HHS Public Access

Author manuscript

J Urol. Author manuscript; available in PMC 2016 April 18.

Published in final edited form as:

J Urol. 2015 August ; 194(2): 378–385. doi:10.1016/j.juro.2015.02.084.

Radical Prostatectomy or External Beam Radiation Therapy versus No Local Therapy for Survival Benefit in Metastatic Prostate Cancer - A SEER-Medicare Analysis

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Abstract

Purpose—To assess survival following radical prostatectomy (RP), intensity modulated radiation therapy (IMRT) or conformal radiation therapy (CRT) versus no local therapy (NLT) for metastatic prostate cancer (MPCa), adjusting for patient comorbidity, androgen deprivation therapy (ADT) and other factors.

Materials and Methods—Men ≥66 with MPCa undergoing treatment by RP, IMRT, CRT or NLT identified from SEER-Medicare linked database (2004–2009). Multivariable Cox proportional hazards models, before and after inverse propensity score weighting, were used to assess all cause and PCa specific mortality. Competing risk regression analysis was used to assess PCa specific mortality.

Results—Among 4069 men with MPCa, RP (n=47), IMRT (n=88), CRT (n=107) were selected as local therapy versus NLT (n=3827). RP was associated with a 52% (HR: 0.48, 95% CI: 0.27–0.85) reduction in the risk of PCa specific mortality, after adjusting for socio-demographic, primary tumour characteristics, comorbidity, ADT and bone radiation within 6 months of diagnosis. IMRT was associated with a 62% (HR: 0.38, 95% CI: 0.24–0.61) reduction in the risk of PCa specific mortality, respectively. CRT was not associated with improved survival compared to NLT. Propensity score weighting yielded comparable results. Competing risk analysis revealed a 42% (SHR: 0.58, 95% CI: 0.35–0.95) and 57% (SHR: 0.43, 95% CI: 0.27–0.68) reduction in the risk of PCa specific mortality for RP and IMRT.

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Conclusions—Local therapy with RP and IMRT, but not CRT, was associated with a survival benefit in MPC and warrants prospective evaluation in clinical trials

MeSH

Prostatic Neoplasm; Prostatectomy; Intensity-Modulated Radiotherapy; Conformal Radiotherapy; Cytoreduction Surgical Procedures; SEER Program

Introduction

The standard of care for metastatic prostate cancer (MPCa) is continuous androgen deprivation therapy (ADT)[1,2]. A secondary analysis of SWOG 8894 suggesting radical prostatectomy (RP) prior to MPCa was associated with a decreased risk of death implicated a potential role for local therapy[3]. Recent population based studies utilizing the Surveillance Epidemiology and End Results (SEER) database have demonstrated a potential survival benefit to RP in MPCa[4–6].

Population-based studies have not assessed the role of intensity modulated radiation therapy (IMRT) or conformal radiation therapy (CRT) for local treatment in MPCa. Further, these studies have not investigated the differential utilization of androgen deprivation therapy (ADT) and patient comorbidity, which can dictate treatment selection and confound the relationship between treatment type and survival. To disentangle the relationship between these factors and survival we utilized the SEER-Medicare linked database to assess survival outcomes of RP, IMRT, CRT and no local treatment (NLT) for MPCa.

Materials and Methods

Study Subjects

The SEER registry captures 28% of the US population and contains information on patient demographics, tumour characteristics and choice of primary treatment modality[7]. Linkage to Medicare, which provides benefits to 97% of Americans aged ≥65 years, offers additional treatment data, including therapies administered in the outpatient setting such as ADT[8,9].

We identified a source population (N= 240,663) based on the International Classification of Diseases for Oncology (third edition, code 8140) of the prostate (site code 61.9) diagnosed between 2004–2009. Figure 1 details the exclusion process to optimize data reliability. MPCa was defined by radiographic and/or pathologic confirmation of metastatic cancer (SEER-collaborative stage) as per the American Joint Committee on Cancer (AJCC) Cancer Staging Manual 6th.

Outcome Measures, Treatment Categories and Covariates

The outcomes of interest were all cause mortality (ACM) and PCa specific mortality (PCSM). Survival time was determined from registry vital statistics from the date of diagnosis to the date of death, last known to be alive or last follow-up (December 2010), whichever occurred first. Patients receiving intensity-modulated radiotherapy (IMRT) or conformal radiotherapy (CRT) were identified from Medicare inpatient, outpatient, and

carrier component files based on Current Procedural Terminology, Fourth Edition (CPT-4) codes as previously described using prostate diagnosis codes for treatment claims[10]. Patients with ≤15 treatment claims were excluded as this likely represented palliative radiation (e.g. bone) or treatment for local symptom control[11]. The practice pattern for palliative radiation varies, however, we selected a cut-off of 15, which represents the largest number of fractions reported from published randomized trials on palliative regimes[12,13]. We also identified patients who received EBRT to bone within 6 months of diagnosis as a marker of advanced disease. RP was defined using SEER surgery site codes 50 or 70[4]. In order to assess possible discrepancies between SEER and Medicare data on treatment assignment[14], we also identified patients that underwent RP using Medicare billing codes[15]. Accuracy of staging and treatment for each individual RP patient (n=47) was re-confirmed by directly contacting SEER registry directors for repeat patient-to-patient data reconfirmation. On review of 228 cases identified from SEER (2004–2010) as having metastatic PCa and receiving RP, 65% were confirmed as correct after registry audits, with individual registries varying from 45–100% with respect to accuracy of classification (Supplemental Figure 1). Patients receiving NLT for PCa never received RP, EBRT, brachytherapy[10], or prostate cryotherapy (CPT-4 code 55873)[16].

