

Breast-conserving therapy leads to better survival outcomes compared to mastectomy in patients with early breast cancer: evidences from the recent literature

Questa è la versione Post print del seguente articolo:

*Original*

Breast-conserving therapy leads to better survival outcomes compared to mastectomy in patients with early breast cancer: evidences from the recent literature / Fancellu, Alessandro; Porzani, Silvia; Prior, Margherita; Cottu, Pietrina; Giuliani, Giuliana; Sanna, Valeria; Porcu, Alberto. - In: MINERVA SURGERY. - ISSN 2724-5691. - 78:2(2023). [10.23736/s2724-5691.22.09820-3]

*Availability:*

This version is available at: 11388/343913 since: 2024-09-14T05:59:13Z

*Publisher:*

*Published*

DOI:10.23736/s2724-5691.22.09820-3

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note finali coverpage

(Article begins on next page)

**Breast-conserving therapy leads to better survival outcomes compared to mastectomy in patients with early breast cancer: evidences from the recent literature.**

Journal: Minerva Surgery (formerly: Minerva Chirurgica)

Paper code: Minerva Surg-9820

Submission date: November 13, 2022

Article type: Review Article

Files:

1. Manuscript

Version: 1

Description: Main file

File format: application/msword

<https://dx.doi.org/10.23736/s2724-5691.22.09820-3>

1 **Breast-conserving therapy leads to better survival outcomes compared to**  
2 **mastectomy in patients with early breast cancer: evidences from the**  
3 **recent literature.**  
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7 *breast-conserving therapy and survival*  
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46 **BREAST-CONSERVING THERAPY LEADS TO BETTER SURVIVAL**  
47 **OUTCOMES COMPARED TO MASTECTOMY IN PATIENTS WITH EARLY**  
48 **BREAST CANCER: EVIDENCES FROM THE RECENT LITERATURE.**  
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52 **ABSTRACT**  
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1 Classical studies comparing breast-conserving therapy (BCT) and mastectomy (Mx)  
2 focused on the non-inferiority of BCT in terms of survival outcomes. However, recent  
3 large retrospective studies have provided evidence that BCT could confer a survival  
4 advantage over Mx. The prognostic benefit of BCT was observed in all molecular  
5 subgroups, including triple negative breast cancer, and also in young patients affected  
6 from the disease, who are often submitted to Mx irrespective of tumor size. This new  
7 concept, regarding the prognostic importance related to the type of surgical treatment of  
8 breast cancer, is of particular relevance in current times. In fact, in the last two decades  
9 there has been a rise in Mx rates in BCT-eligible women, as well as a rise in bilateral  
10 mastectomy in patients with unilateral breast cancer. This phenomenon occurs despite lack  
11 of scientific evidence supporting the necessity of a more extensive surgery, and is  
12 primarily a patient-driven trend. The results of recent studies, demonstrating that BCT  
13 achieves better overall survival than Mx, should be incorporated in the multidisciplinary  
14 decision-making process. Patients with early breast cancer for whom either BCT or Mx  
15 are surgical options, should be properly informed that the prognosis of their disease is  
16 largely dependent from the biological behaviour of the tumor, and that Mx should not be  
17 considered equal to BCT in terms of survival. The present review underscored that BCT,  
18 when feasible, should be considered the option of choice also due to its advantage in  
19 survival outcomes.

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32 **KEYWORDS:** Breast-conserving surgery; Mastectomy; Survival

### 33 34 35 **INTRODUCTION**

36 Breast-conserving therapy (BCT) and mastectomy (Mx) continue to be the keystones of  
37 surgical treatment for early breast cancer. In the 1980s, large population-based trials with  
38 long-term follow-up demonstrated that patients submitted to BCT, i.e. breast-conserving  
39 surgery followed by radiotherapy (RT) achieved survival outcomes comparable to those  
40 submitted to Mx.<sup>1,2</sup> These studies represented a crucial landmark, as they opened the  
41 way to a new era in the management of breast cancer. The chance to preserve the breast  
42 has dramatically improved the quality of life of millions of women affected from the  
43 disease.<sup>2-5</sup> In current clinical practice, BCT is considered the option of choice, when  
44 feasible according to the clinical and radiological picture.

