

## **ABSTRACT**

**OBJECTIVES.** The Movember Foundation launched the Global Action Plan Prostate Cancer Active Surveillance (GAP3) initiative to create a global consensus on the selection and monitoring of men with low-risk prostate cancer (PCa) on active surveillance (AS). The aim of this study is to present data on inclusion and follow-up for AS in this unique global AS database.

**SUBJECTS/PATIENTS (OR MATERIALS) AND METHODS.** Between 2014 and 2016, the database was created by combining patient data from 25 established AS cohorts worldwide (USA, Canada, Australasia, UK, Europe) (n=15,101).

**OUTCOME MEASUREMENTS AND STATISTICAL ANALYSIS.** Descriptive statistics were used to report clinical/demographic characteristics at time of PCa diagnosis, clinical follow-up, discontinuation of AS and subsequent treatment. Cumulative incidence curves were used to report discontinuation rates over time.

**RESULTS AND LIMITATION.** At diagnosis, median age was 65 yr (IQR 60-70) and median PSA was 5.4 ng/ml (IQR 4.0-7.3). Most men had a clinical stage T1 (71.8%), a biopsy Gleason score of 6 (88.8%) and one tumor-positive biopsy core (60.3%). Men on AS had a median follow-up time of 2.2 years (IQR 1.0-5.0 years). After 5, 10 and 15 years of follow-up, respectively, 58%, 39% and 23% of men were still on AS. The current version of GAP3 has limited data from MRI, quality of life and genomic testing.

**CONCLUSIONS.** GAP3 is the largest worldwide data effort integrating patient data from men with PCa on AS. The results will allow individual patients and clinicians to have greater confidence in the personalized decision to either delay or proceed with active treatment. Longer follow-up and the evaluation of imaging (MRI), new genomic markers and patient-related outcomes will result in even more valuable data and eventually in better patient outcomes.

## **INTRODUCTION**

Prostate cancer (PCa) is the second most common cancer in men, with nearly a million new cases diagnosed worldwide[1]. The numbers of men living with a diagnosis of PCa will likely continue to increase, as the population in many countries continues to age, and cancer is detected earlier, owing to the more widespread use of serum prostate specific antigen (PSA) testing[2, 3]. As a result, active surveillance (AS) was introduced as a management strategy for men with low-risk PCa, with the intention to start curative treatment at the time of progression and to avoid overtreatment and its associated morbidities. In recent years, AS has evolved from an experimental protocol to a broadly accepted management strategy for men diagnosed with low-risk PCa[4]. Contemporary data suggest that use of AS has increased globally[5-7].

Nevertheless, identification of those patients whose disease is at low risk for progression is a critical and much debated issue when deciding which men will benefit from AS for their PCa[8]. Numerous agencies have endorsed clinical practice guidelines for the management of low-risk PCa, which include criteria for enrolment of patients in AS programmes and their subsequent management[3]. However, no consensus is available today. Variability in enrolment criteria and follow-up has been demonstrated in international and national series of AS[9]. Moreover, robust data from men with clinically insignificant PCa who are undergoing AS, especially from studies with long follow-up durations, is still limited. Hence, many important questions on AS remain unanswered: Which newly-diagnosed men should be considered suitable candidates for AS[10]? What constitutes an appropriate follow-up regimen for AS[10]? There is a need for a worldwide consensus regarding the optimal criteria and protocols for AS and more comparative data on patient selection and testing protocols[11].

In August 2014, the Movember Foundation launched the Global Action Plan Prostate Cancer Active Surveillance initiative (GAP3). Milestones of the project include a global AS database for clinical, marker-related and imaging data. Its primary goal is to create a global consensus on the selection and monitoring of men with low risk PCa. Ultimately, worldwide uniform guidelines will be developed. The aim of the current study is to present data of this unique global dataset on inclusion and follow-up for AS in low-risk PCa.

## **SUBJECTS/PATIENTS (OR MATERIALS) AND METHODS**

### ***Study population***

Between 2014 and 2016, a global database was created by combining patient data from established AS cohorts worldwide. To assemble existing cohorts into a large consortium of cohorts, a new collaborative framework was needed. The GAP3 partners therefore developed documentation required for sharing and use of clinical data within the global database. The database has been developed at the site of Philips Electronics Nederland B.V. (“Philips”), Eindhoven, the Netherlands and is currently hosted by the Erasmus Medical Centre, Rotterdam, the Netherlands [12]. The GAP3 initiative is initiated and coordinated by the Erasmus Medical Centre, Rotterdam, the Netherlands. The Movember Foundation is the sole funder of the project. Funding has now been secured to provide sustainability of the GAP3 database until February 2019.