Covariates of interest included age at diagnosis (years, continuous), race (African American, Hispanic, Non-Hispanic White, Asian and Other/Unknown), marital status (single, married, unknown or other), year of diagnosis (categorical 2004–2009), pre-treatment PSA (highest recorded, continuous and categorical), Gleason score and clinical AJCC staging from registry data. Approximately 15% of patients had unknown PSA values. In order to ensure that missing PSA was non-informative, PSA was assessed as a categorical variable with an unknown category. PSA was also assessed as continuous variable after excluding unknown values, however, a sensitivity analysis showed comparable effect estimates (data not shown). Specifically, for Gleason score, we used the SEER Collaborative Stage Site-Specific Factor 6 grade variable, categorized as well (≤ 4) or moderately differentiated (5–6), intermediate (7) and poor (≥ 8) differentiated. A validated algorithm was used to derive the Charlson comorbidity index (CCI) from claims one year prior to the diagnosis of MPCa[17]. Lastly, androgen deprivation therapy (ADT) exposure was determined as previously reported[18]. Specifically, ADT exposure in this study included administration of GnRH agonists 3 months before to 12 months after diagnosis, or bilateral orchiectomy within 3 months of diagnosis.

Propensity Score Adjustment

In observational studies there can be significant bias introduced by inherent differences between patients based on treatment selection. In order to decrease the risk of biased estimates of treatment effect, we computed propensity scores by multinomial logistic regression with a four-level outcome variable (RP, IMRT, CRT or NLT) with predictor variables age at diagnosis, year of diagnosis, race, marital status, pre-treatment PSA (categorical), clinical tumour stage and grade, CCI, ADT use and bone radiation within 6 months of diagnosis. Propensity scores were then utilized for inverse propensity score weighted adjustment in the final cox proportional hazards models[19].

Statistical Analysis

Differences between the distributions of socio-demographic and primary tumour factors according to RP, IMRT, CRT and NLT were examined using the Chi-square test. The hazard function of overall survival and PCa specific survival by treatment type was described using the Kaplan–Meier method. Cox proportional hazard models were fitted to assess the crude and adjusted hazard ratios (HRs) comparing RP, IMRT and CRT to NLT for ACM and PCSM. Covariates that were a priori deemed clinically important were mutually adjusted in multivariable models; the final adjusted model included registry, age at diagnosis, year of diagnosis, race, marital status, PSA, Gleason grade, AJCC T, N and M staging, CCI, and bone radiation within 6 months.

We hypothesized that ADT might modify the effect of treatment modality on survival, however, interaction (likelihood ratio test) was not significant (p=0.1) and ADT was included as a covariate in the final model. The proportional hazards assumption was satisfied in all variables except for ADT, where there was statistically significant interaction with time. Modeling ADT as a time-varying covariate did not significantly change the effect estimates (data not shown).

Given the possibility that Cox proportional hazard regression estimates of disease specific survival can overestimate risk, we also performed competing risk regression analysis to compute sub hazard ratios (SHR) as described by Fine and Gray[20,21]. All statistical analyses were performed using SAS version 9.4 (SAS Inc, Cary, NC, USA) and Stata S/E 12.1 (Stata Corporation, College Station, TX). A p-value < 0.05 was considered statistically significant.

Results

A total of 4069 cases with MPCa were identified as receiving RP (n = 47), IMRT (n=88), CRT (n=107) or NLT (n=3827). Total treatments by claim number for CRT (median: 23 [IQR: 19–30]) was less than for IMRT (median: 38 [IQR: 28–42], p<0.001). RP and IMRT groups were younger, had lower pre-treatment PSA, lower Gleason score, lower stage AJCC T and N stage compared to CRT and NLT (Table 1). The metastatic AJCC stage distribution between the treatment groups was relatively comparable. Additionally, RP and IMRT groups were less likely to receive ADT or bone radiation within 6 months of diagnosis (Table 1). The overall median follow up was 20 months (IQR: 10–36) with a total of 2872 total deaths (71%), of which 2058 (72%) deaths were attributable to PCa.

RP and IMRT when compared to NLT were associated with 57% (HR: 0.43, 95% CI: 0.26–0.70) and 55% (HR: 0.45, 95% CI: 0.31–0.65) lower risk of ACM respectively, after adjusting for socio-demographic, primary tumour characteristics, CCI, ADT and bone radiation within 6 months of diagnosis (Table 2). The adjusted PCa specific mortality was 52% (HR: 0.48, 95% CI: 0.27–0.85) and 62% (HR: 0.38, 95% CI: 0.24–0.61) lower in patients undergoing RP and IMRT respectively, compared to NLT (Table 2). In contrast, CRT compared to NLT, was not associated with lower risk of death from prostate cancer (HR: 0.85, 95% CI: 0.64–1.14). IMRT and CRT as a combined category was associated with a decreased risk of PCSM (HR: 0.64, 95% CI: 0.50–0.82. Older age, higher PSA, more aggressive primary tumour pathology (AJCC Stage), increasing CCI and bone radiation

within 6 months of diagnosis were independently associated with increase risk of PCSM. The 3-year overall survival rate was 73% for RP, 72% for IMRT, 37% for CRT, and 34% for NLT (Figure 2A). The 3-year disease specific survival rate was 79% for RP, 82% for IMRT, 49% for CRT, and 46% for NLT (Figure 2B).

Using Medicare billing codes, we identified 39 patients with MPCa as receiving RP. RP and IMRT when compared to NLT were associated with 66% (HR: 0.34, 95% CI: 0.15–0.76) and 62% (HR: 0.38, 95% CI: 0.24–0.61) adjusted lower risk of death from prostate cancer, respectively (data not shown).

Competing risk regression analysis showed that RP (SHR: 0.58, 95% CI: 0.35–0.95) and IMRT (SHR: 0.43, 95% CI: 0.27–0.68) were associated with decreased risk of PCSM compared to NLT (Table 3). Increasing age, PSA, Gleason score, more advanced primary tumour pathology (AJCC Stage), and bone radiation within 6 months of diagnosis were associated with PCSM.

