The long-term outcomes of Gleason grade groups 2 and 3 prostate cancer managed by active surveillance: Results from a large population-based cohort
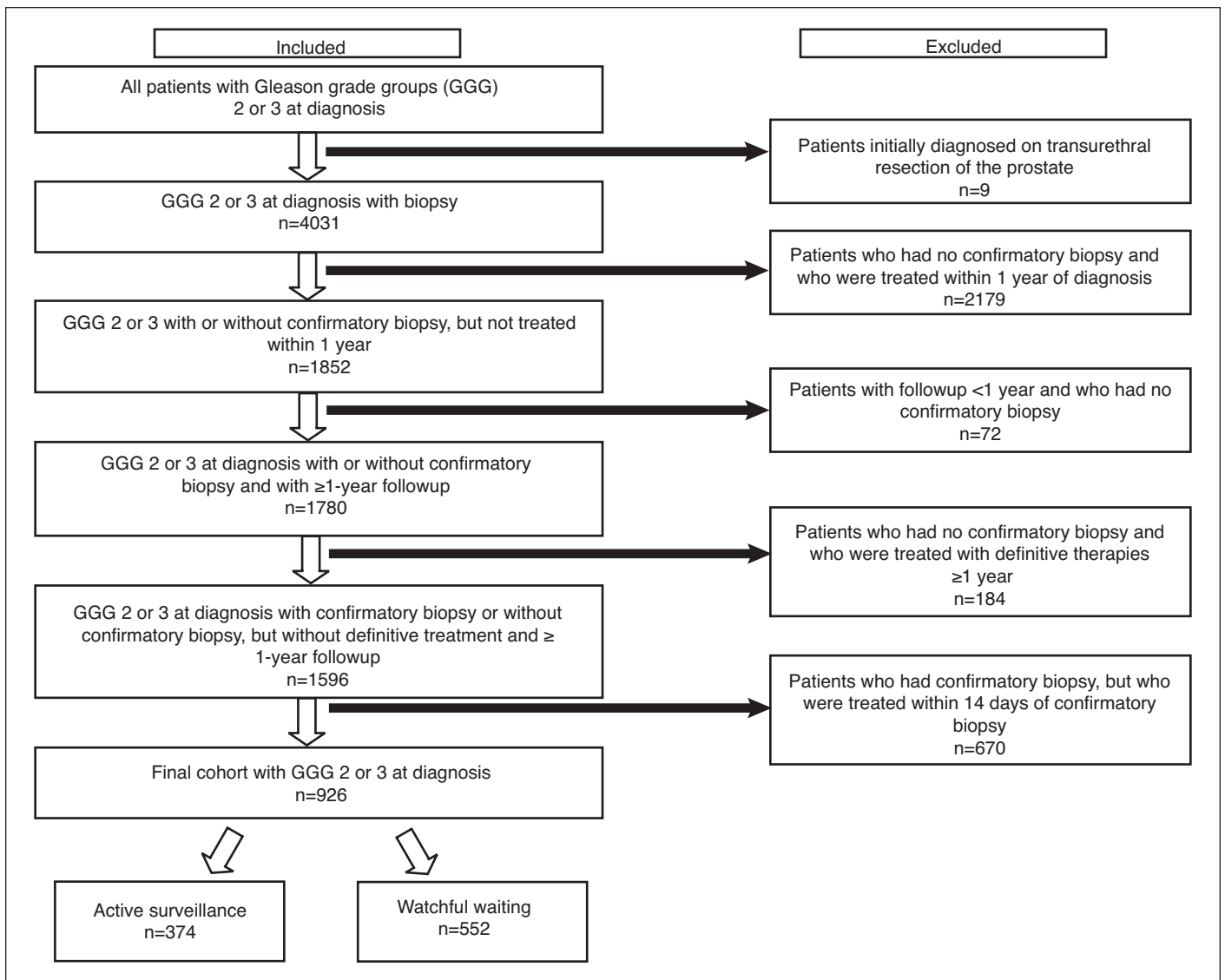
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Supplementary Table 1. Ontario Health Insurance Plan (OHIP) physician billing claims used to identify prostate cancer-related management

