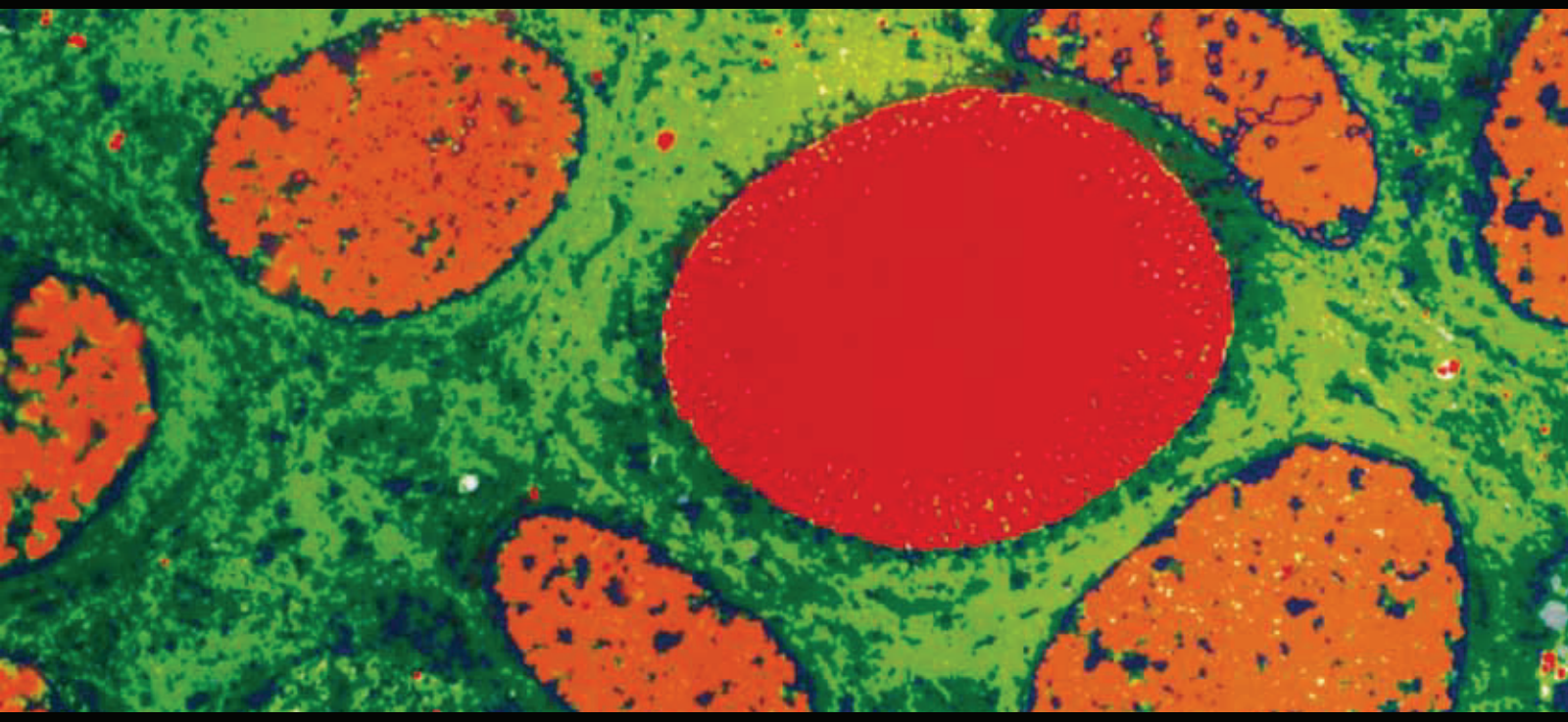
International Journal of Breast Cancer

The Optimization of Breast Conservation

Guest Editors: William C. Dooley, Mo Keshtgar, Tibor Tot, Daigo Yamamoto, and Mahmoud B. El-Tamer



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Editorial Board

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Editorial

The Optimization of Breast Conservation

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This issue includes information from the innovative research ongoing in breast cancer to increase our efficacy and therapeutic choices to adequately treat breast cancers with breast conservation. First a couple of articles address the biologic issues that form the basis of current therapies and how these may be improved with new biologic understandings. We are beginning to recognize that the breast is not one paired organ but two collections of intertwined ductal lobular trees. Most if not all breast cancers only involve a single ductal tree at the time of clinical detection. All the other ductal trees are at risk and may have both synchronous and metachronous lesions that can progress or regress based on biologic and environmental pressures. As we understand breast cancer biology better we may have opportunities to detect cancers earlier, prevent cancers, and optimize conservation with more accurate and precise treatment.

Oncoplastic surgery has given the prospect of breast conservation with reasonable cosmetic outcomes to more and more patients. It now becomes more important through biology and imaging that we accurately predict the extent of disease and treat with a single surgical intervention. Articles in this issue highlight these issues, challenges, and potential successful resolutions. It would seem now that 50–80% or more of stage 0–2 breast cancers could be treated equally as well through modern conservation techniques.

One of the requirements for most patients now for breast conservation is radiation therapy. This has been historically very costly in both equipment and time commitment. New technologies and approaches are leading to much shorter treatment times and treatment volumes than the classic whole breast treated 5 days/week for 6–8 weeks. To make breast conservation more accessible in the less affluent parts of the world, we need short treatment times with minimal equipment and infrastructure investments. Several authors have presented data in this issue on evolving technologies including accelerated partial breast irradiation and targeted intraoperative radiotherapy. A single fraction of radiotherapy given during surgery directly to the tumor bed (intraoperative radiotherapy) avoids many of the prior problems. The rationale and level 1 evidence for the safety and efficacy of these approaches are reviewed and suggest that our ability to bring robust effective breast conservation irradiation to the entire world is soon going to be within our grasp.

The next two decades will see an explosion of breast cancer cases worldwide. Breast cancer becomes more common as countries gain in GDP (Gross Domestic Product). Rates for breast cancer in many parts of the world will reach that of Western Europe and North America. With this impeding public health problem, we need better screening, precise and cost effective treatment, and survivorship not unencumbered by complications and toxicities of our therapies. This issue brings data and ideas that offer a glimmer that breast conservation can become the most common treatment worldwide-not just in the affluent West.

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Research Article

Redefining Lumpectomy Using a Modification of the "Sick Lobe" Hypothesis and Ductal Anatomy

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Objectives. The "Sick Lobe" hypothesis states that breast cancers evolve from entire lobes or portions of lobes of the breast where initiation events have occurred early in development. The implication is that some cancers are isolated events and others are truly multi-focal but limited to single lobar-ductal units. *Methods*. This is a single surgeon retrospective review of early stage breast cancer lumpectomy patients treated from 1/2000 to 2/2005. Ductal endoscopy was used direct lumpectomy surgical margins by defining ductal anatomy and mapping proliferative changes within the sick lobe for complete excision. *Results*. Breast conservation surgery for stage 0–2 breast cancer with an attempt to perform endoscopy in association with therapeutic lumpectomy was performed in 554 patients (successful endoscopy in 465 cases). With an average followup of >5 years for the entire group, annual hazard rate for local failure in traditional lumpectomy without ductal mapping was 0.97%/yr. and for lumpectomy with ductal mapping and excision of entire sick lobe was 0.18%/yr. With endoscopy, 42% of patients were found to have extensive disease within their "sick lobe." *Conclusions*. Targeting breast cancer lumpectomy using endoscopy and excision of regional associated proliferation seems associated with lower recurrence in this non-randomized series.

1. Introduction

The "Sick Lobe" hypothesis was proposed by Tibor Tot in 2005 [1]. His work was really a culmination of collecting relevant clinical and pathologic observations of the last century and a half. His first observations and predictions were based upon DCIS. The breast is defined as a single organ made of multiple lobes. Each lobe is identified by a single orifice on the nipple papilla connecting to branching tree of ducts and hundreds to thousands of individual lobules in the periphery. He proposed that for many cases of DCIS (especially extensive ones) the initiating events of carcinogenesis occurred perhaps as early as in the womb. Then throughout life as the lobe both grew and contracted from hormonal and other influences progression would occur at varying rates in different regions of the ductal tree. This led to the situation of apparent multifocality within the ductal tree and pathologic "skips" between DCIS patches. With further whole mount examination, extensive dissection of extensive intraductal component small invasive cancer cases, and multifocal invasive cancers, the findings support this theory [2–7]. Further molecular studies would seem to indicate that serious adverse genetic events are present throughout many ductal trees in what appears to be histologically normal tissue surrounding known cancers [8]. This is in direct conflict with older theories that the initial events all occurred at the terminal ductal lobular interface and spread pagetoid toward the nipple. The new theory then proposes that simultaneous or asynchronous malignant transformation occurs up and down ducts of the entire lobe and not as a result of migration. It also proposes that each lobe is relatively independent of the other so that multifocality within the lobar unit is common but multicentricity (simultaneous transformation in separate lobes) is rare. This last prediction has certainly held true in larger series of breast endoscopy where even widely separate tumors within a single breast are connected to the same duct system.

The problem comes in how do we turn this new theory into something useful to the operative surgeon trying to do

the best job at breast conservation. The vast majority of early stage tumors we treat seem to involve relative small region of the ductal tree, and with current breast conservation surgery and radiation, few ipsilateral new tumors appear. If the whole ductal tree was genetically predisposed, then it would seem that we still should have more local failure events than we currently encounter. The Tibor Tot version of the sick lobe hypothesis would seem to indicate that a certain margin of histologically normal tissue may be inadequate to prevent recurrence. This clearly flies in face of work such as Mel Silverstein's Van Nuys index where margin seems paramount in predicting recurrence [9]. If followed to its full conclusion, Tot's theory would have us excising the entire lobe (ductal tree) associated with any new breast cancer. While feasible it does seem too extensive and because of complex branching technically difficult for the average breast cancer.

From 2000–2005, we performed a series of lumpectomies where the duct connecting the tumor with the nipple was attempted to be identified. When the duct identified, that duct was endoscoped to detect subclinical intraductal proliferative disease [10]. As has been previously reported this resulted in finding intraductal proliferative growths in 42% that extended beyond the image and clinical 1 cm planned excision margin. The ductal mapping revealed that often cancers were relatively distally located and associated proliferative disease seen endoscopically was limited to very short segments of adjoining ducts. In the case of EIC, ducts were extensively involved for long distances and had skips of greater than 2 cm commonly. Multifocal tumors arose in separate regions of the ductal tree at varying rates. Using the endoscopic ductal tree mapping of intraluminal disease, we elected to remove all intraductal proliferative disease associated with a known cancer independent of its histology (i.e., DCIS, ADH, ALH, DH, etc.). This was done back to at least a 1 cm length of normal duct in the nippleward direction. Once the duct was filled with tumor more distal branches could not be endoscoped so the resection was carried out in a pie-shaped wedge to the periphery to encompass those additional portions of the ductal tree.

New proposed Modified Sick Lobe Hypothesis-Surgical Practical Application.

We propose these changes/additions to the Tot "sick Lobe" hypothesis to address surgical planning.

(1) Most breast cancers begin as isolated genetic events in a single-stem cell during expansion of the ductolobular tree.

(2) The extent of the ductal tree involvement is reflective of the position of the stem cell where initiation events occurred. If occurring early and close to the nipple the tree will have extensive involvement distally manifested by large regions sharing abnormal genotype. If occurring relatively late in the development of the ductolobular tree, then regions derived from the initiating stem cell will be peripheral and limited within the tree. True pagetoid spread or spread by random migration up and down the ducts would be exceedingly rare.

(3) Surgical lumpectomy should be best defined as the adequate removal of the potions of the genetic tree sharing the initiating genotype changes with the known breast cancer. This approach should decrease recurrence by eliminating metachrounous changes within the same ducto-lobular tree.

This hypothesis could then be tested by examining the local failure rates and patterns of local failures in the endoscopically directed lumpectomies as compared to those which were not.

2. Methods

This is a single surgeon review of patients treated at two institutions (Johns Hopkins and University of Oklahoma) from 1/2000 through 2/2005 with stages 0–2 breast cancer with breast conservation without any neoadjuvant chemo- or hormonal therapies.). All patients with prior periareolar resections, prior open surgical biopsies, or large hematomas associated with prior biopsy were not attempted. Otherwise this series includes all those with small tumors (<3 cm) requesting conservation as previously reported. Each patient had careful dekeratinization of the nipple in the operating room and then underwent centripetal breast massage using hand lotion. After the massage (which was also done after lymphazurin injection if sentinel node was also being performed), the retroareolar space was carefully compressed to identify all fluid producing orifices in the nipple papilla. The orifice yielding fluid closest to the position of the known cancer or yielding lymphazurin in the case or peritumoral injection was chosen for ductoscopy to identify the ductal connection to the tumor and associated proliferative disease. This was even done in cases of radiographic apparent multifocality or multicentricity. Ductal anatomy was drawn on the breast surface through the aid of transillumination in a darkened room. Regions of intraductal filling defects caused by epithelial proliferative growths were then marked as well. Lumpectomies were designed to remove known cancer and associated intraluminal growths as previously discussed and in keeping with the new modified sick lobe hypothesis.

3. Results

During this interval (2000–2005), there were 554 patients with early-stage breast cancer in which endoscopy was attempted (Table 1). Endoscopy was successfully completed and identified correctly the duct connecting with the tumor or immediate tumor region in 465 cases. In 16% of cases where no fluid producing duct was found or duct contained no abnormalities and did not connect to tumor region, lumpectomy was performed on the basis of clinical, radiographic, and ultrasonographic guidance as is standard for most breast surgeons. The average followup of these patients was 5.9 years for the endoscopically directed lumpectomies and 5.7 years for those not endoscopically directed (ranges 1.2–8 years). The annual hazard rate for local failure was 0.97% for traditional lumpectomy and 0.18% for those

Table 1: Case distribution and results.

Age	Mean	
Range 32–89	57	
Tumor stage		
DCSIS	155	28%
Stage 1 or 2	399	72%
# of successful endoscopies	465	84%
# BC with additional lesions		42.1%
If endoscopy not successful margin +		19.1%
If endoscopy successful margin +		4.7%
If endoscopy successful nipple ward margin +		0.36%
Annual hazard rate for L/R recurrence with endoscopic guidance		0.18%
Annual hazard rate for L/R recurrence without endoscopic guidance		0.97%

who had endoscopically directed excision of tumor and associated endoscopic lesions. This reaches statistical significance with the recurrence rate of 1.1% for endoscopically directed lumpectomy and 5.6% for traditional lumpectomy ($P = 0.019$; Chi Square, SPSS Ver.10 Chicago, IL). Diffuse involvement of the lobe was defined as extensive proliferative changes seen endoscopically greater than 1 cm from all clinical, radiographic, and ultrasonographic evidences of tumor. In some these involved the whole ductal tree but in most were subsegmental in distribution. At the time of these resections we had not anticipated the need to document volume and weight so we do not have consistently obtained information to compare these parameters in these cases.

Since all patients were treated by NCCN guidelines or on clinical trials, there were no patients who did not receive radiation. All ER+ patients received hormonal therapy. Event rates of local recurrence remain low enough that no other treatment-related factors reach significance. Local ER- recurrences seem higher than ER-proportion in the entire group but this also fails significance.

4. Conclusions

The initial description of the "sick lobe" does fit many patients with extensive DCIS or multifocal DCIS and invasive disease [1]. Breast endoscopy strongly suggests that the clinically relevant genetic changes may be more widespread than initially radiographically appreciated changes but are still often subsegmental within an individual lobe [10, 11]. Much has been argued over the benefits of breast endoscopy since so many of the intraluminal defects are not invasive cancer or DCIS. Certainly the Cleveland Clinic experience directly shows that these additional lesions would not normally raise concern if found at the margin of traditionally performed lumpectomy [12]. As noted previously we took an alternate philosophical approach believing that regional proliferative changes present close to a cancer and not elsewhere were potentially sinister independent of the histopathologic changes they showed. Our prior report confirms that this assumption was associated with dramatic improvements in clear margins at first resection. This can rightfully be criticized in that these resections were bigger than those of nonendoscopically directed lumpectomy so of course margins would be better. However if we are truly affecting the natural history of breast cancer metachronous development within a sick lobe, we should see much fewer ipsilateral recurrences just as we have shown. Even though the absolute number of events is small, we are struck by the fact that contralateral breast cancers in these same patients seem to be occurring at almost identical rates as ipsilateral events in those patients with endoscopically directed proliferative disease included lumpectomies. Further in these patients the ipsilateral events seem randomly distributed and not clustered in the same quadrant as the initial primary as seen in nonendoscopically directed lumpectomy—either this series or others. Several other ductoscopy-directed lumpectomy series find regional proliferative disease in patterns identical to what we initially described in this series [11, 13–15].

Further we need to consider the classic idea of migration of DCIS up and down the ducto-lobular tree. If shed cells into the ductal fluid are totipotent, then we would expect that ductal installation of saline lavage or distending fluids associated with endoscopy would likely result in spreading of disease. This should be manifested by increased local failure events in the ipsilateral breast. Our data does not find this. Similarly researchers using ductal lavage in cancer patients did not see increased local failures. One could argue that such events are masked by the use of radiation for breast conservation in these patients and that it is a valid possibility for suppression of local recurrences. As more surgical investigators become facile with ductal endoscopic mapping, a clinical trial of endoscopically mapped lumpectomy could test whether radiation therapy is still needed if we actually can do an anatomically defined lumpectomy. We therefore find that our follow-up data on ductoscopically directed lumpectomy supports a new version of the "sick lobe" hypothesis that directly addresses how surgeons think and procede to surgical planning around the time of lumpectomy. We view that breast cancer is a lobar disease isolated to the section of the lobe where the initiation events occurred and all subsequent outgrowth from those stem cells. With this change, breast cancer may be isolated to a distal branch of the ducto-lobular tree when initiation events occurred late in lobar growth. These would be the common tumors with little surrounding proliferative disease and well treated by our current techniques. If these could be better defined by the genetic mapping of changes in ducts in their region, simple excision or ablation of all genetically abnormal epithelium of the duct without radiation might be adequate for their control. Some tumors develop from earlier initiation events but still isolated to larger segmental regions within the ducto-lobular tree. Here excisions would need to either be wider or have associated radiation to eliminate the potential progression of genetically altered proliferative cells.

The extent of this abnormal proliferation within the segment would determine also how much irradiation if any needed (i.e., no radiation, partial breast irradiation, or whole breast irradiation). Finally as in the classic Tibor Tot description, the entire lobe is occasionally involved because the initiation events occurred in some of the first stem cells of the lobe early in its development. Here either complete lobe excision or whole breast treatment may be required. We agree with Tibor Tot that true multicentricity of cancers developing in differing lobes of the same breast should be extremely rare [5]. In fact we would propose given our preliminary data that it should be no more common than synchronous or metachronous contralateral breast cancers.

This new hypothesis then raises important clinically relevant questions. Can a better lumpectomy be performed when guided by ductal anatomy and the plan to completely excise proliferative changes sharing genetic signatures with the primary tumor? Are our current tools adequate to embark on an exploration of this hypothesis? If not, what needs to be developed? Most submillimeter endoscopy systems currently have limited biopsy capabilities. Can these be changed or improved so that molecular mapping of the ductal tree can be efficiently performed and a more biologically appropriate surgical approach be taken to lumpectomy? If an anatomic molecular mapped lumpectomy is feasible, can we begin to consider elimination of radiation therapy in early-stage breast cancer without LVI as an appropriate arm in a clinical trial? As our molecular understanding and genotyping of breast cancers become more commonplace, we as surgeons need not to consider that these techniques are only ways to choose better adjuvant therapies but reassess our technical approaches to breast cancer. We are still doing the lumpectomy technique of Bilroth in the mid 1800's with only more careful attention to histopathologic margin. It is time for us to consider applying new and evolving breast cancer biology information to improving the technical aspects of local therapy.

Our data suggests that this new approach to lumpectomy may be valid but can be criticized since increasing volume of resection in certain cases would naturally be expected to decrease recurrence. The Tot theory and our guidelines for application to lumpectomy represent a major deviation from traditional breast cancer biology theories. We encourage others to consider these theoretical proposals and test them against their own observations. The evolution of this new sick lobe hypothesis and the ability to do real time ductal mapping via ductoscopy should strongly motivate surgical innovators to perform multicenter prospective randomized trials to test the validity of this new theory and approach. If accurate, this approach would fundamentally change local therapy for breast cancer.

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Review Article

Subgross Morphology, the Sick Lobe Hypothesis, and the Success of Breast Conservation

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Breast carcinoma has a complex subgross morphology in the majority of cases. The malignant transformation usually involves a single breast lobe and may demonstrate peripheral, segmental, or lobar growth patterns in the in situ phase. During the invasive phase, the tumor may grow beyond the borders of the affected lobe. The dimensions of the involved lobe and the pattern of its involvement determine the extent of the disease in the early phase, with the size, type, and position of the invasive foci being additional determinants in more advanced cases. Breast carcinomas of limited extent (occupying a tissue area <40 mm) are proper candidates for breast-conserving surgery. In other cases, careful individual preoperative assessment of disease extent is necessary in making decisions about the most appropriate surgical approach, taking into account the position of the lesion(s) within the breast, the dimensions of the breast, and patient preference.

1. Introduction

Breast-conserving surgery completed with postoperative irradiation results in good local control of the disease, with relatively few ipsilateral local recurrences [1, 2]. A considerable number of patients, however, still experience local recurrence, even in some of the cases when the surgical margins of the resection have been judged to be cancer free. This number is much higher if postoperative irradiation is omitted [1, 2]. In addition to the possibility of erroneous assessment of the surgical margins as an explanation, another possibility is the leaving behind of foci of cancer or risk tissue within the breast after seemingly complete surgery [3].

Most breast carcinomas have a complex morphology that is often evident already at an early stage of the disease [3–8]. Early lesions are often nonpalpable, small, and hardly visible to the naked eye. Nevertheless, despite their small size, early breast carcinomas are often multifocal and extensive [4, 8, 9], and the small individual foci may be spread over an area of several centimeters in volume, resulting in a large extent of the disease. These seemingly contradictory facts indicate the need for using special nonfragmenting histology techniques in all such cases and also emphasize the paramount importance of a detailed radiological-pathological correlation in diagnosing breast carcinoma in the modern era.

Factors influencing the success of breast-conserving therapy are numerous, with the final determinants of treatment choice being the extent of the disease, ability to tolerate radiotherapy, and patient preference [10]. In this paper, the subgross morphology of breast cancer is discussed in relation to the success of local control of the disease with a special focus on disease extent.

2. Theoretical Background

Breast is a glandular organ with lobar morphology. A breast lobe comprises a single lactiferous duct opening on the nipple, its segmental, subsegmental, and terminal branches with the terminal ductal-lobular units (TDLUs) at the end of the branching tree. The reported number of lobes within a mature breast varies considerably in the literature, 27 being the median in one detailed study [11]. The lobes are individual units with no anastomotic connections between them.

According to our hypothesis of the sick lobe [12–14], breast carcinoma is a lobar disease in that the simultaneously or asynchronously appearing in situ or invasive tumor foci develop within a single sick lobe and the cancerous structures are confined to the area of the sick lobe at the early stage of

the disease. The sick lobe probably contains more or more-sensitive committed progenitor cells than the other lobes of the same breast and is more sensitive to endogenous or exogenous oncogenic stimuli. This hypothesis is congruent with the concept of committed progenitor cells [15], as well as with the concept of mammary field cancerization [16]. The most important implication of these concepts is that an area several centimeters in size of genetically altered tissue may exist in the breast and breast cancer develops within this area rather than at one single point. According to our related hypothesis, the theory of biological timing [9, 13], the time of complete malignant transformation of the committed progenitor cells, is determined by the number of required additional genetic alterations, which are mostly acquired during the division of these cells. This transformation may appear in a single locus within the sick lobe, at more than one locus at the same time or with a considerable time difference, or at a large number of loci leading to a unifocal, multifocal, or diffuse malignant process, respectively. Although the variations in breast cancer morphology are practically unlimited, three patterns of cancer development seem to be the most typical at the early stage: the peripheral pattern (involving the TDLUs), the segmental pattern (involving a segmental duct together with its branches and terminal units), and the lobar pattern (involving the entire sick lobe or large parts of it) [14]. Figure 1 illustrates these patterns for in situ carcinoma.

As demonstrated in numerous studies [17–19], further mutations in the malignant cells and the cells of the surrounding stroma may result in cancer cells losing their ability to maintain the myoepithelial layer and the basal membrane around the ducts and terminal units, and the normal periductal, intralobular, and interlobular stroma undergoes remodeling. Both individual cancer cells and groups of such cells may come into direct contact with stromal elements and be entrapped in the remodeled stroma. They may also come into contact with the prelymphatic spaces and lymphatic vessels, invade them, and be transported via the lymphatic spaces and lymphatic system within (or outside) the breast. In this way, the invasive tumor may spread beyond the area of the sick lobe. Through proliferation of the malignant cells, the invasive component of the tumor may grow, not only around the pre-existing in situ process but also, following its intramammary spread, at distant sites. The tumor foci may eventually coalesce, giving a larger tumor mass with more complex morphology. By further mutations and dedifferentiation, new cell clones may appear in the invasive foci, leading to intratumoral and intertumoral heterogeneity within the same breast. Via these mechanisms, the tumor gradually enters the advanced phase.

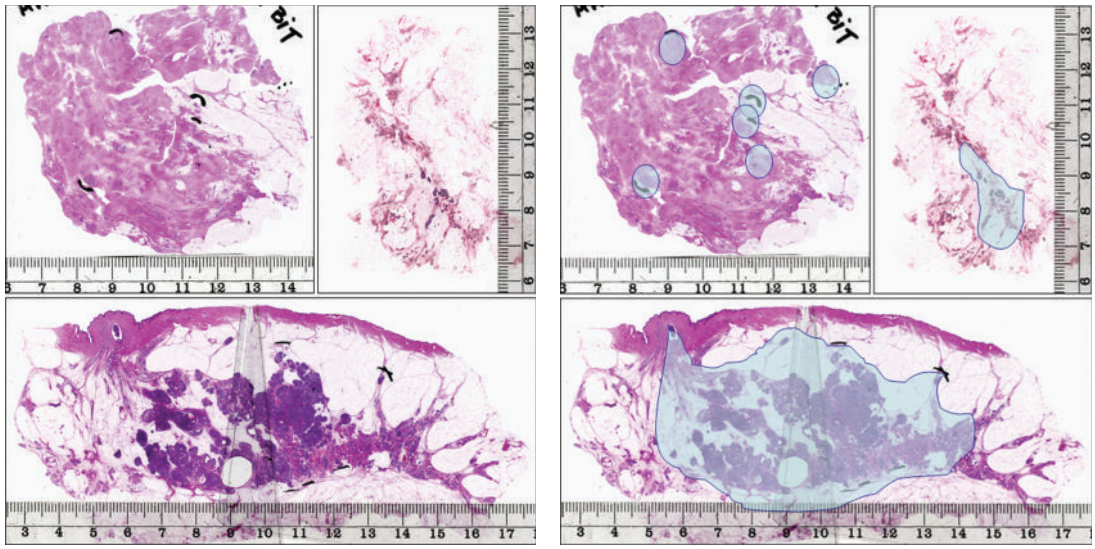
3. Assessing the Subgross Morphology of Early Breast Cancer

In our approach, the distributions of the invasive and in situ components of the same cancer are determined separately. In situ carcinomas are regarded as "unifocal" if they appear to involve a single TDLU or several neighboring TDLUs together with the belonging subsegmental or segmental duct(s). They are designated as "multifocal" if they involve several distant TDLUs with uninvolved breast tissue in between and as "diffuse" if they involve mainly the larger ducts [6–9]. The unifocal pattern of in situ carcinomas corresponds to the segmental pattern, the multifocal pattern to the peripheral pattern, and the diffuse to the lobar pattern of cancer development, as discussed above and as illustrated in Figure 1. These alternative terms reflect two approaches: the peripheral-segmental-lobar designations reflecting the biological approach based on the sick lobe hypothesis and the unifocal-multifocal-diffuse designations reflecting the practical routine diagnostic approach.

Invasive lesions are considered to be "unifocal" if only one invasive focus is observed, which may or may not contain an in situ component. "Multifocal" invasive lesions are characterized by the presence of multiple, well-delineated invasive tumor foci separated from each other by uninvolved breast tissue, regardless of the distance between the foci. Tumors dispersed over a large area in the section, much like a spider web, with no distinct tumor mass are classified as "diffuse," but they are usually large and are not represented among early cancers (Figure 2). Cancers may lack an in situ or an invasive component although most of them have both; any further combination of the in situ and invasive components may characterize an individual case. Theoretically, there are 16 such combinations [6]. In our practical approach, however, after the initial separate assessment of the distribution of the in situ and invasive foci, we combine the findings so that diffuse distribution of the in situ or the invasive component qualifies the lesion as a tumor having a diffuse combined lesion distribution. Multifocality of either the in situ or invasive tumor component, or both, results in multifocal combined lesion distribution.

Figure 3 demonstrates the percentages of different subgross tumor distribution (growth patterns) regarding the in situ component, the invasive component, and the combined patterns, respectively. The material comprises 565 consecutive cases newly diagnosed at our department, all documented in large-format histology slides. Forty tumors (7%, 40/565) lacked an in situ component, while 80/565 (14%) were purely in situ lesions lacking an invasive component. A total of 25% (138/565) of in situ tumors were diffuse (involving large parts of the ductal system of the sick lobe), but only approximately 5% (26/565) of the tumors showed the typical spider web-like diffuse pattern of the invasive component. The in situ component was unifocal in 33% (189/565) and multifocal in 35% (198/565), while the invasive component was unifocal in half of the cases (48%, 274/565) and multifocal in one third of cases (33%, 185/565). The combined distribution of the in situ and the invasive components was as follows: unifocal in 37% (209/565), multifocal in 35% (198/35), and diffuse in 28% (158/565).

Thus, the subgross distribution of the lesion is complex in the majority of breast carcinomas, and for its proper assessment, a close and detailed radiologic-pathologic correlation is as important as using adequate nonfragmenting histology techniques. Assessment of lesion distribution is essential because it represents independent morphologic



(a) (b)

Figure 1: The three basic growth patterns of in situ carcinoma within the sick breast lobe. Upper left: the peripheral pattern; upper right: the segmental pattern; lower image: the lobar pattern. The structures involved by in situ carcinoma, corresponding to the extent of the disease, are marked in the series of images on the right-hand side.

prognostic parameters in breast carcinoma, which are as important as tumor size. Specifically, multifocal and diffuse distribution of the invasive lesions is associated with an increased propensity for metastatic tumor spreading [6–8, 20, 21] and with shortened breast cancer-specific survival [22–25].

4. The Extent of the Disease

While lesion distribution is often complex, disease extent is a morphologic parameter that is easier to communicate within the breast team. This parameter is defined as the area or volume of the breast tissue containing all the in situ, invasive, and intravascular malignant tumor foci. Of importance, disease extent and tumor size (defined as the largest dimension of the largest invasive tumor focus within the breast) differ from each other in the vast majority of cases, being equal only in cases of unifocal invasive carcinomas having no in situ component outside the invasive focus, which comprise no more than 15% of our cases.

Breast morphology as perceived in a histology specimen reflects the status of the balance between dynamic progressive and regressive processes that were stopped at the moment of tissue fixation; it is a still frame from an ongoing process. Microscopic analysis of the specimen gives us only limited information about these processes but represents an important checkpoint in the attempt to reconstruct the natural history of a lesion. This reconstruction is particularly valid for determining disease extent.

It has to be underlined that the extent of the disease is a term relating not to a single component of the tumor, but to all malignant structures within the same breast. The parameter of extensive intraductal component (EIC) [26] is not identical to disease extent. Using our approach, we visualize malignant transformation of the large parts of the ductal tree and/or the lobules within the sick lobe leading to extensive disease in a considerable number of cases. This situation represents a negative prognostic parameter [27], similarly but not identically to that evidenced in cases with EIC [26, 28].

4.1. Extent of the Disease: The Dimensions of the Involved Breast Lobe. The dimensions of the breast lobes vary considerably within the same breast and also individually. The largest lobe demonstrated in one of the very few related studies comprised 25% of the breast volume, the smallest only 1% of the breast volume [29]. Lobes are larger in the upper outer quadrant of the breast than in the medial parts [30]. In addition, the dimensions of the lobes are also age related; they are larger in younger women and undergo involution around and after menopause. Lobes in the medial quadrants of the breast develop later and undergo involution earlier than the lobes in the lateral quadrants [30]. During the malignant transformation of the structures of the sick lobe, new cancerous TDLUs and ducts [27] may develop and increase the dimension of the involved lobe.

Young age strongly correlates with a high risk of local recurrence after breast-conserving surgery, whether or not radiotherapy is given [31]. This relationship is associated with the dimensions of the sick lobe, which is an important factor in determining the success of breast-conserving surgery.

