Impact of prostate cancer screening on de novo and progressive metastasis

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Abstract

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Background: Clinical trials of cancer screening tests present results in terms of deaths prevented due to screening. We developed a framework for projecting overall metastasis prevented using prostate cancer screening as a case study.

Methods: Mechanistic simulation model in which screening shifts a fraction of cases that would be metastatic at diagnosis to being non-metastatic. This shift increases the incidence of non-overdiagnosed, organ-confined cases under screening. We use estimates of the risk of metastatic progression for these cases to project how many progress to metastasis after diagnosis. We use data on stage shift from the European Randomized Study of Screening for Prostate Cancer (ERSPC) and data on the risk of metastatic progression from the Scandinavian Prostate Cancer Group-4 (SPCG-4) trial. We estimate the relative risk and absolute risk reductions in metastatic disease at diagnosis and compared these with the reduction in overall metastasis due to screening.

Results: Assuming no effect of screening beyond initial stage shift at diagnosis, the model projected a 43% reduction in metastasis at diagnosis but a 22% reduction in the cumulative probability of metastasis over 12 years in favor of screening. These results are consistent with the empirical findings from the ERSPC.

Conclusion: The reduction in metastatic disease at diagnosis under screening is likely to be an overly optimistic predictor of the impact of screening on disease-specific mortality. Our framework permits projecting the impact of screening on overall metastasis which should provide a closer approximation of the effect of screening on mortality.

Keywords: *prostate cancer, screening, radical prostatectomy, watchful waiting, metastasis*

Introduction

A key rationale underlying cancer screening is that detecting tumors early when they are still localized will translate into a reduction in cancer mortality. In the European Randomized Study of Screening for Prostate Cancer (ERSPC), the incidence of metastatic disease at diagnosis was reduced by 40% and prostate cancer mortality was reduced by 20% at 12 years of follow-up.[1-3] The incidence of metastatic prostate cancer declined similarly in the US population after the rapid adoption of prostate specific antigen (PSA) screening, with a 60% drop from pre-PSA era rates.[4, 5] A recent uptick in distant metastases from 2010-2014 has been associated with declines in early detection following national guidelines that recommended against routine screening for prostate cancer.[6-9]

The expectation that early detection will reduce advanced-stage cancer, referred to as stage shift, is a key motivation for the development of novel screening tests.[3, 10] However, stage shift at diagnosis does not account for progressive cases that may develop after diagnosis. Any reduction in advanced-stage disease at diagnosis will translate into a commensurate increase in organ-confined diagnoses, thus increasing the pool of cases eligible to progress to metastasis. Progressive cases could attenuate any initial difference in the incidence of metastatic disease at diagnosis, leading the metastatic cases in a screened group to catch up with a non-screened group over time. Indeed, in the ERSPC, there was a 50% reduction in the hazard of de novo metastatic disease at diagnosis that attenuated to 30% after 12 years of follow-up.[1]

Most population-based screening trials do not compare the overall risk of metastasis in the screening and control arms during follow-up, but focus instead on metastasis at diagnosis and disease-specific mortality. Empirical observation of the effect of screening on overall metastasis can be onerous and time-consuming, requiring similarly rigorous follow-up of localized cases on both trial arms for disease progression and recurrence. Being able to project the likely consequences of an observed stage shift at diagnosis for the overall difference in advanced-stage disease could help investigators to develop realistic projections of long-term screening impact.

Currently, a framework is lacking for projecting from the reduction in metastasis at diagnosis to the reduction in overall metastasis under screening. We develop a simulation model for doing this and uses it to project de novo and progressive metastases in a population-based screening trial setting, using prostate cancer as a case study. Our modeling framework clarifies the data and assumptions needed in general to project long-term outcomes of screening based on information about disease stage at diagnosis.

