Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2010 July 15; 77(4): 1066–1071. doi:10.1016/j.ijrobp.2009.06.013.

A NEW METHOD FOR SYNTHESIZING RADIATION DOSE RESPONSE DATA FROM MULTIPLE TRIALS APPLIED TO PROSTATE CANCER

Patricia Diez, MSc*, Ivan S. Vogelius, PhD^{†,††}, and Søren M. Bentzen, PhD, DSc^{††}

*Clinical Physics Department, Mount Vernon Centre for Cancer Treatment, Northwood, Middlesex, UK

[†]Department of Oncology, Vejle Sygehus, Vejle, Denmark

^{††}Department of Human Oncology, University of Wisconsin School of Medicine and Public Health, Madison, WI 53792, USA

Abstract

Purpose—A new method is presented for synthesizing dose-response data for biochemical control of prostate cancer according to study design (randomized vs. non-randomized) and risk group (low vs. intermediate-high)

Methods and materials—Nine published prostate cancer dose escalation studies including 6539 patients were identified in the MEDLINE and CINAHL databases and reviewed to assess the relationship between dose and biochemical control. A novel method of analysis is presented in which the normalized dose-response gradient, γ_{50} , is estimated for each study and subsequently synthesized across studies. Our method does not assume that biochemical control rates are directly comparable between studies.

Results—Non-randomized studies produced a statistically significantly higher γ_{50} than randomized studies for intermediate-high risk patients ($\gamma_{50}=1.63$ vs $\gamma_{50}=0.93$, $p=0.03$) and a borderline significantly higher ($\gamma_{50}=1.78$ vs $\gamma_{50}=0.56$, $p=0.08$) for low risk patients. No statistically significant difference in γ_{50} was found between low and intermediate-high risk patients ($p=0.31$). From the pooled data of low and intermediate-high risk patients in randomized trials, we obtain the overall best estimate of $\gamma_{50}=0.84$ with 95% confidence interval 0.54–1.15.

Conclusions—Non-randomized studies over-estimate the steepness of the dose-response curve as compared to randomized trials. This is probably the result of stage migration, improved treatment techniques and a shorter follow-up in higher-dose patients that were typically entered more recently. This over-estimation leads to inflated expectations regarding the benefit from dose-escalation and could lead to under-powered clinical trials. There is no evidence of a steeper dose-response for intermediate-high risk compared to low risk patients.

© 2009 Elsevier Inc. All rights reserved.

Corresponding Author: Søren M. Bentzen, D.Sc., Department of Human Oncology, University of Wisconsin Comprehensive Cancer Center, K4/316 Clinical Science Center, 600 Highland Avenue, Madison, WI 53792, USA, Tel: 608-265-8572, Fax: 608-263-9947, bentzen@humonc.wisc.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflict of interest: none

Keywords

Prostate cancer; dose response; radiotherapy; systematic review

INTRODUCTION

Recent advances in radiation delivery techniques, such as conformal (1) and intensity modulated radiotherapy (IMRT), proton therapy and image guided therapy (2,3), have allowed delivery of external beam radiotherapy doses exceeding 80 Gy in prostate cancer therapy with acceptable toxicity. A key quantity in rational consideration of the clinical gain from target dose escalation - and thereby the cost-effectiveness of advanced radiation therapy technologies - is the steepness of the radiation dose-control curve. Several studies, many of them non-randomized, have shown a benefit from dose escalation in this disease. Some authors have simply plotted outcome data from multiple studies on the same graph to obtain a dose response curve from the available data (4). As the analyzed studies are performed over a period of more than a decade of rapid technological and medical development, it is questionable whether this procedure is valid. On one hand, study-to-study variability in patient selection and treatment details will introduce variability in study outcomes which in turn will lead to more shallow dose response relationships. On the other hand, the fact that higher doses have been introduced more recently, could bias the outcome of these due to stage migration, improved therapy and shorter follow-up, which could create an artificially steep dose-response relationship. This has led us to propose an alternative analytical strategy presented here. A convenient measure of the steepness of the dose-response curve is the normalized dose-response gradient (5,6), the γ_{50} , and the method pools these intra-study steepness estimates across studies using a mathematical method similar to a meta-analysis. This paper presents a review of 9 published studies and a pooled analysis of γ_{50} in order to gain understanding of the shape of the underlying dose response curve for low and intermediate-high risk patients. Additionally, we perform a comparative analysis between randomized and non-randomized studies inspired by previous concerns that the latter may be upward biased.

