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Effect of *BRCA* Mutations on Metastatic Relapse and Cause-specific Survival After Radical Treatment for Localised Prostate Cancer

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Abstract

Background: Germline *BRCA* mutations are associated with worse prostate cancer (PCa) outcomes; however, the most appropriate management for mutation carriers has not yet been investigated.
Objective: To evaluate the response of *BRCA* carriers to conventional treatments for localised PCa by analysing metastasis-free survival (MFS) and cause-specific survival (CSS) following radical prostatectomy (RP) or external-beam radiation therapy (RT).
Design, setting, and participants: Tumour features and outcomes of 1302 patients with local/locally advanced PCa (including 67 *BRCA* mutation carriers) were analysed. RP was undergone by 535 patients (35 *BRCA*); 767 received RT (32 *BRCA*). Median follow-up was 64 mo.
Outcome measurements and statistical analysis: Median survival and 3-, 5-, and 10-yr survival rates were estimated using the Kaplan-Meier method. Generated survival curves were compared using the log-rank test. Cox regression analyses were used to assess the prognostic value of *BRCA* mutations.
Results and limitations: A total of 67 *BRCA* carriers and 1235 noncarriers were included. At 3, 5, and 10 yr after treatment, 97%, 94%, and 84% of noncarriers and 90%, 72%, and 50% of carriers were free from metastasis ($p < 0.001$). The 3-, 5- and 10-yr CSS rates were significantly better in the noncarrier cohort (99%, 97%, and 85%, respectively) than in

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carriers (96%, 76%, and 61%, respectively; $p < 0.001$). Multivariate analysis confirmed *BRCA* mutations as an independent prognostic factor for MFS (hazard ratio [HR]: 2.36; 95% confidence interval [CI], 1.38–4.03; $p = 0.002$) and CSS (HR: 2.17; 95% CI, 1.16–4.07; $p = 0.016$).

Conclusions: *BRCA* carriers had worse outcomes than noncarriers when conventionally treated for local/locally advanced PCa.

Patient summary: Prostate cancer patients with germline *BRCA* mutations had worse outcomes than noncarriers when conventionally treated with surgery or radiation therapy.

1. Introduction

Advances in prostate cancer (PCa) diagnosis and treatment during the last 25 yr have improved patients' survival [1], and the focus is now shifting towards individualising treatment options according to disease biology.

Several predictive tools have been developed to estimate the risk of relapse following the main standard treatment options for localised PCa [2]. However, PCa is very heterogeneous, and some patients who *a priori* have good prognostic features still relapse and succumb to the disease. This is particularly applicable to men who harbour germline mutations in the *BRCA1* or *BRCA2* genes. We recently demonstrated that *BRCA2* germline mutations not only confer a high risk of PCa (8.6-fold in men ≤65 yr) [3] but are also an independent prognostic factor for cause-specific survival (CSS) in all stages of PCa including localised disease [4].

BRCA1 and *BRCA2* play central roles in DNA repair by homologous recombination, which is the mechanism that cells use to repair double-strand breaks induced, for instance, by platinum-based chemotherapeutic agents or ionising radiation. Previous studies have demonstrated that *BRCA1* and *BRCA2* mutations are predictive factors for response to platinum-based chemotherapy in breast and ovarian cancer, respectively [5,6]. However previous studies in breast cancer have failed to show a relevant difference in local relapse or toxicity following radiation therapy (RT) compared with noncarriers [7–9].

We hypothesise that *BRCA* status may have prognostic implications when considering radical treatment options for localised PCa. We have compared the outcomes of PCa patients (*BRCA* carriers and noncarriers) who underwent radical prostatectomy (RP), and separately, the outcomes of those who received external-beam RT to treat localised or locally advanced PCa.

2. Patients and methods

2.1. Study design

In this retrospective analysis the outcomes of local/locally advanced PCa patients known to be *BRCA* mutation carriers or noncarriers were compared. Briefly, 67 *BRCA* mutation carriers with PCa treated with curative intent were identified from two studies: the United Kingdom Genetic Prostate Cancer Study [UKGPCS] (NIHR869) and the Epidemiological Study of BRCA1/2 Mutation Carriers [EMBRACE] (NIHR1358) study (Fig. 1). These numbers include 55 carriers previously reported [4] and 12 new cases enrolled in EMBRACE or UKPGCS. A total of 1235 patients out of 1774 known noncarriers [3,10,11] enrolled in UKGPCS and treated with RT or RP for local or locally advanced disease for whom clinical and follow-up data were available were included as controls.