4.2. Extent of the Disease: The Biological Timing of Malignant Transformation. The committed progenitor cells dispersed unevenly within the sick lobe may undergo malignant transformation under the influence of exogenous and endogenous

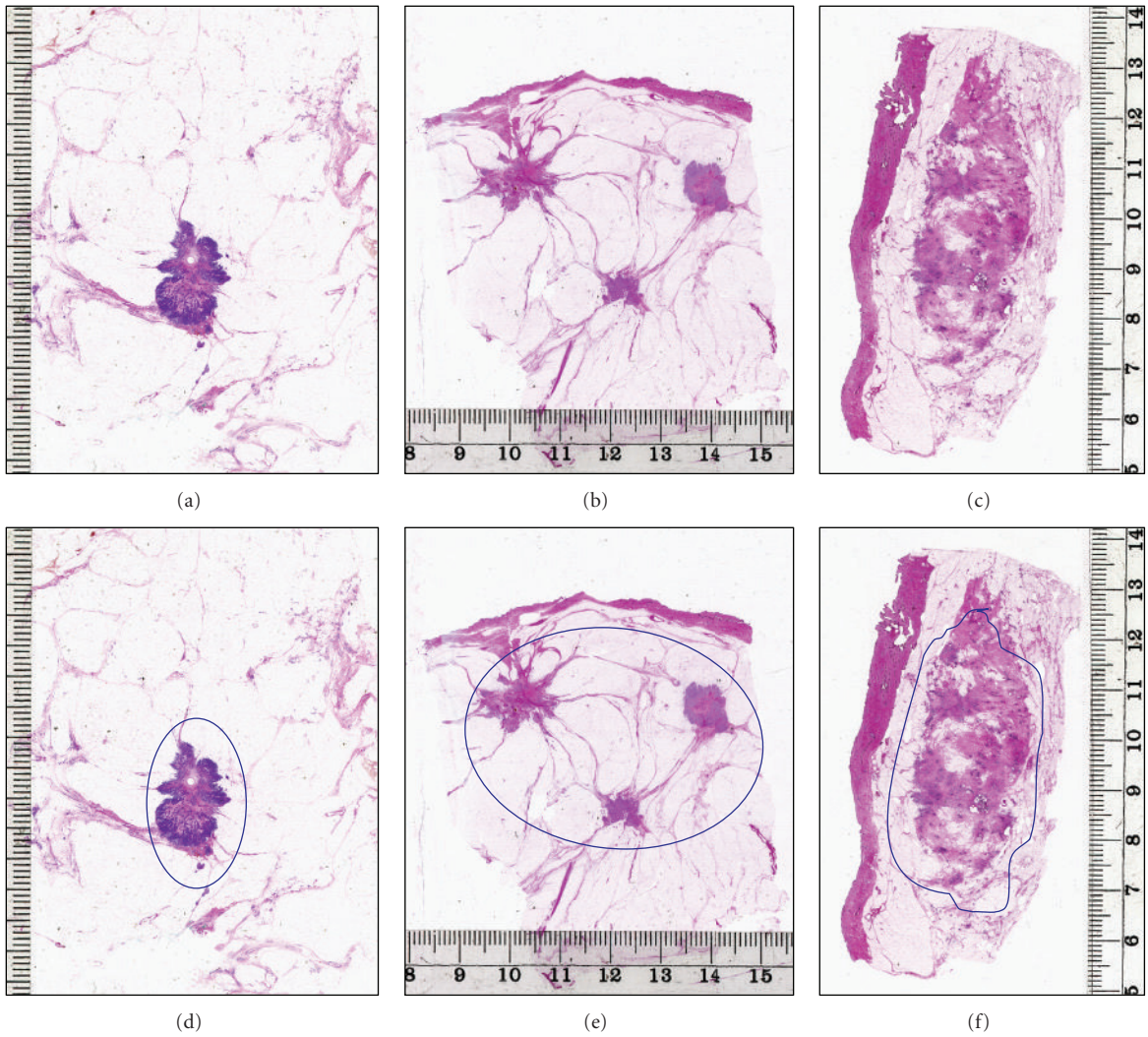


Figure 2: The three basic growth patterns of invasive breast carcinoma. Upper left: unifocal; upper central: multifocal; upper right: diffuse growth pattern. The extent of the disease is marked in the lower series of images.

oncogenic stimuli [15]. According to our hypothesis, the timing of this transformation is determined by the number of required genetic alterations, which are mostly acquired during the division of these cells. This hypothesis has been termed the hypothesis of biological timing. Malignant transformation may appear in a single locus within the sick lobe, more than one locus at the same time or with considerable time difference, or at a large number of loci, yielding the segmental, peripheral, and lobar patterns of malignant transformation, respectively, as discussed above.

The timing and the pattern of malignant transformation within the sick lobe are the main determinants of disease extent, in addition to the dimensions of the lobe. Malignant transformation may appear in a small segment of a large lobe, giving rise to a unifocal early breast cancer of limited extent (segmental pattern). Additional tumor foci may develop within the same lobe years or decades later and will be perceived as a local recurrence after the initial tumor has been excised. If the malignant transformation targets distant individual TDLUs (peripheral pattern), the process will be multifocal from its beginning. The extent of such malignancy will be determined by the dimensions of the sick lobe and the distance between the affected TDLUs; the disease may be extensive or of limited extent. Asynchronous involvement of additional TDLUs leads to local recurrence if the sick lobe was not completely removed by surgery. The lobar pattern of malignant transformation develops as a result of simultaneous alteration of the progenitor cells at many loci, and, in the extreme, the entirety of the sick lobe. Such tumors involve diffusely the larger ducts and many TDLUs within the sick lobe. These tumors are often extensive from the very beginning of their development (Figure 1). In one of our studies, diffuse in situ carcinomas had an average disease extent of 52.7 mm (range 16–180 mm) [32].

4.3. Extent of the Disease: Invasion beyond the Borders of the Sick Lobe. Invasion may appear at a single locus or (simultaneously or asynchronously) at several loci of the sick

Table 1: Ipsilateral local recurrence rates by disease extent and type of surgery: extensive tumors defined as those occupying an area 4 cm or larger in the greatest dimension. Falun 1996–1998, 10-year followup.

	Extensive tumors ≥4 cm	Nonextensive tumors <4 cm	Total	Relative risk	Significance level
Mastectomy	7.3% (9/124)	9.3% (8/86)	8.1% (17/210)	RR = 0.7802 (CI: 0.3135–1.9429)	$P = .5937$
Breast-conserving surgery	20.5% (9/44)	7.4% (20/269)	8.9% (29/313)	RR = 2.7511 (CI: 1.3401–5.6478)	$P = .0058$
Sum	10.7% (18/168)	7.9% (28/355)	8.6% (46/523)	RR = 1.3584 (CI: 0.7736–2.3852)	$P = .2862$
Relative risk	RR = 2.8182 (CI: 1.1955–6.6435)	RR = 1.2512 (CI: 0.5717–2.7380)	RR = 0.8737 (CI: 0.4928–1.5490)		
Significance level	$P = .0179$	$P = .5749$	$P = .6440$		

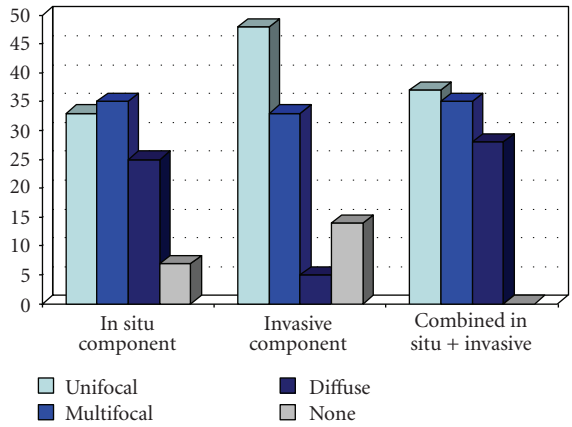


Figure 3: Percentages of carcinomas with unifocal, multifocal, and diffuse subgross patterns regarding the in situ component of the tumor, the invasive component, or both combined. Falun 2008–2010.

lobe involved by an in situ cancer. The invasive component may invade beyond the area of the sick lobe, especially in a more advanced stage of the disease. Two mechanisms may lead to the multifocality of the invasive component in breast carcinoma: separate invasive foci may develop independently from each other from in situ carcinoma in different parts of the sick lobe, or they may be a result of intramammary tumor spread via the (pre-)lymphatic system. The latter possibility may explain the influence of multifocality on the metastatic capacity of the tumors and on survival.

The rare diffuse invasive carcinomas develop simultaneously at many loci of the sick lobe and often invade without provoking any stromal reaction, which in other cases may limit the tumoral growth (Figure 2). The outcome is an extensive invasive process involving large parts of the breast and not confined to the area of the sick lobe. Most of these tumors are of the lobular type [33] and are large and extensive at the moment of their clinical or radiological detection. In one of our studies, these tumors had an average size of 55.9 mm (range 27–91 mm) [32].

4.4. Extent of the Disease: Cutoffs. There is no international consensus regarding the definition of extensive breast carcinoma. Two cutoffs, 15 mm and 40 mm, are used in the Van Nuys Prognostic Index scoring system [34], but this scoring system is limited to cases of ductal carcinoma in situ. Faverly et al. [5] defined extensive carcinoma as tumors having foci more than 1 cm apart, in contrast to breast carcinomas of limited extent, which were proposed by the authors as adequate candidates for breast-conserving surgery. Because the extent of the disease is defined as volume or area of the breast tissue including all the malignant structures within the breast, we prefer to use a cutoff defining the volume or the area and not the distance between the foci.

We define extensive tumors as those occupying a tissue area at least 40 mm in the largest dimension in contrast to breast carcinomas of limited extent [7, 9]. The most important reason for choosing this cutoff is the 10-year followup results regarding our material (1996–1998), presented in Tables 1, 2, and 3.

Testing different cutoffs (20 mm, 30 mm, and 40 mm) led to the conclusion that an extent of 40 mm or more represents the proper target cutoff in selecting cases for breast-conserving surgery. Such tumors comprised in our material one third of carcinomas in this series and exhibited a relative risk of 2.75 for developing ipsilateral local recurrence compared to nonextensive tumors if treated with conserving surgery and irradiation. Further, significant differences were seen in local ipsilateral recurrence rates when extensive tumors treated with mastectomy versus breast-conserving surgery were compared. Such statistically significant differences could not be demonstrated with 20-mm or 30-mm cutoff values. It is worth mentioning that an extent of the disease greater or equal to 40 mm also represents a survival-related negative prognostic parameter [24, 25].

4.5. Extent of the Disease: Relation to Tumor Size. We compared the extent of the disease and the distribution of the lesions in a consecutive series of 120 purely in situ carcinomas, 332 early invasive carcinomas (<15 mm), and 340 more advanced invasive carcinomas (≥15 mm) and found that the proportions of extensive cases in these categories were 45.0%, 42.5%, and 42.4%, respectively [9].

Table 2: Ipsilateral local recurrence rates by disease extent and type of surgery: extensive tumors defined as those occupying an area 3 cm or larger in the greatest dimension. Falun 1996–1998, 10-year followup.

	Extensive tumors ≥3 cm	Nonextensive tumors <3 cm	Sum	Relative risk	Significance level
Mastectomy	7.5% (12/160)	10.0% (5/50)	8.1% (17/210)	RR = 0.7500 (CI: 0.2776–2.0261)	$P = .5707$
Breast-conserving surgery	15.0% (12/80)	7.3% (17/233)	9.2% (29/313)	RR = 2.0559 (CI: 1.0271–4.1152)	$P = .0418$
Sum	10.0% (24/240)	7.8% (22/283)	8.8% (46/523)	RR = 1.2864 (CI: 0.7404–2.2349)	$P = .3716$
Relative risk	RR = 2.0000 (CI: 0.9411–4.2502)	RR = 0.7296 (CI: 0.2824–1.8851)	RR = 1.1445 (CI: 0.6456–2.0291)		
Significance level	$P = .0715$	$P = .5151$	$P = .6440$		

Table 3: Ipsilateral local recurrence rates by disease extent and type of surgery: extensive tumors defined as those occupying an area 2 cm or larger in the greatest dimension. Falun 1996–1998, 10-year followup.

	Extensive tumors ≥2 cm	Nonextensive tumors <2 cm	Sum	Relative risk	Significance level
Mastectomy	7.7% (15/194)	12.5% (2/16)	8.1% (17/210)	RR = 0.6186 (CI: 0.1549–2.4699)	$P = .4965$
Breast-conserving surgery	12.0% (18/150)	6.7% (11/163)	9.3% (29/313)	RR = 1.7782 (CI: 0.8665–3.6407)	$P = .1154$
Sum	9.6% (33/344)	7.3% (13/179)	8.8% (46/523)	RR = 1.3209 (CI: 0.7135–2.4453)	$P = .3758$
Relative risk	RR = 1.5520 (CI: 0.8082–2.9766)	RR = 0.5399 (CI: 0.1310–2.2257)	RR = 1.1445 (CI: 0.6456–2.0291)		
Significance level	$P = .1859$	$P = .3937$	$P = .6440$		

In another study on carcinomas 1–14 mm in size, we found that 96 of 301 (31.9%) had a multifocal invasive component and that none of them demonstrated a diffuse invasive growth pattern [8]. Thus, early breast carcinomas are as often extensive and as often multifocal as their more advanced counterparts; they differ from the advanced carcinomas in the smaller size of the individual invasive lesion(s).

4.6. Extent of the Disease: The Surrounding Normal Tissue. Genetic alterations similar or identical to those in cancer may be found in morphologically normal breast tissue, a finding strongly supporting the sick lobe hypothesis. Such alterations were demonstrated in normal-looking breast tissue as far as 4 cm from the cancer and even in breasts free of histologically verifiable cancer [14, 35]. Although the status of the surgical margins is clearly related to the risk of developing local recurrence, a clear margin, free of microscopic tumor foci, is not a guarantee that already developed distant tumor foci or a risk tissue carrying genetic abnormalities representing potential source of cancer foci have not been left behind after a seemingly complete intervention. Although postoperative irradiation substantially reduces the risk of local recurrence (Table 4), proper preoperative mapping of the disease and identifying the sick lobe are essential in planning adequate surgery.

The surgical intervention in early breast cancer must target excision of the already developed and radiologically and morphologically evident cancer foci together with the surrounding genetically altered but morphologically normal at-risk tissue. In other words, the aim is to remove the entire sick lobe together with the lesions within it; partial excision of the sick lobe represents a risk for tumor recurrence. Because of the above-discussed morphological variability, proper intravital mapping of the breast lobes and identifying the borders of the sick lobe is very difficult. Removing a lobe-like triangular piece of tissue from the breast (segmental excision) seems to be a more appropriate approach in context of the sick lobe theory than a simple lumpectomy. Modern breast ultrasound techniques may visualize the central axis of a lobe and lead the radiologist and the surgeon to excise the proper structures [30]. Figure 4 demonstrates a case of breast carcinoma with a duct leading into the area of the invasive tumor. Dooley propose routine operative breast endoscopy during lumpectomy to direct the surgical intervention towards the diseased part of the sick lobe [36]; his long experience with such an approach is reported in the present issue of the International Journal of Breast Cancer.

Breast carcinomas of limited extent (occupying a tissue area <40 mm) are proper candidates for breast-conserving surgery. In other cases, careful individual preoperative

Table 4: Ipsilateral local recurrence rates by disease extent and postoperative irradiation in extensive tumors and tumors of limited extent treated with breast-conserving surgery, Falun 1996–1998, 10-year followup.

Extent	Irradiated	Nonirradiated	Data missing	Sum	Relative risk	Significance level
≥4 cm	10.7% (3/28)	42.9% (6/14)	0.0% (0/2)	20.5% (9/44)	RR = 4.0000 (CI: 1.1709–13.6643)	$P = .0270$
<4 cm	3.9% (7/178)	15.2% (12/79)	50.0% (1/2)	7.4% (20/269)	RR = 3.8626 (CI: 1.5803–9.2208)	$P = .0030$

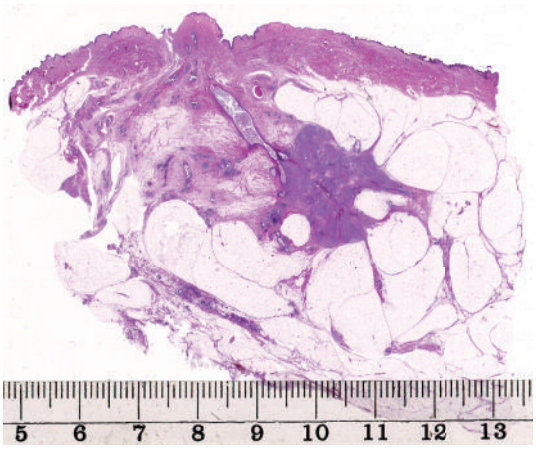


Figure 4: Invasive breast carcinoma with an in situ component involving a lactiferous duct leading to the invasive area.

assessment of disease extent is necessary in making decisions about the most appropriate surgical approach, taking into account the position of the lesion(s) within the breast, the dimensions of the breast, and patient preference.

5. Conclusions

Breast carcinoma is a lobar disease and, in the vast majority of cases, it is confined to the structures of a single sick lobe at its early stage. Finding the ductal tree of the sick lobe and mapping the diseased part(s) of it are essential in guiding adequate surgical intervention. Breast carcinomas of limited extent (<4 cm), whether unifocal or multifocal, are proper candidates for breast-conserving surgery. Adequacy of breast conservation in more extensive tumors should be carefully judged preoperatively in every individual case. In situ carcinomas with a lobar growth pattern (diffuse ductal carcinoma in situ) and invasive breast carcinomas of diffuse type often represent extensive disease, limiting the success of breast-conserving surgery.

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Review Article

Breast Conservation Surgery: State of the Art

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Breast conservation surgery is available to the vast majority of women with breast cancer. The combination of neoadjuvant therapies and oncoplastic surgical techniques allows even large tumours to be managed with a breast-conserving approach. The relationship between breast size and the volume of tissue to be excised determines the need for volume displacement or replacement. Such an approach can also be used in the management of carefully selected cases of multifocal or multicentric breast cancer. The role of novel techniques, such as endoscopic breast surgery and radiofrequency ablation, is yet to be precisely defined.

1. Introduction

The replacement of obligatory mastectomy, be it radical or modified radical, by simple mastectomy or wide local excision and adjuvant radiotherapy, reflected a paradigm shift in the understanding of breast cancer pathology and biology [1]. The combination of multimodal treatments, both locoregional, in the form of conservation surgery and radiotherapy, and systemic endocrine treatment and chemotherapy, has resulted in reduced postsurgical morbidity without compromising oncological outcomes [2]. The concept of downstaging tumours by means of neo-adjuvant chemotherapy or endocrine therapy is increasingly being applied to improve the chance of successful conservation surgery in the same way as it can render operable the inoperable [3, 4]. The adoption of oncoplastic surgical techniques allows larger tumours to be excised safely without compromising cosmetic outcomes. Currently, the only absolute contraindications to breast conservation relate to tumours with chest wall involvement, significant skin involvement, and patients with either extensive malignant microcalcifications or inflammatory carcinoma [5, 6]. Multifocal and multicentric tumours remain relative contraindications to attempts at breast conserving surgery. Such patients need careful counselling regarding the possible need for further surgery if excision is incomplete, and the increased risk of locoregional recurrence. Meticulous preoperative planning is essential if conservation is to be successful in this context [7]. The role of salvage breast conservation surgery in the management of local recurrence, or a metachronous primary cancer, is controversial, and should be considered with caution.

While some studies in the United States have suggested that the increasing incidence of breast cancer may have begun to level off [8], data from European countries does not reflect this change [9, 10]. Survival from breast cancer has certainly improved [11, 12], and it follows, therefore, that there are more patients alive now, having survived breast cancer, than at any other time. Aesthetic concerns and expectations are understandably higher on patients' agenda than previously and remain a source of psychological morbidity after mastectomy or if the results from breast conservation surgery are poor [12, 13]. Thus the importance of the oncoplastic approach, defined as the application of plastic surgery techniques of partial breast reconstruction at the time of breast cancer surgery, to optimising the oncological and cosmetic outcomes of breast conservation, has never been more keenly felt [14–16].

2. Optimisation of Oncological Factors

Tumours may be successfully downstaged with neoadjuvant chemotherapy and/or endocrine therapy, allowing the majority of patients to undergo breast conservation surgery [4, 17]. In this context, the decision to proceed with breast conserving surgery is guided by the clinical and radiological

response to neoadjuvant therapy. Magnetic resonance imaging is superior to mammography or ultrasound in evaluating the response to neoadjuvant therapy and should be used in preference [18–20]. Whereas regimens of neoadjuvant chemotherapy usually last approximately six months, the duration of endocrine therapy in the neoadjuvant context is more varied. Although only used for three months in the IMPACT trial [21], reductions in tumour size were sufficient to allow breast conservation treatment in a large proportion. Neoadjuvant endocrine treatment is sometimes associated with a more gradual reduction in tumour size and can safely be continued for longer durations prior to undertaking curative breast conservation surgery [22].

Small lesions, which are impalpable or difficult to feel, should be localised stereotactically or by ultrasound. A number of techniques are available, utilising hookwire localisation, radioactive beads, or injection of radioisotope colloid, the latter being particularly attractive in cases where breast-conserving surgery is performed in conjunction with sentinel lymph node biopsy [23, 24].

The use of intraoperative specimen X-ray helps confirm complete excision of the radiological abnormality [25]. This has been shown to help reduce the need for further surgery because of margin positivity, as a further cavity shave may be taken intraoperatively if the specimen X-ray gives cause for concern [26].

Optimal oncological treatment demands complete excision of malignant tissues with a negative resection margin. What constitutes a negative margin is not well defined. In early studies, only margins of >1 cm were considered negative [27, 28]. A recent meta-analysis showed equivalent rates of local recurrence with margins as close as 1-2 mm [29, 30], but closer margins have been associated with rates of local recurrence similar to those seen in cases with positive margins [31, 32].

The use of intraoperative frozen section for assessment of margins, where available, is helpful in reducing the number of second procedures required to achieve clear margins [33, 34]. A further cavity shave can be taken from any margin found to be positive on intraoperative frozen section. Intraoperative touch imprint cytology can also be used as a means of margin assessment but, as with frozen section, requires the availability of an expert cytopathologist to report slides intraoperatively [35].

The role of routine cavity biopsies is controversial [36]. Hewes et al. (2009) found poor correlation between the status of the resection margin and cavity biopsies. In their series, the status of cavity biopsies was a better predictor of both breast-cancer-specific and overall survival. The two key benefits of this approach are the reduced need for second operations if the specimen margin is positive and the cavity biopsy negative and the diagnosis of otherwise occult multifocal disease, often necessitating mastectomy [37]. Conversely, it can be argued that the practice is both unnecessary, given that discontinuous small foci of disease are adequately treated by radiotherapy [28] and undesirable, as it inevitably results in the excision of more tissue than strictly necessary, having a potentially adverse effect on cosmetic outcomes.

Rates of local recurrence after breast-conserving surgery are significantly reduced by the use of adjuvant radiotherapy, giving rates of overall survival similar to those following mastectomy [38], and therefore should be viewed as a standard of care, unless distant metastases are discovered soon after surgery [39, 40]. Postoperative external beam whole-breast radiotherapy remains the most commonly used technique, although partial breast radiotherapy is possible, and may be performed intraoperatively or postoperatively, via external beam, brachytherapy, or photon emission [41–44]. There is evidence that partial breast radiotherapy may be superior in terms of cosmetic outcome [45]. This is often cited as a major advantage over whole breast radiotherapy, which is associated with a number of unfavourable cosmetic sequelae, such as breast lymphoedema, fibrosis, and shrinkage of the breast tissue, often leading to accentuation of small parenchymal defects and distortion of the nipple. However, although short-term rates of local recurrence after partial breast irradiation seem similar, long-term data (i.e., over 10 years) showing equivalence with traditional whole-breast external beam radiotherapy are not yet available. The importance of reducing rates of 5-year locoregional recurrence is emphasised by its relationship with 15-year mortality. The 20% reduction in 5-year locoregional recurrence associated with the addition of radiotherapy to breast conservation surgery corresponds to a 5% reduction in mortality at 15 years [46].

3. Optimisation of the Cosmetic Outcome after Breast Conservation Surgery

The cosmetic appearance of the breast after breast conservation surgery depends, firstly, on the relative proportion of breast volume excised in order to satisfy oncological requirements and, secondly, on the location of the tumour within the breast.

The cosmetic defect caused by excision of medial tumours, especially in the upper inner quadrant, is more pronounced than for tumours in the outer half of the breast. Estimation of the proportion of breast volume to be excised is therefore an important consideration when planning surgery [47]. Successful oncological and aesthetic outcome depends on adequate preoperative planning. Mammography and ultrasound alone may underestimate the extent of disease and fail to demonstrate multifocality. Magnetic resonance imaging is being used increasingly in this context, as it has been shown to give a more accurate estimate of the true distribution of malignancy, particularly for lobular carcinomas [48, 49].

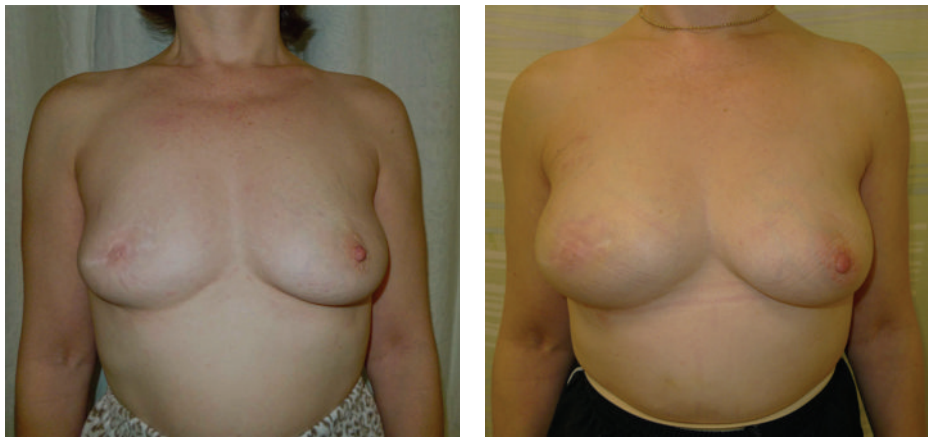
4. Surgical Principles

Overview.

(i) General principles

  (a) choice of incision,
  (b) avoidance of nipple deviation.

(ii) Techniques for excision of <10% of breast volume.



(a) (b)

Figure 1: (a) This patient had previously undergone a central wide local excision and nipple reconstruction at the age of 47. Although the contour of the right breast is similar to that of the left, there is a relative lack of projection and the breast has a blunted appearance. (b) Autologous fat transfer, in the form of lipomodelling, successfully fills the defect from previous surgery. The patient also received a subdermal silicone areola prosthesis to improve projection of the reconstructed nipple.

(iii) Techniques for excision of 10–20% breast volume:

(a) volume displacement,
(b) central tumours,
(c) peripheral tumours.

(iv) Techniques for excision of >20% of breast volume:

(a) tissue transfer.

Incisions should follow Langer's lines, semicircular, concentric to the edge of the areola, or Kraissl's lines, parallel to the horizontal skin creases. Radial incisions can be useful, but care must be taken to ensure that the nipple-areola complex is not likely to be displaced as the scar contracts during the process of wound healing and radiotherapy. A circumareolar incision can give good access to most lesions except those at the extreme periphery of the breast.

The skin overlying the cancer only needs to be excised if there are concerns regarding skin involvement, for example, if there is in-drawing of the skin or fixed dimpling. Following wide excisions, the resultant scarring and radiotherapy changes tend to cause nipple deviation towards the scar. This can be avoided by undermining the skin and disconnecting the ducts behind the nipple-areola complex. If needed, the remaining glandular tissue can also be undermined to allow rotation and approximation of tissue into the defect. If significant NAC deviation is anticipated, then de-epithelialisation of a crescent of skin from the areolar edge that is opposite to the scar and resiting the nipple to adjust for anticipated deviation often is helpful.

In general, excision of up to 10% of breast volume as a simple wide local excision gives an acceptable cosmetic result [47]. The resultant filling defect can be resolved to some degree by generously undermining the surrounding glandular tissue to allow it to fill the wide excision cavity. For those cases with defects despite breast remodelling the use of autologous fat transfer (Figures 1(a) and 1(b)) is emerging as an attractive option [50]. However, dystrophic calcification following fat necrosis may result in increased recall after screening mammography for biopsy [51].

Table 1

Mammoplasty techniques for resection of 10–20% of breast volume:
Glandular remodelling
Inferior pedicle
Superior pedicle
Vertical scar
Round block
Grisotti flaps

For cancers occupying up to 20% of breast volume, some degree of volume displacement may be required to fill the defect [52]. This is achieved by mobilisation and transposition of neighbouring glandular tissue with or without overlying skin (see Table 1). Suitable patients with adequate breast volume may wish to undergo therapeutic mammoplasty [53]. Surgery to the contralateral breast may be requested to improve symmetry and may take the form of a reduction mammoplasty or mastopexy.

For cancers occupying 20–40% of the breast, volume displacement alone may not be sufficient and thus volume replacement by autologous tissue transfer may become necessary.

5. Optimising Cosmesis: Central Tumours Occupying 10–20% of Breast Volume

Subareolar tumours have previously been viewed as an indication for mastectomy but may be safely approached by central excision with resection of the nipple-areola complex [54, 55]. The skin wound can be closed with a purse string or horizontal suture, although this tends to reduce the projection of the breast mound. A central excision

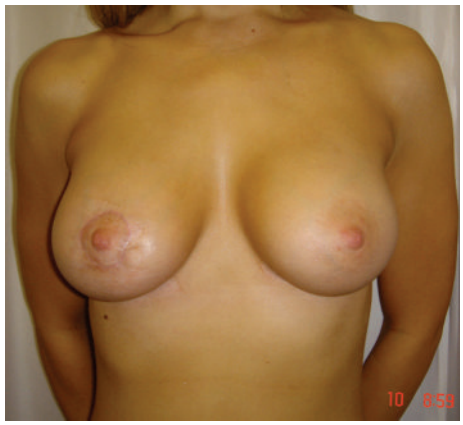


Figure 2: This patient presented with a 1 cm tumour located in the upper inner quadrant of the right breast. The tumour was excised via a periareolar incision and the remaining breast tissue was mobilised to close the defect. The round block technique ensured that the nipple-areolar complex remained in the correct position.

Table 2: Oncoplastic techniques suitable for excision of lesions in specified locations.

Tumour location	Oncoplastic technique
Superior to NAC	Periareolar (Benelli) mammoplasty
	Inferior pedicle (Grisotti) mammoplasty
Lateral to NAC	Lateral mammoplasty
Medial to NAC	Medial mammoplasty
Lower outer/inner quadrant	L-mammoplasty
	J-mammoplasty
Inferior to NAC	Vertical scar mammoplasty
	Inverted T (WISE) mammoplasty
Inframammary fold	IMF-plasty

with volume displacement using a Grisotti dermoglandular flap is more appropriate for larger breasts with greater degrees of ptosis [56]. After excision of the nipple-areola complex and the underlying tumour, a dermoglandular flap is harvested from the inferolateral breast. The flap is then de-epithelialised apart from the circle of skin destined to reconstruct the nipple. Free rotation depends on the flap being freed from the prepectoral fascia. An inverted-T (WISE pattern) mammoplasty [53], excising the nipple-areola complex, is a popular alternative, with the nipple potentially being reconstructed at a later date.

For central tumours not involving the nipple-areola complex an alternate option would be the use of Benelli's round block technique (Figure 2) [57]. Concentric circles are incised around the areola, and the skin resected, allowing access to the periareolar tissue. This allows reshaping of the breast by mobilising adjacent tissue, and the skin is closed by means of a purse string suture [58]. Alternatively such tumours may be excised in combination with a batwing mastopexy, otherwise known as the omega plasty, while preserving the nipple-areola complex [59]. Briefly, semicircular incisions are made: one circumareolar and the other a short distance away, and these are joined by angled "wings" to each side of the areola. After excision of the breast lesion, the defect is closed by advancing the breast tissue and closing the skin.

6. Optimising Cosmesis: Peripheral Tumours Occupying 10–20% of Breast Volume

Different oncoplastic techniques lend themselves to excision of lesions in certain locations (see Table 2). Tumours above the nipple-areola complex may be excised and the defect filled with an inferior pedicle mammoplasty.

Excision of tumours in the lateral aspect of the breast: tumours inferior to the nipple-areola complex may be excised by means of a vertical mammoplasty [60, 61] or nipple-sparing inverted-T mammoplasty [53] (Figures 3(a) and 3(b)). Moderately sized tumours in the lower outer quadrant may be resected using a modified approach, sometimes referred to as the J-mammoplasty, with larger tumours excised via an inverted-T or L-mammoplasty.

