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Patients at high risk of progression after radical prostatectomy: Do they all benefit from immediate post-operative irradiation? (EORTC trial 22911)

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Abstract

EORTC trial 22911 demonstrated that immediate postoperative irradiation significantly improved biochemical failure free survival (BPFS) compared to wait-and-see (W&S) until relapse in patients with pT2-3 tumours and pathological risk factors after radical prostatectomy. In this study, we have investigated the heterogeneity of the treatment benefit across defined subgroups of patients. Data from 972 patients were used. A risk model was developed in the W&S group and the Log-rank test for heterogeneity was applied ($\alpha = 0.05$). Positive surgical margin (SM+), seminal vesicle invasion (SV+), WHO differentiation grade, pre- and post-operative PSA were independent predictors for BPFS in the W&S group. Men with SV+ were at higher risk of relapse whereas those with SM+ but no capsule infiltration (ECE−) did not seem to differ from those with SM−ECE+ or with SM+ECE+. Postoperative irradiation improved biochemical progression-free survival in all patient groups. Longer follow-up is needed to assess the endpoint of clinical progression-free survival.
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1. Introduction

Radical prostatectomy is an effective treatment for patients with organ confined prostate cancer [1–5]. However, the recurrence rate after local surgery is largely

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affected by pathological risk factors such as: extra-prostatic tumour extension (pathological T3), positive surgical margins and high grade disease and by initial PSA. It is estimated that 10–15% without and 40–60% of patients with these factors will experience biochemical or clinical recurrence following surgery [6–8].

More than two decades ago, postoperative radiotherapy was reported to eradicate the microscopic disease left in the surgical bed [9,10] and retrospective series [11,12] confirmed the significant reduction of local relapse without being able to demonstrate any impact on disease free survival.

In 1992, the European Organisation for Research and Treatment of Cancer (EORTC) initiated a randomised, multi-centre, phase III trial to test the hypothesis that immediate radiotherapy following prostatectomy improves biochemical and clinical progression free survival in patients classified as pT2-3N0M0 [UICC 1993] who are at risk of local relapse and distant dissemination. The first results of the trial (EORTC 22911) were recently published with a median follow-up of 5 years [13]: immediate post-operative irradiation resulted in a statistically significant improvement of the primary endpoint, biochemical progression-free survival ($P < 0.0001$) and of clinical progression-free survival ($P = 0.0004$).

We have now explored whether the observed benefit of immediate irradiation is homogeneous across groups of patients with different absolute risk of clinical or biochemical failure. For that purpose, we first assessed prognostic factors in patients who were not irradiated immediately to create risk groups. We then assessed whether the prognostic risk groups were also predictive for the treatment effect. Following Freedland and colleagues [14], we also assessed the prognosis according to the pathological classification in the untreated group and explored the homogeneity of the treatment effect in subsets of patients presenting with various pathological features.

2. Patients and methods

The original trial is a randomised multi-centre phase III study comparing immediate post-operative irradiation (60 Gy, external beam) to wait-and-see policy and treatment after progression in prostate cancer patients presenting poor pathological risk factors after radical prostatectomy. Adjuvant hormonal treatment was not foreseen in the protocol. One thousand and five (1005) patients were accrued to the study of which 972 were eligible. Eligible patients were 75 years old or less, with WHO performance status 0–1 and previously untreated pT2-T3N0 prostate cancer (1993 UICC TNM classification). The radical prostatectomy specimen exhibited at least one of the following risk factors: capsule perforation, positive surgical margins (including at the level of the prostate apex where the capsule is non-existent) or invasion of seminal vesicles. The study was approved by the ethics committee of each participating institution and was conducted in compliance with the Helsinki declaration. Informed consent was obtained from all patients in accordance with national laws. Randomisation was performed centrally by minimisation algorithm with stratification for the treating institution, capsule invasion, positive margins and invasion of seminal vesicles.

2.1. Endpoints

The primary endpoint was biochemical progression free survival counted from the day of randomisation to the day of first biochemical or clinical progression or start of treatment in absence of progression, if any, or death due to any cause. Biochemical progression was defined as every increase over the lowest postoperative value to a value >0.2 ng/ml that is confirmed twice, at minimum 2-week intervals. Local recurrence had to be documented by a digital rectal examination (with or without biopsy) and distant relapse by sonography, radiographic or scintigraphic imaging.

2.2. Pathological examination

The surgical specimen had to be marked with India ink over the entire resection margin. The prostate had then to be sectioned transversely from the distal margin to the bladder neck at 3–4 mm intervals in transverse planes perpendicular to the rectal surface, and fixed overnight in 10% formalin. Specific sections were taken from the distal urethral margin, bladder neck margin and junction of the seminal vesicles with the prostate. Sections were stained with hematoxylin and eosin. Margins were defined as positive if malignant cells were in direct contact with the inked margins. The WHO histopathological grading was used. Gleason grades were not assessed. Central review of the specimens was not available.