All patients in EMBRACE and UKPGCS had previously provided informed consent. In addition, patients had histologic confirmation of PCa and the availability of clinical and follow-up data.

Patients were managed according to departmental protocols, standardised in 1999 by the National Institute for Clinical Excellence [12]. UKGPCS and EMBRACE are observational studies and did not interfere with PCa management.

The aim of this study was to evaluate the response of *BRCA* carriers to conventional treatments for localised PCa by analysing metastasis-free survival (MFS) and CSS following RP or RT in two separate cohorts of PCa patients with and without germline *BRCA* mutations. The local institutional review boards approved this study.

2.2. Data collection

Data from patients enrolled in UKGPCS and EMBRACE were collected at study entry and updated annually. Data sources used in these studies included medical records (electronic and hard copy records) and printed copies of the pathology reports (from initial diagnosis, repeated biopsies, and/or RP when applicable). UKPGCS and EMBRACE study questionnaires collected baseline diagnostic variables and outcomes including date at PCa diagnosis, age, TNM stage, Gleason score, prostate-specific antigen (PSA) levels and dates, administered treatments for PCa, date of metastasis, and date/cause of death. Data collection cut-off for this study was April 20, 2014. During the follow-up period (median: 64 mo; range: 12–233), 127 patients developed metastasis and 144 deaths occurred, of which 96 attributable to PCa.

2.3. Statistical methods

No formal statistical sample size calculations were formulated *a priori* due to the rarity of germline *BRCA* mutations in PCa (<2%) [11]. MFS was estimated from the date of treatment-end until the date of metastatic disease. CSS was calculated from the date of PCa treatment-end until date of death or censored at the last follow-up. If cause of death was different from PCa, CSS time was censored at the time of death.

Associations between patient characteristics and treatment modality and/or *BRCA* mutations were analysed using the chi-square test, Mantel-Haenszel linear-trend test, or the Mann-Whitney *U* test, as appropriate. Median survival was estimated using the Kaplan-Meier method. Survival curves generated for each group were compared using the log-rank test. To assess the independent prognostic value of *BRCA* mutations and/or other baseline characteristics, a multivariable analysis (MVA) model for each outcome was created using a stepwise Cox regression model in which all potential prognostic variables significantly associated with

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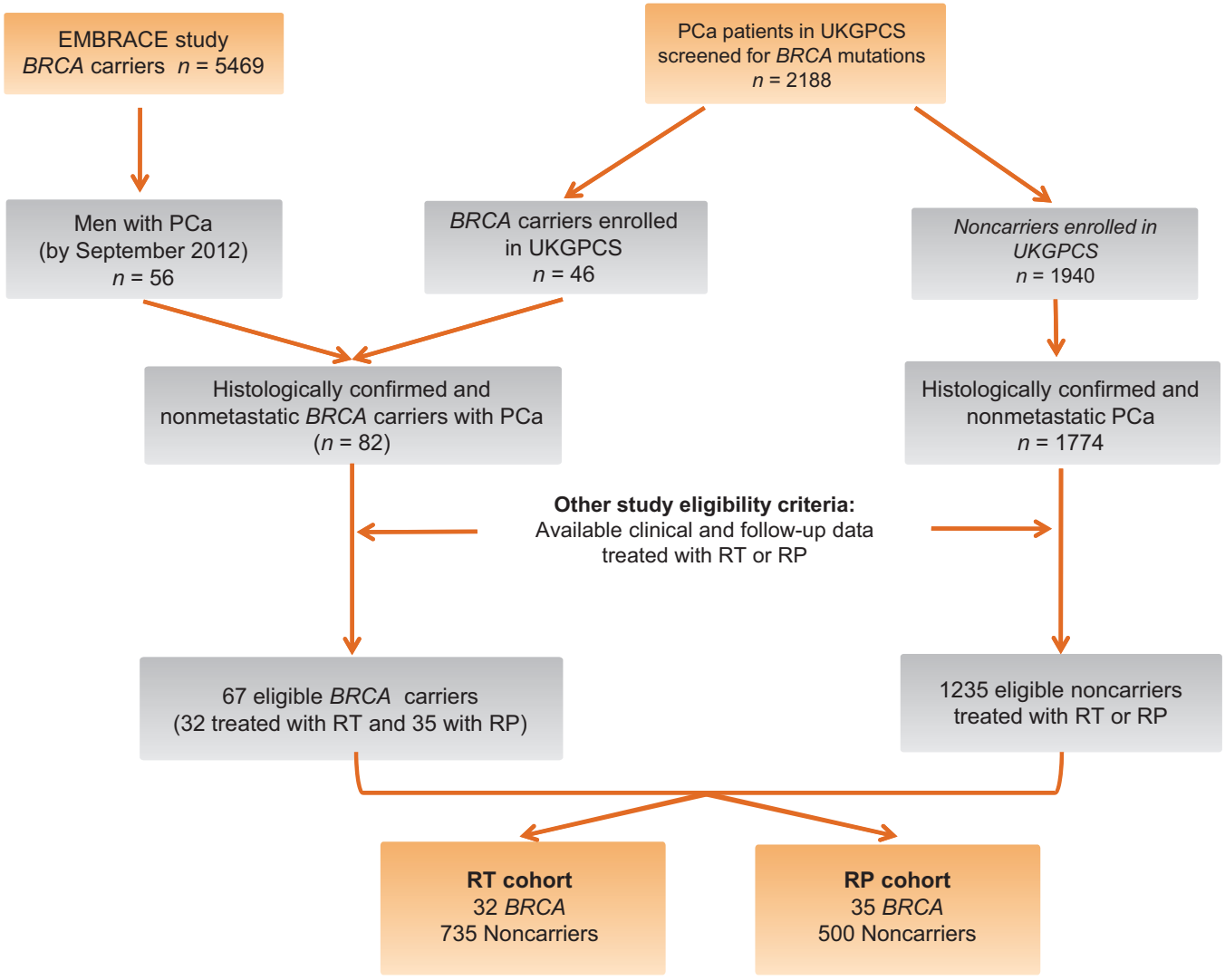