After propensity score adjustment, RP compared to NLT was associated with a 45% lower risk of PCSM (HR: 0.55, 95% CI: 0.30–1.02), although not statistically significant (Table 4). IMRT was associated with a 53% decreased risk of PCSM (HR: 0.47, 95% CI: 0.31–0.72). There was no statistically significant evidence of interaction between local treatment type and CCI, PSA, metastatic stage, ADT exposure, age and bone radiation within 6-months with respect to ACM and PCSM. As these variables are of clinical interest, exploratory analyses were undertaken by relevant subsets, although limited in sample size in several groups. RP was associated with improved PCSM (HR: 0.07, 95% CI: 0.02–0.23) in the subset of patients with PSA ≤ 20, whereas the same protective association was not observed in those with PSA > 20. A consistent pattern was not observed after subsets by age, Charlson comorbidity index, metastatic stage and by ADT exposure.

Discussion

To our knowledge, this is the first population-based study examining the outcomes of RP in comparison to two modalities of external beam radiation therapy (IMRT and CRT) or no local treatment in MPCa. Additionally, in contrast to past studies[4,5], we adjusted for important confounders of survival in the metastatic setting by using billing derived patient comorbidity, receipt of ADT and early (<6 month) bone radiation as a marker of advanced disease. After accounting for these and conventional risk factors, RP and IMRT were associated with a 52% and 62% reduction in the risk of PCa specific mortality, respectively. Similar results were seen after propensity score adjustment and competing risk analysis.

Our results remain consistent with earlier SEER based analyses, which also suggested a benefit to RP and brachytherapy[4,5]. The observation that IMRT but not CRT was associated with improved ACM and PSCM may be indicative that patients receiving CRT have more advanced tumour burden, worse tumour biology and higher comorbidity that are inadequately measured and controlled for by the variables we have utilized in this retrospective study. In contemporary practice, CRT may be viewed as non-definitive therapy, used in the setting of MPCa for local symptom control, wherein lower doses and treatments

are delivered[11]. Consistent with this, we observed a nearly two-fold lower number of treatment claims for CRT compared to IMRT.

The SEER-Medicare database provides important claims derived patient variables, however, there are important limitations. This cohort consists of men > 65 years of age and hence these results may not be broadly generalizable. Further, errors in coding can occur in large databases like SEER and can be more problematic in studies involving small study samples[22]. However, in this study, men undergoing RP were all individually confirmed to have the correct staging and treatment by registry audits. Nonetheless, while the same protective effect of RP was observed when treatment was classified by Medicare billing codes, the discrepancy between SEER and Medicare highlights the need for prospective evaluation and caution related to accuracy of stage and treatment classification. Other limitation of the data include uncertainty regarding radiation doses and whether radiation was indeed delivered to the prostate and not elsewhere (e.g. bone). Further, critical variables including imaging results (e.g bone scan), lab values (e.g. PSA response to ADT) and baseline pain scores, which are necessary to define the metastatic burden, were not available. Moreover, the receipt of docetaxel based chemotherapy, immunotherapy or novel androgen receptor pathway targeted agents after the development of castrate-resistant PCa is unknown and can differentially impact survival if one group receives aggressive treatment. Taken together, selection bias may be driving the conclusions about RP and IMRT, reflecting residual confounding due to the lack critical variables that can be measured, but also concerns about the reliability and quality of measurements, such as comorbidity from claims based data[23]. Despite accounting for the receipt of early bone radiation as a marker of advanced disease, the most important selection bias remains metastatic burden. It remains possible that the survival benefit observed for RP and IMRT is purely on the basis of having less or slowly progressing metastatic deposits than patients whom underwent no local therapy. Despite these limitations, the consistency in findings for ACM and PCSM using traditional multivariable, propensity-weighted and competing risk analyses warrants further investigation.

Adoption of local treatment in MPCa must be judicious as the treatments themselves increase the risk of surgical morbidity and can be detrimental to health related quality of life. Recent data for RP in the setting of MPCa supports its feasibility with acceptable functional outcomes as well as decreased need for percutaneous or surgical interventions for local tumour growth[24]. The mechanism and underlying tumour biology that explains a potential oncologic benefit remains unknown, however, there are several hypotheses. First, eradication of the primary tumour eliminates the source of cytokine signalling that prepares niches for eventual sites of metastases and promotes their growth[25]. Second, the primary tumour may remain a source of circulating tumour cells that are capable of “self-seeding” the primary organ[26]. Lastly, local therapy may eradicate self-renewing progenitor cells persisting after ADT which have been shown to have a immature luminal, androgen receptor low phenotype and are capable of propagating adenocarcinoma[27]. Moving forward, at the very least, tissue banking RP specimens after ADT may facilitate studies of tumour and progenitor cell biology[28] including the use of high throughput genomic and transcriptome analyses to improve patient prognosis and eventually develop targeted therapy.

Conclusions

Local therapy with RP or IMRT but not CRT compared to no local treatment was associated with decreased risk of all cause and prostate cancer specific mortality, after accounting for patient comorbidity, ADT exposure and receipt of early palliative bone radiation. These results should be viewed as hypothesis generating as the lack of information on metastatic disease burden is a critical caveat in this analysis. Future prospective trials are crucial and must aim to access health related quality of life as well as oncological benefits to local therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors acknowledge the efforts of the Applied Research Program, NCI; the Office of Research, Development and Information, CMS; Information Management Services (IMS), Inc.; and the Surveillance, Epidemiology, and End Results (SEER) Program tumour registries in the creation of the SEER-Medicare database and for their generous assistance in individually auditing cases for this study. A.E.K. received support from grant 5T32 ES013678 from the National Institute of Environmental Health Sciences

Funding: None

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Standard Abbreviations

MPCa	Metastatic Prostate Cancer
RP	Radical Prostatectomy
IMRT	Intensity Modulated Radiation Therapy

