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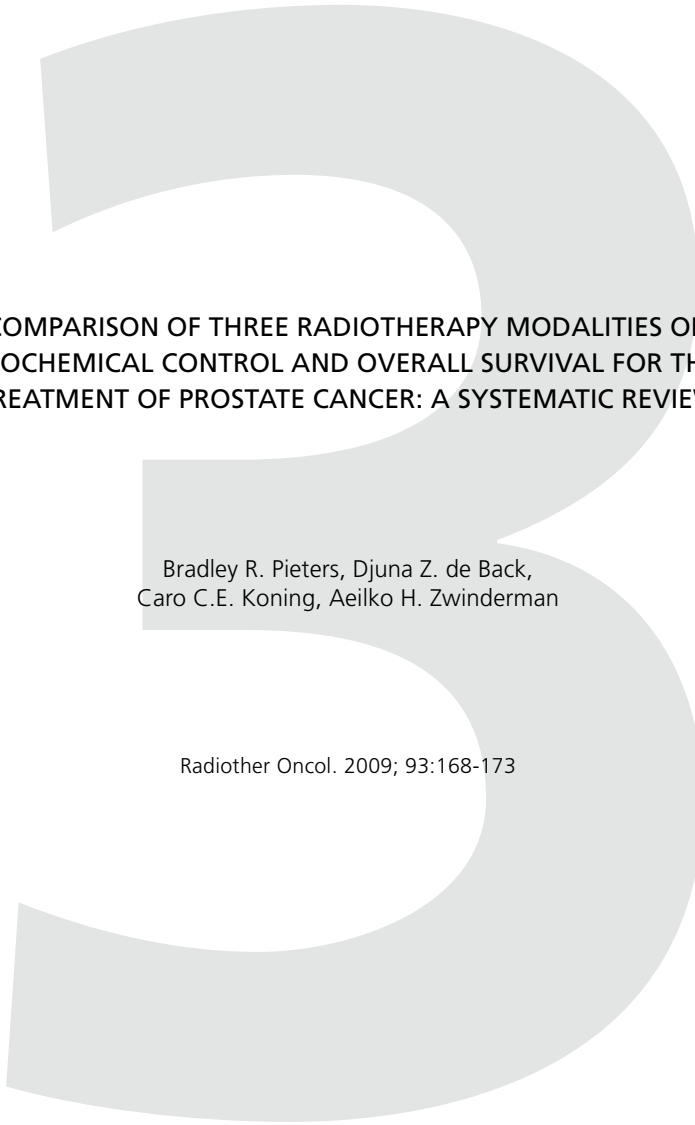
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**COMPARISON OF THREE RADIOTHERAPY MODALITIES ON
BIOCHEMICAL CONTROL AND OVERALL SURVIVAL FOR THE
TREATMENT OF PROSTATE CANCER: A SYSTEMATIC REVIEW**

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ABSTRACT

Background and Purpose. For the radiation treatment of prostate cancer high dose should be delivered for optimal biochemical control. Treatment can be given by dose-escalated external beam radiotherapy (EBRT) or external beam radiotherapy combined with a radioactive seed implantation (EBSeeds) or high-dose rate (HDR) brachytherapy (EBTI). Differences in outcome between the modalities were assessed by a systematic review.

Materials and methods. A systematic search was performed resulting in 40 articles to be used. Data were extracted on biochemical control and overall survival at 3, 5, and 8 years and other time points mentioned in the articles. Also known prognostic parameters were noted. Comparison of the modalities was done by a Weibull survival analysis and estimation of Hazard Ratio's (HR) was done with 95% confidence intervals (95% CI).

Results. The HR for biochemical recurrence was 1.40 (95% CI 1.31 to 1.51) for EBRT relative to EBTI and was 1.37 (95% CI 1.26 to 1.49) for EBSeeds relative to EBTI.

The HR for overall survival was 1.50 (95% CI 1.29 to 1.73) for EBRT relative to EBTI, and was 2.33 (95% CI 2.04 to 2.66) for EBSeeds relative to EBTI, respectively.

Conclusion. The combination of external beam radiotherapy and HDR brachytherapy results in a superior biochemical control and overall survival found in a systematic review on radiotherapy for prostate cancer.

INTRODUCTION

It is obvious that for the treatment of intermediate to high-risk prostate cancer with radiotherapy high doses are needed for high tumor control. In randomized studies of low dose compared to high dose better biochemical control, expressed as prostate specific antigen (PSA)-control, was found in favor of the high-dose groups [1-3].