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1 over Mx.<sup>6-9</sup> Interestingly, in the modern era of multidisciplinary management of breast  
2 cancer, a new question has arisen: can BCT achieve better survival outcomes than Mx?  
3 The “less is more” principle has been developed, based on recent studies comparing long-  
4 term results between patients receiving BCT or Mx.<sup>10</sup>  
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8 It should be recognized that the management of breast cancer has known profound  
9 changes in the last two decades. Nowadays, breast-conserving surgery is quite different  
10 from the original “quadrantectomy”, since the concept of “no tumor on ink” has  
11 dramatically reduced the need to obtain large margins around the tumor mass.<sup>11</sup> On the  
12 other hand, Mx has evolved towards the modern skin-sparing and nipple-sparing  
13 mastectomy, mostly thanks to the advancements of plastic surgery. The extent of axillary  
14 surgery has been progressively reduced since the adoption of sentinel node biopsy in  
15 clinical practice. Side effects of radiation therapy have become less frequent with the  
16 modern CT-based planning techniques. Also, systemic treatments have radically changed  
17 in both the neoadjuvant and adjuvant settings, and have contributed to improve the long-  
18 term survival outcomes in patients with early or advanced breast cancer in all age groups.  
19 Furthermore, the recent acquisitions in the field of molecular profile of breast cancer, have  
20 demonstrated that the prognosis of the disease largely results from the molecular subtype  
21 and efficacy of targeted therapies.  
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24 In this paper, the authors critically appraised the recent literature focusing on long-term  
25 survival outcomes of BCT and Mx, with the aim to evaluate their impact on modern  
26 management of breast cancer.  
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## 35 36 37 **LITERATURE SEARCH AND STUDY SELECTION** 38

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40 The present narrative review focused on the literature investigating the topic of survival  
41 outcomes in patients receiving BCT or Mx for early breast cancer. A systematic literature  
42 search using the PubMed, Scopus, and Web of Science databases was conducted in  
43 September 2022. The following keywords were used and combined for the search: ‘breast  
44 conservation’, ‘breast-conserving surgery’, ‘breast-conserving therapy’, ‘mastectomy’,  
45 ‘breast cancer’, ‘overall survival’, ‘disease-free survival’, ‘outcomes’. Articles published  
46 in English from January 1, 2020 to September 30, 2022 were retrieved, screened and  
47 selected by two independent authors. Relevant data were extracted into a standardized data  
48 collection sheet by two authors and the research coordinator. The most relevant  
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1 observational retrospective or prospective studies that presented numerical analyses and  
2 comparisons of patients with early breast cancer receiving BCT or Mx were included.  
3 Outcomes were defined as percentages or overall proportions. Due to the nature of the  
4 work (review), no formal statistical analyses were conducted.  
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## 8 9 **SURVIVAL OUTCOMES OF BCT AND MASTECTOMY**

