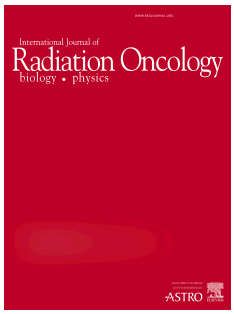
Accepted Manuscript



Salvage Radiotherapy Dose Response for Biochemical Failure of Prostate Cancer after Prostatectomy - A Multi-Institutional Observational Study

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Title

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Summary

Ten academic centers in the United States pooled individual prostate cancer patient data into a centralized database in order to describe the effects of salvage radiotherapy for detectable serum prostate-specific antigen after prostatectomy. The outcomes of 1108 such patients are presented, focusing on the relationship of radiotherapy dose with selected endpoints. The incidence of biochemical failure after radiotherapy was reduced when ≥66.0 Gy was prescribed, supporting higher-dose salvage radiotherapy whenever feasible.

Manuscript pages:

Section	Pages
Title Page	4
Summary	1
Abstract	1
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Contributions	1
Figure Legends	1
Figures	2
Tables	3
Total	20

Figures: 2

Tables: 3

Word count:

Section	Words
Running Title (characters with spaces)	4 (24)
Abstract	248
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Patients & Methods	838
Results	368
Discussion	1192
Total (section headings included)	2634
Remaining	866
References	24

Companion papers or previous versions: 0

Introduction

The relationship between radiotherapy (RT) dose and tumor response forms the basis of RT dose prescription. This relationship has been well-studied in the non-operative treatment of prostate cancer with RT, but to a much lesser extent with its use in the post-operative setting. RT administered when the prostate-specific antigen (PSA) level is elevated post-operatively is termed salvage RT (1), but different conclusions about the dose-response relationship have been noted in this setting (2-5). Our *** did not observe an association between dose and biochemical control previously (***), but a greatly expanded study cohort and longer follow-up of patients (pts) allowed *** to investigate this issue again.

Several tumor-related factors are associated with biochemical failure (BcF) after salvage RT, and these may differentiate to some degree between the presence of prostate cancer in the prostatic bed versus nodal or metastatic sites. Surgical margin status (2, 4), pelvic nodal involvement (2), and PSA level immediately before salvage RT (2, 4, 6, 7) are such factors. Using these factors as selection criteria may enrich a study cohort for a preponderance of prostatic bed recurrences. An investigation of a RT dose-response association is thus focused on a study cohort with lesser likelihood of distant cancer spread as the cause of PSA elevation. We hypothesized that an inverse association of RT dose with BcF exists, and sought to validate dose cut-off points used previously by other investigators (3, 4).

Patients & Methods

Patients

*** were invited to contribute patient data to a central repository if there was similar prior participation (***) or other relevant research productivity. Nine centers in the United States were signatory to an agreement with the ***, the recipient and data center, that obligated all ten sites to comply with Standards for Privacy of Individually Identifiable Health Information issued under the Health Insurance Portability and Accountability Act of 1996, and the American Recovery and Reinvestment and the Health Information Technology for Economic and Clinical Health Acts of 2009. A Limited Data Set of protected health information that excluded direct identifiers of an individual or their relatives, employers or household members was assembled after Institutional Review Board approval at each center. Study inclusion criteria, data elements, and data collection and transference procedures were pre-specified; data elements did not include adverse events, because this was reported previously(***).

The inclusion criteria for case submission to the repository were: men aged ≥18 years, prior radical prostatectomy (RP) and lymphadenectomy with complete prostate and tumor excision grossly, histologically-confirmed pathological Stage II-III prostatic adenocarcinoma (9), no androgen suppression (AS) before RP or planned adjuvantly after RT, no prior orchiectomy, no known local or metastatic recurrence prior to RT, PSA done prior to both RP and RT, and event monitoring with serial PSA determinations after RT. Patients with nodal involvement at RP were excluded. 2460 evaluable patients were contributed in total. Data inconsistencies or incomplete entry were addressed through queries to the contributing center.

