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Prostate Cancer

Active Surveillance for Men Younger than 60 Years or with Intermediate-risk Localized Prostate Cancer. Descriptive Analyses of Clinical Practice in the Movember GAP3 Initiative

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Article info

Abstract

Background: Active surveillance (AS) is a management option for men diagnosed with low-risk prostate cancer. Opinions differ on whether it is safe to include young men (≤60 yr) or men with intermediate-risk disease.
Objective: To assess whether reasons for discontinuation, treatment choice after AS, and adverse pathology at radical prostatectomy (RP; N1, or ≥GG3, or ≥pT3) differ for men ≤60 yr or those with European Association of Urology (EAU) intermediate-risk disease from those for men >60 yr or those with EAU low-risk disease.
Design, setting, and participants: We analyzed data from 5411 men ≤60 yr and 14 959 men >60 yr, 14 064 men with low-risk cancer, and 2441 men with intermediate-risk cancer, originating from the GAP3 database (21 169 patients/27 cohorts worldwide).

[†] The Movember Foundation's Global Action Plan Prostate Cancer Active Surveillance (GAP3) consortium members are presented in the Supplementary material.
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Outcome measurements and statistical analysis: Cumulative incidence curves were used to estimate the rates of AS discontinuation and treatment choice.

Results and limitations: The probability of discontinuation of AS due to disease progression at 5 yr was similar for men aged ≤60 yr (22%) and those >60 yr (25%), as well as those of any age with low-risk disease (24%) versus those with intermediate-risk disease (24%). Men with intermediate-risk disease are more prone to discontinue AS without evidence of progression than men with low-risk disease (at 1/5 yr: 5.9%/14.2% vs 2.0%/8.8%). Adverse pathology at RP was observed in 32% of men ≤60 yr compared with 36% of men >60 yr ($p = 0.029$), and in 34% with low-risk disease compared with 40% with intermediate-risk disease ($p = 0.048$).

Conclusions: Our descriptive analysis of AS practices worldwide showed that the risk of progression during AS is similar across the age and risk groups studied. The proportion of adverse pathology was higher among men >60 yr than among men ≤60 yr. These results suggest that men ≤60 yr and those with EAU intermediate-risk disease should not be excluded from opting for AS as initial management.

Patient summary: Data from 27 international centers reflecting daily clinical practice suggest that younger men or men with intermediate-risk prostate cancer do not hold greater risk for disease progression during active surveillance.

1. Introduction

Active surveillance (AS) can be offered to patients with low-risk disease and to selected patients with intermediate-risk disease [1–4]. However, there is no consensus on the selection criteria for patients with intermediate-risk disease, and the current evidence of including men with intermediate-risk disease on AS with <10% Gleason pattern 4 is classified as weak by the European Association of Urology (EAU) [1]. One argument against the inclusion of *all* men with intermediate-risk disease in AS is the increased risk of biochemical recurrence (BCR) after radical prostatectomy (RP) [5]. However, Abern et al [5] also showed that the risk of BCR resulting from delayed RP was not different for men with low-volume intermediate-risk disease (≤33% positive biopsy cores and ≤cT2a) from that for men with immediate treatment. As an argument to include men with intermediate-risk disease on AS, single-center studies have shown that there is no difference in metastatic progression between men diagnosed with grade group (GG) 2 disease and those diagnosed with GG1 disease when initially managed with AS [6–8]. Other studies show that the cancer-specific survival for men with intermediate-risk disease and managed with AS is over 90% [6,8–10]. For men diagnosed with low-risk disease, this probability is 94–99% [11,12]. However, it was also shown that men diagnosed with GG2 disease and initially managed with AS have a higher risk of adverse pathology at RP than men with GG1 disease and initially managed with AS (ie, 28% vs 22%) [13]. However, one can argue that the resulting increased number of years with good quality of live due to AS could outweigh the small increased risk on adverse pathology at RP and cancer-specific death, making the choice of AS as initial treatment realistic for some patients.

