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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.10.025. 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Reasons for Discontinuing Active Surveillance: Assessment of 21 Centres in 12 Countries in the Movember GAP3 Consortium

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Abstract

Background: Careful assessment of the reasons for discontinuation of active surveillance (AS) is required for men with prostate cancer (PCa).

Objective: Using Movember's Global Action Plan Prostate Cancer Active Surveillance initiative (GAP3) database, we report on reasons for AS discontinuation.

Design, setting, and participants: We compared data from 10 296 men on AS from 21 centres across 12 countries.

Outcome measurements and statistical analysis: Cumulative incidence methods were used to estimate the cumulative incidence rates of AS discontinuation.

Results and limitations: During 5-yr follow-up, 27.5% (95% confidence interval [CI]: 26.4–28.6%) men showed signs of disease progression, 12.8% (95% CI: 12.0–13.6%) converted to active treatment without evidence of progression, 1.7% (95% CI: 1.5–2.0%) continued to watchful waiting, and 1.7% (95% CI: 1.4–2.1%) died from other causes. Of the 7049 men who remained on AS, 2339 had follow-up for >5 yr, 4561 had follow-up for <5 yr, and 149 were lost to follow-up. Cumulative incidence of progression was 27.5% (95% CI: 26.4–28.6%) at 5 yr and 38.2% (95% CI: 36.7–39.9%) at 10 yr. A limitation is that not all centres were included due to limited information on the reason for discontinuation and limited follow-up.

Conclusions: Our descriptive analyses of current AS practices worldwide showed that 43.6% of men drop out of AS during 5-yr follow-up, mainly due to signs of disease progression. Improvements in selection tools for AS are thus needed to correctly allocate men with PCa to AS, which will also reduce discontinuation due to conversion to active treatment without evidence of disease progression.

Patient summary: Our assessment of a worldwide database of men with prostate cancer (PCa) on active surveillance (AS) shows that 43.6% drop out of AS within 5 yr, mainly due to signs of disease progression. Better tools are needed to select and monitor men with PCa as part of AS.

Keywords

Prostate cancer; Active surveillance; Discontinuation; Worldwide

1. Introduction

About 2 decades ago, the concept of active surveillance (AS) was introduced as a management strategy for men with low-risk prostate cancer (PCa) [1]. Men are monitored closely through repeated prostate-specific antigen (PSA) measurements, biopsies, and potentially also magnetic resonance imaging (MRI), with the intention to start curative treatment when their PCa is reclassified as higher risk due to signs of progression (ie, clinical or pathological) and to minimise the harm caused by the overtreatment of indolent cancer [2]. However, even though AS has no long-term physical morbidity, studies continue to report that 1.6–38% of men opt out of AS, often with no or little evidence of disease progression, within 5 yr [3]. Thus, men embarking on AS are likely to transition to an alternative strategy within a decade, which highlights the need for more insight into AS protocols [1,4].

Careful assessment of reasons for discontinuation of AS is required, especially since treatment pathways for men with low-risk PCa vary by country and are managed differently in various healthcare systems [5,6]. It is unclear whether a decrease in health-related quality of life in men on AS precipitates their transition to radical treatment or whether this is driven by the distress over disease progression, physiological symptoms, or the burden of age. Most studies are small and with short follow-up [7–10]. Better understanding of reasons for opting out of AS is thus needed to help define a management strategy for AS.

Hence, in 2014, the Movember Foundation launched the Global Action Plan Prostate Cancer Active Surveillance initiative (GAP3), which covers the largest centralised PCa AS database

to date (https://gap3.movemberprojects.com). Its primary goal is to create a global consensus with uniform guidelines on the selection and monitoring of men with low-risk PCa [11]. Here, we report on adherence to AS and the reasons for discontinuation by comparing data from 10296 men on AS from 21 different centres across 12 different countries.