CRT	Conformal Radiation Therapy
NTL	No Local Therapy
CCI	Charlson Comorbidity Index
ADT	Androgen Deprivation Therapy
ACM	All Cause Mortality
PCSM	Prostate Cancer Specific Mortality
SEER	Surveillance Epidemiology and End Results
HR	Hazard Ratio
SHR	Sub hazard Ratio

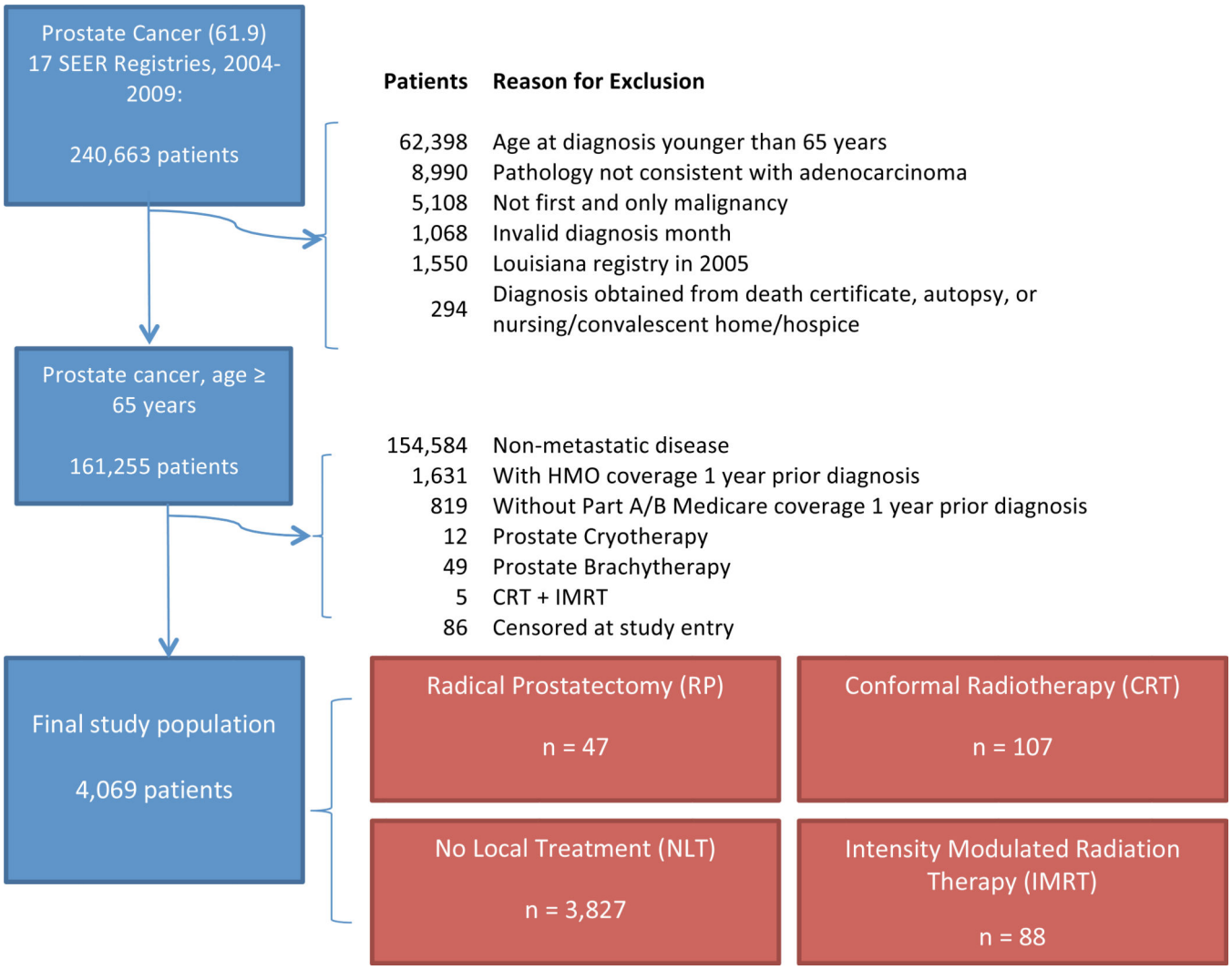

Figure 1.
Exclusion criteria utilized to derive the final study cohort from the SEER-Medicare linked database (2004–2009).