Besides intermediate-risk disease, the suitability of AS for younger patients has not been accepted universally. Most AS registries/programs apply a lower age cutoff, as reflected in the median age of 62–68 yr reported in a review on AS cohorts [14]. However, data are available that men diagnosed under 60 yr show an equal or even lower risk of disease progression to GG3 on AS [15,16]. Furthermore, a study showed that younger men who undergo RP after biopsy upgrading showed a lower risk of upgrading at RP than older men [15]. This suggests that AS could also be a good management strategy for younger men.

Currently, the evidence of including men with intermediate-risk disease or younger men emerges mainly from single-center studies that are likely to represent a homogeneous patient population. Using the largest centralized AS database in the world (the Movember GAP3 database [17]), we have the unique opportunity to analyze pooled data from 27 cohorts worldwide. We aimed to gain insight into the reasons for discontinuing AS, treatment choice after AS, and the rate of adverse pathology at RP in order to assess the safety of AS in younger men and those with intermediate-risk disease. We compared men ≤60 yr with those >60 yr of age at the time of diagnosis and compared men with low-risk disease with those with intermediate-risk disease.

2. Patients and methods

2.1. Study population

Analyses were performed on the GAP3 database version 3.2 containing data from a total of 21 169 patients on AS from 27 AS cohorts worldwide. Inclusion criteria and follow-up protocols differed between centers, as described previously by Van Hemelrijck et al [18]. The general consensus on inclusion criteria were cT1-T2, serum prostate-specific antigen (PSA)

Table 1 – Patient characteristics at inclusion for age group

	Age ≤60 yr (n = 5411)	Age >60 yr (n = 14 959)	p value [a]
Overall follow-up (yr), median (IQR)	2.7 (1.1–5.2)	2.5 (1.1–5.0)	<0.001
Follow-up for men still on AS (yr), median (IQR)	3.1 (1.1–6.0)	2.8 (1.1–5.4)	<0.001
Years of follow-up by reason for discontinuation, median (IQR)			
Anxiety	2.0 (0.9–3.7)	1.5 (0.9–2.8)	<0.001
Conversion without evidence of progression	1.7 (0.9–3.4)	1.9 (1.0–4.0)	<0.001
Disease progression	2.2 (1.2–4.2)	1.9 (1.1–3.8)	<0.001
Lost to FU	3.7 (1.8–6.5)	4.7 (2.3–8.9)	<0.001
Non-PCa death	5.5 (2.8–8.8)	5.8 (3.1–9.6)	<0.001
Age at diagnosis (yr), median (IQR)	57 (53–59)	68 (65–72)	<0.001
Age at discontinuation (yr), median (IQR)	60 (56–62)	71 (68–76)	0.002
PSA (ng/ml)			
Median (IQR)	4.9 (3.8–6.6)	5.7 (4.3–7.5)	<0.001
Unknown, n (%)	237 (4)	619 (4)	
Prostatic volume TRUS (cc)			
Median (IQR)	39 (30–51)	45 (35–62)	<0.001
Unknown, n (%)	1582 (29)	3305 (22)	
PSA density			
Median (IQR)	0.13 (0.09–0.17)	0.12 (0.09–0.17)	<0.001
Unknown, n (%)	1684 (31)	3605 (24)	
cT stage, n (%)			
T1	4127 (87)	11 105 (85)	<0.001
T2	603 (13)	2003 (15)	
Unknown	681 (12)	1851 (12)	
GG, n (%)			
1	5077 (94)	13 328 (90)	<0.001
2	273 (5)	1301 (9)	
>2	37 (1)	224 (2)	
Unknown	24 (0)	106 (4)	
Maximum percentage cancer in any core			
Median (IQR)	10 (5–21)	10 (5–25)	0.03
Unknown, n (%)	2143 (40)	7201 (48)	
EAU Risk group, n (%)			
Low risk	3974 (90)	9970 (82)	<0.001
Intermediate risk	417 (9)	2008 (16)	
High risk	49 (1)	250 (2)	
Unknown	971 (18)	2731 (18)	
Biopsy cores with prostate cancer, n (%)			
1	3102 (60)	8070 (58)	<0.001
2	1127 (22)	3593 (26)	
>2	940 (18)	2366 (17)	
Unknown	242 (4)	930 (6)	

