Breast cancer treatment in mutation carriers - surgical treatment

"BREAST CANCER TREATMENT IN MUTATION CARRIERS"

SURGICAL TREATMENT

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Introduction

The surgical option which should be reserved for patients with BRCA1/2 mutation and breast cancer diagnosis is still debated. For women without BRCA mutation, breast-conserving therapy (BCT), i.e. breast-conserving surgery (BCS) followed by radiation therapy (RT), is the treatment of choice as it offers similar survival to that of unilateral mastectomy[1-2]. However, after a breast cancer diagnosis in BRCA-mutation carriers, the optimal local management remains a matter of debate. Initial concerns about the potential harmful effects of radiation therapy after BCS in patients with mutated BRCA turned out to be unsubstantiated[3-4] and several studies support the conservative surgery as a reasonable option. However, several aspects should be considered before the surgical decision-making: the risk of ipsilateral breast recurrence (IBR), the risk of contralateral breast cancer (CBC), the potential survival benefit of prophylactic mastectomy, and the possible risk factors that could either increase or decrease the risk for IBR or CBC. This aspects may be helpful to identify a goup of patients candidates for more aggressive treatments.

Is the BCT option worse than unilateral mastectomy?

Studies comparing risk of ipsilateral breast cancer recurrence (IBR) following BCT between carriers and non-carriers are largely retrospective and have generated conflicting results. Several studies conclude that breast conservative therapy does not increase the risk for IBR in BRCA mutation carriers compared to non-carriers, however, an increased risk for IBR in carriers was observed in studies with longer follow-up. A recent meta-analysis[5], including 526 BRCA mutation carriers and 2320 controls, analysing ten studies (6 cohort and 4 case-control), demonstrated no significant difference in the rates of IBR for BRCA-mutation and controls (17.3 % and 11 % respectively, RR 1.45, 95 % CI 0.98–2.14, p value = 0.07) (Table 1).

Table 1: Risk for IBR in BRCA mutation carriers versus controls[5]

Cohort studies	**Risk Ratio (95% IC)**
Brekelmans 2007[6]	0.61 [0.33, 1.11]
Chappuis 2000[7]	0.97 [0.22, 4.15]
El-Tamer 2004[8]	3.22 [1.15, 9.01]
Haffty 2002[9]	2.15 [1.13, 4.07]
Robson 1998[10]	0.46 [0.06, 3.34]
Robson 2004[11]	1.57 [0.73, 6.36]
Subtotal (95% IC)	1.32 [0.70, 2.46]
Case-control studies	
Eccles 2001[12]	0.69 [0.30, 1.58]
Garcia-Etienne 2009[13]	4.50 [1.32, 15.35]
Kirova 2010[14]	1.90 [1.22, 2.97]
Pierce 2006[15]	1.51 [0.89, 2.56]
Subtotal (95% IC)	1.60 [0.94, 2.56]
Total (95% IC)	1.45 [0.98, 2.14]

Stratifying patients according to follow up the AA confirm no significant difference in local recurrence between carriers and controls in studies with a median follow-up <7 years (6 studies: 1212 patients, local recurrence 11.7% carriers versus 8.9% controls, RR 1.38, 95% CI 0.53-3.60, p = 0.51); however, in studies with longer follow-up (5 studies, 1634 patients) the incidence of local recurrence among BRCA mutation carriers increased substantially to 23.7% as compared to 15.9% among controls (RR 1.51, 95% CI 1.15 -1.98, p < 0.003). This occurrence may be explained by a higher risk for new primary cancers in carriers, since their mutation-related risks continue to affect the residual breast tissue after removal of the first lesion. No overall survival (OS) difference was observed between BRCA mutated patients and controls who choosed to undergo breast-conserving surgery.

As to the risk for IBR in BRCA mutation carriers after mastectomy versus BCT few data are available in literature. Patients who underwent BCT had higher risk for IBR than patients with mastectomy with a cumulative estimated risk of 23.5% vs. 5.5%, respectively, at 15 years (p<0.0001). However, no significant difference in breast-cancer specific or overall survival was observed by local treatment type at 15 years. Breast cancer-specific survivals with BCT were 93.5% vs. 92.8 with mastectomy (p=0.85). Overall survivals with BCT group were 91.8% and 89.8% with mastectomy (p=0.73)[3]. When the pattern of IBR in each group is analyzed, IBRs in BCT-group are mostly new primary cancers while in mastectomy-group they are true recurrences. The lack of survival difference between mastectomy and BCT may reflect the differences in the type of IBRs between the two groups since new primary cancers have biologically less aggressive phenotype than true recurrences. A recent study comparing breast-conserving therapy and mastectomy in BRCA1/2 mutation carriers reaches the same conclusions. Compared to mastectomy, BCT is associated with an increased risk of IBR also in multivariable analysis adjusting for tumor stage, age, and use of adjuvant chemotherapy (HR 2.9; CI 1.1–7.8). The cumulative incidence of LR in the BCT group was 32 % after 15 years versus 9% in the Mastectomy group, but there were no significant differences between BCT and mastectomy for OS, breast cancer death, or distant recurrence. Following mastectomy, local recurrences (LR) were seen in the first 5 years after breast cancer diagnosis, while following BCT, the rate of LR continued to be high also after the first 5 years (Table 2)[16].