2. Patients and methods

2.1. Study population

Between 2014 and 2016, the global GAP3 database was created by combining patient data from established AS cohorts worldwide. Requirements for participation included, amongst others, ethical approval for sharing digital patient data in a centralised global database and active registry of AS patients over the last 2 yr or more, including at least ~50 patients annually. To date, 25 centres from the USA, Canada, Australasia, the UK, and Europe fulfilled the requirements for participation and joined the initiative [11], resulting in data for a total of 15 101 men on AS. For the current study, we excluded 3084 patients from Dublin, MD Anderson Cancer Centre, Toronto, and University of Michigan and Michigan Urological Surgery Improvement Collaborative, as these centres did not distinguish between progression and anxiety events. Furthermore, to ensure as much homogeneity in our AS cohort as possible, we included only men with a Gleason grade group of 1, leaving 10 296 patients for the final analysis. Each institution obtained institution ethical approval and signed a Movember end user license agreement, an access rights principles agreement, and the commonly agreed upon GAP3 analytical plan.

Although there are many variations in existing protocols, most agreed that the most suitable patients for AS are those with age >18 yr, pretreatment clinical stage T1–T2, serum PSA 10 ng/ml, a biopsy Gleason grade group of 1 or 2, and a maximum of two tumour-positive biopsy core samples. The AS inclusion criteria for the 25 centres are shown in Supplementary Table 1 [11]. Some protocols included PSA density (most often using a cut-off of 0.2 ng/ml), the maximum extent of cancer per core (most often using a cut-off of 50%), life expectancy of >10 yr, and adequate biopsy sampling as inclusion criteria for AS. An overview of contemporary worldwide AS practices across the world (and included in GAP3) can also be found in the systematic review by Kinsella et al. [3] and the cohort profile of the GAP3 database [5].

Following initiation of AS, almost all protocols recommended serial measurements (with a variation in time intervals) of serum PSA levels, digital rectal examination, and surveillance biopsy sampling in order to identify pathological progression. Several protocols considered MRI for routine use in AS, again with many differences between recommended frequencies. An overview of the AS follow-up protocols of the 25 institutes included in GAP3 is given in Supplementary Table 2 [11].

In addition to baseline criteria for selection and monitoring of AS, the GAP3 database also contains information on discontinuation of AS (ie, the reasons for stopping AS), and potential following treatments (eg, radical prostatectomy) and cause of death. Each centre reports for each patient an event time, defined as the time from the patient's AS initiation to discontinuation of AS due to "conversion to watchful waiting", "clinical progression",

"pathological progression", "clinical and pathological progression", "PSA progression (PSA doubling time <3 yr)", "other PSA kinetics", "patient choice/anxiety", "doctor's anxiety", "radiological progression", "death", "loss to follow-up", "other/unknown reasons", or "still being on AS". These events are defined according to the centres' own criteria. We used the following coding for defining the signs of disease progression: "clinical and pathological progression", "clinical progression", "other PSA kinetics", "pathological progression", "PSA progression", and "radiological progression". If the reason for discontinuation was classified as "other/unknown", but the "pathological progression status" reported at the time of AS discontinuation was "Gleason grade group 3 or higher" or the "clinical progression status" was "cT3 or higher" or "PSA progression status" was "PSA >20", the reason for discontinuation was also classified as signs of disease progression. The term "sign of disease progression" as used in this manuscript can thus refer to risk reclassification or disease progression as such. Conversion to active treatment without evidence of disease progression includes those patients for whom there was no information on specific discontinuation or disease progression (according to the criteria described above) and for whom specific treatment information was available, as well as those for whom the reason for discontinuation was registered as "doctor's anxiety" or "patient's choice/anxiety". The distribution of different types of active treatment has been described in detail in our recently published cohort profile [11].

2.2. Statistical methods

Descriptive statistics were used to summarise patient characteristics. The cumulative incidence method was used to estimate the rates of each event for discontinuation of AS. Cox proportional hazards regression analyses were used to estimate hazard ratios for various reasons of discontinuation based on age, PSA, and the number of positive biopsy cores. To account for the heterogeneity between centres, these models used the centre as a stratum. R version 3.3.2 (The R Foundation for Statistical Computing, Vienna, Austria) was used to perform all analyses.