AS = active surveillance; EAU = European Association of Urology; FU = follow-up; GG = grade group; IQR = interquartile range; PCa = prostate cancer; PSA = prostate-specific antigen; TRUS = transrectal ultrasonography.

[a] Categorical variables were analyzed using chi-square test and continuous variables were analyzed using Mann-Whitney U test; p values are not based on the unknowns and are due to the large samples not being informative.

≤10 ng/ml, a biopsy Gleason GG of 1 or 2, and a maximum of two tumor-positive biopsy core samples. During follow-up, most protocols recommend serial measurements of serum PSA levels (every 3–6 mo), digital rectal examination (every 6–12 mo), and surveillance biopsy sampling in order to identify pathological progression (every 1–3 yr).

The GAP3 database contains clinical information from each patient at inclusion, during AS, and at discontinuation of AS, including potential following treatments. Coding of these variables has previously been described by Van Hemelrijck et al [18]. In short, reason for discontinuation includes disease progression (either clinical and/or pathological, PSA, or radiological progression as defined according to centers' own criteria), conversion to active treatment without evidence of progression, watchful waiting, non–prostate cancer (non-PCa) death, anxiety, or "unknown" reasons. If the reason for discontinuation was classified as "other/unknown", but the "pathological progression status" reported at the time of AS discontinuation was "GG ≥3" or the "clinical progression status" was "≥cT3" or "PSA progression status" was "PSA >20", the reason for discontinuation was also classified as signs of disease progression. We should note that the term "sign of disease progression" as used in this manuscript can refer to risk reclassification (ie, disease progression within the 1st year of AS) or disease progression as such (ie, disease progression after the 1st year of AS).

Recorded treatment options after discontinuation of AS include RP, radiotherapy (RT), hormonal therapy (HT), watchful waiting, other treatment, or "unknown". The group of men labeled as those receiving "other treatment" consists predominantly of men receiving RT combined with HT, or those who underwent focal therapy. Information at RP includes GG at RP, pT stage, pN stage, and surgical margin status. Adverse pathology at RP was defined as ≥pT3 stage or the presence of positive surgical margins or lymph node involvement or GG ≥3. If men discontinued AS without evidence of progression and the treatment choice was unknown, reason for discontinuing was labeled as unknown.

We analyzed the reasons for discontinuing AS, treatment choice after AS, and adverse pathology at RP for (1) men ≤60 yr compared with men >60 yr at the time of diagnosis, (2) men of any age with EAU-defined low-risk disease compared with those with intermediate-risk disease, and (3) EAU low- and intermediate-risk groups stratified by age (≤60 vs >60 yr).

