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Original Article

Radiation therapy management in *BRCA1/2* carriers diagnosed with early breast cancer: An international cohort study

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ABSTRACT

Background: The oncological safety of breast-conserving surgery followed by radiation therapy (BCS + RT) in young women carrying pathogenic or likely pathogenic *BRCA1/2* variants remains debated, with mastectomy (MS) often favoured despite limited comparative real-world evidence. We evaluated survival and recurrence outcomes associated with different loco-regional strategies in a large international cohort of young *BRCA* carriers.

Methods: The BRCA BCY Collaboration (NCT03673306) is a retrospective, multicentre cohort including women aged ≤ 40 years with invasive breast cancer and confirmed germline *BRCA1/2* variants treated between 2000 and 2020. Outcomes were compared between patients treated with BCS + RT, MS alone, or MS plus RT (MS + RT). Endpoints were overall survival (OS), breast cancer-free interval (BCFI), and second primary breast cancer events, defined as ipsilateral breast recurrence (IBR) or contralateral breast cancer (CBC). Multivariable Cox models were used for OS and BCFI. Competing-risks models were used for IBR/CBC. Models were adjusted for prespecified prognostic factors, and subgroup analyses were conducted by *BRCA* gene, stage, and tumour grade.

Results: Among 4,837 patients, 1,704 (35.2%) received BCS + RT, 1,488 (30.8%) MS alone, and 1,645 (34.0%) MS + RT. After a median follow-up of 8.2 years (IQR 4.8–12.7), OS did not differ between BCS + RT and MS alone (adjusted hazard ratio [aHR] 1.02, 95% CI 0.78–1.34). BCFI was comparable across groups. BCS + RT was associated with a higher risk of second primary breast cancer events compared with MS alone (aHR 1.33, 95% CI 1.07–1.66), particularly in patients with *BRCA1* variants and stage III disease.

Conclusion: In young *BRCA1/2* carriers, BCS + RT was not associated with worse OS compared with MS alone, despite a higher risk of second primary breast events. Differences in second primary breast cancer events should be interpreted cautiously given differences in *BRCA* testing timing and treatment era across groups. These data support individualised loco-regional management within a multidisciplinary framework.

Introduction

Breast cancer diagnosed at 40 years of age or younger presents distinct clinical challenges and requires tailored multidisciplinary care that considers age-specific priorities and long-term survivorship [1]. In this population, germline genetic testing is of particular importance, as more than 10% are expected to harbour a pathogenic or likely pathogenic variant (PV) in *BRCA1* or *BRCA2* [2,3].

Randomised trials have established that breast-conserving surgery (BCS) followed by radiation therapy (RT), breast-conserving therapy (BCT), achieves overall survival (OS) and breast cancer–specific survival outcomes comparable to mastectomy (MS) in early-stage breast cancer [4–6]. BCT has therefore become a standard approach. Large population-based studies have additionally suggested that BCT may be associated with improved OS compared with MS in selected settings [7–9]. However, the safety and long-term implications of BCT in *BRCA1/2* carriers remain debated. *BRCA* carriers face elevated risks of both ipsilateral breast events and, particularly, contralateral breast cancer (CBC) [10–14]. Consequently, many patients elect to undergo bilateral MS following diagnosis, particularly when germline status is known at the time of initial treatment [15,16].

A clinically relevant subset of *BRCA* carriers nonetheless choose BCT, motivated by preferences for breast preservation and avoidance of the physical and psychosocial consequences of more extensive surgery [17]. This may occur in the setting of delayed genetic testing or strong organ-preservation priorities. Although this approach may entail a higher risk of subsequent breast events, current guidelines indicate that *BRCA* status alone should not contraindicate BCT when otherwise clinically appropriate [18]. Observational studies generally report similar survival after BCT versus MS among *BRCA* carriers, despite higher local event rates in BCT cohorts [17,19–22]. Many of these datasets, however, were limited by size, particularly for *BRCA2* carriers, and heterogeneity in case-mix and timing of genetic testing.

Using the same international cohort, we recently reported that risk-reducing mastectomy (RRM) and salpingo-oophorectomy (RRSO) were associated with improved OS in young *BRCA* carriers [23]. In the present analysis, we evaluated survival and recurrence outcomes according to loco-regional treatment strategy among young *BRCA1/2* carriers treated with BCT or MS (with or without RT).

[1] Co-first.
[2] Co-last.

Methods

Study design and participants

The *BRCA* BCY Collaboration (NCT03673306) is an international, multicentre, hospital-based retrospective cohort including female *BRCA* carriers with a history of breast cancer diagnosed at young age [24]. Eligible participants were women diagnosed with invasive breast cancer at age ≤ 40 years between January 2000 and December 2020 and carrying a confirmed germline *BRCA1/2* PV.

We excluded healthy *BRCA* carriers, carriers of variants of uncertain significance, and patients with non-invasive breast cancer. For the present analysis, we additionally excluded patients with concomitant *BRCA1* and *BRCA2* PVs; bilateral breast cancer at presentation; unknown uptake or timing of RRM and/or RRSO; absence of breast cancer surgery (e.g. carcinoma of unknown primary); omission of RT after BCS (e.g. early failure precluding RT, refusal); de novo stage IV disease; and patients with a disease-free survival event within six months of diagnosis.

Procedures and data collection

Collected variables included age at diagnosis; *BRCA* gene and timing of testing relative to diagnosis; grade, hormone receptor status, and histology; type of breast and axillary surgery; clinical and pathological tumour and nodal stage; systemic therapy (type and setting of chemotherapy and endocrine therapy); and uptake and timing of RRM and RRSO.

The Institut Jules Bordet (Brussels, Belgium) was the coordinating centre and served as the central ethics committee. Local approval was obtained by participating institutions where required. Reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [25].

Outcomes

The objective was to evaluate associations between loco-regional treatment strategy and outcomes in young *BRCA1/2* carriers with surgically treated, non-metastatic breast cancer. We compared BCS + RT with MS-based strategies (MS alone and MS + RT). Patients undergoing RRM within one year of diagnosis were classified within the MS groups (MS or MS + RT) according to receipt of RT.

Endpoints were: OS, defined as the time from diagnosis to death from any cause, BCFI, defined as the time from diagnosis to loco-regional recurrence, distant recurrence, second primary breast cancer, or death from breast cancer, and second primary breast cancer events. For the purpose of this analysis, second primary breast cancer events were defined as the occurrence of either ipsilateral breast recurrence (IBR) or contralateral breast cancer (CBC). Other events, including non-breast cancer death, distant recurrence, and second primary non-breast malignancies, were treated as competing events in the statistical analyses.

Statistical analysis

Categorical variables are presented as proportions and continuous variables as medians (IQR). Median follow-up was estimated using the reverse Kaplan–Meier method [26]. Patients without an event were censored at last contact.

Cox proportional hazards models estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for OS and BCFI. For IBR/CBC, competing-risks regression estimated subdistribution HRs and cumulative incidence functions (CIFs), treating non-breast cancer death, second primary non-breast tumours, and distant recurrence as competing events.

Adjusted models included prespecified prognostic and/or imbalanced factors (country, year of diagnosis, axillary surgery, tumour stage, hormone receptor status) and included uptake of RRM as a time-dependent covariate, allowing the procedure to modify the probability of subsequent breast events without assuming complete elimination of risk. To account for potential calendar period effects reflecting changes in treatment strategies over time, year of diagnosis was included as an adjustment variable in the multivariable Cox regression models.

To mitigate potential immortal time bias related to delayed *BRCA* testing, the primary analysis incorporated left truncation at the time of *BRCA* genetic testing, ensuring that follow-up time prior to *BRCA* status ascertainment was not included in the risk period; untruncated models were reported as sensitivity analyses. Additional sensitivity analyses restricted to patients tested within six months of diagnosis were performed [27]. Subgroup analyses examined heterogeneity by *BRCA* gene, tumour stage, and grade (interaction tests reported).

Single imputation was used for missing covariates assuming a monotone missingness pattern, using logistic regression methods. Analyses were two-sided with $p < 0.05$. No multiplicity adjustment was applied. Analyses were conducted in SAS 9.4 (SAS Institute Inc).

Results

Among 5,660 young *BRCA* carriers in the cohort, 4,837 met eligibility for this analysis: 1,704 (35.2%) received BCS + RT, 1,488 (30.8%) MS alone, and 1,645 (34.0%) MS + RT (Fig. 1). Median age at diagnosis was 35 years (IQR 31–38). Most patients were *BRCA1* carriers (3,114; 64.4%), and *BRCA* testing occurred after diagnosis in 2,180 (45.1%).

BRCA2 carriers were more frequently treated with MS + RT (724/1,645; 44.0%) than with BCS + RT (501/1,704; 29.4%) or MS alone (498/1,488; 33.5%). Year of diagnosis and timing of genetic testing differed markedly across groups: BCS + RT was more common in earlier calendar years (diagnosed 2017–2020: 263/1,704; 15.4%) than MS alone (470/1,488; 31.6%) or MS + RT (494/1,645; 30.0%). Accordingly, median time from diagnosis to *BRCA* testing was longer in the BCS + RT group (1.4 years, IQR 0.3–4.8) than in MS alone (0.1 years, IQR 0.0–0.7) or MS + RT (0.3 years, IQR 0.1–1.5).

Nodal involvement was reported in 2,274/4,837 (47.0%) patients, with more advanced nodal disease (N2–3) more frequent in MS + RT (436/1,645; 26.5%) than in BCS + RT (130/1,704; 7.6%) or MS alone (42/1,488; 2.8%). Larger tumours (T3–T4) were also more frequent in MS + RT (473/1,645; 28.8%) than in BCS + RT (135/1,704; 7.9%) or MS alone (87/1,488; 5.8%).

