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Has Active Surveillance for Prostate Cancer Become Safer? Lessons Learned from a Global Clinical Registry

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Abstract

Background and objective: Active surveillance (AS) has evolved into a widely applied treatment strategy for many men around the world with low-risk prostate cancer (or in selected cases intermediate-risk disease). Here, we report on the safety and acceptability of AS, and treatment outcomes for low- and intermediate-risk tumours over time in 14 623 men with follow-up of over 6 yr.

Methods: Clinical data from 26 999 men on AS from 25 cohorts in 15 countries have been collected in an international database from 2000 onwards.

Key findings and limitations: Across our predefined four time periods of 4 yr each (covering the period 2000–2016), there was no significant change in overall survival (OS). However, metastasis-free survival (MFS) rates have improved since the second period and were excellent (>99%). Treatment-free survival rates for earlier periods showed a slightly more rapid shift to radical treatment. Over time, there was a constant proportion of 5% of men for whom anxiety was registered as the reason for treatment alteration. There was, however, also a subset of 10–15% in whom treatment was changed, for which no apparent reason was available. In a subset of men (10–15%), tumour progression was the trigger for treatment. In men who opted for radical

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treatment, surgery was the most common treatment modality. In those men who underwent radical treatment, 90% were free from biochemical recurrence at 5 yr after treatment.

Conclusions and clinical implications: Our study confirms that AS was a safe management option over the full duration in this large multicentre cohort with long-term follow-up, given the 84.1% OS and 99.4% MFS at 10 yr. The probability of treatment at 10 yr was 20% in men with initial low-risk tumours and 31% in men with intermediate-risk tumours. New diagnostic modalities may improve the acceptability of follow-up using individual risk assessments, while safely broadening the use of AS in higher-risk tumours.

Patient summary: Active surveillance (AS) has evolved into a widely applied treatment strategy for many men with prostate cancer around the world. In this report, we show the long-term safety of following AS for men with low- and intermediate-risk prostate cancer. Our study confirms AS as a safe management option for low- and intermediate-risk prostate cancer. New diagnostic modalities may improve the acceptability of follow-up using individual risk assessments, while safely broadening the use of AS in higher-risk tumours.

1. Introduction

Active surveillance (AS) has matured into a widely applied management strategy for low- to favourable intermediate-risk prostate cancer (PCa) [1–3]. However, uptake and usage of AS has varied significantly worldwide. In Europe 75–95%, in Australia 71%, in the USA approximately 50% (with wide regional variation), and in Asia 10–56% of low-risk cancers are treated with AS [4–9].

Autopsy data have confirmed that a significant number of PCa cases never surface to clinical relevance [10]. AS provides a pathway to limit overtreatment of insignificant cancers diagnosed by screening [11,12]. The benefit of AS is the avoidance or delay of complications associated with immediate treatment most commonly with radiotherapy (RT) or surgery. Disadvantages of AS include the need for repeated tumour evaluation, psychological effects of cancer diagnosis without treatment, and potential for missed cancer progression [13].

There has been a continued effort to improve the accuracy of diagnosing and stratifying low-risk PCa to ensure the appropriateness of this strategy in individual patients. In particular, multiparametric magnetic resonance imaging (mpMRI) has allowed for more accurate sampling of the prostate and identification of patients suitable for AS [14]. The development of new diagnostic tests and risk-based

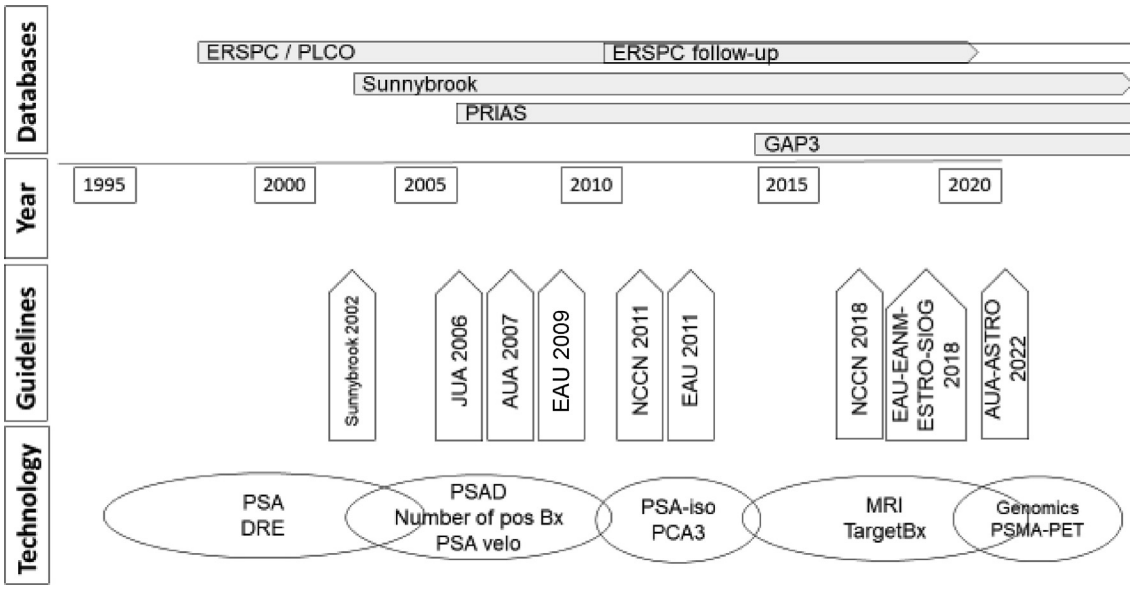

Fig. 1 – Timeline on the introduction of diagnostic tests, guidelines on active surveillance, and related databases. AUA = American Urological Association; DRE = digital rectal examination; EANM = European Association of Nuclear Medicine; EAU = European Urological Association; ERSPC = European Randomized study of Screening for Prostate Cancer; ESTRO = European Society for Radiotherapy and Oncology; GAP3 = Global Action Plan 3 on active surveillance; JUA = Japanese Urological Association; MRI = magnetic resonance imaging; NCCN = National Comprehensive Cancer Network; PCA3 = Prostate Carcinoma gene 3; PLCO = Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; pos Bx = positive biopsy; PRIAS = PRostate cancer International Active Surveillance study; PSA = prostate-specific antigen; PSAD = prostate-specific antigen density; PSA-iso = PSA isoforms belonging to kallekrein-3 gene family; PSA velo = PSA velocity variations; PSMA-PET = prostate-specific membrane antigen positron emission tomography; SIOG = International Society of Geriatric Oncology; TargetBx = image-guided targeted biopsy.

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models has influenced the practice of AS, as summarised in Figure 1.

Owing to advanced diagnostic techniques, higher numbers of intermediate-risk PCa patients have also been managed with AS. However, it is not yet known how the long-term clinical outcomes of these patients have improved.

The Global Action Plan Prostate Cancer Active Surveillance (GAP3) database was established in 2014 based on the existing and new databases from 25 AS cohorts (Supplementary Table 1) [15] and currently includes >26 000 patients. Our aim is to describe whether and how the selection of patients considered eligible for AS has changed over time and provides an update on long-term clinical outcomes such as metastasis-free survival (MFS), in order to assess whether the safety and acceptability of AS have changed. Furthermore, this paper will describe the (historical) geographical variations in the use of AS and explore the potential reasons for variation.