Study Design

This is an observational cohort design reflective of clinical practice during the study period. After treatment was completed and follow-up status determined, we postulated that higher salvage RT dose is associated with a lower incidence of subsequent BcF, the primary endpoint; the incidence of distant metastasis (DM) was a secondary endpoint. Before any data queries were otherwise started, patients were selected for this analysis (Figure 1) from the total cohort (2460 pts) if cancer was present at the RP margin (R1 (9) margin-positive resection), the PSA level before RT start was ≤2.0 ng/mL (as in the randomized clinical trial of the Swiss Group for Clinical Cancer Research [SAKK], NCT01272050) (10), and neoadjuvant and/or concurrent AS was not used. Analysis and reporting were

guided by STrengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations (11).

Treatment

Treatment was not pre-specified or guided by uniform provisions, but differed by practitioner, center, availability of specialized equipment and support services, and practice standards customary at that time. RP was selected by practitioner and patient, and surgical technique is presumed to have varied amongst surgeons and over time. Histological reporting of RP and lymphadenectomy specimens was performed on site without central pathology review. Evaluation to identify an anatomical site of prostate cancer recurrence before RT was not specified, and is assumed to have varied within the boundaries of current consensus guidelines (1).

Patient referral to radiation oncology was at practitioner and patient discretion, with RT use determined by the radiation oncologist and agreed to through informed consent. Treatment planning techniques included orthogonal radiographic and computed tomographic target definition, with two-dimensional, three-dimensional, and intensity-modulated conformal dose-delivery methods. The postoperative prostatic bed (± pelvic lymphatics) target volume was determined by the radiation oncologist, for the most part before emergence of consensus guidelines (12). Image-guidance for target localization was uncommon, with alignment assessed mainly with periodic portal images referenced to skeletal anatomy.

Statistical Methods

The chi-square test was applied to identify differences between the three pre-determined RT dose groupings (<66.0 Gy *vs.* 66.0- 69.9 Gy *vs.* ≥70.0 Gy) for categorical characteristics, and the analysis of variance was used for continuous variables. BcF was defined as a post-RT PSA rising to >0.2 ng/mL with a confirmatory value of >0.2 ng/mL (1), or a single value rising to >0.4 ng/mL. DM was the occurrence of extrapelvic nodal, osseous, or visceral disease attributed to prostate cancer. The cumulative risk estimator provided cumulative incidences of BcF and DM after RT (13), and Fine-Gray competing risks hazard regression (14) models were used to investigate the association between potential predictors and these endpoints; candidate predictors were chosen from *** prior work (***). Univariate models were considered, as were multivariate models that adjusted simultaneously for possible confounders (variables identified in the single models). Variables not significant in the univariate model were not retained in the multivariate model (*i.e.*, forward selection). *P*-value <0.05 was significant.

Time-to-event duration originated at RT completion and ended with data received through December 2014. RT dose was investigated as a numeric continuous variable to assess linear association, and also as a three-level categorical variable (<66.0, 66.0-69.9, ≥70.0-Gy) for possible non-linear association. PSA values obtained before RT start, but after RP, were entered directly into the models without logarithmic conversion, because the value range for study inclusion was truncated at ≤2.0 ng/mL. PSA values were entered into univariate models as continuous and categorical (≤0.20, 0.21-0.50, 0.51-1.0, and >1.0-2.0 ng/mL) variables, and into the multivariate models as a categorical variable only to avoid confounding.

Results

Demographics

Characteristics of the 1108-patient study cohort are shown in Table 1, which provides also the distribution of variables within RT dose grouping and tests for between-group differences. The median interval from RP to salvage RT was 19.3 months (interquartile range [IQR], 7.0-41.0), and the median follow-up duration thereafter was 65.2 months (IQR, 34.0-110.0). A trend toward higher RT dose prescription (≥70.0 Gy) was observed during the later years of the study timeframe, with 1% of patients treated at this dose level between 1985-1999 compared with 27% subsequently.