Billing claims – code	Fee code: OHIP definition
Androgen deprivation therapy	G342: implantation of hormone pellets
Orchiectomy	S589: orchiectomy; S598: radical orchiectomy
Biopsy	Z712: biopsy, needle; Z713 biopsy, needle with drainage of abcess; S644: biopsy, perineal; E780: cystoscopy with needle biopsy of prostate
Transurethral resection of the prostate	S654: transurethral resection of prostate for residual tissue; S655:transurethral resection of prostate
Radical prostatectomy	S645:perineal prostatectomy; S646:perineal prostatectomy with vesiculectomy; S651: radical retropubic prostatectomy; S653:laparoscopic radical prostatectomy;
Pelvic lymph node dissection	S652:staging pelvic lymph node dissection for prostate cancer
Brachytherapy	S640: stereotactic prostate brachytherapy; X322: radium (sealed sources) treatment planning dosage; X323:radium (sealed sources) Intracavit. applic. - 1st applic.; X324: radium (sealed sources) - Interstitial; X325: radium (sealed sources) Applic. plaque/mould; X334: radium (sealed sources) Intracavit. applic. - rep. applic.
Radiotherapy	X310: simple treatment planning; X311: intermediate treatment planning; X312: complex treatment planning; X313: full 3D treatment preparation
Urologist visits	A355: consultation; A935: special surgical consultation; A356: repeat consultation; A353: specific assessment; A354: partial assessment; C355: in-patient consultation; C935: in-patient special surgical consultation; C356: in-patient repeat consultation; C353: in-patient specific assessment; C354: in-patient partial assessment; C352: in-patient subsequent visits – first five weeks; C357: in-patient subsequent visits – sixth to thirteenth week; C359: in-patient subsequent visit – after thirteenth week
Radio-oncologist visits	A340: medical specific re-assessment; A341: complex medical specific re-assessment; A343:medical specific assessment; A345: consultation; A346: repeat consultation; A348: partial assessment; A745: limited consultation; C340: in-patient medical specific re-assessment; C341: in-patient complex medical specific re-assessment; C343: in-patient medical specific assessment; C345: in-patient consultation; C346: in-patient repeat consultation; C348: in-patient partial assessment; C745: in-patient limited consultation; C352: in-patient subsequent visits – first five weeks; C357: in-patient subsequent visits – sixth to thirteenth week; C359: in-patient subsequent visit – after thirteenth week

Included	Excluded
All patients with Gleason grade groups (GGG) 2 or 3 at diagnosis	
	Patients initially diagnosed on transurethral resection of the prostate n=9
GGG 2 or 3 at diagnosis with biopsy n=4031	
	Patients who had no confirmatory biopsy and who were treated within 1 year of diagnosis n=2179
GGG 2 or 3 with or without confirmatory biopsy, but not treated within 1 year n=1852	
	Patients with followup <1 year and who had no confirmatory biopsy n=72
GGG 2 or 3 at diagnosis with or without confirmatory biopsy and with ≥1-year followup n=1780	
	Patients who had no confirmatory biopsy and who were treated with definitive therapies ≥1 year n=184
GGG 2 or 3 at diagnosis with confirmatory biopsy or without confirmatory biopsy, but without definitive treatment and ≥ 1-year followup n=1596	
	Patients who had confirmatory biopsy, but who were treated within 14 days of confirmatory biopsy n=670
Final cohort with GGG 2 or 3 at diagnosis n=926	

Active surveillance n=374	Watchful waiting n=552

Supplementary Fig. 1. Flow chart for identification of cohort.

Supplementary Table 2. Description of covariates used in the multivariable models