Table 2: Five, ten, and fifteen-year cumulative incidences (%) of death of any cause, breast cancer death, distant recurrence, and local recurrence as first recurrence (LR) split on mastectomy (M) or breast conserving therapy (BCT), and the corresponding hazard ratios (HR)[16]

	local recurrence		**distant recurrence**		**breast cancer death**		**death of any cause**	
	M	BCT	M	BCT	M	BCT	M	BCT
Adjusted*HR (95% IC)	1.0	2.9 [1.1-7.8]	1.0	1.8 [0.9-3.5]	1.0	1.6 [0.8-3.3]	1.0	1.4 [0.8-2.5]

** Adjusted for TNM stage, age at diagnosis, and use of (neo)adjuvant chemotherapy*

The potential risk factors for IBR after BCT in BRCA-mutation carriers were extensively studied. Two factors, supported by a moderate level of evidence, were found to be protective against IBR: the use of adjuvant chemotherapy (RR 0.51, 95 % CI 0.31–0.84), and oophorectomy (RR 0.42, 95

% CI 0.22–0.81)[5]. In the same meta-analysis the use of adjuvant tamoxifen was not significantly associated with IBR (level of evidence: moderate), even if another study claims the protective effect of Tamoxifen independent from being mutation carrier or not[3].

Does contralateral prophylactic mastectomy (CPM) offer any additional advantages compared to BCT or unilateral mastectomy?

Patients with BRCA mutation had a higher risk for contralateral breast cancer (CBC) compared with non carriers (RR 3.56, 95 % CI 2.50–5.08, p value < 0.001) and BRCA1-mutation carriers had an increased risk for CBC compared to BRCA2-mutation carriers. Pooled rates of CBC in a meta-analysis of 11 studies (7 cohort and 4 case-control), including 807 carriers and 3163 controls were 23.7% and 6.8% respectively (RR 3.56, 95% CI 2.50-5.08, p < 0.001) (Table 3)[5].

Table 3: risk for CBC: BRCA-mutation carriers versus non-carriers[5]

Cohort studies	**Risk Ratio (95% IC)**
Brekelmans 2007[6]	3.54 [2.28, 5.49]
Chappuis 2000[7]	7.97 [1.39, 45.81]
El-Tamer 2004[8]	1.74 [0.98, 3.11]
Haffty 2002[9]	4.77 [1.86, 12.24]
Robson 1998[10]	4.88 [1.89, 12.58]
Robson 2004[11]	3.51 [2.05, 6.01]
Stoppa-Lyonnet 2000[17]	0.89 [0.39, 2.04]
Subtotal (95% IC)	2.90 [1.85, 4.53]
Case-control studies	
Eccles 2001[12]	3.60 [2.15, 6.03]
Garcia-Etienne 2009[13]	15.0 [1.79, 125.57]
Kirova 2010[14]	3.67 [2.07, 6.48]
Pierce 2006[15]	8.34 [4.45, 15.63]
Subtotal (95% IC)	5.0 [2.97, 8.40]
Total (95% IC)	3.56 [2.50, 5.08]

Among 7 studies investigating the risk difference between BRCA1 and BRCA2 carriers (1,532 BRCA1-mutation carriers, 950 BRCA2- mutation carriers), the rates of CBC were 21.1% and 15.1%, respectively (RR 1.42, 95% CI 1.01-1.95, p <0.04)[5]. Another meta-analysis[18] yielded similar results with a cumulative 5-years risk of CBC for BRCA1 and BRCA2 mutation carriers of 15% and 9%, respectively. The risk increases with time after the first breast cancer diagnosis, growing at 10-years up to 27% and 19%, respectively. In contrast, the 5-years cumulative risk was substantially lower in non-BRCA carriers (3%) and remained the same over the subsequent years (5% at 10 years). Bilateral mastectomy is intended to prevent CBC in BRCA mutation carriers. However, no difference in survival was found if a contralateral prophylactic mastectomy was performed or not, but specific studies are small and the median follow-up relatively short[5]. Two studies[6]-[19] on breast cancer specific survival (BCSS), with a median follow-up time of 4.3 and 3.4 years respectively showed no difference between patients with BRCA-mutation who underwent contralateral prophylactic mastectomy and patients with BRCA-mutation who did not undergo prophylactic