1.1. Geographical and historical trends in AS

1.1.1. North America

In North America, AS is now the preferred treatment option for men with low-risk and selected men with favourable intermediate-risk disease as per the National Comprehensive Cancer Network (NCCN) and American Urological Association guidelines [16,17]. Conservative management as an option was described by Whitmore et al [18] in 1991. AS was a response to the overdetection and overtreatment brought about by widespread and repeated prostate-specific antigen (PSA) screening [19]. The first large clinical experience with AS was in Toronto in 2002 [20,21] and was followed by four other large and multicentre cohorts [22–26]. The inclusion criteria and timing between surveillance biopsies varied amongst cohorts, ranging from those enrolling only very-low-risk patients biopsied yearly [27] to those that allowed men with intermediate-risk features and performed biopsies less frequently. From these cohorts, predictors of progression on AS, such as imaging (mpMRI), surveillance biopsy findings, PSA density, genomic profiling, age, ethnicity, cancer grade group (GG), and volume, have been identified, although not all have been well validated across cohorts [28–30]. The use of such prognostic factors has led to a refined approach to surveillance, with reduced intensity of surveillance in those with a very low likelihood of progression [31]. Owing to risk profiling, the rate of men starting AS stratified by D'Amico risk grouping in low and intermediate risk increased between 2014 and 2019 from 29.6% to 49.5% for low-risk and from 10.4% to 20.4% for intermediate-risk patients in the USA, while in Canada, it increased from 38% in 2008 to 69% in 2014 for low-risk patients [7,8]. In the very-low-risk group, intensive follow-up with annual biopsies and long-term outcomes demonstrated 100% survival for PCa-related death, 100% MFS, and 90.6% biochemical recurrence (BCR)-free survival (BFS) [27], while in a low- and intermediate-risk cohort, 7-yr MFS rate of 99% was reported [32].

The considerable variation in the use of AS [33] in the USA may be financially driven by imaging costs and treatment incentives, and the changing attitude towards the use of systematic 12-core transrectal biopsy for diagnosis and surveillance, contributing to patient and physician anxiety regarding undergrading and understaging in AS [34]. Presently, therefore, most institutional cohorts incorporate magnetic resonance imaging (MRI) into their follow-up protocols.

1.1.2. Europe

Conservative management of low-risk PCa has been practised in Europe since the recognition of cT1a PCa [35]. In the European Randomized Screening study for Prostate Cancer (ERSPC), detection of low-risk tumours by active PSA screening lowered the age of first diagnosis and increased the number of men diagnosed [36]. This led to the development of the registration site Prostate cancer Internationals for Active Surveillance (PRIAS) protocol in 2006 [37]. The PRIAS digital database facilitated data collection with an online tool in the clinical setting. This supported the acceptability of AS by patients and physicians. In order to reduce sampling error secondary to biopsy, sextant biopsies were replaced by protocols using a higher number. In 2015, PSA doubling time became a criterion to trigger repeat biopsy rather than cause an immediate shift to radical treatment. Up until 2020, a PSA value of >20 triggered a bone scan. MRI-targeted biopsies were introduced in a PRIAS side study in 2013, and led to the incorporation of mpMRI into PRIAS entry criteria within few years [12] and the European Urological Association guidelines 2020 for the primary diagnostic pathway [2,38].

However, the uptake and methods of detection of AS also varied between European countries, depending on the different national guidelines and the availability of imaging facilities of individual countries. Overall, the proportion of low-risk cancers managed by AS in Europe has increased. In the UK, there are very high rates of AS, with 95% of low-risk patients opting for AS [5]. Likewise, Sweden has also reported increasing rates of AS use of >95% over time. A review of the National Prostate Cancer Registry demonstrated an increase from 2009 to 2014, with AS in men with very-low-risk PCa increasing from 64% to 93% and in those with low-risk PCa from 50% to 79%. However, the rates for intermediate-risk PCa have remained stable at around 25% [6]. Similarly, in the Netherlands, between 2015 and 2020, AS was reported as the management strategy for 85–95% of patients with low-risk cancers (www.iknl.nl).

1.1.3. Asia

In Asia, the earliest documentation of AS dates to 2002 [39]. In recent times, AS has become increasingly recognised in Asia. Still, the proportion of low-risk patients offered AS remains relatively low (1.3–15%) and varies considerably by region and hospital [9]. Asian men with low-risk PCa may have a higher rate of adverse pathology on radical prostatectomy (RP) than Western men [40,41]. However, these studies only included patients who underwent limited systematic biopsy with ten to 12 cores, did not have mpMRI, and had clinically palpable disease, and thus patients were likely undergraded/staged.

AS protocols were developed based on the data derived from Asian men. These include single- and multi-

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institutional databases including the Korean Study Group of Prostate Cancer (K-CaP), Japan Study Group of Prostate Cancer (J-CaP), and the multinational Asia Study Group of Prostate Cancer (A-CaP) [42–44]. The low proportion of patients on AS, heterogeneous patient population and tumour demographics due to disparate health care policies, and patient selection from high-volume institutions were barriers to establishing a comprehensive AS protocol representing Asian men [45]. In Asia, there is a paucity of public national data. In Malaysia, a national database amongst 1839 patients from nine sites reported AS being used in 56.9% of patients with stage 1 (low risk) disease [46]. In Japan, in the Otokuni district, 169 low-risk patients were eligible for AS between 1995 and 2015, of whom 74 (44%) opted for AS [39]. The A-CaP database comprises demographic and survival data of 34 710 biopsy-proven patients from 14 Asian countries. Amongst them, 1989 (5.7%) are on AS and their outcomes will be reported.

1.1.4. *Australia and New Zealand*

In Australia and New Zealand (ANZ), the rates of AS have increased over time [4], from 54% in 2015 to 74% in 2018, correlating with a fall in surgery for low PCa (39% vs 24%). The shift towards transperineal saturation template biopsy might also have led to increased rates of AS because (temporary) more cores were taken due to the lower risk of sepsis compared with transrectal biopsy allowing for lower risk of undergrading of PCa [47]. In 2018, transperineal biopsy was performed more frequently than transrectal biopsy, 46% versus 43% of diagnoses of all PCa cases.

The high use of mpMRI prior to biopsy was stimulated by the Australian Government funding mpMRI since 2018 to reduce the cost barriers amongst regions [48]. Prebiopsy mpMRI has improved the ability to detect clinically significant cancer and allows regular surveillance to detect cancer progression during AS [49,50]. Furthermore, Australian centres have employed prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) for PCa diagnosis, which may further improve safety and acceptability of AS by looking for unexpected foci of high-grade disease examining the maximum standardised uptake value [51].

The oncological outcomes of AS within Australia are positive and comparable with other geographical regions, with PCa-related survival, MFS, and BFS being, respectively, 100%, 100%, and 99% at a median 55 mo of follow-up. Treatment-free survival (TFS) was 45% at 10 yr [52].

2. Methods

2.1. *Cohort*

A retrospective analysis of the GAP3 database (v4.1.1) was performed, which includes 26 999 patients, from 25 cohorts and 15 countries (Supplementary Table 1). In this analysis, patients who were diagnosed between 2000 and 2016 were included to allow for a potential of 6 yr of follow-up of all patients. The exclusion criteria included patients with D'Amico risk level of high, Gleason score of ≥8, patients enrolled outside of the selected time period, or data insufficiently available for D'Amico risk analysis. For the analysis, patients were stratified into four time periods (2000–2004, 2005–2008, 2009–2012, and 2013–2016). An overall flow chart shows inclusion and exclusion of patients (Supplementary Fig. 1).