Outcomes

The cumulative incidence of BcF after salvage RT was 36.5% (95% confidence interval [CI], 33.2-39.6%) by five years and 50.2% (95% CI, 46.1-54.2%) by ten years; freedom from BcF (Figure 2) was thus estimated at 63.5% (95% CI, 60.4-66.8%) and 49.8% (95% CI, 45.8-53.9%) at five and ten years, respectively. Outcomes within the pre-specified subgroups are provided in Table 2, as is the univariate and multivariate analysis of associations between candidate predictors and BcF. RT target (prostatic bed *vs.* prostatic bed and pelvic nodal) and technique (two-dimensional *vs.* three-dimensional conformal *vs.* intensity-modulated) were not significant (data not shown), and were not considered further. Higher Gleason score and pre-RT PSA level, and the presence of seminal vesicle invasion (T3b classification (9)) were associated with worse outcome. Higher RT dose was significantly associated with a 26% - 35% relative risk reduction, adjusted for the effect of other predictors. For example, 61% of the group that received ≥70.0 Gy was free of BcF at ten years compared with 43% of the <66.0 Gy group. A significant difference between the 66.0-69.9-Gy and the ≥70.0-Gy groups was not observed.

The cumulative incidence of DM was 12.4% (95% CI, 9.6-15.2%) by ten years (Figure 2). Exploratory analysis of candidate predictors for DM is shown in Table 3. Higher Gleason score and pre-RT PSA level, and extraprostatic tumor extension and seminal vesicle invasion were associated with worse outcome. DM was observed in more than one-quarter of patients with a Gleason score 8-10 tumor or with seminal vesicle invasion in the decade following RT. Delayed salvage RT until PSA was >1.0-2.0 ng/mL was associated with more than a three-fold increase in the relative risk of DM.

Discussion

An elevated serum PSA is the most sensitive and specific early indicator of prostate cancer recurrence after RP. Although the risk of death due to prostate cancer is lessened when salvage RT is promptly initiated (7), it is not used frequently in urological practice (15). There are several reasons salvage RT may not be given despite consensus recommendations for its use (1), but a perceived lack of efficacy may have a role. The present study sought to address a central aspect of RT efficacy to support best practices - the dose-response relationship, studied previously by a *** (***) to this *** and supported by a systematic review of the literature (not a meta-analysis of individual patient data) subsequently (5). Our *** analysis of salvage RT is the largest study to date of individual patient data enriched to enhance detection of a dose-response relationship.

Most observational series of salvage RT include patients with a broad spectrum of characteristics (7, 16), some of which are strongly associated with subclinical DM. Inclusion of such patients may confound assessment of a treatment directed only to the prostatic bed, a non-metastatic potential site of disease recurrence. The present study was mindful of such confounding, selecting a study cohort enriched for a greater likelihood of disease recurrence in the prostatic bed only, where salvage RT is apt to be more effective. Our findings validated those of Bernard *et al* (3), who noted also an association between RT dose and the incidence of BcF after salvage RT. We observed associations when dose was modeled as a continuous variable or when categorized at the pre-specified cut-offs of 66-Gy and 70-Gy (Table 2). The prescription of at least 66-Gy to the prostatic bed is supported by our findings and those of Bernard *et al* (3).

We did not identify an association between BcF and prescribed doses at or above 70-Gy, compared with doses between 66-Gy and 70-Gy, as noted by Goenka *et al* also (4). Our study may have been limited however by an inadequate sample size in the highest dose group, by a relatively small dose gradient between dose groupings, and perhaps by factors unknown to us (for example, use of higher RT dose for patients with higher risk attributes not included in the data elements of this study) that may have led to confounding by intention - that is, physician selection of dose was (and is) a complex interplay of considerations that we could not account for. As such, the absence of an identifiable treatment effect beyond 70-Gy should not be interpreted as lack of effect. The finding of

an overall dose-response relationship in our study supports the testing of higher dose levels for safety and efficacy (17) and the conduct of randomized trials (for example, SAKK 09/10) (10) when feasible.

The present study does not identify an optimal singular RT dose for use in all patients, a decision that should balance cancer control, adverse effects, and quality of life. It may be assumed that cancer control varies from one circumstance to another, because of the association of post-RT BcF with Gleason score (2, 6, 7), seminal vesicle invasion (6), and pre-RT PSA level (2, 6, 7) affirmed in this study (Table 2). Patients with a tumor of higher Gleason score or pre-RT PSA level may have a greater tumor volume in the prostatic bed, with such reasoning yielding consideration of higher salvage RT dose prescription. It would be ideal to identify dose-response differences in patient subsets through exploratory analyses of a prospective trial, but the SAKK study 09/10 may not have sufficient subset sample sizes to accomplish this task (10).