2.3. Statistical methods

2.3.1. Baseline factors considered

Ten baseline factors were screened for prognostic significance in the wait-and-see group: age, presence of other chronic diseases, clinical T category, PSA before surgery and PSA within 3 weeks after surgery (all PSA values were transformed into Hybritech equivalent values), nerve sparing radical prostatectomy, seminal vesicles invasion, capsule perforation, positive surgical margin and WHO histopathological grade. Other collected variables were judged not relevant to the purpose or could not be used because all patients were in the same category (eligibility criteria). The pathological factors were reported by the local pathologist and the Gleason

score was not available from that review. Ninety-two patients in the sample had received short term hormonal manipulation prior to surgery (<3 months). This variable was not used because its effect represents a selection of patients for short term neo-adjuvant hormonal treatment, which was not foreseen by protocol and was not applied in all centers and because despite this, the patients remained eligible for the study.

The continuous variables were transformed into categories using published cut points (PSA) or the median (age). Adjacent levels of discrete variables with small numbers were lumped together.

2.3.2. Modeling

The Cox proportional hazards model was used for the prognostic factor modeling. A step-wise multivariate selection procedure was applied to select the independent prognostic factors. Statistical significance was set at 0.05 in all analyses.

Internal model validation was performed by the bootstrap re-sampling technique that generated 5000 random samples from the original sample on which the model-fitting procedure was independently repeated. This provided a bias-corrected estimate of the area under the receiver operating characteristic curve (ROC AUC)

Table 1
Distribution of the ten baseline factors that were assessed as potential predictors

	Included in analysis set		Excluded (ineligible)	Total
	Wait-and-see ($N = 487$)	Postoperative irradiation ($N = 485$)	($N = 33$)	($N = 1005$)
	N (%)	*N* (%)	*N* (%)	*N* (%)
Age				
⩽65 y	225 (46.2)	228 (47.0)	21 (63.6)	474 (47.2)
>65 y	262 (53.8)	257 (53.0)	12 (36.4)	531 (52.8)
Associated chronic disease				
No	349 (71.7)	357 (73.6)	25 (75.8)	731 (72.7)
Yes	137 (28.1)	125 (25.8)	7 (21.2)	269 (26.8)
Missing	1 (0.2)	3 (0.6)	1 (3.0)	5 (1.4)
Nerve sparing surgical procedure				
No	283 (58.1)	288 (59.4)	18 (54.5)	589 (58.6)
Yes	197 (40.5)	182 (37.5)	15 (45.5)	394 (39.2)
Missing	7 (1.4)	15 (3.1)	0 (0.0)	22 (2.2)
Clinical T Category				
T0–1	83 (17.0)	89 (18.4)	5 (15.2)	177 (17.6)
T2	328 (67.4)	304 (62.7)	22 (66.7)	654 (65.1)
T3	76 (15.6)	91 (18.8)	6 (18.2)	173 (17.2)
Missing	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
WHO G Grade				
G1	57 (11.7)	69 (14.2)	0 (0.0)	126 (12.5)
G2	315 (64.7)	295 (60.8)	20 (60.6)	630 (62.7)
G3	111 (22.8)	114 (23.5)	12 (36.4)	237 (23.6)
Missing	4 (0.8)	7 (1.4)	1 (3.0)	12 (1.2)
Pre-operative PSA				
⩽20 ng/ml	365 (74.9)	356 (73.4)	26 (78.8)	747 (74.3)
>20 ng/ml	121 (24.8)	126 (26.0)	6 (18.2)	253 (25.2)
Missing	1 (0.2)	3 (0.6)	1 (3.0)	5 (0.5)
PSA within 3 weeks post-surgery				
⩽0.2 ng/ml	334 (68.6)	342 (70.5)	22 (66.7)	698 (69.5)
>0.2 ng/ml	128 (26.3)	123 (25.4)	9 (27.3)	260 (25.9)
Missing	25 (5.1)	20 (4.1)	2 (6.1)	47 (4.7)
Pathological risk factors (individual stratification factors)				
Seminal vesicle invasion	122 (25.1)	122 (25.2)	12 (36.4)	256 (25.5)
Positive surgical margins	306 (62.8)	306 (63.1)	17 (51.5)	629 (62.6)
Capsule perforation	383 (78.6)	365 (75.3)	26 (78.8)	774 (77.0)
Pathological stage[a]				
SM+, ECE−	79 (16.2)	82 (16.9)	2 (6.1)	163 (16.2)
SM−, ECE+	125 (25.7)	133 (27.4)	8 (24.2)	266 (26.5)
SM+, ECE+	161 (33.1)	148 (30.5)	9 (27.3)	318 (31.6)
SV+	122 (25.1)	122 (25.2)	12 (36.4)	256 (25.5)
Missing	0 (0.0)	0 (0.0)	2 (6.1)	2 (0.2)

[a] SM, surgical margin; ECE, capsule perforation; SV, seminal vesicle invasion.