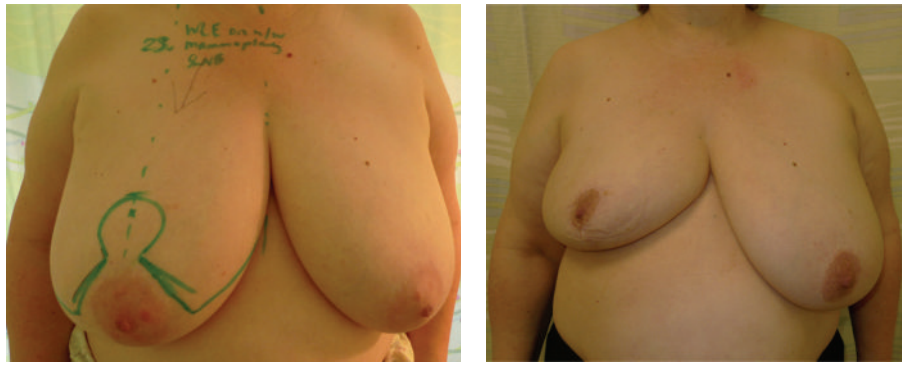
Tumours close to the inframammary fold may be removed by excising an ellipse of skin and breast tissue and simply closing the resulting defect. Although this reduces the distance from nipple to inframammary fold, this is often not apparent in patients with preexisting ptosis.

7. Optimising Cosmesis after Extensive Excision of 20–40% of Breast Volume: Techniques of Tissue Transfer

When more than 20% of breast volume is excised, tissue mobilisation alone may not succeed in achieving a satisfactory result and, unless the patient desires a much smaller breast, volume replacement by tissue transfer may be necessary. Most commonly, this entails use of a pedicled *latissimus dorsi* miniflap (Figures 4(a) and 4(b)), which can be mobilised to fill a defect in any quadrant [62, 63]. The first stage of the procedure involves excision of the breast lesion, and then the latissimus dorsi miniflap is used to fill the defect after a delay of one or two weeks to allow the margin status to be assessed [64]. If intraoperative analysis of surgical margins by frozen section is available, then a single stage procedure is feasible [65, 66]. Alternatives include mobilisation of axillary tissue on a thoracodorsal artery perforator lipodermal flap [7] or use of intercostal artery perforator flaps [66]. One novel approach adopted in our unit is to laparoscopically harvest an omental flap (Figures 5(a) and 5(b)) to fill the local defect [67]. Whereas pedicled flaps usually withstand radiotherapy, albeit with a substantial rate of complications, the use of free flaps in this context is contraindicated.

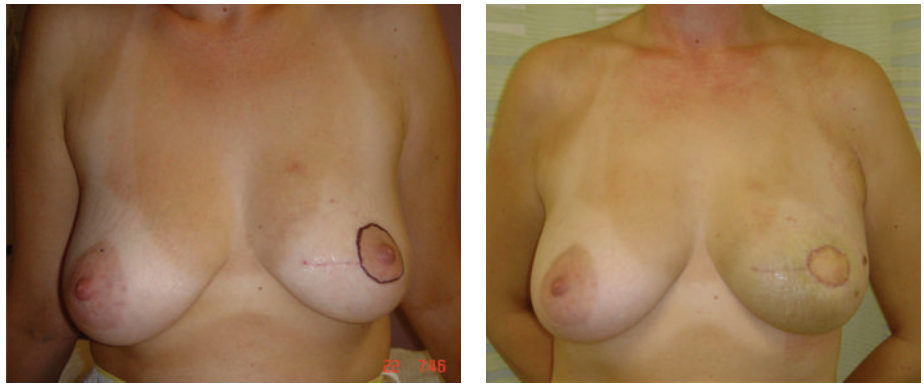
8. Optimising Management of Multifocal and Multicentric Tumours

The management of multifocal tumours, within the same quadrant, and multicentric tumours, in different quadrants



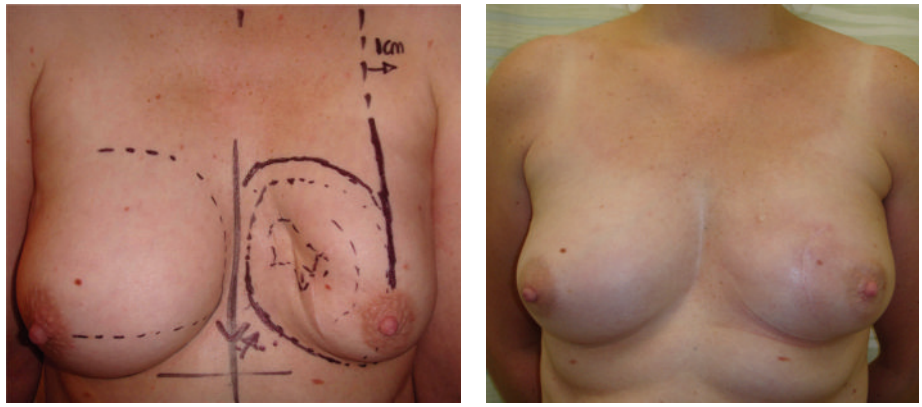
(a) (b)

Figure 3: (a) This 63-year-old patient with large ptotic breasts presented with a tumour in the right breast. The skin markings show the planned incisions for a therapeutic inverted-T mammoplasty. (b) Postoperative images of the same patient after completion of adjuvant chemotherapy and prior to commencing radiotherapy. The inverted-T mammoplasty gives a satisfactory result and is in proportion to the patient's body habitus. Reduction mammoplasty of the contralateral breast, to improve symmetry, is planned to be performed six months after completion of adjuvant radiotherapy.



(a) (b)

Figure 4: (a) This 41-year-old patient had previously undergone wide local excision of a tumour in the left breast. The lateral margin was involved, necessitating a further central wide local excision to include the nipple-areolar complex. (b) In view of the predicted loss of volume, a *latissimus dorsi* miniflap was utilised to both fill the resultant defect and also replace the skin of the areola. The volume of the partially reconstructed breast is very similar to that of the contralateral side, although postoperative swelling is apparent.



(a) (b)

Figure 5: (a) This patient had previously undergone wide local excision and adjuvant radiotherapy for a cancer located in the lower inner quadrant of the left breast. The resulting defect causes significant distortion to the breast shape and nipple deviation toward the midline. (b) An omental flap was harvested laparoscopically in order to partially reconstruct the breast, achieving a high degree of symmetry with the contralateral breast.

or in the same quadrant but widely separated (>5 cm), is controversial. Traditionally these scenarios would dictate mastectomy as the only oncologically sound procedure. If a conservative procedure is to be considered in these patients, careful selection is required with regard to tumour location and breast size and shape and counselled regarding the increased likelihood of further surgery should margins be positive, and possible increased risk of local recurrence, which may entail completion mastectomy. There have been no randomised controlled trials to address the issue of the oncological safety of breast conservation surgery in this context [7]. A retrospective study comparing outcomes of patients with multifocal and unifocal cancers showed equivalent overall survival and no increase in risk of locoregional recurrence [68].

In general, tumours closely spaced within the breast may be removed together utilising an appropriate technique such as an omegaplasty or inverted-T mammoplasty as listed above, whereas separate wide excisions are more appropriate for tumours separated by >5 cm. Careful preoperative planning is of paramount importance. This may often include the use of magnetic resonance imaging, and image-guided localisation of all lesions to be excised is essential. Access to intraoperative frozen section histology, while desirable in terms of reducing the need for further surgery in case of margin involvement, is not an absolute prerequisite.

9. Optimising Management of Local Recurrence or Metachronous Ipsilateral Primary Breast Cancer

The role of further attempts at breast conservation in patients who have previously undergone wide local excision for an ipsilateral cancer is controversial. Whole-breast radiotherapy can only be given once, and therefore further breast conservation surgery alone, versus mastectomy, is subject to the same disparity in efficacy as when wide local excision, without radiotherapy, is compared with mastectomy for primary breast cancer [28]. Thus, perhaps as many as 40% of women treated in this way will have further problems with local recurrence. Given these odds, many women will opt for mastectomy rather than any further attempt at breast conservation, but partial breast radiotherapy may be used in this context in an attempt to reduce the risk of failure [69]. At present, partial breast radiotherapy is only offered to a minority of patients. As these techniques gain wider acceptance and enter routine practice, a greater proportion of patients may be eligible for further breast conservation surgery to manage local recurrence or metachronous ipsilateral primary breast cancer.

10. Optimising Symmetry: When to Perform Contralateral Surgery

Large volume excisions, in patients for whom breast reduction is desirable, often result in noticeable asymmetry, which should be corrected. There is no consensus regarding the optimal timing of contralateral surgery. Simultaneous procedures are attractive in terms of reducing patient inconvenience and the need for a second admission and general anaesthetic (Figures 6(a) and 6(b)). Conversely, postradiotherapy changes can be unpredictable, and, therefore, some prefer to perform the contralateral reduction after these have had time to settle, to improve the chance of achieving good symmetry. A delayed approach also takes into account the possibility that further surgery may be required in the form of excision of margins or completion mastectomy if excision is incomplete [59]. If contralateral reduction is planned as a simultaneous procedure, then slightly more tissue should be excised and the nipple placed marginally higher, to mimic the predicted postradiotherapy shape [55].

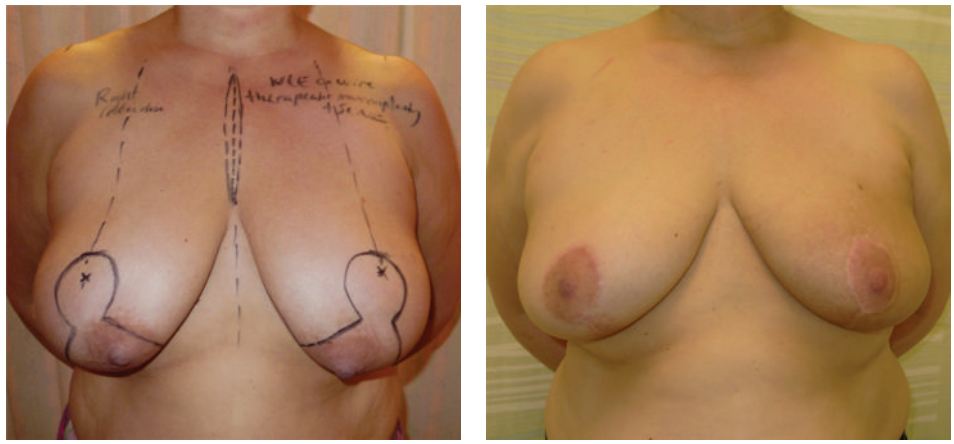
11. Novel Technologies and the Future of Optimising Breast Conservation

Endoscopic breast surgery for benign and malignant disease has been described in a number of small case series [70, 71]. Carbon dioxide insufflation creates a working space and both subcutaneous mastectomy and wide local excision have been performed using this technique. Although usually employed in the management of ductal carcinoma *in situ*, excision of T1 carcinomas has also been successfully performed [72]. The ability to reliably excise tumours with clear surgical margins is not well established due to the small size of these case reports, and more work is needed before they will be readily adopted into routine practice [73].

Radiofrequency ablation for small breast tumours is currently under evaluation [74]. The procedure can be monitored intraoperatively by ultrasound and postoperatively by magnetic resonance imaging. Wide local excision may be performed after radiofrequency ablation to ensure adequate oncological treatment [75]. Concerns regarding the ability to accurately assess response by magnetic resonance imaging alone currently preclude the use of this technique in isolation [76]. Fine-needle aspiration cytology in conjunction with magnetic resonance imaging has been used to assess response in patients not undergoing excision [77], but this approach should not be employed outside of clinical research given its unproven sensitivity and inability to adequately sample the "margin" of ablation and because of the paucity of data related to long-term outcomes.

12. Conclusion

The role of surgery in the management of breast cancer has changed markedly since the days of Halsted, reflecting the change in the way breast cancer is perceived as a systemic, rather than locoregional, disease process. Multimodal therapies, especially in the form of neoadjuvant chemotherapy and endocrine therapy, have increased the proportion of women eligible for breast conservation. The adoption of relatively straightforward surgical techniques to achieve volume displacement can give superior cosmetic outcomes for patients with larger tumours. Techniques of volume replacement are more demanding but are within the



(a) (b)

Figure 6: (a) This 51-year-old patient with large, ptotic breasts and nipple-areola complexes situated medial to the breast meridian presented with a left breast cancer. These images show the skin markings used to plan a therapeutic inverted-T mammoplasty and simultaneous contralateral reduction mammoplasty for symmetrisation. (b) Adjuvant radiotherapy to the left breast has resulted in mild changes in skin pigmentation but symmetry is still good with the contralateral breast being still satisfactory.

remit of surgeons with an interest in oncoplastic surgery or can be performed in conjunction with a plastic surgeon.

The management of multifocal or multicentric cancers and the management of further conservation surgery for recurrence or metachronous ipsilateral primary after previous wide local excision are contentious issues. Ideally, multicentre randomised controlled trials should be designed to address these issues. Surgery to the contralateral breast to improve symmetry should be offered to all patients. The timing of such surgery, and the merits of synchronous versus delayed approaches, should be discussed with patients in full.

In the future, endoscopic breast cancer surgery and radiofrequency ablation therapy are likely to become more popular, but larger studies with longer periods of followup are needed to evaluate their oncological safety prior to their widespread adoption.

Now that patients are benefiting from improved disease-free and overall survival, the cosmetic outcome is of great importance as patients seek to come to terms with the aftermath of breast cancer and its treatment. The importance of cosmesis, in terms of emotional and psychosexual well-being [78–80], demands that the principles of an oncoplastic approach to breast conservation surgery be employed in treating all women with breast cancer.

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Clinical Study

Breast Cancer Preoperative Staging: Does Contrast-Enhanced Magnetic Resonance Mammography Modify Surgery?

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Women with newly diagnosed breast cancer may have lesions undetected by conventional imaging. Recently contrast-enhanced magnetic resonance mammography (CE-MRM) showed higher sensitivity in breast lesions detection. The present analysis was aimed at evaluating the benefit of preoperative CE-MRM in the surgical planning. From 2005 to 2009, 525 consecutive women (25–75 years) with breast cancer, newly diagnosed by mammography, ultrasound, and needle-biopsy, underwent CE-MRM. The median invasive tumour size was 19 mm. In 144 patients, CE-MRM identified additional lesions. After secondlook, 119 patients underwent additional biopsy. CE-MRM altered surgery in 118 patients: 57 received double lumpectomy or wider excision (41 beneficial), 41 required mastectomy (40 beneficial), and 20 underwent contra lateral surgery (18 beneficial). The overall false-positive rate was 27.1% (39/144). CE-MRM contributed significantly to the management of breast cancer, suggesting more extensive disease in 144/525 (27.4%) patients and changing the surgical plan in 118/525 (22.5%) patients (99/525, 18.8% beneficial).

1. Introduction

The primary objective of any diagnostic imaging modality is to accurately define the presence, the type, and the extent of disease in order to optimize patient management decisions and best plan therapeutic and surgical interventions. In women with suspected breast cancer, the aim of diagnostic imaging is to detect and accurately diagnose malignant tumors and to facilitate the correct choice of therapy, being mastectomy or breast-conserving surgery (e.g., lumpectomy) with or without preoperative neoadjuvant chemotherapy. The choice between breast-conserving surgery and mastectomy depends on numerous factors including tumour size, location and grade, the ratio of tumour size to breast volume, multifocality or multicentricity of the tumour, and patient preference. Currently, conventional mammography and ultrasound (US) are standard imaging techniques for the detection and evaluation of breast disease [1]. In recent years, contrast-enhanced magnetic resonance mammography (CE-MRM) has emerged as the most sensitive imaging modality for the detection and diagnosis of breast lesions [2–5]. Numerous studies have confirmed the superior diagnostic performance of CE-MRM compared to conventional mammography and US [6–9]. Studies to evaluate the impact of CE-MRM on patient management decisions have similarly revealed its superiority compared to standard imaging [10–13].

The present analysis was aimed at further evaluating the impact of CE-MRM on surgical decision making compared with those taken solely on the basis of clinical examination, conventional mammography, and ultrasound. The potential impact of CE-MRM on surgical decision making was, thereafter, evaluated for each patient. The CE-MRM was considered to accurately suggest the appropriateness of breast conservation images clearly which demonstrated the respectability of the lesion and in which CE-MRM was the only imaging modality able to do so. CE-MRM was considered to accurately suggest the necessity of changing surgery planning

when images clearly showed more extensive disease than otherwise suspected from conventional mammography or ultrasound. More extensive disease includes larger size of index cancer, additional foci of cancer in the same or in other breast quadrants, and contra lateral lesions. Our purpose was to verify the benefit of preoperative CE-MRM in the surgical planning in our institution.

2. Materials and Methods

This retrospective study includes consecutive patients identified from a prospective database from January, 1, 2005 to November, 30, 2009. A standardized protocol was implemented in the management of all new, biopsy-proven breast cancer starting in January 2005.

The primary inclusion *criterium* was a preoperative CE-MRM in patients with histologically confirmed breast cancer. The study included women 25 to 75 years of age with a new primary breast cancer.

Exclusion *criteria* were mammographic pattern of fatty breast tissue, pregnancy, claustrophobia, planned bilateral mastectomy, preoperative chemotherapy, and history of breast cancer.

All patients underwent mammography and ultrasonography. The evaluation of images was performed in consensus by four observers with 10 years' experience, respectively, in interpretation of conventional mammography and breast ultrasound images. Conventional mammograms and sonograms were evaluated for tumor detection and size.

Needle biopsy was performed in case of suspicious lesion, often with radiographic (US or mammographic) guidance by 14 gauge core needle biopsy (Bard).

Pathological results of core biopsy were in line with UK and European guidelines [14, 15]. Categories are B1: normal tissue/unsatisfactory; B2: benign; B3: lesions of uncertain malignant potential; B4: suspicious of malignancy; B5: (malignant subclassified as ductal carcinoma in situ (DCIS) or invasive cancer) [14, 15].

If the biopsy specimen was positive for malignancy, the patient was referred to surgeons.

A complete clinical examination was performed and a preliminary surgical plan was made. Then, CE-MRM at 1.5 T was performed in the eligible patients.

CE-MRM was performed on a 1.5 T magnet (Achieva 1.5 T Philips) using a bilateral breast surface coil with the patient in the prone position.

An axial 3D dynamic T1-weighted gradient-echo sequence and T2-weighted pulse sequence were employed with images acquired before contrast agent administration (precontrast-unenhanced images) and, at 0, 1.5, 3, 4.5, and 6 minutes after the administration of contrast agent (postcontrast-enhanced images). Postcontrast 3D T1-weighted gradient-echo dynamic images were acquired after the administration of 0.1 mmol/kg bodyweight of gadopentetate dimeglumine Gd-DTPA (Magnevist Bayer Schering Pharma) through an 18 gauge needle cannula positioned in an antecubital vein. Gadopentetate dimeglumine Gd-DTPA was administered using an automatic injector at a rate of 2 mL/sec and was followed by 10 mL of saline solution at the same rate.

The evaluation of images was performed in consensus by two observers with 13 and 8 years' specific experience, respectively, in CE-MRM interpretation (approximately 1500 MR breast images per year).

If CE-MRM revealed more extensive breast disease, other than the index cancer, the patients would return for a second-look examination with mammogram and/or US. More extensive disease included larger size of index cancer, additional foci of cancer in the same or in other breast quadrants, and contra lateral lesions.

Second look was performed by the same radiologists who interpreted the CE-MRM images. If a lesion was confirmed as suspicious, a new radiographic guided needle biopsy was performed. CE-MRM-guided biopsy is not available in our institution.

Whether the patients refused to undergo a core biopsy, additional surgery was strongly suggested. If the lesion was not seen on second look, the patient was counselled to remove it if the image was suspicious on CE-MRM, or to have 6-month followup CE-MRM if the lesion was less concerning in opinion of the attending breast radiologist.

If the pathologic findings of the CE-MRM-discovered lesions biopsy specimen were malignant or high-risk pathology (atypical ductal hyperplasia (ADH), lobular intraepithelial neoplasia (LIN), papillary lesions, radial scar/complex sclerosing lesions), the case was reassessed by the same team of surgeons. A decision was made about the possibility to change surgical planning. There were three change's categories: first, from lumpectomy to double lumpectomy or wider excision, if the new lesions were located in the same quadrant but were separated from the index cancer by at least 1.0 cm of normal-appearing tissue on CE-MRM (multifocal lesions), or if there was a single additional lesion in other quadrant than index cancer (bicentric disease), or if it was in the same quadrant and contiguous with the original cancer or rounding it, but extended at least 4.0 cm beyond the site of the primary lesion (larger size); second, from breast conservative surgery to mastectomy, if lesions discovered were multicentric (more lesions in different quadrants), or if patient was not candidate to conservative surgery (e.g., retroareolar, large cancer in little breast); third, contra lateral surgery, if the lesions identified were in contra lateral breast.

After surgery, all radiographic and pathologic results were examined.

In patients with a change of surgery, we analyzed tumour size and the presence of additional foci on mammographic, US, CE-MRM, and histologic reports to determine if the change of treatment was or not appropriate. Appropriate changes of treatment were defined as those in which pathologic report correlates with CE-MRM findings, but not with mammography and US. Inappropriate changes of surgery were those in which CE-MRM predicted a larger lesion or other foci than mammography or US, but the histological results confirmed the original mammographic and ultrasonographic findings.

Table 1: Breast cancer diagnosis.

	N (%)
Positive MX + positive US	401 (76.4)
Positive MX + negative US	70 (13.3)
Negative MX + positive US	54 (10.3)
Total	525 (100)

MX: mammography.
US: ultrasounds.
N: number of patients.

Table 2: Histopathologic types.

	N (%)
DCIS	67 (12.8)
Invasive carcinomas	458 (87.2)
(i) ductal	287 (63)
(ii) lobular	74 (16)
(iii) others	97 (21)
Total	525 (100)

DCIS: ductal carcinoma in situ.
N: number of patients.
Others: ductal-lobular (49); mucinous (15); tubular (14); medullary (9); metaplastic (3); papillary (7).

Table 3: Axillary nodes status.

Evaluation	*N* (%)
Positive nodes:	
(i) FNAC +	91 (19.9)
(ii) SNB +	99 (21.6)
Negative SNB	268 (58.5)
Total	458 (100)

SNB: sentinel node biopsy.
FNAC: fine needle aspiration cytology.
N: number of patients.

We defined as "false positive" patients, both with positive MRI and negative core biopsy, than with positive MRI and negative pathological report after surgery.

The institutional multidisciplinary breast conference of the Evangelical Hospital of Turin approved the employ of breast CE-MRM in women with newly diagnosed breast cancer, and the procedure was scheduled in the routinely workup of these patients after mammogram and US. The institutional review board of the Evangelical Hospital of Turin did not require the approval of patients, nor their informed consent to review their records on database.

One-year followup was at least required to detect by mammogram or CE-MRM previously undetected lesions. About surveillance, we are in line with NCCN practice guidelines of invasive breast cancer. Physical exam and interval history every 4–6 months for 5 years, then every 12 months. Mammogram and US every 12 months (also MRI in recommended cases) [16].

Statistical analysis was performed using the Statistics Package for Social Sciences, version 15.0 (SPSS Inc., Chicago, Ill). Categorical variables were evaluated with χ^2 analysis. Results were considered statistically significant when $P < .05$.

3. Results

During the 5-year study period, 525 women were defined eligible to undergo bilateral breast CE-MRM, following inclusion criteria.

The mean age was 51.9 (range 25–75 years). Diagnosis of breast cancer was made by mammography and ultrasounds as seen in Table 1.

The median invasive tumour size at study entry was 19 mm (range 1–60 mm), based on mammography/ultrasounds.

In 302/525 patients (57.5%), breast cancer was a palpable mass and in 223/525 women (42.5%) presented with radiographic findings.

Lumpectomy, double lumpectomy, or wider excision was performed for 396/525 patients (75.4%); 129/525 women (24.6%) underwent mastectomy.

In 67/525 patients (12.8%), the definitive diagnosis was ductal carcinoma in situ, whereas in 458/525 (87.2%) cases was invasive carcinoma (Table 2).

A total of 190/458 patients (41.5%) with invasive cancer had lymph node-positive disease, preoperative, or after sentinel node biopsy (Table 3).

At all, 525 women with a newly diagnosed breast cancer underwent CE-MRM according to the study protocol (Figure 1). CE-MRM findings were in concordance with mammogram and/or US in 381/525 patients (72.6%).

In 144/525 patients (27.4%), CE-MRM identified suspicious lesions (Figure 1). In 26 patients, CE-MRM found additional images that resulted less concerning at second look with mammogram and/or US (18 cases) and benign at core biopsy (8 cases). In these cases, preoperative management unchanged and patients had six-month followup CE-MRM recommended.

In 118 patients, CE-MRM detected lesions that the second look confirmed as concerning. A total of 111 patients underwent image-guided biopsy (US- or stereotactic-guided) which found B3, B4, or malignancy in the specimens [14, 15]. In 7 patients (4 patients who refused to have a new core biopsy and 3 patients in which the second look did not identify the additional enhancing lesion detected by CE-MRM), on the basis of high suspect of CE-MRM imaging, patients were strongly recommended to undergo to wider surgery (Figure 1).

CE-MRM altered programmed surgery of newly diagnosed breast cancers in 118/525 (22.5%) patients (Table 4). Fifty-seven patients who were initially candidates for breast-conserving surgery were upgraded, based on CE-MRM findings, to double lumpectomy or to wider excision. In 20/57 patients, CE-MRM found additional foci, and in 37/57 patients, the size of index cancer was larger.

On the basis of CE-MRM imaging, 41 women required a mastectomy. 37/41 patients had multicentric cancer CE-MRM detected, in 4/41 patients, there were a larger lesion with unfavourable cancer size/breast size ratio.

Table 4: Change in surgical management based on CE-MRM.

Treatment change	Change	Beneficial	FP	FN
	N (%)	*N* (%)	*N* (%)	*N* (%)
(A) Double lumpectomy or wider excision	57 (48.3)	41 (71.9)	11 (19.3)	5 (8.8)
(B) Mastectomy	41 (34.7)	40 (97.6)	1 (2.4)	0
(C) Contra lateral surgery:				
(i) alone	6 (5.1)	6 (100)	0	0
(ii) in addition to (A)	8 (6.8)	6 (75)	1 (12.5)	1 (12.5)
(iii) in addition to (B)	6 (5.1)	6 (100)	0	0
Total	118 (100)	99 (84)	13 (11)	6 (5)

N: number of patients.
FP: false positives.
FN: false negatives.

All patients enrolled in the study received bilateral CE-MRM, and 20 women had suspicious lesions discovered in the contra lateral breast (Table 4).

Of these 20 patients, all demonstrated with needle biopsy, 6 women had programmed operation in the ipsilateral breast and a new contra lateral surgery; in 14 patients, the surgical plan changed bilaterally, according to the additional lesions detected by CE-MRM.

A radiographic-pathologic correlation was performed to verify whether the change in surgical management based on CE-MRM was beneficial, owing to better concordance between CE-MRM and surgical pathologic findings than between mammography or US and histological reports.

CE-MRM detected enhanced lesions in 144 cases (Figure 1). The second look identified suspicious lesions in 126 cases, and, in 119 patients, an image-guided biopsy (ultrasonographic or stereotactic) was performed. Pathologic reports confirmed an apparent malignancy in the specimens in 111 patients, whereas 8 patients had benign lesions. The false-positive rate for biopsy of a CE-MRM-detected lesion was 8/119 (6.7%). In 18 patients who refused to undergo core-biopsy after second look, the lesions were considered by our radiologist as less concerning; these patients had six-month CE-MRM followup recommended. Therefore, the total false-positive rate for second look was 26/144 (18%).

As illustrated in Figure 1, 118 patients had a change in surgical plan. In 13 patients, change of surgery was inappropriate (Table 4), in 11 patients, in which wider excision was performed, histological reports did not confirm CE-MRM suggestions, lesions were smaller than 4.0 cm, or the second lesion identified was near the index cancer (distance < 1.0 cm). In one patients in which wider excision and contra lateral surgery were performed, histology demonstrated that surgery was appropriate in the breast with index cancer, but, in contra lateral breast, definitive diagnosis was benign. Finally, in one patient who had >4.0 cm CE-MRM-detected lesion, operation was converted to mastectomy, but the surgical histological report did not confirm CE-MRM findings. The false-positive rate for surgery was 13/118 (11%).

In summary, the overall false positive rate was 39/144 (27.1%).

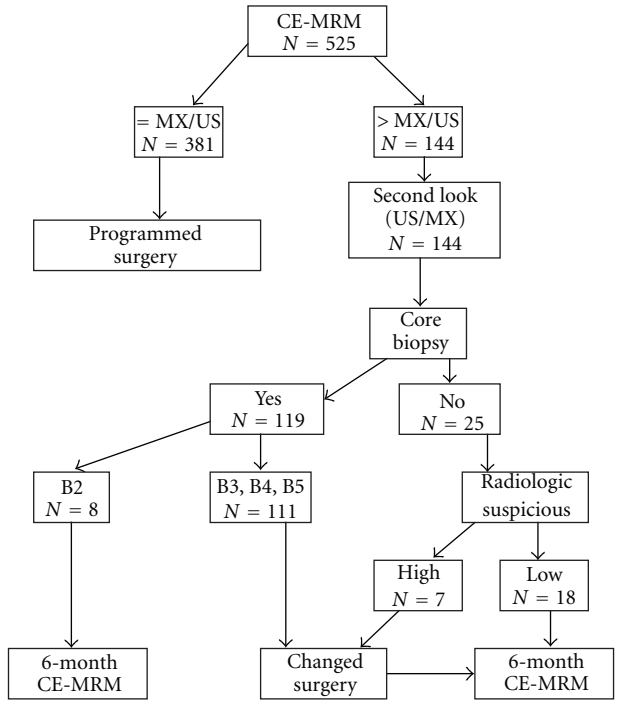

Figure 1: Additional evaluation based on breast CE-MRM findings and change in preoperative management. = MX/US: CE-MRM report in concordance with MX/US. > MX/US: CE-MRM detects more or larger lesions. B2: benign lesion; B3: lesion of uncertain malignant potential; B4: suspiciousnes of malignancy; B5: malignant (B5a: in situ carcinoma (DCIS) or B5b: invasive carcinoma) [14, 15]. *N*: number of patients.

As seen in Table 4, in six-women breast, CE-MRM detected additional separate lesions (4 patients), or it confirmed the presence of the known lesion, but larger (2 patients), which allowed a wider excision (Table 4). Unfortunately, histology demonstrated the presence of more extensive disease (6/118, 5% false-negative rate).

Therefore, among 118 patients who had a change in surgical plan, 99 (84%) were found to have a concordance

Table 5: Histopatologic type in the subgroups.

	Patients	Double lumpectomy/Wider excision*	Mastectomy*	Contra lateral surgery
	N	*N* (%)	*N* (%)	*N* (%)
DCIS	67	6 (9)	5 (7.5)	3 (4.5)
IDC	287	31 (10.8)	25 (8.7)	6 (2.1)
ILC	74	10 (13.5)	7 (9.5)	7 (9.5)**
Others	97	10 (10.3)	4 (4.1)	4 (4.1)

DCIS: ductal carcinoma in situ; IDC: infiltrating ductal carcinoma; ILC: infiltrating lobular carcinoma.
*Patients with synchronous contra lateral surgery were excluded.
**lobular versus ductal histotype $P < .011$.
Others: ductal lobular (49); mucinous (15); tubular (14); medullary (9); metaplastic (3); papillary (7).

Table 6: Negative versus positive nodes in the subgroups.

	Double lumpectomy/Wider excision*	Mastectomy*	Contra lateral surgery
Negative nodes (%)	32/325 (9.8)	16/325 (4.9)	10/335 (3.0)
Positive nodes (%)	25/180 (13.9)	25/180 (13.9)	10/190 (5.3)
P value	(NS)	(P <.0001)	(NS)

* Patients with synchronous contra lateral surgery were excluded.

between CE-MRM findings and final histological reports. Surgical change was defined in these patients appropriate and beneficial (Table 4). Forty one of the 57 women (71.9%) who had an initially planned lumpectomy converted to a double lumpectomy or to a wider excision based on CE-MRM were converted appropriately. Forty of 41 patients (97.6%) who had a lumpectomy converted to a mastectomy had a beneficial change because CE-MRM correlated with final pathologic report. In the 20 women with contra lateral CE-MRM-detected lesions, the histological report correlated with CE-MRM findings in 19 (95%).

In 163/525 patients, breast cancer was multicentric (31%). In 88/163 patients, breast cancer was defined as multicentric before CE-MRM. In seventy-five patients of 163 (46%), we modified surgical planning because CE-MRM detected additional foci of breast cancer (including also bicentric disease, in which double lumpectomy was performed).

On univariate analysis, we considered patient age, radiographic findings, pathologic features, and staging. We considered patients divided into the three types of changed surgery. We focused our attention on interesting results (see Tables 5-7).