Methods

Overview

Our simulation model builds on a previously developed model of prostate cancer natural history, screening, and incidence to project the incidence of metastatic disease at diagnosis among participants in the ERSPC screening and control arms.[11-13] The reduced incidence of metastasis at diagnosis in the screening arm implies an increase in incidence of localized disease at diagnosis in this arm. For non-overdiagnosed localized cases (i.e., cases that would be clinically detected in a patient's lifetime in absence of screening), we project time to progression using data from an established treatment trial (Scandinavian Prostate Cancer Group-4 [SPCG-4] trial)[14], which provided detailed information on metastasis and disease-specific mortality among its participants. Table 1 summarizes the simulation model sources. We do not initially assume any effect of screening on the risk of progression; our model allows only that screening changes the stage distribution at diagnosis, but we explore in sensitivity analyses how our projections might change if screening were to delay metastatic progression as well as reducing de novo metastatic incidence.

ERSPC and SCPG-4 trial data

The ERSPC trial, initiated in 1993, is a large-scale randomized controlled screening trial for prostate cancer that compared PSA-screening every 2-4 years to usual care between the ages 55-69. We used data from N=76,813 men (N=36,270 screening; N=40,543 control) from the four largest centers in the study (Netherlands (N=34,833), Sweden (N=11,852), Finland (Tampere location only) (N=20,225) and Switzerland (N=9903)) with a median 12 years' complete follow-up. The study protocol did not establish a common follow-up scheme for the ascertainment of metastasis; thus, patients were followed according to their center's standard of care. In the ERSPC, metastasis at diagnosis was defined as M1 disease or PSA>100 ng/ml. For the purpose of this analysis and for greater consistency with the simulation model, metastasis at diagnosis also included N1 and T4 disease.

Metastasis (both at diagnosis and during follow-up) was recorded in the study database source documents from medical records reflecting clinical follow-up for metastasis at the discretion of the patients' clinicians.[1] Patients with locally advanced disease were typically followed up every 3-6 months with a PSA-test and clinical exam. Bone scans were performed in men with bone pain or other clinical suspicion of distant metastasis, as well as in men with PSA ≥20 ng/mL and high Gleason score ≥7.[1] Progressive metastasis was defined as M1 or PSA>100 ng/mL – a strong indicator of underlying metastatic disease even in absence of confirmed surgical or imaging data.

The SPCG-4 trial, initiated 1989, is a large-scale randomized controlled treatment trial comparing radical prostatectomy to watchful waiting for localized prostate cancer (<75 years, life expectancy>10 years, moderately high differentiation according to the WHO definition, clinical stage ≤T2, PSA <50 ng/mL and negative bone scan). The average age of the participants was 65 years. We used data from N=695 men (N=347 intervention; N=348 control) in the SPCG-4 trial with 29 years' complete follow-up for metastasis after date of diagnosis. Metastasis was defined as a positive bone scan. As part of the study protocol, all men in both trial arms were actively followed every 6 months for the first two years, and annually thereafter, with PSA-tests and clinical exams. Bone scans were obtained annually until 2003; thereafter, they were

performed biennially unless the patient had a PSA increase or showed other clinical signs of progression. Men in both groups received hormonal therapy if metastases were confirmed, mainly orchiectomy or gonadotropin-releasing hormone analogs as lifelong therapy.[15] The SPCG-4 trial took place at a time when most men in Scandinavia were not PSA-screened (the proportion of PSA-detected T1c tumors was 36/695=5.2%)[15], and collected metastasis and death as outcomes. As a result, it provides high-quality information about the timing of metastasis in men who were clinically diagnosed.

Model of screening and stage-specific incidence

To project the incidence of de novo metastatic disease, we used the Fred Hutchinson Cancer Research Center (FHCRC) microsimulation model of prostate cancer natural history, as described in detail previously.[12, 13] The model links an individual man's PSA growth to the onset and progression of a preclinical prostate tumor so that, on average, an individual with a faster PSA growth rate has a shorter time to clinical diagnosis and a higher probability of metastatic stage at diagnosis. Tumor grade is assigned at disease onset and does not change over time. Under screening, a fraction of preclinical prostate tumors that would have been diagnosed at a metastatic stage in the absence of screening are detected at a localized stage by screening. For each individual, the model generates a date and stage of clinical diagnosis and similarly a date and stage of screen-diagnosis given the screening protocol. This allows for the identification of cases shifted earlier by screening and generates a lead time for each screen-detected case. For non-overdiagnosed cases, post-screen-diagnosis events (e.g. disease progression and survival) are generated beginning at the end of the lead time.