[15] which measures the predictive discrimination of the model: a value of 0.5 indicates no discrimination; a value of 1 indicates perfect discrimination. Model stability was assessed by the frequency of inclusion of each of the component variables into the Cox multivariate models [16] and by the frequency of selection of each admissible multivariate model.

The stratified Log-rank test and Forest plots were used to test for heterogeneity of the treatment effect between risk groups using meta-analysis methodology [17].

3. Results

With a median follow-up of 5 years, EORTC Trial 22911 [13] showed that post-operative irradiation significantly improved the primary trial endpoint, biochemical progression-free survival ($P < 0.0001$, HR = 0.48, 98% CI: 0.37–0.62 based on 351 events) and the secondary endpoint clinical progression-free survival ($P = 0.0009$, HR = 0.61, 98%CI: 0.43–0.87 based on 188 events). For 281 of the 351 patients the first failure was a PSA increase (80.0% overall, 85.5% on wait-and-see and 71.0% on post-operative irradiation).

Of the 1005 patients entered in the trial, 972 eligible patients were used for the purpose of the predictive factor analysis (485 irradiated and 487 on wait-and-see) and only the 487 on wait-and-see were used for identifying prognostic factors. Thirty-three patients were excluded from this analysis for reasons of ineligibility mostly due to previous other cancers or inadequate disease stage. Table 1 showing the distribution of the 10 considered baseline factors indicates no major difference

Table 2
Univariate analysis of biochemical progression-free survival in the wait-and-see arm

	No. patients	No. observed events	Hazard ratio (95% confidence interval)	*P*-value	5-year event-free rate (95% confidence interval)
Age group					
⩽65 y[a]	225	87	1.00	0.0558	58.4 (51.3, 65.6)
>65 y	262	127	1.31 (0.99, 1.72)		47.5 (40.5, 54.5)
Associated chronic disease					
No[a]	349	160	1.00	0.3148	51.6 (45.7, 57.5)
Yes	137	54	0.85 (0.63, 1.16)		54.8 (44.9, 64.6)
Nerve sparing procedure					
No[a]	283	136	1.00	0.0633	48.6 (42.0, 55.1)
Yes	197	73	0.76 (0.57, 1.02)		58.7 (50.7, 66.7)
Clinical T category					
T0–1[a]	83	30	1.27 (1.00, 1.62)	0.0503	61.1 (49.5, 72.7)
T2	328	143			52.6 (46.4, 58.8)
T3	76	41			43.6 (31.1, 56.1)
WHO G Grade[b]					
G1[a]	57	20	1.68 (1.32, 2.13)	<0.0001	63.8 (50.7, 77.0)
G2	315	131			56.8 (50.5, 63.0)
G3	111	63			32.4 (21.9, 43.0)
Pre-operative PSA[b]					
⩽10 ng/ml[a]	194	67	1.41 (1.19, 1.67)	0.0001	62.2 (54.2, 70.1)
10 ⩽ 20 ng/ml	171	74			50.6 (41.7, 59.4)
>20 ng/ml	121	73			40.4 (31.1, 49.7)
PSA within 3 weeks post surgery					
⩽0.2 ng/ml[a]	334	121	1.00	<0.0001	59.2 (53.0, 65.4)
>0.2 ng/ml	128	80	2.09 (1.58, 2.78)		36.3 (27.3, 45.3)
Seminal vesicle invasion					
Not reported[a]	365	139	1.00	<0.0001	59.0 (53.3, 64.7)
Present	122	75	2.10 (1.58, 2.78)		32.6 (22.76, 42.4)
Positive surgical margin					
Not reported[a]	181	71	1.00	0.0308	59.0 (50.6, 67.5)
Present	306	143	1.37 (1.03, 1.83)		48.4 (42.1, 54.7)
Capsule perforation					
Not reported[a]	104	42	1.00	0.5136	52.5 (41.2, 63.8)
Present	383	172	1.12 (0.80, 1.57)		52.4 (46.7, 58.0)

[a] Reference category for the calculation of the hazard ratios.
[b] Linear trend.

between the two treatment groups (see Bolla [13] for more details). The ineligible patients were somewhat dissimilar, as could be expected since their disease status was not adequate for inclusion in the study.

3.1. Prognostic factors for biochemical progression free survival in the wait-and-see arm

In the wait-and-see arm, all baseline factors tested were statistically significant ($P < 0.05$) in the univariate analysis except for the presence of associated chronic disease and capsule perforation ($P > 0.1$), age and nerve sparing procedure ($P = 0.0558$ and $P = 0.0633$, respectively). The univariate effect of clinical T category was borderline statistically significant ($P = 0.0503$) (Table 2). Owing to the likely presence of correlations between factors, the multivariate model selection procedure was initiated with a model that contained all ten variables. After model reduction, five factors were retained as independent predictors of increased risk of clinical or biochemical failure: a PSA > 0.2 ng/ml within 3 weeks post-surgery (and prior to irradiation, if any), invasion of seminal vesicles, elevated (>10 or >20 ng/ml) PSA prior to surgery, poor tumour differentiation (WHO G grade) and positive surgical margins (Table 3). Of note, when this model was applied to the irradiated group, pre-operative PSA and positive surgical margins were no longer statistically significant and the associated hazard ratios were closer to unity ($P = 0.2698$ and $P = 0.1353$, respectively).

