

Post-metastasis Survival of Patients with High-Risk Localized and Locally Advanced Prostate Cancer Undergoing Primary Treatment in the United States: a Retrospective Study

Short title Post-metastasis Survival of Patients with High-Risk Localized and Locally Advanced Prostate Cancer

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Supplementary Materials

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1. Supplementary Methods

These supplementary results present results from an earlier analysis that used a larger dataset than the one included in the main manuscript. This earlier dataset, referred to as the 'INITIAL sample', included all patients from the manuscript plus additional subjects. The data used in the manuscript are termed the 'MANUSCRIPT sample'. Unfortunately, access to all data was lost, but additional analyses are presented here to further support the primary findings that had already been conducted on the INITIAL sample prior to the loss of data access. As noted below, the two datasets markedly overlap and differ only slightly, providing relevant and informative analyses.

The patients in the MANUSCRIPT sample represent a random selection from the ConcertAI Patient360™ database, which forms the basis of their comprehensive prostate cancer dataset. The INITIAL sample was specifically designed to address separate research questions from other investigators and thus comprised the MANUSCRIPT sample along with additional patients specifically chosen from the ConcertAI Patient360™ database. This selection process likely resulted in a slight overrepresentation of certain patient subgroups, leading to a composition that differs modestly from the random sample constituting the ConcertAI Patient360™ prostate cancer dataset. Importantly, this difference in sample composition did not significantly alter the characteristics of the study samples (Table S1).

Compared to the post-metastasis cohort from the MANUSCRIPT sample, the post-metastasis cohort from the INITIAL sample included 224 (18%) additional patients, while the pre-metastasis cohort had 794 (33%) more patients.

2. Comparison of Baseline Patient Characteristics Between Cohorts From the INITIAL and MANUSCRIPT Samples

Patient characteristics of the pre-metastasis and post-metastasis cohorts from the INITIAL and MANUSCRIPT samples are summarized in Tables S1 and S2, respectively. Table S1 shows that the pre-metastasis treatment cohorts defined using these two samples (MANUSCRIPT and INITIAL) maintain a comparable distribution of patient characteristics. A slightly lower proportion of patients developed metastasis in the pre-metastasis cohorts in the INITIAL sample compared with the MANUSCRIPT sample.

Table S1. Characteristics of patients in the pre-metastasis cohort for the MANUSCRIPT and INITIAL samples

PRE-METASTASIS						
Cohort	RP group		RT only group		RT + ADT group	
Sample	MANUSCRIPT	INITIAL	MANUSCRIPT	INITIAL	MANUSCRIPT	INITIAL
Sample size	<i>n</i> = 1696	<i>n</i> = 2243	<i>n</i> = 421	<i>n</i> = 523	<i>n</i> = 264	<i>n</i> = 409
Median age at primary treatment (IQR), years	63 (57.0–68.0)	62 (57.0–68.0)	67 (60.0–72.0)	67 (61.0–72.0)	70 (64.0–75.0)	70 (64.0–75.0)
Developed metastasis, <i>n</i> (%)						
M0	811 (48)	1202 (54)	158 (38)	215 (41)	180 (68)	301 (74)
M1	885 (52)	1041 (46)	263 (62)	308 (59)	84 (32)	108 (26)
Median follow-up (IQR), years	8.4 (4.6–13.4)	8.2 (4.6–13.2)	7.9 (4.2–12.4)	7.6 (4.1–12.2)	3.7 (2.0–6.4)	3.7 (2.0–6.4)

ADT androgen deprivation therapy, *IQR*, interquartile range, *RP* radical prostatectomy, *RT* radiotherapy.

Table S2 shows that the post-metastasis treatment cohorts defined using the MANUSCRIPT and INITIAL samples also maintain a comparable distribution of patient characteristics, with marginally longer times from primary treatment to metastasis in the INITIAL sample compared with the MANUSCRIPT sample.

Table S2. Characteristics of patients in the post-metastasis cohort for the MANUSCRIPT and INITIAL samples

POST-METASTASIS						
Cohort	RP group		RT only group		RT + ADT group	
Sample	MANUSCRIPT	INITIAL	MANUSCRIPT	INITIAL	MANUSCRIPT	INITIAL
Sample size	<i>n</i> = 885	<i>n</i> = 1040	<i>n</i> = 262	<i>n</i> = 307	<i>n</i> = 84	<i>n</i> = 108
Median age at primary treatment (IQR), years	63 (57.0–68.0)	63 (57.0–68.0)	67 (60.0–72.0)	67 (60.5–72.0)	70 (64.0–75.0)	70 (65.0–75.0)
Median age at metastasis (IQR), years	69 (64.0–75.0)	70 (64.0–75.0)	73 (66.0–78.0)	73 (67.0–79.0)	73 (67.0–77.0)	73 (67.8–78.0)
Median time from primary treatment to metastasis (IQR), years	5.5 (2.6–9.8)	5.7 (2.7–10.0)	4.2 (2.6–8.7)	4.4 (2.6–8.6)	2.9 (1.6–4.5)	3.1 (1.6–4.8)
Median follow-up (IQR), years	2.9 (1.5–4.7)	2.9 (1.5–4.7)	2.7 (1.2–4.4)	2.7 (1.2–4.4)	2.3 (1.0–3.8)	2.2 (1.0–3.4)

ADT androgen deprivation therapy, *RP* radical prostatectomy, *RT* radiotherapy, *IQR* interquartile range.

