Original Article

Radiation-Induced Lymphopoenia and Treatment Outcome in Hereditary Breast Cancer Patients

(breast cancer / adjuvant radiotherapy / radiation-induced toxicity / multigene panel testing / hereditary cancer predisposition / germline pathogenic variant / *BRCA1* / *BRCA2* / *ATM* / *PALB2* / *RAD51C* / *RAD51D*)

SOŇA ARGALÁCSOVÁ, ĽUDMILA KŘÍŽOVÁ, MARTIN MATĚJŮ, DOMINIKA SVOBODOVÁ, MICHAL VOČKA

Department of Oncology, First Faculty of Medicine, Charles University and General University Hospital in Prague, Czech Republic

Abstract. Many breast cancer (BC) predisposition genes encode proteins involved in DNA damage repair (DDR). Identification of germline pathogenic variants (PV) in *DDR* genes raises the question whether their presence can influence the treatment outcomes and potential radiation-induced toxicity in their carriers treated by adjuvant radiotherapy, which has not yet been answered conclusively. We retrospectively examined records of 213 BC patients treated by adjuvant radiotherapy, including 39 (18.3 %) *BRCA1/2* PV carriers, 25 carriers (11.7 %) of PV in other breast cancer-predisposing genes, and 149 (70 %) non-carriers. Our goal was to examine 5-year disease-free survival (5y DFS) rates among the study groups and determine the impact of radiotherapy-induced lymphopoenia (RIL) on this outcome. While we found no significant difference in 5y DFS between non-carriers and carriers of *BRCA* mutations (86.4 % vs 78.4 % P = 0.24) or between non-carriers and other studied mutations (86.4 % vs 93.3 %; P = 0.27), respectively, we observed that the entire group of PV carriers had a significantly lower proportion of patients without RIL (P = 0.04) than the non-carriers. In contrast, subsequent analyses indicated a non-significant trend toward an increased 5y DFS in PV carriers with RIL. Our single-centre study indicated that the presence of PV in BC patients has an insignificant impact on DFS but can reduce the risk of RIL associated with adjuvant radiotherapy. It remains unclear whether this may result from the paradoxical activation of anti-tumour immunity in PV carriers with higher lymphocyte consumption resulting from higher immune effectiveness.

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Corresponding author: Soňa Argalácsová, Department of Oncology, First Faculty of Medicine, Charles University and General University Hospital in Prague, U Nemocnice 2, 120 00 Prague 2, Czech Republic. Phone: +420 224 962 219; e-mail: sona.argalacsova@vfn.cz

Abbreviations: 5y DFS – five-year disease-free survival, ALL-PV – carriers of any PV (BRCA-PV+OTHER-PV), BC – breast cancer, BRCA-PV – carriers of PV in the *BRCA1/BRCA2* genes, CBC – contralateral breast cancer, CI – confidence interval, DDR – DNA damage repair, GUH – General University Hospital in Prague, HBOC – hereditary breast and ovarian cancer, HR – hazard ratio, NC – pathogenic variant (PV) non-carriers, OTHER-PV – carriers of PV in other BC predisposition genes (except *BRCA1/BRCA2* PV carriers), PV – pathogenic variants in *DDR* genes, RIL – radiotherapy-induced lymphopoenia, RT – radiotherapy, TNBC – triple-negative BC, WBI – whole-breast irradiation.

Introduction

Breast cancer (BC) is the most frequent cancer type worldwide (Ferlay et al., 2021). Breast cancer is a multifactorial disease; however, about 5–10 % of BC cases are caused by germline pathogenic variants (PV) in breast cancer predisposition genes coding for DNA repair and DNA damage response proteins in majority (incl. *BRCA1, BRCA2*, *CHEK2*, *ATM*, *PALB2*, *RAD51C/RAD51D*, *TP53*, *BRIP1*, *PTEN*) (Desmond et al., 2015; Kleibl and Kristensen, 2016). Tumours in mutation carriers are characterized by specific clinical and histopathological features that, at least in a part, correspond to the DNA repair impairment. Thus, the contribution of impaired DNA repair processes to changes in efficacy and toxicity of genotoxic therapeutic options, including radiotherapy (RT), is a longstanding matter of debate (Lazzari et al., 2021; Chapman et al., 2022; Gonçalves et al., 2022). Moreover, the impact of PV in *BRCA1/BRCA2* and other cancer predisposition genes on the