METHODS AND MATERIALS

Study Identification

A MEDLINE and CINAHL search was conducted to identify published studies correlating radiation dose with biochemical control in the treatment of localized prostate cancer from 1966 to May 2008. Keywords used were: "prostate", "radiotherapy", "biochemical control" and "dose". A study was eligible if it: (1) was published in a peer-reviewed journal; (2) specified the radiotherapy technique and total radiation dose prescribed to the target volume; (3) presented long-term biochemical control rates for two or more different radiation dose levels. Studies involving brachytherapy were excluded due to concerns over possible geographical misses as opposed to dose-limited failures and uncertainties in radiobiological parameters adjusting for dose-fractionation and dose-rate effects. Similarly, two hypofractionation studies (7,8) were excluded to eliminate the effect of uncertainty in the α/β ratio for prostate cancer. If a study was published more than once, the most recently published data were used unless the required data could only be extracted from earlier publications. Studies with less than 200 patients were excluded from the analysis.

The exclusion of hypofractionation and brachytherapy studies obviously results in a smaller total cohort of patients reducing the statistical power of the analysis. This is, however, preferable compared to the possible systematic error that would be introduced by imprecise

parameter estimates when correcting for fraction size, repair effects and inhomogeneous dose distributions.

Data extracted from each study included number of patients treated, risk groups, length of follow-up, type and technique of radiation delivery, dose prescription, and biochemical control (biochemical no evidence of disease, bNED) data.

Statistical Analysis

The idea of the present data analytical strategy is to estimate the value of γ_{50} for each study and then calculate a “best” overall γ_{50} value from the mean of these estimates weighted by their inverse variance. This way the steepness of the dose-response curve for a particular study is based on within-study comparison of outcome only, ideally a comparison between groups of patients randomly assigned to one of two dose levels. Thus, we can replace the commonly applied, strong assumption of homogeneity in response among studies with the much weaker assumption that the steepness of the underlying dose response function does not vary among studies. The analysis was performed separately for low risk patients and intermediate-high-risk patients.

A logistic dose response function, $P_{\text{Survival}} = \frac{\exp(u)}{1 + \exp(u)}$, is assumed, where $u = a_0 + bD$ for

constant fraction size. Since $\gamma_{50} = D_{50} \left. \frac{dP_{\text{Survival}}}{dD} \right|_{D_{50}}$, where D_{50} is the dose required to produce 50% biochemical control at a given follow-up time, we can derive γ_{50} from published tumour control probabilities p_1 and p_2 at two different dose levels, D_1 and D_2 (6).

$$\gamma_{50} = \frac{1}{4} \cdot \frac{1}{1 - \frac{D_1}{D_2}} \cdot \left[\frac{D_1}{D_2} \cdot \ln \frac{p_2}{1 - p_2} - \ln \frac{p_1}{1 - p_1} \right] \quad \text{Equation 1}$$

The standard error of the γ_{50} estimate, $s_{\gamma_{50}}$, may be calculated using one of three methods presented in the Appendix, depending on the published data available for each study. If biochemical control rates for more than two dose levels are reported, γ_{50} and its standard error are estimated from a logistic fit.

With values of γ_{50} and $s_{\gamma_{50}}$ established, a pooled analysis was performed by entering the data in the RevMan software (9) for statistical analysis and estimation of a pooled mean weighted by inverse variance.

RESULTS

Four randomized studies comprising a total of 2201 patients were identified (10-13) along with five non-randomized studies including a total of 4338 patients (14-18). Table 1 lists the included studies together with information on doses applied, follow up, the method of analysis we used to derive γ_{50} and $s_{\gamma_{50}}$ (HR, KM, KM point or regression), definition of biochemical control, and published control rates. One study (19) was excluded from our analysis because the patient cohort overlapped with a more than three times larger study (17).

Unfortunately, risk-group definitions vary between the studies; they do, however, generally involve initial PSA level, usually in combination with criteria on Gleason score and tumour stage. Some studies use low (PSA<10), intermediate (PSA 10–20), and high (PSA>20) risk as stratification whereas others combine the latter two into one intermediate-high risk group.

We have chosen to follow the two-risk-group stratification in order to avoid excluding the two-stratum studies. If three risk groups are used in the original publications, γ -estimates from the intermediate and high risk data are combined using inverse variance weighting.