3. Results

Table 1 shows the distribution of men on AS included in this study according to patient and tumour characteristics, by outcome at 5 yr of follow-up. During 5-yr follow-up, 27.5% (95% confidence interval [CI]: 26.4–28.6%) men showed signs of disease progression, 12.8% (95% CI: 12.0–13.6%) converted to active treatment without evidence of progression, 1.7% (95% CI: 1.5–2.0%) continued to watchful waiting, and 1.7% (95% CI:1.4–2.1%) died from other causes. Of the 7049 men who remained on AS during follow-up, 2339 had follow-up of >5 yr, 4561 had <5 yr of follow-up, and 149 were lost to follow-up. Hence, at 5 yr of follow-up, the cumulative incidence rate of men remaining on AS was 56.4% (95% CI: 55.2–57.6%), and 43.6% (95% CI: 42.4–44.8%) were lost to follow-up or discontinued AS. Furthermore, the distribution of outcomes and tumour characteristics per participating centre are shown in Table 2 and Supplementary Table 3.

The cumulative incidence of signs of disease progression was 27.5% (95% CI: 26.4–28.6%) at 5 yr and 38.2% (95% CI: 36.7–39.9%) at 10 yr. Figure 1 shows the cumulative incidence

for discontinuation based on different events: signs of progression, conversion to active treatment without evidence of progression, watchful waiting, death, and still being on AS. An increase in discontinuation can be observed after 1 yr, with the largest proportion being due to signs of disease progression and conversion to active treatment without evidence of progression. Moreover, it is worth noting that the proportion of men dying from other causes increased gradually throughout the follow-up, which reflects the real-world setting of this database. Finally, it can be seen that the proportion of men converting to active treatment without evidence of progression remained stable from about 7 yr onwards; a similar trend was observed for conversion to watchful waiting. To further understand how patient characteristics may affect discontinuation of AS, we generated a forest plot specifically focussing on the effects of age (in decade), PSA, and more than one positive biopsy core (Fig. 2). As expected, the strongest positive association is seen for age with transferring to watchful waiting and non-PCa death. Furthermore, more than one positive biopsy core positively associates with progression and non-PCa death.

Figure 3 shows the cumulative incidence for discontinuation for each centre included in the GAP3 database. For all centres, an increase in signs of disease progression was also observed after 1 yr, but the slope of this increase varied substantially by centre.

4. Discussion

Based on the data from the largest AS database in the world, we observed that after about 5 yr of follow-up, about 56.4% of men were still on AS. Substantial variation by centre was observed, but the main reasons for discontinuation were signs of disease progression (27.5% of men) and conversion to active treatment without evidence of disease progression (12.8% of men).

As shown in a recent systematic review by Kinsella et al. [12], many factors influence men's adherence to AS on multiple levels. Their thematic assessment of barriers and facilitators for adherence to AS identified many key themes: (1) patient and tumour factors (age, comorbidities, knowledge, education, socioeconomic status, family history, grade, tumour volume, fear of progression/side-effects), (2) family and social support, (3) provider (speciality, communication, attitudes), (4) healthcare organisation (geography, type of practice), and (5) health policy (guidelines, year, awareness) [12]. Interestingly, this systematic review observed that even though a number of studies have shown that emotional distress is relatively high in men at the time of their PC diagnosis [13,14], anxiety in men on long-term AS has been generally reported as favourably low. More studies have suggested that anxiety in men on AS reduces [15–17] or remains the same over time [8,17–22].

Our findings of a drop-out rate of 43.6% after about 5 yr are in line with previous estimations [23]. However, the proportion of men opting out without evidence for progression was only 12.8%. The variation observed between different institutions shows rather distinct patterns with respect to the proportion of men dropping out due to progression and the proportion of men dropping out due to conversion to active treatment without evidence of disease progression. However, part of the reason why the proportion of drop-out due to conversion to active treatment without evidence of disease progression was largest

in Memorial Sloan Kettering Cancer Center, Singapore, Baden, and Goteborg may be explained by the fact that their median follow-up was about 3–4 yr as compared with 1–2 yr in most other centres. Nevertheless, the data from other centres with lengthier follow-up such as John Hopkins University, Valencia, and University of California San Francisco, still showed the largest proportion of discontinuation due to disease progression. In this context, it was also interesting to note that the proportion of men converting to active treatment without evidence of progression in our database remained stable after about 7 yr. It can be speculated that more anxious men (and clinicians) were more likely to make the decision about discontinuing AS during the first years. It might suggest that more emphasis on education and support is required during these first years on AS [12]. Surprisingly, the proportion of watchful waiting also stabilised after 7 yr, which is unexpected as the population is growing older. Again, this observation might be due to different practices across centres.