The FHCRC model was originally calibrated to U.S. population trends in disease incidence by age and stage.[12] For the ERSPC simulation, select natural history parameters of the FHCRC model were adjusted to approximate observed incidence in the trial by age, stage, grade, and study year, while accounting for age distributions at randomization, attendance rates, and biopsy patterns in each center.[11] We used the model to simulate outcomes for individuals in the participating Netherlands, Sweden, Finland, and Switzerland centers, all of which recorded metastasis after diagnosis and were represented in the published analysis of the trial.[1] The model replicated biopsy compliance in the trial that depended on age and PSA in each center. Biopsy sensitivity was assumed to be 80%.[16] All analyses were conducted on data collected up to 12 years following randomization. Metastasis at diagnosis was defined in the model as M1, N1, or T4 disease and progressive metastasis as M1, reflecting the different technologies used for identification of metastatic disease at diagnosis (rectal exam, surgery) and post diagnosis (PSA tests, imaging). The model definitions of metastatic events reflected disease natural history events included in model development, and approximated the ERSPC trial definitions and reported results.

Mechanism of screening benefit

The implements a stage shift induced by screening.[17] Under the stage-shift mechanism, prostate tumors that would have been diagnosed at a metastatic stage in the absence of screening are instead detected when they are screened at a localized stage, and their post-diagnosis progression is based on their localized disease status (**Figure 1**). The base model assumes no additional benefit of screening beyond the stage shift; this assumption is relaxed in a sensitivity analysis.

Model of metastatic progression

Metastasis after diagnosis was projected from the point of clinical diagnosis (post lead time in the screen arm), ensuring that we only projected metastases in non-over-diagnosed cases. The risk of metastasis after diagnosis was based on the SPCG-4 trial that compared radical prostatectomy versus watchful waiting for localized prostate cancer.[14] We fit a Weibull regression model to time to metastasis as a function of age, grade (Gleason Score (GS) <7 versus 7+), and treatment arm and used this model to simulate times of metastatic progression after diagnosis (**Supplementary Appendix, Methods A**). The simulation assumes that the fraction in each arm receiving curative treatment was the same as in the ERSPC (72.5% of men in the control arm received either radical prostatectomy or radiation, as did 70.5% of men in the control arm).[18] At diagnosis, localized cases either receive curative treatment or no treatment. We model benefit of radiation on metastatic progression as equivalent to the benefit of surgery.

Analysis of outcome measures

The goal of our analyses was to compare projected screening benefit in terms of metastasis at diagnosis and overall metastasis. We quantified screening benefit via three different measures: 1) Hazard ratio (HR) comparing the time from entry to metastasis at or after diagnosis in the screen versus the control group; 2) Relative risk (RR) measured at 12 years in the screen versus the control group; and 3) Absolute risk difference (AR) at 12 years (control group minus screen group). All metrics considered other-cause death and end of study as censoring events. (**Supplementary Appendix, Methods B**).

Sensitivity analyses

We considered three types of sensitivity analyses pertaining to the benefit of screening, the benefit of treatment, and the risk of metastasis, as described in **Supplementary Appendix, Sensitivity Analyses**. In brief, the sensitivity analyses allowed us to consider 1) an additional benefit of screening beyond the stage shift 2) an improved benefit of treatments for localized disease (e.g., corresponding to adjuvant or early salvage treatment), and 3) a different risk of metastasis than was observed in the SPCG-4 population.

Results

Metastasis at diagnosis in the simulation

By the end of the 12-year study, the screen arm accumulated fewer de novo metastatic cases at diagnosis than the control arm, reflecting the stage shift effect of screening **(Figure 2)**. Furthermore, the cumulative incidence of de novo metastasis in the screen and control arms in the simulated trial replicates that of the empirical ERSPC trial (**Figure 3**).

