

The Breast Cancer Alternative Hypothesis: Is There Evidence to Justify Replacing It?

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INTRODUCTION

After nearly 50 years of research by one of us (B.F.) that provided scientific justification for replacing the Halstedian hypothesis, it was disheartening to read the editorial by Rabinovitch and Kavanagh entitled, "Double Helix of Breast Cancer Therapy: Intertwining the Halsted and Fisher Hypotheses," which appeared in the *Journal of Clinical Oncology*.¹ The idea that the Halsted and the Fisher hypotheses can be "intertwined" is unwarranted. Halsted's hypothesis was based on empiricism, and his operation was governed by anatomic and mechanistic principles. In contrast, the Fisher alternative thesis was the product of laboratory investigation and was supported by results obtained from a series of randomized clinical trials.²⁻⁴ Moreover, Halsted was attracted to concepts of tumor biology that were formulated by others during the 19th century and that were subsequently disproven, mainly as a result of the studies conducted by Fisher during the last 40 years of the 20th century. Despite those circumstances, however, Rabinovitch and Kavanagh opine that there is "a need to re-evaluate the Fisher hypothesis and consider bringing Halsted back into view," and that it "... might be that the place in which we now find ourselves is a place we may have been before"^{1(p2422)} (one assumes, at the time of Halsted). Has new, credible biologic and clinical information been obtained that would provide justification for rejecting the Fisher hypothesis and accepting Rabinovitch and Kavanagh's thesis, or is their view the result of empirical thought? If the former, then it behooves them to make available the information that supports their position. If the latter, their thesis does a disservice to women with breast cancer and, moreover, repudiates science. Considering a return to "Halstedianism" without scientifically based evidence for doing so would result in therapeutic chaos similar to that which existed before the end of the Halstedian era.

In the Rabinovitch editorial, the authors "rewrite history" by presenting, decades after the fact, their perception of our thoughts and actions with regard to the research and treatment of breast cancer. They also misquote or misinterpret statements

that they have taken from several of our previously published articles and, in some cases, they have omitted important details that accompany those statements. To preserve the accuracy of that part of breast cancer history to which we have made contributions, it is necessary that we set the record straight. Another aim of this commentary is to report on the current status of the Fisher alternative hypothesis. That thesis, which was formulated several decades ago, resulted in rejection of the Halstedian paradigm that governed breast cancer surgery for most of the 20th century.

LOCOREGIONAL RECURRENCE

In Rabinovitch and Kavanagh's editorial, the authors infer that we have failed to both recognize the significance of locoregional tumor recurrence and to appreciate the need for the prevention and treatment of such recurrences. They imply that, as a consequence, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 clinical trial, which provided the first data to justify the use of lumpectomy for the treatment of breast cancer, was flawed in both design and conduct. That notion is without basis in fact. Indeed, the idea that we have been indifferent to local disease control can be refuted by an examination of a few excerpts from some of our publications. We have stated that:

- "Improper surgery, improper radiation therapy, along with inadequate backup systems, such as pathology, will destroy the credibility of breast conservation."^{5(p112)}
- "It continues to remain NSABP policy, however, that all patients treated by lumpectomy have tumor-free specimen margins. It is also our opinion that in no circumstance is there justification for surgeons to not make every effort to obtain tumor-free [specimen] margins. Nor is it justifiable for a radiation oncologist to dismiss the importance of free margins because 'radiation therapy will take care of it.' It is to be emphasized that abandonment of Halstedian principles of cancer surgery does not imply that sloppy surgery can be condoned."^{6(p427)}

- “[We have] emphasized the need for close interrelationships among surgeons, pathologists, and radiation and medical oncologists when a lumpectomy is performed. Orchestration of the event is more complex than that which is necessary for a mastectomy. When a surgeon makes the decision that a lumpectomy is appropriate, he or she must appreciate that a patient’s outcome is apt to depend on the surgeon’s skills as well as those that the other members of the ‘team’ possess.”^{7(p56)}

A more careful reading of our article on the subject of advances in the treatment of breast cancer, which was published in 1999, and which is cited as reference number 2 in the Rabinovitch editorial, would have led the authors to better understand our position with regard to the prevention of locoregional recurrence. The following statements appeared in that article:

- “. . . I [B.F.] do not dismiss the idea that all efforts should be made to prevent local-regional tumour. . . . the treatment of breast cancer was governed by two independent paradigms, one concerned with eradicating local manifestations of the disease without compromising prospects for cure. . . .”^{3(p1968)}

Furthermore, because Rabinovitch and Kavanagh cite no references for their erroneous assertion that, “Local recurrences [in the B-06 trial] were not considered potential sources of subsequent metastatic spread,”^{1(p2422)} this comment is their impression of our position, rather than an actual statement of fact. Although we have maintained that, “IBTR [ipsilateral breast tumor recurrence] proved to be a powerful independent predictor of distant disease,”^{8(p327)} never have we either stated or implied that the presence of an IBTR could not be a potential source of distant disease.

