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Prophylactic Mastectomy:

Challenging Considerations for the Surgeon

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Abstract

The use of bilateral prophylactic mastectomy contralateral prophylactic mastectomy (CPM) has both increased significantly over the last decade. Various risk models have been developed to identify patients at increased risk for breast cancer. Indications for bilateral prophylactic mastectomy in patients without a diagnosis of breast cancer include patients at high risk from BRCA or other genetic susceptibility gene mutations, a very strong family history with no identifiable mutation, and patients with high risk based on breast histology.

Additionally, the use of CPM has more than doubled in the last decade, and this increase is noted among all stages of breast cancer, even in patients with ductal carcinoma in-situ (Stage0). The risk of contralateral breast cancer is often over-estimated by both patients and physicians. Nevertheless, specific risk factors are associated with an increased risk of contralateral breast cancer, including BRCA or other genetic mutation, young age at diagnosis, lobular histology, family history, and prior chest wall irradiation.

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While CPM reduces the incidence of contralateral breast cancer, the effect on disease-free and more importantly overall survival is questionable and is underscored by the fact that the reason most patients choose CPM is ‘peace of mind’. Newer and effective reconstructive options have made the procedure more attractive. This panel addresses the indications and rationale for bilateral prophylactic mastectomy and CPM, the decision-making process by patients, and ethical considerations. Changes in the physician-patient relationship over the past few decades have altered our approach, and ethical considerations are paramount in addressing these issues.

The use of bilateral prophylactic mastectomy contralateral prophylactic mastectomy (CPM) has both increased significantly over the last decade. Additionally, the use of CPM has more than doubled in the last decade. The risk of contralateral breast cancer is often over-estimated by both patients and physicians. While CPM reduces the incidence of contralateral breast cancer, the effect on disease-free and more importantly overall survival is questionable and is underscored by the fact that the reason most patients choose CPM is ‘peace of mind’. This panel addresses the indications and rationale for bilateral prophylactic mastectomy and CPM, the decision-making process by patients, and ethical considerations.

Is there a survival benefit to surgery?

For patients interested in CPM, several endpoints need to be considered. First is an assessment of the risk of contralateral breast cancer (CBC) to determine the absolute potential decrement in CBC risk with CPM. Several factors contribute to risk of a second breast primary: BRCA mutation status, family history (regardless of BRCA), age at diagnosis, hormone receptor status and possibility of adjuvant endocrine therapy. [1,2,3,4,5]. A deleterious BRCA 1 or 2 mutation, family history of breast cancer (particularly first degree relatives), younger age at diagnosis (even without a family history) and hormone receptor negative tumors are all associated with increased risk of CBC.

There are dynamic associations amongst these factors that impact long term CBC risk. Even amongst BRCA mutation carriers, risk of CBC varies based on the age of initial breast cancer diagnosis [6]. Similarly, the number and age of affected family members impacts the CBC risk of a BRCA mutation carrier [3]. Amongst women who are *not* BRCA mutation carriers, age based risk varies with family history [1]. These associations create additional complexity when trying to determine any given woman’s risk of CBC; to date, there is no one single model that comprehensively accounts for all these risk elements and considers their interdependent influence on CBC risk.

A second consideration when counseling patients considering CPM is the impact of operation on disease free survival (DFS). The field is challenged by lack of any clinical trial data. Data is limited and studies rely heavily on population level analyses and statistical modeling. However, these data do suggest a modest association between CPM and DFS in small subsets of women, typically those diagnosed young, with early stage disease that is hormone receptor negative[7.8.9]. In the majority of breast cancer patients, no clear data exists demonstrating association between CPM and DFS, speaking to the unique combination of events that need to be present to affect DFS outcomes; a relatively low risk of dying of the index event coupled with a relatively high risk of CBC and few, if any, other comorbid

conditions that would contribute to early mortality. This combination of findings is relatively uncommon amongst the breast cancer population.