Most patients received chemotherapy (4,483/4,837; 92.7%), most commonly anthracycline-plus-taxane regimens (3,173/4,483; 70.8%). Tumour subtype differed substantially by *BRCA* gene, with triple-negative disease more prevalent in BRCA1-associated tumours than BRCA2-associated tumours (72.9% vs 13.3%). Chemotherapy regimens varied across loco-regional groups: anthracycline-plus-taxane use increased from BCS + RT to MS alone to MS + RT (*BRCA1*: 59.4%, 73.8%, 83.5%; *BRCA2*: 58.8%, 60.1%, 81.8%), whereas anthracycline-only regimens were more frequent in BCS + RT than in MS alone or MS + RT (*BRCA1*: 29.4%, 15.6%, 8.8%; *BRCA2*: 27.9%, 23.3%, 10.4%) (Supplementary Tables S1–S2). Neoadjuvant chemotherapy was more common in MS + RT (985/1,614; 61.0%) than in BCS + RT (481/1,566; 30.7%) or MS alone (527/1,303; 40.5%). Patient, tumour and treatment characteristics in the whole study cohort are summarised in Table 1. Descriptive analyses stratified by *BRCA* mutation type (*BRCA1* vs *BRCA2*) showed that the clinical and pathological characteristics observed in the overall population were broadly consistent within each subgroup, as detailed in Supplementary Tables S1 and S2.

Median follow-up was 8.2 years (IQR 4.8–12.7), longest in BCS + RT (10.5 years, IQR 6.6–14.9), followed by MS + RT (7.1 years, IQR 4.3–11.5) and MS alone (6.9 years, IQR 4.0–11.0).

Event distributions differed across loco-regional strategies (Table 2). Patients treated with BCS + RT had higher rates of loco-regional relapse (1.4 per 100 person-years) and second primary breast cancers (2.6 per 100 person-years) than MS alone (1.1 and 1.1 per 100 person-years) or

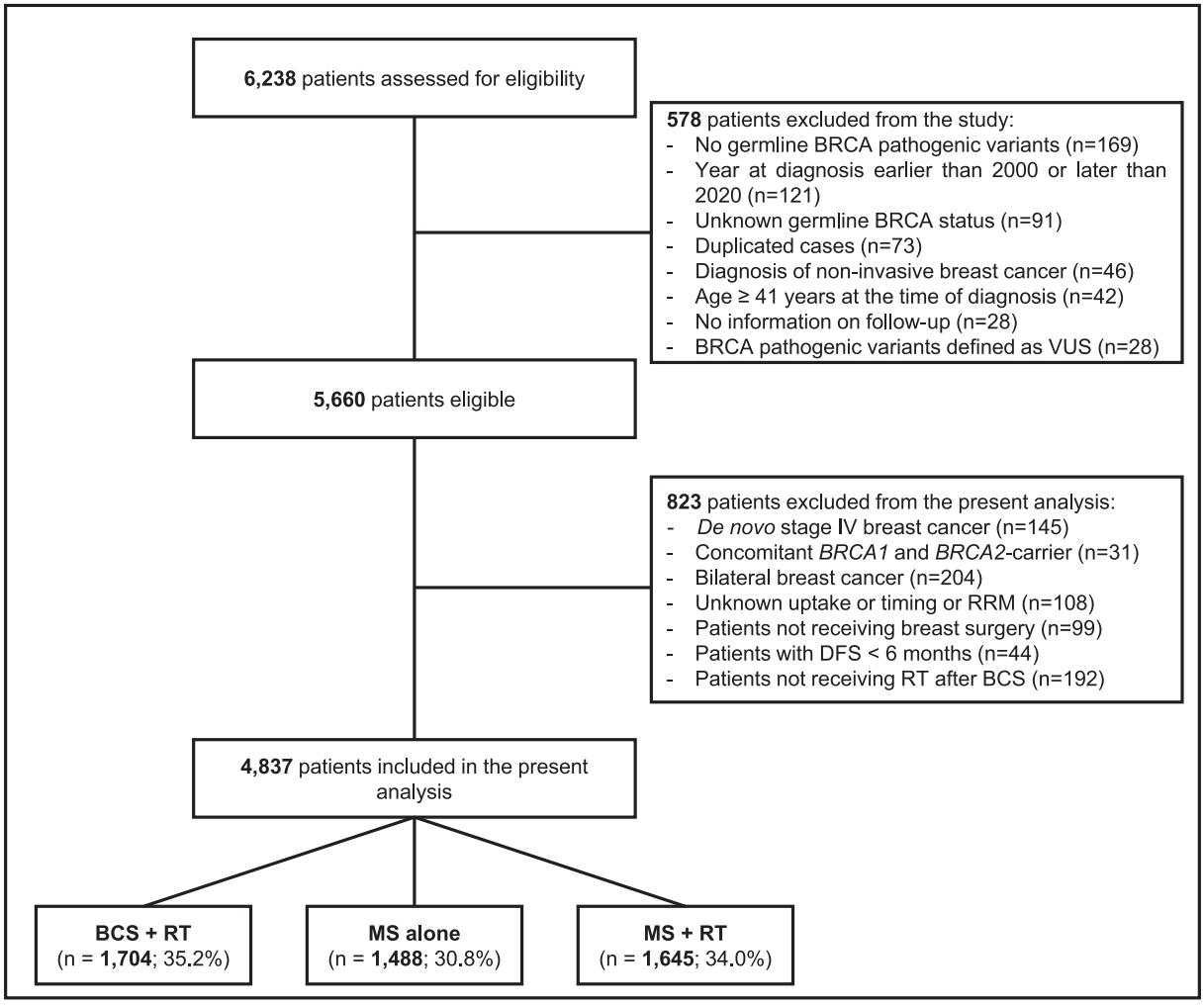

Fig. 1. Study flow diagram and loco-regional treatment allocation.

MS + RT (0.9 and 1.1 per 100 person-years). Loco-regional strategy was independently associated with IBR/CBC (p = 0.003): BCS + RT vs MS alone aHR 1.33 (95% CI 1.07–1.66), and MS + RT vs MS alone aHR 0.90 (95% CI 0.69–1.17).

Distant relapse (a competing event) was more frequent in MS + RT (2.9 per 100 person-years) than MS alone (1.3) or BCS + RT (1.2), consistent with more advanced baseline disease in MS + RT.

Subgroup analyses showed heterogeneity by *BRCA* gene (interaction p = 0.015). Among *BRCA2* carriers, BCS + RT was associated with a numerically lower not statistically significant recurrence risk versus MS alone (aHR 0.86, 95% CI 0.61–1.23), whereas among *BRCA1* carriers, BCS + RT was associated with a significantly higher risk (aHR 1.64, 95% CI 1.24–2.16). Heterogeneity was also observed by grade (interaction p = 0.003): compared with MS alone, BCS + RT was associated with a numerically lower recurrence risk in G1–2 tumours (aHR 0.76, 95% CI 0.51–1.14) and significantly higher risk in G3 tumours (aHR 1.61, 95% CI 1.24–2.09). No evidence of interaction by stage was observed (p = 0.403). Findings were consistent across sensitivity analyses, including models with left truncation and analyses restricted to patients who underwent BRCA testing before or at diagnosis (Table 3; Fig. 2).

BCFI did not differ across loco-regional groups in the overall cohort (p = 0.392). Adjusted analyses showed similar BCFI for BCS + RT vs MS alone (aHR 1.01, 95% CI 0.86–1.17) and for MS + RT vs MS alone (aHR 1.05, 95% CI 0.89–1.23).

Heterogeneity by *BRCA* gene was observed (interaction p = 0.003): among *BRCA2* carriers, BCS + RT was associated with a numerically improved BCFI versus MS alone (aHR 0.74, 95% CI 0.54–1.02), whereas among *BRCA1* carriers BCS + RT was associated with significantly worse BCFI (aHR 1.41, 95% CI 1.11–1.80). Heterogeneity by grade was also present (interaction p = 0.001): BCS + RT was associated with a significantly improved BCFI in G1–2 tumours (aHR 0.66, 95% CI 0.47–0.94) and worse BCFI in G3 tumours (aHR 1.39, 95% CI 1.11–1.75). No interaction by stage was detected (p = 0.605). Findings were consistent across sensitivity analyses, including models with left truncation and analyses restricted to patients who underwent BRCA testing before or at diagnosis (Table 4; Fig. 3).

Loco-regional strategy was associated with OS (p = 0.029). In adjusted analyses, OS was similar for BCS + RT versus MS alone (aHR 1.02, 95% CI 0.78–1.34). MS + RT was associated with significantly worse OS compared with MS alone (aHR 1.35, 95% CI 1.03–1.77), consistent with baseline risk differences and treatment indication.

No evidence of interaction by BRCA gene, stage, or grade was observed for OS (all interaction p > 0.05). Results were consistent in left-truncated and restricted-testing sensitivity analyses (Table 5; Fig. 4).

Discussion

Our analysis provides real-world evidence on the comparative effect of loco-regional treatment approaches in young *BRCA1/2* carriers with breast cancer. OS was comparable between patients treated with BCS + RT and those undergoing MS alone, supporting the oncological safety of breast conservation combined with irradiation [7,9]. This finding is

Table 1
Patient, tumour, and treatment characteristics by loco-regional treatment strategy (breast-conserving surgery plus radiation therapy [BCS + RT], mastectomy alone [MS], and mastectomy plus radiotherapy [MS + RT]).