The rather large proportion of drop-outs due to signs of disease progression also highlights the need for better inclusion/exclusion criteria, better markers of stable disease, and better outcome measures. For instance, a recent review by Nowinski et al. [24] showed the need for novel approaches of classification, including molecular features, to direct therapy for men with low-grade PCa, especially those on AS. They concluded that by combining genome-wide association study data with gene expression and structural rearrangements, risk alleles were identified, which could provide a new basis for developing a prognostication tool to guide therapy for men with early PCa [24,25].

Moreover, the use of MRI as a tool to risk stratify men with low-risk PCa has been emerging over time. A study by Thurtle et al. [26] evaluated data from 157 men enrolled on AS using a protocol including multiparametric MRI, and noted low progression and treatment conversion rates. Changes in multiparametric MRI findings were found to be the principal trigger for detecting progression by imaging alone or pathologically. In addition, the recent findings of the PROMIS trial, which was based on men with PSA concentrations up to 15 ng/ml and with no previous biopsy, have shown us that MRI identified nearly all men with clinically significant PCa (93%) versus the current practice standard (transrectal biopsy), which identified only 48% [27]. The endotype generated by positive MRI was positively associated with grade and volume, and contained cancer in most cases (Likert ≥ 4 = 92%; Likert ≥ 3 = 60%). An update of the current Movember GAP3 database with information on MRI images will hence provide us more insight into the use of MRI as a selection and monitoring tool for AS.

In addition to genetics and MRI, several studies have also investigated the use of serum biomarkers as a tool to monitor men on AS. However, a recent systematic review by Loeb and Tosoian [28] concluded that very few markers have longitudinal results available yet for men on AS, indicating an important area for future research where the GAP3 database will be able to contribute. Furthermore, simple changes in clinical assessment have been proposed as a strategy to reduce rates of discontinuation of AS. Bokhorst et al. [29] have, for example, shown that the number of positive biopsies should no longer be used to trigger immediate active treatment, but rather to indicate further investigation to confirm the suspicion of higher-risk disease.

The GAP3 database is a unique resource covering data from all over the world. Some limitations exist, resulting in not all centres being included in these analyses due to the lack of information on the reason for discontinuation and limited follow up. However, even after a follow-up of 5 yr, we could already observe clear patterns with respect to reasons for discontinuation. The heterogeneity in study protocols and data collection across centres can be seen as a limitation; however, we would like to argue that it is this real-world setting that adds value to our understanding of AS. As outlined by PIONEER, the big PCa data consortium of the European Association of Urology, combination and analysis of the patient records of men diagnosed with PCa can enable healthcare systems to provide more efficient outcome-driven patient-centred interventions [30]. By providing data from a wide variety of centres, GAP3 has the power to transform the perspective of all relevant stakeholders. Recently, Movember has also allocated additional funding to maintain the database and update the clinical data annually, thereby prolonging follow-up time. Furthermore, this provides the opportunity to collect evidence on imaging (MRI), molecular (genomics) markers, patient-related outcomes, and more. In addition, it is worth noting that only qualitative data will not be sufficient to answer the question about adherence to AS—there is a need to combine our observations with qualitative studies to truly understand the patterns of discontinuation [12]. Given the available data on the natural course of low-risk disease, the question about whether active monitoring leads to better outcome and benefit whilst avoiding missing the window of cure in case of reclassification/progression is crucial.

