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Estimating the individual benefit of immediate treatment or active surveillance for prostate cancer after screen-detection in older (65+) men

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A significant proportion of screen-detected men with prostate cancer is likely to be overtreated, especially in older age groups. We aim to find which groups of screen-detected older men (65+) benefit the most from Immediate Radical Treatment or Active Surveillance (AS) for prostate cancer, depending on age, screening history, health status and prostate cancer stage at detection. We used a microsimulation model (MISCAN) of the natural history of prostate cancer based on ERSPC data. Individual life histories are simulated with US comorbidity lifetables based on a random sample of MEDICARE data. Different screening histories are simulated and we count outcomes for men screen-detected from ages 66 to 72. For immediately treated men with low-risk disease ($\leq$ T2a, Gleason 6) the probability of overtreatment ranges from 61% to 86% decreasing to between 37 and 46%, if they are assigned to AS. For intermediate risk men ($\leq$T2, Gleason 3 + 4) overtreatment ranges from 23 to 60%, which reduces to between 16 and 31% for AS. For high risk men (T3, or $\geq$ Gleason 4 + 3), overtreatment ranges from 11 to 51%. The disease stage at screen-detection is a critical risk factor for overtreatment. For low risk men, AS seems to significantly reduce overtreatment at a modest cost. For intermediate risk men, the decision between immediate treatment or AS depends on age and comorbidity status. Men screen-detected in a high risk disease stage may benefit from immediate treatment even beyond age 69.

Overdiagnosis consists of the detection of cancer that would not develop into clinical cancer in absence of screening, or eventually be life-threatening. If an overdiagnosed man is referred for radical treatment then he is considered to be overtreated. In a context of limited healthcare resources, it is crucial to identify which patients are at risk of overtreatment and therefore could be better handled by Active Surveillance (AS) or be left untreated.

Estimates of overdiagnosis in prostate cancer can vary considerably. Depending on, whether an excess incidence approach is used or, on the specific microsimulation model, estimates range between 23 and 60% of screen-detected men.[1,2]

Due to these estimates, and to the controversy surrounding the magnitude of the benefit of screening in the two largest prostate cancer screening randomized control trials,[3,4] the US Preventative Services Task Force recommended in 2012 against PSA screening for prostate cancer.[5] Others, like the AUA recommend shared decision making about screening between ages 55 and 69.[6]

Translating these results from the population level to an individual patient though, can be an arduous task. The probability that an individual benefits from screening and treatment can vary substantially depending on the individual person's characteristics. Namely, age, health status and past screening history could have an influence on the risk of being overdiagnosed and overtreated.

Previous studies[7,8] have assessed the association between PSA, age and overdiagnosis, finding that the majority of overdiagnosed cases occurs in men older than 60. However, Wever *et al.*[9] studied the relationship between overdiagnosis and disease stage at detection and found that for men in age Group 65–69, the probability of overdiagnosis ranges from 9 to 50%. None of these studies included AS as an option for newly screen-detected men.

AS for prostate cancer consists on the frequent monitoring of newly screen-detected men, through PSA tests and repeat biopsies. It has recently emerged as a viable alternative to immediate treatment, namely for low risk men.[10] For men

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What's new?
How can clinicians strike a balance between overtreatment and undertreatment? Large scale screening programs inevitably lead to overdiagnosis, and treatment of cancers that would never develop into life-threatening disease. These authors created a computer simulation of prostate cancer that considered age, screening history, cancer stage, and general health to calculate individualized risk of overtreatment. Unlike previous studies, this model included active surveillance as an option, in addition to immediate treatment. For low-risk men, active surveillance can reduce overtreatment, while for intermediate-risk men, personal factors such as age and comorbidity will determine whether treatment or surveillance is the preferred course.

older than 65, it could be an avenue to significantly reduce overtreatment. Additionally, no study has yet modeled the association between overdiagnosis and comorbidity in prostate cancer for screen-detected men. This association could have a critical impact on the estimates of,[7,9] specially for men with significant comorbidities.