2.2. *Covariates*

Covariates considered in the analysis were the year of enrolment, D'Amico risk group, age at diagnosis, Gleason score, PSA, PSA density at inclusion, clinical T stage, use of MRI within the first 12 mo of diagnosis, total number of biopsy cores taken, and total number of biopsy cores positive.

2.3. *Outcomes*

The GAP3 database also contains clinical information regarding discontinuation of AS, including potential subsequent treatments. Coding of these variables has previously been described by Van Hemelrijck et al [53]. In summary, the reasons for discontinuation include disease progression (either clinical and/or pathological, PSA, or radiological progression as defined according to centres' own criteria), conversion to active treatment without evidence of progression, watchful waiting, non-PCa death, anxiety, or "unknown" reasons. Anxiety reflects all of those emotions contributing to decrease the quality of life seriously, as registered according to the discretion of the physician [54]. 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 the "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, as a reflection of resampling of the pre-existing cancer) or disease progression as such (ie, disease progression towards a higher TNM stage and grade after the 1st year of AS). In the group of "unexplained treatment changes", some of the reasons included stress with spouses, reimbursement problems in the health care system, patients not coping with intensity of follow-up, and repeated biopsies and alterations based on PSA variability between centres.

Recorded treatment options after discontinuation of AS include RP, RT, hormonal therapy (HT), watchful waiting, other treatment, or unknown. The group of men labelled as those receiving "other treatment" consists predominantly of men receiving RT combined with HT, or those who underwent focal therapy. Information at RP included 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 labelled as unknown.

The treatment choice when patients discontinued AS was assessed. Additionally, we assessed the rates of adverse pathology for patients who underwent RP after AS.

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Additionally, we assessed BCR for patients who underwent RP and RT. The definition of BCR as defined in each of the different cohorts was used.

2.4. Statistical analysis

Baseline patient characteristics were described stratified by geographical area of origin (North America, Europe, ANZ, and Asia). Descriptive statistics were used to compare patient and tumour characteristics in the four time periods: 2000–2004, 2005–2008, 2009–2012, and 2013–2016. Cumulative incidence curves were used to estimate the probability of discontinuation of AS and treatment choice, using R version 3.6.0 and R-package cmprsk. Clinical safety of AS over time was assessed using Kaplan-Meier curves with clinical endpoints including TFS, MFS, and overall survival (OS) after diagnosis. Patients were censored in TFS and MFS analyses according to stop of registration or death. The *p* value was calculated using the log-rank test.

Acceptability of AS by patients and clinicians was assessed by describing reasons for discontinuation of AS, as explained previously [53]. These outcomes were stratified into four cohorts over time.

3. Results

3.1. Geographical distribution

There has been an increased use of AS in North America from 2000 onwards, while in Europe, this increase was noticed after the initiation of the PRIAS project, which facilitated online registration (Fig. 2). Most centres in the GAP3 database originate from Western countries; only three centres are localised in Asian areas, and thus the overall enrolment numbers are lower in Asia.

3.2. Overall cohort description

A total of 26 999 patients were included in the GAP3 database with a median follow-up of 4.95 yr by October 2022. Figure 3 depicts the 10-yr OS and MFS of the complete cohort. The rates are presented in the graph and show a 10-yr metastatic probability of 0.9%. In Supplementary Table 1, details are provided on the registration numbers of each participating centre over time.

In total, 14 623 men were included for the final analysis after the exclusion criteria were applied. For the time periods of 2000–2004, 2005–2008, 2009–2012, and 2013–2016,

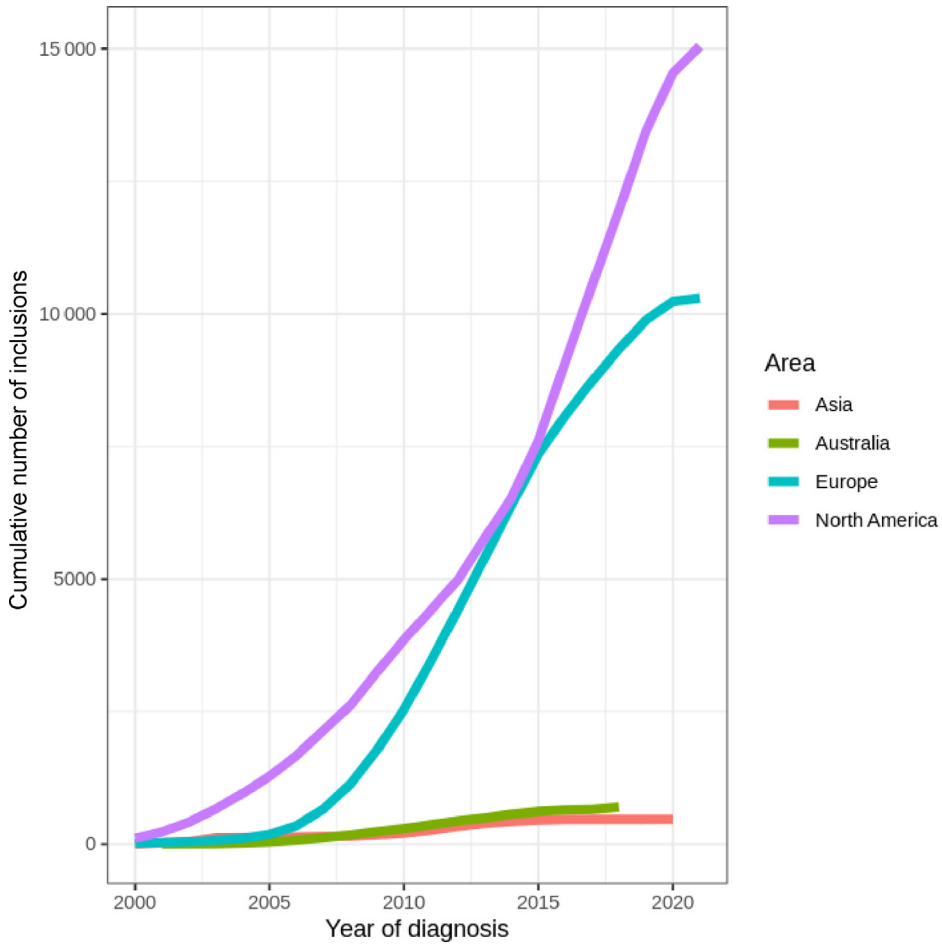

Fig. 2 – Cumulative number of inclusions over time according to geographical area.