mastectomy (HR 0.78, 95 % CI 0.44–1.39, p value = 0.40). Only one study[19] on overall survival (OS), achieved a significant difference between two groups with 94% OS for the prophylactic mastectomy group versus 77% for the non-prophylactic mastectomy group (p value = 0.03). However, when adjusted for other factor as prophylactic oophorectomy women in the first group did not show a significantly better survival than those in the second group (HR 0.35, p value = 0.14). The largest study with the longest follow-up on this topic was reported at the American Society of Clinical Oncology Annual meeting in 2013. A statistically significant improved survival in patients who underwent prophylactic mastectomy compared with those without mastectomy (10 year OS 90% versus 80%, respectively) was reported[20]. However an important bias was that more patients in the prophylactic mastectomy group received adjuvant chemotherapy. This difference could result in improved OS, especially considering the greater sensitivity to chemotherapy of BRCA-associated breast cancers. Therefore, the question whether contralateral prophylactic mastectomy confers a survival benefit in carriers with breast cancer still remains open. Metcalfe et al. published a recent retrospective analysis with the aim to compare the survival rates of women with BRCA associated breast cancer who did and did not undergo mastectomy of the contralateral breast[21]. They conclude that BRCA mutated women treated for early stage breast cancer with bilateral mastectomy are less likely to die from breast cancer than women treated with unilateral mastectomy. At 20 years the survival rate for women who had contralateral mastectomy was 88% versus 66% for those who did not. After controlling for age at diagnosis, treatment, and other prognostic features, contralateral prophylactic mastectomy was associated with a 48% reduction in death from breast cancer (hazard ratio 0.52, 95% IC 0.29-0.93; P=0.03). Authors conclude predicting that of 100 women treated with contralateral mastectomy, 87 will be alive at 20 years compared with 66 of 100 women treated with unilateral mastectomy.

CBC after a first breast tumor in BRCA mutated patients can be attributed to genetic predisposition, but it can also be related to the same external factors that cause CBC among non-carriers, including hormonal and reproductive factors. Analyzing the risk factors for CBC in BRCA-mutation carriers, in they recent meta-analysis, Velakis et al. identify two factors consistently associated with decreased risk: oophorectomy (RR 0.52, 95 % CI 0.37–0.74) and increased age at diagnosis (a cumulative HR is not defined in the meta-analysis). Metcalfe et al.[22] demonstrated that CBC risk is higher for women diagnosed with first breast cancer at younger ages: diagnosis in women <50 years old was associated with increased risk of CBC at 15 years compared to diagnosis at >50 years (37.6% versus 16.8%, p <0.001). Similarly, in an previous study by Graeser et al.[23], age >50 years at diagnosis was associated with decreased risk of CBC in BRCA1 patients. One additional factor that could reduced the risk for CBC is the use of adjuvant **tamoxifen** (RR 0.57, 95 % CI 0.43–0.75). This protective effect seems to be stronger in women who did not undergo oophorectomy (RR 0.42, 95 % CI 0.27–0.63). The use of adjuvant chemotherapy did not alter the risk for CBC (RR 0.90, 95 % CI 0.66–1.22) [5].

Are there any risk factors that identify subgroups of patients that will gain more benefit with more aggressive surgical management?

For higher-risk groups of BRCA mutated patients, a more-aggressive surgical approach may be preferable. However, ER tumor status, stage of the index lesion, and individual patient preferences should all be considered in the surgical decision-making process. As mentioned above, the use of adjuvant chemotherapy and performing oophorectomy are associated with a 50% decreased risk for IBR. As a result, in carriers who have not undergone oophorectomy, a more aggressive surgical approach (unilateral mastectomy or unilateral therapeutic mastectomy with concomitant

contralateral prophylactic mastectomy) might be more appropriate. When considering the risk for CBC, three risk factors were associated with significantly decreased risk: the use of adjuvant tamoxifen, performing oophorectomy and older age at first breast cancer diagnosis. As a result, younger patients that have not undergone oophorectomy and have not received adjuvant tamoxifen might constitute a subgroup of patients that might benefit from a more aggressive surgical approach. Also considering that BRCA1-mutation carriers have an increased risk for CBC compared to BRCA2-mutation carriers, available data suggest that young patients with BRCA1-associated breast cancers would potentially derive the most benefit from an aggressive surgical approach. On the other end older patients with BRCA2-associated ER positive breast cancer may achieve adequate local control and take an acceptable risk of CBC with a less-aggressive surgical approach followed by anti-estrogen therapy. Prophylactic oophorectomy to reduce the risk of ovarian cancer should always be considered.