3.2. Model validation

The bias-corrected area under the ROC curve for this model with five variables was 0.65. The model was also the most frequently selected reduced multivariate model in the bootstrap validation process. Table 4 displays the inclusion frequency of the 10 variables tested in the 5000 Bootstrap samples final multivariate models: pre- and post-operative PSA and seminal vesicles invasion were selected in >85% of the models, WHO G grade and positive surgical margins in >75% of the models, all other variables were selected in less than 30% of the models.

3.3. Risk groups

A prognostic index (PI) was calculated for each patient by adding the coefficients attached to each of the five risk factors in the final model, whenever the risk factor was present for that given patient: $PI = 0 + 0.669 \times [\text{post-operative PSA} > 0.2\ \text{ng/ml}] + 0.653 \times [\text{seminal vesicle invasion}] + 0.314 \times [\text{pre-operative PSA} > 10\ \text{ng/ml}] + 0.314 \times [\text{pre-operative PSA} > 20\ \text{ng/ml}] + 0.412 \times [\text{G grade} - 1] + 0.434 \times [\text{positive surgical margins}]$.

Risk groups were constituted by classifying the patients on the wait-and-see arm according to tertiles of the prognostic index (low risk: 0 to ⩽0.85, intermediate risk: >0.85 to ⩽1.55, high risk: >1.55 to ⩽3.21). Fig. 1 shows the biochemical progression-free survival by risk group in the wait-and-see arm (development set) and Table 5 the 5-year event free rates and hazard ratios.

3.4. Predictive effect of the prognostic risk groups

The forest plot of the effect of post-operative irradiation on biochemical progression-free survival in the three risk groups (Fig. 2) indicated no substantial heterogeneity in magnitude of the hazard ratios for the benefit of postoperative irradiation across the three risk groups (Log-rank for heterogeneity $P > 0.1$) for the endpoint of biochemical progression-free survival.

Table 4
Frequency of inclusion of the individual baseline factors in the final models obtained on the $B = 5000$ bootstrap samples

Variable	Frequency of inclusion among the $B = 5000$ Bootsrap sample models N (%)
Post-operative PSA	4940 (98.8)
Invasion of seminal vesicles	4892 (97.8)
Pre-operative PSA	4385 (87.7)
WHO G grade	4219 (84.4)
Positive surgical margins	3803 (76.1)
Associated chronic disease	1393 (27.9)
Age	1148 (23.0)
Nerve sparing procedure	1088 (21.8)
Clinical T category	940 (18.8)
Capsule perforation	428 (8.6)

Table 3
Multivariate prognostic factor model for biochemical progression-free survival in the wait-and-see arm

Variable label	Parameter estimate[a]	Standard error	χ^2	P-value	Hazard ratio	Hazard ratio 95% confidence interval
Positive surgical margins	0.434	0.153	8.05	0.0046	1.54	1.14–2.08
Invasion of the seminal vesicles	0.653	0.153	18.14	<0.0001	1.92	1.42–2.59
G Grade: G1 *vs.* G2 *vs.* G3	0.412	0.123	11.27	0.0008	1.51	1.19–1.92
Pre-operative PSA: ⩽10 ng/ml *vs.* >10–20 *vs* >20 ng/ml	0.314	0.090	12.13	0.0005	1.37	1.15–1.63
PSA within 3 weeks post surgery: >0.2 ng/ml	0.669	0.146	20.90	<0.0001	1.95	1.47–2.60

[a] Coefficients for building the prognostic index.