The study by Kuban et al (11) is one such case, where the intermediate risk group and the high risk group from the original study should be combined to the intermediate-high risk group used in this analysis. Unfortunately, the two observed control levels of the intermediate risk group are very close and the logistic dose model fails to give a biologically reasonable sigmoid curve, estimating negative values of both γ_{50} and D_{50} . This is a result of our approach forcing the model to fit two data points precisely when the data are inherently noisy. The questionable fit of the sigmoid curve results in an unreasonably low estimate of the variance of γ_{50} for the intermediate risk group. As a result the intermediate risk group would dominate the estimate of γ_{50} from the intermediate-high risk group of the Kuban study after weighting by inverse variance, and the Kuban study would dominate the overall estimate of γ_{50} for the intermediate-high risk group derived in this study. We have therefore chosen to disregard the intermediate risk dataset from Kuban's study. The intermediate-high risk group estimate from the Kuban study used in the remainder of this paper is therefore based on data from the high risk group only. This is an upper limit γ_{50} for the intermediate-high risk group since we disregarded the low estimate of γ_{50} from the intermediate risk group.

The results of the pooled analysis are given in figure 1 and 2 for the low risk group and the intermediate-high risk groups respectively. We note a borderline significant difference in γ_{50} between the randomized and non-randomized studies for low risk patients ($p=0.08$) and a significant difference for intermediate to high-risk patients ($p=0.03$).

A pooled analysis by risk group with randomized studies (Figure 3) shows no evidence of a significant difference between γ_{50} estimates for low risk patients and intermediate-high risk patients ($p=0.31$). Since there is a significant difference between randomized and non-randomized studies, but no evidence of difference between risk groups, the best overall estimate of γ_{50} is obtained by pooling the risk groups of the randomized studies as in Figure 3. Overall, we estimate that the γ_{50} of the radiation dose response curve for prostate cancer is 0.84 with 95% confidence interval 0.54–1.15.

DISCUSSION

Non-randomized studies overestimate the steepness of the dose response curve when patients are stratified by risk group. This is probably because the non-randomized studies are susceptible to bias due to a gradual improvement of multiple aspects of diagnosis and patient care as well as different length of follow-up in the dose groups. All of these factors tend to produce an apparent improvement in outcome which may be erroneously attributed in the data analysis to the higher doses being used in more recent cohorts. The length of follow up has previously been shown to be critical when using the ASTRO definition of biochemical failure (20). The non-randomized study by Kupelian et al (15) included only patients treated in 1995 and 1996 to reduce this problem. Some support for this approach - and the bias issues discussed here - comes from the fact that Kupelian's γ_{50} -estimate for the low and intermediate-high risk groups is lower than those derived from the other non-randomized studies. This also means the tests for differences between γ -estimates from randomized studies and non-randomized studies become more significant if the study by Kupelian is excluded ($p=0.007$ and $p=0.003$ for low and intermediate-high risk patients, respectively).

The over-estimation of γ_{50} from the non-randomized studies relative to the randomized trials may lead to overly optimistic expectations from, say, a 10% dose-escalation(21). Assume

that the 5-year bNED is 80% after a dose of 70 Gy in 35 fractions. We want to design a randomized controlled trial with standard design parameters, significance level $\alpha=0.05$ and statistical power, $1-\beta=0.9$. If we assume $\gamma_{50}=1.63$, the estimate from the non-randomized studies, a target sample size of 548 patients will be required. If $\gamma_{50}=0.93$, the best estimate from the randomized trials, this same trial would need to accrue 1,208 patients. This has implications not only for simple dose escalation studies but also studies of, say, hypofractionated radiotherapy(22) .

Another consequence of the randomized trials being conducted more recently is that two of the four studies (10,11) apply the newer Phoenix (or very similar) definition of biochemical failure (23), whereas all of the non-randomized studies use the 1996 ASTRO definition (24). Cheung et al studied the effect of changing the biochemical failure criteria on γ_{50} and concluded that γ_{50} varies with time for both a threshold definition and the ASTRO definition, but did not see a significant difference between the two measures after five years (19). Also, our results do not indicate that the randomized studies with the Phoenix definition give lower γ_{50} than the other two randomized studies. Thus, the difference in biochemical control definition is unlikely to explain the higher estimates of γ_{50} for non-randomized studies.