	BCS + RT (n = 1704) n (%)	MS alone (n = 1488) n (%)	MS + RT (n = 1645) n (%)	Total (n = 4837) n (%)
Patients' characteristics				
Country				
Centre/South America	85 (5.0)	50 (3.4)	110 (6.7)	245 (5.1)
Australia/Oceania	64 (3.8)	69 (4.6)	45 (2.7)	178 (3.7)
Nord Europe	216 (12.7)	198 (13.3)	293 (17.8)	707 (14.6)
Est Europe	82 (4.8)	100 (6.7)	126 (7.7)	308 (6.4)
Nord America	71 (4.2)	270 (18.1)	236 (14.3)	577 (11.9)
South Europe	685 (40.2)	571 (38.4)	581 (35.3)	1837 (38.0)
Asia	499 (29.3)	230 (15.5)	250 (15.2)	979 (20.2)
Africa	2 (0.1)	0 (0.0)	4 (0.2)	6 (0.1)
Year of diagnosis				
2000–2004	333 (19.5)	130 (8.7)	134 (8.1)	597 (12.3)
2005–2008	355 (20.8)	200 (13.4)	216 (13.1)	771 (15.9)
2009–2012	408 (23.9)	291 (19.6)	341 (20.7)	1040 (21.5)
2013–2016	345 (20.2)	397 (26.7)	460 (28.0)	1202 (24.9)
2017–2020	263 (15.4)	470 (31.6)	494 (30.0)	1227 (25.4)
Median age at diagnosis, years (IQR)	35.0 (31.0–38.0)	35.0 (31.0–38.0)	35.0 (31.0–37.0)	35.0 (31.0–38.0)
Age at diagnosis				
≤30	368 (21.6)	308 (20.7)	331 (20.1)	1007 (20.8)
31–35	610 (35.8)	548 (36.8)	614 (37.3)	1772 (36.6)
36–40	726 (42.6)	632 (42.5)	700 (42.6)	2058 (42.5)
BRCA				
BRCA1	1203 (70.6)	990 (66.5)	921 (56.0)	3114 (64.4)
BRCA2	501 (29.4)	498 (33.5)	724 (44.0)	1723 (35.6)
Median time to BRCA test, years (IQR)	1.4 (0.3–4.8)	0.1 (0.0–0.7)	0.3 (0.1–1.5)	0.4 (0.1–1.5)
BRCA TEST				
Test before diagnosis	74 (4.3)	246 (16.5)	124 (7.5)	444 (9.2)
Test at diagnosis	448 (26.3)	730 (49.1)	777 (47.2)	1955 (40.4)
Test after diagnosis	1113 (65.3)	413 (27.8)	654 (39.8)	2180 (45.1)
Unknown date of BRCA testing	69 (4.0)	99 (6.7)	90 (5.5)	258 (5.3)
Tumours' characteristics				
Tumour histology				
Ductal	1468 (86.2)	1220 (82.0)	1364 (82.9)	4052 (83.8)
Other	204 (12.0)	211 (14.2)	222 (13.5)	637 (13.2)
Unknown	32 (1.9)	57 (3.8)	59 (3.6)	148 (3.1)
Tumour size				
T1	786 (46.1)	729 (49.0)	325 (19.8)	1840 (38.0)
T2	783 (46.0)	672 (45.2)	847 (51.5)	2302 (47.6)
T3/T4	135 (7.9)	87 (5.8)	473 (28.8)	695 (14.4)
Nodal status				
N0	1067 (62.6)	1082 (72.7)	414 (25.2)	2563 (53.0)
N1	507 (29.8)	364 (24.5)	795 (48.3)	1666 (34.4)
N2/N3	130 (7.6)	42 (2.8)	436 (26.5)	608 (12.6)
Tumour stage at diagnosis				
Stage I	572 (33.6)	577 (38.8)	83 (5.0)	1232 (25.5)
Stage II	934 (54.8)	833 (56.0)	901 (54.8)	2668 (55.2)
Stage III	198 (11.6)	78 (5.2)	661 (40.2)	937 (19.4)
Tumour grade				
G1	30 (1.8)	39 (2.6)	27 (1.6)	96 (2.0)
G2	359 (21.1)	387 (26.0)	457 (27.8)	1203 (24.9)
G3	1315 (77.2)	1062 (71.4)	1161 (70.6)	3538 (73.1)
Hormone receptor status				
Negative	1030 (60.4)	790 (53.1)	781 (47.5)	2601 (53.8)
Positive	674 (39.6)	698 (46.9)	864 (52.5)	2236 (46.2)
HER2 status				
Negative	1542 (90.5)	1338 (89.9)	1452 (88.3)	4332 (89.6)
Positive	96 (5.6)	102 (6.9)	137 (8.3)	335 (6.9)
Unknown	66 (3.9)	48 (3.2)	56 (3.4)	170 (3.5)
Tumour subtype				
HER2+	98 (5.8)	105 (7.1)	143 (8.7)	346 (7.2)
TNBC	996 (58.5)	760 (51.1)	743 (45.2)	2499 (51.7)
Luminal B	395 (23.2)	356 (23.9)	480 (29.2)	1231 (25.4)
Luminal A	215 (12.6)	267 (17.9)	279 (17.0)	761 (15.7)
Treatment				
CT use				
No	128 (7.5)	179 (12.0)	26 (1.6)	333 (6.9)
Yes	1566 (91.9)	1303 (87.6)	1614 (98.1)	4483 (92.7)
Unknown	10 (0.6)	6 (0.4)	5 (0.3)	21 (0.4)
CT setting *				
Neoadjuvant	481 (30.7)	527 (40.5)	985 (61.0)	1993 (44.5)
Adjuvant	1076 (68.7)	773 (59.3)	624 (38.7)	2473 (55.2)
Unknown	9 (0.6)	3 (0.2)	5 (0.3)	17 (0.4)
Type of CT *				
Antra + Taxane based	927 (59.2)	910 (69.8)	1336 (82.8)	3173 (70.8)
Antra only	454 (29.0)	232 (17.8)	153 (9.5)	839 (18.7)
Taxane only	68 (4.3)	89 (6.8)	56 (3.5)	213 (4.8)
Other	63 (4.0)	37 (2.8)	33 (2.0)	133 (3.0)
Unknown	54 (3.4)	35 (2.7)	36 (2.2)	125 (2.8)
ET use **				
No	29 (4.3)	53 (7.6)	30 (3.5)	112 (5.0)
Yes	639 (94.8)	636 (91.1)	825 (95.5)	2100 (93.9)
Unknown	6 (0.9)	9 (1.3)	9 (1.0)	24 (1.1)
Type of ET ***				
Tamoxifen alone	304 (47.6)	221 (34.8)	274 (33.2)	799 (38.1)
Tamoxifen + LHRH	182 (28.5)	189 (29.7)	194 (23.5)	565 (26.9)
LHRH alone	11 (1.7)	22 (3.5)	11 (1.3)	44 (2.1)
AI + LHRH	56 (8.8)	111 (17.5)	188 (22.8)	355 (16.9)
Tamoxifen →AI	73 (11.4)	79 (12.4)	140 (17.0)	292 (13.9)
Other	7 (1.1)	8 (1.3)	13 (1.6)	28 (1.3)
Unknown	6 (0.9)	6 (0.9)	5 (0.6)	17 (0.8)
Axillary surgery				
No axillary surgery	15 (2.2)	9 (5.5)	22 (1.8)	46 (2.2)
Sentinel node biopsy only	297 (44.5)	67 (40.6)	607 (48.6)	971 (46.7)
Axillary dissection	346 (51.9)	85 (51.5)	600 (48.1)	1031 (49.6)
Unknown	9 (1.4)	4 (2.4)	19 (1.5)	32 (1.5)
Risk-Reducing Mastectomy				
No	1045 (61.3)	371 (24.9)	602 (36.6)	2018 (41.7)
Yes	659 (38.7)	1117 (75.1)	1043 (63.4)	2819 (58.3)
Risk-Reducing Ovariectomy				
No	763 (44.8)	666 (44.8)	762 (46.3)	2191 (45.3)
Yes	935 (54.9)	814 (54.7)	872 (53.0)	2621 (54.2)
Unknown	6 (0.4)	8 (0.5)	11 (0.7)	25 (0.5)

Note. Values are n (%) unless otherwise specified; age and time to *BRCA* testing are reported as median (interquartile range).
* CT setting and regimen are reported among patients receiving CT.
** ET is reported among hormone receptor- positive patients.
*** ET regimen is reported among patients receiving ET.
***Abbreviations: BCS, breast-conserving surgery; CI, confidence interval; CT, chemotherapy; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; IQR, interquartile range; MS, mastectomy; RT, radiation therapy; TNBC, triple-negative breast cancer; AI, aromatase inhibitors; LHRH, luteinizing hormone-releasing hormone.

particularly relevant for young women, including those unaware of their *BRCA* status at diagnosis or those prioritising breast preservation for personal or reproductive reasons, such as pregnancy or future breast-feeding plans [7,9,28].

Importantly, patients diagnosed in earlier periods of the study, who were more likely to receive BCT, did not experience inferior survival outcomes despite being treated before the availability of contemporary systemic strategies, including multigene assays guiding chemotherapy de-escalation, PARP inhibitors for high-risk *BRCA* carriers, and CDK4/6 inhibitors in the adjuvant setting. Consistent with historical practice, chemotherapy use was high across all groups, reflecting treatment

Table 2
Distribution of loco-regional relapse, second primary breast cancer, and competing events by loco-regional treatment strategy in the overall cohort.

	Overall cohort n = 4837 n (%)	BCS + RT n = 1704 events/100 person-years	MS alone n = 1488 events/100 person-years	MS + RT n = 1645 events/100 person-years
Event	1721 (35.6)	5.96	4.01	5.55
Type of event				
Locoregional relapse	366 (7.6)	1.35	1.08	0.86
Second primary breast cancer	558 (11.5)	2.62	1.06	1.13
Distant relapse (competing)	572 (11.8)	1.22	1.25	2.91
Second primary malignancy non breast (competing)	190 (3.9)	0.71	0.51	0.48
Death without recurrence (competing)	35 (0.7)	0.06	0.11	0.17

Note. For each treatment group, event rates are expressed as events per 100 person-years. Competing events include distant relapse, second primary non-breast malignancy, and death without recurrence.
***Abbreviations: BCS, breast-conserving surgery; MS, mastectomy; RT, radiation therapy.

patterns prior to widespread genomic risk stratification. Although BCS + RT was associated with a higher incidence of loco-regional recurrence and second primary breast cancer events, particularly among *BRCA1* carriers, these differences did not translate into inferior OS. This finding underscores the need to balance oncological outcomes with patient-centred considerations when discussing loco-regional treatment options in this population.

Several large retrospective studies have reported no difference in OS between MS and BCT among BRCA carriers [17,22]. Our results are consistent with this body of evidence and extend prior observations to the largest reported international cohort restricted to patients diagnosed at ≤ 40 years of age. Interpretation must nevertheless consider that loco-regional treatment strategies in our cohort were associated with distinct baseline clinicopathological characteristics, including tumour stage, nodal involvement, grade, systemic therapy patterns, and uptake and timing of risk-reducing procedures, all of which may independently influence outcomes.

In this context, although BCS + RT was associated with a higher cumulative incidence of IBR and CBC, OS remained comparable across loco-regional approaches. These findings should be interpreted alongside prior analyses from this cohort demonstrating a survival advantage associated with bilateral MS [23], likely reflecting the combined impact of reduced future breast cancer events, patient selection, and long-term risk reduction, rather than the effect of the initial loco-regional treatment itself. Taken together, the available evidence supports current guideline recommendations indicating that *BRCA* mutation status alone should not preclude offering breast-conserving approaches when clinically appropriate, while emphasising the importance of individualised, risk-informed decision-making [18].

