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REVIEW ARTICLE

Is breast-conserving therapy adequate in BRCA 1/2 mutation carriers? The radiation oncologist's point of view

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ABSTRACT

Breast conserving therapy (BCT) is currently a recognized alternative to mastectomy for early BC patients. However, the therapeutic index of BCT was considered controversial for decades in BRCA1/2 mutation carriers. The aim of the present review was to investigate the outcome of mutation carriers undergoing BCT regarding local and distant endpoints. A short review was performed from the point of view of the radiation oncologist. Only retrospective data were available regarding local outcome assessment. They generated conflicting results. In studies with limited follow-up, BCT did not increase the risk of local recurrence in BRCA1/2 mutation carriers *versus* non-carriers. Conversely, some studies with longer follow-up supported that local relapse was increased in mutation carriers. Yet, according to some publications, their long-term risk of ipsilateral recurrence post-BCT was not different from general population cohorts. Besides, overall and metastasis-free survivals were the same after BCT regardless of the BRCA1/2 mutation status. Similar survival rates were also reported when BCT and mastectomy were compared in mutation carriers. Regarding acute or late toxicity, normal rates were reported in BRCA mutation carriers after breast radiotherapy. The BRCA1/2 mutation does not seem to widely alter the therapeutic index (efficacy/toxicity ratio) of modern adjuvant breast irradiation. Although the long term equivalence of BCT/mastectomy on local control is still not clearly recognised, BCT can be considered an adequate option for BRCA1/2 mutation carriers. This review highlights that BCT is a reasonable option for BRCA1/2 mutation carriers however litterature is controversial concerning long-term local outcome and results of a large prospective cohort are needed.

INTRODUCTION

Tumour-suppressor genes BRCA1 and 2 (BReast CAncer gene) regulate genome stability, transcription and DNA repair based on homologous recombination (HR).[1] Although BRCA1 and 2 mutations are rare,[2] they have a major impact on mutation carriers. Half of them may have a breast cancer (BC) before 70.[3] Breast conserving therapy (BCT) is a recognized alternative to mastectomy for early BC patients. BCT is based on a lumpectomy followed by breast irradiation. In sporadic BC patients, it was shown to provide a survival equivalent to mastectomy with a cosmetically acceptable breast and a low rate of local recurrence. However, the therapeutic index of BCT was considered controversial for decades in BRCA mutation carriers due to an elevated radiosensitivity of BRCA1 and 2 mutated cells. On the one hand, the two copies of BRCA are regularly missing in tumour cells which results in a full loss of function of the gene.[4] Preclinical and clinical data showed that such cells featured an increased radiosensitivity, supporting the hypothesis that tumours of BRCA mutation carriers might have better responses to radiation.[5–8] On the other hand, most patients are BRCA1/2 heterozygous carriers of an inherited single mutated allele because homozygous BRCA mutations predominantly induce non-viable embryos. Therefore mutation carriers' normal breast tissue still has a functional allele leading to partially maintained DNA repair capacities. This probably explains the normal rates of acute or late toxicity that were reported in BRCA mutation carriers after breast radiotherapy[9–15] (Table 1). However, small decreases in repair capacities were suspected to impact genome stability as evidenced by the increased cancer risk

Table 1. Data about radiation-induced toxicity in BRCA1/2 mutation carriers treated for breast cancer