In this study, we use a simulation model to compute personalized estimates of overtreatment, prostate cancer mortality (PCM), number needed to treat (NNT) and life-years saved given age at screen-detection, health status, disease stage and screening history. We present results for men older than 65, which is the age group where the benefit of immediate treatment is most debatable.

Material and Methods

Microsimulation model

Microsimulation Screening Analysis (MISCAN) is a microsimulation model designed to study the effect of screening on incidence and PCM. A description is available in http://cisnet.cancer.gov/prostate/profiles.html. and in the Online Supporting Information.

Each of MISCAN's health states denote different disease, detection and treatment phases. We model 18 disease stages, consisting of the combination of 3 stages (T1, T2, and T3), 3 grades (which correspond to Gleason Score 2–6, 7 and >7) and whether the cancer is metastasized. Additional disease states were created to model AS, including dividing Gleason 7 cancers in $3+4$, $4+3$ and T2GS6 (GS6 denotes Gleason Score 6 or lower) cancers between T2a and T2bc.

The transition probabilities and durations between different stages, grades until metastasized cancer and clinical diagnosis are calibrated to European Randomized Study of Screening for Prostate Cancer (ERSPC) data.[11,12] The model for PSA growth is based on[13] and is calibrated jointly to SEER incidence and ERSPC PSA distribution data[4] (Supporting Information Tables S1–S3, Fig. 1).

In an "immediate treatment" run, all screen-detected men are assigned with equal chance to either radiation therapy (RT) or radical prostatectomy (RP). In an "AS" run, all low-risk ($\leq$T2a Gleason 6), and intermediate-risk (Gleason $3+4$, T2bc and Gleason 6) screen-detected men are assigned to AS. In absence of treatment, a baseline survival is assigned at clinical detection, which depends on Gleason Score and is based on SEER data from the pre-PSA era. The baseline survival is further corrected by adding a hazard ratio of 0.82, which was found by calibration to the observed PCM in the control (no screening) group of the ERSPC[4] trial (Supporting Information Table S4).

The hazard ratio of prostate cancer survival after treatment equals 0.56 for RP[14] or 0.63 for RT, using the same ratio as in Ref. 15. Additionally, there is an effect of early detection: a probability of cure, which decreases exponentially with lead-time for nonmetastatic cases,

$$\text{Cure probability} = \exp(\text{cure parameter}^{*}\text{lead-time}).$$

The cure parameter was calibrated to the observed PCM reduction due to screening in the ERSPC[4] and equals -0.22 (Supporting Information Table S4 and Fig. 2).

Active surveillance

If a man is assigned to AS, the disease progresses as if not screen-detected. Referral to radical treatment may occur by volume progression (if there is an increase in T-stage), gleason progression, in case the patient would be clinically diagnosed or due to their own personal preference (Table 1). Rates of progression are dependent on the disease stage and are calibrated to John Hopkins cohort data[16] (Supporting Information Table S5). In the basecase, we stop AS after 6 years (six biopsies) if no progression is detected, since we are modeling older men.

Comorbidity lifetables

Three cohorts of 5 million men born in 1960 are simulated with life tables corresponding to no comorbidity, moderate comorbidity or severe comorbidity. Each comorbidity group was identified using a comorbidity index defined by conditions included in the Charlson index,[17] based on a random sample of Medicare data from SEER areas. The estimation of these lifetables, corresponding life expectancies, and prevalences of each comorbidity type are extensively described in Cho *et al.*[18] In Vogelaar *et al.*,[19] the life expectancies corresponding to each comorbidity for several ages are shown.

For instance, moderate comorbidity includes conditions like diabetes or cerebrovascular disease, while severe comorbidity includes chronical renal failure, chronic obstructive pulmonary disease or dementia, among others. This results in an estimated prevalence at age 69 of 75% for no comorbidity, about 12% for moderate comorbidity and 13% for severe comorbidity.[19]

Table 1. Modeling referral to treatment in AS[1]

Event	Modeling	Parameter(s)
Volume Progression	Indirectly modeled, may occur if in absence of screening there would be an increase in T-stage.	Probability of volume progression, given an increase in T-stage.
Gleason Upgrade	Directly modeled, may occur if in absence of screening Gleason would increase.	Sensitivity for Gleason upgrade.
Clinical Diagnosis[2]	Time of clinical detection in absence of screening.	Hazard of clinical diagnosis per stage.
Referral to treatment in absence of progression	Randomly selected from all men in AS.	Probability of treatment in absence of evidence of progression or clinical diagnosis.