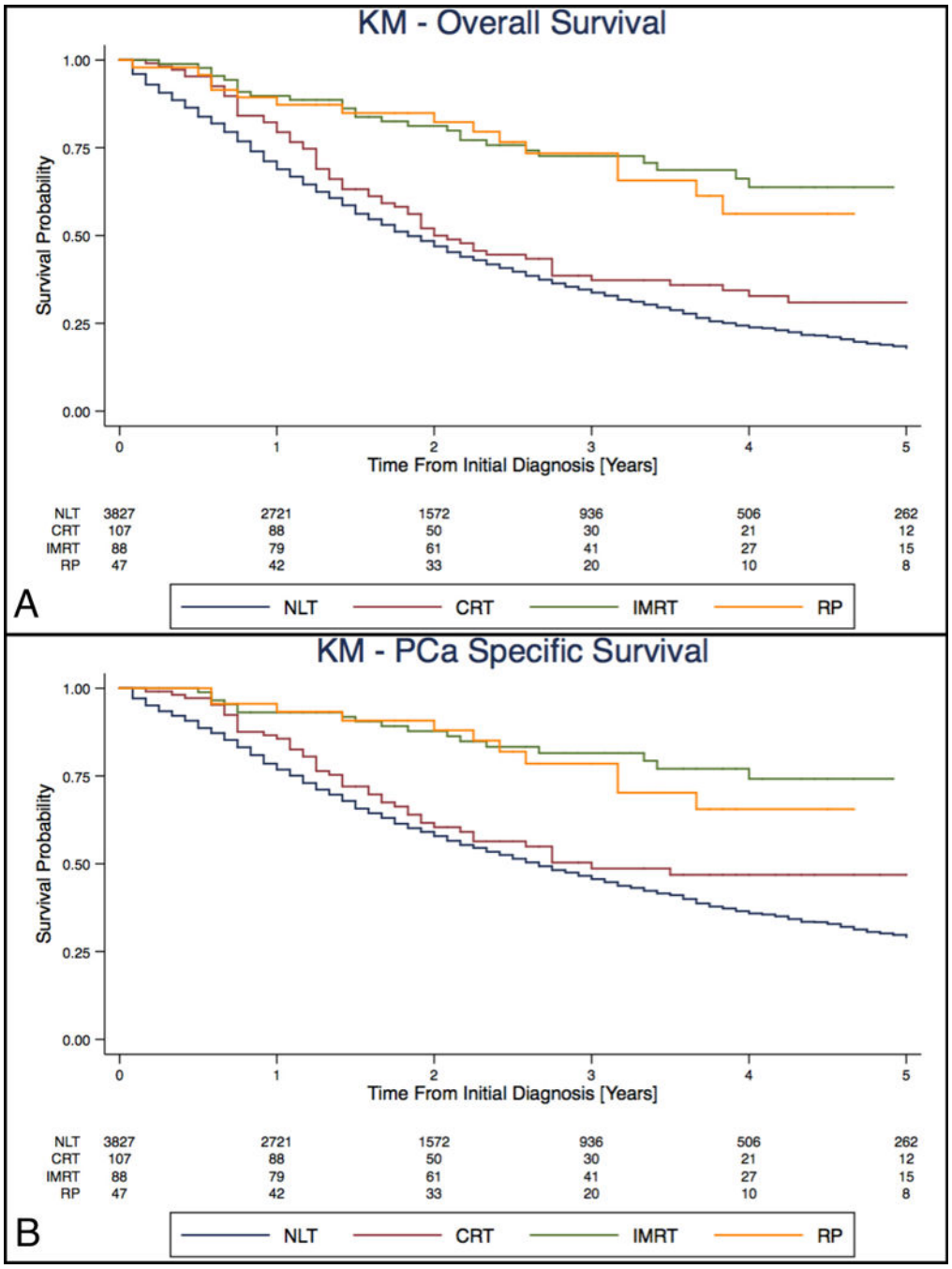

Figure 2.

Kaplan-Meier survival curve of all cause mortality (A) and prostate-cancer specific mortality (B) in patients with metastatic prostate cancer treated by RP, IMRT, CRT or NLT. Curves have been adjusted for treatment group (NLT, CRT, IMRT and RP), age, year of diagnosis, marital status, PSA, Gleason score, AJCC staging (TNM), Charlson Comorbidity Index, androgen deprivation therapy, receipt of bone radiation within 6 months of diagnosis and registry.

Table 1

Socio-demographics, tumour characteristics, comorbidity, ADT use and receipt of bone radiation within 6 months among men with metastatic prostate cancer (N=4069) that received radical prostatectomy (RP), intensity modulated radiation therapy (IMRT), conformal radiation therapy (CRT), or No Local Treatment (NLT). Percentages are shown in parenthesis. One-way ANOVA (PSA and log-transformed age) and two-tailed chi-square tests were used to test the hypothesis that at least one of the proportions/distribution of covariates is different by treatment type. Note that 595 patients (~15%) have unknown PSA values and are not included in continuous description of PSA.

	RP	IMRT	CRT	NLT	*p-value*
	47	88	107	3827	
Year of Diagnosis – N (%)					
2004	6 (13)	12 (14)	21 (20)	709 (19)	0.2
2005	5 (11)	9 (10)	26 (24)	692 (18)	
2006	7 (15)	14 (16)	21 (20)	667 (17)	
2007	11 (23)	21 (24)	16 (15)	619 (16)	
2008	10 (21)	18 (20)	14 (13)	580 (15)	
2009	8 (17)	14 (16)	9 (8)	560 (15)	
Age at Diagnosis					
Mean (SD)	73.0 (6.0)	74.2 (6.1)	76.4 (6.3)	78.2 (7.2)	< 0.001
Race – N (%)					
NHW	38 (81)	75 (85)	81 (76)	2925 (76)	0.5
AA	7 (15)	9 (10)	13 (12)	608 (16)	
Hisp	0 (0)	2 (2)	3 (3)	95 (2)	
Asian	2 (4)	1 (1)	6 (6)	103 (3)	
Other/Unknown	0 (0)	1 (1)	4 (4)	96 (3)	
Marital Status – N (%)					
Single	2 (4)	10 (11)	6 (6)	408 (11)	0.1
Married	35 (74)	60 (68)	68 (64)	2248 (59)	
Separated/divorced/widowed/ domestic partners	9 (19)	12 (14)	27 (25)	933 (24)	
Unknown	1 (2)	6 (7)	6 (6)	238 (6)	
PSA – N (%)					
< 10 ng/ml	25 (53)	35 (40)	9 (8)	401 (10)	< 0.001
10–19 ng/ml	6 (13)	16 (18)	20 (19)	449 (12)	