Variables	Definition	Type of variable	Categories
Patient-specific characteristics			
Age, years	Age at diagnosis	Continuous	Per 10-year increment
Year of diagnosis	Year of diagnosis	Categorical	Years 2002–2004 Years 2005–2007 Years 2008–2011
ADG score	ADG summary score	Continuous	Per 1-unit increment
Area of residency	Primary area of residency	Categorical	Urban Rural
Income quintile	Neighborhood average income quintile	Categorical	1–5, with 1 representing the lowest income quintile and 5 the highest
Initial management	Type of management	Categorical	Watchful waiting Active surveillance
Disease characteristics			
PSA category at diagnosis	PSA level (ng/mL)	Categorical	0–4 4.01–10 >10 Missing
Positive cores at diagnosis and confirmatory biopsy	Number of positive cores at diagnosis and at confirmatory biopsy	Categorical	1 2 3 >3 Missing
Max. % of core involvement at diagnosis and confirmatory biopsy	Maximal percentage of core involvement at diagnosis and at confirmatory biopsy	Categorical	≤50% <50%
Gleason grade group at confirmatory biopsy	Maximal grade group at diagnosis and at confirmatory biopsy	Categorical	2 (Gleason score 3+4) 3 (Gleason Score 4+3)
Institution-level characteristics			
Type of primary physician	Specialty of primary caregiver	Categorical	Urologist Radiation oncologist
Physician annual prostate cancer treatment volume	Annual new PCa-related consultation volume during study period – physician	Categorical	1st tertile 2nd tertile 3rd tertile
Specialized cancer-center	Type of center	Categorical	YES – Cancer center NO – Non-cancer center
Institution annual prostate cancer treatment volume	Annual new PCa-related consultation volume during study period - institution	Categorical	1st tertile 2nd tertile 3rd tertile

Supplementary Table 3. Cancer-specific and overall survival status (watchful waiting vs. active surveillance)†

Variables	Overall (n=926)	Watchful waiting (n=552)	Active surveillance (n=374)	p
Overall deaths, n (%)*				
Overall	371 (40)	300 (54)	71 (19)	<0.001
5 years	158 (17)	136 (25)	22 (6)	<0.001
10 years	341 (37)	274 (50)	67 (18)	<0.001
Prostate cancer related deaths, n (%)				
Overall	63 (7)	48 (9)	15 (4)	0.006
5 years	35 (4)	28 (5)	7 (2)	0.01
8 years	54 (6)	41 (7)	13 (4)	0.01
Followup for overall survival (months), median (IQR)	91 (60–116)	84 (50–110)	97 (72–121)	<0.001
Followup for cancer-specific survival (months), median (IQR)	77 (49–93)	74 (48–91)	81 (50–95)	0.12

†Followup data was available for overall deaths until December 31, 2014 and until December 31, 2012 for cancer-specific survival. *If censored after December 31, 2012, there were 260 (28%) deaths identified (216 in the watchful waiting cohort; 44 in the active surveillance cohort). IQR: interquartile range.

Supplementary Table 4. Cancer-specific and overall survival status (by Gleason grade group)†

Variables	Overall (n=926)	Watchful waiting n=552			Active surveillance n=374		
		Grade group 2 (n=361)	Grade group 3 (n=191)	p	Grade group 2 (n=283)	Grade group 3 (n=101)	p
Overall deaths, n (%)*							
Overall	371 (40)	181 (50)	119 (62)	0.006	47 (17)	24 (26)	0.034
5 years	158 (17)	81 (22)	55 (29)	0.099	15 (5)	7 (8)	0.39
10 years	341 (37)	169 (46)	105 (55)	0.068	45 (16)	22 (24)	0.071
Followup for overall survival (months), median (IQR)	91 (60–116)	82 (52–110)	86 (49–115)	0.57	95 (71–119)	105 (72–125)	0.20
Prostate cancer related deaths, n (%)							
Overall	63 (7)	23 (6)	25 (13)	0.007	9 (3)	6 (7)	0.14
5 years	35 (4)	13 (4)	15 (8)	0.030	3 (1)	4 (4)	0.062
8 years	54 (6)	19 (5)	22 (12)	0.007	7 (3)	6 (7)	0.092
Followup for cancer-specific survival (months), median (IQR)	77 (49–93)	75 (48–91)	73 (45–92)	0.87	80 (48–93)	89 (58–96)	0.072

†Followup data was available for overall deaths until December 31, 2014 and until December 31 2012 for cancer-specific survival. *If censored after December 31, 2012, there were 260 (28%) deaths identified (216 in the watchful waiting cohort; 44 in the active surveillance cohort). IQR: interquartile range.