Fig. 1 – Consolidated Standards of Reporting Trials diagram.
EMBRACE = Epidemiological Study of BRCA1/2 Mutation Carriers; PCa = prostate cancer; RP = radical prostatectomy; RT = radiation therapy; UKGPCS = United Kingdom Genetic Prostate Cancer Study.

outcomes in the univariable analysis (UVA) were included. Two variables, namely, risk stratification for localised PCa and American Joint Committee on Cancer (AJCC) stage, presented high collinearity; therefore only the latter variable was considered in the prognostic analyses. We tested the interaction term between *BRCA* status and treatment modality in the MVA analysis to explore whether the effect of *BRCA* was different in patients treated with RT or RP. The concordance index (C-index) for each Cox regression model was calculated, and models were compared using the likelihood ratio. All *p* values were two sided. SPSS programme v.19.0 (IBM Corp, Armonk, NY, USA) and R v.3.0.1 (R Foundation, Vienna, Austria) were used for the statistical analyses.

3. Results

A total of 1302 patients were included in the study, of which 67 carried a germline *BRCA* mutation (18 *BRCA1* and 49 *BRCA2*). These mutations were spread throughout the coding regions of both genes and not clustered in specific regions. No differences were seen between carriers and noncarriers in age at diagnosis and PSA pretreatment levels (median age: 57 yr; median PSA: 10 ng/ml). Overall, 9% of carriers had T1 tumours, 48% had T2, and 34% had T3, compared with 26%, 39%, and 28% of noncarriers who had T1, T2, and T3 tumours, respectively ($p < 0.02$). Differences between carriers and noncarriers were also observed in tumour grades; 33% of *BRCA*-related tumours presented Gleason scores $\leq$6, 31% Gleason 7, and 34% Gleason $\geq$8 compared with 50%, 34%, and 15% of noncarriers, respectively ($p < 0.001$). Nodal involvement (N1) was present in 6% of carriers and 2% of noncarriers ($p = 0.009$).

3.1. Radical prostatectomy and radiotherapy cohorts

A total of 535 patients were treated with RP, whilst 767 patients received RT. Overall, patients in the RT cohort presented with more aggressive and more advanced disease than those surgically reated. Median PSA pretreatment level

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Table 1 – Characteristics and treatments of patients included in the study