Requirements for participation in GAP3 included, amongst others, ethical approval for sharing digital patient data in a centralized global database, and an active registry of AS patients over the last two years or more, including at least ~50 patients annually. To date, 25 centers from the USA, Canada, Australasia, the UK and Europe fulfilled the requirements for participation

and joined the initiative (Table S1). References to the individual AS cohorts can be found in Table S1. The global database currently comprises data on 15,101 patients (Table S1) (database version ‘gap3data\_2.3’, released in June 2017). A summary of the entry criteria for each individual AS cohort is included in Table S2.

Although many variations in protocols currently exist, most agree that the most suitable patients for AS are those with age >18, pretreatment clinical stage T1-T2 PCa, serum PSA  $\leq$ 10 ng/ml, a biopsy Gleason score of  $\leq$ 6 or (3+4) 7, and a maximum of two tumour-positive biopsy core samples. Some protocols included PSA density (most often using a cutoff of 0.2 ng/ml<sup>2</sup>), the maximum extent of cancer per core (most often using a cutoff of 50%) and life expectancy (>10 years) and adequate biopsy sampling as inclusion criteria for AS. As a result the following baseline host (e.g. age, BMI, race, ethnicity, marital status, educational level, family history of PCa, smoking history and comorbidities/ overall health status) and tumour characteristics (e.g. clinical stage, PSA, prostatic volume, biopsy Gleason score, PSA density, number of biopsy cores with PCa, and maximum extent cancer per core) were recorded.

In addition to baseline information, follow-up information was key for the entire GAP3 project – it will allow us to shed light on current practice and outcomes with the final goal of providing consensus guidelines. A summary of the monitoring strategy for each individual AS cohort is included in Table S3. Following initiation of AS, almost all protocols recommend serial measurement of serum PSA levels, digital rectal examination (DRE) and surveillance biopsy sampling in order to identify pathological progression. Many uncertainties remain surrounding the optimal timing of these surveillance strategies. Some protocols recommend PSA levels measurements every three months, while others state that serum PSA monitoring should be implemented at intervals no more often than every six months after the start of AS. Some

protocols recommend DRE every six months, whilst others do not include DRE in follow up, due to the use of MRI. Substantial variation exists in the recommended frequency at which rebiopsy procedures should be conducted. Further, several protocols consider MRI for routine use in AS, again with differences between the recommended frequency, although most protocols recommend a 12 month interval. PSA kinetics and Quality of Life data are less frequently recommended as methods to identify whether or not a patients' cancer has progressed. We therefore collected follow-up information on e.g. PSA, PSA kinetics (PSA doubling time and PSA velocity), T-stage by DRE, biopsy characteristics and MRI findings (e.g. suspicious lesions found on MRI). Finally, the database contains information on discontinuation of AS (e.g. the reasons for stopping AS), and potential following treatments (e.g. radical prostatectomy (RP)) and cause of death.

### *Statistical analyses*

Descriptive statistics were used to assess the clinical and demographic characteristics at time of PCa diagnosis for all men included in the GAP3 cohort, their clinical follow-up, discontinuation of AS and potential following treatments. Cumulative incidence curves were used to report discontinuation rates over time[13]. R was used to perform all analyses [14].

## **RESULTS**

The GAP3 database currently comprises data on 15,101 patients from 25 centers across 15 countries (database version 'gap3data\_2.3', released in June 2017). At time of diagnosis, median age was 65 yr (IQR 60-70); median PSA was 5.4 ng/ml (IQR 4.0-7.3); median PSA density was 0.12 ng/ml (IQR 0.09-0.17); and median prostate volume was 43.2 cc (IQR 33-59). Most men

had a clinical stage T1 (71.8%), a biopsy Gleason score of 6 (88.8%), one tumor-positive biopsy core (60.3%) and no comorbidity (25%) (Table 1; see table S4 for characteristics at time of PCa diagnosis for all men included in the GAP3 cohort for each participating center). Men on AS had a median follow-up time (i.e. the time until discontinuation or the time until the last known follow-up without discontinuation being reported) of 2.16 years (IQR 1.02-4.47 years). Maximum follow-up time was 21.3 years. The median number of years until their last follow-up while on AS was 1.99 yr (0.83-4.24). (Table 2).