Lastly, consideration needs to be given to CPM and overall survival (OS). Here, data is even more scarce and less compelling in demonstrating benefit of CPM. Although Herrinton showed an improvement in all-cause mortality associated with CPM, this data needs to be taken with caution as this analysis also demonstrated improvement in mortality from causes other than breast cancer as a result of CPM [10]. Since the only potential mechanism by which CPM may improve survival is by reduction of CBC, a finding of CPM improvement in survival not associated with breast cancer, leads to significant concerns of bias. More compelling is data from Portschy, modeling OS outcomes from CPM, show no meaningful improvement[9]. This lack of OS benefit from CPM is due to the fact that most CBC are detected early, thus curable, thus with no impact on OS.

Navigating surgical treatment decisions with patients

Surgeons are surprised by the surge of patient interest and desire for CPM with reconstruction. Only about 5% of women with breast cancer received CPM in 2006, representing about 10–15% of mastectomies performed that year.[11] Most recent data suggests CPM rates have increased to as much as 25% of patients newly diagnosed, representing up to half of women undergoing mastectomy. Nearly 90% of patients who have CPM undergo reconstruction. Most women today who receive CPM do not have elevated risk of a 2nd primary.[12] Thus, CPM provides no benefit of DFS. [13]

Reasons for the increased rates of CPM are largely due to patient heightened awareness and desire for more extensive surgery. Dramatic highly publicized stories of media celebrities undergoing ‘life-saving’ CPM created a powerful image that resonated with patients. These stories conflated scenarios of women with marked elevated risk of a 2nd primary (Angelina Jolie), who realized a documented benefit of risk reduction with CPM, with breast cancer patients at average risk of 2nd primary, in whom there is no benefit of DFS. Patients are more aware of the CPM from media reports but also from neighbors, friends, colleagues, or family members who have undergone and are proponents of the procedure.

Powerful intuitive judgement factors, heuristics and counterfactual thinking, fuel the desire for more extensive treatment. Aversion to uncertainty and the desire for greater peace of mind is endorsed by virtually all women who undergo CPM, the desire to move beyond the threat of the diagnosis as completely and quickly as possible. Another powerful driver is anticipated regret: we make decisions in the moment to minimize future regret. Many patients convey this counterfactual thinking: “I want to do everything I can now because if I get a recurrence I feel that I did what I could”. A fundamental problem with anticipated regret is that it focuses on total threat of recurrence rather than the net benefit of the different treatment options. Furthermore, psychology research has confirmed we are not good at predicting our reactions to future events. Heuristics and counterfactual thinking are cloaked in the abyss of the subconscious and thus difficult to address. A paradox increasingly recognized is that patient satisfaction with surgical treatment decision-making is very high but their knowledge about the tradeoffs between the different treatment options is extremely

low.[14] This paradox underscores that patient deliberation over numbers is not a primary determinant of preference for treatment.

The dominance of intuition over deliberation in patient preferences for treatment poses major challenges for surgeons.[15] One important goal is to focus patient's attention on the net benefit of treatment and away from the total threat of the disease. Surgeons need strategies to focus patient attention on lack of benefit of CPM in disease free survival. The immediate intuitive reaction of patients to the management plan is not the same as long term quality of life. Bigger breast surgery is back on the radar screen. Research is needed to examine how patient, surgeon, and system factors influence utilization of expanding treatment options for women.

The Choice for Contralateral Prophylactic Mastectomy: Autonomy and Ethics

The "epidemic" of requests for CPM often comes from women without genetic or other risk factors for cancer. CPM has been used for both small invasive cancers as well as for DCIS.

Consider a Case: A 39-year-old woman has a 1.7 cm invasive lobular breast carcinoma. Her surgeon discusses options of breast conservation versus mastectomy. The patient requests a mastectomy with CPM because of concerns with recurrence. Despite the surgeon's outlining increased risks and longer operative times, if the patient wants CPM, most surgeons will provide this and most insurance companies will pay for it.