5. Conclusions

Our descriptive analyses of current AS practices around the world showed that about 43.6% of men drop out of AS after 5 yr, mainly due to signs of disease progression—about 12.8% of drop-outs were due to conversion to active treatment without evidence of progression. Improvements in selection tools for AS (eg, biomarkers or MRI) are thus needed to correctly allocate men with PCa to AS, which in turn will also reduce discontinuation due to conversion to active treatment without evidence of disease progression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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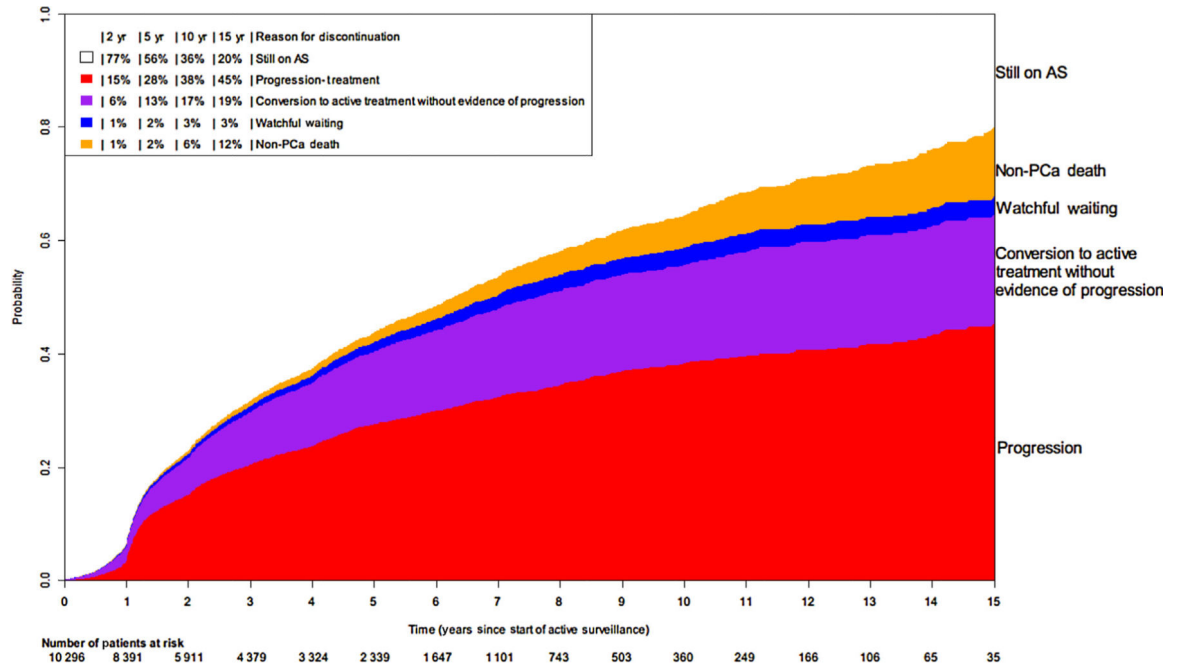[30]. European Association of Urology. PIONEER: the European network of excellence for big data in prostate cancer. 2018. https://prostate-pioneer.eu

Fig. 1 –.

Cumulative incidence of discontinuation of active surveillance over time. AS = active surveillance; PCa = prostate cancer.
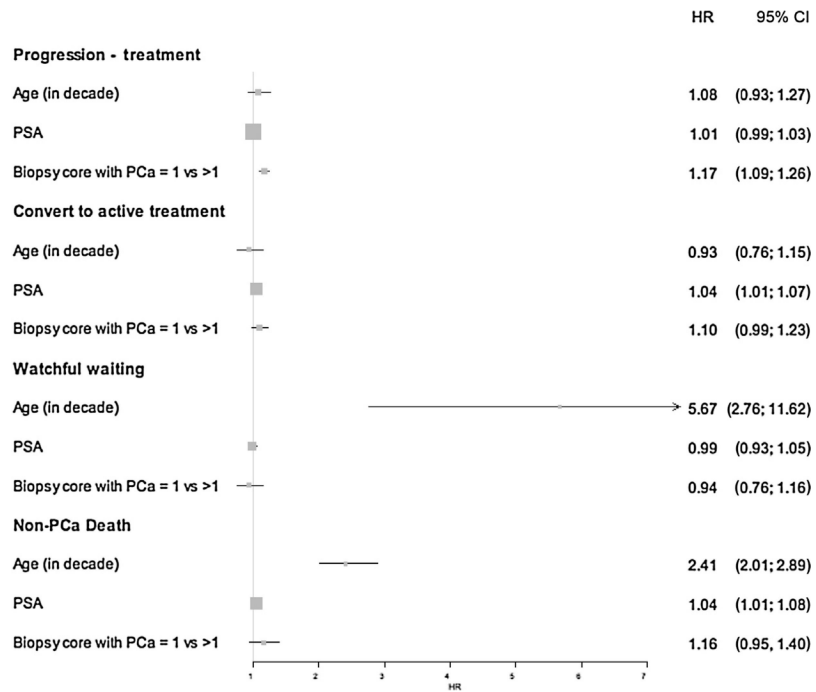
Fig. 2 –.
Forest plot showing the association between age, PSA, positive biopsy cores, and different reasons for discontinuation of active surveillance. CI = confidence interval; HR = hazard ratio; PCa = prostate cancer; PSA = prostate-specific antigen.