It is also alleged in the Rabinovitch and Kavanagh editorial that, “. . . according to the guidelines of that protocol [B-06], disease recurrence in the breast after breast-conserving surgery was treated with mastectomy and considered merely a ‘cosmetic failure’ . . .” and that “recurrence in the breast was not even scored as an event affecting disease-free survival.”^{1(p2422)} The authors’ use of the qualifying words “merely” and “not even” to suggest that we opted to treat disease recurrence after breast conservation in a cavalier fashion has no basis in fact. They have either misinterpreted, or are not familiar with, the specific aims and guidelines of the B-06 protocol with regard to the local control of breast cancer. They state further that, in patients in B-06 who experienced an IBTR, “. . . no other therapy [other than a salvage mastectomy] will be permitted without evidence of tumor elsewhere. This includes radiation therapy, systemic therapy such as chemotherapy, hormonal therapy, and castration.”^{1(p2422)} Their inference seems to be that our treatment of the women in the B-06 trial was inadequate and that, as a consequence, we were putting our patients’ safety at risk. In the reference list that accompanies the Rabinovitch and Kavanagh editorial, the authors list one of our articles⁹ that was purported to contain the above statement about the use of other therapy. Such a statement never appeared, either in our first, or in any subsequent reports, of the findings from that study, but was, instead, part of a 54-page document that was distributed to participating NSABP physicians and that described in detail the Background, Specific Aims, Plan of Investigation, and Conduct of the B-06 trial (National Surgical Adjuvant Breast Project Protocol B-06. A protocol to compare segmental mastectomy and axillary dissection with and without radiation of the breast, and total mastectomy and axillary dissection [unpublished report]).¹⁰ The document also clearly defined the meaning of treatment failure, survival, and cosmetic failure and

specifically indicated that, “No additional therapy will be permitted without evidence of tumor elsewhere.” (National Surgical Adjuvant Breast Project Protocol B-06. A protocol to compare segmental mastectomy and axillary dissection with and without radiation of the breast, and total mastectomy and axillary dissection [unpublished report, p 4]).¹⁰ It seems, however, that Rabinovitch and Kavanagh overlooked a subsequent paragraph included in that document, in which the following statement appears:

“When this [an IBTR] occurs in patients with histologically positive nodes who are receiving chemotherapy, those patients will be managed with total mastectomy. If necessary, chemotherapy [which all node-positive patients received] may be interrupted to permit operation and recovery. Effort should be made to re-establish treatment, ie, [every] 6 weeks cycle as soon as possible and no later than six (6) weeks after operation.” (National Surgical Adjuvant Breast Project Protocol B-06. A protocol to compare segmental mastectomy and axillary dissection with and without radiation of the breast, and total mastectomy and axillary dissection [unpublished report, p 5]).¹⁰

Because Rabinovitch and Kavanagh have taken our statement about the use of additional therapy out of context, the question may be raised regarding whether they are cognizant of the complexities of clinical trial design, for example, the need for proper control groups, as well as the need for eliminating circumstances that could interfere with appropriate biostatistical analyses and conclusions. One wonders whether they are aware that the aim of the appropriately conducted clinical trial is to obtain information in such a way as to obviate empirical thinking. Another example of their misrepresentation of our data involves a statement that has appeared in more than 20 of our articles that were published between 1980^{2(3867),11(p1011)} and 2008.^{4(p10014)} In all of those publications, we stated that, “Variations in local-regional therapy are unlikely to substantially affect survival.” It seems strange that Rabinovitch and Kavanagh cite that article in which the word “substantially” was inadvertently omitted from a sentence quoted from the original source.³ (The importance of the omission of that word will become evident when the benefit in survival outcome after the use of postoperative radiation therapy is discussed later in this commentary.)

Most inappropriate was the assertion in the Rabinovitch and Kavanagh editorial that, before the design of the B-06 trial, the NSABP was firmly committed “. . . to the model that local therapy and local disease control cannot affect survival outcomes (given the presumed presence of occult systemic disease). . . .”^{1(p2422)} It must be noted that no one associated with the NSABP had, a priori, any “commitment” to implement a study based on such a collective or personal bias. When the B-06 trial was designed and conducted to test the worth of the Fisher hypothesis and, consequently, the credibility of treating breast cancer with lumpectomy, the NSABP was an organization of hundreds of doctors, statisticians, nurses, and other professionals who were committed to the performance of clinical trials. Because the design, implementation, and initial reporting of the study were carried out by the principal investigator (B.F.), in collaboration with NSABP biostatisticians and selected radiation oncologists, and with the approval of officials of the National Cancer Institute and their intramural and extramural committees, any suggestion of bias in the design of the B-06 study is a challenge to the probity of all who were involved.

PUTATIVE NEED TO RE-EVALUATE THE ALTERNATIVE HYPOTHESIS?

Another example of the way in which Rabinovitch and Kavanagh have misinterpreted our findings is evidenced by their statement that, “There is now, however, a sizable body of evidence, much of it originating from within the NSABP itself, . . . together with numerous other analyses [that] reveal a constellation of provocative observations” that support the notion that the Fisher hypothesis requires re-evaluation and that Halsted should, perhaps, be brought “back into view.”^{1(p2422)} This so-called evidence is portrayed in the Rabinovitch and Kavanagh editorial in six bulleted (•) statements, each one of which putatively supports the authors’ claim. Three of these statements relate to the effect of an IBTR on distant disease and mortality, whereas the others support the value of radiation therapy after lumpectomy for improving survival.

The following snippets of data from three NSABP publications¹²⁻¹⁴ about lumpectomy-treated women who subsequently developed an IBTR are presented without either explanation or discussion¹:

- “The risk of distant disease. . . was 3.41 times greater in patients who developed IBTR than in patients who did not.”^(p2422)
- “In the NSABP adjuvant trials, the hazard rate for mortality after IBTR was 4.49 in estrogen receptor–negative node-negative patients and 2.33 in estrogen receptor–positive node-negative patients, as reported by Anderson et al.”^(p2423)
- “In the NSABP adjuvant trials, the hazard rate for mortality after IBTR was 2.58 in node-positive patients, as reported by Wapnir et al.”^(p2423)

Although the statements are correct as presented, Rabinovitch and Kavanagh fail to indicate how these assertions support their claim that the NSABP has provided evidence to re-evaluate the Fisher hypothesis. Only by using the findings from the B-06 trial,¹² in which randomized comparisons were made among patients treated with lumpectomy, lumpectomy and radiation therapy, or total mastectomy, can the relationship between the incidence of IBTR and patient survival be appropriately assessed. The results from the NSABP B-06 trial provide no support for consideration of a return to Halsted.

