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Comparative analysis to evaluate various methods for treating primary malignancies of the breast

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A COMPARATIVE ANALYSIS TO EVALUATE VARIOUS METHODS FOR
TREATING PRIMARY MALIGNANCIES OF THE BREAST

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INTRODUCTION

Cancer of the breast is a centuries old disease of mankind. Prior to the late 1800's it was considered to be an almost invariably fatal affliction and there was little to afford a patient in the way of therapy. Therefore, in 1894, when Halsted introduced the radical mastectomy operation and provided evidence that it could accomplish a significant number of cures, the prospects for patients who developed this disease became more optimistic and, accordingly, medical science began to afford it more attention. Yet, since the time the Halsted mastectomy became in vogue, the treatment of this disease has remained a problem area which medical science has not resolved. This problem of treatment in breast cancer is the dominant theme of this paper; however, in order to appreciate problems of therapy, let us first review the current status of breast carcinoma.

STATISTICAL CONSIDERATIONS

Breast cancer, a sex-specific neoplastic entity, accounts for 22% of all malignant female tumors occurring in the United States.¹ The alarming but consistently reported estimate that one of every eighteen women will develop this disease during their lifetime attests to its common occurrence among our female population.² It attacks often and when it does it carries with it a lethal potential. Of the approximately 54,000 women who will develop breast cancer annually, one out of every two will not survive five years.³ Moreover, with carcinoma of the breast, in contrast to the great majority of other malignant diseases, five-year survival is not synonymous with cure. Patients are known to succumb to the ravages of disseminante metastatic breast cancer as long as twenty years after the initial diagnosis was made.⁴ Therefore, death from this disease actually occurs at a rate of approximately 60-70%.

Unfortunately, the information given above would have been quite accurate were it presented three to four decades ago! It is a disappointing fact that the mortality from mammary carcinoma has

remained stable. The age-adjusted mortality for the past forty years has remained at approximately 24 to 25 annual deaths per 100,000 females.⁵ Moreover, it has even been shown that there has actually been a rising death rate from mammary cancer.⁶ One may question whether this might be due to improvement in collection of vital statistics and to the gradual population increase. Yet, alone these factors belie an adequate explanation by which we can claim any net gains in effectiveness of treatment as judged by end results.

REVIEW OF APPROACH TO IMPROVING RESULTS

To state that this disease entity has been a neglected area of medical science as explanation of why the outlook for this neoplasm has not changed is entirely unwarranted and without basis. It is one of the most extensively investigated afflictions of the human race. There are voluminous statistical data which have been compiled and analyzed in order to understand more concerning its natural history. Likewise, in the realm of etiology there has been no neglect. Many certain consistent correlatives, e.g., with parity and lactation, have been established. However, as to specific etiology this malignancy, as

all others, has defied explanation as to why apparently normal tissue begins its lethal autonomous growth. Nevertheless, the latest refinements of scientific investigation are constantly being applied in pursuance of an answer to this vital question. Notable examples in this regard, with particular reference to mammary carcinoma, are the works of Andervont and Dunn⁷ concerning breast cancer in mice. Their work dealing with virus-induced mammary tumors and host-virus relationships lend generous stimulus to research of a virological relationship in this and other human malignancies.

Realizing that natural history and etiological relationships are only part of the quest for improvement in this disease, much focus has centered on diagnosis and treatment. The universal agreement that early diagnosis favors prospects of salvage from carcinoma has stimulated efforts to achieve this goal. Vigorous campaigns have been waged at educating the public concerning the great value in immediate medical consultation when an abnormality of the mammary gland is suspected. Physicians today are being trained in appropriate techniques of clinically detecting breast lesions and encouraged to instruct female patients in the methods of self-exam. Now, we can also view the emergence of newer diagnostic aids, for example, recent

mammographic techniques such as that advocated by Zuckerman,⁸ which may hopefully yield still earlier diagnoses.