	Entire series						RP cohort						RT cohort					
	All patients (*n* = 1302)		*BRCA* (*n* = 67)		Noncarriers (*n* = 1235)		All patients (*n* = 535)		*BRCA* (*n* = 35)		Noncarriers (*n* = 500)		All patients (*n* = 767)		*BRCA* (*n* = 32)		Noncarriers (*n* = 735)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Age																		
Median (range)	57.1 (36.0–85.8)		58.7 (41.7–77.5)		57.1 (36.0–85.8)		56.9 (36.9–85.9)		57.1 (47.1–65.3)		56.9 (36.9–85.8)		57.4 (36.0–79.0)		59.3 (46.0–77.5)		57.3 (36.0–79.0)	
IQR	54.5–60.3		54.0–62.9		54.2–59.7		53.5–59.4		53.6–62.8		53.4–59.3		54.6–60.4		56.0–69.4		54.5–60.3	
T stage																		
T1	331	25.4	6	9.0	325	26.3	171	32.0	2	5.7	169	33.8	160	20.9	4	12.5	156	21.2
T2	516	39.6	32	47.8	484	39.2	247	46.2	24	68.6	223	44.6	269	35.1	8	25.0	261	35.5
T3	371	28.5	23	34.3	348	28.2	91	17.0	7	20.0	84	16.8	280	36.5	16	50.0	264	35.9
T4	19	1.5	1	1.5	18	1.5	1	0.2	0	0.0	1	0.2	18	2.3	1	3.1	17	2.3
Unknown	65	5.0	5	7.5	60	4.9	25	4.7	2	5.7	23	4.6	40	5.2	3	9.4	37	5.0
Nodal involvement																		
N0	1275	97.9	62	92.5	1213	98.2	525	98.1	33	94.3	492	98.4	750	97.8	29	90.6	721	98.1
N1	24	1.8	4	6.0	20	1.6	7	1.3	1	2.9	6	1.2	17	2.2	3	9.4	14	1.9
Unknown	3	0.2	1	1.5	2	0.2	3	0.6	1	2.9	2	0.4	0	0.0	0	0.0	0	0.0
Gleason score																		
≤6	630	48.4	22	32.8	608	49.2	299	55.9	15	42.9	284	56.8	331	43.2	7	21.9	324	44.1
7	440	33.8	21	31.3	419	33.9	171	32.0	10	28.6	161	32.2	269	35.1	11	34.4	258	35.1
≥8	203	15.6	23	34.3	180	14.6	53	9.9	9	25.7	44	8.8	150	19.6	14	43.8	136	18.5
Unknown	29	2.2	1	1.5	28	2.3	12	2.2	1	2.9	11	2.2	17	2.2	0	0.0	17	2.3
PSA pretreatment																		
Median (range)	10.0 (0.5–153.0)		8.5 (0.5–68.5)		10.1 (0.5–143)		7.5 (0.5–138.9)		6.0 (0.5–29.1)		7.6 (0.7–138.9)		14.0 (1.2–143.0)		19.4 (2.1–68.5)		13.9 (1.2–143.0)	
IQR	6.3–20.1		5.3–20.5		6.4–20.1		5.3–11.9		4.7–8.7		5.3–12.2		7.8–28.1		6.9–30.5		7.8–27.6	
Risk stratification for localised PCa																		
Low risk	329	25.3	9	13.4	320	25.9	177	33.1	4	11.4	173	34.6	152	19.8	5	15.6	147	20.0
Intermediate risk	359	27.6	19	28.4	340	27.5	207	38.7	17	48.6	190	38.0	152	19.8	2	6.3	150	20.4
High risk	561	43.1	34	50.7	527	42.7	131	24.5	12	34.3	119	23.8	430	56.1	22	68.8	408	55.5
NA (T4, N1)	24	1.8	4	6.0	20	1.6	47	8.8	1	2.9	6	1.2	17	2.2	3	9.4	14	1.9
Unknown	29	2.2	1	1.5	28	2.3	13	2.4	1	2.9	12	2.4	16	2.1	0	0.0	16	2.2
AJCC stage, prognostic group																		
I	324	24.9	8	11.9	316	25.6	175	32.7	4	11.4	171	34.2	149	19.4	4	12.5	145	19.7
IIa	329	25.3	10	14.9	319	25.8	185	34.6	8	22.9	177	35.4	144	18.8	2	6.3	142	19.3
IIb	246	18.9	21	31.3	225	18.2	78	14.6	15	42.9	63	12.6	168	21.9	6	18.8	162	22.0
III	343	26.3	18	26.9	325	26.3	85	15.9	6	17.1	79	15.8	258	33.6	12	37.5	246	33.5
IV	60	4.6	10	14.9	50	4.0	12	2.2	2	5.7	10	2.0	48	6.3	8	25.0	40	5.4
ADT duration																		
No ADT	655	50.3	35	52.2	620	50.2	486	90.8	30	85.7	456	91.2	169	22.0	5	15.6	164	22.3
<6 mo	294	22.6	8	11.9	286	23.2	18	3.4	2	5.7	16	3.2	276	36.0	6	18.8	270	36.7
≥6 mo	353	27.1	24	35.8	329	26.6	31	5.8	3	8.6	28	5.6	322	42.0	21	65.6	301	41.0

