably, the AS acceptance rate has greatly increased from 10%[33,34] to 40%-50% over the past decade.[35] Our study included 6,522 AS patients between 41 and 86 years old with an estimated pooled median of 65.8 years. Five out of 8 studies had a lower range and /or IQR in the 40s or 50s, while 3 out of 8 studies reported a lower range and/or IQR in the early 60s (Table 1). We found that younger age is associated with lower risk of GS upgrading and biopsy progression. It can be inferred that patients <65.8 years on AS have both lower risk of GS upgrading and biopsy progression compared to older patients (>65.8 years). Furthermore, Leapman et al. found that younger patients (<60 years) had lower risk of GS upgrading with 73% GS upgrading-free rates at 3 years and 55% at 5 years compared to 64% and 48% in older patients (>60 years).[12]

Current usage of AS in younger patients remains controversial. Several studies indicate that patients may miss the chance for curative treatment.[31] Rogers et al. have shown that younger patients who undergo laparoscopic radical prostatectomies may regain urinary function and potency sooner than older patients.[32] However, they stated that 33 out of 116 (28%) patients (<59 years) required pads for incontinence [24 required ≤1 pad/day and 9 > 1 pad/day] at 1-year follow-up and about 23/58 patients (39.6%) did not regain their potency after bilateral nerve sparing at 1-year follow-up. They defined potency as penile rigidity sufficient for intercourse with or without phosphodiesterase-5 inhibitors. In a recent study, Nossiter et al. have shown that there is a small difference between robotic and laparoscopic prostatectomy regarding the sexual function and urinary incontinence improvement at 18 months which is unlikely to be of clinical significance.[36] Satkunasivam et al. showed that radical prostatectomy after AS did not lead to significant adverse pathological outcomes when compared to other patients with similar preoperative histopathology.[37] Leapman et al. showed that there is no significant correlation between