The findings of this study cannot determine whether prescription of salvage RT doses at or above 70-Gy should be used. Patient-specific information (*e.g.*, comorbidity), findings from pre-RT diagnostic imaging (*e.g.*, magnetic resonance imaging), treatment planning (*e.g.*, dose-volume data) and delivery (*i.e.*, intensity-modulation, image-guidance) parameters, and adjunctive therapies (*e.g.*, androgen suppression) may inform shared decision-making in this regard. Use of conformal dose delivery methods, particularly intensity modulation (18), and image-guidance (19) is associated with improved RT tolerance at higher dose levels (17). Adherence to normal tissue dose constraints (20, 21), and restriction of higher dose levels to higher risk regions (22) or imaging abnormalities within the prostate bed may also be considered in dose selection.

Our patient group was chosen to limit the number of variables that might influence the primary outcome (*i.e.*, BcF) of this study, and patients treated with adjuvant AS were specifically excluded for this reason. This is not meant to imply that higher salvage RT dose levels obviate use of AS in some patients, for whom outcomes might be improved further. We also cannot know from this investigation whether AS influences the RT dose-response relationship, and so whether the use of AS should influence RT dose selection presently. First reporting of the Groupe d'Etude des Tumeurs Uro-Génitales randomized trial 16 (NCT00423475) suggests that BcF is reduced with addition of short-term AS to salvage RT (66-Gy), but an effect on DM and cause-specific mortality has not been found, at least not as of yet (23). The NRG Oncology/Radiation Therapy Oncology Group (RTOG) trial 9601 (NCT00002874) observed reduced BcF, DM, and cause-specific mortality with salvage RT (64.8-Gy) and two years of the anti-androgen bicalutamide (150 mg daily). Further analysis of this trial is expected to clarify which patient subsets benefit most from long-term adjuvant anti-androgen use, and this is apt to define the role of long-term adjuvant therapy in these patients. Several other ongoing randomized clinical trials will provide further guidance on AS in the years to come.

The present study methodology is limited by its observational design in which practice patterns varied, screen failures and adverse event rates are unrecorded, and event-monitoring and data collection was not pre-specified - a limitation of nearly all studies that report patient outcomes following salvage RT. There are inherent perils using historical controls to which a more recently treated group is compared, because year of treatment may have prognostic significance of its own (24). However, an association of RT dose with BcF was retained with inclusion of RT year as a covariate in our multivariable regression. We also cannot know whether these findings apply to patients not included in our study; for example, those with higher PSA levels. There are finite resources available to perform studies such as ours in the context of a prospective clinical trial, leaving our study design as the most feasible option to evaluate salvage RT dose-response at the present time. In addition to the SAKK 09/10 trial (NCT01272050) (10), RTOG trial *** (NCT***) allows physician selection of a salvage RT dose within the range of 64.8-Gy to 70.2-Gy. Secondary exploratory analysis from this trial may someday add evidence also to further guide optimal dose selection.

Conclusion

Dose escalation to levels greater than 66-Gy are associated with a reduced likelihood of BcF after salvage RT in patients with post-RP detectable PSA levels. Dose selection may be viewed in the broader context of patient-, tumor-, and other treatment-related factors, but the selection of such doses whenever feasible is supported by evidence presented in this research.

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Figure Captions

Fig 1. Identification of study cohort. RT: radiotherapy; PSA: prostate-specific antigen; AS: androgen suppression; Gy: gray.

Fig 2. Cumulative incidence of (freedom from) biochemical failure (A) and of distant metastasis (B) according to salvage radiotherapy dose groups.