ADT = androgen deprivation therapy; AJCC = American Joint Committee on Cancer; IQR = interquartile range; NA = not available; PCa = prostate cancer; PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiation therapy.

in the RT cohort was 14 ng/ml (range: 1.2–143) and 7.5 ng/ml (range: 0.5–139) in the RP cohort ($p < 0.001$). Gleason scores 7 and ≥8 were present in 36% and 20% of tumours in the RT cohort versus 32% and 10% in the RP cohort, respectively ($p < 0.001$). T1–T2 tumours accounted for 78% of those in the RP cohort; 71% in the RT cohort were T2–T3 ($p < 0.001$). AJCC stages I and IIa represented 66% of cases in the RP cohort; stage IIb and III accounted for 55% of RT cases ($p < 0.001$). As expected, the use of androgen-deprivation therapy (ADT) was more frequent in the RT cohort than in the RP cohort (78% vs 9%; $p < 0.001$).

A total of 35 *BRCA* carriers and 500 noncarriers underwent RP. Overall, 6% of carriers had T1 tumours and 69% had T2 tumours versus 34% and 45% of noncarriers, respectively ($p < 0.01$). Gleason score ≥8 was present in 26% of *BRCA* cases and 9% of noncarriers ($p < 0.001$). As illustrated in Table 1, carriers tended to higher AJCC stages ($p = 0.009$). No relevant differences were observed between carriers and noncarriers in age, PSA, N1, or use of ADT. After a median follow-up of 60 mo (range: 12–245), 24 metastatic progressions and 17 PCa-related deaths occurred.

A total of 32 carriers and 735 noncarriers received RT. In this cohort, carriers and noncarriers presented with similar age, PSA, and T stage, but 43% of carriers presented tumours with Gleason score ≥8 versus 19% of noncarriers ($p < 0.001$). N1 was also more frequent in *BRCA* carriers (9.4% vs 1.9%; $p = 0.005$). Subsequently, *BRCA* carriers tended to more advanced AJCC stages than noncarriers ($p = 0.009$) (Table 1). ADT was received by 78% of patients, with 65% of carriers receiving it ≥6 mo versus 41% of noncarriers ($p = 0.020$). After a median follow-up of 67 mo (range: 12–233), 103 metastatic progressions and 81 PCa-related deaths were observed.

3.2. Metastasis-free survival

Metastatic disease following radical treatment with curative intent was observed in 127 patients. At 3, 5, and 10 yr after treatment, 97%, 94%, and 84% of noncarriers *vs* 90%, 72%, and 50% of carriers were free from metastasis ($p < 0.001$) (Fig. 2A). Exploratory analyses suggested that *BRCA* status may have a prognostic impact on both RP and RP cohorts. Following RP, 99%, 97%, and 91% of noncarriers were free from metastasis at 3, 5, and 10 yr compared with 96%, 89%, and 67% of carriers, respectively ($p = 0.024$) (Fig. 2B). In the RT cohort, 96%, 91%, and 80% of noncarriers were free from metastasis at 3, 5, and 10 yr compared with 85%, 57%, and 39% of *BRCA* carriers ($p < 0.001$) (Fig. 2C).

Initially, a single-risk model was derivative for all patients using UVA and MVA as previously described. MVA confirmed *BRCA* mutations as an independent prognostic factor for MFS in this series (HR: 2.36; 95% confidence interval [CI], 1.38–4.03; $p = 0.002$). Other independent prognostic variables included AJCC stage ($p < 0.001$), Gleason score ($p < 0.001$), and treatment modality ($p = 0.004$) (Table 2). The *BRCA-status*Treatment-modality* interaction term was not significant; therefore, we did not pursue further prognostic analyses by treatment modality. The C-index for the model with all the independent prognostic factors was 0.806. The predictive