Subgroup analyses suggested distinct patterns according to *BRCA* gene and tumour grade. Among *BRCA2* carriers, BCS + RT was associated with numerically more favourable OS compared with MS alone, whereas no OS differences were observed among *BRCA1* carriers. Conversely, in *BRCA1* carriers and in high-grade tumours, BCS + RT was associated with worse BCFI and a higher risk of IBR/CBC compared with MS alone. These findings should be interpreted cautiously, as the observational nature of the study and the potential for residual confounding preclude causal attribution to the loco-regional treatment approach.

The biological mechanisms underlying these differences may relate to intrinsic tumour characteristics associated with BRCA PVs. *BRCA1*-associated tumours predominantly exhibit a triple-negative phenotype with high-grade histology, whereas *BRCA2*-associated tumours more frequently demonstrate hormone receptor positivity and a luminal-like biology, potentially deriving greater benefit from combined systemic and loco-regional treatments, as previously reported [17,22].

In addition to survival outcomes, our data suggest different time-to-event patterns between *BRCA* subgroups. *BRCA1* carriers experienced earlier loco-regional or second primary breast cancer events, whereas *BRCA2* carriers showed a more delayed cumulative incidence [27,29]. These findings support the hypothesis of divergent clinical trajectories and highlight the potential need for time-sensitive, gene-specific surveillance strategies. Nevertheless, the relatively small size of the *BRCA2* subgroup warrants cautious interpretation of the favourable outcomes observed with breast conservation. Despite these limitations, our results reinforce the distinct clinical behaviour of breast cancer in *BRCA1* versus *BRCA2* carriers and the necessity for tailored management strategies in clinical practice.

Our analysis of second primary breast cancer events (IBR/CBC) further clarifies the trade-offs associated with loco-regional treatment selection. BCS + RT was associated with an increased risk of IBR/CBC compared with MS alone in the overall cohort, an effect predominantly driven by *BRCA1* carriers, while *BRCA2* carriers treated with BCS + RT showed numerically more favourable outcomes. Competing events, particularly distant relapse, were frequent, especially among patients treated with MS + RT, likely reflecting more advanced disease at diagnosis and established indications for post-mastectomy RT. These observations underscore that decisions regarding post-mastectomy irradiation should be guided by baseline tumour characteristics and that individualised treatment remains essential [4,30,31].

Notably, previous studies have reported that CBC contributes substantially to the cumulative event rate in patients treated with BCS [17,19,20]. Among BRCA carriers who do not undergo RRM, the cumulative 20-year risk of CBC exceeds 40% for BRCA1 and 26% for BRCA2 carriers [11]. These findings highlight the critical importance of early genetic testing and comprehensive counselling at diagnosis to guide optimal surgical and preventive strategies [10,15].

Beyond oncological outcomes, regional and cultural factors may influence loco-regional treatment selection. In exploratory analyses by ethnicity and geographic region (Table 1), MS rates varied substantially across populations. These differences likely reflect a complex interplay of cultural attitudes, patient risk perception, access to and timing of genetic testing, and regional practice patterns, rather than tumour-related factors alone.

An informed diagnosis not only facilitates decision-making regarding primary treatment approaches but also allows patients to plan appropriate risk-reducing interventions, significantly influencing long-term outcomes and patient satisfaction. Bilateral MS substantially reduces the risk of IBR and CBC in *BRCA* carriers, particularly in *BRCA1*, and evidence from this large international cohort further demonstrated that both RRM and RRSO were associated with favourable survival outcomes [23]. However, other studies have not consistently shown a clear survival advantage of bilateral MS over BCT, particularly among *BRCA1* carriers [21,32]. In contrast, RRSO has been associated with an estimated 40% relative reduction in cancer-specific mortality among *BRCA* carriers [10].

High-quality patient counselling and shared decision-making therefore remain cornerstones of optimal management for BRCA carriers. Although bilateral RRM represents the most effective strategy to minimise future breast cancer events, it carries significant psychosocial consequences, including potential effects on body image, sexual identity, and mental health [18,20]. A staged management approach, initially offering BCT with careful surveillance and the option of deferred risk-reducing surgery, may represent a reasonable alternative for selected patients, balancing oncological safety with quality-of-life

Table 3
Associations between loco-regional treatment strategy and ipsilateral/contralateral breast events (IBC/CBC) in the overall cohort and by subgroup (*BRCA* gene, stage, and grade).

		Unadjusted HR (95%CI)	p	Adjusted* HR (95%CI)	p	Unadjusted HR (95%CI) with left truncation	p	Adjusted* HR (95%CI) with left truncation	p	Unadjusted HR (95% CI) in BRCA testing before or at diagnosis	p	Adjusted* HR (95%CI) in BRCA testing before or at diagnosis	p
	Locoregional treatment		<0.001		0.018		<0.001		0.003		<0.001		0.972
	BCS + RT	1.80 (1.53–2.11)		1.09 (0.90–1.31)		2.00 (1.63–2.45)		1.33 (1.07–1.66)		1.72 (1.28–2.31)		0.96 (0.65–1.41)	
	MS alone	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
	MS + RT	0.84 (0.69–1.02)		0.82 (0.66–1.02)		0.89 (0.70–1.13)		0.90 (0.69–1.17)		0.91 (0.66–1.25)		0.97 (0.68–1.38)	
Subgroups analysis													
			P for interaction		**P for interaction**		**P for interaction**		**P for interaction**		**P for interaction**		**P for interaction**
BRCA			0.003		0.018		0.005		0.015		<0.001		<0.001
BRCA1	**BCS + RT vs MS alone**	2.14 (1.75–2.62)		1.28 (1.01–1.61)		2.49 (1.93–3.20)		1.64 (1.24–2.16)		2.54 (1.80–3.58)		1.52 (0.97–2.37)	
	MS + RT vs MS alone	0.97 (0.75–1.26)		0.89 (0.68–1.17)		1.06 (0.78–1.46)		1.04 (0.74–1.45)		1.18 (0.79–1.76)		1.22 (0.79–1.89)	
BRCA2	**BCS + RT vs MS alone**	1.18 (0.89–1.55)		0.77 (0.57–1.03)		1.20 (0.84–1.71)		0.86 (0.61–1.23)		0.34 (0.14–0.80)		0.16 (0.06–0.46)	
	MS + RT vs MS alone	0.68 (0.50–0.92)		0.72 (0.52–1.00)		0.68 (0.47–0.98)		0.70 (0.48–1.03)		0.55 (0.32–0.94)		0.63 (0.34–1.16)	
Stage			0.055		0.089		0.122		0.403		0.559		0.713
Stage I	**BCS + RT vs MS alone**	2.30 (1.75–3.02)		1.19 (0.88–1.60)		2.66 (1.91–3.69)		1.49 (1.04–2.13)		2.22 (1.42–3.47)		1.32 (0.80–2.17)	
	MS + RT vs MS alone	1.46 (0.86–2.48)		1.25 (0.74–2.12)		1.13 (0.53–2.42)		0.97 (0.45–2.06)		1.34 (0.54–3.35)		0.92 (0.38–2.21)	
Stage II	**BCS + RT vs MS alone**	1.49 (1.20–1.83)		0.98 (0.79–1.23)		1.58 (1.21–2.07)		1.12 (0.84–1.49)		1.39 (0.92–2.10)		0.94 (0.60–1.48)	
	MS + RT vs MS alone	0.77 (0.60–1.00)		0.75 (0.59–0.97)		0.82 (0.60–1.13)		0.82 (0.60–1.12)		0.86 (0.56–1.31)		0.82 (0.55–1.25)	
Stage III	**BCS + RT vs MS alone**	2.71 (1.29–5.69)		1.98 (0.92–4.27)		3.76 (1.34–10.58)		2.93 (0.99–8.67)		2.52 (0.49–12.92)		2.62 (0.43–16.13)	
	MS + RT vs MS alone	1.16 (0.56–2.41)		1.06 (0.50–2.24)		1.58 (0.57–4.33)		1.80 (0.63–5.17)		1.67 (0.40–7.06)		1.98 (0.38–10.27)	
Grade			0.065		0.107		0.007		0.003		0.118		0.003
G1-2	**BCS + RT vs MS alone**	1.33 (0.98–1.80)		0.81 (0.58–1.13)		1.23 (0.83–1.82)		0.76 (0.51–1.14)		0.97 (0.52–1.82)		0.33 (0.15–0.70)	
	MS + RT vs MS alone	0.75 (0.54–1.06)		0.70 (0.49–1.02)		0.86 (0.58–1.30)		0.78 (0.51–1.21)		0.79 (0.45–1.39)		0.71 (0.36–1.39)	
G3	**BCS + RT vs MS alone**	2.01 (1.66–2.44)		1.23 (0.98–1.53)		2.34 (1.85–2.98)		1.61 (1.24–2.09)		2.06 (1.46–2.91)		1.35 (0.88–2.09)	
	MS + RT vs MS alone	0.88 (0.69–1.11)		0.88 (0.68–1.13)		0.89 (0.66–1.20)		0.93 (0.68–1.28)		0.96 (0.65–1.41)		1.12 (0.74–1.69)	

*Models were stratified by country, year of diagnosis, axillary surgery, tumour stage, and hormone receptor status, and adjusted for RRM as a time-dependent covariate.
Note. Subdistribution HRs were estimated using competing-risks regression, with non–breast cancer-related death, second primary non-breast tumours, and distant relapse treated as competing events. Results are shown for unadjusted and adjusted models, with and without left truncation at the time of *BRCA* testing (primary analysis), and in sensitivity analyses restricted to patients tested before or at diagnosis.
****Abbreviations: BCS, breast-conserving surgery; CBC, contralateral breast cancer; CI, confidence interval; HR, hazard ratio; IBC, ipsilateral breast cancer; MS, mastectomy; RT, radiation therapy; RRM, risk-reducing mastectomy.