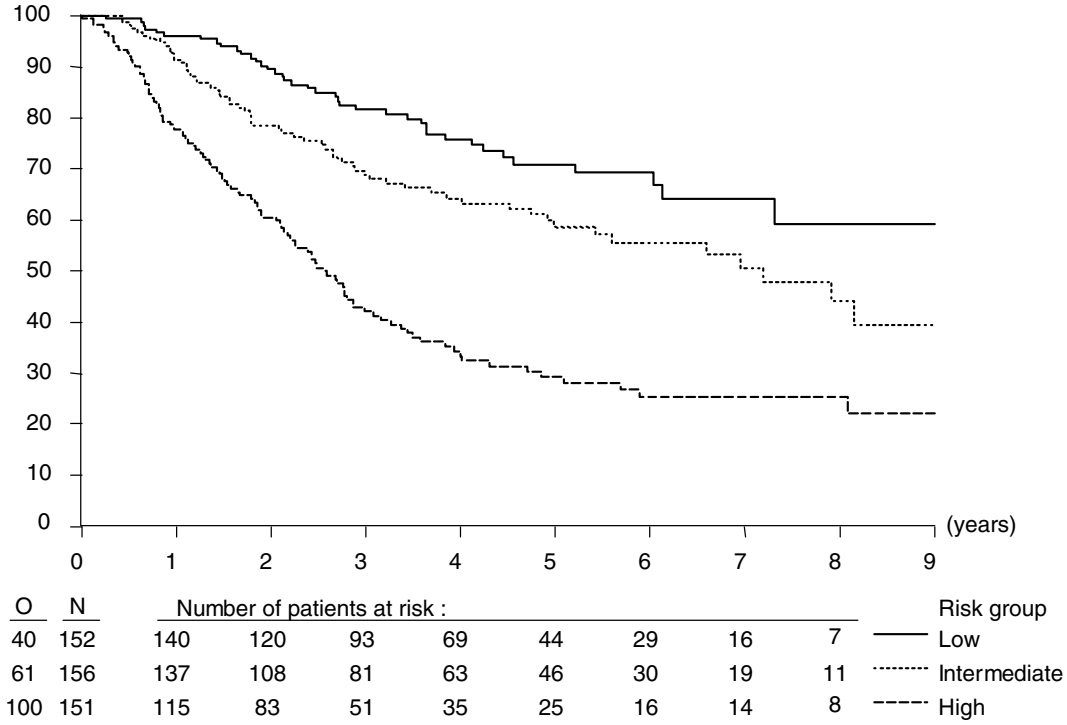

Fig. 1. Biochemical progression-free survival by risk group in the wait-and-see arm (development set).

Table 5
Risk groups in the two treatment arms

Risk group	Wait-and-see arm				Post-operative irradiation arm			
	No. patients	No. events	Hazard ratio (95% CI)	5-year event free rate (95% CI)	No. patients	No. events	Hazard ratio (95% CI)	5-year event free rate (95% CI)
Low	152	40	1.00	70.9% (62.4, 79.4)	146	20	1.00	84.4% (77.4, 91.4)
Intermediate	156	61	1.65 (1.10, 2.46)	58.7% (49.8, 67.5)	179	44	1.83 (1.08, 3.11)	77.9% (70.8, 84.9)
High	151	100	3.63 (2.50, 5.26)	29.3% (21.2, 37.4)	136	51	3.28 (1.95, 5.50)	61.0% (51.8, 70.3)

CI = confidence interval.

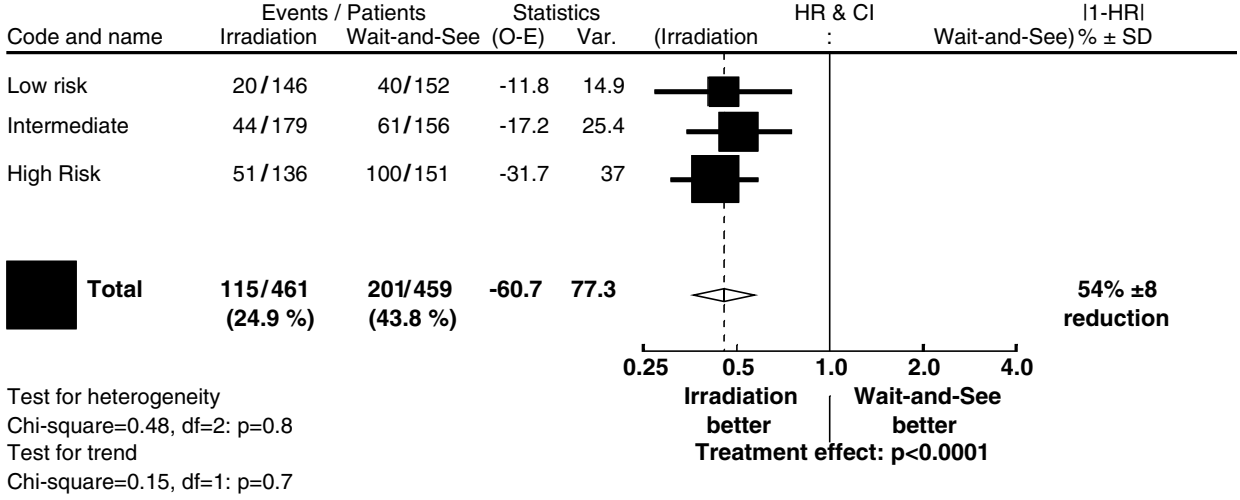

Fig. 2. Forest plot of the effect of post-operative irradiation on biochemical progression free survival, in the risk groups derived from the multivariate Cox model developed in the wait-and-see arm. The center of the squares is the hazard ratio, bars represent 95% confidence interval, the size of the square is proportionate to the number of events.