Modeled effect of screening on metastasis at diagnosis

Screening had a substantial relative and absolute benefit for reducing de novo metastasis in the simulated trial. By the end of the simulated trial, the RR of de novo metastasis in the screen versus control arm was 0.57 in simulated trial, the HR was 0.60, and the ARR was 39.6/10,000 men (**Table 2**).

Progression to metastasis in the SPCG-4 trial

Figure 4 shows the results of the Weibull regression model fit to the SPCG-4 trial used to project progressive metastasis in the simulated trial. The SPCG-4 trial found radical prostatectomy to have a HR of 0.53 on risk of metastasis after diagnosis, in favor of surgery (**Supplementary Appendix, Methods A**).[14] Across the age ranges included, the Weibull regression estimates an approximately 9-10% and 16-19% cumulative probability of metastasis ten years after clinical diagnosis in men with Gleason Score<7 in the treated arm and untreated arms, respectively. Gleason Score $\geq$7 as associated with a 2.8 (95% CI [2.1,3.7]) times higher hazard of metastasis and a correspondingly higher cumulative probability of this event (**Figure 4**).

Modeled effect of screening on progressive and overall metastasis

Figure 5 shows stacked plots of the cumulative incidence of developing progressive and de novo metastasis in the simulated trial; the total curve represents the cumulative probability of developing either type of metastasis. Compared with the effect of screening on de novo metastasis, the accumulation of progressive metastases in the screen and control arms leads to an attenuation in absolute and relative benefit for metastatic disease overall. The RR at 12 years for metastasis overall in screen versus control arms is 0.78 in the simulated trial, and the HR is 0.76. The ARR at 12 years is 30.7/10,000 men (**Table 2**).

Comparison of simulated trial with ERSPC metastasis at diagnosis and overall metastasis

As in the simulated trial, the empirical ERSPC demonstrated the stage shift benefit of screening on de novo metastasis **(Figure 2)**. The simulated trial was broadly in agreement with the empirical ERSPC as far as an attenuation of the absolute and relative benefit of screening on metastasis overall relative to de novo metastasis. At diagnosis, the RR of de novo metastasis in screen versus control arms was 0.60; for overall metastasis, it was 0.74. The ARR was 34.7/10,000 for de novo metastasis and 30.3/10,000 for metastasis overall (**Table 2)**.

There were also some differences between the simulated trial and what was observed in the ERSPC. In particular, the simulated trial projected fewer localized cases at diagnosis and more progressive metastasis cases than the empirical ERSPC (**Table 2).**

Sensitivity analyses

Results of the sensitivity analyses are shown in **Supplementary Appendix, Sensitivity Analyses** and **Supplemental Figures 3A-C**.

Discussion

In this study, we developed a novel modeling framework to estimate the expected benefit of cancer screening on the cumulative incidence of metastasis. Rather than focusing only on the reduction in distant stage disease at diagnosis ("stage shift"), this measure combines de novo and progressive cases and is likely to be a more accurate proxy for mortality reduction than the commonly used stage shift at diagnosis. The model requires data on the stage-specific incidence of disease with and without screening and on the risk of metastatic progression after a localized

diagnosis. We use data from two randomized trials, the ERSPC screening trial and the SPCG-4 treatment trial.

Our framework provides a mechanistic understanding of how screening might impact disease stage at and after diagnosis. Screening reduces the number of men with distant stage at diagnosis in the screening group relative to the control group, but this leads to a larger pool of non-overdiagnosed localized cases eligible to progress to metastatic events over time. The model reflects the ERSPC experience of a greater accumulation of progressive metastases in the screen arm relative to the control arm. This accumulation translates into an attenuation of both the relative and absolute benefit of screening for overall metastasis compared to metastasis at diagnosis.

While we use the ERSPC as a case study, the simulation is not intended to replicate this screening trial. The simulation is an artificial replication of reality and is not subject to the kinds of issues that arise when recording clinical outcomes in a multicenter setting over time. Recognizing this, we defined endpoints in the model in a manner that best replicated the observed data while at the same time not expecting to match exactly. The model-based definition of metastasis at diagnosis was chosen at calibration to enhance compatibility between the model-projected incidence of metastasis at diagnosis and that observed in the ERSPC. After diagnosis, we included ERSPC cases with PSA>100 ng/ml since they were likely clinically metastatic even if they lacked imaging or other clinical records, and their inclusion again leads to greater compatibility with model projections of progressive metastasis based on SPCG-4 data.

