Role of Science in the Treatment of Breast Cancer When Tumor Multicentricity is Present

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During the past 100 years, there have been two major controversies with regard to the treatment of primary breast cancer. The first controversy, which occurred approximately 35 years ago, questioned the performance of radical mastectomy, as originally proposed by Halsted in the 1890s. That controversy was resolved by the use of laboratory and clinical research, hypothesis formulation, and evaluation of the efficacy of the latter through the conduct of randomized clinical trials. A second major controversy arose when magnetic resonance imaging began to detect the presence of tumor multicentricity in many breast cancer patients, resulting in a resurgence in mastectomy in women who could have been treated with breast-preserving surgery. Because the use of science resolved the first controversy, I investigated whether there was scientific evidence to justify the current reversion to mastectomy. Extensive examination of the vast amount of recent medical literature related to that subject, that is, individual articles, review articles, and reports from the use of clinical trials, demonstrated that many physicians are not familiar with the scientific method, and thus, were unable to present, in those articles, credible evidence to support mastectomy in the presence of tumor cell multicentricity. Aside from the randomized clinical trial conducted by the National Surgical Adjuvant Breast and Bowel Project begun in 1976, which demonstrated no statistically significant difference in disease-free survival, distant disease-free survival, and overall survival between mastectomy and lumpectomy with or without radiation therapy, there has been no information in any of the few recently conducted studies involving multicentricity to justify the current resurgence in mastectomy.

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In a 1999 essay (1) in which I described many of the major advances in the treatment of breast cancer, I stated the following:

“Perhaps the most important accomplishment of the twentieth century relates to the change in the process of therapeutic decision making. The transition from non-science to science, i.e. from anecdotalism and inductivism to the testing of scientifically based hypotheses using well-designed clinical trials for determining the worth of a therapy before it is used on a population as a whole, is accountable for most of the advances that have been made in the management of breast cancer. The continued use of this scientific process is imperative if future progress is to be made in breast cancer research and treatment.”

Unfortunately, nonscience has again invaded the process of therapeutic decision making and has generated a new breast cancer controversy. The current dilemma, which has largely resulted from concern about the phenomenon of tumor multicentricity detected by magnetic resonance imaging (MRI), has led to a resurgence in mastectomy in women who would, otherwise, be eligible for breast-conserving surgery.

Having participated, for the past 50 years, in both the scientific and clinical evolution in breast cancer treatment, I am concerned that if mastectomy is again accepted on the basis of nonscientific evidence, countless women will be adversely affected. In this commentary, I will put the current discord into historical perspective and show that there is no scientific justification for mastectomy when tumor multicentricity has been detected.
inductive reasoning. Not until the late 1970s, when science began to play a seminal role in the evolution of breast cancer therapy, did that discord begin to diminish.

Laboratory and Clinical Research
In 1958, my late brother, Dr Edwin Fisher, and I began laboratory investigations related to mechanisms of tumor metastasis (3). The results from those studies led me to formulate a hypothesis (4,5) whose tenets were contrary to those of Halsted. I contended that, at diagnosis, breast cancer was apt to be a systemic disease that involved a complex spectrum of host–tumor interrelations and that variations in surgical management were not likely to substantially affect survival. Moreover, I believed that only with the addition of systemic therapy would a reduction in breast cancer mortality occur.

In keeping with the contention of Claude Bernard, the mid-19th century physiologist, that the “starting point for all experimental reason” is a hypothesis that can be tested to determine its validity (6), I designed and conducted a series of randomized trials (7,8) to test my thesis. Data from those studies, which were subjected to rigorous biostatistical analyses, provided the necessary confirmation. As a consequence of the findings from those trials, there became, for the first time, a biological rationale for performing breast surgery. Consequently, the Halstedian anatomical and mechanistic theses were subsequently displaced. In another study (9), I demonstrated that postoperative breast irradiation and systemic therapy in the form of chemotherapy and/or tamoxifen further improved the outcome obtained with surgery and breast irradiation therapy. One of my concepts supported the eradication of local manifestations of the disease by means of breast-conserving surgery followed by radiation therapy; the other involved the use of postoperative systemic chemotherapy and tamoxifen for the elimination of disseminated tumor. When it was evident that systemic therapy also decreased local tumor recurrence after lumpectomy and radiation therapy, there was justification to conclude that the two concepts could be replaced with a single unified exemplar. Thus, it was no longer appropriate to compare the worth of mastectomy with lumpectomy without taking into account the fact that both postoperative breast irradiation and systemic therapy enhanced the justification for performing lumpectomy. The era in which surgery was the sole treatment for primary breast cancer had come to an end. Evaluating the worth of surgery as a single therapeutic entity became meaningless for the overwhelming majority of invasive cancers.