The final focus of the subject of carcinoma of the breast concerns treating the disease. Until all cases are diagnosed at the earliest stages, therapy remains of two general types. The first designated as primary therapy pertains to treatment of the localized disease where the therapeutic objective is definitive cure. The second type, secondary or palliative therapy, deals with those patients with disseminate systemic breast cancer where salvage of the patient's life is deemed unobtainable. Treatment aims in this type of therapy are to temporarily arrest or decrease the rate of progression of the disease, and provide maximum comfort possible while the malignancy runs its fatal course.

In the past 40 years primary therapy fails to show improvement as judged on the sole basis of increasing the percentage of the number of definitive cures over the total number of patients who develop breast cancer. The investigation of progress with secondary therapies do indicate, however, that some gains have been made. By definition, however, all methods of palliation

cannot improve cure rates but only can show improvement in length of survival time. The latter has not been well documented, but yet, palliative therapies such as ablative endocrine procedures, hormonal administration, cancer chemotherapy, and radiotherapy are felt to give, to a limited extent, the unfortunate patient with advanced disease a somewhat brightened outlook. It is hoped that further evaluation of these methods of treatment eventually crystallize into a pattern representing a rational approach of utilizing these methods to great advantage. Then, the difficult problem of choosing the appropriate palliative therapies and their proper sequential application from the myriad of secondary therapeutic possibilities may be minimized.

ASSESSMENT OF PROGRESS

In spite of the intensive efforts by various methods of scientific investigations to achieve a more favorable prognostic outlook in breast cancer the enigma remains: Why has the ability to validate progress in this disease been so elusive? It may be speculated that there are other unknown factors which obscure what is actual positive gain in this disease, but it cannot be proven. Then what does account for the apparent failure? It is accepted

almost without exception that treatment in the earliest stages of a malignancy is directly proportional to the chance for cure. Then must we accept as fact that efforts at obtaining earlier diagnoses have gone unrewarded? Clinic centers have shown that the disease when discovered is more localized and that tumor size is smaller than 30 years ago.⁹ Yet, if this represents evidence of success in obtaining early diagnosis, why has there been no increase in survival rate? Also, it would be expected that improvements in training of surgeons who are granted the advantages of modern, well-equipped hospitals with modern anesthesiological facilities would produce positive results. In addition, if radiotherapy aids at all in eradicating malignant disease, the improvements in this area such as knowledge of more effective dosage schedules and ability to obtain total field exposures might also be expected to add to the expected therapeutic gains. There are undoubtedly other reasons to expect that a span of 40 years would show better prospects for the patient receiving a diagnosis of breast cancer. Yet, regardless of expectations, the persistent, static mortality rate forces us to admit that in saving lives from the disease, we have been at a dead end street the past three to four decades.

A PRESENT CONTROVERSY

The text of the preceding tends to illustrate that the results of efforts to more effectively deal with breast cancer in the past few decades have, in general, been ungratifying. These efforts have been especially disappointing in the area of primary therapy. As a result, there is much controversy concerning treatment of the localized disease. The time honored and most widely accepted form of therapy, the radical mastectomy, today receives vigorous challenge from those who advocate alternative methods of treatment.

In a broad sense, supporters of methods of therapy other than the classical Halsted mastectomy, can be divided into two groups. The first group holds that the conventional operation denies patients a chance of cure on the grounds that it does not remove all foci of malignant disease. They therefore contend that enlarging the scope of attack to eradicate deposits of tumor cells residing in areas not excised by the Halsted mastectomy, but which have not become disseminated in the blood stream, will result in a greater number of cures. The second group argue that a more modified approach might accomplish results as good as the conventional therapy and add the benefits of less debilitation

from treatment. Hence, the two groups seek separate objectives. The first desires to develop a method of therapy which, if it were universally applied, would then result in the best over-all cure rate. The second seeks to provide the simplest and most humane form of therapy. Those supporting a more radical attack claim that anything less is a step backwards. Those supporting more conservatism in therapy state that we have already stepped out too far and that it is time to consider the quality as well as the quantity of life.