Nipple sparing Mastectomy in BRCA mutated patients and Patients satisfaction after prophylactic mastectomy

Contemporary therapeutic and prophylactic **surgical management options** include total mastectomy, skin-sparing mastectomy (SSM) and nipple sparing mastectomy (NSM), with the latter two surgical options having superior cosmetic results. For women with BRCA mutations candidate to mastectomy, preservation of the nipple-areola complex (NAC) may be highly important due to the generally younger age at time of surgery. In comparison to skin-sparing mastectomy, the nipple-sparing approach may allow a superior cosmetic outcome and higher levels of patient satisfaction[24]. Several studies have shown that preservation of the NAC is safe with no increased risk of local recurrence in women with sporadic breast cancer[25]. The role of NSM in BRCA mutation carriers has not been well clarified, limited data assessing oncologic outcomes in BRCA mutation carriers are currently available. An important concern regarding NSM in women with a BRCA mutation is if this surgical procedure is oncologically safe, because the retained breast ductal epithelium carrying the mutation, may be at risk for breast cancer development. Recent studies demonstrate no higher rates of tumor involvement of the nipple in BRCA-positive patients undergoing NSM and immediate reconstruction, low local–regional recurrence, and low development of new cancers[26].

There is a low probability of nipple involvement by premalignant or malignant lesions at time of prophylactic mastectomy in BRCA mutation carriers. Terminal duct lobular units (TDLUs) found within the NAC would provide a possible nidus for subsequent development of cancer; TDLUs was found in 9-25% of nipple specimens[27], but the significance of this for long-term risk is unknown. The rate of tumor involvement of the NAC in studies with significant numbers of BRCA-positive patients in their cohorts undergoing prophylactic SSM (with NAC excision) is 0–5.6 %[28]-[29]. One analysis of NAC specimens exclusively in BRCA-positive patients undergoing SSM for prophylactic indications showed no in situ or invasive cancer in any cases[30]. Another recent study whit specific analysis of NAC specimens in BRCA-mutated patients showed minimal rates of tumor involvement after either prophylactic or therapeutic mastectomy[26]. Several retrospective studies have shown on the average 18% nipple involvement by tumor in therapeutic mastectomy specimen from the general population; in BRCA mutated patients the rate is comparable (19%)[31]. The rate of NAC involvement is strongly influenced by the patient selection and intraoperative evaluation of the tissue behind the NAC to try and minimize risk. In multivariate models, tumor size, stage, and tumor distance to nipple were predictors for occult nipple-areola involvement[32]-[33].

Concerning the oncological safety, several studies of nipple sparing mastectomy in high-risk woman have shown a low rate of development of new primary carcinoma in residual breast tissue[34].

Data are limited regarding local recurrence after therapeutic mastectomy in BRCA mutation carriers, the rate seems to be similar to the cohort of non-mutation carriers with median follow-up of 50 months[6]. A recent study[26] reports the largest series of BRCA positive patients who underwent NSM and specifically examines oncologic outcomes in this group of patients: at 4-year follow-up equivalent safety has been shown in BRCA carriers and in controls. NSM is an acceptable option for patients with BRCA mutations, with no evidence of compromise to oncological safety at short-term follow-up[35]. Recently published studies have demonstrated oncologic outcomes after NSM comparable to those after skin-sparing mastectomy, with locoregional recurrence as low as 2% at 3-year follow-up[36].