We found that patients with ILC (7/64, 9.5%) were more likely to have contra lateral disease compared with IDC (6/287, 2.1%); $P < .0001$ (Table 5). Patients with positive nodes (25/180, 13.9%) were converted to mastectomy more often than women with negative nodes (16/325, 4.9%); $P < .0001$ (Table 6). Similarly, we found that patients with multicentric disease were more likely to have mastectomy (37/145, 25.5% versus 4/360, 1.1%; $P < .0001$) and contra lateral breast cancer (18/163, 11.0% versus 2/362, 0.5%; $P < .0001$), compared with patients with unifocal breast cancer (Table 7).

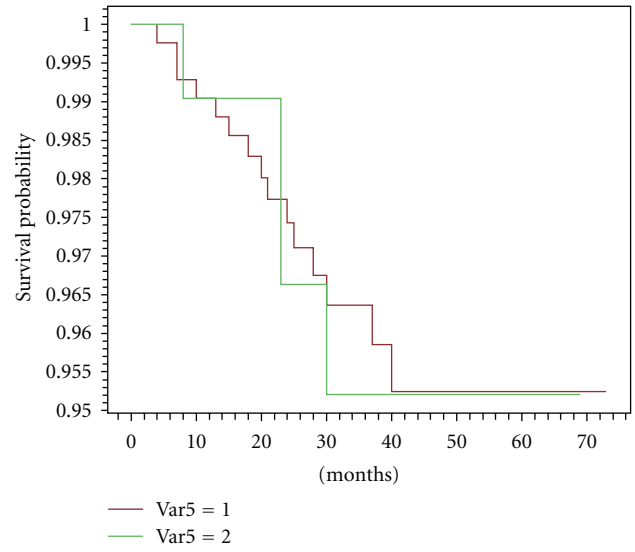

Figure 2: Curves of disease-free survival local recurrences.Var5 1: patients with unmodified surgery after CE-MRM Var5 2: patients with modified surgery after CE-MRM $P = .97$.

The number and the site of recurrences are reported in Table 8. In our series, as expected and hoped, the number of first local failures was similar in women with converted surgery, compared with patients with any change of treatment (Figure 2); however, we notice that the number of distant metastases seems to be higher in cases with modified surgery versus unmodified surgery. Kaplan-Meier survival analysis (distant disease-free and overall survival) showed both curves overlapping around 97% at 5 years (Figures 3

Table 7: Multicentric versus unifocal cancer in the subgroups.

	Double lumpectomy/Wider excision*	Mastectomy*	Contra lateral surgery
Multicentric (%)	20/145 (13.8)	37/145 (25.5)	18/163 (11.0)
Unifocal (%)	37/360 (10.3)	4/360 (1.1)	2/362 (0.5)
P value	(NS)	($P < .0001$)	($P < .0001$)

* Patients with synchronous contra lateral surgery were excluded.

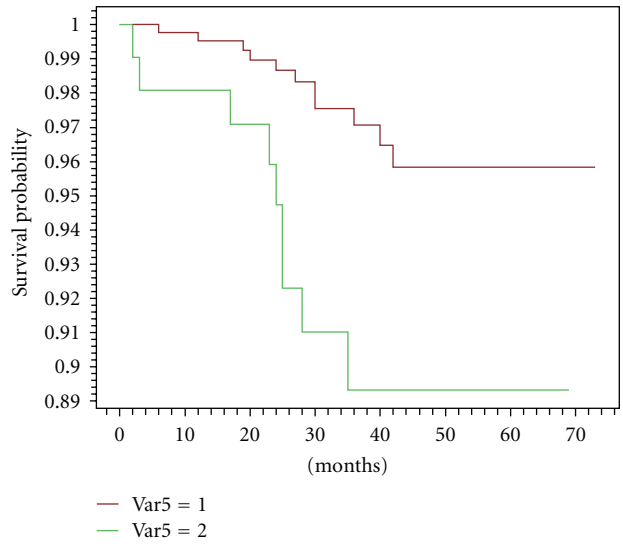

Figure 3: Curves of disease-free survival distant metastases. Var5 1: patients with unmodified surgery after CE-MRM Var5 2: patients with modified surgery after CE-MRM $P = .002$.

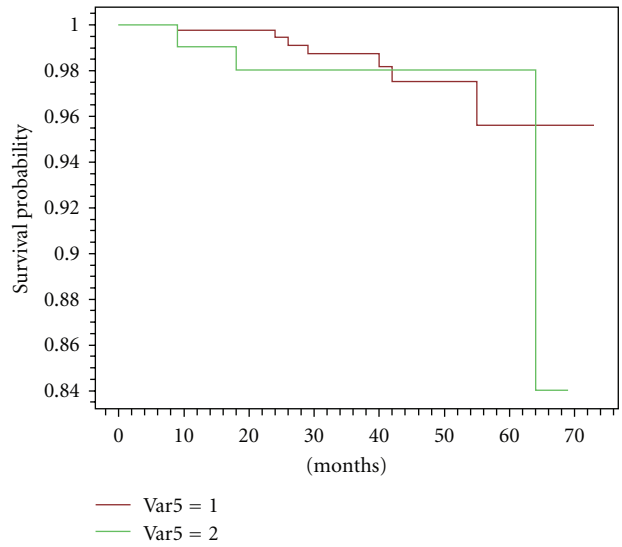

Figure 4: Curves of overall survival.

Table 8: Site and number of first failure after treatment.

	Change surgery	
	No	Yes
Site	*N* (%)	*N* (%)
Local	15*(3.7)	5**(4.2)
Regional	3 (0.7)	1 (0.8)
Contra lateral breast cancer	5***(1.2)	0
Distant	11 (2.7)	9 (7.6)
None	373 (91.6)	103 (87.3)

* Includes one patient with concurrent contra lateral breast cancer and four patients with synchronous distant metastases.
** Includes one patient with concurrent distant metastases.
*** Includes one patients with concurrent ipsilateral local failure.

and 4). Considering the short followup (median 36 months), firm statistical conclusions are hard.

4. Discussion

This retrospective study evaluated the impact of CE-MRM on the surgical management of 525 consecutive patients of 25–75 years of age with newly diagnosed breast cancer.

Since CE-MRM is performed in all the patients in our hospital (except patients >75-year old and patients with mammographic pattern of fatty breast tissue), only few patients were left out of the study.

Patients were treated following a workup in which our breast surgeons assessed all patients before CE-MRM. Women were all revaluated after CE-MRM by the same surgeons to decide if a change in surgical planning was necessary.

CE-MRM-altered programmed surgery in 118/525 (22.5%) of patients and, based on findings founded in the pathologic specimens, the change of surgery planning was confirmed as appropriate in 99/118 (84%) of these patients. Thus, 99/525 (18.8%) of women had a favourable change in surgical management, based on preoperative CE-MRM. Therefore, 5 women must undergo to CE-MRM for 1 to have a beneficial conversion in surgical plan.

Surgical management, other than the histology and the size of the breast, is usually influenced by the real size of index cancer and by the extent of the disease, indicated by the presence of multiple malignant foci in the same quadrant or in different quadrants from the main lesions, or by the presence of contra lateral lesions. CE-MRM has demonstrated that, despite its suboptimal specificity, it is able to offer this kind of information better than conventional radiology.

The first risk of CE-MRM is, in fact, the number of false-positive that may cause unnecessary imaging and biopsies, and that is a major limitation in the use of this procedure [17]. In this regard, false positives (and also false negatives)

after CE-MRM can be attributed to inherent technological limitation of CE-MRM, patients characteristics, quality assurance failures, and human error [18]. The consequences of these factors include missed cancers, with potentially worse prognosis, as well as anxiety and potential harms associated with interventions for benign lesions [18].

In our series, the overall false-positive rate was 39/144 (27.1%), in which CE-MRM-detected lesions were ultimately not malignant. In 13/118 (11%) of patients in which change of surgery was decided (13/118), the conversion was inappropriate (Table 4).

Furthermore, 11 women were upgraded from lumpectomy to wider excision or double lumpectomy, but histological reports did not confirm CE-MRM suggestions. Analyzing these records in our database, we verified that four patients refused to have a guided core biopsy after second look; two patients had a negative second look with high suspiciousess of CE-MRM findings. In these cases, the pathologic specimens revealed the presence of benign lesions. The other cases were B3 and B4 as result of core biopsy. Definitive pathologic reports verified that lesions resulted are not malignant.

In one patient in which ipsilateral wider excision and contra lateral surgery were performed, histology demonstrated that surgery was appropriate in the breast with index cancer, but, in contra lateral breast final diagnosis was LIN 1.

Moreover, in one patient, an unnecessary mastectomy was programmed, because the lesion was overestimated by CE-MRM, and, in the histological specimen, the presence of a LIN 1 near the index cancer was verified.

Considering false negatives, in six of 118 women, CE-MRM detected additional lesions, which allowed a wider excision. These patients were borderline candidates for breast-conserving therapy, and, after an exhaustive counselling with them, the decision to attempt a wider excision was made. Unfortunately, histology demonstrated the presence of more extensive disease (5% false-negative rate), and a subsequent mastectomy was performed.

Numerous reports showed that CE-MRM can detect additional foci in a substantial number of women with a new diagnosis of breast cancer [6–9]. Moreover, numerous nonrandomized studies have attempted to evaluate the effect of CE-MRM on surgical treatment and planning [10–13]. The only evidence from a prospective randomized trial on the impact of CE-MRM on surgical management derived from the COMICE study [19], a controlled randomized trial that was designed to measure the reexcision rate as its primary endpoint (Turnbull et al., 2010). In this trial 1,625 women were randomly evaluated before surgery with breast CE-MRM or not [19]. Reexcision rates were quite similar in women randomized to receive conventional assessment (19.3%) or to receive CE-MRM in addition to standard imaging (18.8%); NS [19].

Previous reports have also described the identification of previously undetected, synchronous lesions in the contra lateral breast using CE-MRM in an average of 5% of women with a recent diagnosis of breast cancer [20–22].

The most of CE-MRM-detected contra lateral breast cancers appear to early stage disease, as indicated in a recent review [23], and, in approximately 2/3 of cases, the specimens were positive for invasive cancer [23, 24].

In patients with invasive lobular carcinoma (ILC), the coexistence of other invasive malignant foci, identified by breast CE-MRM, apart from the index lesion in the ipsilateral breast reached 32% in a recent meta-analysis [25]. Moreover, the detection rate of contra lateral ILC is another 7% of patients by CE-MRM only [25].

Our overall detection rate of contra lateral breast cancer was 20/525 (3.8%). All the contra lateral lesions CE-MRM detected were guided-biopsy proven and only one of them were overestimated. CE-MRM (Table 5) identified bilaterality in 3/67 (4.5%) of DCIS in 6/287 (2.1%) of IDC and in 7/74 (9.5%; $P < .0001$) of ILC, respectively. Finally, the number of the CE-MRM-detected contra lateral breast cancers was unrelated to nodal status (Table 6). The fact that change in treatment was considered correct, as verified by pathologic findings in the specimen, in 19/20 (95%) of cases of contra lateral surgery (Table 4), shows that breast cancer, and especially ILC, is often more extensive than appreciate on conventional imaging.

Our study shows that the CE-MRM can improve the detection of other malignant lesions (ipsilateral and contra lateral) when added to a conventional imaging (mammogram and US) at the time of the initial diagnosis of breast cancer. The current cost of CE-MRM precludes its widespread use in general population, but this imaging tool appears to improve the detection of cancer in women at increased risk, such as women with a recent diagnosis of breast cancer, and a number needed to treat of 5 is reasonable in our opinion.

If CE-MRM is performed, the false-positive rate indicates that abnormal findings should be investigated with image-guided core biopsy to establish a diagnosis before surgical treatment, as emphasized in a recent review [26].

The second risk of this approach to local staging the breast is that more women being treated with more radical surgery without a demonstrated improvement in surgical outcomes or prognosis.

Based on the results of controlled clinical trials with mortality as the endpoint, breast conservation therapy (BCT) and mastectomy confer equivalent risk to the patient [27–29]. As stated by Orel and Schnall [4], the 25–36% of local recurrence rate in the absence of radiotherapy and chemotherapy corresponds to the frequency of multifocal and multicentric tumours found only with conventional imaging [4]. The potential 10-year recurrence rate after breast-conserving therapy followed by standard adjuvant therapies (radiation therapy, chemotherapy, and hormonal therapy) would be 9-10% [30]. Moreover, the absolute risk of contra lateral breast cancer in women with a personal history of breast cancer is up to 3% of synchronous disease, whereas 7% of women will be diagnosed with metachronous disease [22]. This risk is significantly higher than that of the general population [31]. In this regard, adjuvant therapies (local and systemic) play a key role in achieving local control in women treated with breast-conserving surgery. Thus, the goal of breast-conserving therapy is to achieve good local control, and to

provide women who wish to conserve their breast a good cosmetic result.

Some argue that any increase in the rate of mastectomy prompted by CE-MRM findings would represent a setback in the standard of care [32, 33]. And since radiation therapy is presumed to eradicate or delay the progression of residual disease in most women who undergo conservation therapy, preoperative CE-MRM would have little or no impact on rates of recurrence or death [32].

On the other hand, the upper threshold amount of residual disease that can be eradicated by radiation therapy is not yet well established. Although the rate of recurrence after breast conservation is low, it is not zero, and each patient should be offered the best possible chance for successful treatment. Detecting widespread disease can obviate inappropriate attempts at conservation, in which both lumpectomy with positive margins and reexcision with positive margins are carried out before the full extent of the disease burden is understood. A staging CE-MRM examination showing only a single cancer lesion may permit the patient to choose conservation therapy with a degree of confidence that no macroscopic disease will be missed at surgery [34]. About our false positives, as yet explained above, the pathologic reports described four cases of ADH, and two cases of LIN 1. In women with ADH a review of literature suggests a 4- to 5-fold increased risk of invasive breast cancer, compared with a 6- to 10-fold risk ALH/LIN [35]. With regard to lobular neoplasia, the subsequent invasive cancer may be ipsilateral or contra lateral, and more than 50% of these diagnoses occur more than 15 years after the original diagnosis of lobular neoplasia [36, 37]. Thus, in our opinion, the excision of these lesions that were considered clinical risk factors of breast cancer was absolutely correct.

Therefore, if we believe that it is important to clear lumpectomy margins of breast disease (from atypical hyperplasia to in situ and microinvasive carcinoma) to reduce the risk of local recurrence, it should follow that small foci in both breast detected on CE-MRM also warrant identification and excision.

After a median followup of 36 months, we reported 5/118 (4.2%) versus 15/407 (3.7%) (NS) local recurrences in women with converted surgery, compared with patients with any change of treatment (Figure 2). However, the two populations differed as regard the metastatic risk, so much as to be able to undo the effect of possible local benefit. In our series, we observed higher rates of larger cancers > pT1 (39/118, 33.0% versus 92/407, 22.6%) and of nodal involvement (58/118, 49.1 versus 144/407, 35.4; $P < .0001$) in cases with modified versus unmodified surgery. This condition could carry out the higher rate of distant recurrences. In fact, we observed up to this time 9/118 (7.6%) events in former group versus 11/407 (2.7%) in the latter. These few events do not allow us to distinguish any subgroup of risk, that is multicentricity versus larger size of tumour. Kaplan-Meier survival analysis showed both curves overlapping around 97% at 5 years (Figures 3-4). As reported elsewhere [12], larger tumour size is an independent factor of a beneficial change in surgical management of newly diagnosed breast cancer in patients who undergo CE-MRM (odds ratio 1.66; 95% C.I., 1.04–2.66) [12].

Anyway, before to say that CE-MRM have little or no impact on local recurrence rate and on survival rate, because women are at higher risk of distant metastases, the number of observations and the followup should be implemented.

5. Conclusions

The use of CE-MRM results in a beneficial change in surgical management in 99/525 (18.8%) of patients. Additional malignant lesions are detected in about one patient every five who undergo CE-MRM.

These data suggest that CE-MRM plays a role in the staging evaluation of newly diagnosed breast cancers.

Our experience confirms that, when needle-biopsy was missed, the suspiciousness of CE-MRM-imaging findings was not sufficient to advise a change in surgical planning (six high suspicious CE-MRM-detected lesions without preoperative histological confirmation resulted benign after surgery). Thus, we conclude that guided needle biopsy is always recommended to verify additional CE-MRM-detected lesions.

This study has some limitation to be addressed. It is a retrospective report of consecutive patients with a proven diagnosis of newly breast cancer. The number of patients is quite large, but the median followup is not so long to make firm statistical conclusions.

Therefore, future research is mandatory to explore the value of CE-MRM in the improvement of surgical outcome and prognosis by decreasing the need for reoperation and lowering recurrent rates.

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Research Article

Image-Based Treatment Planning of the Post-Lumpectomy Breast Utilizing CT and 3TMRI

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Accurate lumpectomy cavity definition is critical in breast treatment planning. We compared contouring lumpectomy cavity volume and cavity visualization score (CVS) with CT versus 3T MRI. 29 patients were imaged with CT and 3T MRI. Seven additional boost planning sets were obtained for 36 image sets total. Three observers contoured the lumpectomy cavity on all images, assigning a cavity visualization score (CVS) of 1 to 5. Measures of consistency and agreement for CT volumes were 98.84% and 98.62%, for T1 MRI were 95.65% and 95.55%, and for T2 MRI were 97.63% and 97.71%. The mean CT, T1 MRI, and T2 MRI CVS scores were 3.28, 3.38, and 4.32, respectively. There was a highly significant difference between CT and T2 scores ($P < .00001$) and between T1 and T2 scores ($P < .00001$). Interobserver consistency and agreement regarding volumes were high for all three modalities with T2 MRI CVS the highest. MRI may contribute to target definition in selected patients.

1. Introduction

Definition of the lumpectomy cavity is a critical step in treatment planning for irradiation of the intact breast, breast boost, and for partial breast irradiation. Multiple studies have shown the limitations of single modality imaging with interobserver differences in lumpectomy cavity definition [1–4]. CT-based imaging is commonly used for breast treatment planning; but the limited soft tissue contrast of CT can result in poor visualization of the lumpectomy site in patients with dense breast parenchyma, small lumpectomy cavities, or a prolonged delay between surgery and treatment planning [2, 3]. MR imaging provides superior soft tissue contrast and may provide clearer visualization of the lumpectomy cavity. Although the diagnostic role of MRI in breast cancer management is expanding, MRI is rarely used as an imaging modality in post-lumpectomy radiation therapy planning. We compared contouring of the lumpectomy cavity volume and cavity visualization score (CVS) based on CT imaging compared to 3 Tesla magnetic resonance imaging, (3T MRI).

2. Methods and Materials

This is an IRB-approved retrospective review of treatment planning imaging obtained for breast cancer patients following breast conserving surgery.

From September 2008 to July 2009, 29 patients referred for intact breast irradiation had breast imaging performed using both CT and noncontrast 3T MRI. Of these, seven patients had repeat CT and MRI performed at the time of boost planning, providing 36 image sets. Sixteen patients did not receive chemotherapy. The average interval between surgery and image acquisition for this group was 28 days (range 14–52).

Eleven patients received postoperative adjuvant chemotherapy prior to radiation. The average interval between surgery and image acquisition was 137 days (range 68–206) for this group.

Two patients had neoadjuvant chemotherapy followed by surgery, then radiation. The surgery-image intervals of these 2 patients were 38 and 57 days.

Table 1: Patient and imaging data.

	Median	Range
Age (years), $N = 29$	56.9	38–76
Interval from surgery to image acquisition (days), $N = 29$		
No chemotherapy $N = 16$	28	14–52
Adjuvant postoperative chemotherapy $N = 11$	137	38–206
Neoadjuvant chemotherapy-before surgery $N = 2$	47.5	38–57
Lumpectomy volume (cc) (Average of 3 contourers)		
CT ($n = 36^*$)	43.88	4.36–239.85
T1 MRI ($n = 36$)	40.94	4.51–285.97
T2 MRI ($n = 28$)	35.18	5.02–176.76

$^*n = 29$ *patients with 7 boosts*

All 36 image sets included a CT and T1 MRI. 28 image sets also included a T2 MRI. CT scans were performed with patients in the supine treatment position, both arms extended above the head on a commercial arm board, with wires defining the breast and scars. A noncontrast MRI was performed immediately afterward in the same position. MRI scans were obtained with a 3T Scanner (Siemens TRIO TIM) using a flexible six-element body RF matrix coil. The coil was placed over the patient's chest in the supine position. The 3D T1 weighted images were acquired using VIBE (Volumetric interpolated breath-hold exam) sequence with TR/TE: 3.37/1.23 ms, 1 NEX at $2.4 \times 2.0 \times 2.0$ mm spatial resolution in parallel imaging mode (acceleration factor of 2) yielding 104 slices in 0.21 minutes. T2 weighted images were obtained using a 2D Turbo spin echo sequence with TR/TE: 6440/127 ms, 3 NEX at $2.1 \times 1.6 \times 3.0$ mm resolution with acceleration factor of 2 yielding 30–56 slices in 6.02 minutes. Image distortions resulting from gradient field nonlinearity were corrected using a vendor supplied 3D distortion algorithm, which compensates for slice curving effects in addition to in-plane distortions. The distortion corrected images were imported into the treatment planning system (TPS).

The MR images, as they do not contain the intrinsic electron density information of tissues required for radiation therapy planning, were registered/fused with CT images in a two-step process. First, a coarse registration was achieved using a manual interactive registration tool available with the TPS (Pinnacle^3 RTP, Phillips Medical Systems (Cleveland), Inc., Fitchburg, WI, USA), which permits rigid-body transformations (translations and rotations) on the secondary image set (MRI) along and about the three major axes of the primary (CT). Second, an automatic Local Correlation (LC) registration algorithm (available with Syntegra registration module of Pinnacle^3 RTP) was applied to further enhance the accuracy. The visualization tools-sliding window and/or checkerboard were used to verify the clinical accuracy of the fusion process.

Table 2: Cavity visualization score (CVS).

CVS	Description
1	Cavity not visualized
2	Cavity visualized but margins indistinct
3	Cavity visualized with some distinct margins
4	Cavity with majority of margins distinct
5	All margins clearly seen

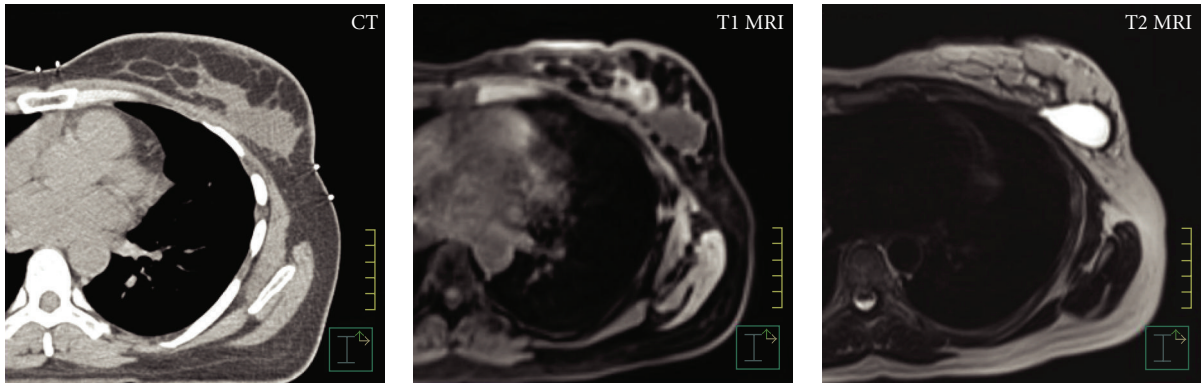
Three observers, a radiation oncologist, a dosimetrist, and a radiation oncology resident independently contoured the lumpectomy cavity on CT and MRI images (Table 1). Surgical clips were occasionally, but not routinely, placed in these patients by referring surgeons. When present, clips were contoured independently as clips, not as part of the lumpectomy cavity. Contourers outlined the visible seroma cavity/tumor bed on CT. Associated stranding was not contoured. For T1 and T2 MRI, the contourers outlined the outermost contour of the boundary between tumor bed and breast tissue. Measures of consistency and agreement between observers for CT volume and MRI volume were evaluated by the Intraclass Correlation Coefficient (ICC) obtained from a random effect ANOVA model. All patients had CT and T1 MRI scans; 28 had an additional T2 MRI scan. Statistics are based on comparing CT images with T1 and T2 MRI images. The observers assigned each image a cavity visualization score (CVS) of 1 (cavity not visualized) to 5 (all cavity margins clearly defined), see Table 2 (1).

3. Results

Measures of consistency and agreement for CT volumes were 98.84% and 98.62%. Measures for T1 MRI were 95.65% for consistency and 95.55% for agreement. Measures for T2 MRI were 97.63% for consistency and 97.71% for agreement. There was a strong and significant agreement between observers. Observations do not differ much in assessment between CT and MRI. However, there was a significant difference in the perceived quality of the image measured by cavity visualization score (CVS), see Figure 1. The mean CT, T1 MRI, and T2 MRI scores were 3.28, 3.38, and 4.32, respectively. Analysis of variance (one-way ANOVA) was used to compare all three CVS at once. There was a significant difference between the scores (P value $< .0001$). Pairwise comparisons showed no significant difference between CT scores and T1 scores ($P = .43$). There was a highly significant difference between CT and T2 scores ($P < .00001$) and between T1 and T2 scores ($P < .00001$). Surgical clips, when present, are easily seen on CT. They can sometimes be visualized on T1 MRI by signal void, as seen in Figure 2.

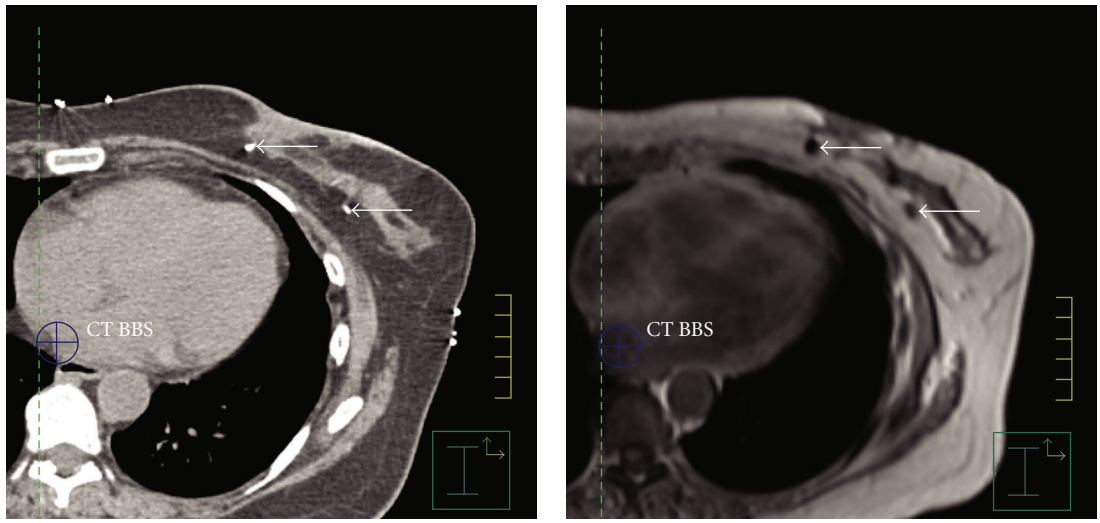
4. Discussion

Breast conservation therapy with tumor directed surgery followed by whole breast radiation has been an accepted management of invasive breast cancer for several decades.



(a) (b) (c)

Figure 1: Comparison of imaging modalities. (a) CT shows homogeneous gray area. Borders are distinct laterally. Medially, the borders between lumpectomy cavity and breast parenchyma and chest wall are poorly defined. CVS 3. (b) T1 MRI, noncontrast, shows cavity with fairly well-defined borders, some rim enhancement. CVS 4. (c) T2 MRI noncontrast shows hyperintense signal consistent with seroma, distinct margins. CVS 5.



(a) (b)

Figure 2: (a) Biopsy clips visible on CT. (b) Biopsy clips seen as signal void on T1 MRI.

Recent trends in radiation oncology have focused on image-based planning for the majority of disease sites including breast cancer. The first step in image-based treatment planning of the intact breast following breast conserving surgery is accurate identification and contouring of the target volume. Most series related to boost definition and partial breast radiation therapy have defined the post-lumpectomy site as the volume on which subsequent planning is based. Numerous studies have demonstrated that there is a great deal of variability and uncertainty in this critical first step. The ability to identify the lumpectomy cavity varies from patient to patient. Several factors, including breast density, interval between surgery and image acquisition, and the volume of the lumpectomy cavity, can present challenges in distinguishing the lumpectomy site from the normal breast with CT images. In a few instances, particularly when several cycles of chemotherapy are delivered between lumpectomy and initiation of radiation, the site of the lumpectomy cavity cannot be identified. Even when visible, postoperative stranding, borders between the lumpectomy site and chest wall or skin, and dense breast parenchyma can obscure the borders of the lumpectomy cavity. In addition to the challenges in identification of the lumpectomy site, several studies have shown interobserver differences in contouring radiation target volumes [5–7]. Rates of discordance in interobserver studies have conformity indices approaching 50% [2, 8]. An RTOG multi-institutional and multiobserver study showed clinically significant differences in target and organ at risk delineation for breast irradiation, with some structure overlaps as low as 10% and volume variations with standard deviations as high as 60% [9].

MRI has improved soft tissue characterization compared to CT and is used in breast cancer screening and presurgical evaluation. As a screening modality, breast MRI has been found to have a sensitivity of 93–100% [10, 11]. In a single institutional retrospective study, presurgery breast MRI changed breast cancer surgical management in 9.7% of newly diagnosed cases [12]. Although MRI has a high resolution and sensitivity in breast tissue, it has not been widely used in radiation therapy treatment planning. Reasons may include lack of access, cost, and lack of data on the utility of MRI imaging for this purpose. In addition, there are issues related to patient position, soft tissue deformation, and spatial accuracy. Ahn et al. designed an MRI imaging protocol for treatment planning with the patient in a prone position and demonstrated adequate contrast and spatial fidelity [13]. Whipp and Halliwell obtained postoperative MRIs in 100 randomly selected breast cancer patients [14]. The images were obtained in a single open MRI scanner using the conventional breast radiotherapy treatment position, without contrast, prior to routine two-dimensional simulation. MRI results were qualitatively different from CT and ultrasound cavities described in the literature. 85% of the MRI volumes were described as heterogeneous, 9% were described as homogeneous. 88% were described as complex/cystic and 5% as simple cystic. Regular concentric rings of differing signal were seen within the postoperative complex in 32% of scans. The postoperative complex was in contact with the chest wall in 53% of patients. A follow-up study by this group reported on local recurrence rates after MRI-assisted radiotherapy planning [15]. The lumpectomy site, described as the postoperative complex (POCx) was visible on MRI of all 221 patients. MRI imaging was used in the context of conventional treatment planning and altered the standard field margins in 69% of patients.

The University of Iowa Hospital and Clinics Department of Radiation Oncology has a 3T MRI device present in the department for treatment planning. Although diagnostic breast MRI is usually obtained in a prone position, we preferred to continue our treatment planning and treatment delivery in the supine position. Many of our patients have a BMI greater than 30 and would be uncomfortable in a prolonged prone position. Image acquisition at 3T using surface coils combined with the parallel imaging approach resulted in an improved SNR and adequate coverage. Since the MRI was obtained for treatment planning and not for diagnosis, we did not use contrast. We used a surface coil and found minimal deformation of breast tissue. Obtaining the noncontrast T1 and T2 images adds an additional 16 minutes to the treatment planning time. As described above, the MRI images provided a greater detail than the CT images, showing heterogeneous cavities and concentric rings of granulation tissue. The lumpectomy cavity is identified by a bright signal on the T2 image and shows clear demarcation between seroma and normal tissue. In this study, the T2 images provided the best cavity visualization score, which was significantly better than that of the CT or T1 MRI. MRI, particularly T2 MRI, better demarcated the interface between seroma and chest wall, seroma and skin, and distinguished between seroma and dense breast parenchyma (Figure 1).

5. Conclusion

MRI provides more detailed visual information than CT in the post-lumpectomy breast. In patients with difficult to visualize cavities, the addition of MRI images to CT treatment planning may contribute to improved target volume definition. In our experience, a noncontrast MRI image can be obtained in the supine treatment planning position in a reasonable period of time during the treatment planning session.

Conflict of Interests

The authors declare that no conflict of interest or potential conflict of interest exists.