It has been argued that the dose-response curve of intermediate-high-risk prostate patients may be intrinsically higher than for low risk patients mainly based on the impression that more studies show differences between dose levels or treatment arms for this group of patients. We tested the null hypothesis that the γ_{50} is independent of risk subgroup for the entire cohort of patients. The result is presented in Figure 3. Our analysis does not support the hypothesis that the dose response curve is steeper in higher risk populations. However, the *local* steepness of the curve at a high tumor control probability will be lower (6). As a result, studies involving intermediate-high-risk patients have a higher power than studies involving the same number of low risk patients.

CONCLUSIONS

Estimates of the steepness of the dose response curve for biochemical control of prostate cancer differ between randomized controlled trials and non-randomized studies when risk group stratification is used. This provides yet another illustration of the role of randomization as a safeguard against systematic bias, even in studies where careful dosimetry and case stratification is performed. The literature data reviewed here provides no support for the hypothesized lack of a dose-response relationship for low risk disease. Our data indicate that, irrespective of risk group, the radiation dose response relationship for biochemical control in prostate cancer is fairly shallow, with a $\gamma_{50}=0.84$ (95% CI: 0.54–1.15). In patient strata with higher control rates, the local value of γ will be lower.

Appendix: Estimation of the standard error of the γ_{50} estimate

Case I: Estimation from the hazard ratio and its confidence interval or reported p-value

If the hazard ratio is available with a confidence interval, the tumour control probability after a dose D_2 is estimated from $\hat{p}_2 = p_1^\theta$, where θ is the hazard ratio and the notation $\hat{p}_2$ is used to distinguish this estimate from the observed Kaplan-Meier [KM] value p_2 . The standard error of θ , s_θ , is estimated as the range of the 95% confidence interval divided by four. It is then possible to derive the relation between s_θ and the desired standard error of γ_{50} , $s_{\gamma_{50}}$, by propagation of error:

$$S_{\gamma_{50}} = \frac{1}{4} \cdot \frac{1}{\frac{D_2}{D_1} - 1} \cdot \frac{-\ln(p_1)}{(1 - \widehat{p}_2)} \cdot S_{\theta}$$

Equation 2

If a 2-tailed p-value is given with the hazard ratio, but no confidence interval is available, we first find a value of the z parameter of the normal distribution, z_0 , corresponding to the

published p-value. It can then be seen that $S_{\theta} = \frac{\theta \ln \theta}{z_0}$ by noting that $\ln(\theta)$ is normally distributed under the null hypothesis.

Case II: Estimation from Kaplan-Meier estimates of p_1 and p_2

If the hazard ratio and confidence interval could not be extracted from the published data as described above, the KM survival curves was used to estimate $s_{\gamma_{50}}$ as follows:

The hazard ratio at a given time was found as $\theta(t) = \frac{\ln(p_2(t))}{\ln(p_1(t))}$. The hazard ratio should be constant in the proportional hazards model, but this is never fulfilled perfectly. We derived θ for a series of time points ranging from one year to the end of reporting, usually five years, and the values of θ were then averaged. The standard error of the estimate of θ can be

approximated by using $S_{\theta} = \frac{\theta \ln \theta}{z_0}$ as previously, but with the p-value from a test of differences between the survival curves. Given s_{θ} , the standard error of γ_{50} can be found from Equation 2.

The derived $s_{\gamma_{50}}$ is an approximation, but the estimate ensures that more of the available observations are used and hence avoids the inherent underweighting of data from studies where only a point estimate from survival curves can be derived.

In one study (15), the KM survival curves of two patient subgroups did not include p-values from a test of differences between survival curves. In these cases we used an estimate of the standard error of the KM survival probability and propagation of error to derive the following expression for the standard error of the normalized slope

$$S_{p_i} = KM_i(t) \cdot \sqrt{\frac{1 - KM_i(t)}{N_i(t)}} \Rightarrow S_{\gamma_{50}} = \frac{1}{4} \cdot \frac{1}{1 - \frac{D_1}{D_2}} \cdot \sqrt{\left(\frac{D_1}{D_2}\right)^2 \cdot \frac{1}{N_2 \cdot p_2 \cdot (1 - p_2)} + \frac{1}{N_1 \cdot p_1 \cdot (1 - p_1)}}$$

Equation 3

where N_i is the number of patients at risk in arm i at time of evaluation.

Case III: Estimation from logistic regression of three dose-response levels

In one case (17), three levels of dose-response were reported. In this case we used a generalized linear regression algorithm to derive the dose response curve from the dose and response levels weighted by their inverse variance.