High dose to the prostate can also be achieved with brachytherapy. The dose can be delivered with low activity radioactive seed sources or by a temporary implant with a higher activity source. Monotherapy with radioactive seeds is preferably reserved for patients with low-risk disease, however some groups have also treated patients with intermediate risk disease. For patients with intermediate to high-risk disease seed brachytherapy can be combined with external beam (EBSeeds) aiming at higher tumor dose and better coverage of the target volume because of presumed extension of cancer cells beyond the prostate boundaries.

Other brachytherapy modality is with high-dose rate (HDR) performed by a temporary implant (EBTI). The largest experience up to now is combined with external beam radiotherapy [4-6]. The reported results are in good agreement with high biochemical control rates and are challenging for high-dose external beam radiotherapy.

Because of the similar results reported by high-dose external beam radiotherapy (EBRT) and external beam radiotherapy combined with a temporary implant, randomized studies were undertaken for the comparison of the two modalities [7, 8]. One study is already published as a full paper showing the preliminary results to be in favor of EBTI. A drawback of this study is that the biological dose in the EBRT-arm is lower than that in the EBTI-arm, hampering a fair comparison between the two modalities [8].

In this study a systematic review of observational studies was performed with the data of EBRT, EBSeeds, and EBTI cohorts for the treatment of prostate cancer. Analysis was restricted to data related to tumor control. The aim was to look for possible differences in outcome between treatment modalities commonly employed in the radiotherapy community.

MATERIALS AND METHODS

A systematic search was performed in the database of PubMed, Embase, Cochrane, and CancerLit from 1980 to December 2007. Terms used for the search were *prostatic neoplasms* in combination with *dose-response relationship*, *treatment outcome*, *survival analysis*, *survival rate*, *survival*, *disease-free survival*, *PSA-free survival*, *biochemical non-evidence of disease*, and combined with *computer-assisted radiotherapy*, *conformal radiotherapy*, *Intensity Modulated Radiotherapy*, *high dose*, *dose escalation*, *brachytherapy*, *high-dose rate*, *pulsed-dose rate*, *iridium*, *iodine*, and *palladium*. Also synonyms and derivatives of the terms were used to enlarge the number of articles to be found. Manual search was

performed on the articles mentioned in the reference list of articles not found in the automatic search. The following data were extracted from the articles: year of publication, year of entry of the first patient, year of entry of the last patient, number of patients, median follow-up time, mean or median age, percentage of patients with an initial PSA-value of ≤ 10 ng/ml, 10-20 ng/ml, > 20 ng/ml, percentage of patients with a Gleason score ≤ 6 and > 6 , percentage of patients with a clinical T1, T2, T3 and T4 stage, percentage of patients with hormonal therapy, the given dose, overall survival (OS) at 3, 5, and 8 years with standard errors, biochemical free survival (BFS) at 3, 5, and 8 years with standard errors, and definition of biochemical recurrence. If additional survival data at other time points were mentioned in the text, these values were also noted. Missing standard errors for survival time were estimated using the number of patients of the subcohort or the number of patients at risk.

Statistics

Comparison of the treatment groups (EBRT, EBSeeds, and EBTI) was done on BFS and OS. Differences between survival curves were assessed by the Weibull survival analysis. To account for differences in the number of patients in each study the fixed-effects model was applied. A stepwise multivariate regression analysis was performed on the $\ln(-\ln(\text{probability of survival}))$ as dependent variable. Covariates entered into the model were: type of treatment (EBRT vs. EBSeeds vs. EBTI), T-stage (T1-2 vs. T3-4), Gleason score (≤ 6 vs. > 6), PSA (≤ 10 vs. 10-20 vs. > 20), hormonal therapy (yes vs. no), year of publication, and median or mean age. Type of treatment was considered the main covariate and remained into the model. The other covariates were entered stepwise into the model and remained if the regression coefficient of treatment type changed with more than 10%. Interaction of treatment type with time was performed to investigate the assumption of proportionality. Associations with a P-value ≤ 0.05 (two-sided) were considered significant. The analysis was performed for both BFS and OS with the Statistical Package for the Social Sciences, version 16.0 for Mac OS X (SPSS, Chicago, IL, USA).