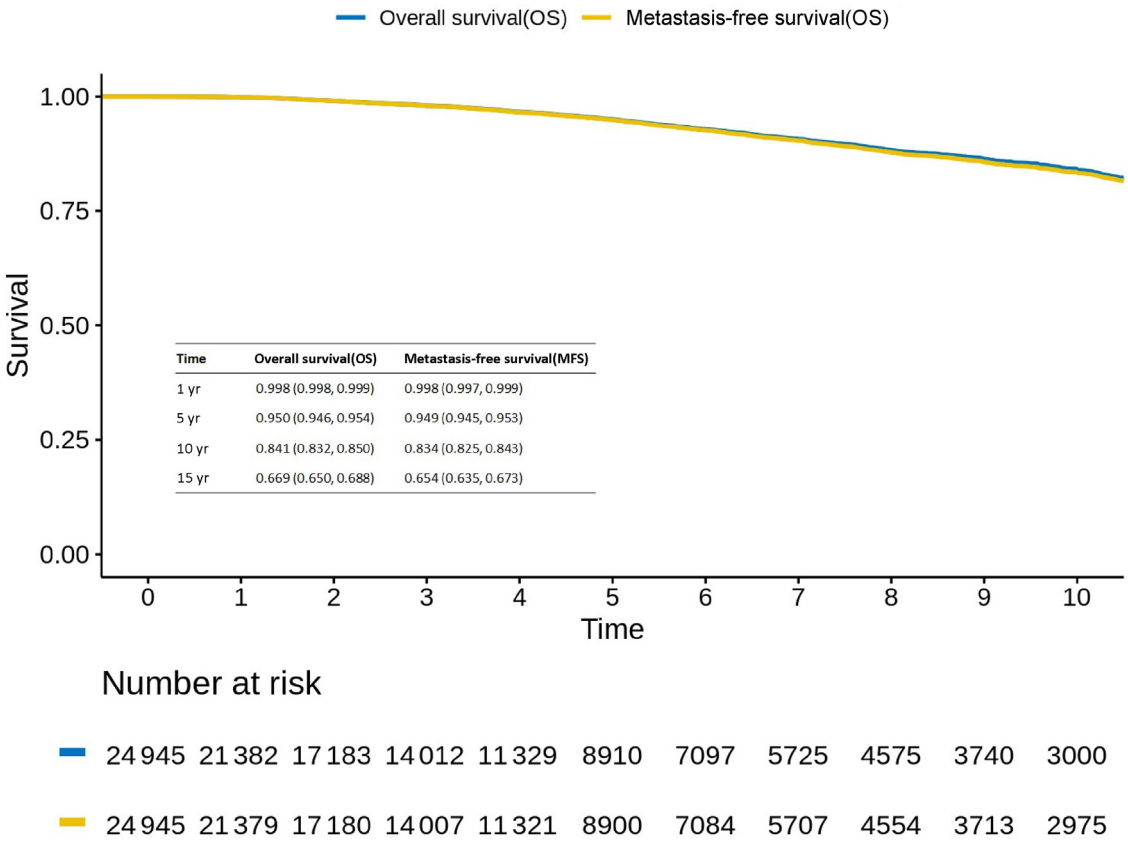

Fig. 3 – Overall and metastasis-free survival in the complete GAP3 cohort. GAP3 = Global Action Plan 3 on active surveillance.

Table 1 – Baseline characteristics and overall inclusion to AS in absolute numbers (percentage)

Characteristics	2000–2004 (800)	2005–2008 (2136)	2009–2012 (4921)	2013–2016 (6766)	Total (14 623)
Risk group					
Intermediate	161 (20.1)	292 (13.7)	721 (14.7)	1451 (21.4)	2626 (18)
Low	639 (79.9)	1844 (86.3)	4199 (85.3)	5315 (78.6)	11 997 (82)
Age at diagnosis	66.0 (7.96)	64.1 (7.62)	64.2 (7.47)	65.0 (14.5)	64.6 (11.3)
Gleason sum					
3 + 3	745 (94.3)	1976 (95.4)	4469 (93.0)	5812 (86.9)	13 001 (90.6)
3 + 4	42 (5.3)	87 (4.2)	303 (6.3)	778 (11.6)	1208 (8.4)
4 + 3	3 (0.4)	10 (0.5)	34 (0.7)	99 (1.5)	146 (1.0)
PSA at inclusion	5.5 (4.2, 7.9)	5.3 (3.8, 7.1)	5.6 (4.2, 7.4)	5.7 (4.4, 7.6)	5.6 (4.3, 7.4)
T stage					
Unknown	23 (2.9)	98 (4.6)	325 (6.6)	345 (5.1)	791 (6.4)
≤T1c	570 (71.2)	1619 (75.8)	3814 (77.5)	5570 (82.3)	11 573 (79.2)
T2	207 (25.9)	418 (19.6)	780 (15.9)	851 (12.6)	2256 (15.4)
MRI					
Baseline MRI	78 (9.8)	85 (4)	158 (3.2)	627 (9.3)	948 (7.8)
MRI during follow-up	16 (2)	15 (0.7)	67 (1.4)	158 (2.3)	256 (1.7)
No MRI	706 (88.2)	2036 (95.3)	4696 (95.4)	5981 (88.4)	13 419 (91.8)
Number of biopsy cores used at diagnosis	10 (7, 12)	12 (8, 13)	12 (10, 14)	12 (12, 14)	12 (10, 14)
Number of biopsy cores with prostate cancer	1 (1, 2)	1 (1, 2)	1 (1, 2)	1 (1, 2)	1 (1, 2)
Percentage biopsy cores with prostate cancer	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)

AS = active surveillance; MRI = magnetic resonance imaging; PSA = prostate-specific antigen.
All mentioned differences are statistically significant.

the median follow-up durations were 10.75, 8.71, 5.82, and 4.06 yr, respectively. Table 1 compares the baseline characteristics of patients enrolled for AS over the different time periods. Age at diagnosis and PSA at diagnosis were similar over the different time periods. In more recent time periods, increasing amounts of patients had T1c disease. The percentage of intermediate-risk patients varied over time, with approximately 20% in the initial and latest cohorts (2000–2004 and 2013–2016 periods) compared with 14% in the cohorts in between. This reflects the alterations in