Significant difference	Study	Year	Nb. of BRCA1/2 mutation carriers	Nb. of matched controls[a]/non-mutation carriers[b]	Median follow-up	Acute toxicities Nb. (%)	Late toxicities
Retrospective case/control studies. LEVEL OF EVIDENCE 3: LOW LEVEL OF EVIDENCE							
NO	Pierce et al.[9]	2000	67 (53 BRCA1, 14 BRCA2)	213[a]	5.3 years	**Skin toxicity:** BRCA = 19 (28%, with 1% of Grade 3) Sporadic = 61 (29%, with 3% of Grade 3) (p = 0.9) **Lung toxicity:** BRCA = 0 Sporadic = 0	**Skin toxicity:** BRCA = 2 (2%) Sporadic = 8 (3%) (p = 0.9) **Subcutaneous toxicity:** BRCA = 7 (10%) Sporadic = 26 (13%) (p = 0.5) **Lung toxicity:** BRCA = 1 (1%) Sporadic = 0 **No bone complication**
NO, except for acute severe breast pain	Shanley et al.[10]	2006	55 (37 BRCA1, 18 BRCA2)	55[a]	6.75 years	**Severe erythema**: BRCA = 10 (18%) Sporadic = 15[16] (NS, p not reported) **Moist desquamation:** BRCA = 8 (15%) Sporadic = 13 (24%) (NS, p not reported) **Severe breast pain:** BRCA = 2 (4%) Sporadic = 1 (2%) (p = 0.03) **Severe fatigue:** BRCA = 13 (24%) Sporadic = 7 (13%) (NS, p not reported)	**Rib fracture:** BRCA = 3 (5%) Sporadic = 3 (5%) (NS, p not reported) **Lung fibrosis:** BRCA = 1 (2%) Sporadic = 0 (NS, p not reported) **Soft tissue/Bone necrosis:** BRCA = 1 (2%) Sporadic = 0 (NS, p not reported) **No cardiac fibrosis**
Retrospective case or cohort studies. LEVEL OF EVIDENCE 4: LOW LEVEL OF EVIDENCE							
NO	Gaffney et al.[12]	1998	21 (11 BRCA1, 10 BRCA2)	none	Not reported	**Moist desquamation:** BRCA = 6 (28.5%) including two treatment discontinuations	N.A.

(Continued)

Table 1. (Continued)

Significant difference	Study	Year	Nb. of BRCA1/2 mutation carriers	Nb. of matched controls[a]/non-mutation carriers[b]	Median follow-up	Acute toxicities Nb. (%)	Late toxicities
NO	Huszno et al.[13]	2013	41 (BRCA1/2 repartition was not reported)	229[b]	Not reported	**Skin erythema:** BRCA = 23 (56%) Sporadic = 117 (53%) (p = 0.6) **Breast pain:** BRCA = 0 Sporadic = 7 (3%) (p = 0.2) **Dry skin desquamation:** BRCA = 2 (5%) Sporadic = 16 (7%) (p = 1) **Moist skin desquamation:** BRCA = 2 (5%) Sporadic = 12 (5%) (p = 1)	N.A.
NO	Park et al.[15]	2014	46 (20 BRCA1, 24 BRCA2, 2 BRCA1 +2)	167[b]	First day of RT until 30 days post RT	**Skin Toxicity:** BRCA1 = 4 (7%) BRCA2 = 9 (15.8%) BRCA 1 + 2=0 (0%) Total BRCA = 13 (28%) Non-mutation = 44 (26%) (p = 0.342 for BRCA1, p = 0.337 for BRCA2, p = 0.785 for BRCA1 +2)	N.A.
NO	Huzno et al.[14]	2015	40 BRCA (repartition between BRCA1 and 2 is not reported)	251[b]	Not reported	**Skin toxicity:** BRCA = 1 (3%) Sporadic = 6 (4%) (p = 0.9) requiring 1 BRCA treatment discontinuation (p = 0.89)	N.A.

BCT, Breast conserving therapy; N.A, not assessed; NS, not significant; Nb, number; PORT, Post-operative radiotherapy; RT, Radiotherapy.

Table 2. Data about efficacy in BRCA1/2 mutation carriers undergoing mastectomy *versus* breast conserving therapy

Study	Year	No. of BRCA1/2 mutation carriers	Median follow-up (years)	Ipsilateral Recurrence	Contralateral Recurrence	Distant recurrence	Overall Survival	Specific Survival
Pierce et al.[17]	2010	655 (302 BCT / 353 Mast.)	BCT = 8.2 Mast.=8.9	BCT = 23.5% Mast.=5.5% ($p < 0.0001$)	NS ($p = 0.44$)	BCT = 11.1%, Mast. = 9.1% (NS)	BTC = 87.3% Mast.=89.8% (NS)	BCT = 91.7% Mast.=92.8% (NS)
Nilsson et al[18]	2014	162 (45 BCT /117 Mast.)	BCT = 14.9 Mast = 12.1	BCT = 32% Mast.=9% ($p < 0.05$)	N.A.	BCT = 35% Mast.=31% (NS)	BCT = 58% Mast = 63% (NS)	BCT = 66% Mast = 71% (NS)

BCT, Breast conserving therapy; Mast, Mastectomy; NA, Not Assessed; NS, non significant; RT, radiotherapy.

in these individuals. The remaining heterozygous BRCA-mutated breast tissue left after BCT could therefore be at higher risk of local recurrences or second primaries than the sporadic BC patients.