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Review Article

Oncoplastic Approaches to Breast Conservation

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When a woman is diagnosed with breast cancer many aspects of her physical, emotional, and sexual wholeness are threatened. The quickly expanding field of oncoplastic breast surgery aims to enhance the physician commitment to restore the patient's image and self-assurance. By combining a multidisciplinary approach to diagnosis and treatment with oncoplastic surgery, successful results in the eyes of the patient and physician are significantly more likely to occur. As a way to aid oncoplastic teams in determining which approach is most suitable for their patient's tumor size, tumor location, body habitus, and desired cosmetic outcome we present a review of several oncoplastic surgical approaches. For resections located anywhere in the breast, the *radial ellipse segmentectomy incision* and *circumareolar approach for segmental resection* are discussed. For resections in the upper or central breast, *crescent mastopexy*, the *batwing incision*, the *hemibatwing incision*, *donut mastopexy*, *B-flap resection*, and the *central quadrantectomy* are reviewed. For lesions of the lower breast, the *triangle incision*, *inframammary incision*, and *reduction mastopexy* are discussed. Surgeons who are interested in adding oncoplastic breast conserving therapies to their skill sets are encouraged to implement these surgical techniques where applicable and to seek out breast fellowships or enhanced training when appropriate.

1. Introduction

The diagnosis of breast cancer is a life-changing experience. Not only does it bring the woman face to face with her mortality, but also surgical treatment of breast cancer is accompanied by physical changes to the breast and body that may significantly, and often permanently, alter her perception of her physical, emotional, and sexual wholeness.

Since the Early Breast Cancer Trialists' Collaborative Group established the equivalency of mastectomy and breast conserving therapy in 1985, breast conserving surgery has remained the optimal surgical treatment for the breast cancer patient [1]. The goals of breast conserving surgery are the removal of breast cancer with an adequate surgical margin and maintenance of a breast that is cosmetically acceptable to the patient. Mastectomy with or without breast reconstruction is the treatment of choice when tumor resection and cosmesis is unattainable. Given the understandable desire to preserve a sense of wholeness, it is not surprising that many women consider mastectomy to be an unacceptable cosmetic alternative to breast conserving surgery.

Increasing use of mammographic screening and neoadjuvant chemotherapy has rendered 70–80% of breast cancer patients as potential candidates for breast conserving surgery (BCS). Nonetheless, BCS remains highly underutilized, with nearly 50% of women either selecting or being advised to undergo mastectomy [2]. Although underutilization of BCS may partly reflect limited access to radiotherapy or the patients' desire to minimize the risk of local recurrence, surgeon judgment is of paramount importance in assessing the potential for cosmesis. In addition, aesthetic success in BCS is dependent upon a variety of patient- and tumor-specific factors. Small breast size, ptotic breast shape, large body habitus, large tumor size, central, medial, or lower quadrant tumor location, segmental or multifocal tumor distribution, tumor re-excision, and resection of >20% breast volume have all been identified as predictors of poor cosmesis [3, 4].

The goal of optimizing the cosmetic and oncologic outcomes of BCS has been addressed in recent years by the emergence of the field of oncoplastic surgery. Originally defined as an assortment of volume replacement techniques performed by plastic surgeons to replace all or part of the resected breast volume with myocutaneous tissue flaps, the definition of oncoplastic surgery has more recently been expanded to include a wide range of volume displacement or volume redistribution procedures performed by breast surgeons and general surgeons to optimize breast shape and breast volume following breast cancer surgery [5–9]. Also included in the definition of "oncoplasty" is the surgical correction of breast asymmetry achieved by reducing or reconstructing the contralateral breast. The emergence of oncoplastic surgery reflects a growing appreciation for the importance of breast cosmesis and the willingness of many surgeons to obtain advanced training to improve cosmetic outcomes for their patients. Thus, the traditional emphasis on scar placement (i.e., Langer's lines and Kraissl's lines) and skin preservation is gradually being replaced or complimented by an appropriate emphasis on breast shape, volume, and symmetry. While traditional volume replacement oncoplastic procedures (e.g., myocutaneous flap reconstruction) remain beyond the skill set of most oncologic surgeons, a wide range of volume displacement procedures are relatively easy to learn and can be gradually incorporated into an oncologic surgery practice.

2. Multidisciplinary Approach

Oncoplastic surgery requires a multidisciplinary approach to breast cancer care characterized by close collaboration between the breast surgeon, radiologist, radiation oncologist, and, when appropriate, plastic surgeon, medical oncologist, genetic counselor, and psychologist all working together to help the patient achieve the best possible surgical outcome [10]. The general requirement for adjuvant radiotherapy calls for coordination with the radiation oncologist. The timing of surgery should also be coordinated with the medical oncologist for patients receiving neoadjuvant chemotherapy or endocrine therapy. Genetic counseling and psychoanalysis should facilitate treatment planning (e.g., contralateral prophylactic mastectomy) and psychological well-being. Upon making a decision that breast conservation is achievable and desirable, the definite approach to management of the index and contralateral breast is selected by consensus between the surgeon, patient, and plastic surgeon. Accurate diagnostic evaluation and lesion localization should be planned with the radiologist.

3. Management of the Contralateral Breast

Breast asymmetry resulting from BCS can be managed with contralateral breast reduction or mastopexy to restore breast symmetry. Symmetrization surgery can be performed at the time of BCS, at a second operation, or may be indefinitely deferred, depending on the interests of the surgeon, the patient's wishes, the clinical setting, and the availability of plastic surgery expertise [11]. The timing of contralateral breast surgery is controversial owing to concerns about surgical margins and the potential need for re-excision or conversion to mastectomy, changes in breast volume following radiotherapy, and breast edema resulting from breast or axillary surgery.

4. Before Getting Started: General Principles

Since oncoplastic procedures may offer the patient her best or last chance of achieving cosmetic success, oncoplastic surgeons must accept a heightened responsibility to achieve oncologic success at the initial breast operation. Inadequate surgical margins not only compromise the oncologic outcome, but breast re-excision may diminish an initially aesthetic result, increase breast asymmetry, or necessitate conversion to mastectomy. To improve the odds of initial success, surgeons contemplating an oncoplastic approach should adhere to the following recommendations.

4.1. Restrict Oncoplastic Surgery to Definitive Care. Oncoplastic surgical procedures should be reserved for definitive therapeutic management of the diagnosed breast lesion. For undiagnosed patients, diagnostic biopsies should be obtained using minimally invasive breast biopsy techniques (e.g., core needle biopsy) to avoid extensive surgery in patients with benign breast conditions that may not require surgical excision. Limiting oncoplastic surgery to the therapeutic management of breast cancer also avoids removal of excess breast tissue or placement of surgical incisions that may jeopardize the perfusion of subsequent glandular or dermoglandular tissue flaps [12]. In the event that surgical excision is required for diagnostic purposes (e.g., for radial scar, atypical ductal hyperplasia, or papillary lesions), incision placement should anticipate the potential use of oncoplastic techniques in subsequent procedures.

4.2. Apply Radiopaque Markers to Surgical Margins. The cornerstone of oncoplastic breast conserving surgery is the mobilization and redistribution of the breast gland to reconstruct the breast mound. Since nearly all patients are expected to undergo adjuvant radiotherapy and infrequently re-excision, placement of multiple radiopaque tissue markers (e.g., Hemoclips) along the surgical margins should be performed to facilitate radiation planning, margin re-excision, and subsequent mammographic surveillance [13].

4.3. Use Multiple Bracketing Wires. Wire localization of nonpalpable or indistinct lesions using multiple bracketing wires is recommended to clearly define the lesion and the desired surgical margins. Placement of only a single wire through the center of the lesion should be avoided for larger lesions as it increases the probability of close or positive margins [14, 15]. Optimal wire localization should include placement of localizing wires on either side of a lesion (e.g., cranial and caudal or medial and lateral), but placement of an additional wire superficial to a lesion may also be used when preservation of the overlying skin is planned. Having the

radiologist mark the skin overlying a nonpalpable lesion will also aid the surgeon in honing in on a lesion and reduces the need for excessive tunneling through the breast parenchyma.

4.4. Utilize Intraoperative Ultrasound for Sonographically Apparent Lesions. Intraoperative ultrasound is recommended for surgeons who are experienced in the use and interpretation of breast ultrasound [16, 17]. The value of intraoperative ultrasound for oncoplastic surgical resection is most apparent when approaching a lesion from the posterior aspect of the breast, such as in the inframammary approach, where direct visualization of the lesion from the posterior surface of the breast eliminates the need to triangulate its location based on skin markings or localizing wires entering the anterior surface of the breast. Intraoperative ultrasound, used alone or in conjunction with wire localization, can also improve the width of surgical margins and minimize the removal of excessive breast tissue [18].

4.5. Consider Breast MRI to Evaluated Disease Extent. There is considerable ongoing controversy regarding the value for contrast-enhanced breast MRI in the preoperative planning of breast cancer surgery [19, 20]. Although there is growing evidence that MRI may not alter the re-excision rate after breast conserving surgery, the breast reshaping or remodeling that occurs in oncoplastic breast surgery makes it imperative to obtain clear surgical margins at the initial operation. For this reason, there may be greater rationale for performing preoperative contrast-enhanced breast MRI in oncoplastic surgery [21]. Nevertheless, the sensitivity of contrast-enhanced MRI and the potential for false positive findings necessitate histological confirmation of MRI findings (ideally with ultrasound or MRI-guided core needle biopsy) before significantly altering the oncoplastic approach or converting to mastectomy.

4.6. Using a Surgical Drain. Contrary to the lumpectomy patient where seroma formation transiently preserves breast contour, the goal of oncoplastic surgery is to provide durable volume reconstruction by redistributing the breast parenchyma. Since large potential spaces are created in performance of oncoplastic surgery, a surgical drain may be considered to prevent accumulation of a large seroma that might complicate wound healing and recovery by exerting excessive tension on the breast and incision.

4.7. Orient the Surgical Specimen. Accurate orientation of the surgical specimen is essential to ensuring quality of breast cancer care. Nowhere is this more important than in oncoplastic surgery, where failure to accurately orient the surgical specimen may necessitate wide re-excision of close or positive margins, compromising the cosmetic outcome and possibly requiring conversion to mastectomy [22].

4.8. Obtain Intraoperative Pathology Consultation. The importance of attaining clear surgical margins at the initial resection cannot be overemphasized in oncoplastic surgery. To lower the risk of oncologic failure, surgeons should liberally utilize intraoperative pathology consultation including gross and frozen section analysis of surgical margins and specimen radiography [23]. If margin re-excision is required, re-excision of the entire affected margin should be performed to ensure that the new final margin mirrors the entire original surgical margin.

4.9. Preserve Sensation of the Nipple-Areolar Complex. The lateral cutaneous branch of the fourth intercostal nerve is the predominant source of sensory innervation for the nipple-areolar complex and maintains a relatively constant course through the breast [24]. In the left breast, the nerve generally exits the chest wall at the lateral border of the pectoralis minor, enters the posterior-lateral surface of breast at approximately the 4 o'clock position, and then traverses the glandular tissue to the inner areola along the 5 o'clock axis. In the right breast, the nerve generally enters the posterolateral surface of the breast at the 8 o'clock position and traverses the gland to enter the right areola along the 7 o'clock axis. Avoiding the trajectory of these nerves, particularly when performing circumareolar incisions and advancement flaps, will preserve nipple-areolar complex sensation and improve the quality of life of breast cancer patients.

4.10. Obtain Preoperative and Postoperative Photos. Documentation of the preoperative appearance and postoperative results of oncoplastic surgery will help the surgeon evaluate and improve his or her results over time. In addition, the confidential sharing of these photos with prospective patients will give them a clearer understanding of what they may expect from oncoplastic surgery.

5. Patient Selection

Oncoplastic surgical procedures may be used for a wide range of breast cancer patients to achieve resection of breast cancers with acceptable and improved breast appearance. Figure 1 shows a list of selected oncoplastic approaches to BCS that may be performed by general surgeons and breast surgeons with appropriate training. Choosing the best operation for a given patient depends upon her tumor features, breast size and shape, and the surgeon's skill. Omitted from this paper are the oncoplastic breast surgery procedures that involve the use of a myocutaneous tissue flap (e.g., latissimus dorsi miniflaps) since these procedures will likely remain beyond the skill set of most general and breast surgeons.

6. The Advancement Flap

The advancement flap or adjacent tissue transfer is a fundamental technique common to all volume displacement oncoplastic procedures and should be mastered by any surgeon seeking to incorporate oncoplastic surgery in his or her surgical practice. The advancement flap is performed by dividing the retromammary fat plane posterior to the breast at the level of the muscular fascia to allow mobilization and

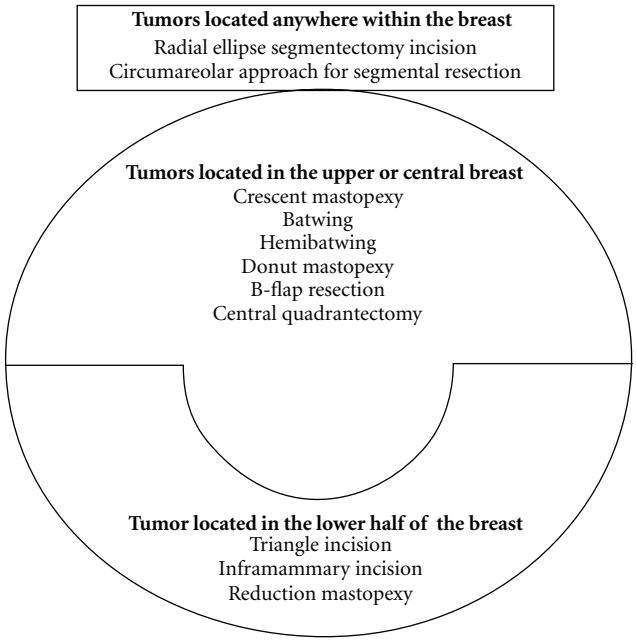


Figure 1: List of oncoplastic breast conserving procedures discussed in this paper, organized by tumor location.

displacement of the breast gland relative to the underlying pectoralis major muscle and chest wall. This technique is most easily practiced in conjunction with the segmentectomy incision, in which skin, parenchyma, and pectoralis fascia surrounding a cancer are excised en bloc, followed by mobilization and redistribution of the adjacent dermoglandular tissue to obliterate the resulting surgical cavity. In dissecting the retromammary fat plane, care should be taken to preserve most of the medial and lateral perforator blood vessels that are important to supporting the dermoglandular tissue flaps. While the breast's redundant blood supply generally lends itself to wide mobilization and undermining, injudicious division of perforating vessels may devascularize glandular or dermoglandular flaps, causing partial or complete flap loss. Extensive mobilization of fatty or elderly breasts may also increase the risk of fat necrosis.

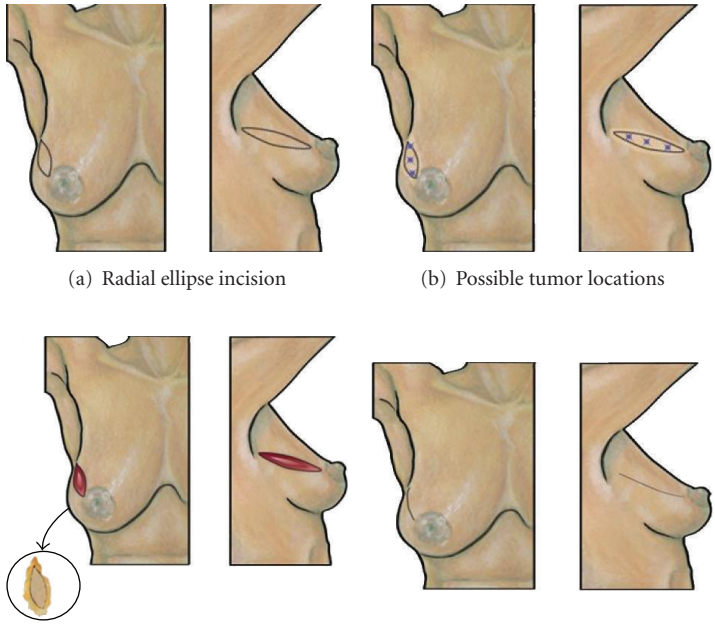
7. Tumors Located Anywhere within the Breast

7.1. Radial Ellipse Segmentectomy. The *radial ellipse segmentectomy* is a versatile procedure that can be used to resect a breast cancer located in any quadrant of the breast [12, 25, 26] (Figure 2). The specimen consists of an ellipse of skin, glandular tissue, and the underlying pectoralis fascia and is an ideal approach for resection of lesions lying adjacent to the skin or chest wall or extending radially toward the nipple. The width of the incision is designed to provide sufficient anterior margin clearance for a superficial lesion. For deep lesions, a narrower skin margin reduces skin removal. As an elliptical incision, the length of the ellipse is generally 3 times the width. The width and length of the glandular component generally approximate the dimensions of the skin margin, with emphasis placed on maintaining a macroscopic glandular margin of 1 cm or more to maximize the potential for microscopically clear margins. Attention should be paid to maintaining a glandular dissection plane relatively perpendicular to the skin surface to avoid unintended widening or narrowing of the specimen as the dissection extends posteriorly through the gland. Avoiding excessive retraction of the highly mobile breast gland can prevent inadvertent tangential dissection through the glandular tissue.

To prepare for wound closure, full-thickness dermoglandular advancement flaps are created by undermining the gland perpendicular to the long axis of the segmentectomy cavity. The degree of undermining depends upon the width of the surgical cavity and should be assessed intermittently by briefly approximating the surgical margins to determine if full-thickness wound closure can be accomplished without excessive tension. Minimal undermining is needed at the two apices of the elliptical cavity since these areas may not require mobilization for wound closure. Full-thickness wound closure is initiated by approximating the long axis of the surgical margins using 2–0 or 3–0 interrupted absorbable sutures placed at the posterior aspect of the glandular tissue, followed by placement of 1 or 2 additional suture layers to close the middle and anterior depth of the glandular tissue. If glandular dissection extended posterior to the nipple-areolar complex, special attention should be given to achieving an adequate full-thickness closure of the central and retroareolar tissue to prevent nipple-areolar complex retraction into an underlying cavity. Wound closure is completed by approximation of the skin in one or two layers using small gauge absorbable sutures.

The oncological advantages of the radial ellipse segmentectomy and advancement flap should be readily apparent: resection of skin makes a close or positive superficial margin irrelevant oncologically and excision of the pectoralis fascia eliminates the need for re-excision of a close or positive deep margin. The obvious disadvantages of this surgical approach (i.e., removal of proportionally more breast tissue near the apices of the ellipse resection and the need for longer incisions) are largely overcome by the advantage of reconstructing the breast mound and expanding the options of breast conserving surgery for patients who may be unsuitable candidates for the standard lumpectomy incision. This approach also minimizes the breast deformity commonly produced by resection of tumors from the central, medial, and inferior quadrants. Use of the radial ellipse segmentectomy is generally discouraged for resection of upper inner quadrant lesions where the resulting scar would be visible in the cleavage or above the bra.

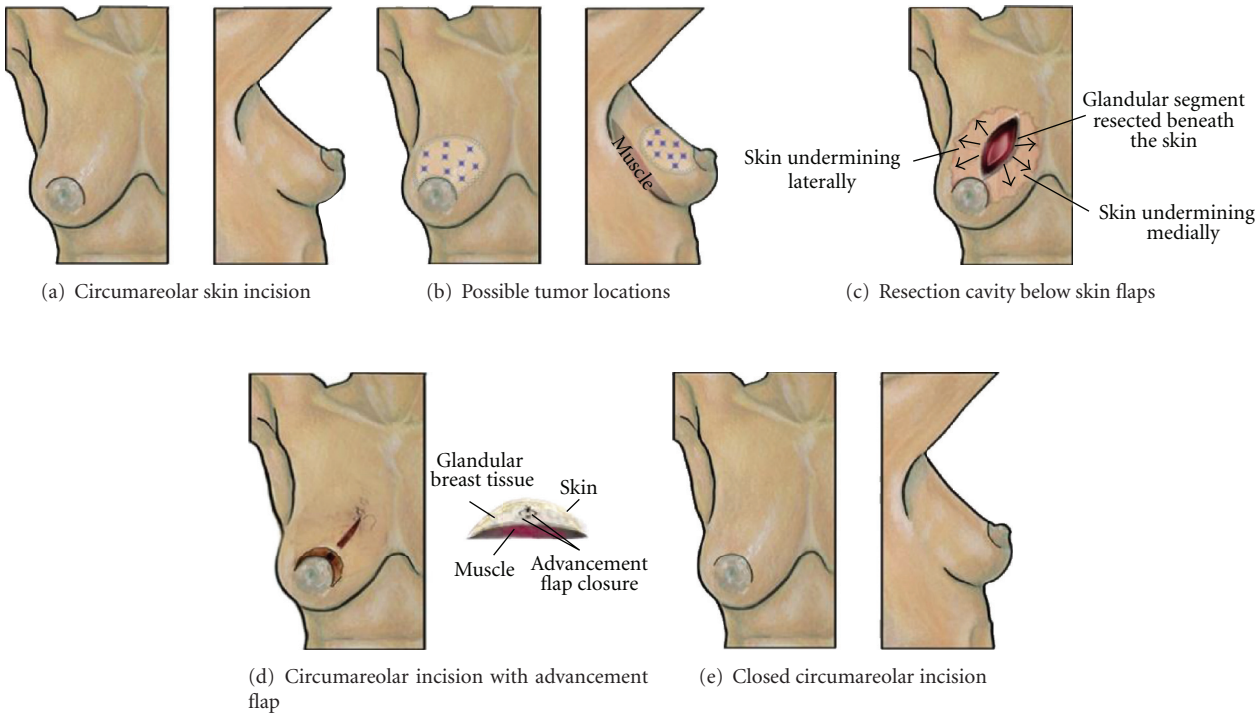
7.2. Circumareolar Approach for Segmental Resection. The *circumareolar approach for segmental resection* is a useful alternative to the radial ellipse segmentectomy when a radially oriented scar is undesired, such as in the upper inner quadrant of the breast (Figure 3). However, this versatile approach may be performed in any quadrant of the breast. Since the circumareolar approach fully preserves the skin overlying the lesion, this method should be restricted to resection of breast cancers that do not approximate the



(a) Radial ellipse incision (b) Possible tumor locations

(c) Radial ellipse resection cavity and specimen (d) Closed radial ellipse incision

Figure 2: Radial ellipse segmentectomy. (a) Shows location of radial ellipse segmentectomy skin incision in upper outer quadrant. (b) Shows multiple "stars" indicating possible tumor locations suitable for this approach. (c) Shows resection cavity following excision of malignancy with excised specimen (inset). (d) Shows breast following closure of the skin incision.



(a) Circumareolar skin incision (b) Possible tumor locations (c) Resection cavity below skin flaps

(d) Circumareolar incision with advancement flap (e) Closed circumareolar incision

Figure 3: Circumareolar approach for segmental resection. (a) Shows location of circumareolar skin incision. (b) Shows multiple "stars" indicating possible tumor locations suitable for this approach. (c) Shows lumpectomy cavity after segmental resection of breast glandular tissue only with arrows denoting the extent of undermining of the overlying skin flap. (d) Shows results of glandular flaps advancements that allow the medial and lateral margins to be sutured together below the skin flap. Frontal and transverse views are shown. (e) Shows breast following closure of the circumareolar incision.

skin to minimize the risk of a positive superficial margin. With skin preservation, the surgical specimen consists of an elliptical or wedge-shaped mass of glandular tissue and the underlying pectoralis fascia. Placement of localizing wires superficial to, as well as on either side of, a nonpalpable lesion will improve margin clearance.

Before beginning the procedure, the location of the lesion is marked on the overlying skin as a reference and the adjacent areolar margin is outlined to indicate the incision placement. A circumareolar incision extending up to 1/3 the circumference of the areola usually provides sufficient access for tumor resection of smaller tumors in patients with medium to large size areolas. Patients with small areolas or larger tumors are best managed using the *donut mastopexy* (*round block*) *resection technique*, which allows greater access to, and mobilization of, the breast gland [7].

The circumareolar approach for segmental resection is initiated by incising the areolar margin to enter the subcutaneous plane, which is then dissected widely over the quadrant of the breast containing the malignancy to create sufficient space for resection of the tumor with adequate margins. In general, the skin flap should extend from the areolar margin to the periphery of the breast and span a minimum of 25% of the breast surface area. Wider skin flap dissection is needed for larger breast resections. The surgeon should obtain an adequate superficial skin margin overlying the malignancy while also maintaining sufficient subcutaneous fat under the skin flap to ensure adequate skin perfusion. Placement of localizing wires superficial to the lesion will improve superficial margin clearance. An elliptical or wedge-shaped incision is then made in the breast parenchyma to encompass the breast malignancy and a gross margin of 1 cm or more. Localizing wires, if used, may be redirected below the skin flap to aid tumor resection. The parenchymal dissection is continued posteriorly until the underlying muscular fascia is encountered, and then dissection is extended posterior to the malignancy to remove the muscular fascia in continuity with the specimen.

Wound closure is accomplished by undermining and performing an advancement flap of the breast gland in a direction perpendicular to the long axis of the segmentectomy cavity. The extent of dissection of the retromammary fat plane should be sufficient to allow tension-free approximation of the surgical margins. Since only the glandular flaps are advanced independent of the overlying skin, widening of the skin flaps may be necessary to prevent skin tethering and to allow free and independent movement of the glandular flaps. The procedure is completed with a layered closure of the glandular tissue using loosely applied 2–0 or 3–0 interrupted absorbable sutures as to avoid tissue strangulation and necrosis. Layered skin closure is completed using smaller gauge absorbable sutures.

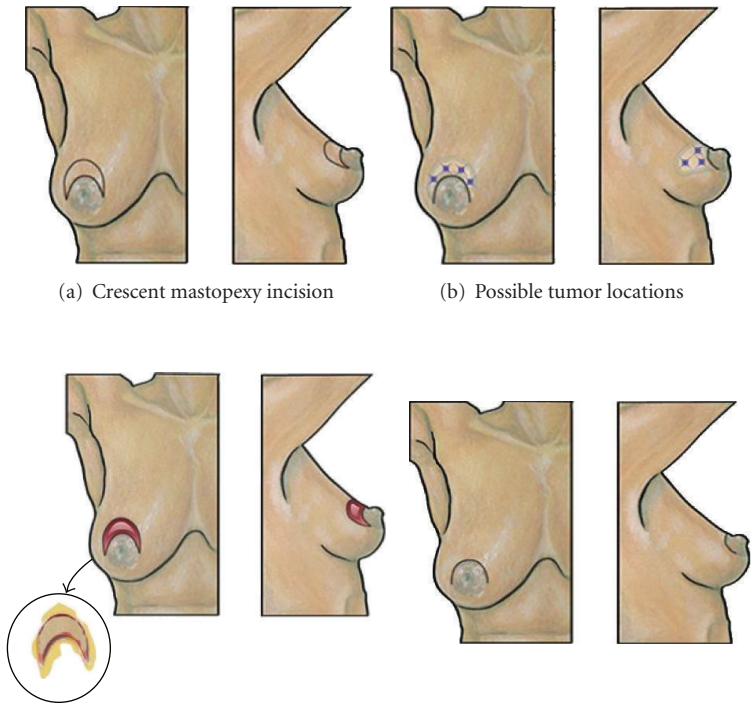
8. Tumors Located in the Upper or Central Breast

8.1. Crescent Mastopexy Resection. The *crescent mastopexy resection* allows removal of a cancer in the central breast superior to but not involving the nipple or areola (Figure 4) [27]. The ideal lesion location for the crescent mastopexy resection is the periareolar 10 to 1 o'clock position. Use of this procedure for more medial or lateral lesions will displace the nipple-areolar complex in a direction that is generally considered undesirable. The crescent mastopexy resection consists of a crescent-shaped area of skin and glandular tissue excised from the superior border of the areola, which has the effect of elevating the nipple-areolar complex and inferior breast and achieving mild correction of ptosis. As an alternative to the standard circumareolar incision, the principle oncological advantage of the crescent mastopexy resection is the removal of skin overlying a tumor in the superficial breast, thus ensuring a clear superficial margin.

The crescent mastopexy incision is designed by drawing two semiparallel "C-" shaped lines superior and adjacent to the areola, encompassing the skin immediately overlying a breast malignancy. The technical limitation to the crescent-shaped incision is the significant skin length disparity between the upper (longer) and lower (shorter) skin margins, which can be partly overcome during closure of the skin incision by taking larger horizontal suture bites along the longer skin margin and shorter vertical sutures bites along the shorter margin. This produces an areola with a slightly larger diameter. In general, breasts with larger areolas or smaller lesions size will be more accommodating of the crescent mastopexy approach. Smaller areolas or larger lesions may necessitate the use of the *batwing* or *hemibatwing resections*.

The procedure is performed with the breast centrally positioned on the pectoralis muscle. The skin and glandular tissue surrounding the breast malignancy are incised to resect the lesion and a wide gross margin. While extension of the dissection to the pectoralis muscle will facilitate wound closure for smaller breasts and larger lesions, dissection to the muscle is generally unnecessary in larger breasts where sufficient central breast volume allows simple approximation of the superior and inferior glandular margins. When small breast size or large lesion size call for full-thickness dermoglandular and pectoralis fascial resection, wound closure is accomplished by undermining the adjacent glandular tissue in the retromammary fat plane and advancement of the superior and inferior dermoglandular margins to permit layered closure of the glandular tissue and skin.

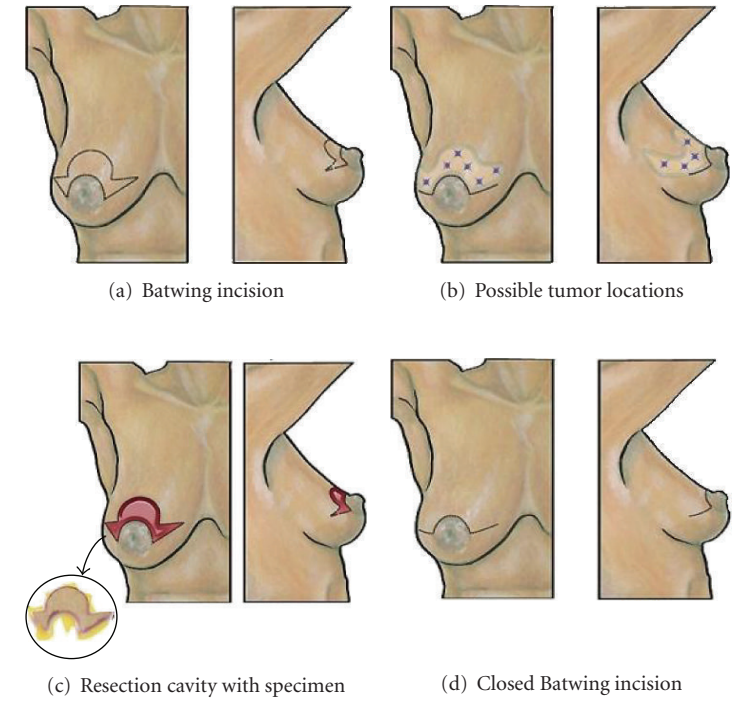
8.2. Batwing Resection. The *batwing resection* may be used as an alternative to the *crescent mastopexy resection* for wide excision of a breast malignancy located in the upper central aspect of the breast within a few centimeters of, but not directly involving, the nipple (Figure 5) [12, 27]. The batwing resection consists of a crescent-shaped central area of skin and gland adjoining 2 triangle-shape or wing-like areas of skin and gland extending from both sides of the areola. Similar to the crescent mastopexy resection, the batwing incision permits correction of breast ptosis by elevating the lower half of the breast and nipple-areolar complex. However, since the skin and glandular incision extends both medially and laterally to the nipple-areolar



(a) Crescent mastopexy incision (b) Possible tumor locations

(c) Resection cavity and specimen (d) Closed crescent incision

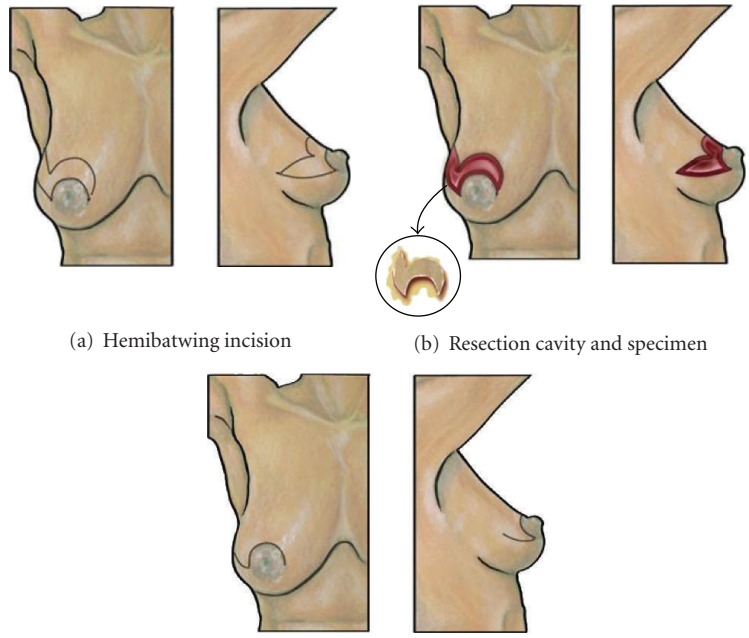
Figure 4: Crescent Mastopexy. (a) Shows location of crescent mastopexy skin incision. (b) Shows multiple "stars" indicating possible tumor locations suitable for this approach. (c) Shows resection cavity following excision of malignancy with excised specimen (inset). (d) Shows breast following closure of the skin incision.