As a result of that scenario, there was reason to believe that a new paradigm for the surgical treatment of breast cancer would arise and that the dilemma that had occurred in the mid-1960s would finally be resolved. Thomas Kuhn, historian and philosopher of physical science, and originator of the term paradigm (10) to encompass “all of the beliefs, values, and techniques shared by members of a [scientific or medical] community,” noted that only when a new set of principles is accepted by a community of practitioners can a paradigm change be said to have taken place. Had the surgical community, indeed, accepted breast conservation?

Replacement of Mastectomy With Breast-Conserving Surgery
In 1985 (8), I reported findings from a randomized clinical trial that indicated that when mastectomy was compared with lumpectomy with or without radiation therapy, disease-free survival, distant disease-free survival, and overall survival outcomes of the groups were equivalent. Before that report (11,12), approximately 10% of women with breast cancer in the United States had undergone lumpectomy. A few years later (11), approximately 25% of women with early-stage breast cancer had that operation. Following a 1990 National Institutes of Health Consensus Development Conference statement (13), which concluded that, “Breast conservation treatment is an appropriate method of primary therapy for the majority of women with stage I and II breast cancer,” treatment with lumpectomy increased to approximately 43%.

Further evidence of that increase appeared in a Surveillance, Epidemiology, and End Results report (14). A little more than half of women who had been diagnosed with primary cancers between 1998 and 2003 were treated with lumpectomy (14). A Mayo Clinic report (15) noted that, at the time of my 1985 publication (8), only about 13% of patients with breast tumors of less than 3 cm had breast-conserving surgery. By 2002, however, approximately 80% of women with such tumors had undergone lumpectomy (15). University of Michigan investigators (16) reported that, between 2002 and 2005, 80% of women deemed to be candidates for breast conservation underwent lumpectomy. They stated that, “Today, the majority of women diagnosed with breast cancer are eligible for breast conservation, and, for stage I or II breast cancer, breast conservation is considered by many to be the standard of care.”

Thus, there was ample evidence to conclude that a new paradigm for the surgical treatment of primary breast cancer had indeed arisen. As a result of the application of science, the surgical dilemma of the 1960s and 1970s had been resolved. However, that period of accord was to be short lived.

The Current Breast Cancer Treatment Controversy
Early in the new millennium, physicians, their patients, and members of the media began to express uncertainty about the appropriateness of the new paradigm. The new controversy can be viewed as being similar to what Kuhn (10) refers to as a “crisis.” Kuhn explains that a crisis that precedes a scientific revolution resembles the one that occurs before a political revolution. In the latter, one part of society defends old institutions while another is introducing a new order. Consequently, society is not being governed at all and chaos results. Similarly, when individuals are discontented with a paradigm, strategies that were previously considered to be inappropriate are often reintroduced. With regard to the current discord, a reversion to Halstedian principles has begun to occur in the form of a resurgence in both unilateral and bilateral mastectomies, with a commensurate decrease in lumpectomies. Women who would have been considered candidates for lumpectomy are now undergoing mastectomy, a circumstance that represents a renunciation of the current scientifically proven paradigm. Is there new and credible scientific evidence for such a procedure, particularly in women with breast cancer multicentricity?

Recent technological advances have provided an abundance of information about changes such as tumor multicentricity that occur at sites in the breast that are remote from the primary tumor. Unfortunately, individuals with a limited historical perspective
have assumed that these findings provide new information that can be used to warrant the rejection of breast-conserving surgery. On the contrary, multicentricity is not a recently discovered phenomenon.