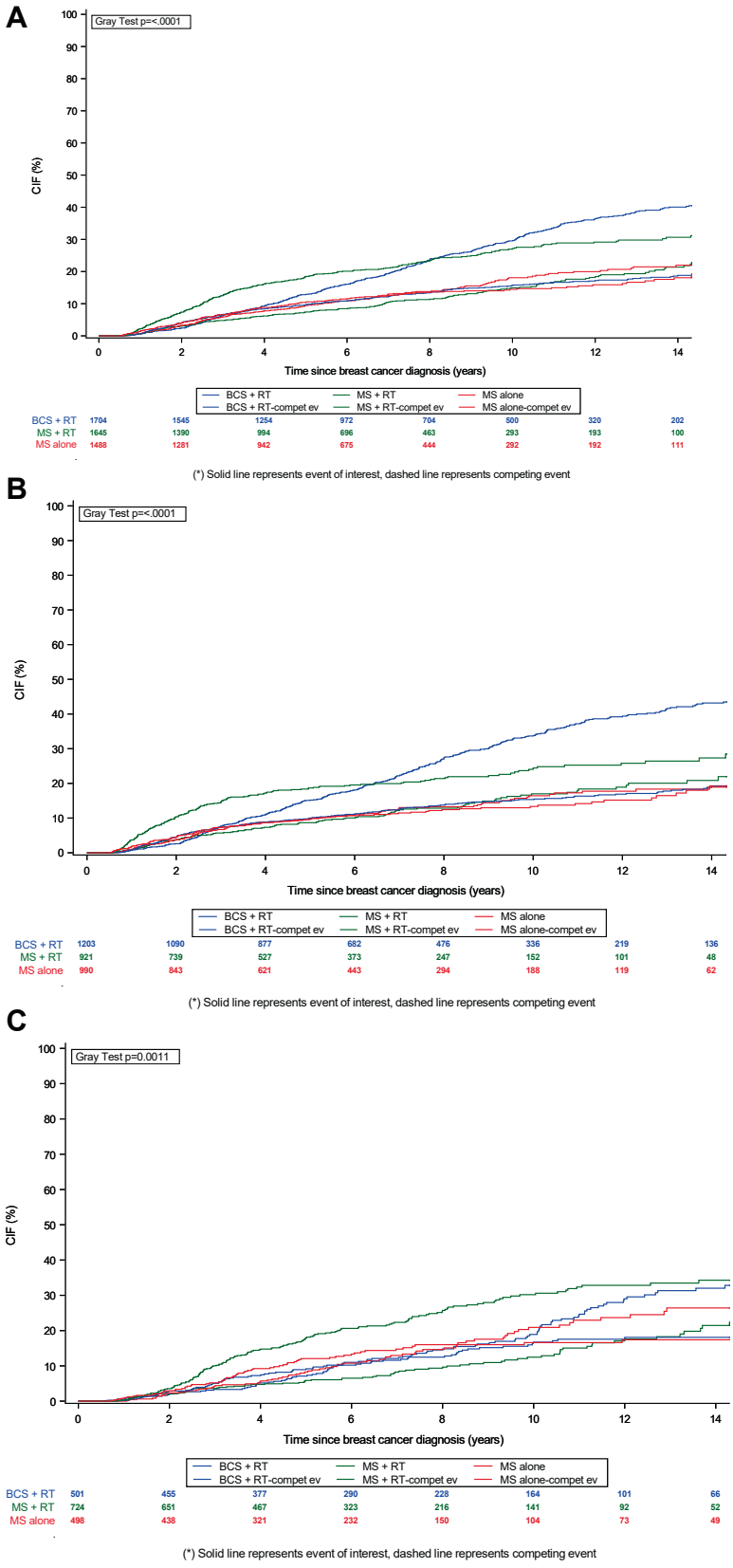

Fig. 2. Cumulative incidence of second primary breast cancer events (IBR/CBC) by loco-regional treatment in **(A)** overall cohort, (**B**) *BRCA1* carriers, and (**C**) *BRCA2* carriers. Competing risks: non–breast cancer death, second primary non-breast tumours, and distant recurrence. Models adjusted for country, year of diagnosis, axillary surgery, tumour stage, hormone receptor status, and uptake of RRM as a time-dependent covariate.

Table 4
Associations between loco-regional treatment strategy and breast cancer–free interval (BCFI) in the overall cohort and by subgroup (*BRCA* gene, stage, and grade).

		Unadjusted HR (95%CI)	p	Adjusted* HR (95%CI)	p	Unadjusted HR (95%CI) with left truncation	p	Adjusted* HR (95%CI) with left truncation	p	Unadjusted HR (95% CI) in BRCA testing before or at diagnosis	p	Adjusted* HR (95%CI) in BRCA testing before or at diagnosis	p
	Locoregional treatment		<0.001		0.822		<0.001		0.392		<0.001		0.274
	BCS + RT	1.53		1.01		1.71		1.13		1.48		0.85	
		(1.34–1.74)		(0.86–1.17)		(1.46–2.00)		(0.93–1.38)		(1.16–1.87)		(0.62–1.17)	
	MS alone	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
	MS + RT	1.47		1.05		1.54		1.12		1.63		1.11	
		(1.28–1.68)		(0.89–1.23)		(1.31–1.81)		(0.92–1.37)		(1.32–2.01)		(0.84–1.45)	
Subgroups analysis													
			P for interaction		**P for interaction**		**P for interaction**		**P for interaction**		**P for interaction**		**P for interaction**
BRCA			0.002		0.017		0.001		0.003		<0.001		<0.001
BRCA1	**BCS + RT vs**	1.78		1.13		2.12		1.41		2.22		1.29	
	MS alone	(1.51–2.09)		(0.93–1.37)		(1.74–2.59)		(1.11–1.80)		(1.68–2.93)		(0.90–1.86)	
	MS + RT vs	1.60		1.06		1.80		1.23		2.15		1.38	
	MS alone	(1.34–1.92)		(0.86–1.31)		(1.45–2.23)		(0.95–1.60)		(1.65–2.82)		(0.99–1.92)	
BRCA2	**BCS + RT vs**	1.10		0.78		1.08		0.74		0.38		0.22	
	MS alone	(0.87–1.38)		(0.60–1.00)		(0.82–1.42)		(0.54–1.02)		(0.21–0.70)		(0.11–0.44)	
	MS + RT vs	1.27		1.02		1.19		0.98		0.97		0.78	
	MS alone	(1.03–1.58)		(0.80–1.31)		(0.93–1.52)		(0.73–1.31)		(0.69–1.37)		(0.51–1.19)	
Stage			0.161		0.756		0.222		0.605		0.261		0.594
Stage I	**BCS + RT vs**	1.89		1.14		2.16		1.38		1.98		1.19	
	MS alone	(1.50–2.38)		(0.88–1.46)		(1.64–2.84)		(1.01–1.88)		(1.35–2.91)		(0.76–1.86)	
	MS + RT vs	1.46		1.31		1.38		1.25		1.68		1.21	
	MS alone	(0.94–2.28)		(0.82–2.08)		(0.78–2.45)		(0.69–2.25)		(0.83–3.41)		(0.57–2.56)	
Stage II	**BCS + RT vs**	1.34		0.96		1.43		1.02		1.20		0.79	
	MS alone	(1.13–1.59)		(0.80–1.16)		(1.16–1.77)		(0.81–1.28)		(0.87–1.67)		(0.55–1.13)	
	MS + RT vs	1.15		1.03		1.15		1.06		1.13		1.05	
	MS alone	(0.96–1.39)		(0.84–1.24)		(0.92–1.43)		(0.84–1.34)		(0.84–1.51)		(0.77–1.43)	
Stage III	**BCS + RT vs**	1.21		0.92		1.49		1.15		1.12		1.01	
	MS alone	(0.80–1.84)		(0.60–1.43)		(0.88–2.52)		(0.67–2.01)		(0.48–2.59)		(0.41–2.51)	
	MS + RT vs	1.04		0.94		1.19		1.18		1.38		1.39	
	MS alone	(0.70–1.53)		(0.63–1.41)		(0.73–1.93)		(0.71–1.96)		(0.72–2.64)		(0.70–2.77)	
Grade			0.003		0.031		0.001		0.001		0.017		0.002
G1-2	**BCS + RT vs**	1.08		0.75		1.04		0.66		0.83		0.39	
	MS alone	(0.84–1.37)		(0.57–0.98)		(0.76–1.41)		(0.47–0.94)		(0.52–1.35)		(0.22–0.68)	
	MS + RT vs	1.26		0.87		1.26		0.83		1.28		0.81	
	MS alone	(0.99–1.60)		(0.66–1.14)		(0.95–1.68)		(0.60–1.16)		(0.90–1.84)		(0.52–1.27)	
G3	**BCS + RT vs**	1.76		1.15		2.05		1.39		1.84		1.17	
	MS alone	(1.51–2.06)		(0.96–1.38)		(1.69–2.47)		(1.11–1.75)		(1.39–2.44)		(0.82–1.67)	
	MS + RT vs	1.57		1.14		1.68		1.28		1.81		1.30	
	MS alone	(1.32–1.86)		(0.93–1.38)		(1.37–2.05)		(1.01–1.62)		(1.40–2.36)		(0.95–1.78)	

*Models were stratified by country, year of diagnosis, axillary surgery, tumour stage, and hormone receptor status, and adjusted for RRM as a time-dependent covariate.
Note. HRs were estimated using Cox proportional hazards models. Results are shown for unadjusted and adjusted models, with and without left truncation at the time of *BRCA* testing (primary analysis), and in sensitivity analyses restricted to patients tested before or at diagnosis.
***Abbreviations: BCFI, breast cancer–free interval; BCS, breast-conserving surgery; CI, confidence interval; HR, hazard ratio; MS, mastectomy; RT, radiation therapy; RRM, risk-reducing mastectomy.