The aim of the present review was to investigate the outcome of mutation carriers undergoing BCT regarding local and distant endpoints (metastasis rate, survival). We should bear in mind that no large randomized prospective study has ever been carried out to answer these questions.

Local relapse in BRCA1 or 2 mutation carriers after BCT

Numerous retrospective studies have focused on local control after BCT in BRCA1/2 mutation carriers, though have generated conflicting results[9,16–28] (Tables 2 and 3). Indeed, in studies with limited follow-up, BCT did not increase the risk of local recurrence in mutation carriers *versus* non-carriers. Conversely, some studies with longer follow-up supported that local relapse was increased in mutation carriers. Yet, sometimes the risk of ipsilateral recurrence post-BCT was not much different from general population cohorts (*i.e.* approximatively 10% at 10 years and 15% at 15 years[29,30]). Listed below are the results of studies with higher levels of evidence (level of evidence 3, Grade C recommendation: low level of evidence):

Garcia-Etienne et al. retrospectively compared 162 sporadic BC patients with 54 BRCA1/2-mutated BC patients. Patients were matched according to their age, tumour size, and date of surgery.[23] All patients underwent a BCT between 1994 and 2007. A significant proportion of mutation carriers received adjuvant chemotherapy (73%) and tamoxifen (63%) in addition to BCT. The characteristics of the whole breast radiotherapy and the presence/absence/dose of a boost to the tumour bed were not reported. Median follow-up was 4 years, results were projected to 10 years. BRCA mutation carriers had a significantly higher incidence of ipsilateral breast recurrence than sporadic BC patients (27% *vs* 4%, $p = 0.03$). However, these results were obtained with a very short follow-up, which is a considerable limitation.

Haffty et al. retrospectively assessed BCT outcomes in BC patients diagnosed under 42. 22 had a BRCA1 or 2 mutation and 105 had a sporadic BC. The characteristics of radiotherapy were not described.[19] With a median follow-up of 12.7 years, ipsilateral breast tumour recurrence significantly increased among BRCA mutations carriers *versus* non-carriers (41% *vs* 19 %, $p = 0.007$). However, despite the patients' young age, neither endocrine therapy nor oophorectomy were performed. This certainly contributed in the unusually high rate of local recurrences in both groups. Since then, adjuvant strategies have been identified in numerous studies as major predictors of local control, especially in BRCA mutation carriers.

Brekelmans et al. retrospectively compared outcomes of 170 BRCA1, 90 BRCA2, and 759 sporadic BC patients.[24] BCT was performed in 46% of BRCA1, 39% of BRCA2, and 55% of sporadic BC patients. In the subgroups of patients who underwent BCT, whatever their mutation status, the local relapse rates were not different. The 10year local relapse respectively rated 16%, 17%, and 21%, ($p = 0.6$). Interestingly, endocrine therapy and chemotherapy were homogeneously performed, respectively in 1/5 and 1/2 of the population. These results suggested that the post-BCT local control did not differ between BRCA mutation carriers and sporadic BC patients when adjuvant treatments were adequately performed,

Robson et al. tested 496 Ashkenazi females undergoing BCT between 1980 and 1995 for BRCA mutation.[21] Genetic analyses identified 56 BRCA1/2 mutation carriers. At a median follow-up of 9.7 years, in both groups local relapse was not different: 12% in mutation carriers *versus* 8% in non-carriers ($p = 0.68$). The only predictor of local relapse in multivariate analysis was age <50 at diagnosis ($p = 0.002$).

Pierce et al. retrospectively studied 655 BRCA1/2 mutation carriers treated either with BCT ($n = 302$) or mastectomy ($n = 353$) for a BC. The results of this study led to major controversies and are hereafter confronted with other publications. The median follow-up was of about 9 years in the study by Pierce et al and data were then extrapolated at 15 years. The 10-year local relapse rate after BCT was 10.5%. This was consistent with a recent study by Metclafe et al. They reported on the risk of ipsilateral recurrence/new primary after BCT in 396 BRCA1/2 mutated patients.[31] The incidence of ipsilateral breast cancer was of 12.9% after a 10 year follow-up. Interestingly, the local control at 10 years in these two major studies was also similar to the one reported in general population cohorts.[29,30] The results of Pierce et al based on extrapolated data were more controversial. The incidence of ipsilateral relapse doubled between assessment at 10

Table 3. Data about efficacy in BRCA1/2 mutation carriers treated with breast conserving therapy and adjuvant breast irradiation