Would this situation be different 50 years ago?

A 39-year-old woman presents with a 2 cm breast lump in 1970. The surgeon likely encouraged her to have a "one step procedure," i.e. a biopsy under general anesthesia and, if cancerous, a radical mastectomy. This approach eliminated any discussion of "controversial" less aggressive procedures. Doctors and patients had long-standing relationships and often shared a common value system. As the medical authority, the doctor made decisions, and medical benefit was equated with patient benefit. Patients were vulnerable and passive.

The evidence of paternalism is clear. The diagnosis of cancer was often not discussed with patients. A study in JAMA in 1961 interviewed physicians regarding what they tell patients about diagnoses, and 88% of physicians stated that they generally did not tell a patient a diagnosis of cancer.[16]

In the past several decades, many changes have occurred in the ethos of medical practice. The concept that doctors always know best was challenged. Physicians came to accept that what is *medically* beneficial might not always be *best* for a patient. The question, "what can be done?" was often replaced with "What should be done?" To answer this latter question when doctors and patients less frequently shared a common value system, patient input became essential.

Respect for patient autonomy became the new paradigm for the doctor-patient relationship. Patients needed information to participate in decisions, and "shared decision-making"

became widely accepted. Evidence for this change is clear: Novack, in 1979, gave the same survey in the same hospital as Oken had given 16 years earlier. But this time, 98% of physicians reported that their "general policy is to tell patients a cancer diagnosis."[17]

Significant changes occurred in breast cancer treatment. Radical mastectomy lost favor. Randomized controlled trials became the standard for evidence. Activism in breast cancer became important. Laws were passed mandating the discussion of options. A 1979 Massachusetts law required surgeons to advise each breast cancer patient of all alternatives to mastectomy. By 1990, 16 states had similar laws. All required presentation of alternatives so that patients could make the choice of treatment for themselves.

Consider CPM and patient "benefit. How should physicians weigh improved quality of life of relative to whether CPM benefits the patient? We are seeing a paradigm shift. Medical progress is no longer determined purely by improvement in the outcome. Benefit previously defined as increased longevity or decreased morbidity and mortality, is now defined relative to the patient's values.

Respect for patient autonomy is central in medical ethics today. However, this principle must be balanced against non-maleficence (avoiding doing harm). If a patient with no risk factors for cancer were to request bilateral prophylactic mastectomy, many surgeons would find this request unacceptable.

A central controversy is the following: Are we seeing the appropriate extension of respect for patient autonomy in going along with all requests for CPM? Or has the pendulum swung too far such that physicians no longer have input on what will benefit patients? Patient choice is critical in breast cancer surgery. Respect for patient autonomy is essential for the ethical practice of medicine. However, respecting autonomy does not require acceding to every patient request. More studies are needed to define the potential risks and benefits of CPM. Physicians should focus on improving communication so that true "shared decision-making" can occur.

Beyond BRCA1 and BRCA2

Mutations in BRCA1 and BRCA2 account for the majority of familial breast cancer cases with an identifiable cause. The invention of massive parallel sequencing and the subsequent commercialization of multi-gene panel tests has greatly expanded the list of breast cancer predisposition genes but has only been able to explain an additional 5–7% of apparent genetic high risk families.[18,19] When a sequence variant is identified on a panel test, the first task is to determine whether that variant increases cancer risk or not. We usually rely on the company performing the test to do this for us. This is the major source of variability in test results reported by different providers. It is important to recognize that some of the genes included on panel tests have not been convincingly linked to breast cancer and there is a 20 – 40% chance that the test will identify a sequence variant that simply cannot be classified as deleterious or not based on existing information. Some approaches to avoiding interpretation difficulties include only testing families with multiple cases of early onset breast cancer, begin testing with the relative with the greatest mutation probability, and restricting the test

to genes for which there are published management guidelines (BRCA1, BRCA2, TP53, CDH1, STK11 and PTEN)[20].