Despite our attempts to define metastasis in a manner that led to similar observed and modeled outcomes, the model-projected risk of progressive metastasis was higher than was observed in the ERSPC. This may additionally be a consequence of using a treatment trial (the SPCG-4 trial) as a source for a critical model input–namely, the risk of progression to metastasis after a localized prostate cancer diagnosis. In the SPCG-4 trial, progression to metastasis was a primary outcome; thus, patients were continuously monitored for evidence of distant metastasis with regular bone scans (annual initially and biennially, if no clinical signs or PSA increases, during later study years).[15] Due to more intensive surveillance for metastasis in the SPCG-4 trial the recorded frequency of metastasis could have been higher in that trial than in the ERSPC, and this could explain the elevated risk of metastasis projected by the model.

For these reasons, and because of the different populations and contexts of the ERSPC and SPCG-4 trials, we do not expect the risks of progressive metastasis to match exactly, but we are gratified to note that the patterns of progression metastasis and the attenuation projected by the model are similar to that observed in the ERSPC.

Our model results match what has been observed in practice, namely that the effect of screening on metastasis at diagnosis appears to be more pronounced relative to the effect on overall metastasis. Our framework provides one explanation for why the ERSPC revealed a dramatic 50% drop in the risk of metastasis at diagnosis under screening but a 20% (still significant) drop in prostate cancer mortality due to screening.

There are several potential current and future applications of our framework. Distant metastasis is an important endpoint of screening trials alongside cancer mortality because it has a tremendous impact on individuals' quality-of-life.[19] Similarly, metastases is a strong surrogate outcome for survival in clinical trials of new therapeutics, due to the long natural history of

prostate cancer for progression to death.[20] For example, the median time from radical prostatectomy to biochemical recurrence is 3 years, from biochemical recurrence to metastases is 8 years, and from metastases to death is 5 years.[21]

In addition to bone pain, pathologic fractures and urinary obstruction caused by distant metastasis and advanced prostate cancer, treatment with lifelong androgen deprivation therapy causes significant declines in quality-of-life and adverse events, such as diabetes, cardiovascular and disease, depression and dementia.[22-25] Moreover, the relatively long natural history of metastatic prostate cancer exacerbates the overall impact on quality adjusted life years and contributes significantly to healthcare cost burdens. Prostate cancer is the fifth most costly cancer, projected to contribute as much as $19 billion to U.S. healthcare costs, and it has the largest projected increase in medical costs for continued cancer care (beyond 12 months after diagnosis) in 2020 vs. 2010 at 42%.[26] For comparison, breast cancer had the second highest increase at 32%.

Our framework offers a short-cut to evaluating the effectiveness of novel tools for cancer screening in terms of this endpoint. Having access to a modeling framework that can project a key intermediate endpoint (metastasis) based on the impact of screening on metastasis at diagnosis may be very useful in projecting the effectiveness of screening in the absence of

A strength of this analysis is in providing a transparent framework for examining how screening affects the overall burden of metastatic disease. It is, however, based on modeling assumptions that may not fully reflect the benefit of screening or the risk of metastasis after localized diagnosis. We addressed several of these assumptions in our sensitivity analyses. In the first sensitivity analysis, we examined the possibility that screening may confer an additional benefit beyond just the stage shift on the risk of progressive metastasis.[27] In the second sensitivity analysis, we reduced the risk of progressive metastasis in treated men on both arms to accommodate adjuvant or early salvage treatments for PSA recurrence. In the third sensitivity analysis, we addressed the possibility that risk of metastasis after diagnosis may be very different for today's cancer patients as compared to the SPCG-4 trial. Our projections were generally robust across all the sensitivity analyses. We did not, however, perform two-way sensitivity analyses, that would explore how the joint effects of metastasis risk and treatment benefits lead to differences compared with the base model.