Tables

Table 1. Characteristics of Study Cohort*

	Overall	<66.0 Gy	66.0 – 69.9 Gy	≥70 Gy	*p*-Value
Study sample, no.	1108 (100)	547 (49)	349 (31)	212 (19)	-
Age at RP, median (IQR)	61 years (55-66)	61 (56-66)	60 (54-65)	61 (56-66)	0.08
Age at RT, median (IQR)	63 years (58-68)	64 (58-69)	62 (57-68)	64 (59-68)	0.36
Follow-up duration, months					<0.0001
Median (IQR)	65 (34-110)	77 (40-126)	42 (19-80)	69 (39-108)	
RP Gleason score, no.					0.01
2-6	282 (25)	161 (29)	83 (24)	38 (18)	
7	659 (59)	302 (55)	218 (62)	139 (66)	
8-10	167 (15)	84 (15)	48 (14)	35 (17)	
Extraprostatic extension, no.†					0.21
Absent	468 (42)	242 (44)	148 (42)	78 (37)	
Present	639 (58)	305 (56)	200 (58)	134 (63)	
Seminal vesical invasion, no.					0.09
Absent	920 (83)	441 (81)	300 (86)	179 (84)	
Present	188 (17)	106 (19)	49 (14)	33 (16)	
Pre-RT PSA, ng/mL					0.008
Median (IQR)	0.48 (0.27-0.80)	0.40 (0.24-0.72)	0.40 (0.21-0.70)	0.40 (0.20-0.62)	
≤0.20	273 (25)	118 (22)	86 (25)	69 (33)	
0.21-0.50	420 (38)	217 (40)	124 (36)	79 (37)	
0.51-1.0	243 (22)	128 (23)	86 (25)	29 (14)	
>1.0-2.0	172 (16)	84 (15)	53 (15)	35 (17)	
RT Dose, Gy					
Median (IQR)	66.0 (64.8-69.0)	64.8 (62.0-64.8)	66.0 (66.0-68.0)	70.0 (70.0-71.0)	-
RT target, no.†					0.01
Prostate bed	948 (86)	452 (83)	314 (90)	182 (86)	
Prostate bed + nodes	159 (14)	95 (17)	35 (10)	29 (14)	
RT year, no.					<0.0001
1985-1994	128 (12)	119 (22)	7 (2)	2 (1)	
1995-1999	223 (20)	162 (30)	58 (17)	3 (1)	
2000-2004	286 (26)	156 (29)	106 (30)	24 (11)	
2005-2013	471 (43)	110 (20)	178 (51)	183 (86)	

* Parenthetical values are percentages, unless otherwise noted. † One patient unknown.
Gy: gray; RP: radical prostatectomy; IQR: interquartile range. RT: radiotherapy; PSA: prostate-specific antigen.

Table 2. Univariate and Multivariate Associations with Biochemical Failure.*

				Univariate		Multivariate	
	No. at Risk	5-yr, %	10-yr, %	Hazard ratio (95% CI)	*p*-Value	Hazard ratio (95% CI)	*p*-Value
RP Gleason score							
2-6	140	21.8	37.6	RL	-	RL	-
7	211	37.7	51.1	1.61 (1.25-2.07)	0.0002	1.84 (1.43-2.38)	<0.0001
8-10	37	57.1	67.9	2.96 (2.17-4.05)	<0.0001	2.93 (2.10-4.08)	<0.0001
Extraprostatic extension			-				
Absent	181	28.6	42.2	RL	-	RL	-
Present	207	42.1	55.4	1.62 (1.32-1.99)	<0.0001	1.24 (0.99-1.56)	0.06
Seminal vesical invasion			-				
Absent	333	55.4	47.0	RL	-	RL	-
Present	55	32.3	64.9	1.98 (1.57-2.51)	<0.0001	1.52 (1.16-1.99)	0.003
Pre-RT PSA, ng/mL			-				
Continuous	-	-	-	2.19 (1.79-2.67)	<0.0001	-	-
≤0.20	90	26.6	35.1	RL	-	RL	-
0.21-0.50	159	32.7	47.2	1.36 (1.01-1.84)	0.04	1.52 (1.13-2.05)	0.006
0.51-1.0	93	37.8	56.7	1.77 (1.29-2.41)	0.0003	2.01 (1.45-2.78)	<0.0001
>1.0-2.0	46	57.0	66.6	2.82 (2.06-3.87)	<0.0001	3.60 (2.52-5.14)	<0.0001
RT Dose			-				
<66.0 Gy	212	40.6	56.9	RL	-	RL	-
66.0-69.9 Gy	84	34.3	42.3	0.76 (0.60-0.97)	0.02	0.76 (0.60-0.97)	0.03
≥70.0 Gy	92	28.5	38.6	0.68 (0.51-0.90)	0.007	0.70 (0.53-0.94)	0.02
RT year							
Continuous	-	-	-	0.98 (0.96-0.99)	0.007	1.01 (0.99-1.04)	0.22

CI: confidence interval; RP: radical prostatectomy; RL: referent level; RT: radiotherapy; PSA: prostate-specific antigen; Gy: gray.
* Cumulative incidence of post-RT PSA >0.2 ng/mL + confirmatory value or single value >0.4 ng/mL.