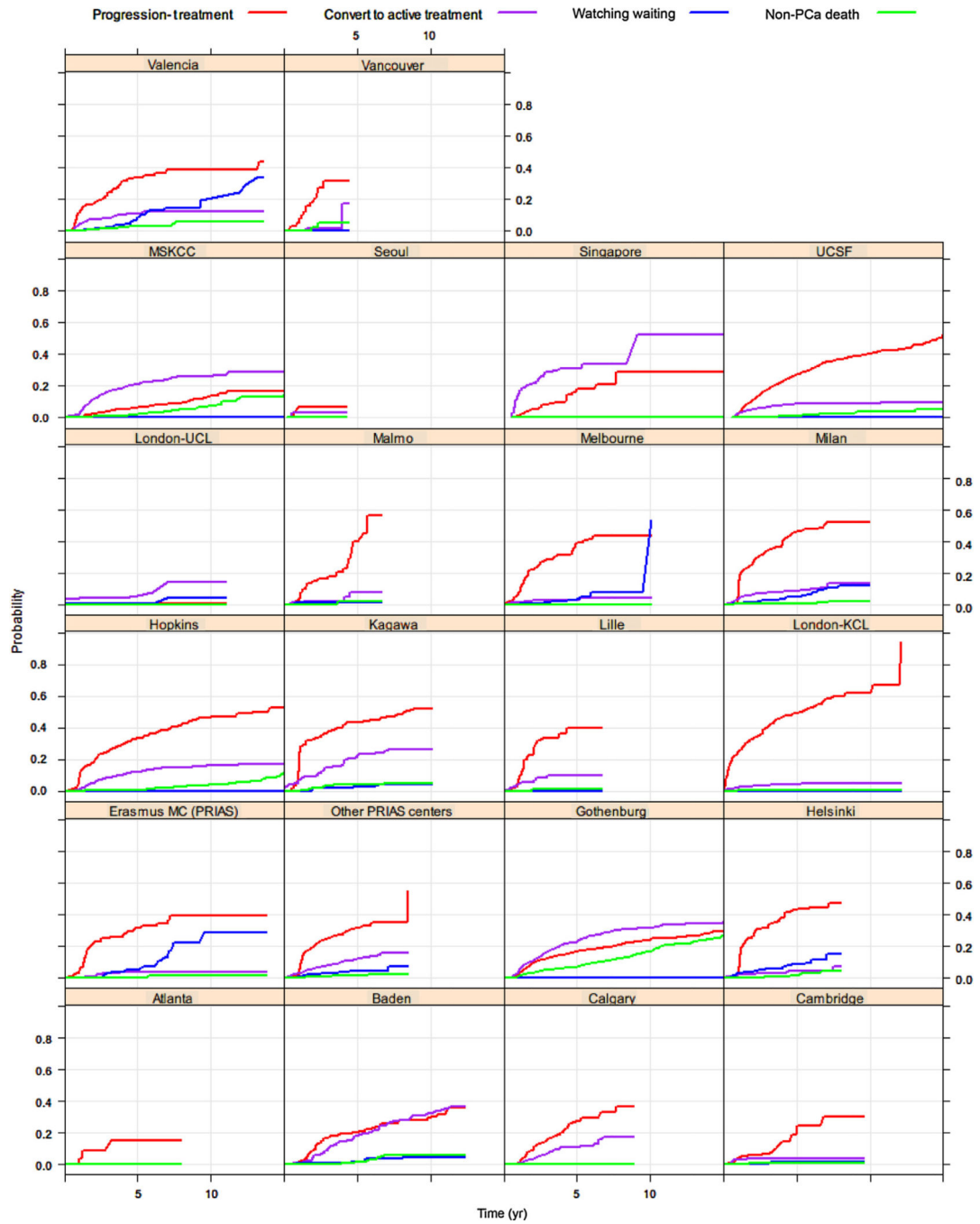**Fig. 3 –.**

Cumulative incidence of discontinuation of active surveillance over time for each centre in the GAP3 database. KCL = King's College London; MC = Erasmus Medical Center; MSKCC = Memorial Sloan Kettering Cancer Center; PCa = prostate cancer; PRIAS = Prostate Cancer Research International Active Surveillance; UCL = University College London; UCSF = University of California, San Francisco.

Table 1 –

Distribution of men on AS according to patient and tumour characteristics, by outcome following AS at 5 yr of follow-up

Variable	Censor or still on AS (N = 7049)	Progression treatment (N = 2061)	Conversion to active treatment without evidence of progression (N = 952)	Watchful waiting (N = 118)	Other cause of death (N = 116)	p value [a]
Years on AS	3.3 (1.4–5.8)	1.4 (1.1–2.5)	1.6 (1.0–2.7)	1.7 (1.2–3.1)	2.3 (1.5–3.4)	<0.01
Year of diagnosis	2010 (2007–2013)	2010 (2007–2011)	2008 (2004–2010)	2010 (2009–2010)	2007 (2003–2010)	<0.01
Age at start of AS (yr)	65 (60–69)	65 (61–69)	65 (60–69)	72 (65–75)	69 (65–73)	<0.01
PSA at start of AS (ng/ml)	5.3 (3.9–7.2)	5.4 (4.2–7.0)	5.6 (4.2–7.3)	5.9 (4.5–7.5)	6.4 (4.2–9.1)	0.01
Number of biopsy cores with PCa	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)	<0.01

AS = active surveillance; PCa = prostate cancer; PSA = prostate-specific antigen.

The median and interquartile ranges are provided for each variable.

[a] Kruskal-Wallis rank sum test.