Until the end of current follow-up, 45 men (0.3%) developed metastases and 566 men (3.7%) died, of which 37 due to PCa (0.2%) (Table 2). The main clinical and demographic characteristics and clinical follow-up for all men that developed metastases during AS (n=45) and for all men that developed metastases and died of PCa (n=17) are summarized in table 3. Of all men that died of PCa until the end of current follow-up (n=37), a total of 32 men switched to curative treatment, of which 21 to androgen deprivation therapy, four to external beam radiotherapy, two to external beam radiotherapy and brachytherapy, one to external beam radiotherapy and androgen deprivation, and four to radical prostatectomy.

A total of 5,625 (37%) men discontinued AS for the following reasons: 46.2% for protocol-based progression, 3.3% switched to watchful waiting (WW), 9.1% discontinued due to patient or clinician choice, 7.0% died, and 25.1% discontinued for unknown reasons. For all men that discontinued AS, treatment was reported in 73% of the cases (n=4124). Treatment after discontinuation was radical prostatectomy in 51.6% of men, external beam radiotherapy in 13.2% of men; brachytherapy in 9.3% of men and primary ADT/hormonal therapy in 8.4% of men (Table 2). Figure 1 shows cumulative incidence curves for reasons of discontinuing AS. The

percentage of total area shaded for each color in the figure can be interpreted, at any time point, as the risk of discontinuing AS for that stated reason.

Of the 15,101 patients, 1068 patients (7.1%) did not have available follow-up data yet. Among the remaining 14,033 patients, after 5, 10 and 15 years of follow-up, respectively, 58%, 39% and 23% of men were still on AS; 23%, 30% and 36% discontinued due to protocol-based progression; 5%, 5% and 6% discontinued due to patient or clinician choice; 1%, 3% and 3% switched to watchful waiting (WW); 2%, 7% and 12% died (mostly of another cause), and 11%, 16%, 20% discontinued for unknown reasons.

## **DISCUSSION**

In recent years, AS has evolved from an experimental protocol to become a broadly accepted—in fact, preferred—management strategy for men diagnosed with low-risk PCa [15].

Nevertheless, consensus on inclusion criteria, surveillance schedules and intervention thresholds for AS of men with low risk PCa is currently lacking. With this in mind, the Movember Foundation launched the GAP3 initiative.

Several findings deserve particular attention. GAP3 is the largest effort of its type to integrate patient data from men with prostate cancer on AS. With more than 15,000 patients, the Movember AS database is the largest centralized prostate cancer AS database to date, comprising the majority of the world's AS patient data. Large volumes of AS data have been collected routinely for many years by the affiliated centers worldwide. Hence, the central data source enables comparisons of determinants for inclusion and follow-up in AS, and subsequent clinical outcomes (e.g. disease progression), between cohorts and countries and it allows us to determine

variable patterns over time. Data capture is nearly complete (i.e. available for at least 90% of the centers) for key variables such as serum PSA levels, Gleason score and clinical stage at time of PCa diagnosis; serum PSA levels, T-stage by DRE and biopsy characteristics during follow-up; reasons to discontinue AS, treatment choices and cause of death. The database thus has a significant amount of highly informative patient data on AS for low risk PCa. It can therefore make significant contributions to the development of evidence-based consensus guidelines for AS, and as a result, improve the lives of men diagnosed with low risk PCa.

There are some limitations that need to be considered when using data from GAP3. The database is ‘ambidirectional’, meaning that it has both a retrospective and a prospective component. Up till now, the GAP3 database is purely a retrospective database. As a consequence, there was limited control over data collection, and the data of interest were sometimes incomplete or inconsistently measured. For instance, in many cohorts (n=18) the reason for discontinuation of AS is not available. For future analyses, the individual centers will be requested to supply the missing data (if available). During the course of the GAP3 project, it has become apparent that there is an urgent need to assess the value of MRI with respect to disease monitoring in men on AS. The current patient series only has limited imaging data from MRI. Currently, almost no data is available for quality of life and genomic testing. However, additional funding has now been secured from the Movember Foundation to sustain the database and to add a prospective element, thereby providing the opportunity to collect evidence on imaging (MRI), molecular (genomics) markers, patient-related outcomes and more.