In general, the estimation by hazard ratio and its confidence interval is preferred since the method uses the entire dataset in the study and allows multivariate statistical analysis if used by the authors. The KM methods and the logistic regression on three dose levels are univariate and use only parts of the dataset as read from figures in the published data.

REFERENCES

1. Cahlon O, Hunt M, Zelefsky MJ. Intensity-modulated radiation therapy: supportive data for prostate cancer. *Semin Radiat Oncol.* 2008; 18:48–57. [PubMed: 18082588]
2. Ghilezan M, Yan D, Liang J, et al. Online image-guided intensity-modulated radiotherapy for prostate cancer: How much improvement can we expect? A theoretical assessment of clinical benefits and potential dose escalation by improving precision and accuracy of radiation delivery. *Int J Radiat Oncol Biol Phys.* 2004; 60:1602–1610. [PubMed: 15590192]
3. Kupelian PA, Langen KM, Willoughby TR, et al. Image-guided radiotherapy for localized prostate cancer: treating a moving target. *Semin Radiat Oncol.* 2008; 18:58–66. [PubMed: 18082589]
4. Fowler JF, Ritter MA, Chappell RJ, et al. What hypofractionated protocols should be tested for prostate cancer? *Int J Radiat Oncol Biol Phys.* 2003; 56:1093–1104. [PubMed: 12829147]
5. Brahme A. Dosimetric precision requirements in radiation therapy. *Acta Radiol Oncol.* 1984; 23:379–391. [PubMed: 6095609]
6. Bentzen SM, Tucker SL. Quantifying the position and steepness of radiation dose-response curves. *Int J Radiat Biol.* 1997; 71:531–542. [PubMed: 9191898]
7. Lukka H, Hayter C, Julian JA, et al. Randomized trial comparing two fractionation schedules for patients with localized prostate cancer. *J Clin Oncol.* 2005; 23:6132–6138. [PubMed: 16135479]
8. Valdagni R, Italia C, Montanaro P, et al. Is the alpha-beta ratio of prostate cancer really low? A prospective, non-randomized trial comparing standard and hyperfractionated conformal radiation therapy. *Radiother Oncol.* 2005; 75:74–82. [PubMed: 15878104]
9. Review Manager (RevMan). 5.0 ed.. The Nordic Cochrane Centre, The Cochrane Collaboration; Copenhagen: 2008.
10. Dearnaley DP, Sydes MR, Graham JD, et al. Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. *Lancet Oncol.* 2007; 8:475–487. [PubMed: 17482880]
11. Kuban DA, Tucker SL, Dong L, et al. Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer. *Int J Radiat Oncol Biol Phys.* 2008; 70:67–74. [PubMed: 17765406]
12. Peeters ST, Heemsbergen WD, Koper PC, et al. Dose-response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. *J Clin Oncol.* 2006; 24:1990–1996. [PubMed: 16648499]
13. Zietman AL, DeSilvio ML, Slater JD, et al. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. *JAMA.* 2005; 294:1233–1239. [PubMed: 16160131]
14. Hanks GE, Hanlon AL, Pinover WH, et al. Dose selection for prostate cancer patients based on dose comparison and dose response studies. *Int J Radiat Oncol Biol Phys.* 2000; 46:823–832. [PubMed: 10705002]
15. Kupelian P, Kuban D, Thames H, et al. Improved biochemical relapse-free survival with increased external radiation doses in patients with localized prostate cancer: the combined experience of nine institutions in patients treated in 1994 and 1995. *Int J Radiat Oncol Biol Phys.* 2005; 61:415–419. [PubMed: 15667961]
16. Lyons JA, Kupelian PA, Mohan DS, et al. Importance of high radiation doses (72 Gy or greater) in the treatment of stage T1-T3 adenocarcinoma of the prostate. *Urology.* 2000; 55:85–90. [PubMed: 10654900]
17. Pollack A, Smith LG, von Eschenbach AC. External beam radiotherapy dose response characteristics of 1127 men with prostate cancer treated in the PSA era. *Int J Radiat Oncol Biol Phys.* 2000; 48:507–512. [PubMed: 10974469]
18. Zelefsky MJ, Leibel SA, Gaudin PB, et al. Dose escalation with three-dimensional conformal radiation therapy affects the outcome in prostate cancer. *Int J Radiat Oncol Biol Phys.* 1998; 41:491–500. [PubMed: 9635694]
19. Cheung R, Tucker SL, Lee AL, et al. Assessing the impact of an alternative biochemical failure definition on radiation dose response for high-risk prostate cancer treated with external beam radiotherapy. *Int J Radiat Oncol Biol Phys.* 2005; 61:14–19. [PubMed: 15629589]