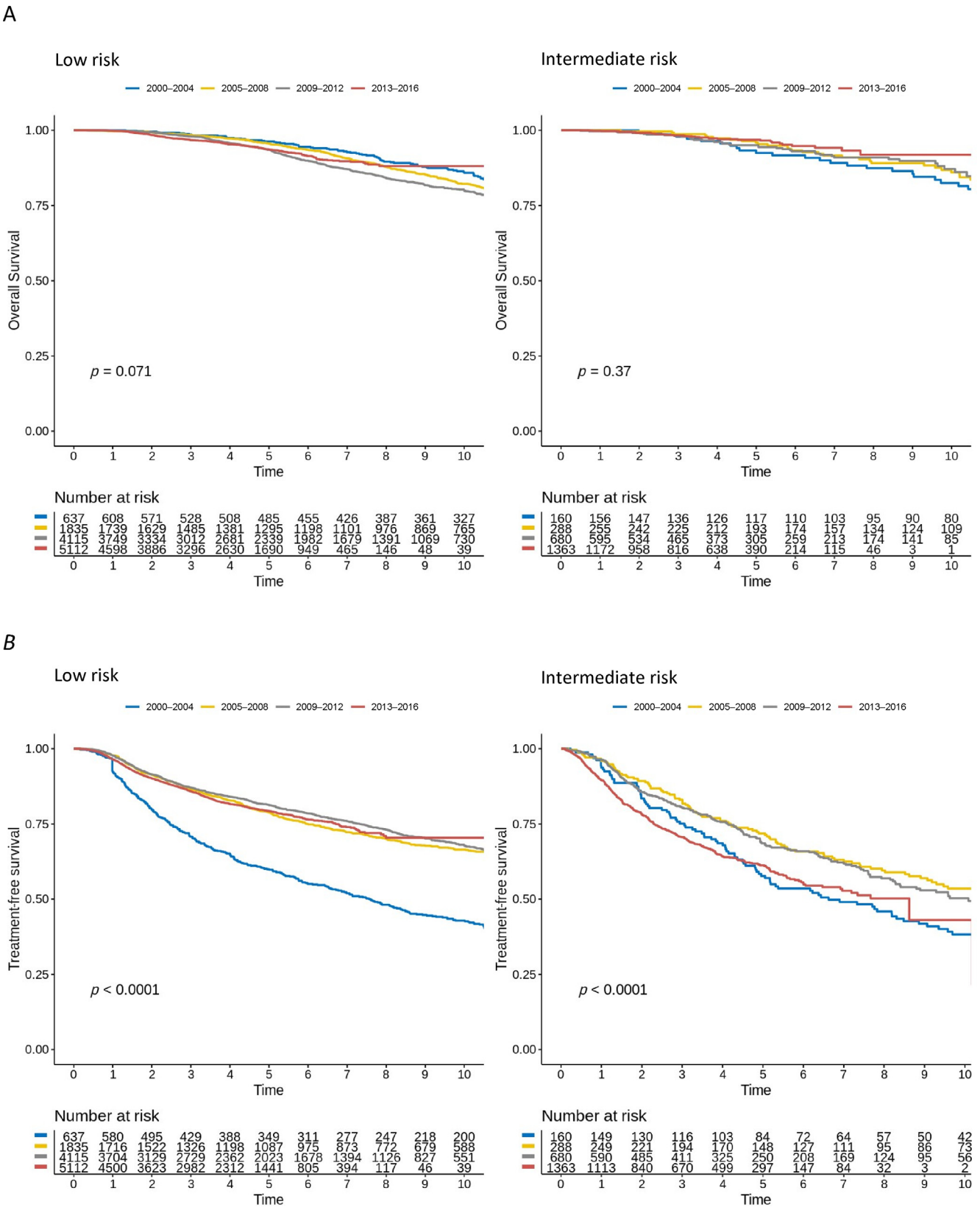

Fig. 4 – (A) Overall survival, (B) treatment-free survival, and (C) metastasis-free survival across four time periods separated by low- and intermediate-risk PCa. The number of events is too small for the calculation of *p* value. PCa = prostate cancer.

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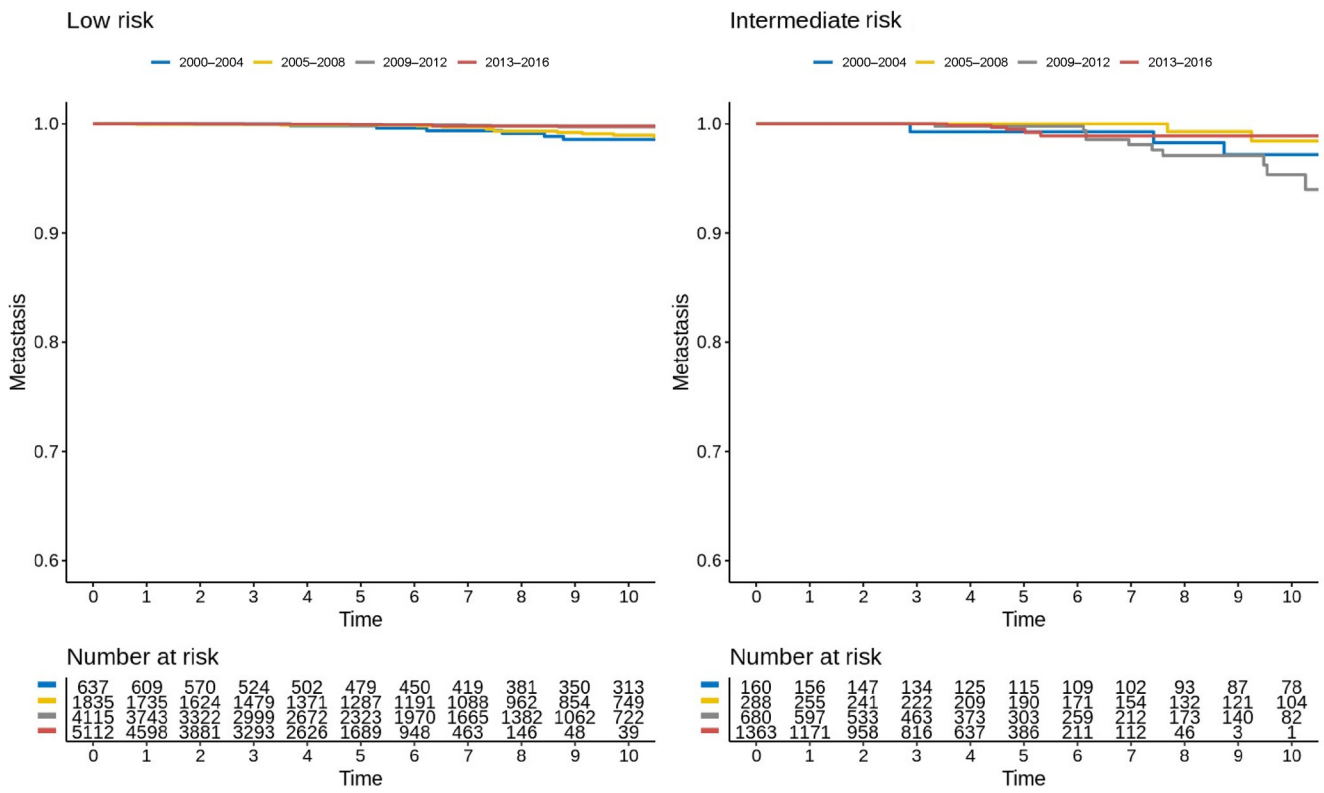

Fig. 4 (*continued*)

AS inclusion criteria, pathology reporting, and protocols over time. In total, 1409 deaths were observed for the participants included. The information on cause of death is often not collected; 1099 (78.0%) were reported as "death due to unknown causes". Only 22 were reported as "death due to PCa"; the rest were reported as "death due to other causes". The use of MRI was documented only at the time of diagnosis in 4–11% of patients, while <1% of patients were recorded as undergoing MRI during follow-up.

3.3. Time-based cohort analysis (N = 14 620)

Clinical outcomes including TFS, MFS, and OS are depicted in Kaplan-Meier curves (Fig. 4A–C). Overall, 20% of men with initial low-risk tumours and 31% of men with intermediate-risk tumours shifted towards invasive therapy after 10 yr. During the four time periods assessed, TFS rates remained similar; however, there was an improvement in MFS in more recent time periods.

3.4. Reasons for discontinuation of AS

Figure 5A depicts the reasons for discontinuation of AS over time for all 26 999 men in the GAP3 database. Overall, the probability of shifting towards invasive therapy over 10 yr was 20% for men with initial low-risk tumours, and 31% for men with intermediate tumours (see Fig. 3).

Figure 5B depicts the reasons for discontinuation of AS across the four time periods during the first 5 yr of following AS.