RESULTS

A total of 884 articles were found. Further selection of relevant articles was done by reading the title and abstract. After this selection 182 articles remained. Articles used for data extraction were only those articles in which data were given on overall survival or biochemical (PSA) free survival. When more than one article was found from the same investigation group only the most recent or the article with the most complete data was selected if it concerned the same cohort. Data from risk groups (combination of initial PSA-value, clinical T-stage, and Gleason score) were not used, but only data of the complete cohort as described in the articles were used. Data from multi-institutional studies were not used if the results were already reported by a single institute to avoid

Table 1. Summary of articles selected.

First author	Year of publication	Number of patients	External beam technique	Target organ external beam	Dose prescribed in BED ₃ (Gy)*
EBRT					
Shipley [14]	1995	103	4F, proton	Lower pelvic Inn, prost	121
Pollack [15]	2000	132	4F, 3D-CRT	NM	130
Pollack [2]	2002	151	4F	Lower pelvic Inn, prost, sem ves	130
Kupelian [16]	2002	116	3D-CRT	Low risk: prost Int and high risk: prost, sem ves	130
Zelefsky [17]	2003	529	IMRT	Prost, sem ves	> 121
Pollack [18]	2004	163	3D-CRT	Low risk: prost Int and high risk: Lower pelvic Inn, prost, sem ves	130
Nichol [19]	2005	120	3D-CRT	Prost	121
Zietman [3]	2005	195	4F, proton	Prost, sem ves	127
Peeters [1]	2006	333	3D-CRT	Prost, sem ves	130
Eade [20]	2007	568	3D-CRT	Low risk: prost Int and high risk: prost, sem ves, lower pelvic Inn	> 120
EBSegs					
Iversen [21]	1989	33	3F	Pelvic Inn	234
Kaye [22]	1995	31	NM	NM	183
Critz [23]	1998	657	Arc, 3D-CRT	Prost, sem ves	183
Ragde [24]	1998	54	4F	Lower pelvic Inn	183
Lederman [25]	2001	348	NM	NM	169-183
Potters [26]	2002	314	4F	Lower pelvic Inn	168-186
Singh [27]	2005	80	3D-CRT	Prost, sem ves	157-161
Jani [28]	2006	54	4F	Prost, sem	169-183
Dattoli [29]	2007	243	NM	Lower pelvic Inn	142-152
Ellis [30]	2007	89	4F	Prost, sem ves	169-185
Sylvester [31]	2007	223	4F	Lower pelvic Inn	169-183
Merrick [32]	2007	204	4F	Pelvic Inn	169
Lee [33]	2007	130	NM	Prost, sem ves	183
EBTI					
Mate [34]	1998	104	Arc, 4F	Prost	105-118
Galalae [5]	2002	144	Arc	Pelvic Inn	139

Table 1. Continued

Pellizzon [35]	2003	108	4F	Prost, sem ves	109-153
Hiratsuka [36]	2004	71	4F	Whole pelvic lnn	119-135
Martin [37]	2004	102	4F	Prost, sem ves	125-146
Åström [38]	2005	214	NM	1988-1993: Pelvic lnn 1993-2000: prost, sem ves	170
Deger [39]	2005	411	4F, 3D-CRT	Low and int risk: prost High risk: prost, sem ves	153-144
Hsu [40]	2005	64	4F, 3D-CRT	Low risk: prost, sem ves Int and high risk: whole pelvic lnn	126
Chin [41]	2006	67	3D-CRT	Low risk: prost Int and high risk: prost, sem ves	134
Izard [42]	2006	165	4F, 3D-CRT	Low risk: prost Int and high risk: prost, sem ves	135
Vargas [6]	2006	197	4F	Whole pelvic lnn	123-188
Yamada [43]	2006	105	3D-CRT	Prost, sem ves	119-151
Hoskin[8]	2007	109	3F, 3D-CRT	Prost	134
Rades [44]	2007	41	4F	Prost, sem ves	153
Phan [45]	2007	309	4F, 3D-CRT, IMRT	Prost, sem ves	126-144
Kälkner [46]	2007	154	3F, 4F	Prost, sem ves	170
Chen [47]	2007	85	3D-CRT, IMRT	Whole pelvic lnn or Prost, sem ves	127