**The Detection of Multicentricity Before the Advent of MRI**

During most of the 20th century, pathologists reported the existence of tumor multicentricity (17–21). Most were concerned with establishing the multicentric origin of mammary cancer rather than with detecting the occurrence of multiple lesions in quadrants that were remote from the dominant mass. One of the first reports to distinguish between foci of cancer in the vicinity of the primary tumor and pathological changes in “opposite positions of the breast” was published in 1957 (20). At that time, because mastectomy was the universal treatment, breast-conserving surgery received no attention. Consequently, from a clinical standpoint, there was little reason for concern about the presence of cancer or of other pathological changes that were present either close to or at a distance from the primary tumor. However, Dr Edwin Fisher and I did state in 1975 (17) that, “One of the major deterrents to the acceptability of such an approach [breast-conserving surgery] is the realization that local excision may ignore residual tumor, particularly that which may occur as clinically and pathologically undetected de novo cancers at sites within the breast quite remote from the dominant mass.”

In our report (17), we also provided information about multicentricity that had been obtained from women with operable invasive breast cancer who had been randomly assigned in a clinical trial comparing radical mastectomy with total mastectomy, that is, only removing the breast, with and without radiation therapy. As a consequence of our findings, we stated that, “The detection of multicentric cancers in mammary quadrants other than that harboring the primary cancer or dominant mass in . . . mastectomy specimens represents a conservative estimate. . . since the probability of identifying such a lesion appeared to increase as the number of [tissue] samples [examined] per patient increased.” Thus, it was evident for more than a half century and before the advent of MRI that tumor multicentricity did occur in women with breast cancer.

During the past 40 years, I have considered the biological significance of tumor multicentricity. In 1977 (22), I noted that it was difficult for surgeons resorting to orthodox principles of cancer management to accept the possibility that a cancer might not be a cancer of clinical significance. There was need for information relating the kinetics of the multicentric foci to those of the primary tumor and about whether the presence of a primary tumor affects their growth.

In 1979 (23), I commented, “Sound justification exists for a clinical test of the hypothesis that multicentricity is not a deterrent to the performance of operations that preserve the breast.” Despite the substantial incidence of multifocal lesions in both breasts of women with cancer, only rarely has there been evidence of two or more overt cancers in the same breast, synchronous bilateral tumors are uncommon, and the incidence of an asynchronous primary tumor in the uninvolved breast fails by far to approach the incidence of occult lesions detected by random biopsy or at autopsy. Under my leadership, the National Surgical Adjuvant Breast and Bowel Project (NSABP) was conducting the only prospective, randomized controlled clinical trial, B-06 (23), to evaluate the efficacy of breast-conserving surgery and the biologic importance of tumor multicentricity.

I indicated in 1983 (24) that there was sound justification to consider the premise that multicentricity was not necessarily a precursor of clinically overt cancer, which would preclude operations that preserve the breast. One year later (5), I considered breast cancer multicentricity from a number of biological perspectives. I questioned whether the presence of a primary tumor inhibits the growth of other tumor foci and if its removal would be followed by stimulation of their growth and whether unremoved occult tumor foci that fail to become overt lesions are a persistent source of disseminated tumor cells that increase the occurrence of distant disease and death.

I also raised issues about whether all multicentric foci of tumor cells are similar to each other and to the primary tumor in terms of their estrogen receptor content (5). I suggested that patients with a primary tumor that contained a high proportion of estrogen receptor–positive cells might be better candidates for local tumor excision because multicentric foci in their breasts are also estrogen receptor–positive and thus might be less likely to develop into a second overt primary tumor. I asked whether all multicentric foci are synchronous in origin, supporting the “multi-field” concept of carcinogenesis, and whether the single overt cancer represents the outcome of a rare transformation in one of them; and I asked whether multicentric tumor foci in the breast are dormant. I subsequently (5) concluded that should the B-06 clinical trial demonstrate that local tumor excision is equivalent to removal of the breast in terms of the development of distant disease and that multicentricity is not a problem to be reckoned with, we will have provided insight into some biological questions of clinical importance.