Table 2 –

Number of patients from each centre in GAP3 at 5 yr of follow-up

Centre	Still on AS	Still on AS, follow-up <5 yr	Lost to follow-up	Progression	Converted to active treatment	Watchful waiting	Death from other causes	Total
EU-Atlanta	5	41	0	2	0	0	0	48
KB-Baden	44	52	0	22	24	2	1	145
UOF-Calgary	82	346	0	80	30	0	0	538
CUHT-Cambridge	21	162	14	18	7	1	1	224
EMC-Rotterdam	49	18	3	33	4	5	0	112
other PRIAS centres	149	1368	26	392	136	51	13	2135
SU-Gothenburg	293	147	1	111	142	0	43	737
HUCH-Helsinki	58	97	1	97	9	17	3	282
JHU-Baltimore	461	315	91	400	141	0	9	1417
KU-Kagawa	29	2	1	45	19	3	5	104
CHU-Lille	4	94	10	36	10	0	1	155
GSTT-London	58	43	0	83	8	0	2	194
UCL-London	30	230	0	0	10	2	0	272
SUS-Malmö	10	90	1	19	4	1	1	126
MEASCAP-Melbourne	53	114	0	63	3	3	0	236
INT-Milan	102	287	0	245	51	23	2	710
MSKCC-New York	443	344	0	56	190	0	16	1049
YUHS-Seoul	0	33	0	2	1	0	0	36
SGH-Singapore	21	93	0	20	46	0	1	181
UCSF-San Francisco	405	487	0	262	94	0	11	1259
IVO-Valencia	22	149	0	61	21	10	5	268
UBC-Vancouver	0	49	1	14	2	0	2	68
Total	2339	4561	149	2061	952	118	116	10 296

GAP3 = Movember's Global Action Plan Prostate Cancer Active Surveillance initiative; KCL = King's College London; Erasmus MC = Erasmus Medical Center; MSKCC = Memorial Sloan Kettering Cancer Center; PRIAS = Prostate Cancer Research International Active Surveillance; UCL = University College London; UCSF = University of California, San Francisco. See appendix A for institute abbreviations.