	RP	IMRT	CRT	NLT	*p-value*
20–29 ng/ml	3 (6)	10 (11)	9 (8)	286 (7)	
> 30 ng/ml	6 (13)	17 (19)	55 (51)	2127 (56)	
Unknown	7 (15)	10 (11)	14 (13)	564 (15)	
PSA (Continuous)					
Mean (SD)	181 (263)	282 (338)	531 (369)	590 (380)	< 0.001
Gleason Score – N (%)					
≤6	5 (11)	10 (11)	8 (7)	167 (4)	< 0.001
7	22 (47)	24 (27)	22 (21)	569 (15)	
≥8	19 (40)	43 (49)	59 (55)	2042 (53)	
Unknown	1 (2)	11 (13)	18 (17)	1049 (27)	
T Stage – N (%)					
T1	0 (0)	27 (31)	31 (29)	839 (22)	< 0.001
T2	21 (45)	36 (41)	28 (26)	1282 (33)	
T3	19 (40)	10 (11)	9 (8)	298 (8)	
T4	6 (13)	9 (10)	17 (16)	461 (12)	
Unknown	1 (2)	6 (7)	22 (21)	947 (25)	
N Stage – N (%)					
N0	34 (72)	59 (67)	63 (59)	1930 (50)	< 0.001
N1	10 (21)	11 (13)	15 (14)	577 (15)	
NX	3 (6)	18 (20)	29 (27)	1320 (34)	
M Stage – N (%)					
M1a	3 (6)	4 (5)	4 (4)	190 (5)	0.2
M1b	26 (55)	65 (74)	72 (67)	2570 (67)	
M1c	17 (36)	16 (18)	31 (29)	922 (24)	
M1 NOS	1 (2)	3 (3)	0 (0)	145 (4)	
Charlson Comorbidity Index – N (%)					
0	32 (68)	60 (68)	67 (63)	2462 (64)	0.9
1	9 (19)	19 (22)	25 (23)	757 (20)	
2	4 (9)	4 (5)	10 (9)	331 (9)	
≥3	2 (4)	5 (6)	5 (5)	277 (7)	
Androgen Deprivation Therapy –					

	RP	IMRT	CRT	NLT	*p-value*
N (%)					
None	27 (57)	30 (34)	13 (12)	1132 (30)	< 0.001
Orchiectomy	3 (6)	0 (0)	5 (5)	331 (9)	
GnRH Agonist	16 (34)	56 (64)	88 (82)	2330 (61)	
Both	1 (2)	2 (2)	1 (1)	34 (1)	
Bone Radiation Within 6 mo of Diagnosis – N (%)					
No	47 (100)	86 (98)	99 (93)	3420 (89)	0.005
Yes	0 (0)	2 (2)	8 (7)	407 (11)	

Table 2

Crude and adjusted probability of all cause and prostate cancer specific mortality after local treatment for metastatic prostate cancer. Hazard Ratios (HR) are adjusted for treatment group (NLT, CRT, IMRT and RP), age, year of diagnosis, race, marital status, PSA, Gleason score, AJCC staging (TNM), Charlson Comorbidity Index, androgen deprivation therapy, receipt of bone radiation within 6 months of diagnosis and registry. The model for prostate cancer specific mortality treats non-prostate cancer deaths as censored observations.

Characteristic	N	All-Cause Mortality	P value	Prostate Cancer Specific Mortality	P value
		Adjusted HR (95% CI)		Adjusted HR (95% CI)	
Treatment					
NLT	3827	1.0 (Ref)		1.0 (Ref)	
CRT	107	0.90 (0.70–1.14)	0.4	0.85 (0.64–1.14)	0.3
IMRT	88	0.45 (0.31–0.65)	< 0.001	0.38 (0.24–0.61)	< 0.001
RP	47	0.43 (0.26–0.72)	0.001	0.48 (0.27–0.85)	0.01
Age					
5 yr. increment	4069	1.17 (1.14–1.20)	< 0.001	1.12 (1.09–1.16)	< 0.001
Year of Diagnosis					
2004	748	1.0 (Ref)		1.0 (Ref)	
2005	732	1.05 (0.93–1.18)	0.4	1.07 (0.93–1.22)	0.4
2006	709	0.98 (0.87–1.11)	0.8	1.05 (0.91–1.20)	0.5
2007	667	0.95 (0.84–1.08)	0.4	0.90 (0.78–1.05)	0.2
2008	622	0.98 (0.85–1.12)	0.7	1.03 (0.88–1.21)	0.7
2009	591	0.88 (0.75–1.04)	0.1	0.87 (0.72–1.06)	0.2
Race					
NHW	3,119	1.0 (Ref)		1.0 (Ref)	
AA	637	0.97 (0.86–1.08)	0.6	0.94 (0.83–1.08)	0.4
Hispanic	100	1.11 (0.87–1.43)	0.4	1.08 (0.80–1.47)	0.6
Asian	112	0.79 (0.61–1.02)	0.1	0.78 (0.57–1.06)	0.1
Other/Unknown	101	0.89 (0.68–1.16)	0.4	0.75 (0.54–1.05)	0.1
Marital Status					
Single	426	1.0 (Ref)		1.0 (Ref)	
Married	2411	0.72 (0.64–0.82)	< 0.001	0.77 (0.66–0.89)	< 0.001

Characteristic	N	All-Cause Mortality	P value	Prostate Cancer Specific Mortality	P value
		Adjusted HR (95% CI)		Adjusted HR (95% CI)	
Separated/Divorced/Widowed	981	0.80 (0.70–0.91)	0.001	0.82 (0.70–0.96)	0.01
Unknown	251	0.70 (0.57–0.84)	< 0.001	0.69 (0.55–0.88)	0.002
PSA					
< 10 ng/ml	470	1.0 (Ref)		1.0 (Ref)	
10–19 ng/ml	491	1.08 (0.92–1.28)	0.3	1.03 (0.84–1.25)	0.8
20–29 ng/ml	308	1.04 (0.87–1.25)	0.7	1.04 (0.84–1.30)	0.7
30+ ng/ml	2205	1.25 (1.09–1.42)	0.001	1.29 (1.10–1.51)	0.002
Unknown	595	1.16 (0.99–1.35)	0.07	1.10 (0.91–1.32)	0.3
Gleason Score					
≤6	190	1.0 (Ref)		1.0 (Ref)	
7	637	0.99 (0.81–1.22)	0.9	1.12 (0.86–1.47)	0.4
≥8	2163	1.39 (1.15–1.68)	0.001	1.72 (1.35–2.21)	< 0.001
Unknown	1079	1.59 (1.30–1.94)	< 0.001	1.92 (1.48–2.49)	< 0.001
T Stage					
T1	897	1.0 (Ref)		1.0 (Ref)	
T2	1367	1.09 (0.98–1.21)	0.1	1.15 (1.01–1.31)	0.03
T3	336	1.10 (0.94–1.30)	0.2	1.05 (0.87–1.28)	0.6
T4	493	1.30 (1.13–1.48)	< 0.001	1.35 (1.15–1.58)	< 0.001
Unknown	976	1.35 (1.19–1.54)	< 0.001	1.34 (1.14–1.57)	< 0.001
N Stage					
N0	2086	1.0 (Ref)		1.0 (Ref)	
N1	613	1.15 (1.03–1.29)	0.02	1.15 (1.01–1.32)	0.04
NX	1370	1.07 (0.97–1.17)	0.17	1.09 (0.98–1.21)	0.13
M Stage					
M1a	201	1.0 (Ref)		1.0 (Ref)	
M1b	2733	1.59 (1.29–1.94)	< 0.001	1.86 (1.44–2.40)	< 0.001
M1c	986	1.93 (1.57–2.39)	< 0.001	2.25 (1.72–2.93)	< 0.001
M1 NOS	149	1.69 (1.28–2.23)	< 0.001	1.97 (1.40–2.77)	< 0.001
Charlson Comorbidity Index					