[1]The parameters of the natural history model are calibrated to ERSPC data. The parameters related to referral to treatment in AS are calibrated to John Hopkins-AS cohort data,[16] including the number of men experiencing volume progression or gleason upgrade, men treated without evidence of progression and the 5 year treatment free survival.
[2]For the clinical diagnosis event, all the related parameters are calibrated to SEER data and denote an additional hazard of clinical detection in the US, relative to the European situation.

Table 2. Overview of included uncertainty in the probabilistic sensitivity analyses

Parameter	Value	Distribution
Hazard ratio improvement baseline survival	0.82	Uniform, Min = −20%, Max = +20%
Hazard ratio of RP[1]	0.56	Normal, Standard Deviation: 0.11[1]
Hazard ratio of RT[1]	0.63	Normal, Standard Deviation: 0.12[1]
Cure parameter	−0.22	Uniform, Min = −20%, Max = +20%

[1]Hazard ratio is relative to the survival without treatment. It is based on Bill-Axelson *et al.*[14] For hazard ratio of RT, we extrapolated based on the same ratio from Etzioni *et al.*[15] The standard deviation was calculated such that the confidence interval in Ref. 14 would include ~95% of random draws.

Outcomes

We present three ages of screen-detection, 66, 69 and 72, and we consider two screening histories. In the first, the person is being screened yearly from age 55 and with a PSA threshold for biopsy referral (PSAt) of 4 until age of screen-detection. In the second, age of screen-detection is the age of first screening. These two screening histories provide a range for the outcomes that will contain most screening histories.

We follow men from screen-detection to PCM or other causes death. These are divided by age and disease stage at screen-detection, comorbidity status and screening history. The low risk group consists of men detected in stages $\leq$ T2aGS6. The intermediate risk group contains $\leq$ T2 stage, Gleason 7 (3 + 4) men. And finally the high risk group contains any men in either T3 disease stage and/or Gleason equal or higher than 4 + 3.

The main outcome measures are NNT to save a life, probability of overtreatment (defined as a treated man, who is overdiagnosed) and life years (LY) saved. A man is counted as overtreated, if he is referred to radical treatment and in absence of screening, he would not be clinically diagnosed during his lifetime.

Scenario analyses

We examine the effects of considering different AS follow-up protocols on our estimates. We vary the stop age of AS from 6 years after diagnosis to 10 years, and we change the biopsy frequency from yearly to every 3 years after the first year.

Sensitivity analyses

We run an univariate sensitivity analysis where the cure parameter and the probabilities of detection in AS decrease or increase by 20%. Additionally, we run a multivariate probabilistic sensitivity analysis, where parameters related to the benefit screening and treatment benefit are varied simultaneously (Table 2).

Results

In Table 3, we show estimates of the probability of overtreatment, PCM, and NNT, divided by age of screen-detection (66,69,72), comorbidity levels, prostate cancer disease stage at detection and screening history.

The prostate cancer stage at detection has a large influence both on NNT and the probability of overtreatment. For men detected in a low-risk stage, the NNT ranges from 11 to 47 and overtreatment from 61 to 86%. By contrast, men detected in a high risk disease stage have a NNT ranging from 2 to 8 and overtreatment between 12 and 51%.

The probability of overtreatment and NNT increases with age at screen-detection. For men detected at age 66 and screened once, with low risk disease and no comorbidity, the NNT increases from 11 to 15, for age 69, and to 20, for age 72. In a similar fashion, overtreatment and NNT increase with the level of comorbidity. For instance, at age 66 the probability of overtreatment for men with no comorbidity is 61% while for men with severe comorbidity is 77%.