3F: 3-field technique

4F: 4-field technique

Arc: Arc technique

3D-CRT: 3-Dimensional radiotherapy

IMRT: Intensity modulated radiotherapy

Prost: Prostate

Sem ves: seminal vesicles

Lnn: lymph nodes

Int: Intermediate

NM: Not mentioned

*Prescription dose expressed as Biologically Effective Dose (BED₃), calculated for an α/β -ratio of 3 Gy.

making an entry of data of the same patient group more than once into the analysis. From EBRT-articles only data of patients treated with 75 Gy or more were used. The results should explicitly be mentioned in the article. From EBSeeds articles only data with the transperineal implantation technique were used and if data of the combined external beam radiotherapy and seed implant results were explicitly mentioned in the article. From EBTI articles only articles using HDR or PDR were selected. One PDR-article was found in which study a 37-mBq iridium-192 source was used in a fractionated treatment of 3 fractions of 6 Gy. In total 40 articles were used in this systematic review; 10 EBRT, 13 EBSeeds, and 17 EBTI (Table 1). In Table 2 an overview of the characteristics of the patient groups of each treatment modality is given. The distribution of initial PSA-value, clinical T-stage, and the use of hormonal therapy were not well balanced between the groups.

Table 2. Frequencies of parameters of the 3 different radiotherapy modalities.

	EBRT	EBSeeds	EBTI
Year of publication	1995-2007	1989-2007	1998-2007
Median number of patients	236	189	144
Range	151-568	31-657	41-411
Median Follow-up time (months)	50.6	54.5	50.6
Range	32-66	24-113	30-96
Median age (years)	68.9	68.0	68.0
Range	66.0-72.0	65.0-71.6	64.0-71.0
Median % of patients with PSA \leq 10 ng/ml	65.0	54.7	44.6
IQR	19.4	22.5	21.0
Median % of patients with PSA 10-20 ng/ml	26.9	29.0	32.6
IQR	19.1	12.2	8.3
Median % of patients with PSA $>$ 20 ng/ml	8.0	11.1	20.0
IQR	10.3	18.3	23.2
Median % of patients with PSA unknown	0.1	5.2	2.8
Median % of patients with clinical stage T1-2	74.9	93.0	68.4
IQR	37.8	5.4	25.9
Median % of patients with clinical stage T3-4	25.1	7.0	31.6
IQR	37.8	5.4	25.4
Median % of patients with Gleason score 2-6	49.5	45.6	47.8
IQR	33.3	39.6	33.7
Median % of patients with Gleason score 7-10	50.5	54.4	52.2
IQR	34.1	39.6	33.7
Median % of patients with hormonal therapy	9.3	28.9	57.3
IQR	5.3	41.9	40.5

EBRT (External Beam Radiotherapy), EBSeeds (External Beam Radiotherapy with seeds implantation), EBTI (External Beam Radiotherapy with Temporary Implant), PSA (Prostate Specific Antigen), IQR (interquartile range).

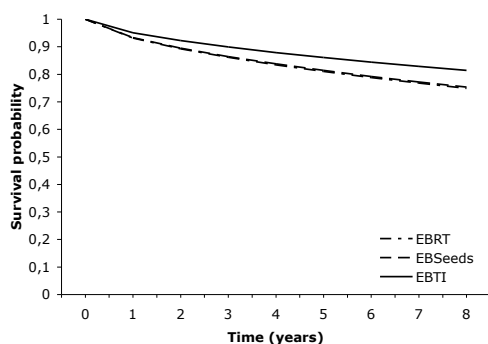


Figure 1. Biochemical free survival curves for External Beam Radiotherapy (EBRT), External Beam Radiotherapy with Seeds implantation (EBSeeds), and External Beam Radiotherapy with Temporary Implants (EBTI) adjusted for confounders.

Biochemical free recurrence rate

Different definitions of biochemical recurrence were used among the different studies (Table 3). The majority have used the 1997 ASTRO Consensus Panel definition of biochemical failure, being three consecutive rises after reaching a nadir with a minimal of 3-month interval between the measurements [9].

With univariate analysis a statistically significant association was found between treatment modality and BFS ($P < 0.001$). The hazard ratio (HR) of biochemical recurrence for EBRT relative to EBTI was 1.05 (95% confidence interval (CI) 1.01 to 1.10) and for EBSeeds relative to EBTI was 0.66 (95% CI 0.63 to 0.69).