Rabinovitch and Kavanagh have also elected to present information from their “constellation of provocative observations” to bolster their claim that the use of postlumpectomy radiation has not only reduced the rate of IBTR but also resulted in increased survival. They state the following:

- “Lumpectomy followed by breast irradiation, as compared with lumpectomy alone, was associated with a marginally significant decrease in deaths due to breast cancer ($P = .04$), as reported in the 20-year follow-up of the NSABP B-06 trial.”^{1(p2422)}

At the time of our 2002 report of the B-06 study,¹² as a consequence of radiation therapy administered after lumpectomy, there was a 7.2% decrease (43.6% v 36.4%) in breast cancer-related mortality. That advantage was mainly offset by a 6% increase in deaths from other causes in the irradiated group. Thus the 20-year decrease in all-cause mortality was only 1.2%. That small mortality decrease was associated with a substantial (24%) reduction in the incidence of IBTR as a result of radiation therapy. Thus those results support one of the tenets of our alternative hypothesis, that is, that variations in locoregional therapy are unlikely to substantially affect survival.

With regard to the effect of radiation therapy on survival, Rabinovitch and Kavanagh also assert the following:

- “There was a highly significant reduction in the annual breast cancer mortality rate for patients treated with radiotherapy after lumpectomy versus lumpectomy alone (breast cancer death rate ratio, 0.83; 95% CI, 0.75 to 0.91; $2P = .0002$), as reported in a meta-analysis by Early Breast Cancer Trialists’ Collaborative Group [EBCTCG].”^{1(p2423)}

Unfortunately, this statement fails to indicate the whole story with regard to the relationship between the use of postoperative radiation and survival outcome. In the 2000 EBCTCG overview,¹⁵ the favorable, as well as the unfavorable, effects of radiation therapy on long-term survival were considered. In their report, the authors of that meta-analysis presented a “forest-plot” that depicted the all-cause mortality in each of 40 randomized trials involving 20,175 women, half of whom received radiotherapy after surgery, and half of whom did not. Twenty-seven of the trials began in the 1960s and 1970s; 13 started in the 1980s. The trials were grouped according to the type of surgery performed, that is, mastectomy alone (five trials), mastectomy with axillary sampling (six trials), mastectomy with axillary clearance (23 trials), and breast conservation with axillary clearance (six trials). On examination of that plot, it is clearly evident that, among the 40 trials, with one exception, there is little, and mostly no significant difference in the annual death rates between the group that received radiation therapy and the control group. In all of the 40 trials combined, a nonsignificant 3.9% reduction in the mortality rate ratio was reported. In three of the four groups of trials, the reduction in the death rate resulting from postoperative radiation was not significant. Only in the group of trials in which patients were treated with mastectomy and axillary sampling was there a significant reduction in the ratio of the annual death rate due to the favorable results obtained from two large trials conducted by the Danish Breast Cancer Study Group.¹⁶ Thus, in keeping with the findings that we obtained in the B-06 trial, the evidence from the year 2000 EBCTCG meta-analysis demonstrated that, although postoperative radiation therapy resulted in a substantial benefit in local recurrence, there was only a small benefit (proportional reduction of 3.9%) in overall mortality.¹⁵

The information in Table 1 is from several figures that appeared in the year 2000 EBCTCG overview and is related to the absolute effect of radiation therapy on cause-specific survival after 20 years of follow-up.¹⁵

Because the previous statement by Rabinovitch and Kavanagh that there was a “highly significant reduction in annual breast cancer mortality rate from patients treated with radiotherapy. . .”^{1(p2423)} was selected from the vast amount of data and commentary in a more recent EBCTCG overview (year 2005), we deemed it appropriate to provide balance to that statement by presenting additional information from that document. The authors of that overview noted

Table 1. Absolute Effect of Radiation Therapy on Cause-Specific Survival After 20 Years of Follow-Up

Deaths	20-Year Survival (%)		
	No RT	RT	Difference
Breast cancer–related	48.6	53.4	4.8 increase
Nonbreast cancer–related	73.8	69.5	4.3 decrease
Overall	35.9	37.1	1.2 increase

Abbreviation: RT, radiation therapy.

that although the 5-year local recurrence was reduced in patients who received breast-conserving surgery, with and without radiation therapy (from 26% to 7%), they also indicated that radiation therapy produced a moderate absolute reduction not only in 15-year breast cancer mortality but also in 15-year overall mortality, ie, 5.4% and 5.3%, respectively.¹⁷

Although almost all of the information presented in the 2005 EBCTCG overview was related to breast cancer mortality and only a small amount to all-cause mortality, it was noted by the authors that there was a “significant excess incidence of contralateral breast cancer. . . and a significant excess of non-breast-cancer mortality in irradiated women. . . .”^{17(p2087)} The latter was mainly the result of heart disease and lung cancer. Thus, this significant excess in non-breast cancer mortality reduced the impact of the reduction in breast cancer mortality putatively related to radiation therapy. The authors of the 2005 meta-analysis demonstrated that radiation therapy produced a moderate absolute reduction not only in 15-year breast cancer mortality but also in 15-year overall mortality, that is, 5.4% and 4.4%, respectively.¹⁷