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12 Several recent retrospective population-based and institutional-based studies have reported  
13 better overall survival (OS) and breast cancer specific survival in patients who underwent  
14 BCT compared to those who underwent Mx with or without RT. The first evidence had  
15 been observed in the late 1990s, when a meta-analysis of 10-year survival of patients with  
16 early-stage breast cancer submitted to BCT or Mx was carried out. Patients receiving BCT  
17 had survival rates at least as high as those receiving Mx. However, under certain  
18 conditions, particularly for node-positive patients, BCT was found to confer a relative  
19 survival advantage over Mx. Interestingly, Mx without adjuvant radiation appeared to be  
20 inferior to BCT for node-positive patients.<sup>12</sup>  
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29 More recently, a cohort study from Swedish national data including 48,986 women, of  
30 whom 59.9% had breast-conserving surgery plus RT, 25.3% Mx, and 14.7% Mx + RT.  
31 OS and breast cancer specific survival were significantly worse after Mx (hazard ratio  
32 [HR], 1.79; and HR, 1.66, respectively) and Mx + RT (HR, 1.24 and HR 1.26,  
33 respectively) than after breast-conserving surgery + RT. The authors concluded that  
34 breast-conserving surgery + RT yielded better survival than Mx irrespective of RT, and  
35 stated that Mx should not be regarded as equal to breast conservation, in patients in whom  
36 both interventions are valid options.<sup>13</sup>  
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43 A retrospective study from the Surveillance, Epidemiology, and End Results (SEER)  
44 database on a total of 132,149 breast cancer patients, found that the 5-yr breast cancer-  
45 specific survival after BCT, Mx alone, or Mx with RT were 97%, 94%, and 90%,  
46 respectively ( $P < .001$ ), and that 10-yr breast cancer-specific survival rates were 94%,  
47 90%, and 83%, respectively ( $P < .001$ ). Therefore, BCT resulted in a higher breast cancer-  
48 specific survival rate compared with Mx or Mx + RT.<sup>14</sup>  
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1 In a Norwegian cohort of about 10,000 women with breast cancer aged 50-69 years, BCT  
2 was associated to a significantly better breast cancer-specific survival and a lower risk of  
3 death from breast cancer compared to Mx, independent of detection mode, prognostic and  
4 predictive tumor characteristic. In fact, adjusted analyses showed a 1.7 (95% CI: 1.3-2.4)  
5 higher risk of breast cancer death among women who underwent Mx.<sup>15</sup>  
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10 Similar results were observed in a registry-based follow-up study of 13,015 women with  
11 early breast cancer operated on between 1998 and 2008. Five-year breast cancer specific  
12 survival for women who underwent primary BCT or primary Mx was 97 and 88 %,  
13 respectively. Moreover, women who underwent Mx had a HR of 1.64 (95 % confidence  
14 interval 1.43-1.88) for breast cancer specific death compared with women who underwent  
15 BCT after adjusting for the year of diagnosis, age at diagnosis, stage, histology, and tumor  
16 grade.<sup>16</sup>  
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23 Breast-conserving surgery plus RT achieved better locoregional recurrence rate and OS  
24 for patients than Mx in another retrospective cohort study of 5,335 alone women. The  
25 authors argued that survival benefit of BCT may be related to the addition of adjuvant  
26 RT.<sup>17</sup>  
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30 A retrospective review collected from the National Cancer Database (NCDB) included  
31 more than 200,000 patients with early-stage lymph node-negative breast cancer operated  
32 on between 2006 and 2014. The authors reported that OS was higher with BCT compared  
33 to Mx. In particular, 5-year OS of 94.4% vs. 91.8% ( $P < 0.001$ ) and 7-year OS of 90% vs.  
34 85.2% ( $P < 0.001$ ) were reported, for BCT and Mx respectively. Multivariable analysis  
35 showed an association between BCT and improved OS (HR 0.66, 95% CI, 0.64–  
36 0.69,  $P < 0.001$ ).<sup>18</sup>  
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42 By using using well-matched, contemporary data, another study from National Cancer  
43 Database Participant User Files found that the 5-year overall survival was superior for  
44 BCT compared with Mx (92.9% vs. 89.7%,  $p < 0.001$ ), and that, as expected, this survival  
45 advantage persisted for both stage I ( $p < 0.001$ ) and stage II ( $p < 0.001$ ) disease on subgroup  
46 analysis.<sup>19</sup>  
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50 A great deal of evidence on the survival benefits of BCT over Mx comes from a meta-  
51 analysis collecting more than 1 500 000 patients from 30 retrospective studies, published  
52 in May 2022. Breast conservation was associated with improved OS compared with Mx  
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1 [relative risk (RR) 0.64, 95% CI 0.55–0.74]. To note, that effect was similar when analysis  
2 was made in cohorts and multi-institutional databases (RR 0.57, 95% CI 0.49–0.67).  
3 Moreover, the benefit of breast-conserving surgery was stronger in patients who had less  
4 than 10 years of follow-up (RR 0.54, 95% CI 0.46–0.64).<sup>20</sup>  
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## 9 **SURVIVAL OUTCOMES BY MOLECULAR SUBTYPE**