3.5. Predictive effect of the pathological risk factors

The potential predictive value of the individual pathological risk factors was assessed, as well as that of pre- and post-operative PSA and WHO differentiation grade. The three pathological factors were stratified for at randomisation. The test for heterogeneity of treatment effects indicated borderline statistically significant heterogeneity in relation to margin status (Fig. 3, $P = 0.0568$). The hazard ratio was 0.61 (95% CI: 0.43–0.88, $P = 0.0082$) in the margin negative group and 0.40 (95% CI: 0.30–0.52, $P < 0.0001$) in the group with positive margins. The analysis indicated no heterogeneity of the trial results according to pre-operative PSA, post-operative PSA or tumour differentiation ($P > 0.1$).

3.6. Prognostic and predictive effect of pathological stage

The biochemical progression-free survival for the groups presenting with positive margins without extra capsular extension (SM+, ECE−), extra capsular extension only (SM−, ECE+), with both factors (SM+, ECE+) or with seminal vesicle invasion, irrespective of margin status (SV+) is depicted in Fig. 4 (also see Table 1 for the distribution in the two treatment arms). The SV+ subgroup fared much worse than the other three subgroups ($P = 0.0003$). Based on the available data, there was no significant difference between the SM−, ECE+ subgroup and the two subgroups with SM+ ($P > 0.1$). There was no statistically significant heterogeneity in treatment effect across patient groups defined by this classification (Fig. 5, Log-rank $P > 0.1$) although the SM−, ECE+ subgroup appeared on the right of the forest plot closer to the unity hazard ratio.

4. Discussion

Today, the urologists' and radiation oncologists' opinion regarding the value of post-prostatectomy

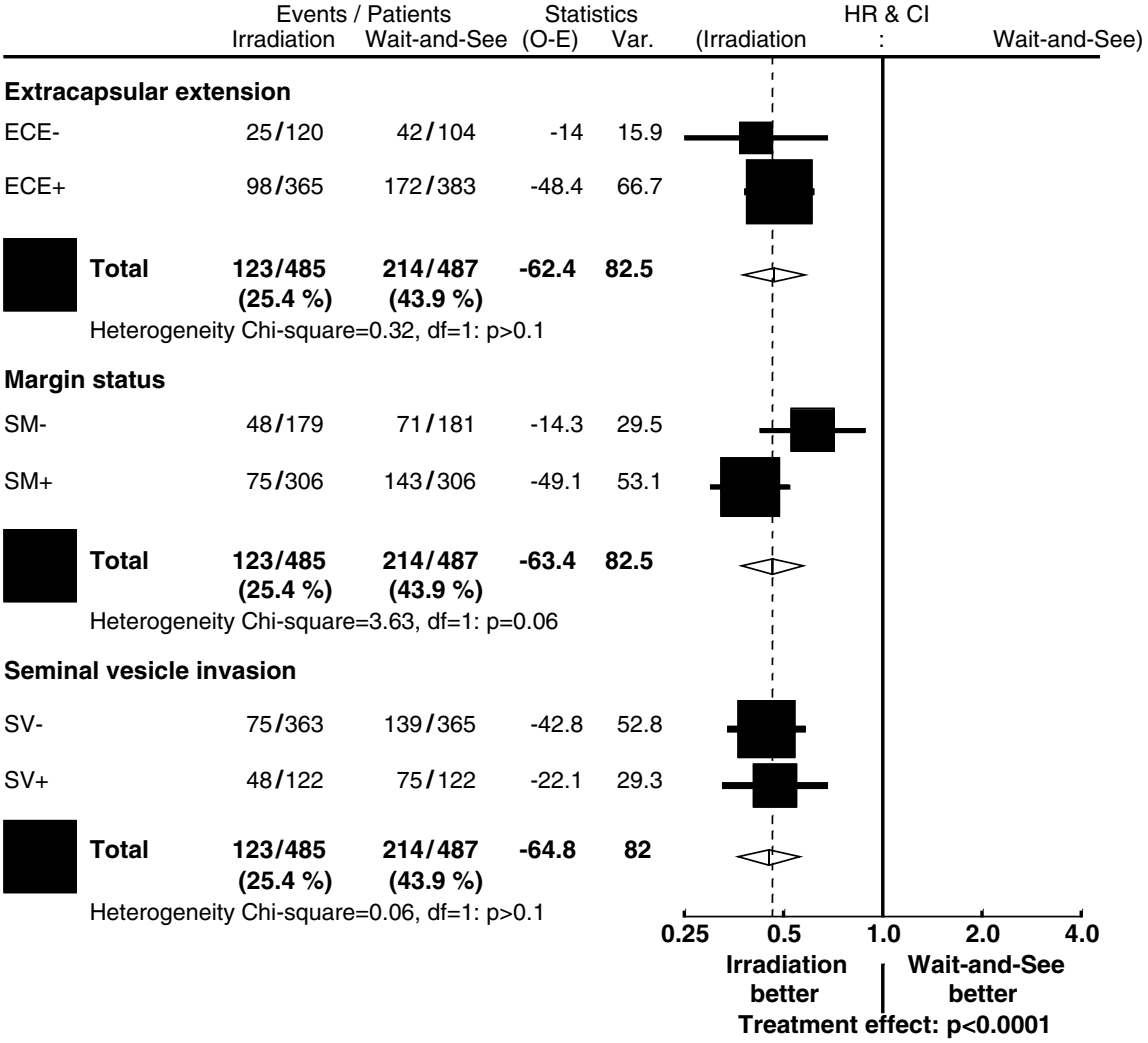

Fig. 3. Forest plot of the effect of post-operative irradiation on biochemical progression-free survival in subgroups defined by the pathological stratification factors extracapsular extension (ECE), surgical margin (SM) and seminal vesicle invasion (SV).