3. Baseline Distribution of LAPC Versus HR-LPC (Defined by D'Amico Factors) at Diagnosis

Table S3 displays the distribution of i) patients at diagnosis with HR-LPC and one D'Amico factor; ii) patients with HR-LPC and two or more D'Amico factors; and iii) patients with locally advanced disease (LAPC) in both the INITIAL sample pre- and post-metastasis cohorts. Half of the patients in the post-metastasis cohort who were treated with RP had LAPC at diagnosis versus 18% in the RT group and 29% in the RT + ADT group. While 48% of the patients in the post-metastasis RT group had HR-LPC with one D'Amico factor at diagnosis and 34% of patients had HR-LPC with two or more factors, only 30% of patients in the RT + ADT group had HR-LPC with one D'Amico factor at diagnosis, and 41% of the patients had two or more factors. Similar distributions of LAPC versus HR-LPC (D'Amico factors) at diagnosis are found in the pre-metastasis treatment cohorts.

Table S3. Baseline distribution of HR-LPC defined by D'Amico factors and LAPC in the pre- and post-metastasis cohorts defined using the INITIAL sample

	Total	RP	RT	RT + ADT
Pre-metastasis cohort (INITIAL sample)	<i>N</i> = 3175	<i>n</i> = 2243	<i>n</i> = 523	<i>n</i> = 409
LAPC vs HR-LPC (D'Amico factors) at diagnosis, <i>n</i> (%)				
HR-LPC (1 factor)	1109 (35)	682 (30)	263 (50)	164 (40)
HR-LPC (≥ 2 factors)	714 (22)	434 (20)	163 (31)	117 (29)
LAPC	1352 (43)	1127 (50)	97 (19)	128 (31)
Post-metastasis cohort (INITIAL sample)	<i>N</i> = 1455	<i>n</i> = 1040	<i>n</i> = 307	<i>n</i> = 108
LAPC vs HR-LPC (D'Amico factors) at diagnosis, <i>n</i> (%)				
HR-LPC (1 factor)	489 (34)	309 (30)	148 (48)	32 (30)
HR-LPC (≥ 2 factors)	356 (24)	208 (20)	103 (34)	45 (41)
LAPC	610 (42)	523 (50)	56 (18)	31 (29)

ADT androgen deprivation therapy, *HR-LPC/LAPC* high-risk localized or locally advanced prostate cancer; *RP* radical prostatectomy, *RT* radiotherapy.

4. Impact of LAPC Versus HR-LPC on the Relationship Between Primary Treatment and Post-Metastasis Survival (PMS)

These observed differences in LAPC versus HR-LPC (D'Amico factors) at diagnosis may influence both the association between the decision on the initial treatment and the PMS, and between time to metastasis and PMS. Table S4 presents unadjusted and adjusted hazard ratios from Cox proportional-hazard regression models estimated using the post-metastasis cohort derived from the INITIAL sample, which additionally control for LAPC versus HR-LPC (D'Amico factors) when assessing the relationship between primary treatment type and PMS. Model results show that the incremental impact of LAPC versus HR-LPC (D'Amico factors) on the hazard ratio for the relationship between primary treatment type and PMS is minimal when adjusting for these factors (Model 3) relative to a model with only age as covariate (Model 2).

An important observation from the results in Table S4 is that even after controlling for age (Model 2) the differences between treatment groups remain statistically significant, with patients in the RT only and RT + ADT groups experiencing higher hazard rates compared with those patients undergoing RP. In the MANUSCRIPT sample, hazard ratio [95% CI] estimates for the same model are slightly lower (RP vs RT only: 1.19 [0.98–1.43]; RP vs RT + ADT: 1.32 [0.97–1.81]) and suggest independence between primary treatment and PMS. Nevertheless, in both models 95% CIs are large indicating uncertainty in the point estimates. These differences in model results may be driven by specific patient characteristics used to select the additional patients into the INITIAL sample but are most likely driven by unmeasured confoundedness resulting from important baseline characteristics such as Eastern Cooperative Oncology Group performance status and Charlson Comorbidity Index, which we do not account for due to high level of missingness.

Table S4. Unadjusted and adjusted associations between primary treatment type and PMS among those who developed metastasis (INITIAL sample)

Model 1	Unadjusted hazard ratio	95% CI
RP vs		
RT only	1.31	1.10–1.55
RT + ADT	1.59	1.22–2.09
Model 2	Adjusted (for age) hazard ratio	95% CI
RP vs		
RT only	1.21	1.02–1.44
RT + ADT	1.41	1.08–1.85
Model 3	Adjusted (for age and LAPC vs HR-LPC) hazard ratio	95% CI
RP vs		
RT only	1.23	1.03–1.47
RT + ADT	1.43	1.08–1.88

ADT androgen deprivation therapy, *CI* confidence interval, *HR-LPC/LAPC* high-risk localized or locally advanced prostate cancer, *PMS* post-metastasis survival, *RP* radical prostatectomy, *RT* radiotherapy.