2.2. Statistical analyses

Descriptive statistics were used to compare patient and tumor characteristics at the initiation of AS and the rate of adverse pathology (defined as R1, N1, ≥GG3, or ≥pT3) at RP (1) between men ≤60 and >60 yr of age,
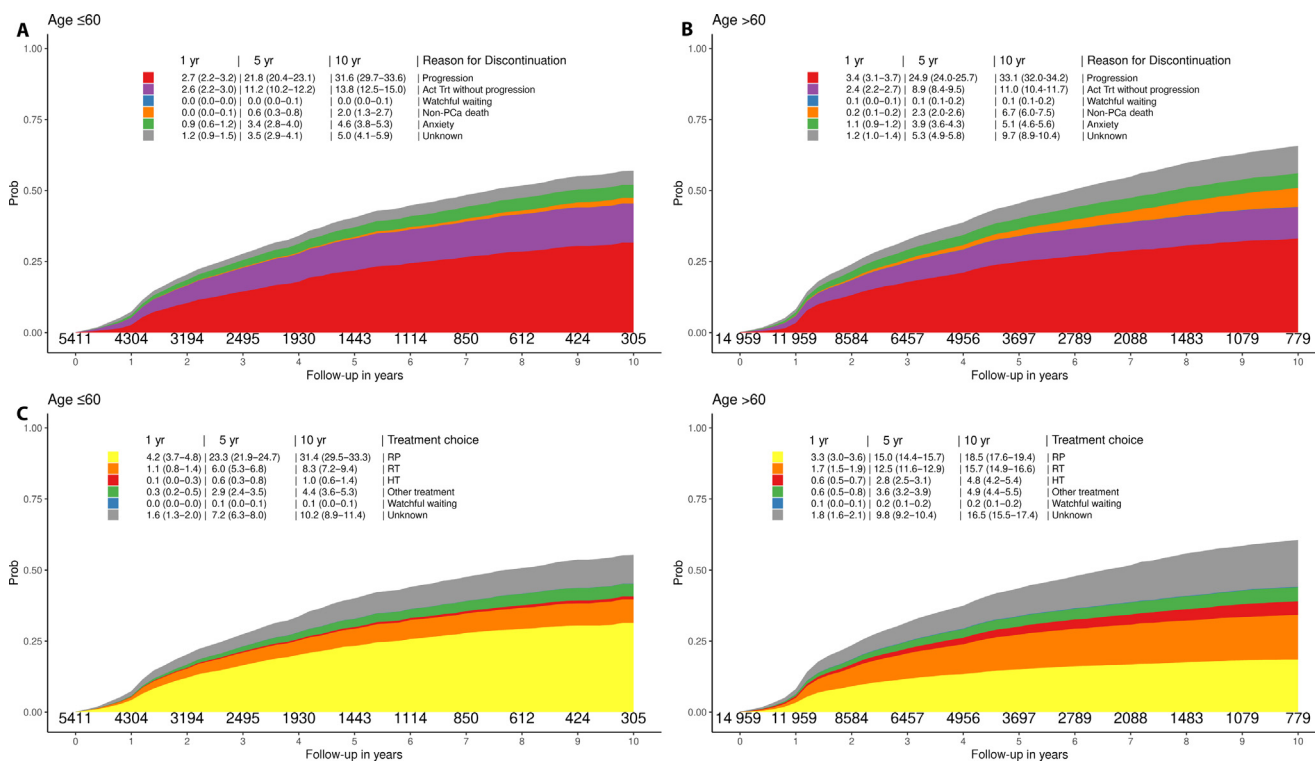
Fig. 1 – (A and B) Reason for discontinuation and (C and D) treatment choice for men diagnosed at age ≤60 yr and >60 yr. The 95% CI values are shown in parentheses. Act trt = active treatment; CI = confidence interval; HT = hormonal therapy; PCa = prostate cancer; Prob = probability; RP = radical prostatectomy; RT = radiotherapy.

and (2) between men with EAU low-risk and intermediate-risk disease. Cumulative incidence curves were used to estimate the probability of discontinuation from AS and treatment choice using R version 3.6.0 [19] and R-package cmprk [20]. For estimating the cumulative incidence of the reason for discontinuing AS, censoring included men still on AS and men lost to follow-up; for the estimation of treatment choice, censoring also included those men who died. As a sensitivity analysis, we also used d'Amico risk group classification.

3. Results

3.1. Age groups

At diagnosis, a total of 5411 men were ≤60 yr and 14 959 >60 yr. Table 1 shows the different patient and tumor characteristics for the two age groups. The median follow-up of men still on AS was 3.1 yr (interquartile range [IQR] 1.1–6.0) for men ≤60 yr and 2.8 yr (IQR 1.1–5.4) for men >60 yr. Data of >5-yr follow-up were available for 1443 men ≤60 yr and 3697 men >60 yr.