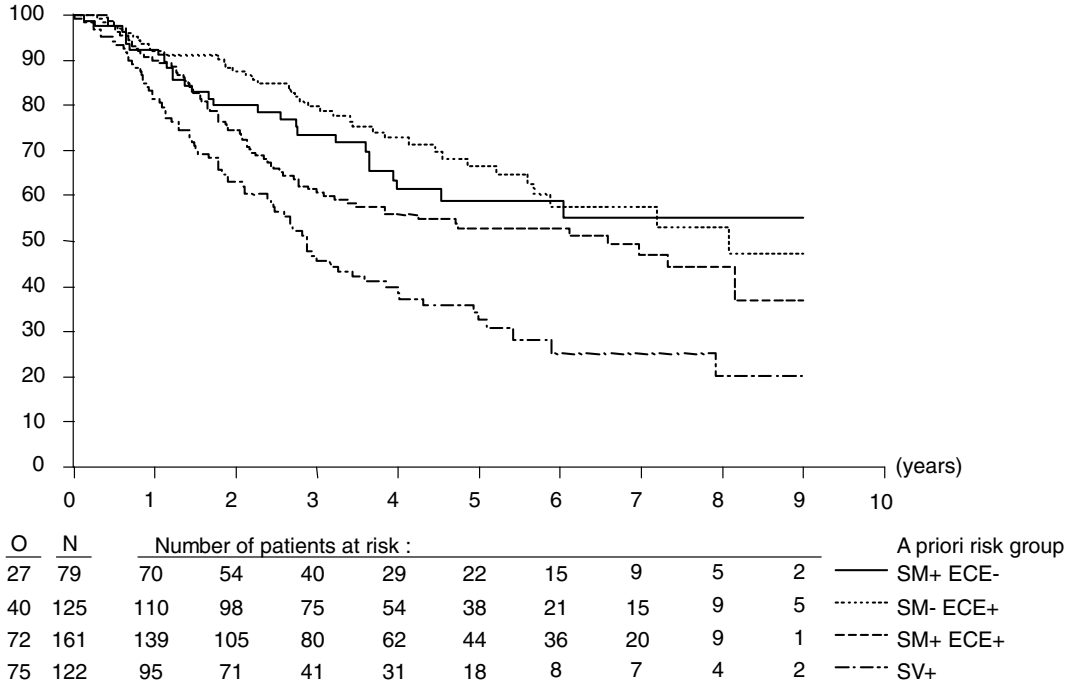

Fig. 4. Biochemical progression-free survival by pathological stage in the Wait-and-see arm. HR for SM−ECE+ *vs.* SM+ECE−: 0.82 (95% CI: 0.50–1.33, $P = 0.4194$). HR for SM+ECE+ *vs.* SM+ECE−: 1.30 (95% CI: 0.83–2.01, $P = 0.2486$). HR for SV+ *vs.* SM+ECE−: 2.25 (95% CI: 1.45–3.48, $P = 0.0003$). Log-rank $P < 0.0001$ for the overall comparison of the three groups.

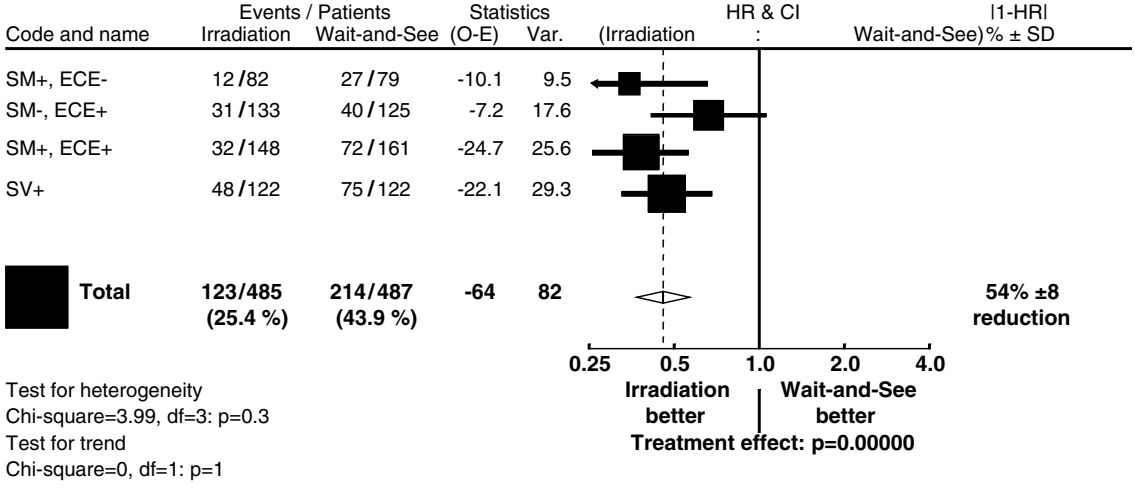

Fig. 5. Forest plot of the effect of post-operative irradiation on biochemical progression-free survival by pathological stage.