After scrutiny of the plethora of analyses conducted and the data obtained from the years 2000 and 2005 EBCTCG meta-analyses, several uncertainties exist with regard to both the process by which the findings were obtained and the interpretation of their meaning. In that regard, the question may be asked as to why, in the year 2000 overview, breast cancer–related mortality, nonbreast cancer–related mortality, and mortality from any cause were reported through 20 years of follow-up, whereas, 5 years later, in the report of the 2005 analyses, results were presented through 15 years. Also, why were data regarding nonbreast cancer deaths, and, consequently, all-cause mortality, less available than were data for estimating death due to cancer? Moreover, it seems that insufficient attention has been directed to the fact that, in the 2005 overview, women in 34 (74%) of the 46 trials received a variety of systemic therapy regimens in addition to radiation therapy. The composition of the regimens administered is often difficult to determine and to categorize by an examination of the data presented in a web table.¹⁷ Tamoxifen was given in some trials with—and in others without—single- or multiagent chemotherapy. In some instances, the use of tamoxifen was related to the estrogen content of tumors, and in others, it was not. Ovarian irradiation or ablation was performed in some of the trials with, and in others without, chemotherapy. Also, one cannot ignore the fact that the dosage of radiation therapy administered among trials varied relative to both site and dose. Finally, it remains a matter of concern regarding whether or not all of those variables might have confounded the findings with respect to radiation therapy.

Despite these concerns, it must be concluded that the expansive findings from the various overviews seem to indicate that the use of radiation therapy markedly reduced the incidence of local recurrence and somewhat, but not substantially, improved overall survival. That conclusion is reinforced by the Plain Language Summary that appears in The Cochrane Collaboration, which indicates that, “Radiotherapy following surgery for early breast cancer substantially reduces the chances of a cancer recurrence but the effects on long term survival seem small.”¹⁸ It is also stated in that report that, “Radiotherapy regimens able to produce the two-thirds reduction in local recurrence seen in these trials, but without long-term hazard, would be expected to produce an absolute increase in 20-year survival of ap-

proximately 2% to 4% (except for women at particularly low risk of local recurrence).”^{18(p1)}

Those findings provide further support for our original thesis that variations in locoregional therapy are unlikely to substantially affect survival. Moreover, they clearly indicate that the impression created in the Rabinovitch and Kavanagh editorial that there has been a “substantial” reduction in mortality after radiation therapy¹ is not in keeping with what was found after a detailed examination of those authors’ sources of information.

The final “provocative observation” that Rabinovitch and Kavanagh cite in support of their claim that the “Fisher hypothesis be re-evaluated and that Halsted be brought back into view” is the following:

- “In numerous trials and meta-analyses, improved regional control with postmastectomy radiotherapy was associated with improved survival.”^{1(p2423)}

That statement relates to information obtained from two randomized trials, 82 b & c, that were conducted by the Danish Breast Cancer Study Group.¹⁶ As previously noted, of the 40 trials included in the year 2000 EBCTCG overview, only the Danish studies demonstrated a significant difference in annual death rates between the radiotherapy and control groups. In a report of the findings, it was concluded that, “The survival benefit after postmastectomy RT [radiation therapy] was substantial and similar in patients with 1-3 and 4+ positive lymph nodes.”^{16(p247)} Those findings were obtained from “Only high-risk patients. . . , defined as patients who were node positive and/or [had] a T3 or T4 tumor and/or skin or deep fascia invasion.”^{16(p248)} Although most of the women failed to have a complete axillary dissection, almost half had four or more positive lymph nodes, two thirds of the tumors were more than 2.0 cm, and two thirds were grades 2 and 3. Thus the women, when first seen by their physicians, were at increased risk for distant disease and death because they already had disseminated tumor cells. Those were the patients who would seem to have been most unlikely to have had a reduction in mortality as a consequence of their receiving postoperative radiation therapy.

The radiation therapy used in the Danish studies was targeted to the chest wall and supraclavicular, axillary, and parasternal lymph nodes and avoided the heart. According to Overgaard et al,¹⁶ a major effort was made to optimize the radiation treatment so that no radiation-related excess of nonbreast cancer deaths or unacceptable toxicity was found. Those investigators concluded that, “Avoiding such negative effect of radiotherapy in the Danish trials is probably one of the reasons for the positive outcome. . . .”^{16(p251)}; ie, there was no increase in nonbreast cancer–related deaths as a result of radiation therapy. In view of the improvement in the radiation therapy techniques used by the investigators in the Danish trials, the authors’ conclusion seems plausible.

Because the Danish studies have played an important role in validating the premise that a survival benefit from radiation therapy exists when that modality is given with systemic therapy, providing further information from those trials would seem to be appropriate. In women with one to three positive nodes, locoregional recurrences at 15 years were substantially reduced from 27% to 4%, a decrease of 23%, and the overall survival was improved by 9% (from 48% to 57%). In women with four or more positive nodes, there was an even greater reduction in locoregional recurrence, from 51% to 10%, a decrease of 41%, and the survival, as in women who had fewer positive

nodes, increased by 9% from 12% to 21%.¹⁶ Because in each of the nodal groups, the survival of irradiated and nonirradiated women was so poor, such a survival increase can hardly be viewed as noteworthy.

In the Danish trials, a large number of premenopausal and postmenopausal women received cyclophosphamide, methotrexate, and fluorouracil with or without radiation therapy. Almost half of those who were postmenopausal were randomly assigned to receive tamoxifen with or without radiation therapy. Because such therapy unequivocally reduces the incidence of breast tumor recurrence, and because the addition of chemotherapy and tamoxifen further diminishes such recurrence and also improves survival, it may be speculated as to what degree, if any, radiation, a locoregional therapy, played when it was used in conjunction with systemic therapy in the reduction of mortality in those high-risk women.