Comorbidity and age play a special role for men screen-detected in an intermediate risk disease stage. Men with no comorbidity younger than 70 have a NNT ranging from 5 to 6 and a probability of overtreatment from 23 to 28%, which is closer to the estimates for high risk men. By contrast, men older than 70 with disease burden have a NNT between 10

Table 3. Probabilities of PCM and overtreatment at screen-detection by current age, comorbidity, screening policy and disease stage[1]

	Age at detection		66			69			72		
Screen	Disease	Comorbidity	No	Mod	Sev	No	Mod	Sev	No	Mod	Sev
Policy	Risk										
55?Age	Low	Overtreat. [IRT]	64.2	71.0	80.3	68.8	75.5	83.5	73.5	80.3	86.4
		PCM [IRT]	0.8	0.7	0.4	0.8	0.6	0.4	0.6	0.5	0.1
		Overtreat. [AS]	39.3	41.4	38.4	41.9	44.0	39.8	44.2	45.5	39.4
		PCM [AS]	2.5	1.9	1.3	2.2	1.7	1.1	1.6	1.2	0.3
		NNT #	12	15	24	16	22	35	21	31	45
	Interm.	Overtreat. [IRT]	30.7	37.9	50.7	35.5	43.1	54.6	41.1	49.4	59.8
		PCM [IRT]	5.1	4.4	3.3	4.7	3.8	2.8	4.2	3.3	2.4
		Overtreat. [AS]	20.3	24.2	28.1	23.2	27.1	29.7	26.2	30.1	31.3
		PCM [AS]	10.5	8.8	6.4	9.5	7.6	5.5	8.3	6.3	4.4
		NNT	5	7	10	7	8	12	8	11	16
	High	Overtreat. [IRT]	19.9	28.9	46.1	22.9	31.9	47.9	26.9	36.8	51.1
		PCM [IRT]	16.5	14.9	11.4	14.9	12.8	9.6	13.5	11.3	8.4
		NNT	2	2	3	4	4	6	4	5	8
Once	Low	Overtreat. [IRT]	60.6	67.6	77.1	65.7	72.8	81.4	71.0	78.3	84.8
		PCM [IRT]	1.0	0.8	0.5	0.9	0.7	0.5	0.9	0.7	0.5
		Overtreat. [AS]	36.7	39.4	36.8	39.8	42.4	38.1	41.8	43.9	38.2
		PCM [AS]	2.8	2.4	1.6	2.3	1.67	1.2	2.0	1.5	1.0
		NNT	11	14	22	15	20	32	20	29	47
	Interm.	Overtreat. [IRT]	22.7	29.5	41.7	28.2	35.5	47.4	33.2	40.8	51.5
		PCM [IRT]	5.1	4.6	3.3	5.2	4.4	3.0	4.6	3.7	2.8
		Overtreat. [AS]	15.9	20.1	24.2	19.2	23.5	26.6	22.6	26.6	28.4
		PCM [AS]	10.5	9.0	6.8	9.1	7.6	5.4	8.4	6.6	4.8
		NNT	5	6	8	6	8	11	7	10	15
	High	Overtreat. [IRT]	11.5	17.3	32.8	13.9	21.4	35.8	18.6	27.0	41.4
		PCM [IRT]	18.1	16.3	12.6	16.3	13.8	10.7	16.2	13.7	10.4
		NNT	3	4	5	3	4	6	4	5	7

[1]Screen-Policies include annual screening starting at age 55 and stop at the age of screen-detection (55-Age), and one time screening at the age of screen-detection (Once). Disease Risk at screen-detection is divided in Low ($\leq$ T2aGS6), Intermediate ($\geq$ T2aGS6, Gleason 3 + 4) and High (either Gleason 4 + 3 or higher, or stage T3 or higher). The outcome measures are probability of overtreatment (Overtreat), probability of PCM and NNT to save one life. NNT is measured as the inverse of the absolute risk difference of PCM between treated and untreated men. Treatment modalities are Immediate Radical Treatment (IRT), which comprises RP and RT or AS. Comorbidity categories include no comorbidity ("No"), moderate comorbidity ("Mod") and severe comorbidity ("Sev").