ALTERNATIVES TO TREATMENT

In reviewing the treatment of localized carcinoma of the breast, let us look at the vast array of primary therapies available today. A list would include local extirpation of the primary tumor, irradiation alone, simple mastectomy, the classical Halsted radical mastectomy, and the super-radical operation which adds to the classical mastectomy dissection of internal mammary and/or supraclavicular nodes. There are also modifications of surgical attack which lie in extent between the simple mastectomy and radical mastectomy, e.g., Patey's operation.¹⁰ The list becomes larger when we consider that any of the above surgical attacks can be supplemented by irradiation (in actual practice

it has not been tried with the super-radical operation). In addition, when irradiation is used to supplement surgery, one has the option of administering it either pre-operatively or post-operatively.

The numerous possibilities of primary therapy are increased by considering the addition of adjunctive chemotherapy, prophylactic removal of the uninvolved breast, or a method of endocrinological alteration to the above mentioned therapies. This list should offer dramatic illustration that universal satisfaction from any one procedure has not been obtained! It should further point out that the primary treatment of mammary carcinoma is not a field of neglect!

OBJECTIVES AND METHOD OF STUDY

I would wish at this point to clarify important features of this study. First of all, it is a literature review which attempts to present a comparative analysis of the dominant methods of primary therapy. The inherent difficulty in comparing separate series of data are ever present. Different methods used for selecting patients for therapy, and inconsistency in the reporting of results, often make accurate comparative analysis an impossibility. Further problems also

arise due to the difference in statistical methods used and the frequently great disparity of series size.

I would also like to point out that many therapeutic approaches will not receive detailed analysis. To deliberate on all approaches to primary therapy would reach textbook proportions. I have decided, therefore, to avoid a voluminous report, which I believe would only add to the confusion rather than aid in any clarification of the issue. However, where any form of therapy has received considerable support and has been duly tested or although not well tested, has shown impressive results, it will be discussed. Any therapy advanced which is not included here, I have taken the liberty to omit because the work with that therapy is either poorly documented, insufficiently tested, or without impressive result to date.

My specific goals are to bring into sharp focus the significant results and the underlying rationale of the forms of therapy which are to be discussed. I intend to give a fair comparative analysis and will undoubtedly have to expose the limitations of achieving that aim. An adherence to objectivity is desired and in this respect I can only offer the advantage of not having personal involvement with any particular form of therapy. Many of the articles on the subject

of primary treatment of breast cancer are reported by authors who have a bias for the method which they advocate, and this may result in limited objectivity.

THE CLASSICAL RADICAL MASTECTOMY

To begin the discussion I have chosen the classical Halsted radical mastectomy as the "ground breaking" form of therapy to be reviewed. It is the time honored form of primary treatment which, although being under full attack in the controversy of primary treatment, probably still maintains dominant support. It embraces the principals of primary cancer therapy in its being an attempt to eradicate the primary tumor and its regional lymphatic routes of spread. In other words, it is an attempt to completely remove all malignant tissue before the lesion has become disseminate.

The radical mastectomy was introduced as a method of treatment for carcinoma of the breast by Dr. William Halsted to the clinical society of Maryland in 1894 as the complete operation for the cure of breast cancer.¹¹ The operation soon came to emphasize four common principals:

- (1) Excision of the skin over the whole breast, covering the defect that remains with a Theirsch graft when necessary;
- (2) Excision of both pectoral muscles;
- (3) A complete axillary dissection;
- and (4) Removal of the excised tissues in one block.¹²

In 1943, Haagensen and Stout¹³ presented their study on the criteria of operability where they outlined what they considered to be those cases of advanced carcinoma which could not be cured by radical mastectomy. These authors reviewed 1,040 cases of cancer of the female breast, 640 of which received a radical mastectomy, at the Presbyterian Hospital in New York during the period 1915 to 1934. This study was designated to correlate the clinical descriptions of the individual cases with the end results of operation. Twenty-one different factors were examined which had been presumed to be evidences of unfavorable prognostic significance. Of these twenty-one, eight were considered in their opinions to be mandatory contraindications to radical mastectomy. Five other factors, not of themselves categorical contraindications, were shown to become so when more than one of them is present in the same patient. Their detailed analyses of these cases resulted in these rules which they advanced for judging operability.¹⁴