In the multivariate analysis with adjustment for potential confounders, such as initial PSA-value, clinical T-stage, Gleason score, median age, hormonal therapy, and year of publication, also a significant association was found between treatment modality and BFS. However, the BFS of EBTI appeared now to be better than that of EBSeeds. The HR of EBRT relative to EBTI was 1.40 (95% CI 1.31 to 1.51), and that of EBSeeds relative to EBTI was 1.37 (95% CI 1.26 to 1.49). The estimated BFS curves are illustrated in Fig. 1.

Table 3. Definition of biochemical recurrence found in the articles and distribution according to treatment modality.

		N
EBRT	3 consecutive rises	8
	Nadir + 4 ng/ml or + 10%	1
	Not reported	1
EBSeeds	2 consecutive rises	1
	3 consecutive rises	4
	> 0.2 ng/ml	1
	> 0.5 ng/ml	2
	> 1.0 ng/ml	1
	> 4.0 ng/ml or nadir + 2 ng/ml	1
	Other	2
	Not reported	1
EBTI	3 consecutive rises	14
	> 1.0 ng/ml	1
	Nadir + 2 ng/ml	1
	Other	1

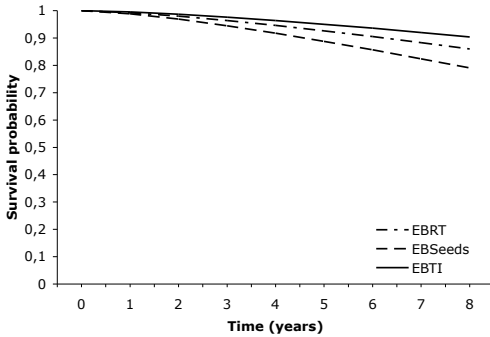


Figure 2. Overall survival curves for External Beam Radiotherapy (EBRT), External Beam Radiotherapy with Seeds implantation (EBSeeds), and External Beam Radiotherapy with Temporary Implants (EBTI) adjusted for confounders.

Biochemical free recurrence restricted to ASTRO biochemical failure criteria

The same multivariate analysis on biochemical failure was performed restricted to those 26 studies, which used the ASTRO criteria for biochemical failure. Studies of EBSeeds are underrepresented in this analysis (Table 3), however the endpoint is uniform. The HR of EBRT relative to EBTI was 1.12 (95% CI 1.04 to 1.20), and that of EBSeeds relative to EBTI was 2.73 (95% CI 2.43 to 3.06).

Overall survival

A statistically significant difference in OS was found between treatment modalities with univariate analysis. The HR of OS was 1.38 (95% CI 1.27 to 1.51) for EBRT relative to EBTI, and was 1.06 (95% CI 0.98 to 1.14) for EBSeeds relative to EBTI. In multivariate analysis the HR was 1.50 (95% CI 1.29 to 1.73) for EBRT relative to EBTI, and 2.33 (95% CI 2.04 to 2.66) for EBSeeds relative to EBTI (Fig. 2).

DISCUSSION

Vicini et al. also performed a review on the optimal radiation modality for prostate cancer [10]. In this review the studies included comprised external beam radiotherapy alone, seed implantation alone, seed implantation combined with external beam radiotherapy, and HDR brachytherapy combined with external beam radiotherapy. No apparent difference in biochemical control was noticed between treatment modalities. However, they made no effort to combine the data of the studies and to control prognostic factors as we did.

In our systematic review a comparison was done between high-dose external beam radiotherapy only vs. external beam radiotherapy with a radioactive seed implantation boost vs. external beam radiotherapy with an iridium-192 high-dose rate boost for the treatment of prostate cancer. The selection for EBRT included only studies with a cohort treated to at least 75 Gy. This selection was chosen because randomized studies have shown that high dose is needed for optimal biochemical control especially for the intermediate to high-risk groups [1-3]. By combining external beam radiotherapy with

brachytherapy also high doses are delivered on the prostate. The doses of the combination treatment are not fully comparable with external beam radiotherapy because of the specific dose distribution with brachytherapy giving high doses in the center of the implant. In a model study, Pieters et al. have shown the higher doses that are given with a combination treatment when doses are expressed in biologically equivalent doses [11]. Because of the different doses applied by the different modalities in the same patient groups it is necessary to compare these modalities to each other and to find out if differences in survival exist between these common and often used therapies.