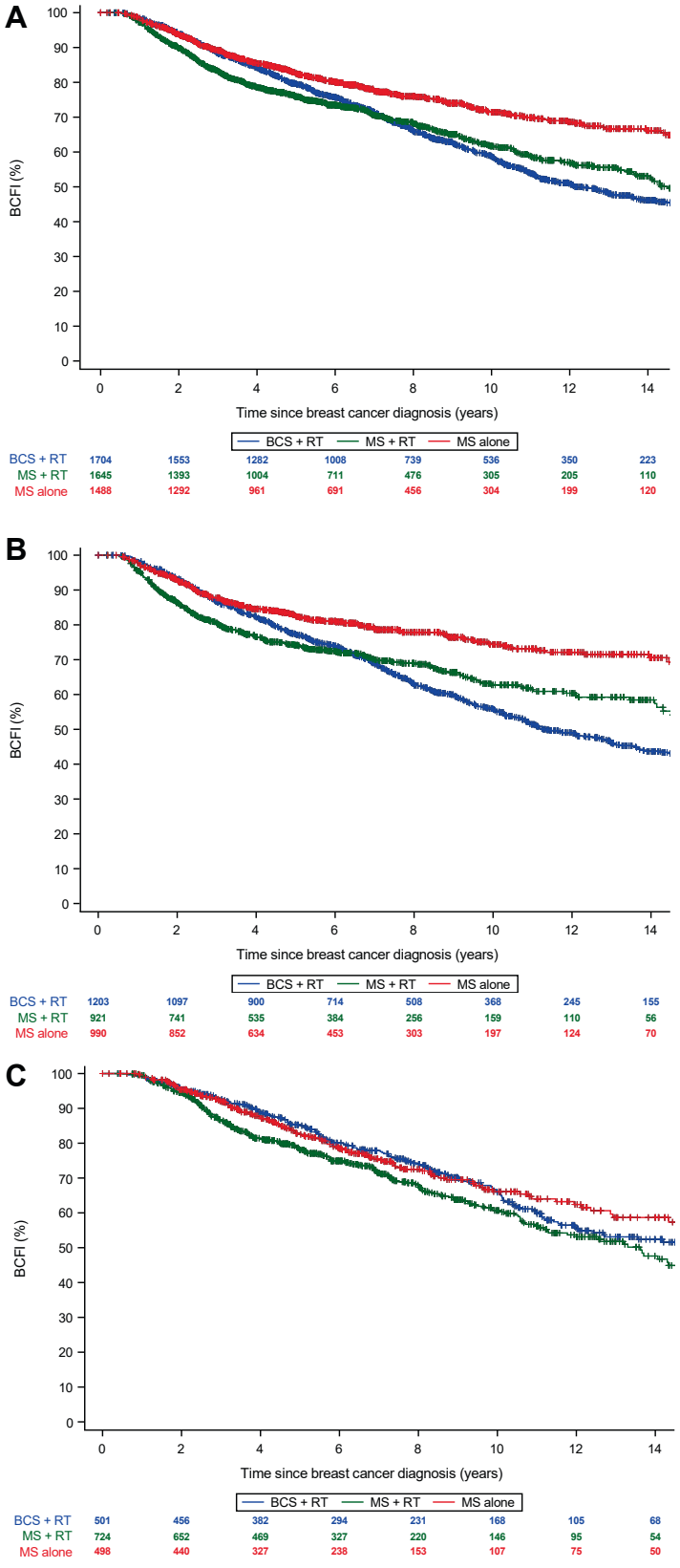

Fig. 3. BCFI by loco-regional treatment in (**A**) overall cohort, (**B**) *BRCA1* carriers, and (**C**) *BRCA2* carriers. Multivariable Cox models adjusted for country, year of diagnosis, axillary surgery, tumour stage, hormone receptor status, and uptake of RRM as a time-dependent covariate; primary analyses included left truncation at *BRCA* testing.

Table 5
Associations between loco-regional treatment strategy and overall survival (OS) in the overall cohort and by subgroup (*BRCA* gene, stage, and grade).

		Unadjusted HR (95%CI)	p	Adjusted* HR (95%CI)	p	Unadjusted HR (95%CI) with left truncation	p	Adjusted* HR (95%CI) with left truncation	p	Unadjusted HR (95% CI) in BRCA testing before or at diagnosis	p	Adjusted* HR (95%CI) in BRCA testing before or at diagnosis	p
	Locoregional treatment		<0.001		0.018		<0.001		0.029		<0.001		0.022
	BCS + RT	1.12 (0.89–1.40)		0.93 (0.72–1.21)		1.42 (1.12–1.80)		1.02 (0.78–1.34)		1.06 (0.69–1.62)		0.68 (0.39–1.16)	
	MS alone	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
	MS + RT	2.27 (1.83–2.82)		1.27 (0.98–1.63)		2.45 (1.96–3.07)		1.35 (1.03–1.77)		2.65 (1.93–3.66)		1.34 (0.90–2.01)	
Subgroups analysis													
			P for interaction		**P for interaction**		**P for interaction**		**P for interaction**		**P for interaction**		**P for interaction**
BRCA			0.642		0.212		0.890		0.239		0.052		0.079
BRCA1	**BCS + RT vs MS alone**	1.08 (0.82–1.41)		0.86 (0.63–1.17)		1.40 (1.06–1.86)		0.93 (0.67–1.29)		1.36 (0.84–2.21)		0.88 (0.48–1.64)	
	MS + RT vs MS alone	2.14 (1.63–2.80)		1.09 (0.80–1.49)		2.39 (1.80–3.16)		1.14 (0.82–1.60)		3.36 (2.27–4.99)		1.51 (0.93–2.46)	
BRCA2	**BCS + RT vs MS alone**	1.17 (0.76–1.79)		1.00 (0.63–1.58)		1.42 (0.92–2.20)		1.09 (0.67–1.75)		0.40 (0.14–1.18)		0.20 (0.06–0.73)	
	MS + RT vs MS alone	2.62 (1.80–3.80)		1.65 (1.09–2.52)		2.62 (1.79–3.83)		1.75 (1.13–2.71)		1.68 (0.97–2.93)		1.06 (0.55–2.04)	
Stage			0.181		0.147		0.367		0.236		0.091		0.123
Stage I	**BCS + RT vs MS alone**	1.13 (0.71–1.81)		1.00 (0.61–1.64)		1.46 (0.90–2.35)		1.13 (0.68–1.87)		1.85 (0.86–4.00)		1.38 (0.59–3.23)	
	MS + RT vs MS alone	1.79 (0.85–3.80)		1.60 (0.73–3.50)		2.01 (0.91–4.43)		1.58 (0.69–3.61)		2.92 (0.95–8.96		2.47 (0.75–8.12)	
Stage II	**BCS + RT vs MS alone**	1.11 (0.82–1.50)		0.96 (0.70–1.31)		1.34 (0.98–1.84)		0.96 (0.69–1.34)		0.76 (0.41–1.40)		0.52 (0.27–1.02)	
	MS + RT vs MS alone	1.79 (1.33–2.41)		1.54 (1.13–2.10)		1.77 (1.30–2.42)		1.56 (1.13–2.16)		1.80 (1.16–2.81)		1.62 (1.01–2.60)	
Stage III	**BCS + RT vs MS alone**	0.66 (0.39–1.11)		0.50 (0.29–0.87)		0.89 (0.51–1.56)		0.62 (0.34–1.12)		0.62 (0.23–1.62)		0.44 (0.15–1.29)	
	MS + RT vs MS alone	0.87 (0.55–1.40)		0.71 (0.43–1.15)		0.98 (0.59–1.62)		0.78 (0.46–1.32)		0.83 (0.43–1.61)		0.76 (0.37–1.57)	
Grade			0.330		0.378		0.410		0.309		0.114		0.101
G1-2	**BCS + RT vs MS alone**	0.86 (0.56–1.32)		0.73 (0.46–1.14)		1.11 (0.71–1.73)		0.75 (0.46–1.21)		0.47 (0.18–1.25)		0.27 (0.09–0.80)	
	MS + RT vs MS alone	1.88 (1.30–2.72)		1.03 (0.68–1.57)		2.07 (1.41–3.05)		1.10 (0.71–1.72)		1.93 (1.12–3.35)		0.99 (0.50–1.96)	
G3	**BCS + RT vs MS alone**	1.25 (0.95–1.65)		1.05 (0.77–1.43)		1.58 (1.19–2.10)		1.17 (0.84–1.62)		1.38 (0.84–2.25)		0.93 (0.51–1.71)	
	MS + RT vs MS alone	2.48 (1.90–3.24)		1.40 (1.03–1.90)		2.64 (2.00–3.48)		1.49 (1.07–2.06)		3.07 (2.07–4.57)		1.55 (0.97–2.50)	

*Models were stratified by country, year of diagnosis, axillary surgery, tumour stage, and hormone receptor status, and adjusted for risk-reducing mastectomy (RRM) as a time-dependent covariate.
Note. HRs were estimated using Cox proportional hazards models. Results are shown for unadjusted and adjusted models, with and without left truncation at the time of *BRCA* testing (primary analysis), and in sensitivity analyses restricted to patients tested before or at diagnosis.
****Abbreviations: BCS, breast-conserving surgery; CI, confidence interval; HR, hazard ratio; MS, mastectomy; OS, overall survival; RT, radiation therapy; RRM, risk-reducing mastectomy.