Women of all age groups, who are in good condition to run the risk of major surgery, should be treated by radical mastectomy, except as follows:

1. When the cancer is one which developed during pregnancy or lactation.
2. When extensive edema of the skin over the breast is present.
3. When statellite nodules are present in the skin.
4. When intercostal or parasternal tumor nodules are present.
5. When there is edema of the arm.
6. When proved supraclavicular metastases are present.
7. When the carcinoma is the inflammatory type.
8. When distant metastases are demonstrated.
9. When any two or more of the following signs of locally advanced cancer are present.
 - a. Ulceration of the skin
 - b. Edema of the skin of limited extent (less than 1/3 of the skin over the breast involved.)
 - c. Fixation of the tumor to the chest wall
 - d. Axillary lymph nodes measuring 2.5 c.m., or more, in transverse diameter, and proved to contain metastases by biopsy
 - e. Fixation of axillary lymph nodes to the skin or the deeper structures of the axilla, and proved to contain metastases by biopsy.¹⁵

The authors further stated that "if these criteria had actually been followed in judging operability in the series of 640 radical mastectomies, a total of 109 of the patients would not have been operated upon. Yet,

the number of patients permanently cured would not have decreased by a single one." This is shown in the following table.

TABLE I*

Group	No. of Cases	5 Yr. Clinical Cures	
		No.	Per Cent
Cases in which radical mastectomy was actually performed	640	231	36.1
Cases classified as inoperable by above criteria	109	3**	2.8
Cases which would be classified as operable by above criteria	531	228	42.9

*Haagensen-Stout criteria of operability applied to Presbyterian Hospital series of radical mastectomies, (1915-1934), from Haagenson and Stout.¹⁷

**All dead of breast cancer in 8 years.

In addition to avoiding needless operations, these authors gave evidence that applying surgery to inoperable cases actually shortens the patient's life. This is shown in Table II.

TABLE II*

No. of Cases	Duration: Onset to Death
118 Presbyterian Hospital cases (1915-1934), untreated	42.3 mo.
104 Presbyterian Hospital inopera- ble cases, 1915-1934 series, treated by radical mastectomy**	32.3 mo.

*Mean total duration of breast carcinoma. Onset to death in various groups of cases. From Haagensen and Stout.¹⁸

**Inoperability as judged by Haagensen-Stout criteria.

It is interesting to next examine the results obtained by Haagensen after actual application of his clinical rules for operability and compare them to the results which would have been obtained had the criteria of operability been used in the retrospective study. Table III, comparing five-year clinical cure rates of the retrospective study and of a series of 495 patients receiving operations at Presbyterian Hospital in 1935-1942¹⁹ which were selected by Haagensen-Stout criteria, is presented.

TABLE III*

Group	No. of Cases	5 Yr. Clinical Cures	
		No. Cases	Per Cent
1. Radical mastectomies-- 1935-1942 inclusive**	495	241	48.7
2. Radical mastectomies-- Haagenson-Stout criteria-- no exceptions (1935-1942 inclusive)	470	241	51.3
3. Cases operable according to Haagensen-Stout criteria-- from retrospective study (1915-1934)	531	228	42.9

*Five year clinical cure rates; criteria of operability in practice vs. its retrospective application

**Twenty-five patients in this group received radical mastectomy although inoperable by Haagensen-Stout criteria--have survived five years

To evaluate the difference in results observed, I made an assessment of statistical significance by using the χ^2 method. Groups 1 and 3, which show a difference in cure rate of 5.9% (48.7% - 42.9%), is of borderline significance, i.e., $P = 0.05 - 0.10$. The difference of 8.4% between groups 2 and 3 is, however statistically significant, P less than 0.05.