Characteristic	N	All-Cause Mortality	P value	Prostate Cancer Specific Mortality	P value
		Adjusted HR (95% CI)		Adjusted HR (95% CI)	
0	2621	1.0 (Ref)		1.0 (Ref)	
1	810	1.09 (0.99–1.20)	0.09	1.04 (0.93–1.16)	0.5
2	349	1.41 (1.24–1.61)	< 0.001	1.21 (1.03–1.43)	0.02
≥3	289	1.85 (1.61–2.12)	< 0.001	1.51 (1.27–1.79)	< 0.001
Androgen Deprivation Therapy					
None	1202	1.0 (Ref)		1.0 (Ref)	
Orchiectomy	339	0.82 (0.71–0.94)	0.006	0.87 (0.74–1.02)	0.09
GnRH Agonist	2490	0.68 (0.62–0.74)	< 0.001	0.72 (0.65–0.80)	< 0.001
Both	38	0.59 (0.40–0.87)	0.007	0.67 (0.44–1.04)	0.07
Bone Radiation Within 6 mo of Diagnosis					
No	3652	1.0 (Ref)		1.0 (Ref)	
Yes	417	1.36 (1.21–1.53)	< 0.001	1.53 (1.34–1.75)	< 0.001

Table 3

Multivariable competing risk regression analysis by Fine and Gray method of patients receiving local therapy for metastatic prostate cancer. Sub Hazard Ratios (SHR) are reported after adjustment for treatment group (NLT, CRT, IMRT and RP), age, year of diagnosis, race, marital status, PSA, Gleason score, AJCC staging (TNM), Charlson Comorbidity Index, androgen deprivation therapy, receipt of bone radiation within 6 months of diagnosis and registry.

Characteristic	N	Adjusted SHR (95% CI)	P value
Treatment			
NLT	3827	1.0 (Ref)	
CRT	107	0.87 (0.65–1.18)	0.4
IMRT	88	0.43 (0.27–0.68)	< 0.001
RP	47	0.58 (0.35–0.95)	0.03
Age Group			
5 yr. increment	4069	1.05 (1.02–1.08)	0.003
Year of Diagnosis			
2004	748	1.0 (Ref)	
2005	732	1.06 (0.92–1.21)	0.4
2006	709	1.04 (0.91–1.19)	0.5
2007	667	0.83 (0.72–0.97)	0.02
2008	622	0.94 (0.81–1.10)	0.5
2009	591	0.73 (0.60–0.88)	0.001
Race			
NHW	3,119	1.0 (Ref)	
AA	637	0.97 (0.85–1.11)	0.7
Hispanic	100	0.96 (0.71–1.29)	0.8
Asian	112	0.82 (0.59–1.15)	0.3
Other/Unknown	101	0.71 (0.50–1.03)	0.07
Marital Status			
Single	426	1.0 (Ref)	
Married	2411	0.88 (0.76–1.02)	0.1
Separated/divorced/widowed	981	0.88 (0.75–1.04)	0.1
Unknown	251	0.77 (0.61–0.98)	0.04
PSA			
< 10 ng/ml	470	1.0 (Ref)	
10–19 ng/ml	491	1.01 (0.83–1.23)	0.9
20–29 ng/ml	308	1.06 (0.86–1.31)	0.6
30+ ng/ml	2205	1.26 (1.08–1.48)	0.003
Unknown	595	1.07 (0.89–1.29)	0.5
Gleason Score			
≤6	190	1.0 (Ref)	
7	637	1.14 (0.88–1.47)	0.3
≥8	2163	1.66 (1.32–2.10)	< 0.001

Characteristic	N	Adjusted SHR (95% CI)	P value
Unknown	1079	1.73 (1.35–2.22)	< 0.001
T Stage			
T1	897	1.0 (Ref)	
T2	1367	1.16 (1.02–1.31)	0.02
T3	336	0.97 (0.80–1.16)	0.7
T4	493	1.25 (1.07–1.46)	0.005
Unknown	976	1.23 (1.05–1.44)	0.009
N Stage			
N0	2086	1.0 (Ref)	
N1	613	1.13 (0.98–1.29)	0.08
NX	1370	1.07 (0.96–1.19)	0.2
M Stage			
M1a	201	1.0 (Ref)	
M1b	2733	1.76 (1.37–2.25)	< 0.001
M1c	986	1.93 (1.49–2.51)	< 0.001
M1 NOS	149	1.82 (1.29–2.56)	0.001
Charlson Comorbidity Index			
0	2621	1.0 (Ref)	
1	810	1 (0.89–1.12)	> 0.9
2	349	1.01 (0.85–1.19)	> 0.9
≥3	289	1.06 (0.89–1.27)	0.5
Androgen Deprivation Therapy			
None	1202	1.0 (Ref)	
Orchiectomy	339	1.01 (0.85–1.19)	> 0.9
GnRH Agonist	2490	0.87 (0.78–0.97)	0.01
Both	38	0.91 (0.59–1.40)	0.7
Bone Radiation Within 6 mo of Diagnosis			
No	3652	1.0 (Ref)	
Yes	417	1.54 (1.34–1.77)	< 0.001