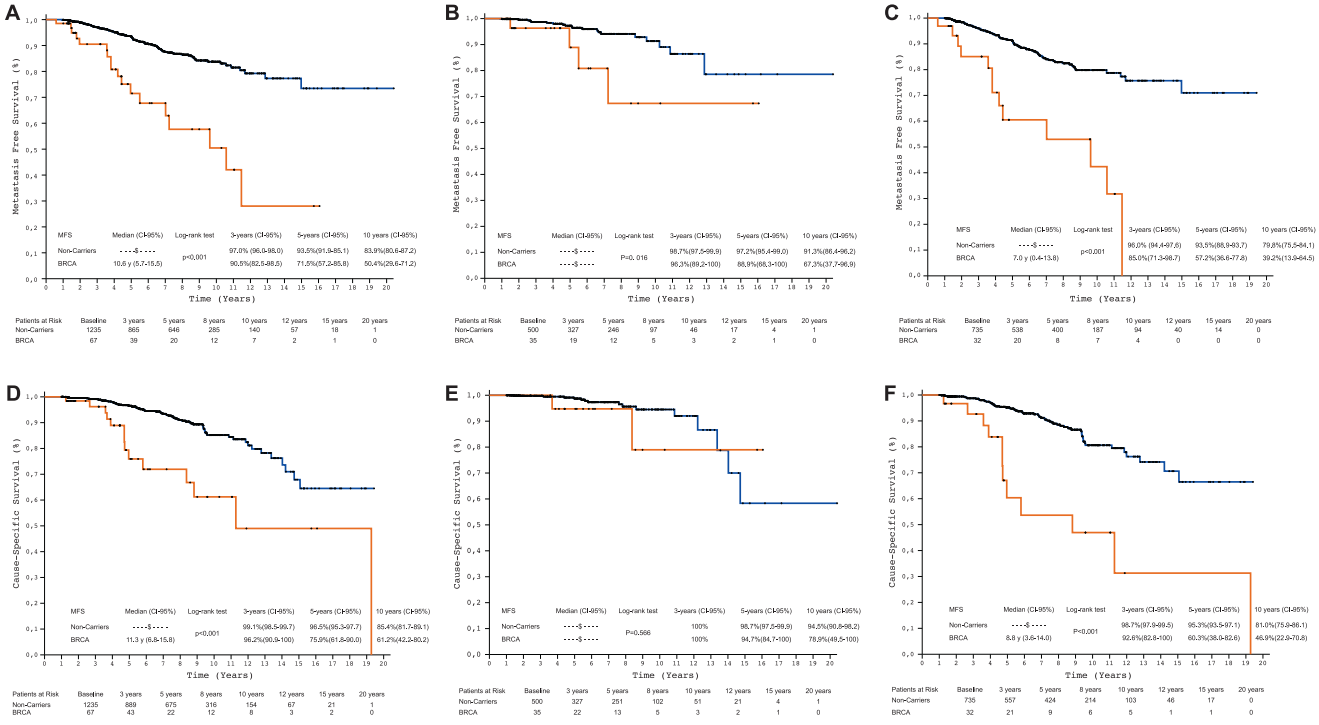

Fig. 2 – Kaplan-Meier survival curves in all patients, radical prostatectomy (RP) cohort, and external-beam radiation therapy (RT) cohort. (A) Metastasis-free survival (MFS) in all patients; (B) MFS in the RP cohort; (C) MFS in the RT cohort; (D) cause-specific survival (CSS) in all patients; (E) CSS in the RP cohort; (F) CSS in the RT cohort. Survival curves for noncarrier patients are blue; *BRCA1* and *BRCA2* mutation carriers are orange. S Median survival in this group was not reached after a median of 64-mo follow-up in the study.
CI = confidence interval; CSS = cause-specific survival; MFS = metastasis-free survival; RP = radical prostatectomy; RT = radiation therapy.

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Table 2 – Multivariable analyses for metastasis-free survival

	HR	95% CI	*p* value
BRCA carrier vs noncarriers	2.36	1.38–4.03	0.002
Tumour stage (T)			0.639
T2 vs T1	0.77	0.40–1.46	0.421
T3 vs T1	0.57	0.17–1.91	0.358
T4 vs T1	0.87	0.25–3.02	0.827
Nodes: N1 vs N0	1.59	0.67–3.75	0.289
Gleason score			<0.001
7 vs ≤6	2.25	1.29–3.90	0.004
≥8 vs ≤6	4.46	2.48–8.01	<0.001
PSA level	1.00	1.00–1.01	0.272
Treatment: RP vs RT	0.48	0.29–0.79	0.004
ADT			0.280
≤6 mo vs no ADT	1.55	0.83–2.89	0.171
>6 mo vs no ADT	1.12	0.62–2.04	0.705
AJCC stage			<0.001
IIa vs I	2.12	0.75–6.01	0.156
IIb vs I	2.13	0.75–6.00	0.155
III vs I	3.25	1.19–8.82	0.021
IV vs I	8.35	2.94–23.72	<0.001
Age at diagnosis	NA	NA	NA
Metastasis-free survival: Kattan, *BRCA*, and treatment (T4 excluded)			
BRCA carrier vs noncarriers	3.23	1.92–5.43	<0.001
Kattan score	1.02	1.01–1.02	<0.001
Treatment: RP vs RT	0.58	0.36–0.93	0.026

ADT = androgen-deprivation therapy; AJCC = American Joint Committee on Cancer; CI = confidence interval; HR = hazard ratio; NA = not applicable; PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiation therapy.

value of this MVA model was significantly superior to a model including all baseline variables except *BRCA* status (C-index: 0.798; $p = 0.028$) (Table 3).