(a) Batwing incision (b) Possible tumor locations

(c) Resection cavity with specimen (d) Closed Batwing incision

Figure 5: Batwing resection. (a) Shows location of batwing skin incision. (b) Shows multiple "stars" indicating possible tumor locations suitable for this approach. (c) Shows resection cavity of batwing resection with excised specimen (inset). (d) Shows breast following closure of the hemibatwing incision.



(a) Hemibatwing incision

(b) Resection cavity and specimen

(c) Closed hemibatwing incision

Figure 6: Hemibatwing resection. (a) Shows location of hemibatwing skin incision. (b) Shows resection cavity of hemibatwing resection with excised specimen (inset). (c) Shows breast following closure of the hemibatwing incision.

complex, the batwing incision also permits resection of a larger lesion that extends a few centimeters medial and/or lateral to the nipple-areolar complex. In addition, the large area of skin and glandular tissue that may be resected with the batwing resection allows for greater correction of ptosis than is possible with the crescent mastopexy resection. The cosmetic result is a smaller, less ptotic breast possessing two horizontal scars (at the 9-10 o'clock and 2-3 o'clock positions) connected by a less visible circumareolar incision at the upper half of the areola. A mastopexy of the opposite breast will correct breast asymmetry.

To perform the batwing resection, a batwing-shaped incision is drawn on the skin to encompass the skin overlying the breast malignancy. The lower half of the drawing should extend along the upper half of the areolar margin. The upper central edge of the batwing incision will ultimately become the new superior areolar margin. To prevent excessive lateral displacement of the nipple-areolar complex, the nipple should remain centered on a line extending from the native nipple location to the junction of the inner and middle thirds of the clavicle (approximately 8–10 cm from mid-sternal notch). This will move the nipple-areolar complex slightly more medial as it is moved to a higher position in the breast.

The batwing incision is performed with the breast positioned centrally on the pectoralis muscle. After planning the incisions, the skin and glandular tissue are incised and dissection is carried out posterior to the breast malignancy. Depending on the position of the lesion, the surgeon may bias the glandular resection in one direction or the other to gain greater clearance around the malignancy and to preserve glandular tissue where it may be advantageous to do so. For wound closure, the glandular tissues cranial and caudal to the resection cavity are advanced together to permit layered closure of the glandular tissue and skin with absorbable sutures.

8.3. Hemibatwing Resection. As its name suggests, the *hemibatwing resection* is similar to the *batwing resection* except that only one "wing" is excised (Figure 6) [27]. The optimal use of the hemibatwing resection is wide local excision of an upper outer quadrant periareolar lesion that extends along the 9-10 o'clock (right) or 2-3 o'clock (left) axis, where removal of skin, glandular tissue, and pectoralis fascia can optimize the surgical margins and provide mild correction of ptosis. Hemibatwing resections are less commonly used for medial quadrant lesions where an incision extending into the upper inner quadrant would leave a visible scar in the cleavage. Aside from these important distinctions, the hemibatwing resection is performed in a manner essentially identical to the batwing resection.

8.4. Donut Mastopexy Resection. The *donut mastopexy* or *round block technique* (Figure 7) allows generous access to any quadrant of the breast while confining the incision to the areolar margins [7, 12, 28, 29]. Similar to the nipple-areolar sparing mastectomy, the donut mastopexy technique is best utilized in the setting of a malignancy that does not extend to the skin or nipple-areolar complex. The donut mastopexy utilizes a pair of concentric circumareolar skin incisions; one placed at the areolar margin and a second whose radius is at least 1 cm longer. The intervening ring of skin is excised (either full thickness or partial thickness) and wide skin flaps are developed over the index and flanking quadrants to enable wide local excision of the malignancy

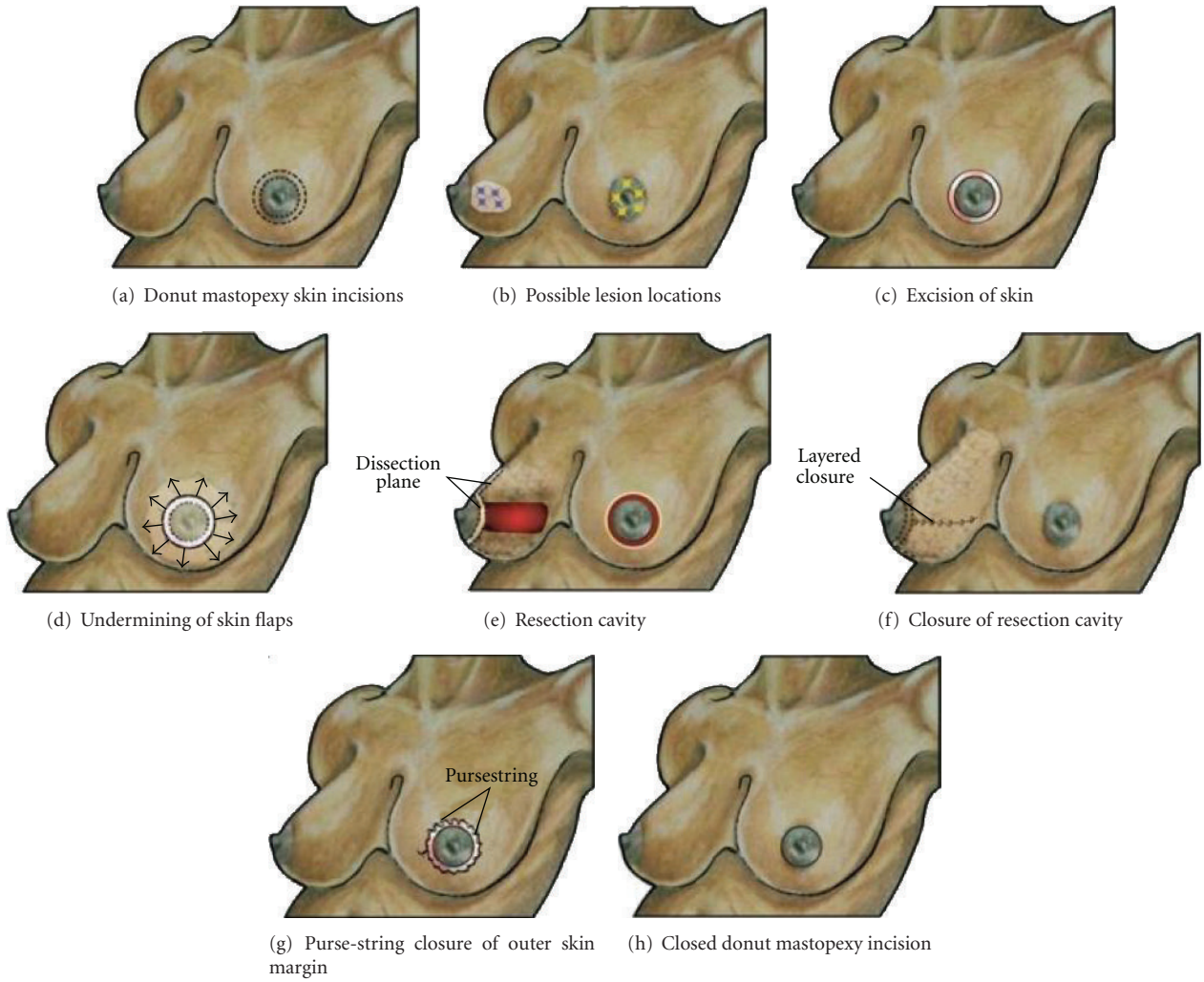


Figure 7: Donut mastopexy resection. (a) Shows location of two circumareolar incisions. (b) Shows frontal and profile views of the breasts with multiple "stars" indicating possible tumor locations suitable for this approach. (c) Shows the area of de-epithelized or excised skin at edge of areola. (d) Shows arrows denoting undermining of skin flaps in the central breast. For illustration purpose, (e) shows medial profile view of the right breast with central lumpectomy cavity and area of undermined skin flaps. Frontal view of left breast shows central lumpectomy behind nipple-areolar complex. (f) Shows results of advancement of glandular tissue which is mobilized and sutured together to fill the central breast. (g) Shows reduction of the diameter of the outer skin margin using a purse-string suture. (h) Shows breast following closure of the skin incision.

and the adjoining pectoralis fascia. Placement of localizing wires anterior and adjacent to the malignancy will improve margin clearance. Following tumor resection, reconstruction of the gland is undertaken by undermining, advancing, and performing a layered closure of the flanking glandular breast tissue using 2–0 absorbable sutures. If full-thickness, full-circumferential, skin incisions are utilized, special attention must be taken to minimize the undermining of the nipple-areolar complex which would compromise the blood supply from the underlying glandular tissue. For skin closure, an absorbable purse-string suture is placed in the outer skin margin to reduce its diameter to that of the normal areola. Skin closure is then completed with the suturing of these two skin margins together, forming the new areolar margin.

A primary advantage of the donut mastopexy resection and the reduction of the skin envelope is the lifting effect that it has on the breast. Cosmesis can further be enhanced by the asymmetric, more cephalad placement of the larger concentric circle, which produces further elevation of the nipple-areolar complex upon wound closure. The principle technical disadvantages of this approach are its greater complexity and the nipple-areolar complex denervation that results from full-thickness circumferential incision of the areolar margin.

8.5. B-Flap Resection. When proximity of the tumor to the nipple-areolar complex necessitates resection of the nipple-areolar complex, the *B-flap resection* (the Grisotti mastopexy technique) is the ideal approach for reconstructing the central breast in a woman with sufficient breast volume or moderate breast ptosis (i.e., ≥ 8 cm distance from the nipple to the inframammary skin fold) (Figure 8) [30–33].

The B-flap resection is named for the "B-" shaped incision that is created to resect and reconstruct the breast. The circumareolar incision makes up the upper portion of the "B" and the lower portion of the "B" is defined by a disk of skin from the lower part of the breast that is preserved and transposed (along with an inferior pedicle of glandular tissue) to the central breast to replace the resected areola and reconstruct the central breast defect. The resulting surgical specimen is comprised of the nipple-areolar complex and the central cylinder of glandular tissue extending to the pectoralis fascia.

In designing the B-flap resection, the breast is positioned centrally on the pectoralis muscle and the areolar margin is outlined. The diameter of the areola is measured and then a disc of skin of equal diameter is drawn on the skin of the breast just inferior to the nipple-areolar complex. This disc of skin will form the new areola. For an eccentrically placed tumor, a larger circumareolar incision can be designed to encompass the skin anterior to the lesion. In this instance, the diameter of the disc of skin should be based on the diameter of the normal areola to maintain symmetry. On the other hand, use of a larger circumareolar incision allows flexibility in positioning the nipple-areolar complex to correct ptosis. Next, two curvilinear lines are drawn from the lateral and medial edges of the native areola and skin disc. As the lines pass inferior to the skin disc, both are curved inferolaterally to converge at the lateral aspect of the inframammary skin fold.

B-flap resection begins with incision of the areolar margin. Dissection is continued posteriorly while maintaining a generous gross margin around the malignancy until the pectoralis muscle is encountered. After resecting the specimen, the area of skin outlined in the inferolateral breast is de-epithelialized except for the encircled disc of skin that will form the future areola. De-epithelization is easily accomplished using tenotomy scissors to excise the pigmented epithelial layer, leaving intact the white reticular "deep" dermis layer.

Wound closure is initiated by incising the breast and inframammary fold along the medial edge of the de-epithelialized skin, extending this incision through the underlying glandular tissue to the chest wall. The lower outer quadrant of the breast is then dissected off the underlying chest wall to allow superior and medial rotation and advancement of the skin disc and underlying glandular tissue to the central breast. This brings the skin disc to the position of the original nipple-areolar complex and partially restores the volume of the central breast using glandular tissue from the inferior and outer quadrants. The central breast mound is further reconstituted by suturing the transposed tissue to the surgical margin using interrupted 2–0 or 3–0 absorbable sutures in multiple layers. Partial undermining of the lower inner quadrant facilitates full-thickness approximation of the lower breast gland. Layered closure of the skin is then performed by suturing the edge of the skin disk to the original areolar skin margin and approximating the epithelialized skin margins of the inferolateral breast after burying the de-epithelialized dermis below the skin surface. Reconstruction of the nipple and tattooing of the areola may be completed at a later date.

8.6. Central Quadrantectomy. *Central quadrantectomy* is performed through a circumareolar incision spanning up to 50% of the areolar circumference and may be used in patients with widely ranging breast sizes [30, 31] (Figure 9). The surgical specimen consists of a cylinder of breast tissue extending from the subareolar plane to the pectoralis muscle encompassing the breast malignancy with a generous surgical margin. Localizing wires inserted along the anterior medial and anterior lateral aspects of the malignancy will facilitate dissection of the subareolar tissue plane and optimize clearance of the surgical margins. When proximity of tumor to the nipple requires resection of the nipple-areolar complex, the nipple-areolar complex is removed in continuity with the cylinder of underlying glandular tissue.

Beginning with the circumareolar skin incision, the dissection is carried out subareolarly to create a dermoglandular flap of the nipple-areolar complex. Dissection of this plane is then extended peripherally in all directions for several centimeters to separate the central breast skin from the central breast gland. This will facilitate resection of the specimen and subsequent wound closure. Maintaining a relatively thick areolar skin flap is important to ensuring adequate perfusion. Once the areolar flap and adjacent skin are detached from the central breast mound, the localizing wires bracketing the lesion are then identified in the subcutaneous plane and used to define the gross margins of the central breast resection. Dissection of the central cylinder is then extended to the pectoralis muscle from which it is detached along with the muscular fascia.

Wound closure is initiated by placement of 2-3 layers of purse-string sutures at the posterior, middle, and anterior depths of the cylindrical resection cavity to bring the central breast mound together in the retroareolar position. Additional undermining of the skin flaps may be needed to release areas of skin that become tethered when the central gland is approximated. Closure of the areolar margin is completed by reapproximation and layered closure of the subcutaneous tissue and skin.

9. Tumor Located in the Lower Half of the Breast

9.1. Triangle Resection. Resection of a breast malignancy from the lower half of the breast has significant potential to cause breast disfigurement. The standard lumpectomy performed in this location may produce a "bird beak" deformity in which the nipple-areolar complex or central breast overhangs a concave area in the inferior breast. Such disfigurement can be avoided by the use of the triangle resection which is capable of achieving wide excision of lesions in the 5–7 o'clock region of the breast while allowing reconstitution of the inferior pole of the breast by advancement of adjacent tissues into the surgical cavity (Figure 10). The triangle incision is ideally suited for lesions that are radially oriented or approximate the skin, but it is also useful for deeper lesions. Using this technique, the

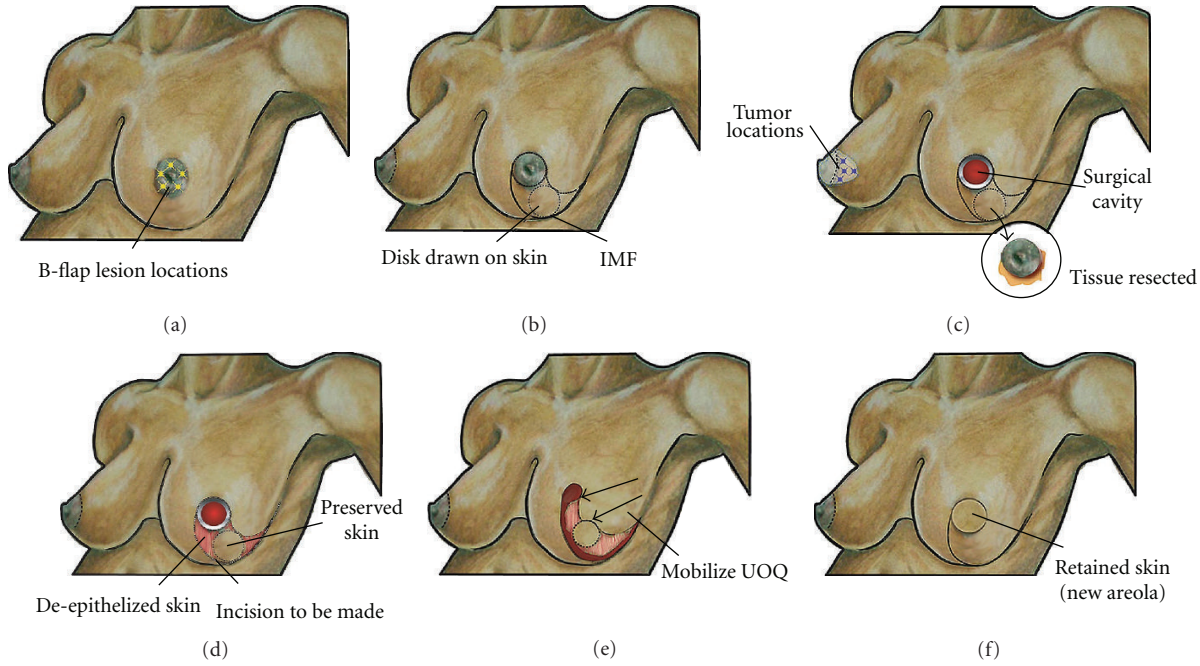


Figure 8: B-flap resection. (a) Shows multiple stars with possible tumor locations. (b) Shows location of skin incision, including disk of skin to be preserved. (c) Shows surgical cavity after excision of central lumpectomy with removal of nipple-areolar complex (inset). For illustration purposes, medial profile view of right breast shows multiple "stars" indicating possible tumor locations suitable for this approach. (d) Shows surgical cavity, areas of de-epithelized skin, preserved disk of epithelized skin, and location of incision to be made in the glandular tissue. (e) Shows advancement and clockwise rotation of lower outer quadrant until disk of skin occupies the nipple-areolar complex position. (f) Shows breast following approximation and closure of the skin incisions. De-epithelized skin is buried below the skin of the lower inner quadrant and the disk of skin forms a new areola.

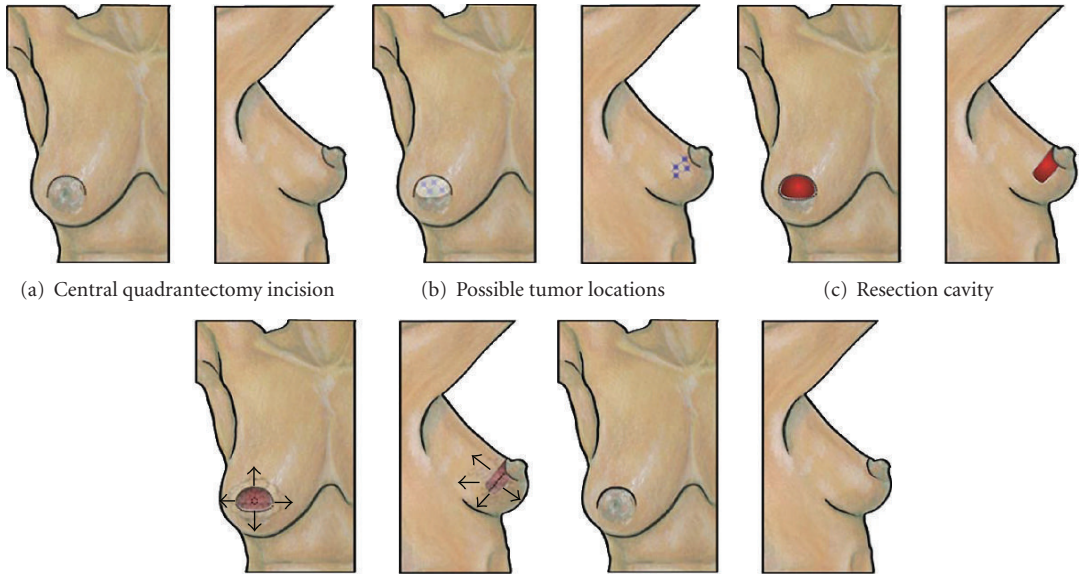
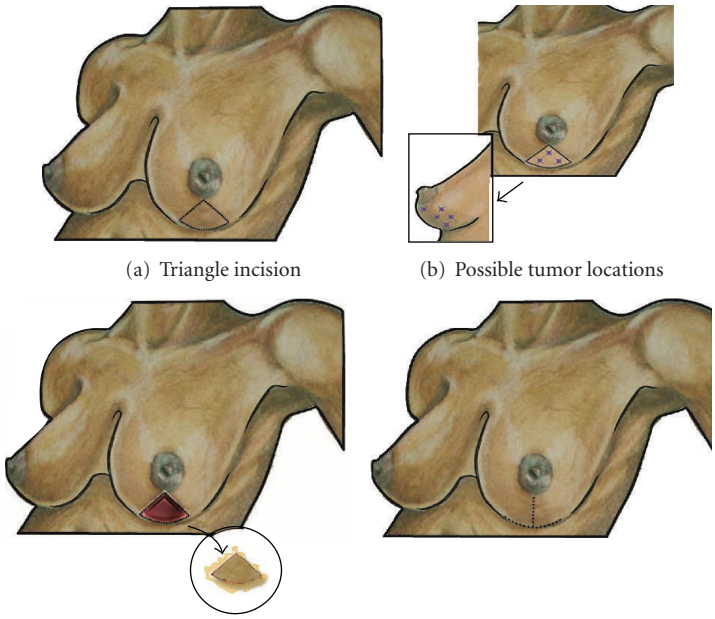


Figure 9: Central quadrantectomy. (a) Shows location of central quadrantectomy skin incision. (b) Shows multiple "stars" indicating possible tumor locations suitable for this approach. (c) Shows resection cavity following excision of malignancy. The nipple-areolar complex was omitted in the left image to allow visualization of surgical cavity. (d) Shows results of glandular flap advancements that allow the surgical margins to be sutured together using purse-string sutures to obliterate the surgical cavity. Arrows showing undermining of skin flaps in the central breast. Nipple-areolar complex omitted in the left image to allow visualization of the approximated glandular tissue. (e) Shows breast following closure of the skin incision.



(a) Triangle incision (b) Possible tumor locations

(c) Resection cavity and specimen (d) Closed triangle incision after extension of IMF incisions

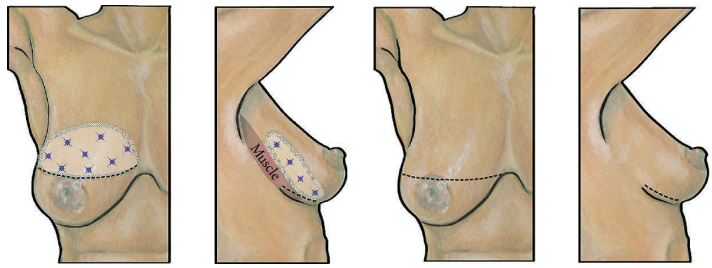
Figure 10: Triangle resection. (a) Shows location of the triangular skin incision. (b) Shows multiple "stars" indicating possible tumor locations suitable for this approach. (c) Shows resection cavity following excision of malignancy with excised specimen (inset). (d) Shows breast following closure of the skin incision, including extensions of incision along the inframammary skin fold.

resulting full-thickness wedge-shaped specimen of skin and glandular tissue is allows removal of a relatively large lesion in this location [27].

To perform the triangle resection, a triangular or wedge-shaped incision is drawn on the skin overlying the breast lesion. The base of the triangle should intersect the inframammary skin fold and the apex of the triangle should point toward, but not necessarily extend to, the inferior areolar margin. Dissection is begun by incising the triangular area of skin and dividing the underlying glandular tissue down to the chest wall. Resection of the specimen is completed by extending the plane of dissection posterior to the specimen at the surface of the serratus anterior muscle or rectus fascia down to the inframammary fold, which is subsequently divided. If necessary, the rectus fascia and/or serratus anterior may be resected to ensure a negative deep margin posterior to the specimen. Special attention should be paid to maintaining a glandular dissection plane that is relatively perpendicular to the skin to facilitate approximation of the surgical margins. Caution should also be taken to avoid excessive traction of the specimen during the course of dissection, as this may lead to inadvertent dissection behind and cephalad to the nipple and removal of excessive normal glandular tissue.

For wound closure, the adjacent lower outer and lower inner quadrants must be brought together to allow full-thickness approximation of the glandular tissue. This is accomplished by extending the inframammary fold incision toward the medial and lateral edges of the breast, undermining the lower half of the breast to create lower outer quadrant and lower inner quadrant dermoglandular flaps, and approximating the dermoglandular flaps using multiple layers of 2–0 or 3–0 absorbable sutures. The resulting length discrepancy between the breast and inframammary fold skin edges can generally be easily overcome by temporary approximation of the edges with skin staples, redistribution of the shorter edge along the longer edge, and use of suturing techniques described above (see Section 8.1). To avoid excessive tension on the breast skin edges, the inframammary fold incision may be extended medially and laterally to allow additional mobilization of the dermoglandular flaps. To complete the procedure, the inframammary fold is closed in multiple layers by approximating the glandular and fibrous tissue of the breast with the fibrous tissue of the inframammary fold using 2–0 or 3–0 interrupted absorbable sutures, followed by closure of the skin with a smaller gauge suture.

From a perfusion perspective, the most vulnerable parts of the breast dermoglandular flaps are the distal corners of the medial and lateral flaps where they converge at the inframammary fold [27]. Limited collateral blood flow at these corners makes them susceptible to ischemia, leading to partial- or full-thickness necrosis of the corners. This can be minimized with delicate tissue handling of the corners, minimizing tension in wound closure, and avoiding the use of retracting instruments on these corners which have the tendency to further traumatize the skin and underlying breast tissue. An additional strategy is to "round off" these corners to reduce the risk of underperfusion of the distal corners. The resulting "skin defect" can be filled by preserving a comparable area of skin at the midpoint of the inframammary fold.



(a) Possible tumor locations (b) Closed incision in the IMF

Figure 11: Inframammary Resection. (a) Shows location of inframammary skin incision. "Stars" indicate multiple possible tumor locations suitable for this approach. (b) Shows breast following closure of the inframammary incision.

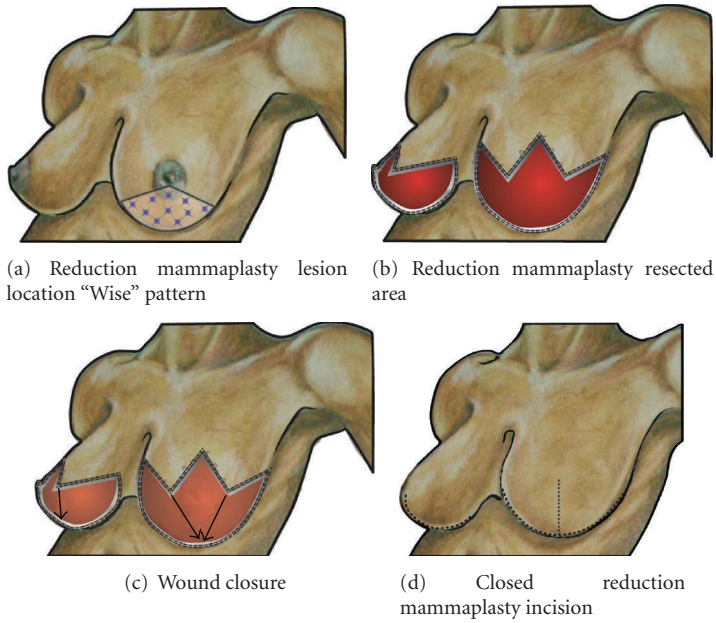
9.2. Inframammary Resection. The *inframammary resection* is a versatile incision for removal of cancers from a variety of locations in the lower or posterior aspects of the breast [27] (Figure 11). Resection of a breast malignancy via the inframammary approach places the incision in the inframammary skin fold where it is "hidden" behind and below the breast. Since the skin overlying the lesion is fully preserved, the inframammary approach should be restricted to resection of breast cancers that are not located in the superficial breast to minimize the risk of a positive superficial margin. Given the indirect or "back-door" approach of this resection, it is imperative that surgeon use multiple bracketing wires and/or intraoperative ultrasound when appropriate to ensure wide excision of the malignancy.

Using the inframammary approach, an incision is made in the skin of inframammary fold and extended through the subcutaneous and fibrous layers to the chest wall. The length of the incision depends, in part, on the size of the lesion, location of the lesion, and the degree of mobilization required to access the lesion and to close the surgical cavity. Larger and more cephalad lesions will require a longer incision to facilitate access to the upper breast. Smaller and more caudal lesions may be accessed through a shorter incision in the medial, central, or lateral inframammary skin fold. Dissection is then extended through the retromammary fat plane to a position at least 3 cm cephalad to the malignancy, the position of which is determined using bimanual palpation, skin markings, localizing wires, ultrasound, or some combination of these techniques. An incision is then made in the posterior surface of breast in the perimeter of the lesion and then extended anteriorly to widely resect the tumor with a generous superficial margin. Placement of localizing wires superficial to the lesion will improve superficial margin clearance. If localizing wires are used, the localizing wires should be identified within the substance of the gland and the external ends of the wires should be redirected so that they project out of the posterior surface of the breast into the surgical cavity. With the localizing wires in view, resection of the specimen is carried out by widely excising the localizing wires and the bracketed specimen. Resection of the corresponding area of muscular fascia should also be considered for deeper lesions.

Wound closure is initiated by approximating the surgical margins to prevent or minimize retraction of the skin into the underlying surgical cavity. This step can be performed relatively easily since the breast has already been widely mobilized from the chest wall. However, if additional mobilization is needed, dissection of the retromammary fat plane or subcutaneous tissue plane can be carried out to facilitate cavity closure. Final wound closure is completed by reapproximation of the inframammary using 2–0 or 3–0 absorbable sutures followed by layered closure with smaller gauge absorbable sutures.

9.3. Reduction Mammaplasty. The *reduction mammaplasty resection* combines wide local excision of a breast malignancy with reduction mammaplasty in a patient who desires breast reduction. Reduction mammaplasty resection may be performed with or without nipple preservation depending on the location of the cancer. When the nipple-areolar complex is preserved, recentralization of the nipple is generally performed to move the nipple-areolar complex to a more anterior and superior position on the breast mound. The principal oncological advantage of the reduction mammaplasty is the ability to achieve wide local excision of large breast malignancies, especially those that might not be amendable to breast conserving surgery using the standard lumpectomy. Breast rearrangement is useful for masking larger segmental defects and simultaneously creating an aesthetic breast mound. The versatility of this approach makes it suitable for resection of lesions located between the 4–8 o'clock axes of the breast, as well as in the retroareolar or supra-areolar position. The reduction mammaplasty resection is regarded to be among the more complex oncoplastic breast conserving procedures and should not be performed by surgeons lacking appropriate training in plastic or oncoplastic surgery. Its inclusion in this paper is meant to provide a broad overview of the approach for surgeons considering appropriate training in oncoplastic surgery.

The key foundations of any reduction technique include the preservation of the vascular supply to the nipple-areolar complex and vascular supply to the remaining breast parenchyma. The first technical aspect of the reduction mammaplasty resection is the planning of the skin incision. While the traditional approach has been the "Wise pattern" (keyhole) incision (Figure 12) [34, 35], vertical reduction



(a) Reduction mammaplasty lesion location "Wise" pattern

(b) Reduction mammaplasty resected area

(c) Wound closure

(d) Closed reduction mammaplasty incision

Figure 12: Reduction mammaplasty. (a) Shows multiple "stars" indicating possible tumor locations suitable for this approach. (b) Shows surgical cavity after resection of nipple-areolar complex and inferior breast using Wise pattern. A symmetrical reduction is shown in the opposite breast. (c) Shows advancement of medial and lateral pedicles to inframammary fold. (d) Shows the breasts after closure of the wounds.

techniques have become very popular as well [36]. The "Wise pattern" creates the classic inverted "T-" or anchor-shaped incision upon closure of the wound and is usually incorporated with an inferiorly based dermoglandular pedicle. When resection of the nipple-areolar complex is required, the central skin incision consists of an inverted "V", the apex of which is placed just above the nipple-areolar complex. In general, the apex of the "V" is placed at the intersection of a longitudinal line extending from the junction of the inner and middle-third of the clavicle to the nipple (i.e., the breast meridian) and a second transverse line drawn at the level of the inframammary fold transposed onto the superior breast skin in the upright position. The apex of the "V" is usually 18–20 cm from the suprasternal notch. The point of intersection is the superior areolar point. From the superior areolar point, the two legs of the "V" should pass inferiorly to the left and right of the nipple-areolar complex for a length of 3–5 cm, plus an additional length of 5 cm or more for a total length of approximately 10 cm. From this point, lines are extended horizontally in the medial and lateral directions to join the medial and lateral ends of the inframammary fold. Skin marking is performed with the patient in the upright sitting or standing position [37].

When the position of the malignancy enables preservation of the nipple-areolar complex, the initial markings are drawn as described above, substituting an inverted "U-" shaped incision instead of a "V-" shaped incision with placement of the apex of the inverted "U" at the new superior areolar point. When the breast wound is closed, the vertical lines will span the distance from the inferior areolar point to the inframammary fold, and the horizontal lines will form the superior skin margin of the new inframammary fold. Modifications of the standard inferior, medial, or lateral incisions have also been described for breast conservation and include adjusting the incisions to incorporate the resected area [38].