Table 4

Inverse propensity score weight adjusted probability of all cause mortality and prostate cancer specific mortality in patients with metastatic prostate cancer at diagnosis. Results are shown for full study cohort and after stratification by age, Charlson Comorbidity Index, PSA level, metastatic stage and androgen deprivation therapy exposure. Patients with unknown PSA levels or metastatic stage were excluded for stratified analysis.

			All-Cause Mortality	P value	Prostate Cancer Specific Mortality	
	Treatment Type	**N**	**Adjusted HR (95% CI)**		**Adjusted HR (95% CI)**	**P value**
Non-Stratified	NLT	3827	1.0 (Ref)		1.0 (Ref)	
	CRT	107	1.01 (0.73–1.39)	0.9	0.97 (0.66–1.43)	0.9
	IMRT	88	0.57 (0.41–0.79)	0.001	0.47 (0.31–0.72)	0.001
	RP	47	0.42 (0.18–0.96)	0.04	0.55 (0.30–1.02)	0.057
Stratified Analyses						
AGE						
≤ 75	NLT	1400	1.0 (Ref)		1.0 (Ref)	
	CRT	49	1.15 (0.72–1.86)	0.6	1.26 (0.72–2.20)	0.4
	IMRT	54	0.57 (0.37–0.88)	0.01	0.44 (0.25–0.76)	0.004
	RP	35	0.76 (0.36–1.61)	0.5	1.12 (0.56–2.22)	0.8
> 75	NLT	2427	1.0 (Ref)		1.0 (Ref)	
	CRT	58	1.41 (0.96–2.08)	0.08	1.25 (0.80–1.97)	0.3
	IMRT	34	0.54 (0.33–0.89)	0.02	0.41 (0.22–0.78)	0.006
	RP	12	0.36 (0.11–1.20)	0.10	0.38 (0.16–0.89)	0.03
Charlson Comorbidity Index						
< 2	NLT	3219	1.0 (Ref)		1.0 (Ref)	
	CRT	92	0.99 (0.72–1.36)	> 0.9	0.98 (0.66–1.44)	> 0.9
	IMRT	79	0.41 (0.24–0.70)	0.001	0.34 (0.17–0.66)	0.002
	RP	41	0.61 (0.26–1.46)	0.3	0.60 (0.28–1.29)	0.19
≥ 2	NLT	608	1.0 (Ref)		1.0 (Ref)	
	CRT	15	1.34 (0.35–5.13)	0.7	0.82 (0.25–2.63)	0.7
	IMRT	9	0.61 (0.26–1.39)	0.2	0.62 (0.15–2.63)	0.5
	RP	6	0.37 (0.16–0.83)	0.02	0.36 (0.15–0.88)	0.03

		All-Cause Mortality		P value	Prostate Cancer Specific Mortality		P value
	Treatment Type	N	Adjusted HR (95% CI)			Adjusted HR (95% CI)	
PSA							
	NLT	850	1.0 (Ref)			1.0 (Ref)	
	CRT	29	0.85 (0.47–1.55)	0.6	1.14 (0.56–2.31)		0.7
≤ 20	IMRT	51	0.61 (0.32–1.17)	0.1	0.40 (0.15–1.09)		0.07
	RP	31	0.07 (0.02–0.24)	< 0.001	0.07 (0.02–0.23)		< 0.001
	NLT	2413	1.0 (Ref)		1.0 (Ref)		
	CRT	64	1.50 (1.03–2.18)	0.03	1.29 (0.81–2.06)		0.3
> 20	IMRT	27	0.55 (0.35–0.86)	0.009	0.44 (0.27–0.74)		0.002
	RP	9	0.69 (0.22–2.14)	0.5	0.62 (0.29–1.30)		0.2
Metastatic Stage							
	NLT	2760	1.0 (Ref)		1.0 (Ref)		
	CRT	76	1.43 (0.97–2.12)	0.07	1.56 (1.03–2.35)		0.04
M1a + M1b	IMRT	69	0.69 (0.47–1.00)	0.051	0.60 (0.37–0.98)		0.04
	RP	29	0.73 (0.27–1.93)	0.5	0.64 (0.32–1.30)		0.2
	NLT	922	1.0 (Ref)		1.0 (Ref)		
	CRT	31	0.90 (0.57–1.44)	0.7	0.75 (0.40–1.41)		0.4
M1c	IMRT	16	0.48 (0.22–1.01)	0.054	0.37 (0.16–0.85)		0.02
	RP	17	0.33 (0.13–0.82)	0.017	0.34 (0.12–0.95)		0.04
Androgen Deprivation Therapy							
	NLT	1132	1.0 (Ref)		1.0 (Ref)		
	CRT	13	1.14 (0.62–2.11)	0.7	1.34 (0.67–2.66)		0.4
No	IMRT	30	0.60 (0.34–1.08)	0.09	0.54 (0.23–1.27)		0.2
	RP	27	0.78 (0.30–2.04)	0.6	0.83 (0.31–2.27)		0.7
	NLT	2695	1.0 (Ref)		1.0 (Ref)		
	CRT	94	1.21 (0.86–1.71)	0.3	1.10 (0.75–1.61)		0.6
Yes	IMRT	58	0.55 (0.37–0.82)	0.003	0.43 (0.25–0.72)		0.002
	RP	20	0.47 (0.24–0.92)	0.03	0.82 (0.45–1.50)		0.5