10 In the modern era of precision medicine and targeted therapy, it is logical to address the  
11 issue of surgical treatment of breast cancer according to its molecular classification. Some  
12 recent studies have investigated the outcomes of BCT and Mx by molecular subtype. It is  
13 a common experience that the breast cancers with worse prognosis, namely HER2 positive  
14 and triple negative breast cancer (TNBC), are often treated with Mx irrespective of tumor  
15 size and locoregional extension.<sup>21</sup> This attitude can be partially explained by the fact that  
16 HER2 positive and TNBC subtypes are associated with higher risk of locoregional  
17 recurrence than Luminal subtypes after BCT.<sup>21-23</sup> In general, the risk of locoregional  
18 recurrence after BCT have decreased over time and is now similar to that after  
19 mastectomy. TNBC, specifically, is the tumor with the worst prognosis among breast  
20 cancers, because of its aggressive biologic behaviour and the lack of targeted therapies.  
21 However, studies have demonstrated that even in patients with TNBC, BCT might better  
22 of Mx in terms of survival outcomes.  
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32 A meta-analysis published in 2021 focused on the impact of the surgical treatment on  
33 oncological outcomes in patients with TNBC. The primary endpoints were locoregional  
34 recurrence, distant metastases, and OS in patients who had BCT versus those who had Mx  
35 for TNBC. Among more than 19 000 patients from 14 comparative studies, women who  
36 underwent BCT resulted in a significantly lower odds of locoregional recurrence (OR  
37 0.64, 95% CI 0.48-0.85), distant metastases (OR 0.70, CI 0.53-0.94), and a significantly  
38 lower hazard for all-cause mortality (HR 0.78, CI 0.69-0.89) relatively to those who  
39 underwent Mx.<sup>21</sup> In another study, including about 13,000 TNBC patients from the SEER  
40 database, the survival benefit of breast-conserving surgery with RT was higher than or  
41 similar to that of total Mx.<sup>24</sup> From the same database, in a study on almost 25,000 TNBC  
42 patients with a survival longer than 5 years, the subgroup analyses for patients with tumors  
43  $\leq 20$  mm displayed a superior OS and breast cancer-specific survival for breast-conserving  
44 surgery when compared with Mx. Interestingly, breast-conserving surgery provided at  
45 least an equivalent prognosis to a Mx in patients with tumors larger than 20 mm.<sup>25</sup>  
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1 Therefore, this study demonstrated that breast conservation can be safely proposed to  
2 patients with TNBC larger than 2 cm. A recent paper also showed that BCT for patients  
3 with T1-2N0M0 TNBC has better survival than Mx, regardless of age of patients, tumor  
4 grade or size.<sup>26</sup> Among 1 242 consecutive patients with T1-2N0 TNBC treated with  
5 multimodality therapy at a single institution from 1999 to 2008, a low 5-year risk of  
6 locoregional recurrence (4.7 %) was achieved.<sup>27</sup> This result suggests that aggressive  
7 multimodality treatment in patients with TNBC may results in low local relapses after  
8 either BCT or Mx. In a propensity-score analysis including almost 100 000 patients, of  
9 whom 77.6% received BCT and 22.4% Mx, the 5-year OS rate was 94.7% in the BCT  
10 group and 87.6% in the Mx group, and the 5-year breast cancer-specific survival was  
11 97.2% in the BCT and 94.3% in the Mx group.<sup>28</sup>

12 In a series of almost 200,000 patients who received surgical treatment for breast cancer,  
13 multivariate analyses were performed separately for patients with low-, intermediate-, and  
14 high-risk tumors. The adjusted HR for disease-specific survival for patients who  
15 underwent Mx versus BCT for low-, intermediate-, and high-risk tumors were 1.66 (95%  
16 CI 1.54-1.79; P < .001), 1.40 (95% CI 1.29-1.53; P < .001), and 1.27 (95% CI 1.19-1.35; P  
17 < .001), respectively. The authors concluded that patients with ER-positive, low-grade  
18 breast cancers who underwent Mx had a 66% increase in disease-specific mortality versus  
19 those who underwent BCT.<sup>29</sup> In a retrospective review including 4,876 patients  
20 undergoing treatment of Stage 0-3 breast cancer, analysis of Stage II patients revealed  
21 that patients receiving breast-conserving surgery vs. Mx had lower rates of distant  
22 recurrence in all molecular subgroup (Luminal A-B, HER2 positive, and TNBC). That  
23 finding was most evident in TNBC, where the BCT group had significantly lower rates of  
24 distant recurrence (p= 0.03) and significantly higher survival (p = 0.007).<sup>30</sup> A study from  
25 California Cancer Registry highlighted that BCT was associated with a significant  
26 increase in OS and disease-specific survival, and that the greatest OS benefit was observed  
27 in patients older than age 50 years with hormone receptor positive tumors.<sup>31</sup>