After designing the skin incision, resection of the breast malignancy is undertaken by incising the inframammary fold, the affected skin, and the glandular margins down to the chest wall, maintaining the dissection plane at right angles to the skin surface. If nipple and areola preservation is intended, care should be taken to preserve vascular supply to the nipple-areolar complex either by avoiding undermining the nipple-areolar complex for a parenchyma pedicle or by maintaining the retained dermis along at least two-thirds of the areolar circumference. In addition, de-epithelialization of the skin between the remaining areolar margin and new superior skin margin may be used to optimize perfusion and innervation of the nipple-areolar complex. For lesions that are eccentrically located (e.g., in the 3-4 o'clock or 7-8 o'clock positions) the surgeon may chose to "cheat" the glandular resection medially or laterally to gain adequate clearance around the malignancy. After complete excision of the malignancy, dermoglandular flaps using the remaining breast tissue can also be incorporated to fill in significant defects [39].

Wound closure is initiated by tailor-tacking the previous incisions with staples, starting with the inferior, medial, and lateral incisions. If the originally drawn circular pattern at the apex of the Wise pattern ("U" shape) is symmetric, the nipple can also be inset, burying the de-epithelialized tissue under the incision. If better symmetry of the nipple-areolar complex is required, a cookie-cutter can be used to create a new superior incision margin after closure of the

inverted "T" incisions only. Any additional skin removal is performed by de-epithelialization. When the nipple-areolar complex has been resected, the skin can be closed in either a transverse or vertical pattern, depending on the type of reduction performed. Layered closure of the parenchyma, dermis, and skin ensures maintenance of the final breast shape over time.

Complications of combined reduction mammaplasty and malignancy excision occur in 17% of patients [39]. Skin and fat necrosis are the most common complications and occur more often in smokers and obese patients. Nipple-areola necrosis occurs in approximately 3% of patients.

10. Summary

The procedures presented herein constitute a broad overview of the most commonly performed oncoplastic breast conserving procedures for optimizing tumor resection and cosmesis. This overview provides a starting point for surgeons interested in adding oncoplasty to the surgical options that they offer to their patients. While some of the procedures can be introduced without specialized training, breast and general surgeons seeking advanced training in oncoplastic surgery should participate in a breast fellowship program or an oncoplastic surgery course. Oncoplastic surgery courses are offered by several specialty societies, including the American Society of Breast Surgeons and the American Society of Breast Diseases.

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Review Article

Intraoperative Radiotherapy in the Treatment of Breast Cancer: A Review of the Evidence

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The surgical treatment of early breast cancer has evolved from the removal of the entire breast and surrounding tissues (mastectomy) to the removal of the tumour together with a margin of healthy tissue (lumpectomy). Adjuvant radiotherapy, however, is still mainly given to the whole breast. Furthermore, external beam radiotherapy is often given several months after initial surgery and requires the patient to attend the radiotherapy centre daily for several weeks. A single fraction of radiotherapy given during surgery directly to the tumour bed (intraoperative radiotherapy) avoids these problems. The rationale and level-1 evidence for the safety and efficacy of the technique are reviewed.

In 1867, a surgeon at the Middlesex Hospital in London published a paper providing evidence for the local origin of breast cancer; after partial removal of the breast, recurrences were generally near the scar [1]. He thought that the recurrences spread centrifugally from the focus through the lymphatics, and the best treatment was to remove as much breast and surrounding tissue as possible. In 1894, Halsted published the results of a radical mastectomy in 50 patients—a local recurrence rate of 6%, which was extremely low by the standards of the time [2]. The technique was adopted enthusiastically and developed further with the extended radical mastectomy (sometimes together with amputation of the upper arm), culminating in the super-radical mastectomy [3].

Coincidentally, Wilhelm Röntgen discovered X-rays in 1895 and the Curies discovered radium in 1898; soon after, radiation was used to treat breast cancer, with variable results [4]. However, surgical removal of the whole breast remained the treatment of choice until the 1970s when results from trials comparing mastectomy with a combination of breast-conserving surgery and whole-breast radiotherapy showed that they were equally effective in terms of survival and considerably less traumatic for the patient [5]. In addition, radiotherapy reduced the risk of local recurrence by 75%, which resulted in a disease-free survival advantage [6] and indeed overall survival [7].

Currently, postoperative radiotherapy to the whole breast with a boost to the tumour bed is regarded as an adjuvant treatment to breast-conserving surgery. However, if the surgical component of the therapy has moved from whole breast (mastectomy) to local (lumpectomy), why cannot the same logic be applied to radiotherapy particularly in this era of mammography where screen-detected lesions are very small?

It is interesting to note that pioneering work on local treatments was performed by Geoffrey Keynes, a surgeon at St Bartholomew's Hospital in London. In 1922, he experimented with the use of radium encased in hollow platinum needles that were inserted around the tumour and lymphatics. Keynes combined this local radiotherapy with local excision (lumpectomy) [8]. Unfortunately, radium was difficult to obtain and handle, so the technique never caught on.

The results of many observational studies and clinical trials have demonstrated that around 90% of recurrent disease

Table 1: Summary of evidence regarding the location of in-breast recurrences.

Year	Description	All LR	IBNP	True LR	Reference
2007	5318 patients with early breast cancer; all had lumpectomy and EBRT ± boost	91	17	81%	[36]
1993	567 women ± EBRT, 39 m median FUP. IBNP ">2 cm from primary site"	25	4	84%	[37]
1992	837 women ± EBRT, 43 m median FUP	131	19	85%	[38]
1992	488 women all with lumpectomy plus EBRT, 103 m mean FUP. "True" LR—"at or close to same quadrant as index case"	42	2	95%	[39]
1990	783 women, 80 m median FUP	91	17	81%	[40]
1990	381 women ± EBRT, 30 m FUP	15	2	87%	[41]
1990	496 women, 71 m median FUP	61	15	77%	[42]
1990	1593 women, 11 y median FUP	178	38	79%	[43]
1989	861 women, 5-6 years median FUP	93	19	80%	[44]
1984	231 women, 44 m median FUP	12	2	83%	[45]
1982	680 women	509	3	>99%	[46]
1982	28 women with DCIS treated by biopsy alone, FUP > 3 y	7	1	86%	[47]
1981	176 patients, median FUP 47 m	15	1	93%	[48]

LR = local recurrence (any recurrence in the ipsilateral breast).
IBNP = ipsilateral breast new primary (a LR that is some distance away from the site of the original tumour; precise definitions vary by study).
True LR = (All LR-IBNP)/(All LR) expressed as a percentage.

in the breast after breast conserving surgery is within the index quadrant, whether or not whole-breast external beam radiotherapy has been given, see Table 1. Furthermore, after adjuvant endocrine therapy, the chance of a local recurrence outside the index quadrant is no more than the risk of a new contralateral tumour [9].

There is evidence (described below) that ipsilateral breast cancer recurrence is in fact two distinct diseases, namely: true recurrence where the cancer is not completely removed and remaining cells grow to form a recurrence; and a second primary cancer, a tumour arising independently of the index tumour. This distinction is important as localised therapy should be judged on its ability to reduce true recurrences, but it will not be expected to have an effect on new primary cancers.

In a retrospective review of 397 patients with ipsilateral breast tumour recurrence, Yi et al. [10] reported that about half were classified as new primary cancers by two methods of assessment using data such as tumour location, histologic subtype, and hormone receptor status. Patients classified as having new primary cancers had better outcomes than those with true local recurrences, specifically 10-year overall and disease-specific survival rates and likelihood of developing subsequent metastatic disease. However, they were more likely to have a contralateral breast cancer.

Komoike et al. [11] described a cohort of 161 Japanese patients with ipsilateral breast tumour recurrences and classified them as either true recurrences or new primary cancers, based on tumour location and pathological findings. The true recurrences were associated with a high rate of lymph node metastases and a shorter disease-free interval than new primary cancers.

The records of 130 patients with ipsilateral breast tumour recurrence were reviewed by Smith et al. [12] and classified as true recurrence if located in the same position from the primary tumour bed, was of the same histologic subtype, or had the same DNA flow cytometry (remained aneuploid). Patients with new primary cancers were found to have better overall, distant disease-free, and cause-specific survival.

So, it is entirely possible that dormant cancers in the breast, distant the primary tumour, do not need any intervention. In other words, not all cancers will grow to become a clinical problem in an individual's lifetime, a situation analogous to prostate cancer, where many men die with, but not of, prostate cancer; men with nonlethal disease do not benefit from treatment [13]. The evidence to support the notion of latency amongst microscopic foci of breast cancer has been well documented [14, 15].

Whole-breast radiotherapy is not without risk. Treatment regimens have become safer since the identification of long-term side effects such as increased mortality from myocardial infarction after radiotherapy for left-sided breast cancer [16]. But, no matter how carefully applied, healthy tissues such as the heart, ribs, and lungs do receive a dose of radiation.

Other issues with whole-breast radiotherapy include the following.

(i) The fractionated doses take between 3 and 7 weeks to deliver, which is a great inconvenience for women who work or look after grandchildren or ill adults or for the elderly who find the daily journeys exhausting. Women in the developing world or those in wealthy countries who live in rural areas more than 100 miles from a centre are denied the chance of breast-conserving surgery and must have a mastectomy, or else are at great hazard of local recurrence if the treatment is omitted [17, 18].

(ii) The radiotherapy equipment is expensive to purchase and to run and requires installation in a shielded

building. In the UK, the treatment of breast cancer accounts for approximately a third of the workload of radiotherapy departments.

(iii) Geographic misses are commonplace in postoperative attempts to target the tumour bed [19].

(iv) Cosmesis is often impaired by the short- or long-term radiotoxicity.

(v) Delays in the start of chemotherapy or delays in the start of radiotherapy in order to accommodate chemotherapy might compromise either modality [20]. A delay of over six weeks has been shown to significantly increase the risk of recurrence at 5 years [21].

Risks associated with accelerated partial breast irradiation include persistent seroma, postprocedural infection, erythema, telangiectasia, edema, blistering, skin thickening, fibrosis, tenderness, and pain; in general, these toxicities are modest and acceptable [22, 23].

Clinicians are increasingly adopting the view that perhaps it is not necessary to irradiate the whole breast, but rather to restrict treatment to the immediate area around the tumour bed or index quadrant. Accelerated partial breast irradiation (APBI) aims to decrease the volume of breast treated and increase the daily fraction size of radiation so that the entire dose can be delivered within 1 week (instead of 3–7 weeks). Techniques include linac-based intensity-modulated radiotherapy, multicatheter interstitial brachytherapy, balloon-based APBI using the MammoSite brachytherapy applicator (Hologic, Inc., Mass, USA), and a newly developed, modified form of balloon-based brachytherapy called Xoft Axxent Electronic Brachytherapy (Xoft, Inc., Calif, USA). A review of randomised trials and prospective single-arm studies led the American Society for Therapeutic Radiation Oncology to issue a consensus statement regarding groups of patients who could be treated by APBI, while urging that further research was required [24].

There are currently seven ongoing randomized trials testing various methods of APBI against whole-breast radiotherapy [25]. However, they are not comparable since they vary in inclusion criteria, total dose, fractionation, volume, and timing related to chemotherapy and hormone treatment. The National Surgical Adjuvant Breast and Bowel Project and the Radiation Therapy Oncology Group have noted this shortcoming which is being addressed in an intergroup study randomising patients with early-stage breast cancer to whole-breast irradiation versus APBI (using either interstitial brachytherapy, Mammosite balloon catheter, or 3D conformal external beam); accrual is expected to be completed soon (NSABP B-39/RTOG 0413, [26]).

There is, however, one type of APBI that has already generated level-1 evidence—intraoperative radiotherapy (IORT) given as a single fraction to the tumour bed during surgery.

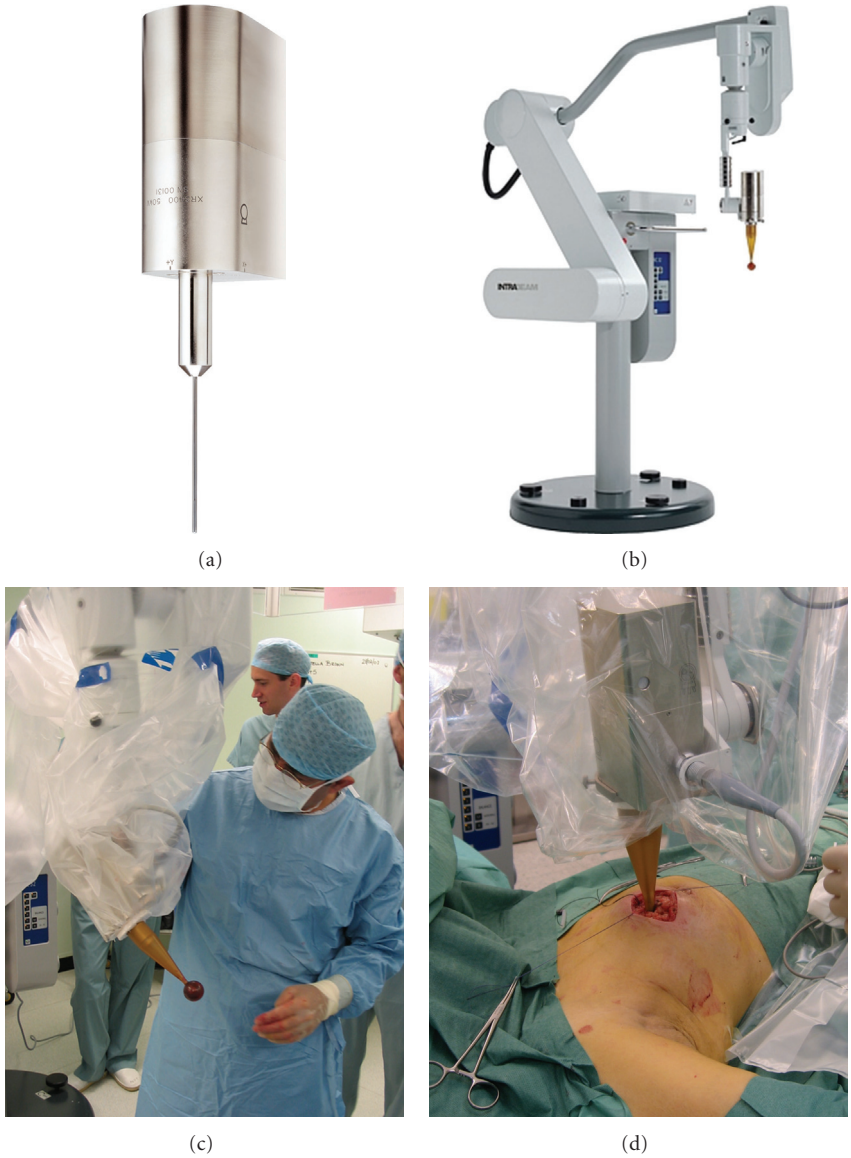
The technique of IORT using INTRABEAM (Carl Zeiss Surgical, Oberkochen, Germany), termed TARGIT, was pioneered in London [27] and allows the patient to receive a single fraction of radiotherapy as soon as the primary tumour is excised, during the same anaesthetic. Advantages of this approach include delivering the radiation immediately, ensuring the radiation is delivered to the tumour bed under direct vision, thus avoiding a "geographical miss", and decreasing costs to the healthcare providers.

INTRABEAM is a mobile, miniature X-ray generator powered by a 12-volt supply. Accelerated electrons strike a gold target at the tip of a 10 cm long drift tube with a diameter of 3 mm, resulting in the emission of low-energy X-rays (50 kV) in an isotropic dose distribution around the tip. The irradiated tissue is kept at a fixed, known distance from the source by spherical applicators to ensure a more uniform dose distribution. The tip of the electron drift tube sits precisely at the epicentre of a spherical plastic applicator, the size of which is chosen to fit the cavity after the tumour is excised, see Figure 1. Using this method, the walls of the tumour cavity are irradiated with a biologically effective dose (20 Gy to the tissue in contact with the applicator) that rapidly attenuates over a distance of a few centimetres. As a result, healthy tissue such as the vital organs is spared and the device can be used in an unmodified operating theatre as there is no need for lead shielding [27].

Another IORT approach is electron intraoperative therapy, pioneered at the European Institute of Oncology in Milan, Italy. In this technique, a portable linear accelerator is used to deliver a single dose of 21 Gy radiation during the surgery [28]. With this approach, it is necessary to perform the procedure in a specially shielded operating theatre for radiation safety considerations. The technique is currently being tested in a clinical trial, and results are eagerly awaited, as results from associated studies look promising [28, 29].

The safety and tolerability of the TARGIT technique has been established in a phase II study [30]. Starting in 1998, all 299 patients (with 300 cancers) who underwent breast conserving surgery for their breast cancer management received a single 20 Gy dose of radiotherapy during surgery. In these patients, this replaced 1 week of radiation to the tumour bed (boost radiation), and all patients received standard external beam radiotherapy to the whole-breast. A total of 32% of the patients were younger than 51 years; 57% of cancers were between 1 and 2 cm (21% >2 cm); 29% had a grade 3 tumour; 27% were node positive. The treatment was well tolerated by all patients, and with median followup of 60.5 months (range: 10–120 months), eight patients had developed ipsilateral recurrence: the 5-year Kaplan-Meier estimate for ipsilateral recurrence is 1.74% (standard error: 0.77). Based on the success of this study, a phase III superiority trial comparing TARGIT boost versus conventional boost will soon be launched.

In March 2000, an international, randomized controlled trial was launched comparing TARGIT versus whole breast external beam radiotherapy as a noninferiority study with the primary outcome of local recurrence. The original recruitment goal of 2232 (powered to test noninferiority; hazard ratio <1.25) was reached in early 2010, and the results were published [31]. 1113 patients were randomly allocated to TARGIT and 1119 to external beam radiotherapy. 14% of the TARGIT group also received external beam radiotherapy.



(a) (b) (c) (d)

Figure 1: (a) The portable X-ray accelerator (Intrabeam). Soft X-rays are produced at the tip of the drift tube. (b) The intrabeam device mounted on the stand. The unit is portable and can be moved into the operating theatre as and when required. (c) Sterile drape and applicator in place, ready for positioning by the surgeon. (d) The applicator has been placed in the tumour bed and a purse-string suture is being applied to ensure conformity of the tissue to the applicator.

At 4 years, there were six local recurrences in the TARGIT group and five in the external beam radiotherapy group. The Kaplan-Meier estimate of local recurrence in the conserved breast at 4 years was 1.20% (95% CI 0.53–2.71) after TARGIT compared with 0.95% (0.39–2.31) in the external beam radiotherapy group; the difference between the groups was not significant. The frequency of any complications and major toxicity was similar in the two groups, and radiotherapy toxicity was lower in the TARGIT group. The results of this study provide level-1 evidence that, for selected patients with early breast cancer, a single dose of radiotherapy delivered at the time of surgery using the TARGIT technique should be considered as an alternative to external beam radiotherapy delivered over several weeks.

Recruitment to the TARGIT Trial has been extended primarily to allow completion of subprotocols (quality of life, patient preference, health economics, and cosmesis). A pilot of the cosmesis subprotocol in 118 patients indicated a superior cosmetic outcome in the first year for those receiving TARGIT [32]. Results from a pilot patient preference study of 58 patients were used to determine if patients would accept the additional risk of 10-year recurrence in order to have TARGIT instead of conventional external beam radiotherapy. 54 (93%) of the subjects said they would undergo TARGIT if it offered equivalent or some added risk compared to EBRT [33].

Not all patients with early breast cancer were suitable for inclusion in the TARGIT Trial. In three major centres in

the UK, Germany, and Australia, we offered IORT off-trial to a highly selected group of 80 patients with exceptional circumstances who could not receive standard external beam radiotherapy. Reasons for using TARGIT included 21 patients who had in-breast tumour recurrence in previously irradiated breasts, and 31 patients had clinical reasons such as systemic lupus erythematosus, motor neuron disease, Parkinson's disease, ankylosing spondylitis, morbid obesity, and cardiovascular or severe respiratory disease. 28 patients were included for compelling personal reasons, usually on compassionate grounds. After a median followup of 38 months, only two local recurrences were observed, which is an annual local recurrence rate of 0.75% (95% confidence interval, 0.09%–2.70%). These results indicate that TARGIT provides acceptable toxicity and good local control and offers an alternative to mastectomy in highly selected cases in whom conventional radiotherapy is not feasible or possible [34].

It has been found that wound fluid (taken from the drain over the first 24 h after surgery) stimulated proliferation, migration, and invasion of breast cancer cell lines; however, the stimulatory effect almost completely disappeared when fluids from TARGIT-treated patients were used. This was due to an alteration in the molecular composition and biological activity of the wound fluid and could provide some explanation for the very low recurrence rates found using TARGIT [35].

In summary, the evidence is mounting for TARGIT to replace whole-breast external beam radiotherapy for selected patients with early breast cancer. The technique is relatively easy to use, does not require shielding of the operating theatre, and largely protects healthy tissues. Furthermore, TARGIT is suitable for developing countries—an unusual example where a new health technology is more affordable than the existing standard and can optimise treatment and reduce the number of unnecessary mastectomies.

Looking forward, these encouraging results have prompted the initiation of new clinical trials using the TARGIT technique, for example, as the sole radiotherapy treatment in elderly women where long-term outcomes are less of a consideration; in nipple-sparing mastectomy to treat residual breast tissue behind the nipple-areolar complex; in cases of screen-detected DCIS with small focal lesions.

The treatment of breast cancer has undergone an evolution and is now poised for a revolution. New adjuvant hormonal therapies, novel chemotherapy, and targeted biological therapies are all helping to drive down mortality rates, and as this happens, cost effectiveness and patient acceptability become relatively more important. The radical approach of radiotherapy in early breast cancer is now being questioned. If IORT proves to be a suitable replacement for external beam radiotherapy, then many women will be spared several weeks of travelling back and forth to the radiotherapy centre.

Furthermore, tens of thousands of women in the developing world who live hundreds of miles from a radiotherapy unit, or in countries that cannot afford the multimillion pound investment, will be able to enjoy the advantages of breast conservation instead of having to undergo mastectomy.

The quest for the optimal treatment for early breast cancer has come a long way in the past 100 years or so. New technology, rigorously tested, will enable us to go a lot further.

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Review Article

Optimization of Adjuvant Radiation in Breast Conservation Therapy: Can We Minimize without Compromise?

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Adjuvant breast radiation therapy after breast conservation surgery is recommended as it yields significant reduction in the risk of local recurrence, and confers a potential overall survival benefit. Although the standard breast radiation regimen has historically been delivered over 5–7 weeks; more novel, shorter courses of breast radiation are currently being employed, offering the advantage of more convenience and less time-commitment. Herein, we review the recent literature substantiating these abbreviated radiation treatment approaches and the methods of delivery thereof. In addition, we discuss imaged guided techniques currently being utilized to further refine the delivery of adjuvant breast radiation therapy.

1. Introduction

Multiple randomized studies have demonstrated equivalent survival outcomes with mastectomy versus breast conservation therapy (BCT, breast conservation surgery (BCS), and adjuvant radiation therapy) in the treatment of early stage breast cancer [1, 2]. In addition, the Oxford meta-analysis convincingly demonstrated not only a significant local control benefit but also an overall survival benefit with adjuvant breast radiation therapy after BCS [3]. As such, BCT has been established as the standard of care for limited stage breast cancer offering the advantage of breast preservation, improved quality of life, and cosmesis. Breast conservation surgery, except in rare cases, is followed by adjuvant radiation therapy (RT). A typical adjuvant radiation course is 45 to 50 Gy in 25 to 28 fractions (1.8 to 2 Gy per fraction) delivered to the whole affected breast. A boost of 10–16 Gy in 5 to 8 fractions is usually prescribed to the lumpectomy cavity for additional local control benefit as demonstrated by two seminal studies [4, 5].

With the standard RT schedule, a 5–7 weeks commitment is required. For most patients, this is quite inconvenient and cumbersome because of employment or social responsibilities, often confounded by remote distance from the treatment center to their place of work or residence. In fact, this treatment time commitment has been cited as one of the main reasons for noncompliance with adjuvant breast radiation [6]. This demand served as impetus for the development of abbreviated regimes for whole breast radiation.

One such schedule is the widely adopted Canadian fractionation, 42.5 Gy in 16 fractions (2.65 Gy per fraction) given over 3 weeks [7]. This and other regimens, 40 Gy in 15 fractions and 39 Gy in 13 fractions delivered over 3 weeks, partly borne from its inception, are discussed in detail herein [7–11].

Conceptually, a shorter course of radiation therapy necessitates hypofractionation utilizing a higher dose per fraction to achieve radiobiological equivalent effectiveness of the standard, more protracted schedule [12]. From radiobiological principles, since late reacting normal tissues are more sensitive to increasing dose per fraction, a priori, larger dose per fraction should yield more long-term toxicity [12]. Thus, the tenable, reserved position among some physicians is that the abridged regimens may be "tagged" with the high clinical price of long-term treatment toxicities. Thus the lingering question is can we minimize treatment time without compromising toxicity?

The utilization of hypofractionated whole breast RT has been contemporaneous with a more focused approach,

accelerated partial breast radiation therapy (APBI). As the name implies, radiation is targeted to the partial breast only, defined by the lumpectomy cavity borders and up to a 2 cm margin diametrically [13]. This regime employs several different treatment methods to deliver an accelerated hypofractionated course of radiation, with a schedule ranging from 20 Gy administered in 1 fraction as in the case of intraoperative radiation therapy (IORT) to 38.5 Gy in 3.85 Gy fractions twice daily over 5 consecutive days with external beam radiation.

The underlying principle of partial breast irradiation is that over 85% of all ipsilateral breast recurrences occur in the same quadrant within a 1-2 cm radius of the index lesion. By this premise, partial breast RT should not significantly compromise treatment outcomes compared to whole breast radiation, in low-risk patients [13]. In addition, organs at risk (OAR) for radiation-induced toxicity such as the unaffected contralateral breast, lungs and heart should be less threatened by partial breast than with whole breast radiation therapy.

Partial breast radiation offers a clinically desirable constellation of advantages over conventional radiation, including shortened treatment duration and reduction of normal tissue toxicity. However, this approach inherently assumes accurate definition of the lumpectomy cavity. This begs the question: can we confidently *minimize* target volume *without compromising* treatment outcomes? Image guidance promises to provide improved accuracy in target localization that should allow target volume reduction.

Herein, we review the results from the most relevant hypofractionated whole and partial breast studies and discuss the implications thereof. We conclude with a brief discussion of image guidance and its utility in whole and partial breast radiation.

2. Hypofractionated Whole Breast Irradiation

Several randomized clinical trials have compared the efficacy of whole breast radiotherapy with conventional fractionation (i.e., 1.8–2.0 Gy fractions) requiring five to six weeks of daily treatments versus hypofractionated (i.e., >2 Gy fractions) radiotherapy requiring fewer treatments. Overall, these trials have shown equivalent local control of breast cancer and breast cosmesis with conventionally fractionated versus hypofractionated regimens. A Canadian trial compared hypofractionated whole breast regimen delivering a dose of 42.5 Gy in 16 fractions of 2.66 Gy daily fractions over 22 days to conventional fractionation of 50 Gy in 25 daily fractions of 2 Gy each [14]. Both regimens were prescribed without a sequential lumpectomy cavity boost. With median followup of 12 years, the 10-year local control was 93.3% versus 93.8% ($P > 0.05$) for the conventional versus hypofractionated radiation, respectively, with both regimens yielding equivalent cosmesis.

Another trial centered at the Royal Marsden Hospital compared conventional 50 Gy in 2 Gy fractions to two hypofractionated arms, delivering 39 Gy or 42.9 Gy in thirteen 3.0 Gy or 3.3 Gy fractions, respectively, over 35 days. That study yielded equivalent 10-year local control rates of 87.9%, 85.2%, and 90.4% for conventionally fractionated and the two hypofractionated radiotherapy regimens, respectively [15].

Two additional UK trials, START A and START B (Standardization of Breast Radiotherapy), with shorter followup (5-year) similarly demonstrated equivalent local control between treatment arms [16, 17].

In contrast, an ongoing UK FAST trial (Faster Radiotherapy for Breast Cancer Radiotherapy) randomized patients between conventionally fractionated radiotherapy and two hypofractionated schedules, 28.5 Gy in five 5.7 Gy fractions and 30 Gy in five 6 Gy fractions delivered over 35 days. The results of this trial have not yet been reported in full-text form [18, 19].

The question of feasibility of delivering lumpectomy cavity boost after Canadian and other fractionated whole breast schedules has been posed. Both START and the Royal Marsden trials prescribed a boost in more than 30% of the study cohort [15–17]. This has also been addressed by a single institution Memorial Sloan Kettering Cancer Center retrospective series in which hypofractionated whole breast radiation therapy (42.4 Gy in 16 fractions of 2.65 Gy each) was delivered to 128 patients followed by a conventionally fractionated boost of (10 Gy in 5 fractions of 2 Gy each) [20]. That study showed comparable cosmetic outcomes to conventional fraction, and there were no grade 3 or more toxicities recorded after median followup of 1.5 years. Another large single institution UK series confirmed feasibility and favorable outcomes with Canadian fraction followed by boost [21].

In 2010, the American Society for Radiation Oncology (ASTRO) published evidence-based guidelines for hypofractionated whole breast radiotherapy [22]. Suitable candidates for hypofractionated radiotherapy are identified as women aged ≥50 years with pT1-2 N0 M0 tumors and who do not receive cytotoxic chemotherapy. With the latter criterion, there is the advantage of less delay in the delivery of radiotherapy. It is still uncertain whether all women benefit equally from hypofractionated as compared to conventionally fractionated radiotherapy regimens. A retrospective exploratory subgroup analysis of the Canadian trial revealed that the hypofractionated regimen was less effective among women with high-grade tumors (10-year local recurrence 15.6% versus 4.7%, hypofractionated versus conventional fractionation regimens, resp.) [14]. Additional data and continued followup from randomized trials will be important in determining the long-term efficacy and cosmesis from hypofractionated whole breast radiotherapy regimens.

3. Accelerated Partial Breast Irradiation

Accelerated partial breast irradiation (APBI) is another technique used to deliver a course of radiotherapy over an even shorter time frame of, usually, 5 days. This regimen is offered to a select subset of patients [23]. APBI targets

the tissue in the periphery of the lumpectomy tumor bed only. This volume can be targeted with various radiotherapy techniques such as external beam radiotherapy (either 3-D conformal, intensity modulated, or electron radiation therapy), brachytherapy (interstitial or balloon catheter), and intraoperative radiotherapy (electrons or superficial photons). Several randomized clinical trials comparing whole breast to accelerated partial breast irradiation are ongoing. The NSABP B-39/RTOG 0413 trial, goal accrual of 4300, randomizes patients between whole breast irradiation or accelerated partial breast irradiation (with choice of either high-dose rate interstitial brachytherapy, MammoSite balloon catheter, or 3D conformal external bream radiotherapy technique) to a dose of 34 Gy or 38.5 Gy in 3.4 Gy or 3.85 Gy fractions over 5–10 days. Final results of this trial have not yet been reported.

The largest reported APBI trial to date, TARGIT (Targeted Intraoperative Radiotherapy) trial, randomized 2232 women (excluding patients with certain high-risk clinicopathologic features) between whole breast irradiation and a single dose of 20 Gy with intraoperative radiotherapy with superficial low-energy photons. At 4 years, there was no difference in local control between the whole breast (99.1%) and partial breast (98.8%) arms [24].

Results employing Electron Intraoperative Therapy (ELIOT) in 1822 women with early stage breast cancer have been published, demonstrating 97.7% local recurrence rate at 3 years and a 5- and ten-year survivals of 97.4 and 89.7%, respectively, while offering reduction of normal tissues to radiation exposure [25].

GEC-ESTRO (Groupe Européen de Curiethérapie—European Society for Therapeutic Radiology and Oncology); RAPID (Randomized Trial of Accelerated Partial Breast Irradiation); IMPORT LOW (Intensity Modulated and Partial Organ Radiotherapy) are examples of current randomized trials evaluating accelerated partial breast radiotherapy versus whole breast irradiation in the treatment of low-risk breast cancer.

The treatment and cosmetic outcomes of mature and ongoing clinical trials should help to clarify treatment criteria and appropriately stratify patients to partial breast versus whole breast irradiation.

4. External Beam Radiotherapy for Breast Cancer Using Image Guidance

Image guided radiotherapy (IGRT) involves the use of localization techniques at the time of daily treatment to verify accurate positioning. The goal of this endeavor is to reduce patient setup variation, in order to facilitate the use of smaller margins around target volumes to be used. Smaller margins should translate into significantly smaller volume of normal tissue radiated which should in turn reduce acute and late normal tissue toxicity.