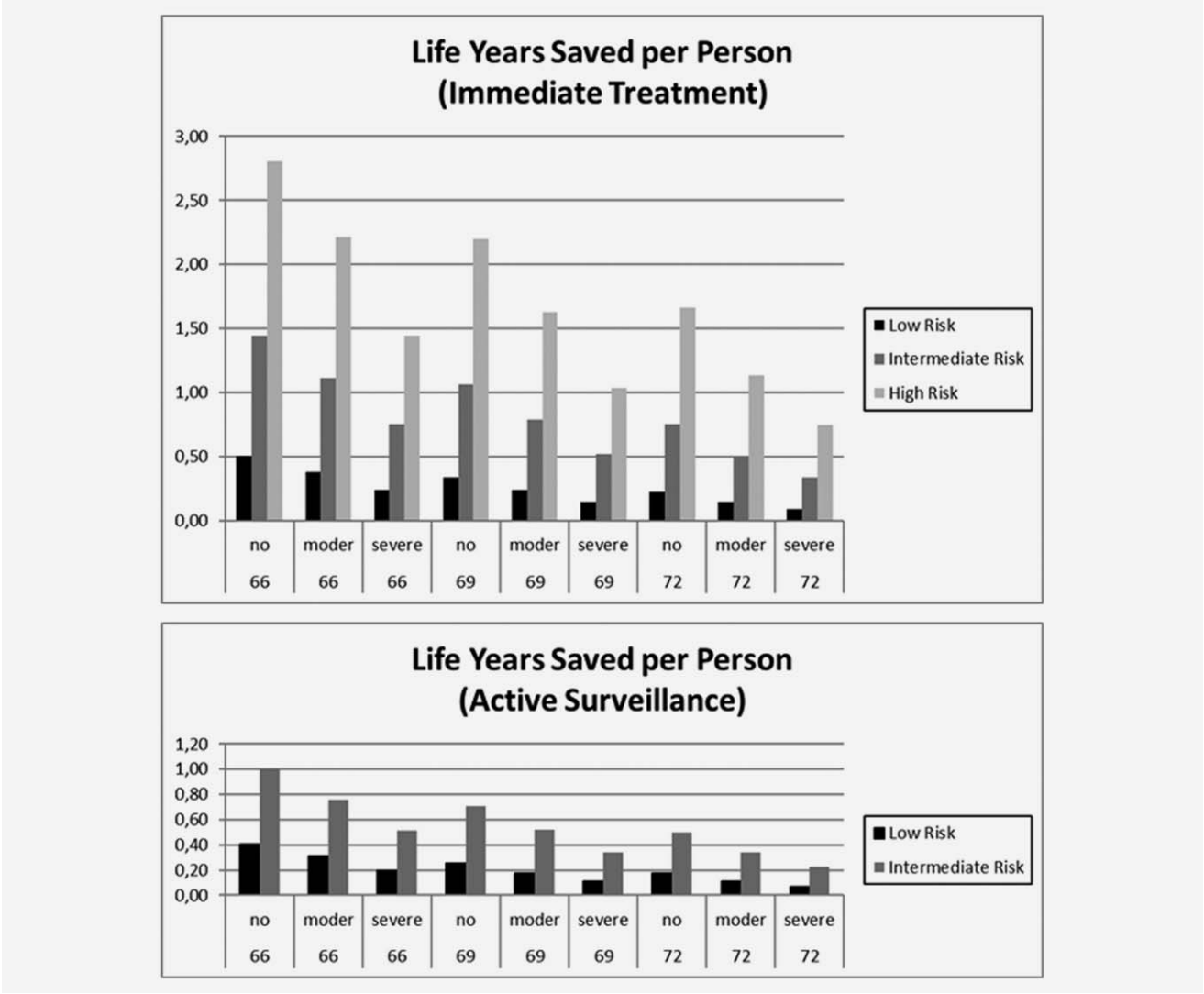

Figure 1. LY Saved by treated person presented by age, comorbidity status and disease stage at detection. Disease Risk at screen-detection is divided in Low Risk ($\leq$ T2aGS6), Intermediate Risk ($>$ T2aGS6, Gleason 3 + 4) and High Risk (either Gleason $\geq 4+3$, or stage-$\geq$T3). LY saved is the difference between the LY per screen-detected person with radical treatment or AS and no treatment.

and 15 and overtreatment between 41% and 52%, which is close to the predicted ranges for low risk men.