clinical outcome in BC patients (the rate of radiation-induced toxicity and the risk of radiation-induced contralateral and/or secondary malignancies) has been studied (Pollard and Gatti, 2009; Fan et al., 2018; Vocka et al., 2019; Reiner et al., 2020; Lazzari et al., 2021; Chapman et al., 2022; Gonçalves et al., 2022). Although the findings are neither systematic nor complete, the American Society of Clinical Oncology, the American Society for Radiation Oncology, and the Society of Surgical Oncology have developed recommendations for the management of BC patients carrying PV in BC predisposition genes (Bergom et al., 2019; Tung et al., 2020). There are no conclusive data supporting increased radiation toxicity in patients with PV in *BRCA1*, *BRCA2*, *PALB2*, *CHEK2*, etc. Therefore, RT recommendations for these patients should not be altered based on PV in DNA repair and DNA damage response proteins. Although pathogenic *ATM* mutations may increase the risk of contralateral BC (CBC) after RT and RT-induced toxicity, RT should not be abandoned in *ATM* carriers but only carefully indicated, especially in young patients (Bergom et al., 2019). Currently, pathogenic variants in *ATM* and *TP53* may be associated with worse radiation-related toxicity (Bergom et al., 2019; Tung et al., 2020; Chapman et al., 2022).

The association between reduced baseline immunity or low lymphocyte counts with cancer prognosis and outcome has been described in several studies (Venkatesulu et al., 2018; Abravan et al., 2020; Xie et al., 2020; Damen et al., 2021; Ni et al., 2022) demonstrating that severe radiotherapy-induced lymphopoenia (RIL; G3 and G4) significantly affects survival parameters in many solid tumours (e.g., oesophageal cancers, pancreatic cancers, and lung tumours) and represents an important prognostic factor. Sun and colleagues (2020) demonstrated a significantly lower 5y DFS for BC patients with more severe RIL (71.8 % vs 82.6 %; P = 0.01) and a lower RIL rate for the patients irradiated with hypofractionated adjuvant chest wall radiotherapy compared with normofractionated radiotherapy. Chemotherapy, lung doses, and radiation technique are reported to be the most important risk factors for the development of RIL in BC patients after adjuvant radiotherapy (Chen et al., 2021). The rate of RIL in BC patients carrying PV in BC predisposition genes has not been systematically investigated yet.

The aim of our study was to determine the rate of acute and late toxicity and specifically RILs in different groups with respect to the presence of specific PV and to analyse its effect on 5y DFS in each subgroup.

Patients and Methods

The clinical and histopathological data from BC patients who underwent germline genetic testing between March 2015 and May 2021 were retrospectively obtained from the institutional database of the Department of Oncology of the General University Hospital (GUH) in Prague. The enrolled patients fulfilled the following criteria:

- histologically or pathologically confirmed BC diagnosed at the age ≥ 18 years,
- treated for non-metastatic cancer (clinical stage I-III) with radical surgery and adjuvant radiotherapy with or without any systemic therapy (e.g., hormonal therapy, chemotherapy, anti-Her2 therapy, or immunotherapy),
- tested for hereditary cancer predisposition.

Hereditary predisposition testing was performed in BC patients who either met national testing guidelines (approved by the Czech Society for Medical Genetics; https://slg.cz/doporuceni/testovani-brca-lecba/) or were part of a research project in patients not indicated for germline genetic testing. All patients provided their informed consent approved by the Ethics Committee of the General University Hospital in Prague and the First Faculty of Medicine, Charles University. The germline genetic testing used a standard procedure that involved germline next-generation sequencing analysis with the CZECANCA multigene panel targeting 226 cancer predisposition and candidate genes (ver. 1.22; http://www.czecanca.cz/panel.html), followed by a bioinformatic pipeline to identify PV. The analysis, bioinformatics, and variant prioritization have been described in detail previously (Soukupová et al., 2016; Soukupova et al., 2018; Lhotova et al., 2020; Kral et al., 2023). Based on the presence of PV in the established BC predisposition genes, the BC patients were assigned to the following groups: carriers of *BRCA1/BRCA2* PV (referred to as BRCA-PV), carriers of PV in other BC cancer predisposition genes (OTHER-PV), carriers of any PV (BRCA-PV+OTHER-PV referred to as ALL-PV), and PV non-carriers (NC).