Because there was no statistically significant difference in outcome among the three treatment groups in the B-06 trial after 20 years of follow-up (25), tumor multicentricity was deemed not to affect outcome. Moreover, because a specific aim of the study was to estimate the effect of tumor multicentricity on outcome, it cannot be claimed that the findings were the result of making a post hoc decision to examine the data. We also noted (26) that, “. . . the findings at this time clearly minimize the clinical significance of multicentric foci of cancer within the breast as a deterrent to performing such a breast-conserving operation as lumpectomy. . . .” Because that conclusion was the result of the findings obtained from NSABP B-06 (26), it lent credibility to my statement, which was subsequently supported by findings from the clinical trials of other investigators (27–32). Is our conclusion still valid, or have new findings been obtained with MRI to justify replacing the paradigm that currently governs breast cancer surgery?

**The Detection of Multicentricity by MRI**

At the onset of the 21st century, multicentric lesions in women with primary tumors of the breast began to be detected by MRI. As a result, information relating MRI to tumor multicentricity, and multicentricity to surgical treatment, has been reported in peer-reviewed medical journals, in high-circulation “throwaway” medical journals, and in review articles and editorials that reflect
the opinions, prejudices, and beliefs of editorialists who have been chosen because of their putative expertise in the subject matter. Unfortunately, physicians have made the claim (33) that, “. . . articles published in throwaway journals were easier to read, . . . were rated consistently better than articles published in peer-reviewed journals. . . .” and, most disturbing, that, “Although lower in methodologic and reporting quality, . . . possess characteristics that are appealing to physician readers.” Many in the scientific community, however, consider such articles to be of questionable importance (34). It is evident that an overabundance of articles containing nonscientifically obtained and often incomprehensible information continue to be published, frequently in journals of questionable value. Hence, any attempt to perform a credible evaluation of such a disparate body of information would seem to be impossible.

Despite those circumstances, I recently examined a large number of individual and review articles to ascertain whether the authors obtained the evidence by scientific means and, thus, provided justification for the resurgence in mastectomy and concomitant decrease in lumpectomy that has recently occurred as a consequence of MRI-detected multicentricity. To aid in my effort, I submitted to the National Library of Medicine PubMed database both individual and combinations of search terms that related to MRI-detected multicentricity in breast cancer patients with tumors that would have met the criteria for treatment with lumpectomy, and thus, were deemed likely to supply the information that I desired.

The Search for Scientific Evidence to Resolve the Multicentricity Controversy

Pathway of Science

Although I have repeatedly emphasized the need for making therapeutic decisions that are contingent upon scientific evidence, increasing numbers of physicians continue to recommend treatments on the basis of what they consider to be good information that they believe is scientifically based. It would appear that few of them, however, are aware that their decisions might be the result of inductive reasoning.

As I have already noted in this commentary, beginning with Frances Bacon in the early 17th century and extending through much of the 20th century, the treatment for breast cancer, and for other cancers as well, was governed by concepts that were based upon empiricism. Generalizations were made from concepts that dictated therapeutic decision making by a process referred to as “inductivism.” Sir Peter Medawar aptly stated (35) that, “Induction is the arguing from the particular to the general.” Or, as Kuhn (10) remarked, “It is a scheme of reasoning in which ideas, observations, results of experiments, and anecdotal experiences give rise to general statements that do more than summarize the information imparted by the data.” According to Medawar (35), “it [such information] expands our pretensions to knowledge.” Furthermore (10), “In the view of the inductivist, this enlargement of experience leads to an enlargement of understanding. Such a misconception continues to plague physicians who attach more significance to anecdotal experience than is justified.”

Clinical trials provide information that can lead to rejection, modification, or support of a hypothesis. The greater the number and quality of investigations that give rise to a hypothesis, the more credible the latter becomes and the more likely that a new paradigm will result. Consequently, more attention must be given to the results obtained from testing a hypothesis than to the plethora of anecdotal reports of inductivist-generated findings, which result only in clinical confusion. Thus, the process of inductivism, which supports current decision making, should be replaced by deductive reasoning.