The parameters were defined as follows [53]: progression: red; conversion towards active treatment registered as without evidence of progression including those patients for whom there was no information on specific discontinuation or disease progression: purple; watchful waiting: blue; non-PCa death: orange; registered patient anxiety: green; and unknown (no registered classification): grey. It is realised that anxiety is an umbrella definition of stress enhancing emotions of any kind. Given the multicultural setting of the observed cohort, it is extremely difficult to find a universal definition and, more importantly, quantification of the various aspects of anxiety. A sensitivity analysis restricted to centres contributing data to all four time periods was performed; these showed similar results to the overall analysis (results not shown).

3.5. Treatment choices after discontinuation

The treatment choices of patients after discontinuation of AS separated by time periods are demonstrated in Table 2 and Figure 6. It appears that compared with RT, overall RP was offered more frequently as an alternative treatment than radical surgery, and that this did not change overtime. A sensitivity analysis was performed to illustrate the weight of individual contributing centres, but no differences were observed between centres (data not shown).

For registered centres, BCR was defined by PSA >0.1 ng/ml on three consecutive measurements. Figure 7 illustrates the BFS across four time periods separated by low- and intermediate-risk PCa ($p < 0.05$). In the initial cohort

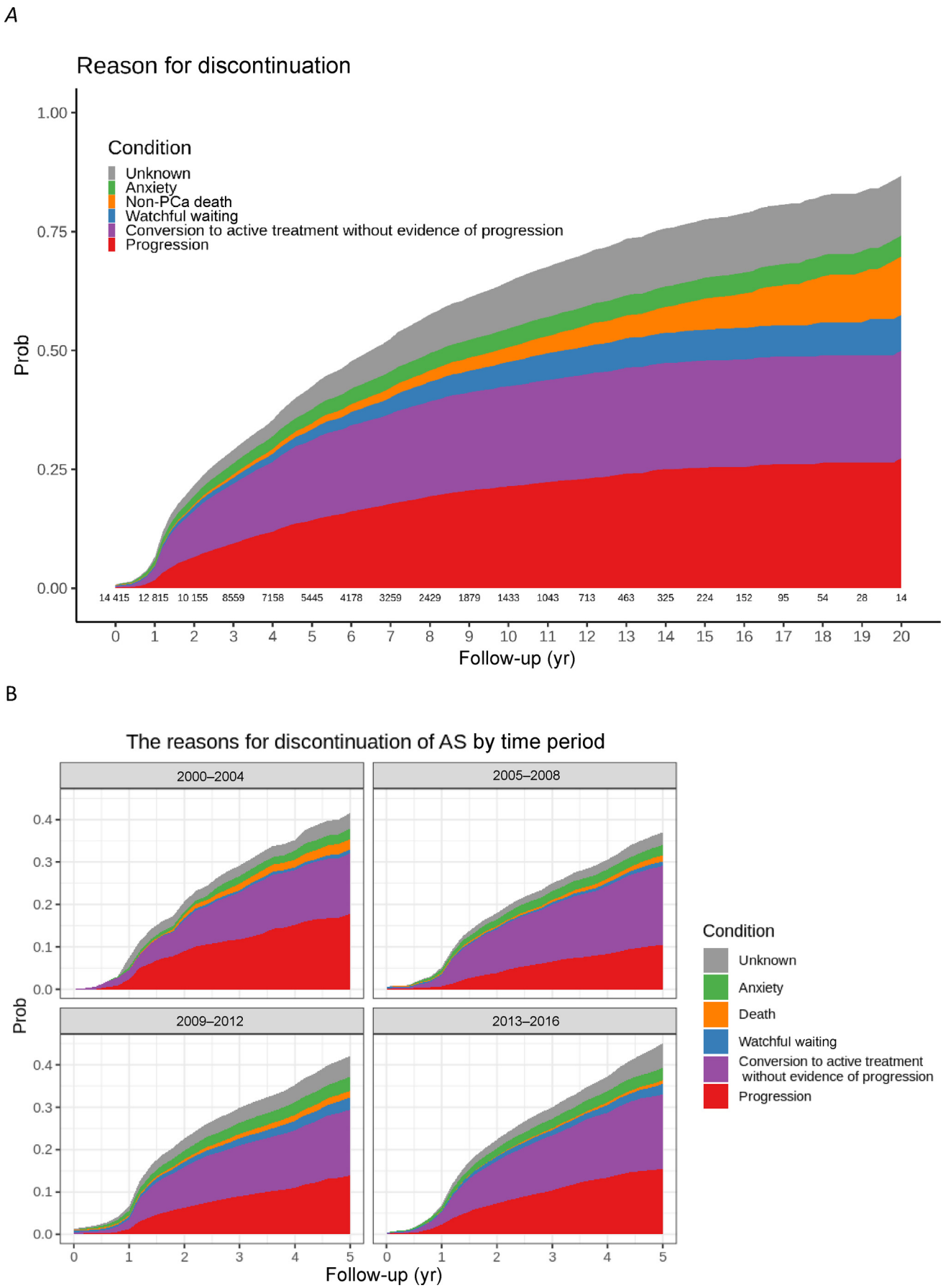

Fig. 5 – The reasons for (A) discontinuation of AS over the time on follow-up and (B) discontinuation during four time periods. AS = active surveillance; PCa = prostate cancer; Prob = probability.

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Table 2 – Treatment choices after shift towards invasive therapy per 4-yr period in absolute numbers (percentages)

Treatment	2000–2004	2005–2008	2009–2012	2013–2016	Total
Radiotherapy	110 (36)	209 (31)	410 (27)	471 (25)	1200 (28)
Radical prostatectomy	169 (56)	408 (61)	967 (65)	1166 (63)	2710 (63)
Adjuvant hormonal therapy	30 (10)	42 (6)	100 (7)	76 (4)	248 (5)
Other treatment	21 (7)	56 (8)	120 (8)	209 (11)	406 (10)
Total	300	673	1497	1846	4316