In the case of breast cancer treatment, this approach may reduce late effects to the breast tissue, heart, and lungs. Used in conjunction with localization of the target volume, particularly in the case of partial breast irradiation, IGRT may additively improve daily target dose coverage and therefore improve local control outcomes as well. Even in the setting of whole breast treatment, the use of IGRT may facilitate smaller margins as well as advanced techniques such as simultaneous integrated boost and intensity-modulated radiation therapy (IMRT), both of which require a much higher degree of setup certainty to be effectively used in treatment [26, 27].

Aligning to bony anatomy, as is done in MV and KV or cone beam CT imaging, improves setup accuracy compared to the traditionally employed surface tattoos [28, 29]. Using either breast surface or location of intraparenchymal surgical clips improves localization over strictly bony alignment, even when using CT guidance [30]. Still, there is some uncertainty associated with the delineation of the tumor bed target volume because of significant interobserver variability [31, 32]. For example, the Radiation Therapy Oncology Group (RTOG) conducted a multi-institutional interobserver study among nine radiation oncologists specializing in breast cancer, to determine the degree of variability in target volume and organs at risk delineation among three sample cases [33]. They found structure mean overlap of only 72% for the lumpectomy cavity in one case and poor agreement on nodal structures, with percent overlap as low as 10% among different observers [33]. This variation resulted in substantial variations in treatment planning and dose coverage. Consequently, the RTOG has published an atlas of breast, chest wall, nodal regions, and organs at risk to guide a more consistent reproducible approach to contouring [34].

We have recently reported our experience at Moffitt Cancer Center using fiducial-based IGRT in prospective cohort of both whole breast and partial breast patients. We used textured gold fiducial markers, which adheres to the surrounding soft tissue, increasing the likelihood of fiducial stability and consistent visualization. In fact, 100% fiducial visualization on MV imaging and minimal variation, we were able to verify fiducial migration [35].

In the partial breast cohort, there was minimal motion due to intrafraction motion from respiration or changes in respiratory motion between 4D CT scans at the time of simulation to the end of treatment [35]. The mean change in distance between fiducials inter- and intrafraction had a small range 2 to 3 mm, well within the range of error of the total size of the fiducial. Fiducial markers position was stable during treatment with no evidence of substantial fiducial migration within a 5 mm range. The position of the center of fiducial mass relative to the center of the seroma was also stable, confirming the stability and applicability and textured fiducials in IGRT in the setting of APBI [35].

Similarly, in the whole breast cohort, small ranges in inter- and intrafraction motion, respiratory motion, and fiducial migration were observed [36]. Our data suggest that, with fiducial-based image guidance, the PTV margin may be safely reduced from the more standard 10 mm to about 5 mm, substantially reducing the volume of normal tissue irradiated unnecessarily. Other investigators using surgical clips or fiducials for breast cancer radiotherapy have reported similar results [37–41].

5. Newer Techniques for Breast IGRT

Although online cone beam CT (CBCT) allows much more accurate and reproducible alignment in 3 dimensions to the bony anatomy as compared to surface tattoos or port films alignment, pretreatment CBCT does not guarantee accurate intrafraction delivery [42, 43]. Prolonged treatment times and couch rotation can significantly reduce treatment delivery accuracy [44]. To address this confounder, patient surface setup systems and real time tracking systems have been recently explored. Data suggest that surface imaging may offer more precise setup than laser or tattoo with a similar reduction in error as fiducial-based IGRT [45]. Ultrasound systems for localization and tracking of the tumor bed for daily treatment have also been investigated and have shown good correlation between the position of the tumor bed on 3D ultrasound and CT, forecasting the utility of 3D US in the near future [46]. Similarly, implantable electromagnetic transponder fiducials have been used to track breast tumor bed motion in real time [47]. With the rising concern of cumulative radiation doses with multiple CT imaging and the lifetime risk of secondary cancers, modalities such as 3D ultrasound image guidance may offer an attractive alternative.

6. Conclusions

Hypofractionated breast radiation therapy offers the attractive alternative of shorter treatment course which is not only convenient for patients, but also time and cost-effective. The overarching question remains, can we minimize without compromise? Results of randomized and large single-institution studies seem to support the edict that attaining this desirable balance is indeed possible.

Reducing target volume, as in the case of external beam APBI techniques, calls for more refinement of treatment delivery with image-guided radiation therapy to ensure accurate delivery of high-dose radiation while sparing normal tissue such as heart and lungs.

Various methods of performing IGRT, including implanted fiducials, CBCT, surface mapping, and ultrasound afford measurable improvement in setup error allowing for PTV margin reductions to as much as 5 mm. Each institution should apply the optimal IGRT technology for their clinical practice commensurate with the center's equipment availability, physician, and technician experience. For, whole breast radiation, wherein a larger volume of heart and lung is irradiated, there is a compelling argument to incorporate IGRT in our daily set up, to achieve optimal results with minimal toxicity. For accelerated partial breast irradiation in particular, IGRT should be systematically incorporated into our daily treatment algorithm.

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Clinical Study

Prophylactic and Therapeutic Breast Conservation in *BRCA1/2* Mutation Carriers

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Breast-conserving therapy (BCT) for sporadic breast cancer has been widely accepted by surgeons and patients alike. While BCT is associated with a higher risk of ipsilateral breast tumor recurrence (IBTR), it has not been shown to decrease overall survival (OS) in comparison with mastectomy. Many women with a *BRCA1/2* mutation opt for mastectomy instead of breast-conserving measures at the time of a breast cancer diagnosis. In some cases, this is due to fear of aggressive disease, but to date, there have been no studies offering strong evidence that breast conservation should not be offered to these women. *BRCA1/2*-associated breast cancer has not been found to be more aggressive or resistant to treatment than comparable sporadic tumors, and no study has shown an actual survival advantage for mastectomy in appropriately treated affected mutation carriers. This paper reviews the available literature for breast conservation and surgical decision making in *BRCA1/2* mutation carriers.

1. Introduction

Knowledge about *BRCA1* and *BRCA2* and how patients with mutations should be treated has been slow to develop since the discovery of these genes in 1990 and 1994, respectively [1, 2]. Many factors have limited collection of data on this subject, such as availability of testing, expense, fear of testing, and the small number of patients available for study. The resultant lack of knowledge drives and sustains patient anxiety, sometimes prompting them to select mastectomy in hopes of a cure while sacrificing cosmesis, body image, and perhaps sexuality [3, 4]. In a 2003 study by van Oostrom et al., 21 of 23 BRCA1/2 mutation carriers underwent prophylactic mastectomy [5]. These patients reported a less favorable body image, while 70% of them reported changes in their sexual relationships. Prophylactic mastectomy has been shown to reduce the risk of breast cancer incidence or recurrence, but there is insufficient data to support an improvement in survival in affected or unaffected carriers, as discussed later [6–8]. Management decisions in *BRCA1/2* carriers prophylactically or at the time of diagnosis of an invasive cancer are complex. Patients will put different weights on different aspects of treatment, some favoring reducing the anxiety associated with surveillance and testing and some favoring body image. There is insufficient evidence at this time to forgo surveillance and breast conservation as viable options for *BRCA1/2* mutation carriers, options offered to patients with most other forms of breast cancer.

2. Tumor Characteristics of *BRCA1/2*-Associated Breast Cancer

BRCA1/2 mutation carriers are known to have an increased incidence of breast cancer and premalignant lesions [9–13]. Histological differences in *BRCA1*-associated tumors as compared to sporadic tumors have been well described. *BRCA2*-associated tumors differ from those of noncarriers to a lesser extent. Invasive ductal carcinoma, NOS (not otherwise specified) type, is the most common histologic

form of all hereditary breast cancers, including *BRCA1*- and *BRCA2*-associated breast cancers [14]. Most *BRCA1*-associated tumors have the basal-like phenotype and are more frequently ER−, PR−, Her2−, grade III, and of the medullary subtype. The majority of studies show no difference in tumor size or nodal status, factors known to be more important for survival based on our current staging of breast cancer [15–26]. The basal-like phenotype is rarely found in *BRCA2* breast cancers. *BRCA2* breast carcinomas tend to be ER+, PR+, Her2−, and higher grade than sporadic age-matched controls [27]. The growth rate of *BRCA1/2*-associated breast tumors is not accelerated. Multivariate analysis revealed that the apparent faster rate of growth in *BRCA1/2*-associated tumors was found to be associated only with a younger age at diagnosis and premenopausal status [16, 28].

No study has shown that *BRCA1/2*-associated breast cancer is more resistant to chemotherapy than are sporadic breast cancer controls. This issue was specifically addressed in a paper by Robson et al. in 2004, who found that the addition of chemotherapy negated any survival difference in the *BRCA1* mutation carriers compared with sporadic controls [19]. Kriege et al. was similarly able to show that *BRCA2*-associated tumors were more sensitive to anthracyclines than sporadic tumors [29]. Both preclinical and clinical studies have found that *BRCA1*-associated breast tumors are sensitive to platinum agents and cyclophosphamide [30–34]. These studies are small but confirm an increased complete clinical response in *BRCA1/2*-associated cancers compared to sporadic cases.

There was early concern that *BRCA1/2*-associated tumors were particularly radiosensitive [35], and because of the role of these genes in DNA repair [35–37], that radiation therapy may stimulate additional tumor formation. Studies by Gaffney et al. and Pierce et al. found no evidence that radiation therapy in this patient population is associated with increased complications, recurrence, or with increased tumorigenesis [24, 38].

Many women fear that *BRCA1/2*-associated cancers are more aggressive than are sporadic tumors. The most important question to answer here is whether there is a difference in breast cancer specific survival (BCSS) or overall survival (OS) between hereditary and sporadic tumors. Numerous studies have addressed this issue, but they are limited by small patient numbers and differences in treatment. To date, we have found no studies that show a statistically significant difference in BCSS or OS after a breast cancer diagnosis when *BRCA1/2* carriers are compared with matched sporadic controls [15, 18–21, 23, 25, 38–41].

3. Breast Conservation Therapy in Affected Mutation Carriers

There are limited studies evaluating breast conservation for *BRCA1/2* mutation carriers diagnosed with breast cancer (affected carriers). The information we seek to learn is in regard to the risk of ipsilateral breast tumor recurrence (IBTR), the risk of contralateral breast cancer (CBC), breast cancer-specific survival (BCSS), and OS. In general, the evidence available for evaluation is found in small retrospective studies, most with relatively short followup. The small number of patients and lack of long-term followup are important concerns, as it is the number of events that provides the needed information (Table 1). Ipsilateral or contralateral disease can be new or recurrent disease. In the ipsilateral breast, different quadrants or different histology can be indicators of new primaries. Contralateral tumors, invasive or noninvasive, are assumed to be new primaries.

Several reports by Pierce et al. about breast conservation in *BRCA1/2* mutation carriers stand out, as they directly compare mastectomy to breast conserving therapy (BCT) [40]. Their latest study, published in 2010, compares breast conservation to mastectomy in 655 women with *BRCA1/2* mutations diagnosed with breast cancer. 302 of these women who underwent BCT and 353 who underwent unilateral mastectomy were followed for 8.2 years and 8.9 years, respectively. The estimated 15-year rate of IBTR was 23.5% in the BCT group and 5.5% in the mastectomy group ($P = 0.0001$, HR 4.5). The ipsilateral recurrences were felt to be second primaries in 16 of 23 (70%) cases. Two other studies published in the last 10 years also show a difference in IBTR between these two groups. Haffty et al. reported findings of 22 patients with a *BRCA1/2* mutation compared to 105 women without this mutation, all of whom underwent BCT [22]. All of the study participants were diagnosed with breast cancer by the age of 42 and were followed for a median of 12 years. These researchers reported an IBTR rate of 49% in the mutation carriers compared to 21% in the controls ($P = 0.007$). They similarly believed that these ipsilateral recurrences were second primaries rather than true recurrences. Garcia-Etienne et al. followed 54 *BRCA1/2* patients and 162 sporadic controls treated with BCT with a median followup of 4 years [23]. They reported a projected 10-year rate of IBTR of 27% in mutation carriers compared to 4% in the sporadic controls, HR 3.9, $P = 0.03$ based on 6 events in the carrier arm and 4 events in the control arm. Criticisms of these studies include the observations that there was a statistically significant difference in the mean age of the *BRCA1/2* mutation carriers (33 years) and the sporadic controls (37 years), ($P = 0.001$) and that none of the mutation carriers underwent bilateral salpingo-oophorectomy (BSO), nor did they receive hormonal therapy (as compared to the 15% in the sporadic group, $P = 0.05$) in the study by Haffty et al. [22]. Both studies by Pierce et al. and Garcia-Etienne et al. project their data over longer time points to estimate a difference in tumor recurrence [23, 40].

Several other informative studies have been published reporting a rate of IBTR in patients undergoing BCT that contradicts the findings reported above. An earlier study by Pierce et al. revealed that there was no difference in IBTR between 160 *BRCA1/2* mutation carriers and 445 matched controls all undergoing BCT with a median followup of 6.7 to 7.9 years [21]. Kirova et al. found no difference ($P = 0.13$) in IBTR when they compared 27 *BRCA1/2* mutation carriers to 104 patients with a family history of breast cancer to 261 matched controls with a 13.4 year followup [20]. Kirova at al. found age to be the most significant predictor of IBTR, with

Table 1: Outcomes of affected BRCA1/2 mutation carriers.

Study	Design	Patients	Followup	IBTR	BCSS	OS
Pierce et al. [40]	1	BCT = 302 Mast. = 353	8.2 to 8.9 years. Data projected to 15 years	BCT = 23.5% Mast. = 5.5%	BCT = 91.7% Mast. = 92.8% $P = 0.85$	BCT = 87.3% Mast. = 89.8% $P = 0.73$
Haffty et al. [22]	2	BRCA = 22 Sporadic = 105	12.7 years	BRCA = 41% Sporadic = 19% $P = 0.007$		
Garcia-Etiene et al. [23]	3	BRCA = 54 Sporadic = 162	4 years. Data projected to 10 years	BRCA = 27% Sporadic = 4% $P = 0.03$		
Pierce et al. [21]	4	BRCA = 160 Sporadic = 445	6.7 to 7.9 years. Data projected to 15 years	BRCA = 24% Sporadic = 17% $P = 0.19$		
Kirova et al. [20]	5	BRCA = 27 Familial = 104 Sporadic = 261	13.4 years	BRCA = 45% Familial = 31% Sporadic = 24% $P = 0.33$		Not significant at 20 years. Actual rates not reported.
Brekelmans et al. [25]	6	BRCA = 326 Familial = 311 Sporadic = 759	4.3 to 5.1 years. Data projected to 10 years	BRCA = 20 to 25% Familial = 6% Sporadic = 5% $P = 0.001$	BRCA = 62 to 68% Familial = 70% Sporadic = 59% $P = 0.17$	BRCA = 50 to 60% Familial = 66% Sporadic = 55% $P = 0.32$
Robson et al. [41]	7	BRCA = 28 Sporadic = 277	10.3 years	BRCA = 22% Sporadic = 7% $P = 0.25$	BRCA = 72% Sporadic = 87% $P = 0.02$*	BRCA = 66% Sporadic = 81% $P = 0.05$*
Robson et al. [19]	8	BRCA = 56 Sporadic = 440	9.7 years		BRCA1 = 63% BRCA2 = 86% Sporadic = 86% $P = < 0.0001$**	

Abbreviations: IBTR: in-breast tumor recurrence; BCSS: breast cancer-specific survival; OS: overall survival; BCT: breast conserving therapy; Mast.: mastectomy; BRCA: *BRCA1/2* unless otherwise specified.

Study design: 1, *BRCA1/2* carriers diagnosed with breast cancer treated with BCT or mastectomy. 2, *BRCA1/2* carriers versus sporadic cancer diagnosis in women ≤42 years of age undergoing BCT. 3, *BRCA1/2*-associated cancer matched with sporadic controls for age and year of surgery treated with BCT. 4, *BRCA1/2*-associated cancer matched with sporadic controls treated with BCT. 5, *BRCA1/2*-associated cancer versus patients with family history of breast or ovarian cancer versus sporadic controls matched for age and year of diagnosis treated with BCT. 6, breast cancer patients with versus without a family history of *BRCA1/2* mutation versus sporadic controls matched for age and year of diagnosis treated with BCT or mastectomy. 7, Ashkenazi Jewish women with versus without the *BRCA1/2* founder mutation undergoing BCT. 8, Ashkenazi Jewish women with versus without the *BRCA1/2* founder mutation undergoing BCT.

*Reached significance on univariate analysis but was lost on multivariate analysis.

**This result was mitigated by and was no longer significant after the addition of chemotherapy.

a relative risk (RR) of 1.05 for each decreasing year of age ($P = 0.01$). Two other studies have reported no difference in IBTR, but these differ in their methods. Brekelmans et al. reported no difference in IBTR in 226 patients with a family history of *BRCA1/2* compared with 311 patients with a family history of breast cancer but testing negative for *BRCA1/2* in the family, and compared to 759 patients with sporadic breast cancer, with a mean duration of followup from 4.3 to 5.1 years [25]. Robson et al. also found no difference in IBTR at 10 years when they compared 28 women of Ashkenazi descent with *BRCA1/2* mutations to 277 women of Ashkenazi descent without mutations, but they did find age <50 to be a statistically significant risk of IBTR on univariate analysis (16% versus 6%, $P = 0.01$) and on multivariate analysis (RR 2.51, $P = 0.01$) [41]. Interestingly, it appears that age at diagnosis rather than *BRCA1/2* mutation status is prognostically important in predicting IBTR [20, 22, 41].

With regard to the risk of contralateral breast cancer, Pierce et al. reported no significant difference in the rate of CBC between the 302 *BRCA1/2* mutation carriers who underwent BCT and the 353 *BRCA1/2* mutation carriers who underwent unilateral mastectomy [40]. All of the other studies we reviewed did reveal a difference in CBC ranging from 1% to 11% in controls to 25% to 42% in mutation carriers when *BRCA1/2* mutation carriers were compared to patients with familial, non-*BRCA1/2*-associated breast cancer and/or sporadic controls [20–23, 25, 41, 42].

We found no study that showed a survival difference when BCT was compared to mastectomy in *BRCA1/2* mutation carriers or when BCT was compared in *BRCA1/2* mutation carriers and familial, non-*BRCA1/2*-associated breast cancer and/or sporadic controls [19–21, 23, 25, 40, 41]. Survival is influenced by stage of disease at diagnosis, tumor characteristics, and treatment. Triple-negative tumors

appear to influence survival; therefore, the mix of *BRCA1* and *BRCA2* cases in a given paper may also influence survival data. Because of the small patient population reported in these papers, we are not able to separately evaluate *BRCA1* and *BRCA2* for IBTR, CBC, BCSS, and OS in triple-negative breast cancer. Due to the increased risk of IBTR and the elevated risk of CBC in *BRCA1/2* mutation carriers, risk-reducing strategies such as BSO or the use of tamoxifen, for those with ER-positive tumors, should be employed as they have been shown to reduce breast cancer recurrence [43].

4. Risk Reduction with Bilateral Prophylactic Mastectomy (BPM), Bilateral Salpingo-Oophorectomy (BSO), and Tamoxifen in Unaffected Mutation Carriers

Many women elect to undergo bilateral prophylactic mastectomy (BPM) sometime after learning of their *BRCA1/2* mutation status. The reasons for this decision are complex and will be discussed in the next section. The benefits of BPM in unaffected mutation carriers are known primarily through the results of a few published studies. The Prose study group has published two papers that detail the benefits of BPM. Their first paper, published in 2004, followed 483 women with a *BRCA1/2* mutation for a mean of 6.4 years [6]. They reported a 1.9% prevalence of breast cancer in 105 women who underwent BPM compared with 48.7% of 378 women undergoing surveillance only**.** Women who had undergone prophylactic BSO were excluded. Their followup study with additional patients, reported in 2010 by Domchek et al. with three years of prospective followup, also noted a difference in breast cancer diagnosis, from 0% in the BPM group to 7% in the non-BPM group [44]. A study predating these, by Meijers-Heijboer et al. [7] prospectively followed 139 women with *BRCA1/2* mutations for a mean of 2.9 to 3 years [7]. 76 of these women underwent BPM and were found to have no breast cancers diagnosed, compared with 8 of 63 women (12.7%) who underwent screening only ($P = 0.003$). The authors do not provide data related to survival differences in these papers, as the number of events is too small, as is the length of followup [6, 7, 44].

The preventive benefit of prophylactic BSO does appear to reduce the prevalence of breast cancer as well as to improve BCSS and to improve OS in premenopausal *BRCA1/2* mutation carriers [25, 40, 44]. Therefore serious consideration should be given to this preventive measure in women after they complete their families, ideally between 35 and 40 years or individualized based on the earliest age of ovarian cancer diagnosis in the family. Women who are *BRCA1/2* mutation carriers and choose not to undergo prophylactic BSO may wish to consider the use of tamoxifen, as it has been shown to reduce breast cancer incidence in that group [43, 45]. For young women with *BRCA1/2* mutations or who are otherwise at high risk for breast cancer, the current American Cancer Society guidelines recommend the inclusion of screening MRI, which has been shown in several studies to have increased sensitivity (79.5% to 91%) for T2 or smaller breast cancer compared to mammography with or without the addition of ultrasound (33% to 50%) [46–49]. No recommendations exist for surveillance after a diagnosis of breast cancer in this population.

5. Surgical Decisions in Affected and Unaffected *BRCA1/2* Mutation Carriers

Several studies have addressed surgical decision making in unaffected *BRCA1* and *BRCA2* mutation carriers. The reported proportions of women who adopt risk-reducing bilateral mastectomy versus intense surveillance are highly variable. A limited review of the literature revealed six studies that analyzed the utilization of risk-reducing mastectomy versus surveillance in unaffected women identified as carrying a *BRCA1* or *BRCA2* gene mutation [50–55].

In a study of 279 adult male and female members of families with an identified *BRCA1* gene mutation from a registry maintained by the Creighton University Hereditary Cancer Institute, 43% requested *BRCA1* test results [50]. Of those tested for the previously identified familial mutation, 46% (53 of 115 electing to receive results) were mutation carriers. Among the unaffected *BRCA1* mutation carriers with no previous prophylactic surgery, 17% (2 of 12) intended to have risk-reducing bilateral mastectomy, but none had actually undergone surgery 1 month after *BRCA* testing. Likewise, Botkin et al. documented a low rate of risk-reducing bilateral mastectomy among 37 unaffected *BRCA1/2* mutation carriers [51]. At 2 years after testing, no women had undergone mastectomy for cancer prophylaxis; however, some reported that they were strongly considering surgery. Of those women, 2 of the 20 women in the younger (25–39 years) age group stated that they were considering this procedure, and 2 of the 12 women in the older (40 years and older) carrier group stated that they were considering it. In addition, Botkin et al. reported an increase in the utilization of mammography and self-breast examination among unaffected carrier females who did not chose surgery.

In contrast, three studies demonstrated a larger number of unaffected *BRCA* carriers who elected to undergo BPM. In a Rotterdam-based study of unaffected women with an identified mutation who were eligible for prophylactic surgery, 51% (35 of 68 women) opted for risk-reducing bilateral mastectomy [52]. The authors reported that of these women, there was a tendency towards mastectomy at younger ages; most were between 30 and 44 years old. Also, the decision to undergo BPM was often made within the first year following receipt of their *BRCA* test results. Lodder et al. found that 53.8% of mutation carriers (14 of 26 unaffected *BRCA* carriers) underwent BPM one year after genetic testing [53]. They reported that often the decision for preventive surgery was made before the disclosure of test results for women who had a 50% *a priori* risk of carrying a known familial *BRCA* mutation. Lastly, in the largest prospective study of 251 individuals with confirmed *BRCA* mutations at Memorial Sloan-Kettering Cancer Center, 29 of 194 women (14.9%) who had breast tissue at risk at the time they received genetic test results underwent bilateral mastectomy for cancer prophylaxis within a median of 5.3 months after

receiving results [54]. Twenty of the 233 *BRCA* carriers had previously elected BPM based on family history alone. Data presented at the Facing Our Risk of Cancer Empowered *Joining FORCEs* conference in 2007 by Dr. Steve Narod and published in 2008 by Metcalf et al. discussed international variation in the decision to undergo prophylactic surgeries [55, 56]. Narod introduced data from an ongoing study of 8,058 known *BRCA1* or *BRCA2* mutation carriers from 11 countries. Within a four-year followup period, 36% of unaffected carriers from the United States chose BPM. Overall 248 (18%) of the 1382 unaffected carriers from all countries chose prophylactic mastectomy.

Many BRCA1/2 mutation carriers diagnosed with breast cancer (affected carriers) opt for bilateral mastectomy rather than BCT for initial treatment of disease. Therefore, hereditary cancer risk assessment at the time of diagnosis may significantly affect a woman's treatment decisions. Four studies investigating surgical decision making in *BRCA* carriers at breast cancer diagnosis were identified through our literature search. Weitzel et al. found that 7 of 32 (22%) women with a newly diagnosed breast cancer carried a deleterious *BRCA* mutation [57]. All 7 of these women opted for contralateral prophylactic mastectomy. In a prospective study of 194 newly diagnosed breast cancer patients at Lombardi Cancer Center, 31 women were identified as carrying a *BRCA* mutation [58]. Forty-eight percent of these carriers chose bilateral mastectomy as the definitive surgical treatment for their breast cancer. Evans et al. identified 20 of 70 newly diagnosed breast cancer patients younger than 50 as *BRCA* mutation carriers [59]. Four of these women were aware of their genetic status at the time of diagnosis and three elected bilateral mastectomy. Four women were told of their mutation status within four weeks of diagnosis. Of these, two opted for bilateral mastectomy although one chose delayed contralateral mastectomy. The remaining 12 mutation carriers were told of their genetic status 3–36 months after diagnosis. Of these 12 women, one opted for contralateral mastectomy. In the data presented by Narod, the percentage of breast cancer survivors choosing contralateral prophylactic mastectomy was outlined for 8 countries, with Israel showing the largest proportion of prophylactic surgery (52%) followed by the United States (49%), Canada (28%), France (20%), Austria (16%), Italy (6%), and Poland (4%) [55].

For women and families who are found to carry a variant of uncertain clinical significance (VUS) in either *BRCA1* or *BRCA2*, screening recommendations are offered according to personal and family history of cancer. There are few reports documenting prophylactic surgery and screening behaviors of individuals whose *BRCA* test results revealed a VUS, which is most likely a reflection of medical management guidelines published by the National Comprehensive Cancer Network, the National Society of Genetic Counselors, and the American Society of Clinical Oncology [60–62]. Surgical decision making in the context of a *BRCA* VUS is also based on personal and family history, as a VUS is uninformative with respect to cancer risk. Those individuals with classic hereditary breast-ovarian cancer syndrome may elect risk-reducing surgery based on family history alone and their own level of concern and anxiety. There are no published data to support prophylactic surgery in the equivocal risk population based on a *BRCA* VUS. Weitzel et al. reported that one of three women identified with a VUS at the time of a breast cancer diagnosis elected risk-reducing mastectomy even though they were counseled that the results of the *BRCA* sequencing were uninformative [57]. Those patients cited fear of cancer and uncertainty associated with the finding of a VUS as reasons for pursuing mastectomy.

Although the risk of breast cancer in other hereditary cancer predisposition syndromes, such as Li-Fraumeni and Cowden syndrome, is known to be significantly elevated above that in the general population (as high as 50%), the efficacy of appropriate medical management and cancer prevention options for these patients has not been widely studied; therefore, they are based mainly on expert opinion. Current recommendations suggest discussing the option of prophylactic mastectomy on a case-by-case basis, including a detailed discussion reviewing the risk reduction benefit, cancer risks, and available reconstruction options [60].

Many factors contribute to the decision-making process with respect to increased surveillance and prophylactic surgeries for mutation carriers. The process is complex and can have a strong psychological impact, a subject that has also been extensively explored in the literature. Unaffected *BRCA* carriers who elect prophylactic mastectomy often report a higher perceived risk of developing breast cancer, higher levels of cancer-related worry, and higher levels of cancer-related distress than those who opt for surveillance. Individuals choosing risk-reducing surgery may also be aware of the hereditary nature of cancer in the family for a longer period of time and report a greater number of relatives affected with breast and ovarian cancer in the family, resulting in more first-hand experience with cancer and making them more apt to consider surgery for risk reduction [53, 63, 64]. Many studies have shown that women who choose bilateral mastectomy tend to be younger (between 30 and 43 years of age), have young children, and have a fear of leaving behind young children [52, 53, 64]. Surgical risk reduction is also sought with the intent to prolong life, the relief associated with a significant reduction in cancer risk, the negative pathologic characteristics of the tumor, and the desire to avoid further surgery at a later stage of cancer [53, 54, 59].

In contrast, *BRCA* mutation carriers who opt for surveillance cite reasons relating to possible dissatisfaction with general body image following mastectomy, the sexual relationship, and their trust in surveillance modalities. Women who opt for surveillance report being worried that they will not feel feminine, will not feel sexually attractive, and will have problems in the intimate relationship following mastectomy [53]. Unaffected *BRCA* carriers opting for surveillance specifically say that prophylactic bilateral mastectomy is too drastic an intervention and that they are reluctant to have healthy breast tissue removed. In addition, these women feel that they have time to explore the options of surgical risk reduction while undergoing surveillance. However, it is recognized that these attitudes may change over time, especially after a longer period of

intensive breast surveillance and failure to comply with followup recommendations [64].

The majority of women who elect risk-reducing mastectomy are satisfied with their decision [65]. Those women who do regret undergoing mastectomy report that the dissatisfaction stems from surgery complications, poor cosmetic outcome, residual pain, fear that reconstruction will impede breast cancer detection, poor self-image, sexual dysfunction, lack of psychological support after surgery, and the fact that the subject of mastectomy was initiated by the physician rather than by the patient herself [53, 65–67]. With regard to the latter, many studies have illustrated that physician recommendations are an important determinant of surgical decisions, especially for women with a newly diagnosed breast cancer [58].

The decision to undergo prophylactic mastectomy for both unaffected *BRCA* mutation carriers and newly diagnosed carriers is a major, irreversible decision. Although a minority of *BRCA* carriers choose prophylactic mastectomy over intense surveillance, the majority of women who choose mastectomy are satisfied with their decision, report reduced cancer-related anxiety about developing breast cancer following surgery, and report favorable psychosocial outcomes.

6. Conclusions

It is clear that women with *BRCA1/2* mutations have a much higher risk of developing breast cancer than the 12.5% lifetime risk of the general population [68]. The risk of developing breast cancer by the age of 70 for carriers of *BRCA1* is 57% to 65%, while the risk in *BRCA2* carriers is slightly lower, at 45% to 49%, based on the findings of two recent metaanalyses [12, 13]. Many women choose to undergo bilateral prophylactic mastectomy, which has been shown to reduce the incidence of breast cancer in these patients, after learning that they are mutation carriers [6–8, 44]. Reduced BCSS in unaffected carriers is assumed although it has not been objectively quantified because of the short duration of followup and low number of events in these studies.

It appears that many women diagnosed with an invasive breast cancer associated with a *BRCA1/2* mutation or a strong family history choose mastectomy as their definitive surgical therapy in lieu of breast conservation with irradiation. Other authors have reported the increased use of mastectomy over breast conservation in the general population with sporadic breast cancers for a variety of reasons as well [69, 70]. It has been shown that affected carriers undergoing mastectomy rather than BCT have a lower incidence of IBTR [19–23, 25, 40, 41]. Perhaps there is the benefit of "peace of mind" that comes with the reduced IBTR that those treated with BCT, and therefore, still subject to screenings and biopsies, do not have.

It has not been established that mastectomy at the time of a cancer diagnosis is the best therapeutic option, as several studies have shown that the BCSS and/or the OS in *BRCA1/2* is no different than that of sporadic cancers [15, 18, 39, 71, 72]. Studies evaluating breast conservation for the treatment of invasive disease in *BRCA1/2* carriers compared to that in sporadic controls reveal mixed results related to IBTR, but none have shown a difference in BCSS and/or OS [20, 22, 23, 25, 41, 71]. One study that compared mastectomy to breast conservation in *BRCA1/2* carriers noted an increased IBTR but no difference in OS [40]. For *BRCA1/2* mutation carriers who opt for BCT, risk-reducing strategies, such as the use of tamoxifen (for ER+ tumors) or BSO, are appropriate, as they appear to reduce the risk of IBTR and CBC [21, 22, 40, 43, 45]. No individual recommendations can be made for *BRCA1* apart from *BRCA2* mutation carriers, as most studies consider them together and have thus far had inadequate numbers to segregate the two despite their histologic differences and the proposed differences in cell function that *BRCA1* and *BRCA2* control [73].

At this time, the use of breast-conserving therapy in patients who are mutation carriers or who have a very strong family history for breast cancer should be handled on a case-by-case basis. Patients should be evaluated and informed about the current existing data and outcomes before an ultimate surgical decision is made. Consultation with a genetic counselor may be of benefit in helping the patient make an informed decision.

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