Metastatic disease or death from PCa are ultimate end points by which AS should be evaluated[16]. However, because of the slow growing nature of low-risk PCa, prospective evaluation of these endpoints requires at least another 10–15 years of follow-up[16]. To date,



mainly data from non-mature prospective clinical trials of AS, that have a mean follow-up of <10 years, are available. The GAP3 database currently also suffers from limited follow-up time, but will in future provide the main resource of real world data on AS management.

In the global database, PCa death and metastasis remain rare events (both <1%). Current analyses therefore make use of surrogate endpoints such as discontinuation of AS and/or changes in PCa treatment. Nevertheless, follow-up is ongoing until at least 2019, so that in the future GAP3 will contain even more valuable data and provide better insight into patient outcomes.

Active surveillance is evolving into a well-accepted management strategy for appropriately selected men. Unless the over-diagnosis of indolent PCa is reduced by alternative diagnostic strategies, AS will continue to play an important role. The GAP3 initiative will make significant contributions to this field of research by offering standard, evidence-based guidelines [3]. Clinicians will be able to use these guidelines to more confidently identify men that are suitable for active surveillance and to also decide whose PCa has progressed and will, therefore, require treatment. Such guidelines will provide reassurance to men that they have made the best treatment choice for their type of disease [3]. Longer follow-up, achieved by ongoing commitment of GAP3 participating centers, and the evaluation of, for instance, imaging and new biomarkers, will result in more valuable data and eventually in better patient outcomes.

## **Acknowledgements**

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## **Legends to illustration**

*Figure 1. Discontinuation of Active Surveillance over time (n=14,033)*

Protocol based progression= clinical and pathological progression, clinical progression, other PSA kinetics, pathological progression, PSA progression (PSADT<3 yrs), or radiological progression; FU = follow-up; WW = watchful waiting.

**Table 1 Characteristics at time of PCa diagnosis for all men included in the GAP3 cohort\***

<b>Characteristics</b>	<b>Distribution of characteristics (N = 15101)</b>	<b>Number of centers reported (N<sub>total</sub>=25)</b>
Age, Median (Q1-Q3)	65 (60-70)	25
Age, n (%)		25
≤55	1547 (10.3)	
56-60	2402 (16.1)	
61-65	3579 (23.9)	
66-70	4002 (26.8)	
71-80	3256 (21.8)	
>80	172 (1.1)	
Year of diagnosis, n (%)		25
1992-1997	260 (1.8)	
1998-2004	1743 (11.6)	
2005-2008	3011 (20.2)	
2009-2011	4101 (27.5)	
2012-2014	4228 (28.4)	
2015-2016	1565 (10.5)	
Charlson Comorbidity Index, n (%)		10
0	3775 (25.0)	
1	669 (4.4)	
2	761 (5.0)	
≥3	563 (3.7)	
Missing	9333 (61.8)	
T-stage (at DRE), n (%)		23
T1	10841 (71.8)	
T2	2034 (13.5)	
T3	11 (0.1)	
T4	1 (<0.1)	
Unknown	2214 (14.6)	
Gleason grade group, n (%)		25
<6	400 (2.7)	
6	13198 (88.8)	
>6	1263 (8.5)	
Unknown	240 (1.6)	
PSA ng/mL, n (%)		25
0-3.0	1826 (12.6)	
3.1-6.0	6913 (47.8)	
6.1-10.0	4511 (31.2)	
>10.0	1207 (8.3)	
Median (Q1-Q3)	5.4 (4.0-7.3)	
Missing, n (%)	644 (4.3)	
Prostate volume, cc		22
Median (Q1-Q3)	43.2 (33.0-59.0)	
Missing, n (%)	4069 (26.9)	
PSA density ng/mL/mL		22
Median (Q1-Q3)	0.12 (0.09-0.17)	
Proportion missing, n (%)	4221 (28.0)	
Positive cores		24
Median (Q1-Q3)	1 (1-2)	
Missing, n (%)	1305 (8.6%)	
Positive cores		24
0	78 (0.6)	
1	8321 (60.3)	
2	3270 (23.7)	
≥3	2127 (15.4)	
Percentage of cancer in any one core		17
Median (Q1-Q3)	10 (5-20)	
Minimum, maximum	0, 100%	
Proportion missing, n (%)	6114 (40.5)	