3.3. *Cause-specific survival*

During the follow-up period, 144 deaths occurred, 96 of them attributed to PCa. The 3-, 5-, and 10-yr CSS rates from radical treatment were significantly better in the noncarrier cohort (99%, 97%, and 85%, respectively) than in carriers (96%, 76%, and 61%, respectively; $p < 0.001$) (Fig. 2D). Just to illustrate the outcome of these two cohorts, we performed separate survival analyses. No significant differences in CSS were seen between carriers and noncarriers after RP (100%, 99%, and 95% of noncarriers vs 100%, 95%, and 79% of carriers at 3, 5, and 10 yr after surgery; $p = 0.566$) (Fig. 2E). On the contrary, carriers treated with RT had shorter survival than noncarriers. CSS was 93%, 60%, and 47% at 3, 5, and 10 yr for carriers compared with 99%, 95%, and 81% in noncarriers (Fig. 2F). Nonetheless, MVA demonstrated that these differences in outcomes could not be attributed to the interaction between *BRCA* status and treatment modality.

MVA for the complete series confirmed the independent value for CSS of *BRCA* mutations (HR: 2.17; 95% CI, 1.16–4.07; $p = 0.016$). Additional significant factors in this MVA included Gleason score ($p < 0.001$), PSA pretreatment level ($p = 0.033$), treatment modality ($p = 0.035$), and AJCC stage ($p = 0.016$) (Table 4). Because the interaction term *BRCA status*Treatment modality* was not significant, we did not carry out further prognostic model analysis for this outcome according to treatment group. The C-index value for this MVA prognostic model was 0.813 and was significantly superior to a model with all baseline variables but *BRCA* status (C-index: 0.796; $p = 0.048$) (Table 3).

4. Discussion

We have previously demonstrated that *BRCA* mutation carriers have a worse prognosis than noncarriers when diagnosed with PCa at any stage without considering treatment modality [4]. In this study, we have shown that those carriers who were treated at diagnosis with curative intent using conventional radical treatment modalities (RT or RP) developed metastasis earlier and had shorter survival than noncarriers, independent of other prognostic factors. This is the first genetic event proven to be a prognostic factor for localised PCa treated with conventional radical treatment.

The recommendation for the general population to undergo RT or RP is usually based on PSA levels at diagnosis, Gleason score, tumour stage, performance status, life expectancy, and patient preferences [12]. *BRCA* carriers with localised PCa are currently treated following the same protocols used for noncarriers because until this study, no data were available to indicate that they may have a different outcome from the treatment strategies used in noncarriers. Our initial results showed that *BRCA* carriers treated with RT have significantly shorter MFS and CSS than those who underwent RP. Although one could be tempted to conclude that RP is a better curative option, our study

Table 3 – Predictive value with different prognostic models for metastasis-free survival and cause-specific survival

Variables in the model	C-index
Models for metastasis-free survival	
MVA model: *BRCA*, Gleason, treatment, AJCC stage	0.806
Significant variables in univariate analyses: *BRCA*, Gleason, treatment, AJCC stage, T stage, PSA, N stage, ADT	0.809
Baseline without *BRCA* status: all variables but *BRCA*	0.796
Baseline with *BRCA* status: all variables including *BRCA*	0.811
Models for cause-specific survival	
MVA model: *BRCA*, Gleason, PSA, treatment, AJCC stage	0.813
Significant variables in univariate analyses: *BRCA*, Gleason, PSA, treatment, AJCC stage, T stage, N stage	0.814
Baseline without *BRCA* status: all variables but *BRCA*	0.802
Baseline with *BRCA* status: all variables including *BRCA*	0.823

ADT = androgen deprivation therapy; AJCC = American Joint Committee on Cancer; C-index = concordance index; MVA = multivariable analysis; PSA = prostate-specific antigen.