Conclusions

Cancer metastasis is a key endpoint that impacts both quality-of-life and cancer mortality. We developed a novel framework for assessing the effect of screening on the overall, cumulative risk of cancer metastasis. This framework offers one explanation for why the reduction in mortality in the ERSPC was lower than the reduction in the incidence of metastatic disease at diagnosis, and suggests that, in general, expectations of screening benefit that are based on stage-shift at diagnosis should be tempered when considering the endpoint of disease mortality.

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Table 1. Components of the simulation model for projecting de novo and progressive metastasis

Event	Empirical data definition (ERSPC)	Model definition (FHCRC)
De novo metastasis	T4, N1, M1, PSA >100	T4, N1, M1
Progressive	M1, PSA >100	M1

ERSPC=European Randomized Study of Screening for Prostate Cancer

FHCRC=Fred Hutchinson Cancer Research Center

Table 2. Simulated and observed trial events after 12-year trial

Trial	Metastasis	Events per 10,000 Control	Screen	RR	HR	ARR/10,000
ERSPC--observed						
	Localized disease at diagnosis	647.6	1168.1			
	De novo metastasis	87.4	52.8	0.60	0.63	34.7
	Progressive metastasis	29.4	33.8			
	Overall metastasis	116.8	86.5	0.74	0.75	30.3
Simulated						
	Localized disease at diagnosis	470.4	1134.6			
	De novo metastasis	92.4	52.8	0.57	0.6	39.6
	Progressive metastasis	44.3	53.2			
	Overall metastasis	136.6	105.9	0.78	0.76	30.7

ERSPC = European Randomized Study of Screening for Prostate Cancer
ARR = Absolute Risk Reduction
RR = Relative Risk Reduction
HR = Hazard Ratio

Figure 1. Stage shift mechanism

The same man diagnosed with metastatic (M+) disease in absence of screening at the point of clinical diagnosis (T_c) may be detected with localized disease (M-) disease under screening. Under the stage shift mechanism, he retains M- disease post lead time and at T_c.

T0 = Time zero, start of screening trial
Tc = Clinical diagnosis
Ts = Screen-diagnosis
Dx = Diagnosis