\*Database version 'gap3data\_2.3', released in June 2017

**Table 2 Characteristics of clinical follow-up, discontinuation of AS and subsequent treatment\***

	Patient age group at PCa diagnosis						All** <i>N=15101</i>
	50-55 years (n=1547)	56-60 years (n=2402)	61-65 years (n=3579)	66-70 years (n=4002)	71-75 years (n=2412)	>75 years (n=1016)	
Median number of years on AS (Q1-Q3)	2.38 (1.04-4.63)	2.21 (1.07-4.51)	2.17 (1.05-4.58)	2.23 (1.03-4.50)	2.12 (1.04-4.45)	1.91 (0.85-3.84)	2.16 (1.02-4.47)
Median number of years until last follow-up while on AS (Q1-Q3)	2.63 (1.00-5.04)	2.51 (1.02-5.07)	2.50 (1.02-5.22)	2.55 (1.02-5.19)	2.29 (1.02-4.85)	2.04 (0.87-4.32)	2.44 (1.01-5.02)
Remaining on AS, n (%)	1083 (70.0)	1584 (66.0)	2236 (62.5)	2379 (59.5)	1460 (60.5)	607 (59.7)	9476 (62.8)
Metastasis, n (%)	4 (0.3)	4 (0.2)	9 (0.3)	11 (0.3)	13 (0.5)	4 (0.4)	45 (0.3)
Death, n (%)							
Alive	1535 (99.2)	2371 (98.7)	3481 (97.3)	3808 (95.2)	2273 (94.2)	927 (91.2)	14535 (96.2)
Death due to other causes	11 (0.7)	28 (1.2)	94 (2.6)	180 (4.5)	129 (5.3)	84 (8.3)	529 (3.5)
Death due to PCa	1 (0.1)	3 (0.1)	4 (0.1)	14 (0.3)	10 (0.4)	5 (0.5)	37 (0.2)
<i>Discontinuing AS due to different reasons, n (%)</i>							<i>N=5625 (37%)</i>
Progression	225 (14.5)	435 (18.1)	698 (19.5)	746 (18.6)	386 (16.0)	107 (10.5)	2599 (46.2%)
Pathological progression	150 (9.7)	276 (11.5)	383 (10.7)	401 (10.0)	190 (7.9)	52 (5.1)	1452 (25.8)
Other progression	75 (4.8)	159 (6.6)	315 (8.8)	345 (8.6)	196 (8.1)	55 (5.4)	1147 (20.4%)
Converting to WW	4 (0.3)	10 (0.4)	22 (0.6)	38 (0.9)	63 (2.6)	42 (4.1)	180 (3.3)
Death	10 (0.7)	18 (0.8)	67 (1.9)	131 (3.3)	95 (3.9)	69 (6.8)	391 (7.0)
Patients anxiety	53 (3.4)	77 (3.2)	139 (3.9)	138 (3.5)	73 (3.0)	25 (2.5)	511 (9.1)
Lost-to-follow up	46 (3.0)	72 (3.0)	106 (3.0)	151 (3.8)	105 (4.3)	50 (4.9)	531 (9.4)
Unknown	128 (8.1)	206 (8.6)	311 (8.7)	419 (10.5)	230 (9.5)	116 (11.4)	1413 (25.1)
<i>Treatment received following AS, n (%)</i>							<i>N=4124 (73%)*</i>
ADT or hormonal therapy	4 (0.3)	18 (0.8)	44 (1.2)	102 (2.5)	105 (4.3)	71 (7.0)	348 (8.4)
Brachytherapy	34 (2.2)	61 (2.5)	105 (2.9)	113 (2.8)	62 (2.6)	10 (1.0)	385 (9.3)
Brachytherapy and ADT	1 (0.1)	2 (0.1)	3 (0.1)	5 (0.1)	1 (0.04)	1 (0.1)	13 (0.3)
EBRT and ADT	2 (0.1)	7 (0.3)	27 (0.8)	62 (1.6)	57 (2.4)	27 (2.7)	182 (4.4)
EBRT and Brachytherapy	7 (0.5)	28 (1.2)	51 (1.4)	107 (2.7)	46 (1.9)	12 (1.2)	251 (6.1)
EBRT and Brachytherapy and ADT	2 (0.1)	1 (0.04)	8 (0.2)	8 (0.2)	1 (0.04)	0 (0)	20 (0.5)
EBRT alone	17 (1.1)	46 (1.9)	115 (3.2)	148 (3.7)	157 (6.5)	62 (6.1)	545 (13.2)
Focal therapy	4 (0.3)	8 (0.3)	11 (0.3)	13 (0.3)	8 (0.3)	5 (0.5)	54 (1.3)
Radical prostatectomy	293 (18.9)	462 (19.2)	658 (18.4)	555 (13.9)	145 (6.0)	11 (1.1)	2127 (51.6)
Radical prostatectomy and ADT	0 (0)	0 (0)	3 (0.1)	4 (0.1)	0 (0)	0 (0)	7 (0.2)
Radical prostatectomy, ADT and EBRT	0 (0)	0 (0)	1 (0.03)	0 (0)	0 (0)	0 (0)	1 (0.02)
Radical prostatectomy and EBRT	0 (0)	1 (0.04)	2 (0.1)	0 (0)	1 (0.04)	0 (0)	4 (0.1)
WW	1 (0.1)	7 (0.3)	12 (0.3)	20 (0.6)	31 (1.3)	13 (1.3)	86 (2.1)