Study	Year	Nb. of BRCA1/2 mutation carriers	Nb. of matched controls	Median follow-up (years)	Ipsilateral Recurrence	Contralateral Recurrence	Distant recurrence	Overall Survival	Specific Survival
META-ANALYSIS of 10 retrospective studies (6 cohorts and four case-controls). LEVEL OF EVIDENCE 2 : SCIENTIFIC PRESUMPTION									
Valachis et al.[22]	2014	526	2320		BRCA = 17.3% Sporadic = 11% (NS)	BRCA = 23.7% Sporadic = 6.8% ($p < 0.001$)	N.A.	N.S.	N.A.
Retrospective case/control cohort studies. LEVEL OF EVIDENCE 3: LOW LEVEL OF EVIDENCE									
Verhoog et al.[28]	1998	18 BRCA1	90 Sporadic	5	BRCA1 = 14% Sporadic = 16% (NS)	BRCA1 = 19% Sporadic = 5% ($p = 0.02$)	N.A.	BRCA1 = 63% Sporadic = 69% (NS)	BRCA1 = 64% Sporadic = 71% (NS)
Robson et al.[21] *	1999	28 (21 BRCA1, 6 BRCA2, 1 BRCA1 +2)	277 Sporadic	10.3	BRCA = 22% Sporadic = 7% (NS)	BRCA = 27% Sporadic = 9.5% ($p = 0.002$)	N.A.	BRCA = 66% Sporadic = 81% (NS)	BRCA = 72% Sporadic = 87% (NS)
Verhoog et al.[27]	1999	28 BRCA2	112 Sporadic	5	BRCA2 = 48% Sporadic = 48% (NS)	BRCA2 = 12% Sporadic = 2% ($p = 0.02$)	N.A.	BRCA2 = 74% Sporadic = 75% (NS)	N.A.
Pierce et al.[9]	2000	71 (54 BRCA1, 17 BRAC2)	213 Sporadic	BRCA = 5.3 Sporadic = 4.6	BRCA = 2% Sporadic = 4% (NS)	BRCA = 20% Sporadic = 2% ($p < 0.001$)	N.A.	BRCA = 86% Sporadic = 91% (NS)	BRCA = 92% Sporadic = 91% (NS)
Haffty et al.[19] *	2002	22 (15 BRCA1, 7 BRCA2)	105 Sporadic	12.7	BRCA = 49% Sporadic = 21% ($p = 0.007$)	BRCA = 42% Sporadic = 9% ($p = 0.001$)	N.A	N.A	N.A
Robson et al.[25] *	2004	56 (42 BRCA1, 13 BRAC2, 1 BRCA1 +2)	440 Sporadic	9.7	BRCA = 12% Sporadic = 8% (NS)	BRCA = 27% Sporadic = 8% ($p < 0.0001$)	N.A.	NS	NS
Seynaeve et al[16]	2004	26 (21 BRCA1, 5 BRCA2)	174 Sporadic	BRCA = 5.7 Sporadic = 6	BRCA = 15% Sporadic = 12% (p not calculated)	BRCA = 15.4% Sporadic = 6.3% (p not calculated)	N.A.	Genetic = 78% Sporadic = 82% (NS)	N.A.
Pierce et al[26] *	2006	160 (123 BRCA1, 37 BRCA2)	445 Sporadic	BRCA = 7.9 Sporadic = 6.7	BRCA = 24% Sporadic = 17% (NS)	BRCA = 39% Sporadic = 7% ($p < 0.0001$)	N.A.	N.A.	N.A.
Brekelmans et al.[24] *	2007	326 (103 BRCA2, 223 BRCA1)	311 Familial 759 Sporadic	BRCA = 4.3 Familial = 4.8 Sporadic = 5.1	BRAC = 17% Familial = 15% Sporadic = 21% (NS)	BRCA = 20–25% Familial: 6% Sporadic = 5% ($p = 0.001$)	N.A.	BRCA = 50 to 61% Familial = 66% Sporadic = 55% (NS)	BRCA = 62 to 68% Familial = 70% Sporadic = 59% (NS)
Garcia-Etienne et al.[23] *	2009	54 (26 BRCA1, 28 BRCA2)	162 Sporadic	4	BRCA = 27% Sporadic = 4% ($p = 0.03$)	BRCA = 25% Sporadic = 1% ($p = 0.03$)	N.A	N.A	N.A

(Continued)

Table 3. (Continued)

Study	Year	Nb. of BRCA1/2 mutation carriers	Nb. of matched controls	Median follow-up (years)	Ipsilateral Recurrence	Contralateral Recurrence	Distant recurrence	Overall Survival	Specific Survival
Kirova et al[20] *	2010	27 (19 BRCA1, 8 BRCA2)	54 Sporadic	BRCA = 13.9 Sporadic = 13	BRCA = 36% Sporadic = 33% (NS)	BRCA = 40.7% Sporadic = 11% ($p = 0.001$)	N.A.	NS	N.A.