Overgaard¹⁶ has addressed that issue and provides an explanation that supports our alternative hypothesis. In that report, Overgaard stated the following:

“The aim of radiotherapy is to secure loco-regional control and to improve survival. Radiotherapy can eradicate residual loco-regional tumor deposits after surgery with adjuvant systemic therapy, and thereby improve local control and reduce the risk of secondary dissemination from these deposits. But only patients who have not yet developed distant metastases or patients who will have their limited occult distant metastases controlled by adjuvant systemic therapy can obtain additional survival benefit from irradiation. Other patients may only benefit in terms of loco-regional tumor control. . . . in patients who have many nodes involved, the likelihood of developing distant metastases is very large, and, therefore, only a limited proportion of these patients can obtain survival benefit, despite their possibly obtaining a large reduction in loco-regional failures. . . . Thus, the improvement in survival may not directly be linked and proportionate to the improvement in loco-regional control.”^{16(p251)}

Unfortunately, Rabinovitch failed to mention this aspect of the Overgaard report, which emphasizes what has been our view for decades, ie, that when a patient is diagnosed with breast cancer, every effort must be made to control locoregional disease to prevent further tumor cell dissemination. And, to do so does matter. However, tumor and host factors that are in play before the diagnosis and treatment of cancer are of primary importance with regard to determining survival.

OPPOSITION TO THE ALTERNATIVE HYPOTHESIS

Before concluding their editorial on the intertwining of the Halstedian and Fisher hypotheses, Rabinovitch and Kavanagh abruptly deviate from their circuitous path by stating the following:

“In 1995. . . [Dr. Samuel] Hellman and Weichselbaum advanced the concept of oligometastases in *JCO* [the *Journal of Clinical Oncology*], describing an intermediate phase of cancer progression falling somewhere between the hypotheses of Halsted and Fisher. They [Hellman and Weichselbaum] hypothesized that there exists an opportunity for local therapy—targeting limited and measurable sites of metastatic disease—to meaningfully affect disease-free and overall survival. This concept has already been evaluated in prospective clinical trials, with provocatively encouraging results to date.”^{1(p2423)}

The extensive criticism of our alternative hypothesis by Hellman¹⁹ is likely to have influenced the beliefs of Rabinovitch and Kavanagh, as well as those of other radiation oncologists.²⁰ In fact, the

Rabinovitch and Kavanagh editorial is an abbreviated version of a prior article by Punglia et al²¹ and is the forerunner of a recent report by Winkfield and Harris.²²

Because Hellman's views continue to attract disciples, both in this country and elsewhere, his conception of our alternative hypothesis requires comment. To familiarize the reader with the alternative hypothesis, a brief summary of the origins and tenets of the alternative hypothesis is presented.

As a consequence of findings obtained by one of us (B.F.) from laboratory investigations in the biology of tumor metastasis,^{2,23-34} conducted during the 1950s and 1960s, we formulated a new hypothesis that has relevance to breast cancer.² Each principle of our thesis pertained to a different aspect of tumor biology, and none was the result of either conjecture, impression, or reinterpretation of findings reported by others. Because the tenets of our thesis were contrary to those of Halsted, it was designated the “alternative hypothesis.” (In 1994, our thesis began to be referred to by Hellman as the “systemic” hypothesis, a title that is inappropriate because that term relates to only one of the multiple precepts of our thesis.¹⁹) A comparison of the tenets comprising the Halsted and alternative hypotheses is presented in Table 2. The comparison in Table 2 clearly demonstrates the dissimilarity of the tenets of the two hypotheses.

Because we recognized the importance of the admonition by French physiologist Claude Bernard, who focused attention on deductive scientific research, and who stated that, “A hypothesis. . . is the obligatory starting point of all experimental reasoning,” and is only of value if it can be tested,³⁵ we proceeded to conduct randomized clinical trials to provide information that could lead to either rejection,

Table 2. Comparison of the Tenets Comprising the Halsted and Alternative Hypotheses

Halstedian Hypothesis (1894)	Alternative Hypothesis (1968)
Tumors spread in an orderly, defined manner based on mechanical considerations.	There is no orderly pattern of tumor cell dissemination.
Tumor cells traverse lymphatics to lymph nodes by direct extension, supporting en bloc dissection.	Tumor cells traverse lymphatics by embolization, challenging the merit of en bloc dissection.
The positive lymph node is an indicator of tumor spread and is the instigator of distant disease.	The positive lymph node is an indicator of a host-tumor relationship that permits development of metastases rather than the instigator.
RLNs are barriers to the passage of tumor cells.	RLNs are ineffective as barriers to tumor cell spread.
RLNs are of anatomical importance.	RLNs are of biologic importance.
The bloodstream is of little significance as a route of tumor dissemination.	The bloodstream is of considerable importance in tumor dissemination.
A tumor is autonomous of its host.	Complex host-tumor inter-relationships affect every facet of the disease.
Operable breast cancer is a locoregional disease.	Operable breast cancer is a systemic disease.
The extent and nuances of operation are the dominant factors influencing patient outcome.	Variations in locoregional therapy are unlikely to substantially affect survival.
No consideration was given to tumor multicentricity in the breast.	Multicentric foci of occult tumor are not of necessity a precursor of clinically overt cancer.

Abbreviation: RLN, regional lymph node.

modification, or support of our hypothesis. The first trial that we implemented in 1971 (NSABP B-04) compared the outcome of patients with clinically node-negative breast cancer who were treated with a Halsted radical mastectomy with the outcome of similar women who underwent either a total (simple) mastectomy followed by locoregional irradiation but no axillary dissection or total mastectomy with no irradiation and removal of axillary nodes only if they became clinically positive. Despite this therapeutic nonconformity, no significant differences in overall treatment failure, distant metastases, or survival were noted among the three groups during 25 years of follow-up.³⁶ The findings from that trial supported the credibility of our alternative hypothesis, thus providing, for the first time, a biologic basis for breast cancer treatment. Moreover, they eliminated biologic considerations that might have contraindicated evaluating breast-conserving operations.