Compared with men >60 yr, men ≤60 yr were more often included with low-risk disease characteristics, as presented by a lower PSA value (median 4.9 ng/ml [IQR 3.8–6.6] vs 5.7 [4.3–7.5]) and fewer cores positive for PCa (two or more cores, 40% vs 42%). After 5 and 10 yr on AS, the probability of remaining on AS was slightly higher for men ≤60 yr (59.5% and 43.0%, respectively) than for men >60 yr (54.6% and 34.3%, respectively). After 5 yr on AS, the probability of discontinuation due to disease progression was slightly lower for men ≤60 yr (21.8%, 95% confidence interval [CI], 20.4–23.1) than for men >60 yr (24.9%,

95% CI 24.0–25.7; Fig. 1A and 1B). After 10 yr on AS, this difference was limited (31.6% vs 33.1%; see Fig. 1A and 1B). Furthermore, the probability of discontinuing AS after 5 yr without evidence of disease progression was slightly higher for men ≤60 yr (11.2%, 95% CI 10.2–12.2) than for men >60 yr (8.9%, 95% CI 8.4–9.5), which was also seen at 10 yr (13.8% vs 11.0%; see Fig. 1A and 1B).

When discontinuing AS, the probability of opting for RT or HT was higher for men >60 yr at the start of AS than for men ≤60 yr, while men ≤60 yr more often opted for RP than men >60 yr (at 5 yr: 23.3%, 95% CI 21.9–24.7, vs 15.0%, 95% CI 14.4–15.7; Fig. 1C and 1D). Any adverse pathology at RP was observed for 339 out of the 1067 (32%) men ≤60 yr and 661 of the 1845 (36%) men >60 yr ($\chi^2(1)$ = 4.8, p = 0.029). See also Supplementary Table 1 for more definitions of adverse pathology for both the different age groups and the risk groups.

Since dichotomization of age categories in this study can be argued, we also stratified age per 2 yr, and compared the proportion of discontinuing AS per reason and the treatment choices at 5 yr after diagnosis. The proportions of men stopping AS overall as well as due to progression remain similar from 44 to over 70 yr (Supplementary Fig. 1).

3.2. EAU risk group

A total of 14 064 (85%) men with low-risk disease and 2441 (15%) with intermediate-risk disease were included. In comparison with the EAU risk strata, d'Amico risk classification showed a different risk group for only 158 men (1%): all

Table 2 – Patient characteristics at inclusion with EAU risk classification

	Low risk (n = 14 064)	Intermediate risk (n = 2441)	p value [a]
Overall follow-up (yr), median (IQR)	2.6 (1.2–5.1)	1.9 (0.7–4.1)	<0.001
Follow-up for men still on AS (yr), median (IQR)	3.0 (1.2–5.7)	1.9 (0.5–4.1)	<0.001
Years follow-up by reason for discontinuation, median (IQR)			
Anxiety	1.5 (0.9–2.9)	1.0 (0.7–1.6)	0.004
Conversion without evidence of progression	1.9 (1.1–4.0)	1.2 (0.5–2.3)	<0.001
Disease progression	1.9 (1.1–3.8)	2.1 (1.2–3.8)	0.6
Lost to FU	4.2 (2.1–8.7)	5.8 (3.0–8.1)	0.14
Non-PCa death	6.1 (3.0–9.5)	5.0 (3.1–9.1)	0.23
Age at diagnosis (yr)			
Median (IQR)	65 (60–70)	68 (63–73)	<0.001
Age ≥75 count, n (%)	1061 (8)	459 (19)	
Unknown, n (%)	120 (1)	16 (1)	
Age at discontinuation (yr)			
Median (IQR)	68 (63–73)	71 (65–76)	<0.001
Unknown, n (%)	120 (1)	16 (1)	
PSA (ng/ml)			
Median (IQR)	5.3 (4.1–6.7)	9.0 (5.4–11.7)	<0.001
Unknown, n (%)	0 (0)	0 (0)	
Prostatic volume TRUS (cc)			
Median (IQR)	43.0 (33.0–58.2)	46.2 (33.0–65.0)	<0.001
Unknown, n (%)	2728 (19)	665 (27)	
PSA density			
Median (IQR)	0.12 (0.09–0.16)	0.17 (0.12–0.24)	<0.001
Unknown, n (%)	2728 (19)	665 (27)	
cT stage, n (%)			
T1	12 598 (90)	2001 (82)	<0.001
T2	1466 (10)	440 (18)	
Unknown	0 (0)	0 (0)	
GG, n (%)			
1	14 064 (100)	1074 (44)	<0.001
2	0 (0)	1209 (50)	
>2	0 (0)	158 (6)	
Unknown	0 (0)	0 (0)	
Maximum percentage cancer in any core			
Median (IQR)	10 (5–20)	20 (8–40)	<0.001
Unknown, n (%)	7333 (52)	746 (31)	
Biopsy cores with prostate cancer, n (%)			
1	8280 (61)	974 (42)	<0.001
2	3451 (26)	554 (24)	
>2	1769 (13)	769 (33)	
Unknown	564 (4)	144 (6)	