For those clinicians who currently make decisions about therapy on the basis of information in the medical literature that they believe is “research based,” it is necessary that they have a clear understanding of the meaning of that term. In a discussion of the concept of “research” (36), it has been stated that, “The word ‘research’ is used today in so many ways by so many different kinds of people that each . . . accepts the word without thinking exactly what we mean by it.” For example, the Nobelist Peyton Rous distinguished REsearch from reSEARCH, the former term indicating an activity of repeated searching in a pedestrian manner, the latter signifying discovery (36).

Finally, physicians must also be aware of some of the comments of Kuhn (10) about the evolution of a paradigm. He indicated that, “Although a paradigm is accepted because it seems better than its competitors, it seldom explains all of the enigmas that confront it.” To resolve problems with a paradigm, disciples resort to the conduct of “normal science.” Most of their efforts, he says (10) “. . .are mainly fact-gathering endeavors carried out by experimentation and observation to resolve ambiguities and solve the problems generated by the paradigm.”

Examples of normal science appear in publications that report information from studies determining how much skin or normal breast tissue surrounding a breast cancer should be excised, how extensive a lymph-node dissection should be, or how, when, and to what area of the breast radiation therapy should be given following a lumpectomy. Although all are examples of normal science, they are not science. Too often, the findings from such efforts give rise to conclusions that have been generated by inductive reasoning.

Highlights of the Search

I began my review of articles with the aim of determining whether the pathway of science or any of its components, such as randomized clinical trials, had been used in an attempt to resolve the dilemma that has occurred as a result of screening with MRI. I found that although there were no scientifically obtained data in the literature to justify performing a mastectomy in women who had been deemed eligible for a lumpectomy before multicentricity was detected, mastectomy was more frequently performed because of the findings obtained with MRI.

Randomized Clinical Trials. The authors of many of the publications that I reviewed (37–43) did, indeed, express the view that rigorously designed randomized clinical trials would be necessary to determine whether mastectomy would result in a statistically significant reduction in ipsilateral tumor recurrence, disease-free survival, and overall survival compared with lumpectomy among women in whom multicentricity had been detected by MRI. The frequency of that recommendation might be viewed as an indication of the authors’ awareness that an absence of scientifically obtained
information hindered them from making an appropriate decision about the type of surgery to employ when multicentricity was present.

Since the 1985 report of results from B-06 (8), as well as reports from trials that confirmed those results (28–31), only one other such trial has reported findings. The British COMICE trial (44) was implemented in 2001 to assess the clinical efficacy and cost-effectiveness of contrast-enhanced MRI in women with primary breast cancer who were scheduled for lumpectomy. That study also addressed the uncertainty about preoperative identification of multicentric disease. The authors concluded (44) that “MRI might be unnecessary in this population of patients to reduce repeat operation rates. . . .”, and that they “. . . identified no evidence that MRI improved surgical treatment or outcomes.”

An editorial (45) that accompanied the report of this trial pointed out that, “COMICE does not fully answer whether preoperative breast MRI adds benefit [by detecting multicentricity] because recurrence and overall survival were not examined.” Thus, no information was presented to indicate whether mastectomy, compared with lumpectomy, will result in better disease-free survival and overall survival outcomes in women with tumors associated with MRI-detected multicentricity.

Another trial that has recently attracted attention is the ongoing MONET study (46): “The aim of the MONET-study is to assess the diagnostic and therapeutic consequences of performing MRI . . . in patients with nonpalpable suspicious breast lesions.” Like the COMICE trial, the MONET study was not designed to provide information about how the surgical treatment of MRI-detected multicentricity would affect outcome.

Thus, it is appropriate to conclude that, since B-06 (8), no study has addressed the issue of whether mastectomy is necessary for improving disease-free survival or survival when multicentricity is present in women eligible for lumpectomy. Because there was no evidence to indicate that any of the authors of articles related to tumor multicentricity had obtained their information from clinical trials, I decided to find out whether any information from individual papers or review articles contained scientifically derived information that might aid in defining the type of surgery that should be performed when multicentricity is detected by MRI.