BCT, breast conserving therapy; Mast, mastectomy; NS, non significant; Nb, number; OS, overall survival; RT, radiotherapy; SS, specific survival.
* = data pooled in [22]

years and projection at 15 years. At 15 years, ipsilateral breast tumour recurrences/second primaries were more frequent in case of BCT *versus* mastectomy [23.5% *vs* 5.5%, HR = 4.5, 95% CI (2.3–8.9); $p < 0.0001$]. However, this higher risk of local relapse could be lessened by chemotherapy (11.9% of local relapse at 15 years with BCT + chemotherapy, $p = 0.08$ when compared to mastectomy).[17] Furthermore, 70% of ipsilateral "recurrences" were suggested to be new primaries since they were in a different quadrant or of different histology compared to initial BC. The 15 year local recurrence rate with BCT (23.5%) was considerably higher in the study by Pierce et al than in other publications.[25,32] For instance, Metcalfe et al reported that the risk of ipsilateral recurrence post-BCT at 15 years was of 15.8% in BRCA mutation carriers, which was not much different from the general population. The discrepancy between the two studies was attributed to differences regarding patient's eligibility. Indeed, unlike the study by Metcalfe et al., Pierce et al included patients at very high risk of local relapse, especially with positive surgical margins (5.3% of patients undergoing BCT).

Nilsson et al. retrospectively studied local outcomes of 162 BRCA mutation carriers undergoing either BCT or mastectomy. Chemotherapy, age, and tumour stage were adjusted in multivariate analysis. Median follow-up was of approximatively 15 years. BCT resulted in significantly more local recurrences/second ipsilateral primaries than mastectomy [(32% *vs 9%,* HR: 2.9; CI (1.1–7.8)]. However, chemotherapy and adjuvant endocrine therapy were significantly more prescribed in patients undergoing mastectomy. Furthermore, 53% of mastectomy patients underwent post-operative radiotherapy which certainly contributed to increase the local control in the mastectomy group. Finally, the authors acknowledged a survivorship bias since a large proportion of the mastectomy patients were treated before 1989. Mastectomy patients—who relapsed locally and died of cancer before BRCA1/2 testing was introduced in the mid-90s—could therefore not be included in the study.[18]

The most recent study with a long follow-up was published in 2010 by Kirova et al.[20] Patients with a family history of ovarian or breast cancer ($n = 131$) were studied and compared with sporadic BC patients ($n = 261$). After genetic analyses, 20.6% were BRCA1/2 mutation carriers. Groups were matched according to their age at diagnosis, year of treatment, and follow-up. All patients received BCT. The characteristics of adjuvant radiotherapy were comparable in both groups. The mean dose to the whole breast was 52 Gy and 70% of patients had a boost to the tumour bed. With a median follow-up of 13.9 years, the rate of ipsilateral recurrence in mutation carriers was no higher than in non-carriers (36% for BRCA1/2 mutated patients *vs* 33% for matched sporadic controls, $p = 0.43$). In multivariate analysis, only the age was predictor of local relapse.

Finally, a recent meta-analysis based on published data from 10 studies compared BCT in BRCA1/2 mutation carriers *versus* non-carriers (level of evidence 2, Grade B recommendation: scientific presumption). Some of the aforementioned studies and other of lower methodological quality were included with six cohorts and four case-control studies.[22] The outcomes of 526