In October 1973, we began the planning of another study (NSABP B-06), which was implemented in 1976. Its intent was to re-evaluate the alternative hypothesis by appraising the worth of breast-conserving surgery. The findings from that trial, through 20 years of follow-up,¹² revealed no significant difference in distant disease-free survival or survival among patients treated with total mastectomy, lumpectomy alone, or lumpectomy followed by breast irradiation. Those results further supported the merit of our hypothesis and demonstrated that there was neither a biologic nor a clinical rationale for opposing the treatment of stages I and II breast cancer patients by breast-conserving surgery followed by breast irradiation. Thus there resulted a new paradigm for the surgical treatment of breast cancer, one based on biologic principles formulated in the laboratory and confirmed in the clinical setting via randomized clinical trials.

During the past two decades, as a consequence of our previously noted efforts, there has been widespread acceptance of lumpectomy followed by radiation therapy and appropriate systemic therapy for the treatment of breast cancer. Over that time, however, Hellman has expressed criticism of the Fisher alternative hypothesis by challenging its credibility. His criticisms have not been based on information obtained via laboratory or clinical investigation. The subsequent eight bulleted statements by him are followed by our comments.

- “That [the alternative] hypothesis suggests that breast cancer is a systemic disease and implies that small tumors are just an early manifestation of such systemic disease, which, if it is to metastasize, has already metastasized.”^{19(p2229)}

This remark minimizes the alternative hypothesis by “suggesting” that breast cancer is a systemic disease. Actually, the hypothesis states that, based on extensive experimental findings, breast cancer “is” a systemic disease. Moreover, in neither the alternative hypothesis (Table 2), nor in any of our publications, has it been stated or intimated that a tumor of any size, “. . . if it is to metastasize, has already done so.” That assertion implies that “predeterminism” has dictated our concept of breast cancer biology, an assumption that is incorrect.

- “The systemic hypothesis is binary: metastases either do or do not exist. If present, even if microscopic, they are extensive and widespread.”^{37(p8)}

This statement is antithetical to our understanding of breast cancer biology and, to our knowledge, has never been made by us.

- “Local control, according to this theory [the alternative hypothesis], is unimportant to survival,” and that “The systemic disease hypothesis suggests that these [distant metastases] occur before clinical

detection and argues that [according to Fisher] local eradication of disease makes little or no difference.”^{19(pp2229,2230)}

In these two statements, Hellman, and, consequently, Rabinovitch and Kavanagh,¹ indicate that because breast cancer is considered by me (B.F.) to be a systemic disease, I believe that “local control. . . is unimportant to survival” and “that local eradication of disease makes no difference.” The impropriety of both of those statements, which seem to be a fundamental basis for their criticism, has already been extensively addressed in this commentary (Locoregional Recurrence).

- “Nodal involvement [according to the alternative hypothesis] is not an orderly contiguous extension, but rather a marker of distant disease.”^{19(p2229)}

This statement seemingly relates to the manner in which tumor cells spread from a primary tumor. It was Halsted’s view that tumor cells did not disseminate via the bloodstream but, instead, traversed lymphatics to lymph nodes by contiguous [touching each other] extension.³⁸ Those nodes then became the source of distant tumor spread, also by contiguous extension via the lymphatics. Halsted viewed the lymph node as a “way station” on the road to distant disease. The alternative hypothesis, on the other hand, has contended, based on experimental findings, that metastases are the result of disseminated tumor cells via both the blood and lymphatic systems, which are so interrelated that a specific route of dissemination is highly unlikely.³³ Thus the view that the lymph node (and not the tumor in the breast) is the initial source of metastasis seems implausible. Contrary to Hellman’s interpretation of our thesis, it has never been denied that an unremoved tumor-bearing lymph node could be a source of further tumor spread. Moreover, we have clearly stated that, “The lymph node that contains tumor cells is important in that it reflects an interrelationship between host and tumor that permits the development of metastases rather than that it is an [the initial] instigator of distant disease.”^{2(p3866)} With regard to the statement that we think that positive lymph nodes are markers of distant disease, we have previously shown that a positive lymph node is an indicator (marker) of the probability of distant disease. We first demonstrated a relationship between the number of positive nodes (one to three *v* four or more) and the prognosis of a patient.³⁹

- “While lumpectomy plus radiation is based on the Halsted model of disease pathogenesis, it is very different than en bloc surgical extirpation.”^{19(p2230)}

Lumpectomy plus radiation is, indeed, different from a radical mastectomy! However, the statement that the former is based on the Halsted model of disease pathogenesis is incomprehensible.

- “Detection by screening mammogram has allowed effective locoregional treatment before distant spread of sufficient number of cells capable of metastatic growth. In my judgment, this is strong argument against the systemic thesis.”^{19(p2230)}

Several years before that statement was made, one of us (B.F.) asserted the following with regard to mammography:

“Current biological concepts indicate, however, that as a result of genetic alterations some occult tumors detected by mammography have populations of cells that have already attained competence for successfully establishing metastases; [others] have not yet achieved that capability but will do so as their cells continue to replicate, or will never demonstrate that capacity, even after they are detected by clinical examination. (A substantial proportion of patients with clinically detected cancers do not develop metastatic disease during their lifetime.) . . . the value or limitations of mammography relate not so much

to the number of clinically occult tumors detected as to the biological nature of the cells in the tumors that are discovered. Perhaps. . . it will be possible to detect and remove more tumors whose cells have not yet undergone the biological changes required for them to attain the metastatic capability that would occur if the tumors were not recognized and not removed.”^{34(p2379)}

Although the first sentence of his statement about screening mammography is correct, the reason that “this is a strong argument against the systemic thesis” is not clear.