Patients' age at diagnosis, sex, lymph node involvement, initial stage of disease according to the American Joint Committee on Cancer staging manual 7th edition (Edge et al., 2010), date of diagnosis, histological type of tumour, oestrogen receptor status, HER2/neu status, extent of the resection, pathological stage of disease, neoadjuvant and adjuvant systemic therapy, duration and extent of radiotherapy, and acute radiation-induced toxicity during and within 90 days after RT and occurrence of lymphedema were recorded.

The primary endpoint of our analysis was 5y DFS and its comparison between the studied groups. DFS was calculated from the day of the end of the radiotherapy course to the event (death, disease progression, or day of the last follow-up visit).

Standard descriptive statistics were used to summarize the patients' characteristics. The primary endpoint (5y DFS) was estimated using the Gehan-Breslow-Wilcoxon test. The primary analysis included the hazard ratio (HR) estimate and its 95 % confidence interval (CI) using the Cox proportional hazards model comparing the treatment groups. The HR and CI were compared with the non-inferiority margin, which was set to 5 %.

Statistical analysis was performed using GraphPad Prism Software (Version 5, El Camino True, CA).

The project was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the General University Hospital in Prague and the First Faculty of Medicine, Charles University (No. 1858/14); informed consent was obtained from all participating subjects.

Results

Between March 2015 and May 2021, 213 BC patients meeting the inclusion criteria underwent germline genetic testing. The results revealed 39 patients (18.3 %) with *BRCA1/BRCA2* gene, 25 patients (11.7 %) with PV in other BC cancer predisposition genes including *CHEK2* (11), *ATM* (4), *PALB2* (4), *RAD51C/RAD51D* (3), *BARD1* (1), *TP53* (1), and *FANCM* (1) and 149 non-carriers (70 %).

The baseline patients' characteristics are summarized in Table 1. As expected, BC was diagnosed at a significantly younger age in the BRCA-PV group (42.9 vs 45.1 in NC group; P = 0.010) that included a higher proportion of triple-negative BC (TNBC) patients (48.7 % vs 28.8 % in NC group; P = 0.023). Compared to the NC group, the BRCA-PV group had a significantly higher mastectomy rate (61.5 vs 30.9; P < 0.001) and, reciprocally, lower rate of whole-breast radiation (WBI; 41.0 vs 59.7; P = 0.046) when compared with breast/chest wall radiation including locoregional lymphatics (59.0 vs 40.3; P = 0.046). We observed a non-significant trend towards a higher prevalence of more advanced stage III

Table 1. Clinicopathological characteristics of BC patients assigned to the groups according to the absence of any germline pathogenic variant in cancer predisposition gene (non-carriers; NC), carriers of PV in BRCA1/BRCA2 (BRCA-PV), carriers of PV in other BC cancer predisposition genes (OTHER-PV), or carriers of PV in any BC predisposition gene (ALL-PV), respectively

	NC (N = 149)			BRCA-PV (N = 39)			OTHER-PV (N = 25)			ALL-PV (N = 64)		
	N	(%)	P	N	(%)	P	N	(%)	P	N	(%)	P
Median age at diagnosis												
year (25–75 % percentile)	45.1	(25.6–76.8)	Ref.	42.9	(27.9–73.8)	0.010	46.2	(30.5–73.2)	0.90	45.0	(27.9–73.8)	0.07
Age diagnosis categories (known)												
< 35 y	12	(8.1)	Ref.	11	(28.2)	0.003	4	(16.0)	0.17	15	(23.4)	**0.005**
35–44 y	62	(41.6)		12	(30.8)		6	(24.0)		18	(28.2)	
≥ 45 y	75	(50.3)		16	(41.0)		15	(60.0)		31	(48.4)	
Gender												
male	2	(1.3)	Ref.	1	(2.6)	0.50	0	(0.0)	1.00	1	(1.6)	1.00
female	147	(98.7)		38	(97.4)		25	(100.0)		63	(98.4)	
Primary tumour (T)												
Tis (in situ)	1	(0.7)	Ref.	0	(0.0)	0.31	0	(0.0)	0.81	0	(0.0)	0.65
T1 (< 2 cm)	81	(54.3)		15	(38.5)		14	(56.0)		29	(45.3)	
T2 (2–5 cm)	57	(38.3)		19	(48.7)		9	(36.0)		28	(43.8)	
T3 (> 5 cm)	6	(4.0)		2	(5.1)		2	(8.0)		4	(6.2)	
T4	4	(2.7)		3	(7.7)		0	(0.0)		3	(4.7)	
Regional lymph node (N)												
N0	80	(53.7)	Ref.	17	(43.6)	0.23	12	(48.0)	0.88	29	(45.3)	0.23
N1	63	(42.3)		18	(46.2)		11	(44.0)		29	(45.3)	
N2–3	6	(4.0)		4	(10.2)		2	(8.0)		6	(9.4)	
Tumour stage												
0 (Tis)	1	(0.7)	Ref.	0	(0.0)	0.18	0	(0.0)	0.59	0	(0.0)	0.16
I (T1N0-1mi)	62	(41.6)		10	(25.7)		9	(36.0)		19	(29.7)	
II (T2-3N0, T1-2N1)	70	(47.0)		21	(53.8)		11	(44.0)		32	(50.0)	
III (T3N1, TXN2-3, T4N0-3)	16	(10.7)		8	(20.5)		5	(20.0)		13	(20.3)	
Breast tumour morphology												
ductal	133	(89.2)	Ref.	34	(87.2)	0.16	24	(96.0)	0.43	58	(90.7)	0.31
lobular	14	(9.4)		2	(5.1)		0	(0.0)		2	(3.1)	
mucinous	1	(0.7)		2	(5.1)		0	(0.0)		2	(3.1)	
other	1	(0.7)		1	(2.6)		1	(4.0)		2	(3.1)	