20. Vicini FA, Kestin LL, Martinez AA. The importance of adequate follow-up in defining treatment success after external beam irradiation for prostate cancer. *Int J Radiat Oncol Biol Phys.* 1999; 45:553–561. [PubMed: 10524405]
21. Bentzen SM. Radiobiological considerations in the design of clinical trials. *Radiother Oncol.* 1994; 32:1–11. [PubMed: 7938673]
22. Bentzen SM, Ritter MA. The alpha/beta ratio for prostate cancer: what is it, really? *Radiother Oncol.* 2005; 76:1–3. [PubMed: 15990189]
23. Roach M 3rd, Hanks G, Thames H Jr. et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *Int J Radiat Oncol Biol Phys.* 2006; 65:965–974. [PubMed: 16798415]
24. American Society for Therapeutic Radiology and Oncology Consensus Panel. Consensus statement: guidelines for PSA following radiation therapy. *Int J Radiat Oncol Biol Phys.* 1997; 37:1035–1041. [PubMed: 9169810]

Figure 1.

Pooled analysis of studies reporting the steepness of the dose response curve for low risk patients. Non-randomized and randomized studies are analyzed separately using inverse variance weighting. Horizontal lines in the forest plot indicate the range of the 95% CI of individual studies, while the left and right corner of the diamond shapes depict the 95% CI of the combined estimate.

Figure 2. Pooled analysis of studies reporting the steepness of the dose response curve for intermediate to high risk patients. Non-randomized and randomized studies are analyzed separately and a significant difference between the pooled estimates is seen ($p=0.03$). The meaning of the symbols is explained in Figure 1

Figure 3.

Pooled analysis of the steepness of the radiation dose response curve in randomized trials compared between the low risk group and the intermediate-high risk group. No evidence of difference is seen ($p=0.31$).

Table 1

Summary of the data extracted from 9 included studies

STUDY	Randomized	No of patients	Dose (Gy)			Follow-up Median (y)	Failure rate reported (y)	Method of analysis *	bNED (%)				bNED definition [†]
			Low (median)	Int (median)	High (median)				Risk group	Low dose	Int dose	High dose	
Zelevsky 1998	–	530	70.2		75.6	3	5	KM	Low	84		95	ASTRO
								KM	Int	55		79	
								KM	High	19		53	
Hanks 2000 ^{††}	–	618	70 (<10f)		73 (<10f)	4.4	5	KM	<10 f	77		89	ASTRO
			<10 unf						70	92			
			73 (rest)		10–19.9 f				72	86			
					10–19.9				51	82			
					>=20 f				23	63			
					>=20 unf				29	26			
Pollack 2000	–	1127	66	70	78	4.3	4	KM	Low	73	85	84	ASTRO
								Int-high	31	51	68		
Lyons 2000	–	738	68.4		74	3.4	5	HR	Low	81		98	ASTRO
								KM	Int-high	41		75	
Zietman 2005	+	393	70.2		79.2	5	5	KM	Low	60		81	ASTRO
									Int-high	63		80	
Kupelian 2005	–	1325	68.4		75.6	5.8	5	KM point	Low	75		79	ASTRO
								KM	Int	63		72	
								KM point	High	38		46	
Peeters 2006	+	664	68	78	4.2	5	5	HR	Low	88		84	ASTRO
									Int	64		79	
									High	48		66	
Dearnaley 2007	+	843	64	74	5	5	5	HR	Low	79		85	PSA >2 And PSA >nadir + 50%
									Int	70		79	
									High	43		57	
Kuban 2008	+	301	70		78	8.7	8	KM	Low	63		88	Phoenix

STUDY	Randomized	No of patients	Dose (Gy)			Follow-up Median (y)	Failure rate reported (y)	Method of analysis*	bNED (%)				bNED definition [†]
			Low (median)	Int (median)	High (median)				Risk group	Low dose	Int dose	High dose	
									Int	76		86	
									High	26		63	

* The method of analysis is used to derive s_{y50} as detailed in the text.

[†] Biological No-Evidence of Disease definition used

^{††} Hanks divide in six risk subgroups according to PSA level and f (favourable) and u (unfavourable) parameters. We combine in two groups by inverse variance with groups defined by PSA only in this study.