## 50 SURVIVAL OUTCOMES IN YOUNG WOMEN

51 Young women with breast cancer are considered those who develop the disease before the  
52 age of 40.<sup>32,33</sup> In the real world, many young women are commonly treated with Mx,  
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1 irrespective of tumor size and possible indications to breast-conserving surgery.<sup>34</sup> It has  
2 been reported that about 65% of young patients with breast cancer undergo Mx in some  
3 US institutions.<sup>35</sup> The concept that a bigger surgical treatment is better in patients  
4 developing breast cancer at a young age, continues to resist to some extent, despite the  
5 evidences from the recent literature.<sup>36</sup> The reasons behind this phenomenon are various  
6 and complex. A reason explaining the high rate of Mx is that young women have an  
7 increased risk to develop locoregional recurrence after BCT when compared to their old  
8 counterpart.<sup>5,33,37-39</sup> However, locoregional recurrence rates have decreased over time in  
9 young women, and current rates are far lower from than reported in previous studies.  
10 Young women with breast cancer are more likely to have familial cancer predisposition  
11 genes. In germline-mutated patients, Mx has become the preferred option in both the  
12 curative and prophylactic settings. Breast cancers occurring in young women are  
13 characterized by higher biological aggressiveness, higher likelihood to develop  
14 phenotypes with bad prognosis and, in general, are associated to al less favorable  
15 oncological outcomes when compared to older women. Nonetheless, a large amount of  
16 data in the literature have shown that survival outcomes after BCT are at least equal, if not  
17 even better, than Mx in young women with early breast cancer.

18 A meta-analysis of studies that compared OS between BCT and Mx in more than 22,000  
19 young patients ( $\leq 40$  years) with T1-T2 N0-N+ M0 breast cancer, has been published in  
20 2015. After all the adjustments, there was no difference in risk of death between the two  
21 groups, although a not significant risk reduction in patients who underwent BCT  
22 compared to Mx was observed.<sup>40</sup> In a recent study, 1,520 breast cancer patients aged 35  
23 or less were stratified into three groups by surgical options: (breast-conserving surgery,  
24 mastectomy alone, and mastectomy with reconstruction). Interestingly, multivariate Cox  
25 analysis demonstrated that disease-free survival and OS were significantly improved in  
26 patients undergoing breast-conserving surgery compared with those undergoing Mx, with  
27 HR of 0.448 (95% CI 0.276-0.728; P = 0.001) and 0.405 (95% CI 0.206-0.797, P = 0.009),  
28 respectively. The authors' conclusion was that breast-conserving surgery is to be  
29 considered the preferred option for early young women breast cancer.<sup>26</sup> The influence of  
30 breast-conserving surgery on OS and breast cancer-specific survival was evaluated in  
31 more than 15,000 women aged 35 or less from the SEER database. Breast-conserving  
32 surgery was an independent protective factor for OS (P = 0.028) and breast cancer specific  
33 survival (P = 0.042), thus breast conservation may bring better survival outcomes than  
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1 mastectomy in young women. To note, the authors advised that not all patients benefit  
2 from breast conservation and built a nomogram to help surgical decision making in breast  
3 cancer women aged  $\leq 35$ .<sup>41</sup> In another study from the same database, the survival benefits  
4 of BCT or mastectomy were compared in 23 810 breast cancer patients under 40 with  
5 early-stage breast cancer, of whom 44.9% received BCT and 55.1% Mx, with a median  
6 follow-up of 116 months. Results showed that BCT had survival benefits that were  
7 defined 'at least no worse than mastectomy', and these benefits were even better in the 36  
8 to 40 years age group.<sup>42</sup> A retrospective analysis found that 5-year OS, as well as breast  
9 cancer-specific survival, was significantly higher in patients with BCT compared to Mx  
10 alone (89% vs. 84.5%, and 93% vs 91%; p-value <0.001) among 2 761 patients with T1-  
11 2N0M0 TNBC. On subgroup analysis, patients younger than 40 had similar survival  
12 outcomes after either Mx alone or BCT.<sup>43</sup>

13 In a cohort of 1,331 breast cancer patients younger than 40 years who had BCT between  
14 1997 and 2010, local control and overall prognosis have improved significantly during the  
15 years, especially after 2005 when the stratification of breast cancer into molecular  
16 subtypes entered in routine clinical practice and the use of trastuzumab in HER2 positive  
17 cancers was implemented.<sup>44</sup> This finding emphasizes the role of molecular classification  
18 in prognosis of breast cancer, even in young women. In fact, rates of locoregional  
19 recurrence have decreased over time, mainly due to the appropriate use of subtype-  
20 directed systemic therapy in all age groups. Evidence has emerged that the higher rates of  
21 local recurrence observed in younger patients are largely driven by molecular subtype and  
22 are not overcome by choice of a more extended surgery.<sup>38</sup>