	NC (N = 149)			BRCA-PV (N = 39)			OTHER-PV (N = 25)			ALL-PV (N = 64)		
	N	(%)	P	N	(%)	P	N	(%)	P	N	(%)	P
Grade												
low (1)	29	(19.5)	Ref.	3	(7.7)	0.13	1	(4.0)	0.25	4	(6.2)	0.06
intermediate (2)	54	(36.2)		12	(30.8)		10	(40.0)		22	(34.4)	
high (3)	43	(28.9)		18	(46.1)		8	(32.0)		26	(40.6)	
unknown (X)	23	(15.4)		6	(15.4)		6	(24.0)		12	(18.8)	
ER status												
positive	103	(69.1)	Ref.	20	(51.3)	0.06	19	(76.0)	0.64	39	(60.9)	0.27
HER-2 status												
positive	20	(13.4)	Ref.	7	(17.9)	1.00	6	(24.0)	0.22	13	(20.3)	0.22
TNBC												
yes	43	(28.8)	Ref.	19	(48.7)	0.023	4	(16.0)	0.23	23	(35.9)	0.33
Surgery – primary tumour												
mastectomy	46	(30.9)	Ref.	24	(61.5)	<0.001	8	(32.0)	1.00	32	(50.0)	**0.013**
breast-conserving surgery	103	(69.1)		15	(38.5)		17	(68.0)		32	(50.0)	
Surgery – lymph nodes												
axillary dissection	63	(42.3)	Ref.	22	(56.4)	0.15	9	(36.0)	0.66	31	(48.4)	0.45
sentinel node biopsy	86	(57.7)		17	(43.6)		16	(64.0)		33	(51.6)	
Radiotherapy												
WBI +/– boost	89	(59.7)	Ref.	16	(41.0)	0.046	15	(60.0)	1.00	31	(48.4)	0.13
WBI/PMTW + lrLN	60	(40.3)		23	(59.0)		10	(40.0)		33	(51.6)	
Chemotherapy												
NACT	61	(40.9)	Ref.	24	(61.6)	0.008	7	(28.0)	0.034	31	(48.4)	**0.010**
ACT	30	(20.2)		10	(25.6)		11	(44.0)		21	(32.8)	
No chemotherapy	58	(38.9)		5	(12.8)		7	(28.0)		12	(18.8)	
Chemotherapy type												
Antra	88	(59.1)	Ref.	30	(76.9)	0.042	17	(68.0)	0.55	47	(73.4)	0.06
Tax.	80	(53.7)	Ref.	33	(84.6)	<0.001	16	(64.0)	0.39	49	(76.5)	**0.021**
Platinum	6	(4.0)	Ref.	6	(15.4)	0.019	0	(0.0)	NA	6	(9.4)	0.19

WBI – whole-breast irradiation; PMTW – postmastectomy thorax wall; lrLN – locoregional lymph nodes; NACT – neoadjuvant chemotherapy; ACT – adjuvant chemotherapy; TNBC – triple-negative BC; Antra – anthracyclines; Tax – taxanes; Ref. – reference

in the BRCA-PV subgroup compared with the NC group (20.5 % vs 10.7 %; P = 0.16). Due to the higher proportion of TNBC and a slightly higher rate of the more advanced stage in the BRCA-PV group, significantly more patients in this group received chemotherapy (P = 0.008).