Once a deleterious mutation has been identified, the next step is to estimate the cancer risk for the specific family in question. Apart from BRCA1 and BRCA2, the genes most commonly identified on panel tests are CHEK2, PALB2 and ATM. These genes have traditionally been classified as moderate penetrance genes and in most families this is likely the case. No cancer predisposition gene acts in isolation, however. Each can be made more virulent or less virulent depending on the genetic background of the family. For example, one study that genotyped CHEK2 for four founder mutations in 7,494 BRCA1 mutation-negative patients with breast cancer and 4,346 control women, estimated lifetime breast cancer risk for truncating mutations at 20% for a woman with no affected relative, 28% for a woman with one affected second-degree relative, 34% for a woman with one first-degree relative, and 44% for a woman with both a first- and second-degree relative[21]. Similarly, most missense mutations in ATM are unlikely to significantly increase breast cancer risk, but certain rare mutations have been associated with up to 60% lifetime risk in some families[22,23]. The situation is similar for PALB2 where, increasingly, families are being identified with breast cancer risk similar to high risk BRCA2 families.

When confronted with a deleterious mutation in any gene, including BRCA1 or BRCA2, the clinician must first go back to the extended pedigree in order to estimate the family-specific penetrance. Lifetime breast cancer risk in some families will be high enough to warrant risk-reducing mastectomy, but for others, less invasive alternatives, such as enhanced surveillance, may be more reasonable.

CPM and Implications for Reconstruction

While a woman's choice to undergo contralateral prophylactic mastectomy (CPM) is clearly multifactorial, reconstruction is an important consideration and potential influence. Post-mastectomy reconstruction may be performed using either breast implants or a woman's own tissue (autologous reconstruction). While both approaches create a breast mound, there are subtle but significant differences in long-term outcomes. These differences are most pronounced among women undergoing unilateral mastectomy and reconstruction. Specifically, unilateral implant reconstruction generally fails to fully 'match' the contralateral breast without a bra. Patient-reported outcomes studies suggest that over time, this asymmetry actually worsens as the contralateral natural breast becomes more ptotic and changes in size with patient weight gain or loss [24]. In contradistinction, unilateral autologous reconstruction creates a breast that more closely matches the contralateral breast and remains more stable over time [25].

In the United States, breast reconstruction rates are steadily rising [26], with the majority of this increase is attributably to an upsurge in implant reconstruction [27]. This is perhaps puzzlingly, given the superior long-term outcomes associated with autologous reconstruction. Limited access to autologous reconstruction may be a factor. Autologous tissue transfer has evolved from pedicled flaps to more technically-challenging, microvascular perforator flaps that are generally performed in specialized, higher volume

centers. For a woman with breast cancer, her request for autologous reconstruction may thus mean delays in treatment and/or surgery outside her local community.

This is where the decision to undergo CPM intersects with the approach to reconstruction. Women generally want their breasts to match [28] and when only offered implant reconstruction, some will choose bilateral mastectomies as a means to achieve better symmetry. While psychological factors, individual perceptions of risk and societal trends are likely the central influences on a woman's decision to pursue CPM, expectations for reconstruction are also a component of the decision-making matrix. Few patients would request removal of their contralateral breast purely for aesthetic reasons, but many will factor this in. The solution is more uniform access to autologous reconstruction [29]. While not all women will be candidates for autologous reconstruction nor willing to accept longer surgery and donor site scars, it is nevertheless important that all patients have access to the full spectrum of reconstructive techniques. When only implant reconstruction is offered, removal of the contralateral healthy breast may otherwise seem like the most appropriate decision.

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Synopsis

Panel summary from the American Society of Breast Surgeons providing a comprehensive analysis of the rationale and indications for prophylactic mastectomy. Reasons for increased request for this procedure, and clinical, genetic, ethical and reconstructive considerations are addressed.