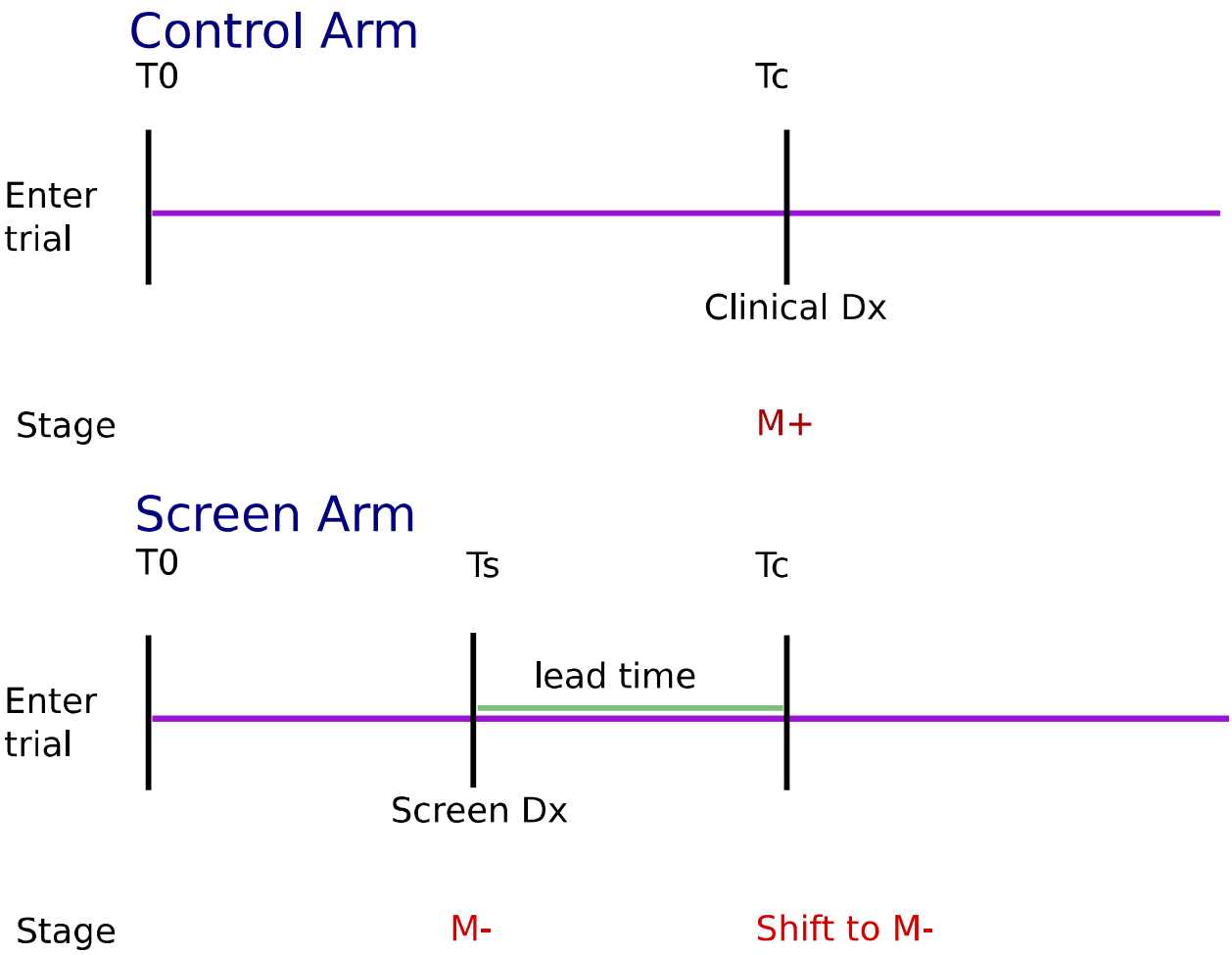


Figure 2. Model-projected and observed cases of localized disease, de novo metastasis, and progressive metastasis at 12 years follow-up in screen and control arms.

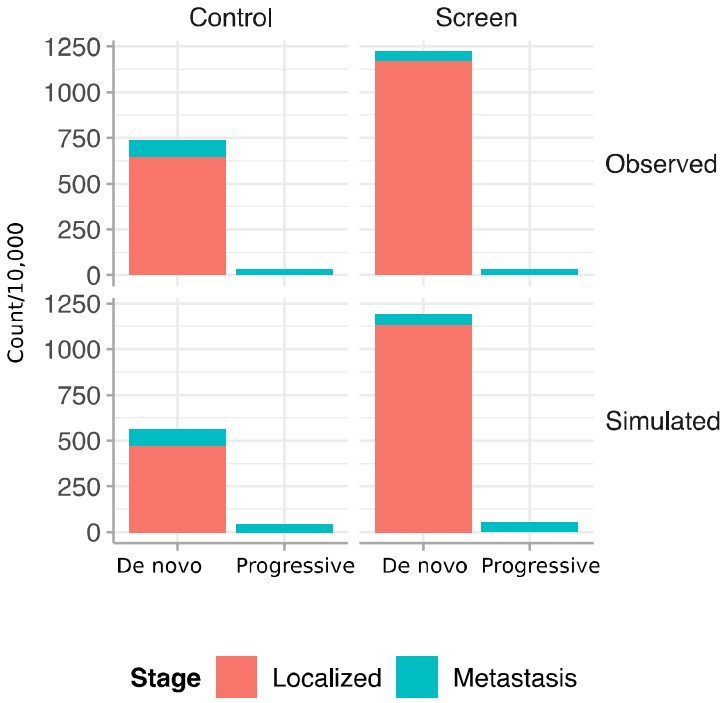


Figure 3. Comparison of cumulative incidence of de novo metastasis in observed ERSPC and simulated trial.

Note: jumps in the simulated screen arm are due to simplified scheduling of the predominantly quadrennial PSA screening in the model.