In terms of acute radiation-induced (RI) toxicity (Table 2), carriers of PV in cancer predisposition gene groups exhibited a significantly lower rate of BC patients with no RIL (G0) compared to the NC group (46.2 % in BRCA-PV, 40.0 % in OTHER-PV, and 43.5 % in ALL-PV vs 61 % in NC). The more severe RIL (≥ G2) did not exhibit any significant differences between the studied groups, as well as the other analysed characteristics and parameters. No other differences in RI toxicity (development of acute toxicity) were found among the studied groups.

Table 3 summarizes the primary assessment of the 5y DFS rates for the BRCA-PV, OTHER-PV, ALL-PV, and NC groups. The overall 5y DFS for all BC patients in the study was 85.7 %. No difference was found in the 5y DFS between NC and BRCA-PV (86.4 % vs 78.4 %; HR 1.83, 95 % CI = 0.67–5.03; P = 0.24) and between NC and OTHER-PV (86.4 % vs 93.3 %; P = 0.27; HR 0.48, 95 % CI = 0.13–1.78) groups, respectively. However, the BRCA-PV group exhibited a tendency towards a lower 5y DFS, while the OTHER-PV group displayed a higher 5y DFS in comparison to the NC group (Fig. 1).

The primary statistical analysis showed a significantly lower proportion of patients without RILs in all subgroups of patients with PV in cancer predisposition genes. In this context, we analysed the relationship between RIL rates and 5y DFS in each subgroup (BRCA-PV, OTHER-PV, ALL-PV, and NC groups). The differences in 5y DFS rates for each subgroup were compared between patients with no or mild radiation-induced lymphopoenia (G0–G1) and those with more severe lymphopoenia (≥ G2; Table 4). In all groups, there was a trend toward higher 5y DFS rates in patients with more severe lymphopoenia.

Table 2. Acute radiation-induced toxicity during and within 90 days after RT

	NC (N = 149)			BRCA-PV (N = 39)			OTHER-PV (N = 25)			ALL-PV		
	N	**%**	**P**	**N**	**%**	**P**	**N**	**%**	**P**	**N**	**%**	**P**
RI-toxicity – Acute dermatitis												
G0	27	(18.1)	Ref.	4	(10.2)	0.37	1	(4.0)	0.09	5	(7.8)	0.25
G1	84	(56.4)		28	(71.8)		13	(52.0)		41	(64.1)	
G2	32	(21.5)		6	(15.4)		8	(32.0)		14	(21.9)	
G3	6	(4.0)		1	(2.6)		3	(12.0)		4	(6.2)	
≥ G2	38	(25.5)	Ref.	7	(17.9)	0.40	11	(44.0)	0.09	18	(28.1)	0.74
RI-toxicity – Neutropoenia												
G0	127	(85.2)	Ref.	31	(79.5)	0.23	24	(96.0)	0.14	55	(85.9)	0.37
G1	17	(11.4)		4	(11.4)		0	(0.0)		4	(6.3)	
G2	2	(1.3)		1	(2.5)		0	(0.0)		1	(1.6)	
G3	1	(0.7)		2	(5.1)		0	(0.0)		2	(3.1)	
NA	2	(1.3)		1	(2.5)		1	(4.0)		2	(3.1)	
≥ G2	3	(2.1)	Ref.	3	(7.7)	0.10	0	(0.0)	NA	3	(4.7)	0.36
RI-toxicity – Lymphopoenia												
G0	91	(61.1)	Ref.	18	(46.2)	0.018	10	(40.0)	0.002	28	(43.5)	0.004
G1	1	(0.7)		3	(7.7)		3	(12.0)		6	(9.3)	
G2	38	(25.5)		14	(35.9)		6	(24.0)		20	(31.6)	
G3	17	(11.4)		3	(7.7)		5	(20.0)		8	(12.5)	
NA	2	(1.3)		1	(2.5)		1	(4.0)		2	(3.1)	
≥ G2	55	(36.9)	Ref.	17	(43.6)	0.46	11	(44.0)	0.50	28	(43.8)	0.35
Toxicity – Lymphedema												
G0	95	(63.7)	Ref.	24	(61.5)	0.34	16	(64.0)	0.94	40 12	(62.5)	0.97
G1	6	(4.0)		1	(2.6)		1	(4.0)		2	(3.1)	
G2	45	(30.2)		14	(35.9)		7	(28.0)		21	(32.8)	
G3	3	(2.1)		0	(0.0)		1	(4.0)		1	(1.6)	
NA	0	(0.0)		0	(0.0)		0	(0.0)		0	(0.0)	
≥ G2	48	(32.2)	Ref.	14	(35.9)	0.70	8	(32.0)	1.00	22	(34.9)	0.75