5. Impact of LAPC Versus HR-LPC on the Relationship Between Time to Metastasis (TTM) and PMS

Table S5 presents unadjusted and adjusted hazard ratios from Cox proportional-hazard regression models estimated using the post-metastasis cohort derived from the INITIAL sample, which additionally controls for primary treatment received and LAPC versus HR-LPC (D'Amico factors) when assessing the relationship between TTM and PMS. Model results show that there is no incremental impact of LAPC versus HR-LPC (D'Amico factors) on the hazard ratio for the relationship between TTM and PMS when adjusting for these factors (Model 4), in addition to age and primary treatment (Model 3). Importantly, these estimates are similar to those obtained from the MANUSCRIPT sample and accurately estimated, which offers reassurance regarding the independence between TTM and PMS.

Table S5. Unadjusted and adjusted associations between TTM and PMS among those who develop metastasis (INITIAL sample)

Model 1	Unadjusted hazard ratio	95% CI
Time from RP/RT to metastasis, years	1.01	1.00–1.03
Model 2	Adjusted (for age) hazard ratio	95% CI
Time from RP/RT to metastasis, years	0.99	0.97–1.00
Model 3	Adjusted (for age and primary treatment) hazard ratio	95% CI
Time from RP/RT to metastasis, years	0.99	0.97–1.00
Model 4	Adjusted (for age, primary treatment; and LAPC vs HR-LPC) hazard ratio	95% CI
Time from RP/RT to metastasis, years	0.99	0.97–1.01

CI confidence interval, *HR-LPC/LAPC* high-risk localized or locally advanced prostate cancer, *PMS* post-metastasis survival, *RP* radical prostatectomy, *RT* radiotherapy, *TTM* time to metastasis.

6. Distribution of Subsequent Treatments Received After Primary Treatment and Prior to Metastasis

Table S6 displays therapies received after primary treatment for each of the post-metastasis treatment cohorts (RP, RT, RT + ADT) derived from the INITIAL sample. ADT is considered as concurrent treatment to RT if given within 180 days before or after RT. For the remaining treatment profiles, only the sequence of the treatments was considered because disease recurrence could not be identified in our data. Most patients in the RT + ADT group received RT + ADT only, and similarly in the RT only group the majority of the patients were treated with RT alone. In both groups, very few patients underwent subsequent treatment with RT or RP. The RP group was slightly more heterogenous: 42% received RT following RP, 40% received RP only, and 11% received ADT following RP.

Table S6. Distribution of pre-metastasis subsequent treatments among patients who developed metastasis (INITIAL sample)

	(N = 1455)
Primary treatment with RP, <i>n</i> (%)	
RP > RT	436 (42)
RP only	413 (40)
RP > ADT	118 (11)
RP > RT + ADT	73 (7)
Total	1040 (100)
Primary treatment with RT, <i>n</i> (%)	
RT only	293 (95)
RT > RP	14 (5)
Total	307 (100)
Primary treatment with RT + ADT, <i>n</i> (%)	
RT + ADT	105 (97)
RT + ADT > RP	3 (3)
Total	108 (100)

ADT androgen deprivation therapy, *RP* radical prostatectomy, *RT* radiotherapy.

7. Impact of Subsequent Treatments on the Relationship Between TTM and PMS

Differences in the distribution of treatments received after primary treatment and prior to metastasis may impact the relationship between TTM and PMS. Table S7 shows unadjusted and adjusted hazard ratios for the relationship between TTM and PMS from Cox proportional-hazard regression models estimated using the post-metastasis cohort derived from the INITIAL sample, which additionally controlled for whether a patient received a subsequent treatment. Further controlling for whether a patient received subsequent treatments had no impact on the hazard ratio (Model 5).

Table S7. Unadjusted and adjusted associations between TTM and PMS among those who develop metastasis (INITIAL sample)

Model 1	Unadjusted hazard ratio	95% CI
Time from RP/RT to metastasis, years	1.01	1.00–1.03
Model 2	Adjusted (for age) hazard ratio	95% CI
Time from RP/RT to metastasis, years	0.99	0.97–1.00
Model 3	Adjusted (for age and primary treatment) hazard ratio	95% CI
Time from RP/RT to metastasis, years	0.99	0.97–1.00
Model 4	Adjusted (for age, primary treatment and LAPC vs HR-LPC) hazard ratio	95% CI
Time from RP/RT to metastasis, years	0.99	0.97–1.01
Model 5	Adjusted (for age, primary treatment, LAPC vs HR-LPC and subsequent treatment) hazard ratio	95% CI
Time from RP/RT to metastasis, years	0.99	0.97–1.01

CI confidence interval, *HR-LPC/LAPC* high-risk localized or locally advanced prostate cancer; *PMS* pre-metastasis survival, *RP* radical prostatectomy, *RT* radiotherapy, *TTM* time to metastasis.