### 23 **INCREASING RATES OF MASTECTOMY**

24 The current debate, regarding the survival outcomes according to the type surgical  
25 treatment of breast cancer, is of particular importance in the current scenario. In fact,  
26 recent data have reported an increasing trend in mastectomy rates.<sup>46,46</sup> In the US, odds of  
27 mastectomy in BCT-eligible women increased 34% during the timeframe 1998-2011.<sup>45</sup>  
28 This phenomenon can be seen as a paradox, inasmuch as a growing number of women are  
29 diagnosed with small or even nonpalpable breast tumors due to the widespread of  
30 mammographic screening. In addition, there is a diffuse trend to de-escalation of  
31 treatments in many fields of surgical oncology. There are many motivations explaining the  
32 increasing tendency of Mx rates. The use of breast MRI in patients with both invasive and  
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1 in situ breast cancer has increased the discovery of multicentric carcinomas, for which Mx  
2 is the considered the standard surgical treatment. In patients with a diagnosed breast  
3 carcinoma, preoperative MRI has a high sensitivity in identifying additional foci of  
4 neoplasia in either the ipsilateral or contralateral breast; nonetheless it has a low  
5 specificity. This finding translates into the necessity to obtain a histological confirmation  
6 of cancer multicentricity suspected with MRI, in order to avoid unnecessary  
7 mastectomies.<sup>47-49</sup> Preoperative MRI has proper indications and should be reserved to  
8 particular situations in which traditional imaging, i.e. mammography and ultrasound,  
9 result insufficient for a precise surgical planning.<sup>50</sup>

10 Another aspect that has contributed to the increasing of Mx rates is the widespread use of  
11 immediate breast reconstruction following breast removal. In fact, a growing number of  
12 patients, even aged over 70 years, nowadays request an immediate reconstruction. In this  
13 regards, it should be recognized that the real contraindications for that intervention have  
14 been reduced over the years, thus a minority of patients receive a mastectomy without  
15 immediate reconstruction in current times.<sup>5,51</sup> Advancements in plastic surgery have led to  
16 a substantial improvement of quality of life of patients who receive surgery for breast  
17 cancer, especially for those candidates to Mx. Immediate autologous or implant-based  
18 reconstruction, in fact, have a positive impact on sexual function and body image.

19 The introduction of nipple sparing mastectomy has largely contributed to the rise of Mx in  
20 clinical practice, since several studies have demonstrated its oncological safety in selected  
21 patients.<sup>52,53</sup> The benefits of nipple-areola preservation are understandable, and lead to  
22 optimal esthetical and psychological outcomes, especially when prepectoral immediate  
23 prosthetic reconstruction is performed.<sup>54</sup>

24 Up to 10% of breast cancers are hereditary and develop due to a genetic mutation, the  
25 most common being BRCA1 and BRCA2 germline mutations. It is estimated that 55%–  
26 72% of women who inherit a harmful BRCA1 variant and 45%–69% of those who inherit  
27 a harmful BRCA2 variant, will develop breast cancer by 70–80 years of age.<sup>55,56</sup> When  
28 compared to sporadic breast cancer, BRCA-associated cancers develop at a younger age,  
29 are of higher histologic grade, are more likely to be estrogen/progesterone receptor  
30 negative, and are more likely to fall within the category of TNBC. The surge in genetic  
31 testing has resulted in a more frequent use of Mx in mutation carriers who developed the  
32 disease, and also in those who requested a risk-reducing surgery. In the therapeutic setting  
33 of BRCA-mutated women with breast cancer, Mx is considered the treatment of choice.

1 However, the surgical decision-making process remain ill-defined since there are no  
2 randomized controlled trials that directly compares BCT and Mx in that subgroup. Recent  
3 studies have suggested that BCT might be a safe option in BRCA mutation carriers who  
4 develop breast cancer. In a systematic review of 18 studies including BRCA carriers,  
5 pooled analysis of OS at 5-, 10- and 15-year were comparable between breast-conserving  
6 surgery and Mx (88.7%, 89.0% and 83.6% in BCT; comparing to 83%, 86.0% and 83.2%,  
7 in Mx). To note, the pooled ipsilateral breast cancer recurrence rates at 5-, 10- and 15-  
8 year resulted higher in the BCT group (8.2%, 15.5% and 23% in BCT; comparing to  
9 3.4%, 4.9% and 6.4% in Mx). These data highlight that breast conservation, although  
10 associated with higher ipsilateral breast cancer recurrence, is not related to adverse short  
11 and long-term survival outcomes. This study also implies that breast-conserving surgery  
12 should be considered as a surgical option even in selected BRCA mutation carriers.<sup>57</sup>  
13 Indubitably, in that particular subgroup, the surgical decision requires a thorough  
14 multidisciplinary approach and an exhaustive pre-operative balancing of risks and benefits  
15 of surgical choice.