Other	16 (1.0)	18 (0.8)	19 (0.5)	23 (0.6)	15 (0.6)	9 (0.9)	101 (2.5)
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\*Database version 'gap3data\_2.3', released in June 2017; \*\* The percentage in the last column (All) is based on the total number of patients, the number of patients who discontinued AS, or the number of patients who received treatment following AS, respectively; AS: active surveillance; WW: watchful waiting; EBRT: External beam radiotherapy; ADT: Androgen deprivation therapy; PCa: prostate cancer; \*\*\* The proportion refers to the % of men that received treatment after stopping AS

**Table 3 Clinical and demographic characteristics and clinical follow-up for all men that developed metastases during AS and for all men that developed metastases and died of PCa\***

Characteristics	Distribution of characteristics of men that developed metastases (N = 45)	Distribution of characteristics of men that developed metastases and died of PCa (N = 17)
Age, Median (Q1-Q3)	66 yr (IQR 62-72)	66 yr (IQR 64-72)
Charlson Comorbidity Index, n (%)		
0	45 (100%)	17 (100%)
1	0 (0%)	0 (0%)
2	0 (0%)	0 (0%)
≥3	0 (0%)	0 (0%)
Missing	0 (0%)	0 (0%)
T-stage (at DRE), n (%)		
T1	21 (46.7%)	6 (35.3%)
T2	15 (33.3%)	7 (41.2%)
T3	2 (4.4%)	1 (5.9%)
T4	1 (2.2%)	1 (5.9%)
Unknown	6 (13.3%)	2 (11.8%)
Gleason grade group, n (%)		
<6	3 (6.7%)	0 (0%)
6	28 (62.2%)	10 (58.8%)
>6	21 (46.7%)	5 (29.4%)
Unknown	4 (8.9%)	2 (11.8%)
PSA ng/mL, n (%)		
Median (Q1-Q3)	6.9 ng/ml (IQR 4.8-8.7)	7.9 ng/ml (IQR 4.3-12.5)
Missing, n (%)	4 (8.9%)	1 (5.9%)
Prostate volume, cc		
Median (Q1-Q3)	44 cc (IQR 31-55)	41 cc (IQR 29-50)
Missing, n (%)	23 (51.1%)	9 (52.9%)
PSA density ng/mL/mL		
Median (Q1-Q3)	0.14 ng/ml (IQR 0.10-0.19)	0.14 ng/ml (IQR 0.11-0.19)
Proportion missing, n (%)	25 (55.6%)	10 (58.8%)
Positive cores		
0	-	-
1	14 (42.4%)	5 (29.4%)
2	10 (30.3%)	4 (23.5%)
≥3	9 (27.3%)	3 (17.6%)
Time to metastasis, Median (Q1-Q3)	6.4 yr (IQR 3.5-9.9)	-
Time to death, Median (Q1-Q3)	-	10.0 (IQR 6.1-12.7)

\*Database version 'gap3data\_2.3', released in June 2017

**Conflicts of Interest:** None declared.

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