- “If differences [in outcome] are found, they must be due to differences in the persistence of disease in the primary tumor or nodal site resulting in differences in distant metastases.”^{19(p2231)}

That differences in outcome must be due to differences in the persistence of disease is arguable. There are biologic explanations such as the heterogeneity of a tumor and of its host that are of equal or greater significance.

- “Both the Halsted and the systemic hypotheses are too restricting.”^{19(p2233)}

Hellman¹⁹ goes on to state that, “Like all dogma in science, . . . [those hypotheses] tend to limit our inquiries and deny the conditional and approximate nature of scientific knowledge.”^{19(p2234)} This point of view is a philosophical one, rather than a scientific justification for condemning the alternative hypothesis.

In context with his criticism of our hypothesis, Hellman, in 1994, introduced a third hypothesis: one that “is most consistent with the data,” namely, the “spectrum” hypothesis.^{19(p2233)} The statements presented in Table 3 are provided to compare the tenets of the “spectrum” thesis with those comprising the Halstedian and alternative hypotheses (Table 2).

Hellman’s idea that breast cancer is a heterogeneous disease and that metastases are a function of tumor growth and progression was hardly new when he considered it worthy of being a tenet of his “new” hypothesis. Almost 15 years before the formulation of his thesis, I (B.F.) stated that “. . . the term breast cancer is an eponym used to describe a biologically heterogeneous group of cancers of the breast

residing in a biologically heterogeneous group of women. The varied ‘natural history’ following treatment by operation and no other therapy is an indicator of that host-tumor heterogeneity.”^{2(p3868)} I also affirmed that “Tumors possess differing histopathological characteristics which relate to patient outcome,” and that “. . . not only is there heterogeneity between tumors but also that individual tumors are comprised of a heterogeneous population of cells which express their differences in innumerable ways.”^{2(p3869)} Hellman also ignored the statement that I (B.F.) made in 1980 that “. . . the profile of the disparate cells comprising a tumor is almost certainly continuously changing and [that] evaluation at one point in time [after tumor removal] may be akin to examining a single frame removed from a motion picture film.”^{2(p3873)}

Hellman’s statement that his theory suggests that, even if tumor cells spread early, metastases do not regularly occur, is a replica of my statement in 1980 that, even though “. . . a tumor is a systemic disease. . . that premise never implied that all patients will develop overt metastases in their lifetime. Conversely, it does not imply that only those with metastases represent the population with disseminated disease.”^{2(p3866)}

Hellman’s contention that a most important factor for determining the likelihood of metastasis is tumor size is “Halstedian” in concept and has been addressed in my (B.F.) 1970 monograph as follows:

“More than 2,000 patients entered into the National Surgical Adjuvant Breast Project were utilized to evaluate the validity of the concept that the size of breast neoplasms influences prognosis. It was concluded that size alone is not as consequential to the fate of the patient as are other factors relative to the tumor and/or host that determine the development of metastases. . . . Since size (ie, growth) is now recognized to be dependent on such factors as the number of proliferating cells, the length of the cycle—which is not always uniform—the extent of cell death or cell loss and the number of nonproliferating cells, . . . it is difficult to relate size to the age of a tumor.”^{40(pp42,43)}

I (B.F.) also noted that “a large tumor that had not metastasized prior to its removal may be considered early and a small one that had already disseminated may be considered late.”^{40(p43)}

Thus, unlike the tenets of the alternative hypothesis, which were based on laboratory and clinical investigation, the spectrum hypothesis consists of a heterogeneous collection of empirical thoughts and generalities (Table 3). That contention is supported by several statements that Hellman made in a subsequent publication. In that article he stated that, “A third paradigm [the spectrum thesis], one that synthesizes the contiguous-systemic dialectic [presumably the Halsted and Fisher hypotheses], has been suggested by one of us to explain the natural history of breast cancer. This thesis argues that cancer comprises a biologic spectrum extending from a disease that remains localized to one that is systemic when first detectable but with many intermediate states. Metastases are a function of both tumor size and tumor progression.”^{37(p8)}

Finally, it is to be noted that 15 years have passed since the spectrum thesis was first introduced. During that time, it has not been subjected to verification. Consequently, no scientific evidence has been presented to challenge the alternative hypothesis, any of its tenets, or the paradigm that currently governs the treatment of breast cancer.

Another aspect of the criticism of our alternative hypothesis is that associated with the concept of oligometastases. According to

Table 3. The Spectrum Hypothesis (1994)

A third hypothesis [the spectrum thesis] considers breast cancer to be a heterogeneous disease that can be thought of as a spectrum of proclivities [tendencies] extending from a disease that remains local throughout its course to one that is systemic when first detectable.
This hypothesis suggests that metastases are a function of tumor growth and progression.
Lymph node involvement is of prognostic importance not only because it indicates a more malignant tumor biology, but also because persistent disease in the lymph nodes can be the source of distant disease.
This model requires that there are meaningful clinical situations in which lymph nodes are involved, but there has not yet been any distant disease.
Persistent disease, locally or regionally, may give rise to distant metastases and, therefore, in contrast to the systemic theory, locoregional therapy is important.
This third, or spectrum, theory suggests that even if, as the systemic theory suggests, tumor cells spread distantly early in the natural history of the disease, metastases do not regularly occur.
A most important parameter determining the likelihood of their presentation [metastases] is tumor size.
Therefore, there are significant times in the clinically relevant natural history of the disease when metastases have not occurred, but, if the tumor is left inadequately treated, metastases will occur.