Supplementary Table 5. Univariable and multivariable Cox proportional hazard model testing for factors associated with overall survival

Variables	Univariable HR (95% CI)	p	Multivariable[†] HR (95% CI)	p
Patient-specific characteristics				
Age, per 10 years increase	2.38 (2.06–2.77)	<0.001	1.79 (1.49–2.14)	<0.001
Year of diagnosis				
2002–04	REF		REF	
2005–07	0.89 (0.71–1.11)	0.3	1.19 (0.93–1.52)	0.16
2008–11	0.74 (0.49–1.12)	0.16	1.41 (0.91–2.18)	0.13
ADG scores, per 1-unit increase	1.04 (1.04–1.04)	<0.001	1.03 (1.02–1.03)	<0.001
Area of residency (rural vs. urban)	1.23 (0.91–1.65)	0.17	1.17 (0.85–1.60)	0.3
Neighborhood Income quintile				
1st quintile (lowest)	REF		REF	
2nd quintile	0.71 (0.51–0.98)	0.04	0.68 (0.48–0.96)	0.03
3rd quintile	0.84 (0.61–1.16)	0.3	0.66 (0.48–0.92)	0.01
4th quintile	0.78 (0.57–1.07)	0.12	0.71 (0.52–0.98)	0.03
5th quintile (highest)	0.66 (0.49–0.91)	0.009	0.65 (0.47–0.91)	0.01
Initial management (watchful waiting vs. active surveillance)	3.44 (2.65–4.46)	<0.001	1.92 (1.31–2.79)	<0.001
Disease-specific characteristics				
PSA category at diagnosis (ng/mL)				
0–4	REF		REF	
4.01–10	1.56 (0.83–2.91)	0.3	0.58 (0.30–1.13)	0.11
>10	0.72 (0.39–1.38)	0.16	0.82 (0.43–1.59)	0.6
Missing	1.55 (0.84–2.85)	0.16	1.08 (0.57–2.04)	0.8
Positive cores at diagnosis				
1	REF		REF	
2	1.12 (0.71–1.76)	0.6	0.80 (0.50–1.28)	0.4
3	1.49 (0.96–2.32)	0.08	1.15 (0.72–1.83)	0.6
>3	1.79 (1.22–2.63)	0.003	1.13 (0.76–1.70)	0.5
Missing	1.94 (1.26–2.97)	0.003	0.95 (0.59–1.55)	0.9
Max. % of core involvement at diagnosis (>50% vs. ≤50%)	1.26 (0.98–1.63)	0.07	1.03 (0.78–1.37)	0.8
Gleason grade group at diagnosis (3 vs. 2)	1.37 (1.12–1.69)	0.003	1.03 (0.83–1.28)	0.8
Definitive treatment (yes vs. no)	0.23 (0.16–0.33)	<0.001	1.37 (0.84–2.49)	0.2
Prostate cancer treatment-specific characteristics)				
Primary physician (urologist vs radiation oncologist)	1.22 (0.87–1.71)	0.3	0.48 (0.29–0.76)	0.002
Physician annual prostate cancer treatment volume				
1st tertile (lowest)	REF		REF	
2nd tertile	1.07 (0.68–1.65)	0.6	1.00 (0.64–1.60)	0.9
3rd tertile (highest)	1.01 (0.67–1.51)	0.7	0.89 (0.58–1.43)	0.6
Specialized cancer center (yes vs. no)	0.55 (0.43–0.70)	<0.001	0.79 (0.54–1.14)	0.20
Institution annual prostate cancer treatment volume				
1st tertile (lowest)	REF		REF	
2nd tertile	0.77 (0.49–1.19)	0.2	0.83 (0.52–1.44)	0.5
3rd tertile (highest)	0.73 (0.49–1.09)	0.12	0.82 (0.51–1.31)	0.4

[†]All variables were fit in final multivariable model. ADG: aggregated diagnosis groups; CI: confidence interval; HR: hazard ratio; PSA: prostate-specific antigen.

Supplementary Table 6. Grade group on radical prostatectomy specimen (n=119)

		Diagnostic biopsy		
		Gleason grade group 2 (n=94)	Gleason grade group 3 (n=25)	Overall (n=119)
Radical prostatectomy Gleason grade groups, n (%)	N/A	0 (0)	3 (12.0)	3 (2.9)
	1	12 (12.8)	3 (12.0)	15 (12.5)
	2	62 (66.0)	10 (25.0)	72 (60.5)
	3	19 (20.2)	7 (28.0)	26 (21.8)
	4	1 (1.1)	0 (0)	1 (0.8)
	5	0 (0)	2 (8.0)	2 (1.7)