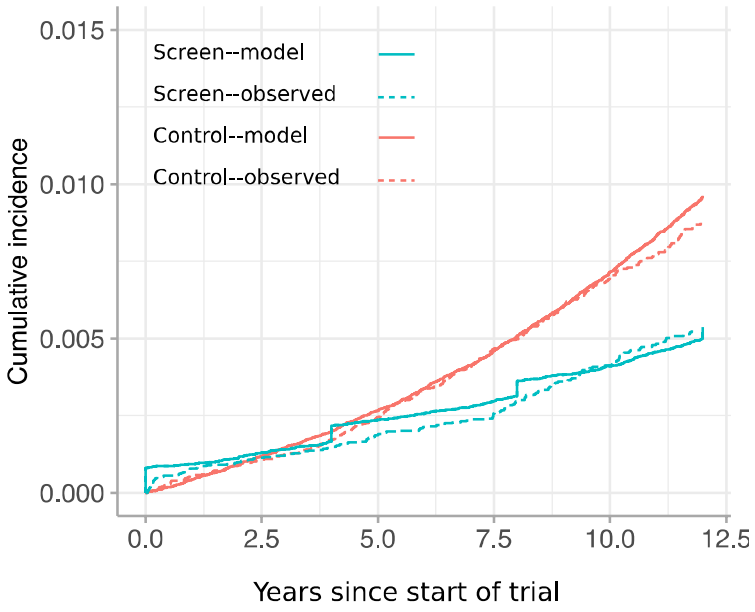
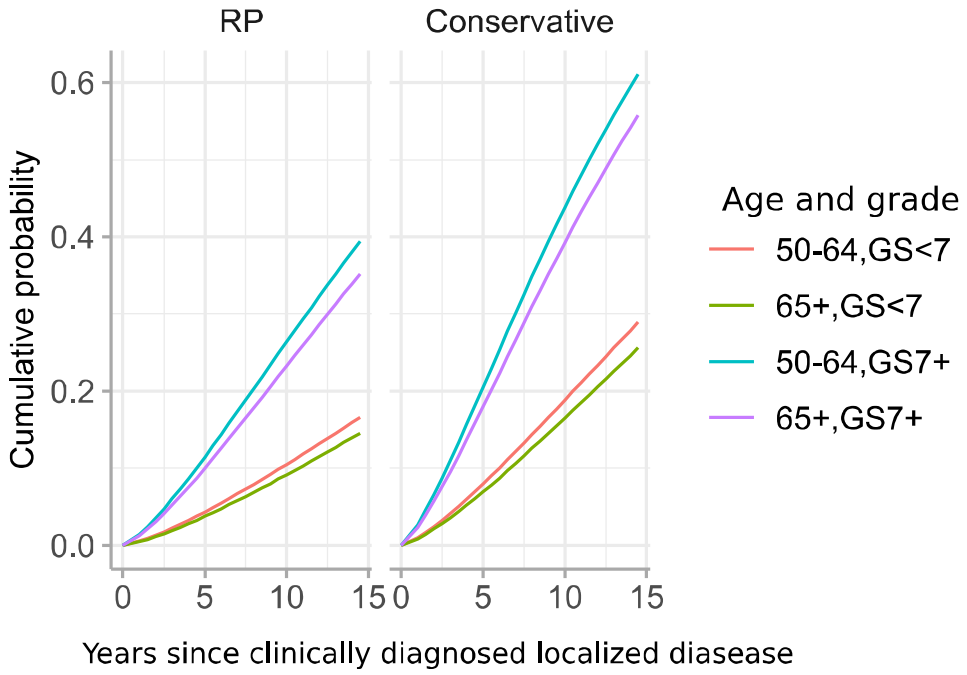


Figure 4. Cumulative distribution functions used to project metastasis after diagnosis based on Weibull models fit to the Scandinavian Prostate Cancer Group-4 (SPCG-4) trial



GS = Gleason Score, RP = Radical Prostatectomy, Conservative = Watchful Waiting

Figure 5. Cumulative incidence of de novo and progressive metastasis in

A. The simulated trial and B. Observed ERSPC trial