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Table 4 – Multivariable analyses for cause-specific survival

Variables	Multivariable		
	HR	95% CI	*p* value
BRCA carrier vs noncarriers	2.17	1.16–4.07	0.016
Tumour stage (T)			0.597
T2 vs T1	1.22	0.54–2.77	0.635
T3 vs T1	0.54	0.12–2.44	0.425
T4 VS T1	0.96	0.21–4.30	0.952
Nodes: N1 vs N0			
Gleason score			<0.001
7 vs ≤6	2.50	1.23–5.07	0.011
≥8 vs ≤6	5.99	2.86–12.55	<0.001
PSA level	1.01	1.00–1.02	0.033
Treatment: RP vs RT	0.52	0.28–0.95	0.035
ADT			
≤6 mo vs no ADT	NA	NA	NA
>6 mo vs no ADT			
AJCC stage			0.016
IIa vs I	1.55	0.46–5.18	0.481
IIb vs I	1.27	0.38–4.24	0.696
III vs I	2.07	0.65–6.62	0.218
IV vs I	3.73	1.10–12.66	0.035
Age at diagnosis	NA	NA	NA
Cause-specific survival: Kattan score, treatment, and *BRCA* (T4 excluded)			
BRCA carrier vs noncarriers	2.78	1.53–5.04	0.001
Kattan score	1.02	1.01–1.02	<0.001
Treatment	0.60	0.34–1.05	0.071

ADT = androgen deprivation therapy; AJCC = American Joint Committee on Cancer; NA = not applicable; PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiation therapy.

cohorts (RT and RP) were not balanced because those patients with more tumour burden and aggressive histology were more often treated with RT rather than RP, according to international clinical practice guidelines, and therefore the risk of metastatic recurrence and death from PCa was higher. Therefore, direct comparisons between the two cohorts are not possible. Because there was not significant statistical interaction between *BRCA* status and treatment modality for MFS and CCS outcomes in our series, independent prognostic analyses for RT and RP subgroup were not justified. Consequently, we should conclude that *BRCA* status seems to affect both cohorts similarly.

A randomised study would be ideal to establish the most appropriate management of localised PCa in *BRCA* carriers. This might be difficult to perform because a large randomised trial comparing RT and RP has never been conducted in the general population. To date, only indirect comparisons of these modalities can be performed by retrospective analyses of population-based data sets [13–16]. The poor response to RT observed in *BRCA* carriers may be due to either radio resistance or to the development of new primary tumours. Previous studies conducted in breast cancer patients with *BRCA* mutations showed that radiosensitivity in those patients does not differ from that in the general population because local relapses and toxicity do not occur more frequently than in noncarriers [17]. However, RT to treat breast cancer is usually administered after surgical removal of the tumour and, in most cases, after adjuvant chemotherapy, and it is therefore delivered in a different context to current management strategies for PCa. Moreover, PCa patients are not usually rebiopsied at biochemical relapse after RT, and we cannot differentiate PSA failures due to local relapse from those due to new primary tumours.

Our results also raise the question of whether adjuvant treatments may be beneficial for *BRCA* carriers. ADT is routinely added to RT for localised and locally advanced disease to improve outcomes. Currently no data are available about the most appropriate scheme of ADT for *BRCA* carriers. However, because androgen receptor–maintained activity has been shown to increase chromosomal instability [18], an increased duration of ADT may possibly benefit patients with DNA repair defects.

No data are available regarding the efficacy of neoadjuvant or adjuvant chemotherapy for *BRCA* carriers. Adjuvant chemotherapy is not a standard of care for PCa because its clinical impact remains to be examined through randomised clinical trials [19]. However, previous studies have demonstrated that *BRCA*-mutated tumours are especially sensitive to compounds that induce double-strand breaks. *BRCA2* mutations in patients with ovarian cancer are associated with better long-term survival, reflecting the increased sensitivity of these tumours to adjuvant platinum-based chemotherapy regimens [6,20,21]. Inhibitors of poly (ADP-ribose) polymerase (PARP) have been proven to be active in *BRCA*-mutated tumours including metastatic PCa [22,23], but their role in the adjuvant setting of PCa has not yet been investigated.

Despite our results, the screening of unselected patients for germline *BRCA* mutations is not justified due to the current cost of the procedure and the low frequency of those events in sporadic PCa. However, as technologies evolve and the cost of sequencing genomes and specific gene panels continues to decrease, the screening of *BRCA* mutations may prove cost effective, especially if further studies support the need of personalised treatment for patients with germline and/or somatic *BRCA* alterations.

5. Conclusions

Our study demonstrates that *BRCA* carriers treated for localised PCa have worse outcomes than noncarriers because they relapse and progress earlier to lethal metastatic disease. Pending future studies confirming the biologic role of *BRCA* genetic alterations in this setting, our results support closer follow-up of these patients and the need for clinical trials to tailor the best radical/adjuvant treatments.

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