BRCA mutation carriers and 2320 controls were analysed. The pooled rates of ipsilateral recurrence for BRCA-mutation patients and controls were 17.3% [95 % CI (11.4–24.2%)] and 11% [95% CI (6.5–15.4%)]. No significant difference was evidenced regarding the mutation status [RR 1.45, 95% CI (0.98–2.14), $p = 0.07$]. Yet, when statistical analyses were restricted to studies with at least a 7 year follow-up (five studies, 1634 patients), the local recurrence rate of mutation carriers was of 23.7 *vs* 15.9% for non-carriers ($p < 0.003$). Authors highlighted that this was possibly due to an increased risk for new primaries in mutation carriers. The most commonly found hypothesis is that, after removal of the first lesion, the residual breast tissue is still affected by the BRCA-mutation. Therefore, it is more likely develop a *de novo* cancer in mutated patients than in the general population. Yet, we should be careful. Indeed, according to valuable studies not taken into account by the meta-analysis, the post-BCT risk of ipsilateral recurrence in BRCA1/2 mutation carriers may not be much different from the general population.[9,27,28,31] Furthermore, direct comparisons of BCT with mastectomy -and therefore trustworthy data on conservative treatment efficacy in BRCA1/2 mutation carriers- are rare with only two retrospective studies[17,18] (Table 2). Local outcome and subanalyses exploring the impact of BRCA1/2 status in the prospective POSH study will probably bring helpful data.[33] A cohort of 3024 females aged between 18 and 40 with BC was treated either with mastectomy or BCT. At 10 years, the rate of local recurrence was higher with BCT (11.7% *vs* 4.9%, $p < 0.001$). However, the final genotyping of the entire cohort has not been completed yet. Therefore, the effect of BRCA mutations on the efficacy of BCT/mastectomy is not available so far.

Overall survival and distant relapse in BRCA1 or two mutation carriers after BCT

Although the long-term equivalence of BCT/mastectomy on local control is still not clearly recognised, BCT can be considered an adequate option for BRCA mutation carriers. Indeed, overall and metastasis-free survivals were the same after BCT regardless of the BRCA1/2 mutation status (Table 3). Similar results were also reported when BCT and mastectomy were compared in BRCA1/2 mutation carriers (Table 2). The only available meta-analysis corroborated these results.[22] Recently, a prospective analysis performed on young BC BRCA mutation carriers confirmed all the retrospective data.[34] Mutation carriers had the same overall and metastasis-free survival as non-carriers at 2, 5, and 10 years, regardless of the type of local management.[34]

DISCUSSION

Altogether, at least in the short term, BCT is equivalent to mastectomy regarding local control for BRCA1/2 mutation carriers. In the long term, BCT is equivalent to mastectomy regarding overall and metastasis-free survival for BRCA1/2 mutation carriers. The most recent studies indicate that BRCA mutation carriers benefit from radiation as much as those with sporadic BC.[35] However, our review of the literature reveals major recurrent limitations. First, all studies were retrospective and mainly included a limited number of patients.[36] Secondly, the relatively infrequent use of endocrine therapy and chemotherapy would not be considered adequate enough given the standard of care today. This is certainly a major limitation given that these risk reducing strategies would have likely decreased the rate of ipsilateral breast relapse and second primary.[20,21,23] Thirdly, the accurate distinction between "true recurrences" and "new primaries" was rarely made. Fourthly, the characteristics of radiotherapy were rarely reported. Thus, in most cases, we have no information about tumour bed irradiation although it is one important element that does improve local control.

Finally, after being regarded as a possible source of complication for decades, the BRCA1/2 mutation doesn't seem to widely modify the therapeutic index (efficacy/toxicity ratio) of modern adjuvant breast irradiation. One of the most frequent argument against BCT in BRCA mutation carriers is that the patients do not undergo a contralateral prophylactic mastectomy, which therefore may increase their risk of breast cancer mortality from new disease on the contralateral breast.[37,38] Although the specific survival from a second *de novo* breast cancer was not explored in the present review, this is certainly a moot point given the MRI era. Furthermore, targeted therapies may induce great changes in the near future. The BRCA1/2 mutation could finally turn into a precious ally for radiation oncologists thanks to the development of PARP inhibitors,[35] which alter DNA single strand break repair. As DNA repair is already deficient in BRCA1/2 mutation carriers, the PARP inhibition is expected to increase radiosensitivity. In pre-clinical and early phase clinical studies, PARP inhibitors successfully sensitized tumours to radiation.[35] However, to our knowledge, trials assessing the efficacy and the toxicity of the concomitant administration of PARP inhibitors with breast irradiation have not been designed yet.

CONCLUSION

BCT is a reasonable option for BRCA1/2 mutation carriers as it results in the same local control in the short term, the same metastasis-free survival and the same overall survival as in sporadic BC patients. Long-term local outcome remains a controversial issue but results of a large prospective cohort will probably provide additional arguments.

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