Men can also choose to delay treatment with AS. For low risk men, this results in a large reduction of overtreatment. For instance, for a men aged 66 with no comorbidity, overtreatment decreases from 61 to 37%, with PCM increasing from 1 to 2.8%. This reduction in overtreatment becomes larger with higher age and comorbidity, while the increase in PCM becomes smaller. For intermediate risk men, aged 66 with no comorbidity, overtreatment reduces from 23 to 16%, with PCM increasing from 5 to 10%.

In Figure 1, LY saved per screen-detected men, by disease stage, comorbidity and age are shown, for men, which were yearly screened. LY saved by treatment decrease with both age and comorbidity. There are large differences in LY saved per disease stage at detection. In most cases, the amount of LY saved more than doubles if a man is detected in a higher risk disease stage than another. Referring men to AS results in a decrease in LY saved, especially for intermediate risk men.

Scenario analyses

Increasing the biopsy interval to three years after the first year, and stopping AS after 10 years reduces overtreatment from 39.3 to 30.2% and increases PCM from 2.5 to 3.8%, compared with basecase AS. By contrast, increasing the maximum time on AS from 6 to 10 years reduces PCM from 2.5 to 1.8% and increases overtreatment to 50%. (Supporting Information Table S6).

Sensitivity analyses

In Supporting Information Table S7, the univariate sensitivity analyses are shown. Varying the cure rate by 20% has little effect on NNT. Changing the probabilities of detection by 20%, has a maximum effect on overtreatment of 4 percentual points. Both analyses have a modest impact on PCM. The

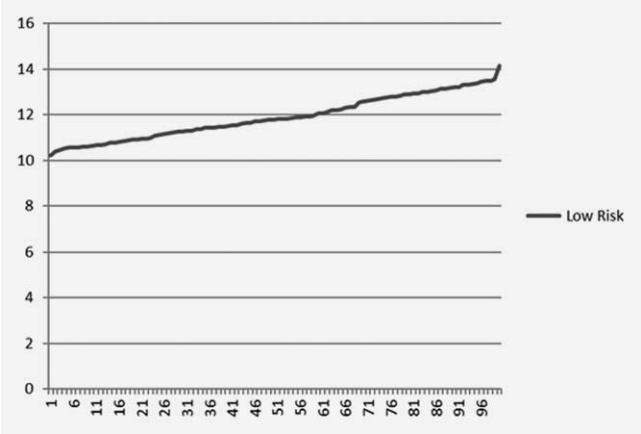

Figure 2. Distribution of the NNT for low risk men, aged 66 and no comorbidity. In the x-axis the percentile of the NNT distribution is shown, and in the y-axis the corresponding NNT. See Table 2 for details on included uncertainty and Appendix Figure 1 and 2, for intermediate and high risk men.

probabilistic sensitivity analysis resulted in a range for NNT of men screen-detected at age 66, with low risk prostate cancer, between 10 and 14 (1th and 99th percentile runs; Fig. 2, Supporting Information Figs. S3 and S4).

Discussion

Individual characteristics, like age, comorbidity status and disease stage at detection have a decisive effect in the risk that a man does not benefit from prostate cancer screening, AS or treatment. The main strength of this study is that the effects of these individual factors are, as far as we know, for the first time quantified together when deciding between immediate treatment, AS and no treatment.

If we consider a man screened yearly since age 55 and screen-detected at age 66 with no comorbidity and in a low risk disease stage then the probability of overtreatment is 64% and NNT is 12. If this person was in a high risk disease stage this probability would decrease to 20% and NNT to 5. By contrast, if he had a severe comorbidity, NNT increases to 24 and the probability of overtreatment to 80%. If he was detected at age 69, his NNT would be 16 and probability of overtreatment would equal 69%.