Rabinovitch and Kavanagh, that construct is “an intermediate phase of cancer progression falling somewhere between the hypotheses of Halsted and of Fisher,”^{1(p2423)} and by “targeting limited and measurable sites of metastatic disease,”^{1(p2423)} more favorable disease-free and overall survival will result. Rabinovitch and Kavanagh claim that “This concept has already been evaluated in prospective clinical trials with provocatively encouraging results to date.”^{1(p2423)}

The initial description of oligometastases by Hellman and Weichselbaum,^{37(p8)} in their 1995 *Journal of Clinical Oncology* editorial, was more complex. They conveyed the “thought processes” that resulted in their oligometastases thesis in a series of statements, such as the following:

- “. . . there are tumor states intermediate between purely localized lesions and those widely metastatic. Such clinical circumstances are not accounted for by either the contiguous [Halsted] or the systemic [alternative] hypotheses. [In both of those theses, when metastases occurred,] they were ‘extensive and widespread’.”
- “From considerations of these theories of cancer dissemination, in the light of the emerging information on the multistep nature of cancer progression, we propose the existence of a clinically significant state of oligometastases. For certain tumors, the anatomy and physiology [host factors] may limit or concentrate these metastases to a single or a limited number of organs.”
- “The likelihood of the oligometastatic state should correlate with the biology of tumor progression, rough clinical surrogates of which, for many tumors, might be primary tumor size and grade” [tumor factors].
- “Metastasizing cells may seed specific organs as a function of the seeding tumor cell number and characteristics as well as the receptivity of the host organ [tumor and host factors].”
- “The importance of ‘seed and soil’ [tumor and host factors] have [sic] been considered elsewhere. . . .”
- “An attractive consequence of the presence of a clinically significant oligometastatic state is that some patients so affected should be amenable to a curative therapeutic strategy.”

None of the above statements present new concepts, data, or biologic information related to the influence of host and tumor factors on metastases that might justify considering replacement of any of the tenets comprising the alternative hypothesis. Some, in fact, even support the tenet of our hypothesis, which indicates that “complex host-tumor interrelationships affect every aspect of the disease” (Table 2).

The idea that some patients may have a single or a few metastases that “should be amenable to curative therapeutic strategy”^{37(p8)} by stereotactic body irradiation (SBRT) or other targeted therapies seemed, in 1995, and perhaps remains to this day, worthy of further consideration. However, until the value of such therapies is proven by current laboratory and clinical research strategies, their biologic and clinical significance remains tenuous. Although Rabinovitch and Kavanagh state in their editorial that information has been obtained from prospective clinical trials with “provocatively encouraging results to date,” the article that they refer to [Milano et al⁴¹] provides data that is less convincing. Findings reported in that article were not obtained from clinical trials but, rather, from anecdotal reports from only 40 patients with five or fewer metastatic lesions who were treated by SBRT with curative intent and from only 11 patients who were similarly treated with palliative intent. Al-

though a plethora of findings were obtained from those few women, Milano et al⁴¹ also noted that “Additional studies are needed to further explore SBRT for oligometastatic disease from breast cancer.” They also noted that “. . . longer follow-up is needed to confirm the hypothesis that oligometastatic disease is potentially curable with multimodality therapy [chemotherapy and hormonal therapy] incorporating local treatment” [SBRT].^{41(p607)} Finally, in contrast to Rabinovitch and Kavanagh’s contention, Milano et al state that “. . . our results do not compellingly support the hypothesis that decreasing disease bulk in patients with breast cancer has the potential to reduce distant metastatic progression.”^{41(p607)}

Before the publication of that report, Hellman had appropriately stated that, “The limited effectiveness of these treatments of oligometastases has been primarily the result of an inability to recognize all metastases and the fact that these seemingly limited lesions were too often a manifestation of undetected widespread cancer. The importance of oligometastases depends on how commonly they are present.”^{37(p9)} He reinforced that admonition by stating further that “Effective treatment of oligometastases will require identification of all of the lesions and, most importantly, of the state of intermediate tumor progression likely to be consistent with the oligometastatic state.”^{37(p9)}

Unfortunately, those issues have not been resolved and, in fact, have become more complex. As a result of improving technology, an increasing number of reports demonstrate that “. . . tumor cell dissemination starts already [sic] early during tumor development and progression,”^{42(p5013)} and that “Tumor cells are frequently detected in the blood and bone marrow of cancer patients without clinical or even histopathologic signs of metastasis.”^{42(p5013)} The statements noted above fail to completely address the issues of identifying and removing not only all metastases, but dormant tumor cells and stem cells as well. Overlooked by those who promote the oligometastases concept is the report by one of us (B.F.) in 1959 that provided experimental evidence about the dormant tumor cell. In that report, I concluded that, “. . . cancer cells, alive to begin with, may be enduringly capable of growth if conditions are favorable.”^{23(p919)} Finally, 15 years have passed, and, as with the spectrum thesis, the oligometastases hypothesis has not given rise to a new paradigm for governing the treatment of breast cancer.

SUMMARY

In conclusion:

- During the last two decades, as a result of the use of systemic therapy in conjunction with breast-conservation surgery and radiation therapy, the incidence of locoregional recurrence has been reduced to a level where further reduction, a goal worthy of achieving, is likely to have little impact on survival.
- Despite the extensive information presented in this commentary, there is no new scientifically based evidence to justify replacing the current breast cancer hypothesis.
- It is likely that findings from research related to molecular biology and genetics will be the source of information that will result in a new, testable thesis that will eventually replace the alternative hypothesis and thus the paradigm that currently governs the treatment of breast cancer.

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The author(s) indicated no potential conflicts of interest.

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