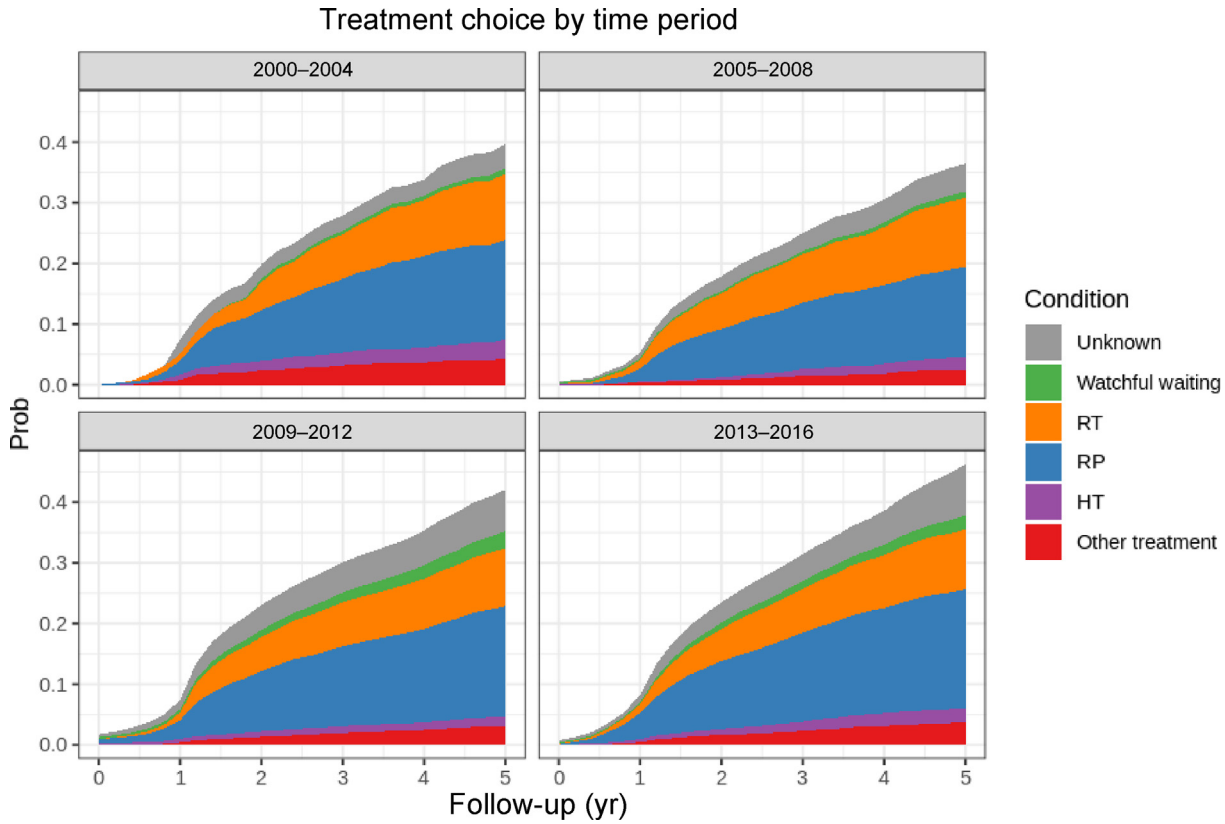

Fig. 6 – Treatment choices after shift towards invasive therapy per 4 yr period over time. HT = hormonal therapy; Prob = probability; RP = radical prostatectomy; RT = radiotherapy.

(2000–2004), BCR was slightly more frequent than in later cohorts; however, the absolute numbers for BCR were very low after 4–5 yr of follow-up. In the later cohorts, BCR occurred in 10% of men undergoing RP after 5 yr, in both low- and intermediate-risk patients. In 26.9% of men, the RP specimen demonstrated locally extended tumour pT3 and, in 2.6%, regional dissemination with positive nodes. Upgrading with Gleason >7 was observed in 10.4%.

4. Discussion

4.1. AS recruitment and regional variation

The current study documents the increasing use of AS worldwide as a treatment option for low-risk and favourable intermediate-risk PCa. Over time, the clinical outcomes of AS have remained stable for both low- and intermediate-risk tumours. In the latter group, AS is increasingly accepted as a primary treatment choice. This is reflected in the GAP3 database (Fig. 2), and in national statistics and cohort studies across the world. The GAP3 database represents the largest centralised consortium for AS and demonstrates an increase in men opting for AS across four geographical continental areas. The data also indicate that the criteria for enrolment into AS have widened over time to include high-volume International Society of Urological Pathology (ISUP) GG 1 cancers and favourable GG 2 cancers.

The growing uptake of AS may also be attributed to the long-term clinical outcomes of multiple large cohorts that have demonstrated favourable TFS, MFS, and OS for low- and favourable intermediate-risk PCa [11,32,52]. However, a review of national statistics and population data on the rates of AS has shown that there is a wide variation between different geographies regarding uptake of AS. The rates for

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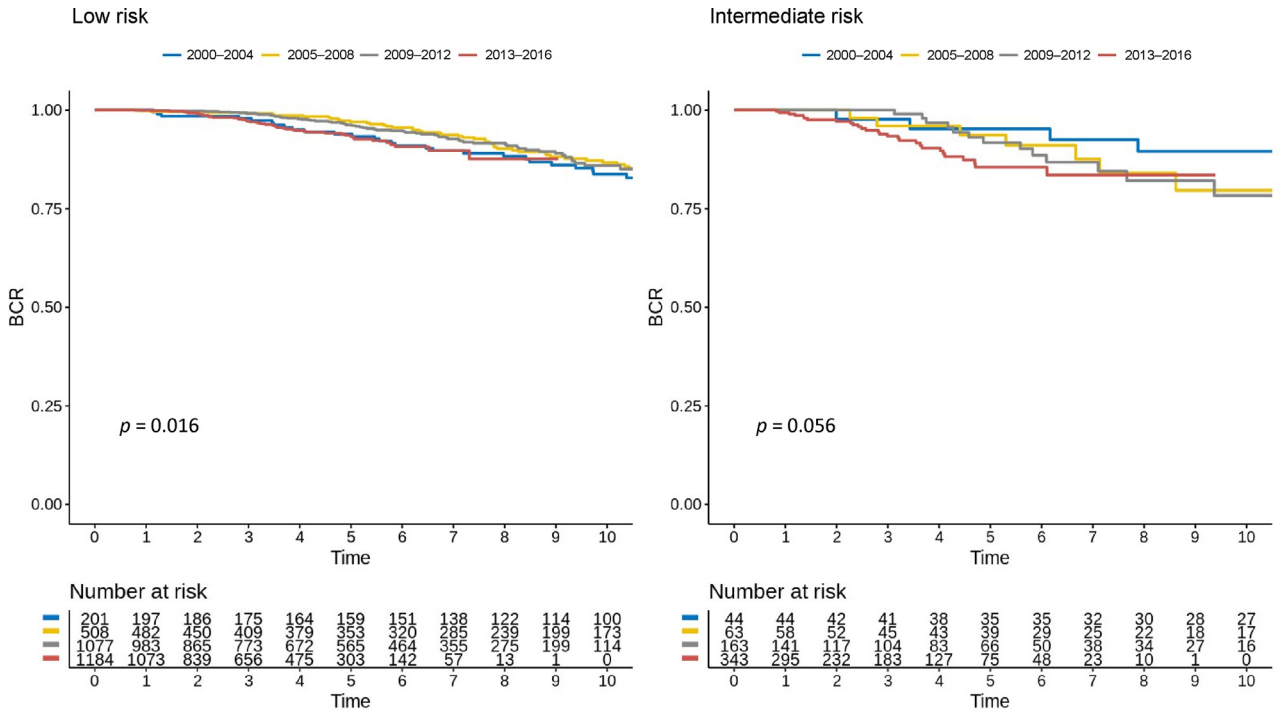

Fig. 7 – BCR-free survival in men after RP across four time periods separated by low- and intermediate-risk PCa ($p < 0.05$). BCR = biochemical recurrence; PCa = prostate cancer; RP = radical prostatectomy.

low risk are ≥90% in some European countries, >70% in ANZ, just under 50% in North America, and between 1% and 15% in Asia [4–9]. This is reflected in the overall uptake in GAP3.

There are several potential reasons for geographical variation. Alterations in clinical guidelines may be influential. In 2022, the NCCN guidelines temporarily changed AS from the preferred treatment for men with very-low-risk PCa to one of three options, including surgery and radiation [55]. However, in 2023, the NCCN guidelines and other institutions in Europe reinstated the status of AS as preferred treatment for (very) low-risk PCa [16]. The access to diagnostic tools such as mpMRI or genomic profiling is dependent on the individual health care policies of governments. In ANZ and Europe, funding and broad access to mpMRI are widespread. However, until recently, in North America, there was limited access to mpMRI. This was associated with the use of systematic biopsies without imaging in many cases, which in turn may have resulted in a higher likelihood of underestimating PCa grade and stage. In line with this, poorer AS outcomes may cause disincentive to AS enrolment. In Asia, risk stratification improves with increasing utility of mpMRI and targeted biopsy strategies, which may better select candidates to enter or continue on AS [56].