16 Among the causes explaining the rise in Mx rates, the patient's choice plays an important  
17 role. It is a common experience that many women eligible for BCT, instead choose to  
18 undergo a Mx. This occurs in up to 25% of BCT-eligible women in some reports, in spite  
19 of the fact that there are not any advantages in terms of survival outcomes.<sup>58</sup> The  
20 phenomenon of rise in Mx rates among women suitable of BCT has been reported in many  
21 studies from US databases.<sup>45,46,59</sup> while this tendency has been less frequently observed in  
22 European countries.<sup>5,60</sup> It is important to note that patient choice is the major determinant  
23 of the rise of Mx rates among US women.<sup>59</sup>

24 Moreover, many women with unilateral breast cancer who meet the criteria for BCT,  
25 request a bilateral Mx.<sup>59,61</sup> In a retrospective study using the US National Cancer Data  
26 Base, the rates of bilateral Mx for unilateral disease increased from 1.9% in 1998 to 11.2%  
27 in 2011 ( $P < .001$ ).<sup>45</sup> The reasons for such a choice include an overestimation of risk of  
28 developing a contralateral breast cancer, and anxiety is often at the origin of the patient's  
29 choice.<sup>59,62,63</sup> Only patients at high risk for multiple primary breast cancers should be  
30 considered appropriate candidates for bilateral mastectomy.

31 It is undoubtful that there is a need to optimize communication strategies in order to  
32 implement the decision making process for surgical treatment of breast cancer.

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## DISCUSSION AND CONCLUSIONS

Breast conservation, compared to Mx, is known to be associated with superior cosmetic outcome, better psychological well-being, smaller surgical wound, and quicker post-operative recovery. The present study focused on the issue of survival outcomes related to the surgical treatment of breast cancer. In particular, evidences from studies demonstrating better survival outcomes of BCT were resumed.

The majority of patients with early breast cancer are eligible for BCT. Mx is still appropriate in many clinical situations and continues to be a cornerstone in the treatment of breast cancer. Breast cancer is a clinically heterogeneous disease and not all patients are suitable for breast conservation. In fact, Mx is generally indicated when the tumor area is too large to be removed with acceptable cosmetic results, in presence of multicentric disease or diffuse malignant calcifications, in situations preventing postoperative RT, and when margins are persistently positive after lumpectomy attempts.<sup>5,59</sup> However, many women in whom BCT should be the treatment of choice on the basis of clinical and radiological pictures, instead undergo a Mx. Patients eligible for BCT who elect for Mx should be extensively informed on the possible consequences of such a decision. Even after an immediate reconstruction, Mx is a permanent organ loss, sometimes leading to troublesome sequelae from the psychological, sexual, and relational perspective. Patients undergoing nipple-sparing Mx, compared to breast conservation, are significantly less satisfied with appearance, less comfortable being seen undressed, and experience decreased persistence of breast intimacy.<sup>4</sup> Furthermore, the cosmetic outcome of a Mx and reconstruction is sometimes worse than expected, especially when a bilateral Mx is carried out or in cases where adjuvant post-mastectomy RT is required. Also, a possible delay in medical adjuvant treatments may occur, due to implant-related complications. Some authors question whether patients with early breast cancer should still be offered the choice of breast-conserving surgery or mastectomy.<sup>64</sup>

Another issue that needs to be briefly discussed is the role of BCT in the setting of neoadjuvant chemotherapy. In the last ten years, there has been a surge in the use of neoadjuvant chemotherapy, especially in HER2 positive and TNBC, with the main aims of delivering primary systemic treatment and down-staging the cancer at presentation. Pathologic complete response is commonly observed in 36.4% of HER2 positive tumors (range 17.5-74.2%), 32.6 of TNBC (range 20.3-62.2%), and 9.3% of hormone receptor-positive/HER2 negative tumors (range 5.5-31.3%).<sup>65</sup> One of the reasons to perform