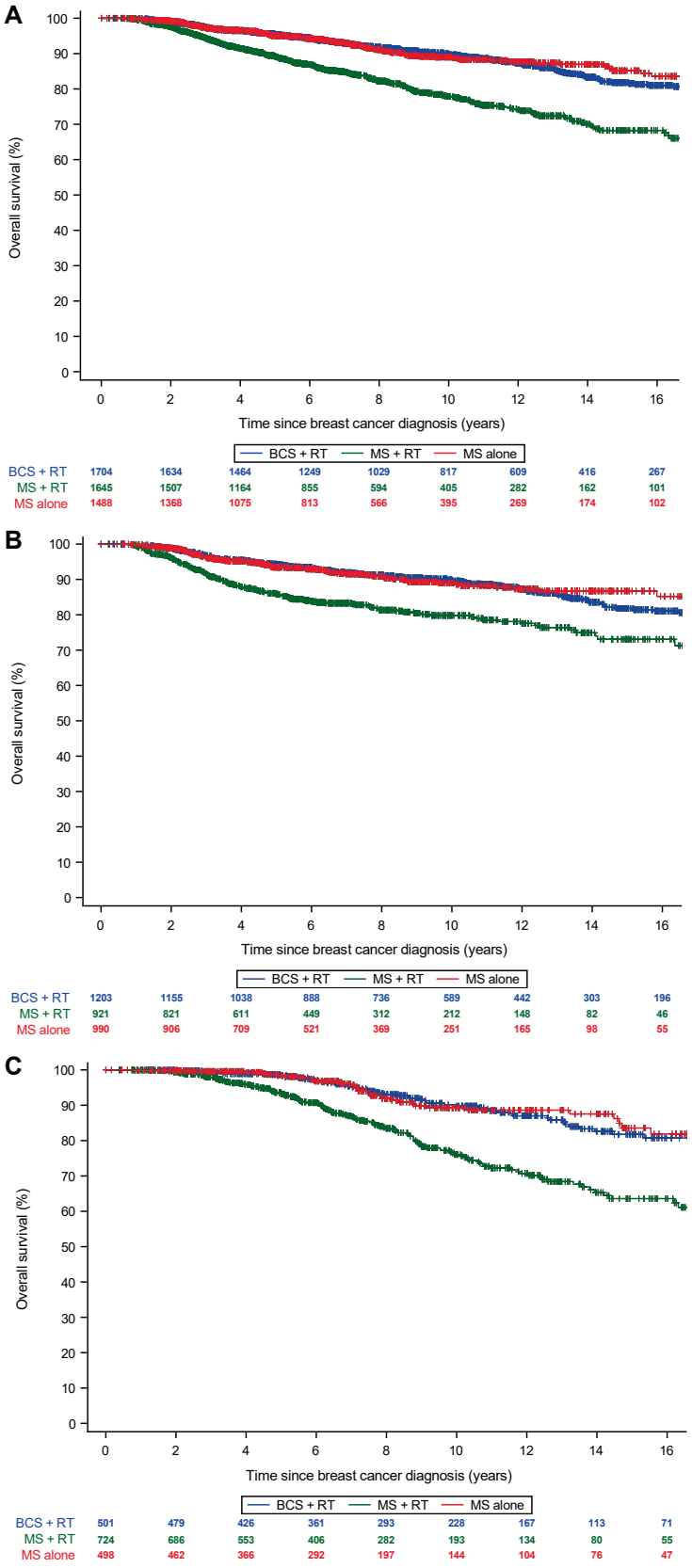

Fig. 4. OS by loco-regional treatment in (**A**) overall cohort, (**B**) *BRCA1* carriers, and (C) *BRCA2* carriers. Multivariable Cox models adjusted for country, year of diagnosis, axillary surgery, tumour stage, hormone receptor status, and uptake of RRM as a time-dependent covariate; primary analyses included left truncation at *BRCA* testing.

considerations [9,17]. Importantly, recent evidence indicates that awareness of *BRCA* mutation status prior to diagnosis is associated with earlier-stage detection and may improve survival outcomes, further underscoring the value of timely genetic testing and counselling in shaping both prognosis and therapeutic choices [27].

Finally, we do not advocate breast-conserving strategies universally for young *BRCA* carriers. Rather, organ preservation should be considered a viable, evidence-based option for patients who explicitly prioritise this approach, provided that disease characteristics and clinical context are favourable. Clinicians should carefully evaluate patient age, *BRCA* gene, tumour stage, and grade when discussing loco-regional options. Equally important, these data provide reassurance to patients who underwent BCS + RT before learning their *BRCA* status. Ultimately, treatment decisions should arise from multidisciplinary discussions that integrate individual risk profiles, life circumstances, and reproductive goals, while respecting patient autonomy.

Study limitations

Several limitations merit consideration. First, the definition and classification of ipsilateral breast events in *BRCA1/2* carriers are inherently complex, as such events may represent either true recurrences or new primary tumours; in addition, CBC contribute substantially to the overall event burden. Grouping IBR and CBC as second primary breast cancer events facilitates analysis but may obscure differences in biological mechanisms and timing. Second, loco-regional treatment strategies were strongly associated with baseline clinicopathological characteristics, calendar period, and timing of *BRCA* testing, introducing confounding by indication and the potential for residual confounding despite multivariable adjustment. In particular, patients undergoing BCS + RT were more likely to receive *BRCA* testing after the initial treatment decision and to have a lower uptake of immediate RRM, which may have contributed to the higher incidence of CBC observed in this group. Although the primary analysis accounted for delayed testing through left truncation at the time of *BRCA* identification, residual bias related to treatment selection cannot be fully excluded. Third, differences in surveillance intensity may have influenced event detection. Patients diagnosed with *BRCA* mutations during follow-up may have undergone more intensive imaging surveillance, potentially increasing the likelihood of detecting second primary breast cancer events. As detailed information on surveillance protocols was not consistently available across participating centres, this represents an additional source of unmeasured confounding. Accordingly, differences in second primary breast cancer events between treatment groups should not be interpreted as a direct causal effect of the loco-regional strategy. Fourth, variation in follow-up duration across treatment groups, with longer follow-up in the BCS + RT cohort, may have influenced cumulative event capture despite the use of time-to-event analyses.

Finally, the retrospective observational design limits causal inference. Although sensitivity analyses addressing delayed *BRCA* testing (including left truncation and restriction to early tested patients) yielded consistent results, unmeasured confounding cannot be excluded. In addition, the long enrolment period spans substantial changes in systemic therapies and diagnostic approaches, including the introduction of neoadjuvant immunotherapy, adjuvant CDK4/6 inhibitors, and PARP inhibitors, which were not standard of care during much of the study period and may have influenced both treatment decisions and long-term outcomes. An additional limitation relates to the lack of detailed and standardised information on RT technical parameters across participating centres. Given the long study period, RT techniques, planning approaches, and delivery modalities have evolved substantially over time, and year of diagnosis may act as a surrogate for these changes. The absence of granular data on RT technique precluded stratified analyses and limits the ability to explore potential differences related to technological advances. This reflects a broader challenge in retrospective multicentre studies, where heterogeneity in RT reporting and the lack of harmonised datasets may impact interpretability. These findings underscore the importance of prospective collection of RT parameters and the implementation of robust RT quality assurance programmes, as recommended in contemporary guidelines for clinical trials, to ensure consistency, reproducibility, and adequate integration of RT within multidisciplinary oncological research [33].

Conclusions

In this large international cohort of young *BRCA1/2* carriers with breast cancer, BCS + RT was associated with a higher risk of second primary breast cancer events (IBR/CBC) compared with MS, without a difference in OS. These findings reinforce the importance of early *BRCA* testing at or before diagnosis to inform surgical decision-making and consideration of risk-reducing strategies such as RRM and RRSO. Loco-regional management should remain personalised and multidisciplinary, balancing oncological safety with long-term quality-of-life implications. Further prospective studies are warranted to refine treatment strategies and optimise care for this high-risk population.

Data sharing

De-identified individual participant data, the data dictionary, and the statistical analysis plan will be available for 5 years after publication upon reasonable request to the corresponding author (matteo.lambertini@unige.it), following appropriate review of the data transfer agreements of each participating centre and subject to approval by the relevant ethics committees.

CRediT authorship contribution statement

Carlotta Becherini: Writing – review & editing, Writing – original draft, Supervision, Data curation, Conceptualization. **Eva Blondeaux:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Virginia Delucchi:** Methodology, Formal analysis, Data curation. **Luca Visani:** Writing – review & editing. **Hee Jeong Kim:** Writing – review & editing. **Florence Coussy:** Writing – review & editing. **Rinat Bernstein Molho:** Writing – review & editing. **Antonio Di Meglio:** Writing – review & editing. **Florentine S. Hilbers:** Writing – review & editing. **Katarzyna Pogoda:** Writing – review & editing. **Ava Kwong:** Writing – review & editing. **Elisa Agostinetto:** Writing – review & editing. **Adinda Baten:** Writing – review & editing. **Jyoti Bajpai:** Writing – review & editing. **Judith Balmana:** Writing – review & editing. **Halle C.F. Moore:** Writing – review & editing. **Ann H. Partridge:** Writing – review & editing. **Christine Rousset-Jablonski:** Writing – review & editing. **Kelly-Anne Phillips:** Writing – review & editing. **Angela Toss:** Writing – review & editing. **Tiphaine Renaud:** Writing – review & editing. **Alberta Ferrari:** Writing – review & editing. **Fedro A. Peccatori:** Writing – review & editing. **Lucas Sanchez:** Writing – review & editing. **Shani Paluch-Shimon:** Writing – review & editing. **Wanda Cui:** Writing – review & editing. **Stephanie M. Wong:** Writing – review & editing. **Jai Min Ryu:** Writing – review & editing. **Robert Fruscio:** Writing – review & editing. **Minna K. Lee:** Writing – review & editing. **Claudio Vernieri:** Writing – review & editing. **Alexios Matikas:** Writing – review & editing. **Fergus J. Couch:** Writing – review & editing. **Laura De Marchis:** Writing – review & editing. **Maria Vittoria Dieci:** Writing – review & editing. **Dione Aguilar y Mendez:** Writing – review & editing. **Shelley E. Hwang:** Writing – review & editing. **Mariya Rozenblit:** Writing – review & editing. **Deniz Can Güven:** Writing – review & editing. **Bela Mrinakova:** Writing – review & editing. **Nadia Harbeck:** Writing – review & editing. **Rodrigo Sanchez-Bayona:** Writing – review & editing. **Luca Boni:** Writing – review & editing, Methodology. **Matteo Lambertini:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Investigation, Data curation, Conceptualization. **Icro Meattini:** Writing –