AS = active surveillance; EAU = European Association of Urology; FU = follow-up; GG = grade group; IQR = interquartile range; PCa = prostate cancer; PSA = prostate-specific antigen; TRUS = transrectal ultrasonography.

[a] Categorical variables were analyzed using chi-square test and continuous variables were analyzed using Mann-Whitney U test; p values are not based on the unknowns and are due to the large samples not being informative.

of these men had EAU intermediate-risk disease and d'Amico high-risk disease. The median follow-up for men still on AS with low-risk disease was 3.0 yr (IQR 1.2–5.7), and it was 1.9 yr (IQR 0.5–4.1) for men with intermediate-risk disease (see Table 2). More than 5 yr of follow-up data was available for 3587 men with low-risk disease and 439 with intermediate-risk disease.

The probability of remaining on AS at 5 and 10 yr was higher for men with low-risk disease (57.2% and 38.1%, respectively) than for men with intermediate-risk disease (49.2% and 32.9, respectively). However, the probability of disease progression at 5 yr was similar for men with low-risk disease (23.9%, 95% CI 23.1–24.8) and those with intermediate-risk disease (24.1%, 95% CI 21.9–26.4), which was also seen at 10 yr (Fig. 2A and 2B). Similar results were observed with d'Amico risk classification (Supplementary Fig. 2). Furthermore, the probability of discontinuing AS without evidence of disease progression was higher for men with intermediate-risk disease than for men with low-risk disease (at 1 and 5 yr, respectively, 5.9% and 14.2% for intermediate risk vs 2.0% and 8.8% for low risk).

The probability of opting for RP at 5- and 10-yr follow-up was very similar between EAU low-risk disease (17.2% and 22.3%, respectively) and intermediate-risk disease (18.3% and 21.3%, respectively; Fig. 2C and 2D). Adverse pathology at RP was observed for 34% of men with low-risk disease (676/1993) and for 40% of men with intermediate-risk disease (131/330; $\chi^2(1) = 3.92$, $p = 0.048$). When using d'Amico risk classification, 39% of men with intermediate-risk disease (119/308) experienced adverse pathology, which was not significantly different from the 34% of men with low-risk disease ($\chi^2(1) = 2.42$, $p = 0.12$).

In the available follow-up, 11 633 biopsy sessions were performed among men with low-risk disease and 1633 biopsy sessions among men with intermediate-risk disease. The incidence rate ratio (taking into account the time on AS) showed a small significant effect of 1.08 (95% CI 1.03–1.14, $p = 0.002$) for men diagnosed with intermediate risk.