1 neoadjuvant chemotherapy is to make breast conservation possible in patients who would  
2 be otherwise candidates to Mx at the time of diagnosis. However, rates of BCT in patients  
3 responding to neoadjuvant chemotherapy remain lower than expected.<sup>66</sup> In a recent study,  
4 data from 1.383 women with stage I-III breast cancer treated with neoadjuvant  
5 chemotherapy and subsequent surgery from 2013 to 2018 were analyzed. Downstaging to  
6 BCT eligibility post-neoadjuvant chemotherapy among initially BCT-ineligible patients  
7 was similar across age groups. However, women aged 40 or less chose breast-conserving  
8 surgery less often than their older counterpart ( $p < 0.001$ ), although they were more likely  
9 to obtain a pathological complete response.<sup>67</sup> Percentages of women who are eligible for  
10 and ultimately undergo BCT after neoadjuvant systemic therapy, range between 30% and  
11 60%.<sup>67,68</sup> There is an urgent need to optimize breast-conserving strategies in patients  
12 undergoing neoadjuvant chemotherapy.

13 Although many articles in the literature have demonstrated survival advantages of BCT  
14 over Mx, the reasons of this phenomenon are still to be elucidated. In this context, RT  
15 probably plays an important role. In fact, while whole-breast RT is routinely performed in  
16 all women undergoing breast-conserving surgery for invasive or intraductal carcinoma, a  
17 minority of patients receive RT after a Mx. The effect of RT is beyond the local control  
18 the disease, and many studies have suggested that radiation treatment may influence and  
19 modulate the immunological systemic response. Also, the higher level of  
20 immunodepression and longer operative time due to extensive surgery (i.e. Mx plus  
21 immediate reconstruction) might impact on the prognosis. Certainly, the existing  
22 relationships between surgery, anesthesia, RT, systemic treatments and immunological  
23 system remain largely unclear. Moreover, the better quality of life observed in women  
24 undergoing BCT might contribute to a better survival; the effects of psychological factors  
25 on the natural history of neoplastic diseases are also to be better elucidated. All the  
26 hypotheses formulated to explain the survival advantages of BCT open fascinating fields  
27 of translational research that worth to be explored.

28 Like all reviews, the present study certainly has some limitations. First, no randomized  
29 trials comparing survival outcomes in patients undergoing BCT or Mx were conducted.  
30 Therefore, the conclusions came from retrospective studies. Second, there was a big  
31 heterogeneity across studies and survival outcomes were reported in different contexts;  
32 consequently, we cannot exclude that biases in patients' selection might have had  
33 influenced some of the reported results, despite appropriate statistical adjustments for  
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confounding factors. Nonetheless, this review provide evidence that many data in the recent literature highlighted the superiority of BCT over Mx in terms of survival outcomes. This advantage of BCT seems to exist also for patients with tumors with unfavorable prognostic factors, such as TNBC. Studies evaluating survival by surgical treatment have demonstrated that BCT is the preferred option also in young patients with breast cancer, although rates of local recurrences are higher when compared to their older counterpart. This information needs to be included when discussing breast cancer treatment with young patients, for whom there is a common tendency to offer upfront Mx despite a lack of evidence that a more extended surgery translates into better outcomes.

What emerges from the present paper is a further confirmation of the concept that a bigger surgery does not overcome a bad tumor biology. With this in mind, it is reasonable to question whether Mx is an appropriate treatment option to offer breast-conserving therapy candidates.

The survival of patients with breast cancer is largely driven from tumor molecular subtype and biological behavior, irrespective of the extension of surgery. These concepts need to be clearly explained to the patient from the members of the multidisciplinary team, which plays a pivotal role in the decision-making process. Preoperative evaluation should be focused primarily on oncological safety and quality of life. The results of the recent studies in favour of survival advantages of BCT over Mx need to be included in the shared surgical decision making.

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31 *Conflicts of interest.* The authors certify that there is no conflict of interest with any financial  
32 organization regarding the material discussed in the manuscript.  
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36 *Funding.* The authors report no involvement in the research by the sponsor that could have  
37 influenced the outcome of this work.  
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41 *Authors' contributions.*— AF and VS have given substantial contributions to the conception or the  
42 design of the manuscript, SP, MP, PC and GG to acquisition, analysis and interpretation of the  
43 data. All authors have participated to drafting the manuscript, AP revised it critically. All authors  
44 read and approved the final version of the manuscript.  
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