RI-toxicity – radiotherapy-induced toxicity

Table 3. 5y DFS in the observed groups of BC patients

	NC (N = 149)	BRCA-PV (N = 39)	OTHER-PV (N = 25)	ALL-PV (N = 64)
5y DFS (%)	86.4	78.4	93.3	83.9
Hazard ratio (95 % CI; P)	1 Ref.	1.83 (0.67–5.03; P = 0.24)	0.48 (0.13–1.78; P = 0.27)	1.14 (0.48–2.71; P = 0.77)

Discussion

The rate of pathogenic variants in hereditary cancer predisposition genes in our cohort was slightly higher than the reported rates (e.g., *BRCA1/2* 18.3 %, *CHEK2* 5.2 %), but consistent with their prevalence in a selected population of breast cancer patients referred for germline genetic testing (Kleiblova et al., 2019; Vocka et al., 2019; Chapman et al., 2022). Demographic and clinicopathological characteristics (stage, histology type, ER, and HER2/neu positivity) of the patients did not differ significantly among the subgroups, suggesting that the subgroups were well balanced and survival outcomes were not influenced by these factors. The increased rates of TNBC and advanced stages in patients with *BRCA1/BRCA2* PV are in line with established features of BRCA-related tumours as documented previously (Vocka et al., 2019; Lazzari et al., 2021; Chapman et al., 2022). Although it could be hypothesized that germline PV affecting DNA repair genes may have contributed to the higher toxicity rate in the subgroups with PV compared to the NC group, our analyses showed no signifi-

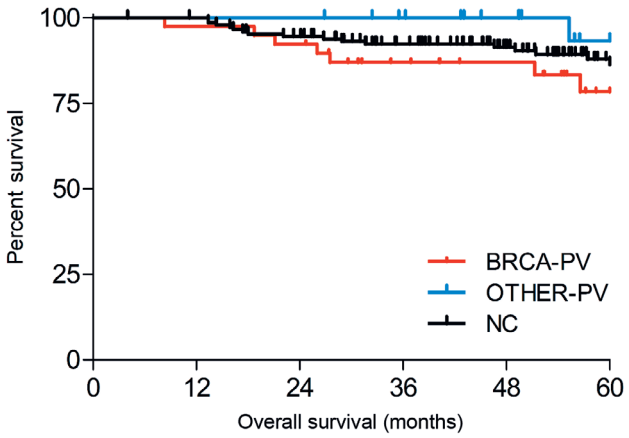

Fig. 1. 5y DFS for all subgroups
5y DFS – five-year disease-free survival; NC – pathogenic variant (PV) non-carriers; BRCA-PV – carriers of PV in the *BRCA1/BRCA2* genes; OTHER-PV – carriers of PV in other BC predisposition genes (except *BRCA1/BRCA2* PV carriers)

Table 4. Radiation-induced lymphopoenia (RIL) in the observed study groups

RIL – whole group	N (%)	5y DFS	Hazard ratio (95 % CI; P)
G0–1	126 (60.3)	85.0 %	1.46 (0.13–1.78; P = 0.38)
≥ G2	83 (39.7)	88.3 %	
NC (N = 147)[a]			
G0-1	92 (62.6)	85.5 %	1.28 (0.46–3.53; P = 0.64)
≥ G2	55 (37.4)	87.3 %	
BRCA-PV (N = 38)[b]			
G0–1	21 (55.3)	80.7 %	1.74 (0.35–8.68; P = 0.50)
≥ G2	17 (44.7)	85.6 %	
OTHER-PV (N = 24)[b]			
G0–1	13 (54.2)	88.9 %	5.29 (0.10–289.63; P = 0.41)
≥ G2	11 (45.8)	100.0 %	
ALL-PV (N = 62)[a]			
G0–1	34 (54.8)	83.6 %	1.94 (0.43–8.62; P = 0.39)
≥ G2	28 (45.2)	90.8 %	