Table 3. Univariate and Multivariate Associations with Distant Metastasis.*

			Univariate		Multivariate	
	No. at Risk	10-yr, %	Hazard ratio (95% CI)	*p*-Value	Hazard ratio (95% CI)	*p*-Value
RP Gleason score						
2-6	75	4.4	RL	-	RL	-
7	109	11.2	2.22 (1.17-4.21)	0.02	2.43 (1.26-4.69)	0.008
8-10	25	30.9	6.91 (3.55-13.44)	<0.0001	6.37 (3.20-12.70)	<0.0001
Extraprostatic extension						
Absent	79	6.2	RL	-	RL	-
Present	130	16.6	2.94 (1.76-4.93)	<0.0001	1.86 (1.06-3.26)	0.03
Seminal vesical invasion		-				
Absent	170	9.2	RL	-	RL	-
Present	39	25.9	3.00 (1.95-4.61)	<0.0001	1.72 (1.05-2.82)	0.03
Pre-RT PSA, ng/mL						
Continuous	-	-	2.02 (1.35-3.03	0.0006	-	-
≤0.20	43	7.2	RL	-	RL	-
0.21-0.50	66	10.6	1.23 (0.64-2.39)	0.53	1.58 (0.81-3.07)	0.18
0.51-1.0	60	14.2	1.66 (0.86-3.22)	0.13	1.86 (0.96-3.63)	0.07
>1.0-2.0	40	19.0	2.46 (1.26-4.80)	0.008	3.36 (1.73-6.53)	0.0004
RT Dose†						
<66.0 Gy	144	12.0	RL	-	-	-
66.0-69.9 Gy	25	11.8	0.76 (0.44-1.31)	0.32	-	-
≥70.0 Gy	40	14.4	0.89 (0.53-1.51)	0.68	-	-
RT year						
Continuous	-	-	0.95 (0.91-0.99)	0.02	0.98 (0.93-1.02)	0.25

CI: confidence interval; RP: radical prostatectomy; RL: referent level; RT: radiotherapy; PSA: prostate-specific antigen; Gy: gray.
* Cumulative incidence. † Excluded from multivariate regression due to lack of association in the univariate model.