review & editing, Writing – original draft, Visualization, Validation, Supervision, Data curation, Conceptualization.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: ML reports advisory roles for Roche, Lilly, Novartis, AstraZeneca, Pfizer, Seagen, Gilead, MSD, Pierre Fabre, Menarini, Exact Sciences, Nordic Pharma, and Bayer; speaker honoraria from Roche, Lilly, Novartis, Pfizer, Sandoz, Libbs, Daiichi Sankyo, Takeda, Ipsen, Menarini, and AstraZeneca; travel grants from Gilead, Roche, and Daiichi Sankyo; and research funding (to his institution) from Gilead. CV reports advisory roles for Roche, Lilly, Novartis, AstraZeneca, Pfizer, Gilead, and Menarini Stemline; speaker honoraria from Roche, Lilly, Novartis, Pfizer, Daiichi Sankyo, Menarini Stemline, AstraZeneca, MSD, and Istituto Gentili; and research funding (to his institution) from Roche and Daiichi Sankyo. AM reports honoraria from Seagen, Roche, AstraZeneca (speaker), Veracyte, MSD, and Novartis; expert testimony for Roche and AstraZeneca; research funding from AstraZeneca; and advisory board participation for Nordic Pharma. IM reports personal honoraria from Menarini StemLine, Eli Lilly, AstraZeneca, Daiichi Sankyo, Novartis, Pfizer, Gilead, MSD, TEMA Sinergie, and Exact Sciences. NH reports honoraria for lectures and/or consulting from AstraZeneca, Daiichi Sankyo, Gilead, High5Oncology, IQVIA, Lilly, MEDSCAPE, Menarini Stemline, MSD, Novartis, Pierre Fabre, Pfizer, Roche, Springer, and Viatris; she is also a Co-Director of the West German Study Group (WSG). RBM reports institutional travel support from Gilead and Pfizer. LDM reports honorary travel support from AstraZeneca and MSD. MVC reports invited speaker roles, advisory board participation, and travel/accommodation support from AstraZeneca, Daiichi Sankyo, Eli Lilly, Exact Sciences, Gilead, Menarini Stemline, MSD, Novartis, Pfizer, Roche, and Seagen. KP reports honoraria for consultations, lectures, training activities, and clinical trials, as well as conference fee payments, from AstraZeneca, Gilead, Roche, Novartis, Eli Lilly, Pfizer, MSD, Sandoz, Swixx, Bayer, Astellas, Exact Sciences, and Menarini. MKL discloses equity interests and professional services and activities related to Biologica. JMR received research funding from Medtronic, Intuitive, Bard, AstraZeneca, and Hanlim. EA reports advisory roles and/or honoraria from Eli Lilly, AstraZeneca, Bayer, Abscint, Gilead, and Novartis; research grants to her institution from Gilead BeLux; and meeting or travel grants from Novartis, Roche, Eli Lilly, Daiichi Sankyo, AstraZeneca, Abscint, Menarini, and Gilead. KAP reports receiving grants from the National Health and Medical Research Council (Australia) to her institution and being an inventor of the iPrevent free online tool used for breast cancer risk assessment and management. All disclosures are outside the submitted work. All remaining authors have declared no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2026.111523.

References

[1] Paluch-Shimon S, Cardoso F, Partridge AH, Abulkhair O, Azim HA, Bianchi-Micheli G, et al. ESO-ESMO fifth international consensus guidelines for breast cancer in young women (BCY5). Ann Oncol 2022;33:1097–118.
[2] Rosenberg SM, Ruddy KJ, Tamimi RM, Gelber S, Schapira L, Come S, et al. BRCA1 and BRCA2 Mutation Testing in Young Women with Breast Cancer. JAMA Oncol 2016;2:730–6.
[3] Copson ER, Maishman TC, Tapper WJ, Cutress RI, Greville-Heygate S, Altman DG, et al. Germline BRCA mutation and outcome in young-onset breast cancer (POSH): a prospective cohort study. Lancet Oncol 2018;19:169–80.
[4] Litiere S, Werutsky G, Fentiman IS, Rutgers E, Christiaens MR, Van Limbergen E, et al. Breast conserving therapy versus mastectomy for stage I-II breast cancer: 20 year follow-up of the EORTC 10801 phase 3 randomised trial. Lancet Oncol 2012;13:412–9.
[5] Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 2002;347:1227–32.
[6] Jacobson JA, Danforth DN, Cowan KH, d'Angelo T, Steinberg SM, Pierce L, et al. Ten-year results of a comparison of conservation with mastectomy in the treatment of stage I and II breast cancer. N Engl J Med 1995;332:907–11.
[7] Wrubel E, Natwick R, Wright GP. Breast-Conserving Therapy is Associated with improved Survival Compared with Mastectomy for Early-Stage Breast Cancer: a Propensity score Matched Comparison using the National Cancer Database. Ann Surg Oncol 2021;28:914–9.
[8] van Maaren MC, de Munck L, Jobsen JJ, Poortmans P, de Bock GH, Siesling S, et al. Breast-conserving therapy versus mastectomy in T1-2N2 stage breast cancer: a population-based study on 10-year overall, relative, and distant metastasis-free survival in 3071 patients. Breast Cancer Res Treat 2016;160:511–21.
[9] van Maaren MC, de Munck L, de Bock GH, Jobsen JJ, van Dalen T, Linn SC, et al. 10 year survival after breast-conserving surgery plus radiotherapy compared with mastectomy in early breast cancer in the Netherlands: a population-based study. Lancet Oncol 2016;17:1158–70.
[10] Cao W, Xie Y, He Y, Li J, Wang T, Fan Z, et al. Risk of ipsilateral breast tumor recurrence in primary invasive breast cancer following breast-conserving surgery with BRCA1 and BRCA2 mutation in China. Breast Cancer Res Treat 2019;175:749–54.
[11] Mavaddat N, Peock S, Frost D, Ellis S, Platte R, Fineberg E, et al. Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. J Natl Cancer Inst 2013;105:812–22.
[12] Garcia-Etienne CA, Barile M, Gentilini OD, Botteri E, Rotmensz N, Sagona A, et al. Breast-conserving surgery in BRCA1/2 mutation carriers: are we approaching an answer? Ann Surg Oncol 2009;16:3380–7.
[13] Pierce LJ, Levin AM, Rebbeck TR, Ben-David MA, Friedman E, Solin LJ, et al. Ten-year multi-institutional results of breast-conserving surgery and radiotherapy in BRCA1/2-associated stage I/II breast cancer. J Clin Oncol 2006;24:2437–43.
[14] Haffty BG, Harrold E, Khan AJ, Pathare P, Smith TE, Turner BC, et al. Outcome of conservatively managed early-onset breast cancer by BRCA1/2 status. Lancet 2002;359:1471–7.
[15] Chiba A, Hoskin TL, Hallberg EJ, Cogswell JA, Heins CN, Couch FJ, et al. Impact that timing of Genetic Mutation Diagnosis has on Surgical Decision making and

Outcome for BRCA1/BRCA2 Mutation Carriers with Breast Cancer. Ann Surg Oncol 2016;23:3232–8.
[16] Croshaw RL, Marshall ML, Williams TL, Erb KM, Julian TB. Prophylactic and Therapeutic Breast Conservation in BRCA1/2 Mutation Carriers. Int J Breast Cancer 2011;2011:481563.
[17] Pierce LJ, Phillips KA, Griffith KA, Buys S, Gaffney DK, Moran MS, et al. Local therapy in BRCA1 and BRCA2 mutation carriers with operable breast cancer: comparison of breast conservation and mastectomy. Breast Cancer Res Treat 2010; 121:389–98.
[18] Tung NM, Boughey JC, Pierce LJ, Robson ME, Bedrosian I, Dietz JR, et al. Management of Hereditary Breast Cancer: American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Guideline. J Clin Oncol 2020;38:2080–106.
[19] Nara M, Ishihara S, Kitano A, Tamura N, Aruga T, Kobayashi D, et al. Does breast-conserving surgery with radiotherapy in BRCA-mutation carriers significantly increase ipsilateral breast tumor recurrence? a systematic review and meta-analysis. Breast Cancer 2022;29:394–401.
[20] van den Broek AJ, Schmidt MK, van 't Veer LJ, Oldenburg HSA, Rutgers EJ, Russell NS,, et al. Prognostic Impact of Breast-Conserving Therapy Versus Mastectomy of BRCA1/2 Mutation Carriers Compared with Noncarriers in a Consecutive Series of Young Breast Cancer patients. Ann Surg 2019;270:364–72.
[21] Nilsson MP, Hartman L, Kristoffersson U, Johannsson OT, Borg A, Henriksson K, et al. High risk of in-breast tumor recurrence after BRCA1/2-associated breast cancer. Breast Cancer Res Treat 2014;147:571–8.
[22] Bernstein-Molho R, Laitman Y, Galper S, Jacobson G, Boursi B, Gal-Yam EN, et al. Locoregional Treatments and Ipsilateral Breast Cancer Recurrence rates in BRCA1/2 Mutation Carriers. Int J Radiat Oncol Biol Phys 2021;109:1332–40.
[23] Blondeaux E, Sonnenblick A, Agostinetto E, Bas R, Kim HJ, Franzoi MA, et al. Association between risk-reducing surgeries and survival in young BRCA carriers with breast cancer: an international cohort study. Lancet Oncol 2025;26:759–70.
[24] Lambertini M, Blondeaux E, Agostinetto E, Hamy AS, Kim HJ, Di Meglio A, et al. Pregnancy after Breast Cancer in Young BRCA Carriers: an International Hospital-based Cohort Study. J Am Med Assoc 2024;331:49–59.
[25] von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007; 370:1453–7.
[26] Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Control Clin Trials 1996;17:343–6.
[27] Lambertini M, Blondeaux E, Tomasello LM, Agostinetto E, Hamy AS, Kim HJ, et al. Clinical Behavior of Breast Cancer in Young BRCA Carriers and Prediagnostic Awareness of Germline BRCA Status. J Clin Oncol 2025;43:1706–19.
[28] Blondeaux E, Delucchi V, Mariamidze E, Bernstein-Molho R, Frank S, Ferrari A, et al. Breastfeeding after breast cancer in young BRCA carriers. J Natl Cancer Inst 2025;117:2229–39.
[29] Arecco L, Bruzzone M, Bas R, Kim HJ, Di Meglio A, Bernstein-Molho R, et al. Impact of hormone receptor status and tumor subtypes of breast cancer in young BRCA carriers. Ann Oncol 2024;35:792–804.
[30] Ebctcg MP, Taylor C, Correa C, Cutter D, Duane F, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet 2014;383:2127–35.
[31] Lancet 2023.
[32] Lambertini M, Ameye L, Hamy AS, Zingarello A, Poorvu PD, Carrasco E, et al. Pregnancy after Breast Cancer in patients with Germline BRCA Mutations. J Clin Oncol 2020;38:3012–23.
[33] Kaidar-Person O, Meattini I, Boersma LJ, Becherini C, Cortes J, Curigliano G, et al. Essential requirements for reporting radiation therapy in breast cancer clinical trials: an international multi-disciplinary consensus endorsed by the European Society for Radiotherapy and Oncology (ESTRO). Radiother Oncol 2024;195: 110060.
[34] for the BBCYC, Becherini C, Blondeaux E, Visani L, Delucchi V, Boni L,, et al. 4041 Radiation therapy management in BRCA1/2 carriers diagnosed with early breast cancer. Radiother Oncol 2025;206:S605.