[a]2 patients without any G of RIL; [b]1 patient without any G of RIL

cant evidence of a higher toxicity rate other than RIL (e.g., skin toxicity, lymphedema). While neither acute nor late skin toxicity differed between PV carrier and non-carrier groups in previous work, RILs were not specifically assessed (Pierce and Haffty, 2011; Bergom et al., 2019; Chapman et al., 2022).

There was no significant difference in 5y DFS between the non-carriers and carriers of PV in *BRCA1/BRCA2* or other BC predisposition genes, respectively. The observed trend towards lower 5y DFS in the BRCA-PV group compared to the NC group are in accordance with previously published reports (Vocka et al., 2019; De Talhouet et al., 2020). In a recent study of 266 *BRCA1/BRCA2* PV carriers and 659 non-carriers by De Talhouet et al. (2020), the *BRCA1/BRCA2* PV carriers showed prolonged DFS (HR = 0.63; 95 % CI 0.44–0.90), a trend towards prolonged disease-specific survival, as well as a prolonged survival in the TNBC subgroup, but unchanged survival in the non-TNBC subgroup. Vocka et al. (2019) enrolled 234 *BRCA1/BRCA2* mutation carriers and 899 non-carriers, although with a non-significant difference in DFS of 71.3 % versus 78.0 % (P = 0.24) for *BRCA1/2* mutation carriers compared to non-carriers. The presumed factor of prolongation of DFS in both studies and the trend towards prolongation of disease-specific survival in prognostically unfavourable *BRCA1/BRCA2* mutation carriers, especially with TNBC, is probably due to increased radiosensitivity and chemosensitivity (Vocka et al., 2019; De Talhouet et al., 2020).

The 5y DFS did not differ significantly between patients with no or only mild RIL and patients with more severe RIL (≥ G2) within each studied subgroup. However, there was a trend toward longer 5y DFS in patients with more severe lymphopoenia compared to patients with no or only mild lymphopoenia observed in the whole group of PV carriers. These observations contrast with previously published reports showing a clear negative effect of RILs on survival parameters in several types of solid tumours, including breast cancer (Venkatesulu et al., 2018; Abravan et al., 2020; Sun et al., 2020; Xie et al., 2020; Ni et al., 2022). Chemotherapy, lung doses, and radiotherapy techniques are reported to be the most important risk factors for the development of RIL in breast cancer after adjuvant radiotherapy (Chen et al., 2021). As no similar analysis of the effect of RILs in hereditary breast and ovarian cancer (HBOC)-associated PV carriers has been found to confirm or refute these conclusions, we can only speculate that radiotherapy-induced cell decay in more sensitive individuals with impaired DNA repair may lead to greater activation of the immune system, and therefore greater efficacy of the anti-tumour immune component than in non-carriers.

The main limitations of our study are its retrospective design and the restricted sample size of patients carrying PV in BC predisposition genes. Despite these limitations, the observed trend towards a potential inverse effect of RILs in carriers of pathogenic variants in HBOC genes is noteworthy and may mirror similar survival patterns in this group of patients (e.g., TNBC), and deserves further investigation in larger cohorts of patients, as well as analysis of other contributing factors.

Conclusion

Toxicity and oncological outcome of the disease do not differ significantly between BC patients with or without pathogenic variants in cancer predisposition genes, according to the previously published studies.

However, our results demonstrated that BC patients carrying germline PV, including patients carrying PV in *BRCA1/BRCA2* or other BC predisposition genes, have significantly lower rates of mild or no lymphopoenia. Additionally, our analysis indicates that severe radiotherapy-induced lymphopoenia in PV carriers can paradoxically extend the 5y DFS. However, further studies will be required to examine this observation and the proposed hypothesis that this effect is a consequence of activation of anti-tumour immunity resulting in increased lymphocyte consumption and thus higher RT efficiency.

Authors' contributions

All authors planned, designed, and participated in the trial. SA and MV drafted the manuscript and performed the evaluation and statistical analysis. All authors contributed to the critical review of the manuscript and approved the final version.

Conflict of interest

The authors declare no conflict of interest.

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