Figures

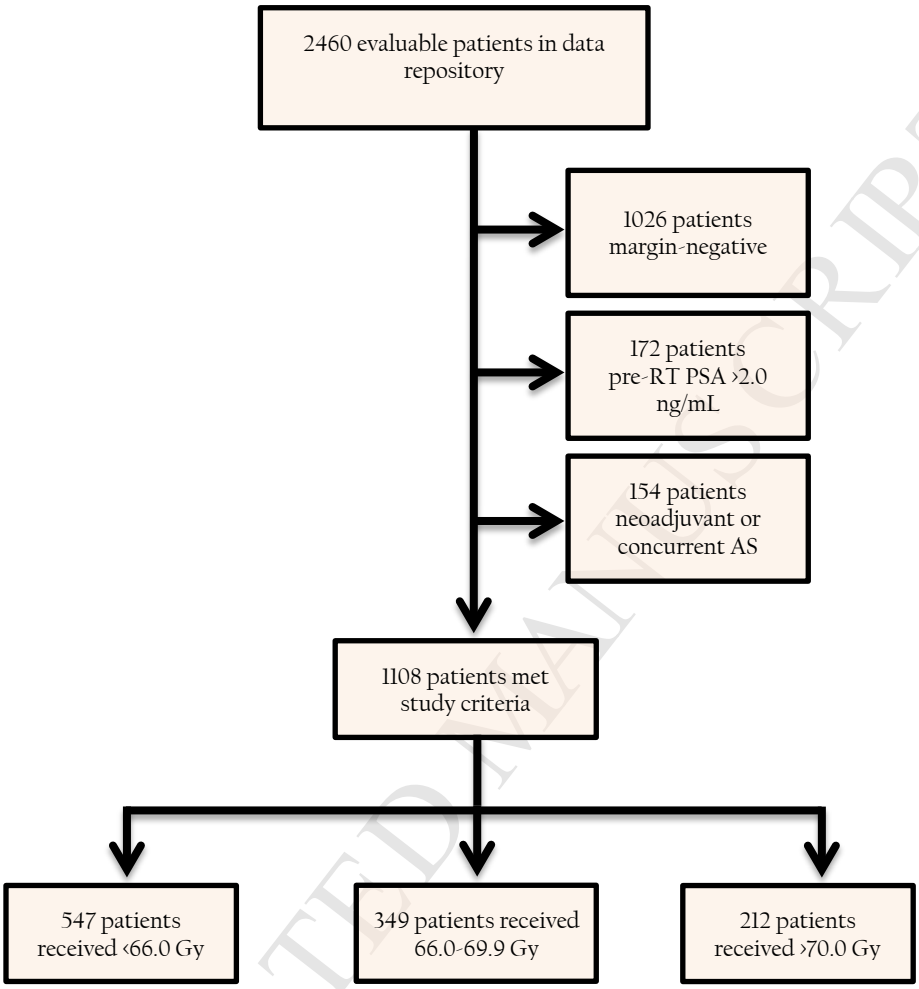
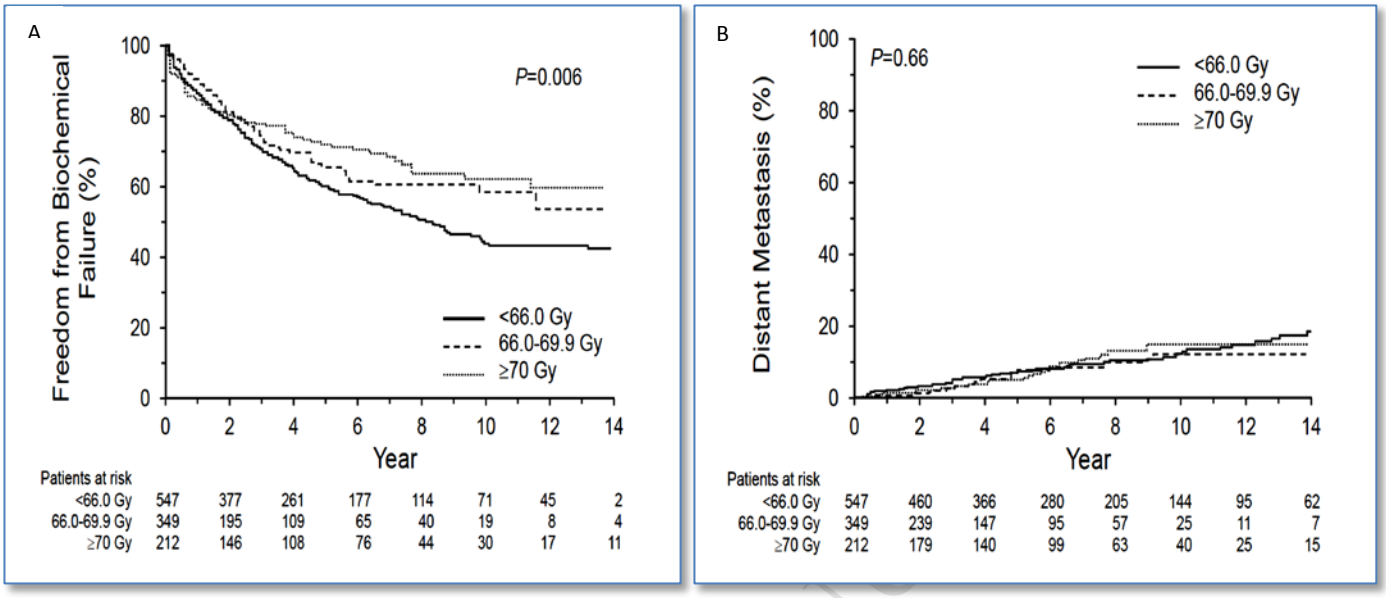


Fig 1. Identification of study cohort. RT: radiotherapy; PSA: prostate-specific antigen; AS: androgen suppression; Gy: gray.



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