adjuvant radiation in patients presenting with poor post-operative risk factors remains varied [18–20]. The EORTC trial 22911 recently demonstrated a benefit of post-prostatectomy irradiation for preventing biochemical and clinical progression in patients with clinical T0-3N0M0 prostate cancer and at least one pathological risk factor of capsule perforation, positive surgical margins and/or invasion of seminal vesicles [13].

We investigated the homogeneity of the benefit observed in trial 22911 across patient subgroups. We postulated that the benefit of immediate irradiation was greatest in patients who were predicted to be at higher risk of relapse.

Our results suggest that the benefit of immediate irradiation as regards biochemical progression-free survival was substantial in all patient subsets, whether formed on trial-based prognostic factors or on pre-defined pathological classification. Statistics supported only the fact that the subset of patients with negative margins may benefit to a somewhat lesser extent than the other subgroups (Heterogeneity $P = 0.0568$). The patients with extra capsular extension as sole risk factor also appeared

on the plots to benefit less of immediate irradiation. This statement was not substantiated statistically (heterogeneity $P > 0.1$). In addition, this further subset represented 70% of the margin negative cases and this strongly suggests that the two observed effects are in fact directly related.

For the purpose of assessing the absolute risk of biochemical progression-free survival, we also assessed prognostic factors in the wait-and-see arm. Our results identified pre-operative PSA, post-operative PSA, WHO differentiation grade, invasion of seminal vesicles and positive margins as prognostic factors. Those factors were already identified in validated pre-operative [21–24] as well as post-operative nomograms [8,25] and in numerous other reports [3,26,27] amongst others]. Our primary objective was not to improve on those models. We did not apply Partin's nomogram in our study, because the Gleason score from the local pathology was not available in the database, as the WHO differentiation grade was used in the study. However, a central review pathology exercise is currently ongoing. The charts of all patients entered at the largest recruiting centers will be reviewed. The results of this review will be the object of a subsequent publication. For similar reasons, other factors were not available, which were shown to improve the prediction models such as the proportion of the gland with tumour-bearing high grade histological features and the extent of positive margins [3,27–29].

When applied to the group of patients who were irradiated post-operatively, pre-operative PSA level and the presence of positive surgical margins were no longer statistically significant. This is obviously related to some predictive value of those two factors, but also suggests that the effect of irradiation superseded the negative impact of these two factors. In a more general perspective, this observation calls attention on the fact that the impact of prognostic factor may be modulated by the (adjuvant) treatments. This ought to be taken into account when designing trials comparing new treatment strategies.

On the basis of the local pathology report, we could identify the pathological stage of all patients. We assessed the biochemical progression-free survival of the non irradiated patients by pathological stage: patients presenting with positive margins only (pT2), with extra capsular extension (pT3a) with or without positive margins and with invasion of the seminal vesicles (pT3b). Like Freedland and colleagues on the SEARCH database [14], we observed that patients with positive surgical margin without extra capsular extension were at similar risk of failure as men presenting with extra capsular extension with or without positive surgical margins but without invasion of seminal vesicles. Although our results are based on a much smaller subgroup, they suggest that men with positive surgical margins following radical prostatectomy might be considered as having pathological stage T3 disease. However, confirmation is required as to the prognosis of this patient subgroup in regard to the risk of distant metastases and disease-related mortality. As indicated earlier, all groups seemed to benefit from immediate irradiation in our series. We also have to observe that current radiation techniques would allow the delivery of an optimised and higher radiation dose and that the overall trial results might have been even more significant in the context of current selection criteria and irradiation standards.

We did not explore the endpoint clinical progression-free survival. The reason is that with currently available five years of median follow-up in EORTC trial 22911, little is known as yet as regards the events of distant relapse and death. As yet, the majority of events of biochemical/clinical relapse consisted in biochemical failure, and only 217 events of clinical relapse or death have been reported, most of which consisted in loco-regional failure. A longer follow-up is therefore needed to assess this endpoint and the endpoint of overall survival. The long term follow-up is eagerly awaited, since PSA failure is not yet validated as a surrogate neither for clinical relapse nor for overall survival in the post-operative indication [30].

Conflict of interest statement

None of the authors of the present paper had any financial or personal relationship with other people or organization that could bias their work.

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