Furthermore, a wide variation in socioeconomic status may decrease access to PCa detection and treatment. In Asia, this is associated with a large discrepancy between incidence and mortality rates of PCa: in China, the PCa incidence is 5.3 per 100 000, while the likely under-reported disease-specific mortality is 2.5. The Korean incidence is 30.3 per 100 000 and disease-specific mortality is 4.6 [57]. Thus, in some Asian countries, patients are more commonly diagnosed at later stages of PCa and not suitable for AS. This is further compounded by other issues, including a large variation in awareness regarding PCa, stigma associated with a cancer diagnosis, lack of support for men regarding treatment choices, and a shortage of multidisciplinary teams to treat cancer [58,59]. Patients within the Asia region may have differing cultural and societal beliefs that encourage radical treatment.

Advancements in diagnostic technologies have affected the inclusion and monitoring of men on AS. There is however a learning curve for each technique. The widening of inclusion criteria for AS could be explained by the improved diagnostic precision of imaging prior to biopsy and the recognition that most GG2 PCa is indolent. With the advent of mpMRI, the likelihood of identifying significant PCa on targeted prostate biopsy has increased considerably compared with systematic sextant biopsies [60,61]. Increasing use of transperineal biopsy with lower infection rates compared with transrectal biopsy provides further acceptability of AS monitoring [62]. Currently, a gradual reduction in the number of biopsies appears to occur.

4.2. *Safety and clinical outcomes*

The GAP3 database demonstrates that the clinical outcomes (MFS and OS) of AS have either improved or at least

remained at high levels in recent times. The 10-yr OS for the cohort is good (78%). The number of reported tumour-specific deaths (22 of 1022) is likely an underestimation. Klotz et al [11] previously demonstrated 15-yr PCa-specific death of 1.5% [63].

MFS for the current cohort in both low- and intermediate-risk PCa has increased in the most recent time period (2013–2016), indicating that the overall safety of AS has improved. This reflects the advancement and future directions in the development of diagnostic tools such as MRI, biomarkers, transperineal biopsy, and PSMA-PET/CT, which may aid in identifying significant PCa. Moreover, somatic gene testing is likely to improve decision-making based on risk calculation and reduce anxiety [64]. Therefore, as intermediate-risk PCa has poorer rates of MFS than low-risk PCa, further research might expand the appropriateness of AS for intermediate-risk PCa, by enhancing selection criteria, improving monitoring protocols, and triggering the correct patients for radical treatment.

4.3. Time-related analysis and acceptability

This study aimed to demonstrate how clinical outcomes for AS have developed over time. However, the outcomes for the cohorts over time are similar. Only TFS is slightly shorter in the oldest cohort than in others. This might be explained in retrospect by the design of the earliest protocols, inclusion bias, and the Will Rogers phenomenon (stage migration) [65]. Correction by risk recalculation based on a review of these earlier cases might confirm this, but will not change the current selection of patients for AS.

The curve for progression (red zone in Fig. 5A) flattens over time, indicating that the selection of nonrelevant cancers by repeated diagnostics occurs more than tumour progression. This emphasises the safety of the monitoring protocol. It might also indicate that the current monitoring protocols can be relaxed over time in those deemed to have very low risk. The curve for cancer-specific death at the time of discontinuation (green zone in Fig. 5B) appears to have become smaller in the recent cohort 2013–2016 (while the age of initiating AS remained identical [Table 1]), indicating that selection (by MRI-based targeted biopsy) and inclusion of overall less aggressive tumours took place.

Over time, the reasons for stopping AS varied in line with growing experience and altering diagnostic techniques. In spite of stable long-term outcomes, patient anxiety did not decrease (Fig. 4B). The large subset of men classified as those with "conversion towards active treatment without evidence of progression" lacks granular detail, but may indicate the lack of confidence that patients, partners, and physicians have in AS. Cancer anxiety is a never-ending reality for a considerable part of our patients. Increased efforts to enhance that understanding of the concept of overdiagnosis and low-risk cancer may lead to a reduction of anxiety [66].

After discontinuation of AS, more men chose radical surgery than radiation options. Many reasons might be supporting their choices, including patient health, marketing of better outcomes of robotics, and availability of treatment options in the local health care systems.

Overall, the GAP3 database demonstrates that more men are enrolled to AS registries, in line with higher rates of patient and clinician acceptability of AS over time. Patients are on AS for longer periods of time (TFS), which correlates with the acceptance and compliance to AS protocols.

4.4. Limitations

Our study has limitations due to the heterogeneity of the registration systems used in a variety of health systems. The analysis is retrospective. Over time, there have been alterations to grading systems such as ISUP classifications for GG and Prostate Imaging Reporting and Data System scoring, which may have affected the results. Many Gleason 6 cancers diagnosed prior to 2015 would be called Gleason 7 (GG2) at the time of writing this article.

A registry such as GAP3 suffers from confounders, known and unknown. Recent developments in radiogenomics, PSMA-PET/CT, and molecular biomarkers were not incorporated into patient management in most cases.

5. Conclusions

The worldwide GAP3 registry is unique in size and duration of follow-up. In appropriate patients initiating AS, the prognosis is excellent and the approach is safe. Long-term trends indicate that, over time, intervention rates have decreased, and eligibility has expanded, likely reflecting increased confidence in the safety of the approach, and incorporation of imaging into the AS algorithm. The clinical outcomes from the GAP3 database robustly support the view that AS should be the gold standard for low-risk PCa management.

Author contributions: Chris Bangma had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Doan, Remmers, Nieboer, Helleman, Roobol, Sugimoto, Carroll, Koo, Thompson, Bangma.
Acquisition of data: Doan, Sugimoto, Chung, Lee, Frydenberg, Klotz, Peacock, Perry, Bjartell, Rannikko, Dasgupta, Moore, Pavlovich, Carroll, Koo, Thompson, Bangma, The Movember Foundation's Global Action Plan Prostate Cancer Active Surveillance (GAP3) Consortium.
Analysis and interpretation of data: Doan, Remmers, Nieboer, Helleman, Roobol, Sugimoto, Carroll, Koo, Hayen, Thompson, Steyerberg, Van Hemelrijck, Bangma.
Drafting of the manuscript: Doan, Remmers, Nieboer, Helleman, Roobol, Sugimoto, Carroll, Koo, Thompson, Bangma.
Critical revision of the manuscript for important intellectual content: Doan, Remmers, Nieboer, Helleman, Roobol, Sugimoto, Frydenberg, Klotz, Perry, Bjartell, Rannikko, Van Hemelrijck, Dasgupta , Moore, Trock, Pavlovich, Steyerberg, Carroll, Koo, Thompson, Bangma, The Movember Foundation's Global Action Plan Prostate Cancer Active Surveillance (GAP3) Consortium.
Statistical analysis: Zhu, Remmers, Nieboer, Roobol.
Obtaining funding: Helleman, Roobol, Bangma.
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Supervision: Helleman, Roobol, Thompson, Bangma.
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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euo.2024.07.003.

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