**Individual Articles.** Individual articles examined included information collected at principal institutions in the United States and Europe. The data in this group of publications were too often deficient because most were obtained by retrospective rather than prospective examination of patient charts and records. Those who are familiar with prospective randomized clinical trials are aware that, in such studies, the experiment is designed, the type of patient is decided upon, and the methods by which the data are to be analyzed are specified in the study protocol that is prepared before the beginning of the trial, hence the term prospective. Moreover, subjects are followed forward in time. On the other hand, in a retrospective study, one looks backward in time by examining medical records and interviews with patients who are already known to have a disease. Most important, it has been emphasized (47) that, “A prospective design has been ranked higher in the hierarchy of evidence than a retrospective design,” and (48) that, “Caution needs to be exercised in particular with retrospective cohort studies because errors due to confounding and bias are more common in retrospective studies than in prospective studies.” It has also been stated (49) that, “Retrospective study designs are generally considered inferior to prospective study designs.”

Although the single articles that I examined presented considerable heterogeneous information related to various aspects of MRI-detected multicentricity, no scientifically obtained evidence was presented to justify reversion to mastectomy.

**Review Articles.** The review articles combined data from a variety of individual papers. In light of my concerns about the value of findings reported in individual articles, which contained information obtained either retrospectively or prospectively, I concluded that the review articles were apt to be of even less value. For example, one such article (37) combined information that had been collected from numerous individual articles. The data in almost half of these articles had been obtained retrospectively. Also in that review, a vast amount of heterogeneous information had been gathered from individual articles, many of which used nonconsecutive patient records, suggesting the possibility of a selection bias.

The fact that the authors were cognizant of the inadequacies and the negative connotations of the information presented in their review articles is evident from the following comments (37): 1) “. . . findings in this review showed consistent evidence that MRI staging results in more extensive surgery in . . . women”; 2) “To date, there is no consensus on whether the use of MRI to detect additional malignant foci within the affected breast improves patient outcomes. . . .”; 3) “. . . even for women in whom MRI correctly detects additional cancer foci, conversion to more extensive surgery may have little long-term clinical benefit because the additional disease may be adequately treated with standard adjuvant therapy”; and 4) “To further our understanding of the value of detecting other disease foci by MRI, measurement of the effect of MRI on surgical, and adjuvant therapy (if any), should be determined in randomized trials.”

A subsequent publication (50) emphasized that, “. . . routine use of preoperative MRI in women with established early-stage breast cancer should be discouraged until (and if) high levels of evidence [clinical trials] demonstrate that preoperative MRI either improves surgical care, reduces the number of required surgeries, or (more importantly) that it reduces at least local recurrence, if not distant metastases and death due to breast cancer.” It also stated that “Surprisingly, preoperative MRI has already been incorporated into clinical practice in the absence of high-level evidence of its clinical utility.”

**Comment**

I have concluded that the data in the individual and review articles that I examined provide no scientific justification for performing mastectomy in women with breast cancer multicentricity. The information in those publications is primarily the product of empiricism, anecdotalism, and inductivism, and not of the use of the scientific method. For the authors and the readers of those articles to assume that information obtained in that manner can be used to resolve a clinical issue reflects fallacious reasoning. Only when such data result in the formulation of a new hypothesis that is testable by a properly conducted, prospectively randomized
clinical trial, or by another method, if and when it becomes available, can such information be meaningful.

I also found during my search that the results from the B-06 clinical trial (25) were cited only infrequently. The failure to acknowledge the information from that study has resulted in the disparate views that currently exist among physicians with regard to how patients with multicentricity should be treated surgically. Although some physicians leave that treatment decision to their patients, others subscribe to the view that the mere presence of multicentricity identified by MRI is an ineligible contraindication to performing breast-conserving surgery. Those who espouse the latter approach continue to regard multicentricity as a surgical, rather than a biological, problem and perhaps unwittingly remain proponents of the disproven Halstedian principle that more expansive surgery, that is, removing one more cancer cell, will cure more women.

Should that inductivist-generated perspective continue to be used to justify mastectomy when MRI-detected tumor multicentricity is present, it could provide the imprimatur for further increasing the performance of mastectomy in all women who have breast tumors that are appropriate for treatment with lumpectomy. That circumstance must be prevented because it represents a reversion to an era when there was no scientific justification for mastectomy and its undesirable consequences.

References


Notes

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