3.3. Age and risk groups combined

The subgroup analysis is presented in Supplementary Fig. 3 and shows no clear relation between the subgroups and
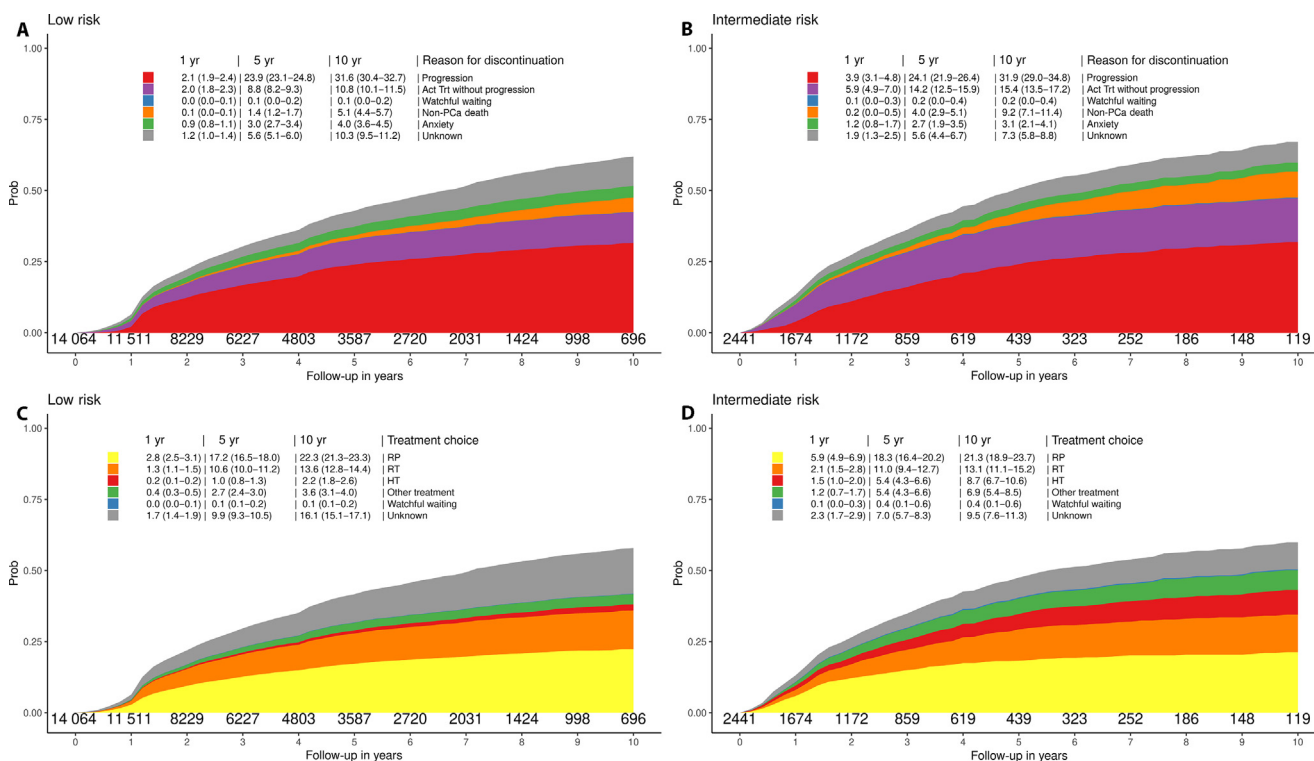
Fig. 2 – (A and B) Reason for discontinuation and (C and D) treatment choice for men diagnosed with EAU low and intermediate risk on AS. The 95% CI values are shown in parentheses. Act trt = active treatment; CI = confidence interval; EAU = European Association of Urology; HT = hormonal therapy; PCa = prostate cancer; Prob = probability; RP = radical prostatectomy; RT = radiotherapy.

discontinuation due to progression or without evidence of progression. For treatment choice after AS, RP is most often opted in men ≤60 yr with intermediate-risk disease, and HT is the more pronounced treatment choice for men >60 yr with intermediate-risk disease (Supplementary Fig. 3). There was no clear relation between the four subgroups and opting for RT.