In patients candidates to conservative surgery for unilateral breast cancer, the decision to perform a contralateral prophylactic mastectomy (CPM) is more difficult to take. However, in general, women with prophylactic breast surgery, report to be **highly satisfied with their decision**, and believe that surgery greatly reduced the risk of developing cancer[37]-[38]. Frost has shown that positive outcomes following surgery include decreased emotional concern about developing breast cancer (75%) and generally favorable psychological and social outcomes. Borgen et al[39] found that only 5% of respondents had significant regrets after prophylactic mastectomy. The majority of women reported no change or improvement of their emotional mood, reduction of the level of stress and no substantial change in sexual relationships and in perception of their woman's image[40]. Depression of mood can occur after surgery, but it's more likely attributable to the general circumstance of having cancer than to surgery and rarely requires drug therapy. Focusing on cosmetic results, most of women reported highly/moderate satisfaction. A large percentage of women lost touch sensitivity, but most of them reported favorable effects or no change in self-esteem, satisfaction with body appearance, feelings of femininity, sexual relationships, level of stress in life, and overall emotional stability[38]. Only few women were negative in their responses reporting a change for the worse of their female image. Frost[40] suggests that the basis for the difference in satisfaction with prophylactic mastectomy may be the possible complications associated with surgery as implant failure, esthetic implant concerns and silicone anxiety. The need for a reoperation was associated with dissatisfaction. Paradoxically, more women with subcutaneous mastectomy than women with simple mastectomy were dissatisfied with their decision and would not choose mastectomy again. In other series, subcutaneous mastectomy was performed more commonly than simple mastectomy; authors reported a small number of surgical complication and women reported the highest level of satisfaction with nipple sparing mastectomy and immediate reconstruction. Any adequate discussion and counseling of BRCA mutated patients with unilateral breast cancer about the possible surgical management should also include the psychosocial and aesthetic dimension of each surgical intervention.

Mastectomy and radiotherapy

When considering the best surgical approach for the patient, it's important to take into account the **impact of adjuvant radiotherapy** on the surgical outcomes following mastectomy and immediate or delayed breast reconstruction. Post mastectomy radiation therapy (PMRT) following breast reconstruction may compromise aesthetic outcomes as well as increase complication rates for both implant (expanders or implants) and autologous reconstructions. The main complication of implant-based reconstruction is the fibroproliferation of the capsular tissue around the breast implant with consequent capsular contracture, which leads to poor expansion due to the stiffening of the tissues. The breast deformation and pain, often require additional surgery and sometimes lead to reconstructive failure. Despite improvements in surgical technique and device manufacturing,

complications requiring reoperation were 37% and reconstructive failure was 16.8% in the study of Bassim el-sabawi at al[41]. Strategies to reduce the incidence of such complication are mainly focused on the timing of PMRT relative to the type of device. If no postmastectomy radiotherapy is planned, skin-sparing mastectomy or nipple-sparing mastectomy with immediate reconstruction involving implants is preferable. If post mastectomy radiotherapy is planned, the physician should consider the advantages and disadvantages of immediate versus delayed reconstruction and the type of device (expanders or implants). The second stage of breast reconstruction can be performed before or after post-mastectomy radiation therapy, but this strategy cannot by applied when performing NSM with one-stage reconstruction and immediate implant placement at the time of mastectomy. In the setting of immediate reconstruction, PMRT to permanent implants seems to be associated with a lower rate of reconstructive failure as compared to tissue expanders (18.8% vs. 14.7%)[41]. In a study focused on the timing of PMRT, Cordeiro et al. compared 94 patients that had PMRT in the setting of tissue expanders to 210 patients that had PMRT in the setting of permanent implants[42]. The reconstructive failure rates were 18.1% with PMRT to tissue expanders and 12.4% with PMRT to permanent implants. The group with the irradiated permanent implants had significantly more Grade III and IV capsular contracture rates (44.6% v. 15.9%). In a similar study, Nava et al. reported reconstructive failures in 40% of women subjected to PMRT in the setting of tissue expanders versus 6.4% in the setting of permanent implants[43].

Another important issue is the **prior chest or breast irradiation before mastectomy**. Prior radiotherapy may increase the risk of complications after NSM and immediate reconstruction, including skin and nipple necrosis as frequent as 20 %[44]. Prior RT is not an absolute contraindication to NSM, although complication rates are higher in irradiated breasts, reconstruction failure and nipple/areola necrosis is infrequent[45]. However, before performing a BCS followed by RT it's important to consider that prior radiotherapy increases the risk of complications in a possible subsequent NSM with immediate breast reconstruction.

Conclusions

Clinical guidelines regarding the surgical management of unilateral breast cancer for BRCA mutated patients are still missing. Mutation carriers with unilateral breast cancer need to be discussed by a multidisciplinary team and the counseling should be managed on a case-by-case basis. The evaluation should include several issues, namely: the current evidence of adequate oncological safety of BCT in BRCA mutated patients, the increased risk for CBC especially in BRCA1 carriers; the feasibility on NSM with a greater patient's satisfaction for cosmetic results with no evidence of compromised oncological safety at short-term follow-up and finally the awareness that breast radiotherapy might increase the risk of complications in a possible subsequent mastectomy with immediate breast reconstruction.

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