Men screen-detected in a high risk disease stage have a relatively low NNT, probability of overtreatment and the largest amount of LY saved by screening. Even beyond the 55–69 age group there seems to be a significant benefit on treating these men. The same holds for intermediate risk men, younger than 70 and no comorbidities.

By contrast, for men detected in a low risk disease stage the probability of overtreatment and NNT are large. Offering AS to low-risk men older than 65 seems to be an attractive alternative to immediate treatment. Our projections show that overtreatment can be sharply reduced (>30%), at the cost of a small PCM increase. For men older than 70 or with significant comorbidity these gains are even more pronounced.

Currently, most ongoing observational cohorts of AS select these men and so far the results seem promising with few or none prostate cancer related deaths.[20–22] However, with the exception of Klotz *et al.*,[23] the median follow-up is small (<5 years).

There is some evidence in favor of including intermediate risk men in AS.[24] We find that for intermediate risk men, the overtreatment reduction and PCM increase due to AS are proportionally similar to low risk men. However, this means for intermediate risk men, aged 66 and with no comorbidity that PCM increases from 5 to 11%, which many could consider to be a bar too high. By contrast, for men aged 72 with severe comorbidity, PCM increases only from 2.8 to 4.8%, which means that personal characteristics are important when choosing between immediate treatment and AS for intermediate risk men.

Running a probabilistic sensitivity analysis with all parameters in the model would be too computationally expensive. Therefore we run an univariate sensitivity analysis for the cure parameter and the probabilities of detection in AS and a multivariate probabilistic sensitivity analysis with parameters related to the benefit of treatment and early detection only. Through this analysis we show that our results are relatively robust, since varying the values of the parameters by 20% would have a small impact in the projections.

In this study, we had to limit our analyses to men older than 65. This is the case since the comorbidity lifetables were based on Medicare data. While this can be considered a serious limitation, it was already shown that a large proportion of overdiagnosis occurs in men older than 60.[7–9]

Compared to Gulati *et al.*,[7] our study tries to address some of the criticisms given in Freidlin and Korn.[25] For instance, they refer that the new USPSTF recommendation, would have a profound impact in screening patterns, and hence, on their estimates. We show that considering once in a lifetime screening (the most limited possible screening policy), changes the estimates of overtreatment and NNT, however the size of the change would have a negligible impact on any recommendation.

This model is a simplification of the natural history of prostate cancer. The comorbidity lifetables do not consider the possibility of interactions between comorbidity and the effect of treatment or cancer biology. Additionally, there is considerable uncertainty regarding the benefit of screening. Nonetheless, our results seem to be consistent with previous literature.[7–9]

In this study, we did not model quality of life. It was previously shown,[26] that the side effects of treatment could decrease the benefit of PSA testing up to 23%. Extrapolating this result to this study would likely mean that the QALY's saved will be of a smaller magnitude than the LY saved shown in Figure 1.

We did not take into account the PSA level at screen-detection. Gulati *et al.*[7] finds that men at lower PSA levels at detection are at a higher risk of being overtreated.

Extrapolating this result to this study would likely translate to lower NNT for men with high PSA values at detection.

Men screen-detected in a low risk disease stage ($\leq$ T2aGS6) and their physicians should carefully consider the potential harms before deciding on aggressive treatment, as they are at great risk of overtreatment. A large majority of them could be safely handled with AS, and then, about a third will avoid treatment. By contrast, those in a high risk disease stage (T3 or $\geq$ Gleason 4 + 3) have a relatively low chance of overtreatment, and unless they have significant morbidities they are likely to benefit from immediate radical treatment even beyond age 69.

Our findings highlight the importance of taking several risk factors into account, when making treatment decisions. We find that the pivotal variable is disease stage at screen-detection. However, age and comorbidity should also play a significant role on the decision to do radical treatment, AS or watchful waiting, especially for intermediate risk men.

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