4. Discussion

The global Movember GAP3 AS database provides the opportunity to analyze combined data from 27 cohorts worldwide reflecting daily clinical practice. We showed that reasons for discontinuation, subsequent treatment choice, and the rate of adverse pathology at RP are very similar for men ≤60 yr and those >60 yr currently included in AS. We observed that younger men were more often included in AS with more favorable tumor characteristics and had a slightly lower probability of discontinuing AS due to disease progression than older men. The latter finding is supported by a meta-analysis showing that younger patients on AS have a lower risk of GG upgrading and biopsy progression than older patients [21] and by Leapman et al [22]. We also observed that younger men more often discontinue AS without signs of disease progression. This is likely due to more concerns on the safety of AS and/or the increasing burden over time associated with repeating visits and biopsies. It may be possible to decrease the rate of discontinuation without evidence of progression by active participation

of the patient in the shared decision process during the choice of the initial treatment or by better education of the patient. This might be beneficial because patients who were actively involved in the shared decision process showed less doubt in their choice of opting for AS [23]. Moreover, since the rates of adverse pathology at RP did not differ between the age groups, this suggests that men ≤60 yr should not be refrained from AS purely based on their age.

We also compared the reasons for discontinuation, subsequent treatment choice, and the rate of adverse pathology at RP for men with intermediate- and low-risk disease. We observed that men included with intermediate-risk disease have a higher probability of discontinuing AS without signs of disease progression than men included with low-risk disease. This could suggest concerns regarding the safety of AS. We also observed that the probability of discontinuing due to disease progression is similar between the risk groups; however, we observed that men included with intermediate-risk disease showed 6% more adverse pathology at RP than men included with low-risk disease (40% vs 34%). However, the difference is slightly smaller and not significant when we would apply the d'Amico classification. It is important to mention that the reported rates of adverse pathology in the current study do not differ from those reported in the literature for nonregistry studies, with rates of 32% [24] and 44% [25] for men with GG1 disease. Since the reasons for discontinuation between EAU low- and intermediate-risk disease are similar, and the rate of adverse pathology at RP differs significantly only with

EAU risk classification, we can conclude that men with intermediate-risk disease should not be excluded from AS purely on the basis of their risk classification.

In clinical practice, it is important to have solid real-life data and to use this in shared decision-making. It is known that AS can delay or even avoid invasive treatment and thus possible side effects such as urinary and sexual dysfunction, thereby increasing the years without burden and in general resulting in better quality of life. The process of shared decision-making should reveal for each patient whether an increased number of years with most likely better quality of life would outweigh the small increased risk on adverse pathology at RP.

This study has some limitations. The AS protocols used over time did not always include magnetic resonance imaging, which may have influenced the outcomes. Owing to the nature of the available data, we cannot make inferences about all men <60 yr or all men with EAU/d'Amico intermediate-risk disease. Furthermore, within this already low-risk PCa patient cohort, a bias toward lower-risk disease may exist in men younger than 60 yr. One study showed that men with low-risk disease were more likely to opt for AS than active treatment if they were ≥60 yr at the time of diagnosis, had more years of education, had more knowledge about PCa, and showed higher levels of awareness of low-risk disease [26]. This suggest that education of PCa is likely to result in more men opting for AS.

5. Conclusions

In conclusion, by analyzing a large amount of real-life data from 27 centers located worldwide, we showed that the proportion of younger men discontinuing AS due to progression is similar to the proportion of men with intermediate-risk disease. Our results suggest that, men ≤60 yrs at time of diagnosis and those with EAU intermediate-risk disease should not be excluded from opting for AS as initial treatment, but should be aided in the shared decision-making.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2022.05.012.

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