Randomized controlled trials (RCTs) provide the strongest evidence of differences in treatment outcome between treatment modalities. Up to now only one trial has been published comparing external beam radiotherapy to external beam radiotherapy with HDR brachytherapy [8]. The results of this trial can be considered preliminary because of a short median follow-up of only 30 months. Because of the lack of randomized trial on the issue of radiotherapy modalities for the treatment of prostate cancer we have chosen to perform a systematic review with metaregression analysis on observational studies. Other reasons to conduct a meta-analysis on observational studies are to analyze risk factors for which no random allocation can be done, to gain information as a preparation to conduct a RCT, or to investigate interventions on community level. We followed the recommendations of the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group in designing, conducting, and analyzing this systematic review [12].

In a multivariate analysis the combination of external beam radiotherapy with HDR appeared to give better biochemical control and better overall survival. No difference was found between EBRT and EBSeeds (HR 1.02, 95% CI 0.96 to 1.08) for biochemical survival. For overall survival a better survival for EBRT was found compared to EBSeeds (HR 0.64, 95% CI 0.59 to 0.70). An explanation why EBRT results in high survival figures could be because of the higher doses applied. When prescription doses of brachytherapy and external beam therapy are compared to each other one has to realize that the doses in the center of a brachytherapy implant are much higher than the prescribed dose. So, a large area within the prostate receives higher doses than the stated BED₃ in Table 1 when brachytherapy is given. In our analysis we have not included dose in the multivariate model. The reason is that in many studies different radiation schedules were applied and therefore it was difficult to control for in the analysis. This review illustrates the common practice showing that with brachytherapy higher doses, particularly with HDR, are easier to achieve and is the reason why better results are reported.

When interpreting the results of systematic reviews of observational studies also possible biases should be considered and taken into account. For example in our study a wide variation was noticed in the selection of patients for the different studies. Because of possible confounding the cohorts were categorized by known risk factors as percentage of patients with a particular clinical T-stage, Gleason score, initial PSA-value, and use of

hormonal therapy and were analyzed in a multivariate model. However, other unknown confounders could play a role and introduce bias and explain the significant interaction found between time ($\ln(t)$) and the type of treatment. Instead of categorizing covariates in dichotomous variables, also continuous variables could have been used such as percentage patients with clinical T1 disease for example. When analyzing the association of the continuous covariates with BFS and OS without dichotomizing we essentially found the same results.

Other bias to consider is the different definition of biochemical recurrence among the studies. This makes comparison between studies difficult, because what is considered a biochemical recurrence in one study does not necessarily to be a recurrence in another one, which is reflected in the different validity and predictive values of the tests [13]. The majority of EBRT and EBTI studies used the ASTRO definition of 3 PSA-rises as recurrence definition in their studies. In contrast, EBSeeds studies more often used a raise of PSA-value above a certain threshold as a criterion for recurrence. The latter definition has a much lower specificity (9%-30%) than the ASTRO definition (about 80%) due to a higher false positive rate and a explanation of the inferior biochemical outcome of the EBSeeds cohorts compared to that of EBTI cohorts. A way to circumvent this problem is to perform an analysis on individual patient data and to analyze all the patients to one common end-point, which means that all these data should be delivered in a uniform way. However, if this effort is not realized selection bias will occur. To analyze the outcome of biochemical control in a more uniform way a second analysis was performed which was restricted to only those studies that used the ASTRO criteria for biochemical failure as an end-point. Similar result was found as in the original analysis indicating that the internal validity of this study is reliable.

The results on overall survival are less robust than those on biochemical control, probably because of the lack in reporting overall survival data. Only 18 studies of the 40 found reported on overall survival whereas 31 studies reported on biochemical control. Not all studies reporting on biochemical control did so on overall survival. This could partly explain the discrepancy found in biochemical control and overall survival between EBRT and EBSeeds. Another criticism on this systematic review is that only a few studies reported 8-year overall survival data. Because of the slow progression of prostate cancer differences in survival curves often become apparent after some years. So, the early differences noticed in this study model should be interpreted with caution.

Because of all these uncertainties randomized studies are needed for definitive answer on which modality will be the preferred treatment considering both tumor control and toxicity as well [7, 8].

CONCLUSION

The combination of external beam radiotherapy and HDR brachytherapy results in a superior biochemical control and overall survival found in a systematic review on radiotherapy for prostate cancer. This outcome is mainly explained by the higher dose that can be prescribed when brachytherapy is used for treatment and by virtue of a higher dose within the implant.

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