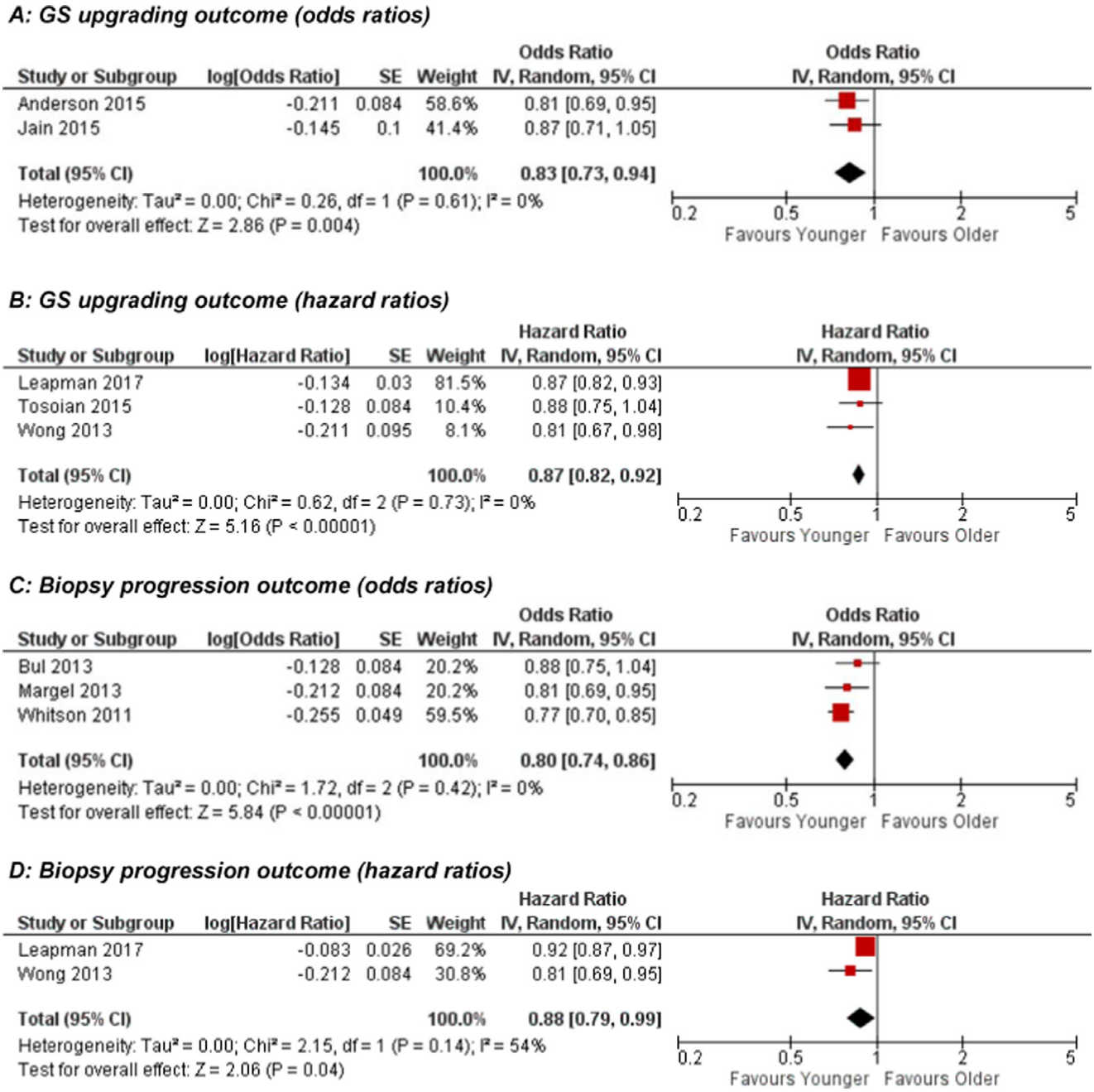

Figure 2. Pooled analyses of age "per decade decrease" as a predictor for GS upgrading (**A**): Studies reporting odds ratios, (**B**) Studies reporting hazard ratios, and age "per decade decrease" as a predictor for biopsy progression (**C**) Studies reporting odds ratios, and (**D**): Studies reporting hazard ratios. (Color version available online.)

younger age and the risk of delayed curative treatment or the risk of biochemical failure after delayed radical prostatectomy.[12] Our study shows that the risk of GS upgrading while on AS is lower in younger patients. We assume that strictly selected patients with very-low risk criteria may benefit from being on AS and avoid operative side effects.

Younger individuals are more likely to have lower incidence of erectile and/or voiding dysfunction at the time of prostate cancer diagnosis.[9] Immediate treatment may impose an increased risk of side effects such as incontinence and impotence. The implications of active treatment may also result in treatment regret coupled with a lower quality of life.[38,39] Anderson et al. surveyed patients on AS who reported having normal overall and prostate-cancer-related anxiety as well as a high quality of life.[40] Furthermore, younger patients diagnosed with prostate cancer are expected to live longer.[41] For these individuals, AS may serve as a useful option in avoiding unintended consequences from active treatment.[9] In contrast, patients on AS might experience possible adverse events from repeated biopsy. Ongoing studies are currently evaluating the adequacy of negative MRI in patients with very low-risk cancer in order to avoid repeated biopsy.[42] Many urologists are skeptical to place younger patients on AS; however, younger patients may in fact have the most to benefit from AS.

While the results do not contradict the use of AS in older patients, physicians should use caution when placing them on AS. At the time of diagnosis, older patients are more likely to have high-risk prostate cancer than younger patients.[5,6]. Some studies have noted that at initial biopsy, there is under-sampling of larger prostates typically found in older patients, which may result in apparent progression on confirmatory biopsy while on AS.[12] The authors believe that the utilization of MRI-targeted prostate biopsies may reduce this risk.

Brassell et al. have demonstrated that aggressive prostate cancer is more prevalent in older patients.[43] In addition, age at the time of diagnosis serves as a significant predictor of prostate cancer specific mortality.[44] Older individuals are more likely to develop cancer due to factors such as genomic instability, epigenetic changes, and increased susceptibility to oncogenic mutations.[45] Another factor is immune senescence, which is the reduced ability to respond to tumors due to immune-surveillance evasion with increasing age and defects in naïve and memory T-cells.[46]

The percentage of GS upgrading and biopsy progression range up to 31.3% and 40.5%, respectively, according to the studies included in this review. However, these values may be inflated due to the varied AS inclusion criteria across studies. The variability in the duration between diagnostic and follow-up biopsies and the number of biopsies could be additional factors potentially skewing these percentages. We assume that adherence to the strict criteria of AS derived from the "very low-risk" disease group defined by the 2017 AUA guidelines[47] may decrease the extent of GS upgrading and/or biopsy progression.

This systematic review is derived from level 1a-2c articles with grade A-B recommendation according to the Oxford Center of Evidence.[48] According to GRADE, the current study certainty ranged from moderate to high level of evidence[14] *(Supplementary table 2)*. To our knowledge, this is the first systematic review evaluating the impact of age on prostate cancer progression for patients on AS. A major limitation of the present study is the small number of studies which constituted this review, which in turn, may affect the fitting of the random-effect model used in the study. However, this can be partially overcome with the large number of total subjects. Additional weaknesses include the presence of inconsistencies in the definitions used for the GS upgrading and biopsy progression outcomes and different regression analyses used in each study.

In summary, while AS is largely offered to older patients, it appears that they are associated with a higher risk of GS upgrading and disease progression. Contrary to many urologists' practice, younger patients may be good candidates if the strict criteria of AS were uniformly enforced. According to this systematic review of the literature, younger age is associated with lower risk of GS upgrading and biopsy progression. In order to avoid interventional-related adverse events and to enhance quality of life, AS may be considered for younger patients. Further randomized control trials are warranted to compare the safety of AS versus other definitive treatments in young patients who are eligible for AS.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.urology.2018.06.048.

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