A safeguard against misinterpreting results such as the above is to compare the absolute five-year cure

rates. The total number of patients in the 1935-42 series, regardless of operability status, was 787.²⁰ The total number in the 1915-1934 was 986.²¹ Absolute 5-year cure rates are 30.6% ($787 \div 241$) for the 1935-1942 series, and 23.1% ($986 \div 228$) for the 1915-1934 series. This observed difference is also statistically significant by the χ^2 method. It is now more justified to suggest that, as judged by comparative results, some gains were apparently being made in dealing with breast cancer. A gain in cure-rate with primary therapy in the face of a gain in absolute cure-rate is difficult to ignore. Were there only improvement shown with primary therapy, but no appreciable change in the percentage of patients saved from the total, the improvement would become suspiciously related to selection. Oddly enough, in the two series of patients compared, there would be little expectations for improved results as the selection of patients was identical and the same method of therapy was used. The reason for the gain in the operable candidates remains one for speculation. Nothing definite can be established and the suggestion that it reflects better surgical technique, etc., should be weighed against the possible vagories of a retrospective study.

The Triple Biopsy in Mammary Carcinoma

In 1953, Macdonald, Haagensen, and Stout²² introduced regional lymph node biopsy as additional criteria of operability for the radical mastectomy. This procedure, as initially described, consisted of incisional biopsy of the primary tumor, biopsy of the nodes in the upper three intercostal spaces on the involved side, and a supraclavicular node dissection. If, in the preliminary biopsy, metastases were located in the internal mammary or supraclavicular nodes, the disease was considered beyond the scope of radical mastectomy. Supraclavicular biopsy, however, did not prove to be a sufficient guide in selecting patients for operation. Haagensen reported his experience that it was not possible to successfully excise carcinoma which had invaded the subclavicular nodes!²⁴ As these nodes were occasionally involved when the supraclavicular nodes were found to be clear, biopsy of the axilla for these nodes were substituted for the supraclavicular biopsy.

The inception of this procedure was inspired by the findings of Dahl-Iverson and Andreassen²⁵ on the incidence of occult supraclavicular metastases and the works of Handley,^{26, 27} Margottini,²⁸ and Urban^{29, 30} which demonstrated the significant incidence of internal

mammary metastases when axillary metastases are present and when the carcinoma is situated in the medial and central sectors of the breast. Exclusion of patients for radical mastectomy when internal mammary or supraclavicular metastases were present was based on the results of experience, and also on the basis of anatomical studies of regional lymphatic routes from the breast. The latter were discussed extensively on the original publication advocating use of the triple biopsy.³¹

Table IV is presented to show preliminary results with the method as compared to using the clinical criteria alone.

TABLE IV*

Columbia Clinical Classification	Clinical and Pathological Criteria of Operability 1952-1955	
	No. Patients	% 5-Yr. Survival
A	116	87.9
B	16	62.5
C	13	61.5
D	1	0.0
	<u>146</u>	<u>82.2</u>

*Five year survival--from Haagensen's personal series (only Series II is presented above; Series I appears on the following page)

TABLE IV (cont)*

Columbia Clinical Classification	Clinical Criteria of Operability - 1935-1951	
	No. Patients	% 5-Yr. Survival
A	228	82.5
B	122	59.0
C	50	38.0
D	10	20.0
	<u>410</u>	<u>68.5</u>

*Series I--from Haagensen's personal series³²

The significant increase in the five-year survival rate can readily be seen. It is a result of selection until proven otherwise. It is a definite contribution to primary therapy to be able to achieve such accuracy in determining the possibility of saving a patient from breast cancer. However, the use of the preliminary biopsy has been debated as to its practicality in a program of therapy. It is not today a widely accepted procedure, the argument usually being that the criteria is too rigid and denies patients who can be salvaged a chance for cure.

THE EXTENDED RADICAL MASTECTOMY

The supraclavicular, internal mammary, and apical axillary nodes, when metastases are present, preclude cure by radical mastectomy if one considers Haagensen's criteria as accurate. It is interesting then to view the results obtained when the operation is extended to include removal of supraclavicular and internal mammary nodes. Trials with supraclavicular node dissection have been unrewarding. Halsted, in the early 1890's added supraclavicular dissection to the radical mastectomy.³⁴ He utilized this procedure in 101 cases of which 44 were found to have supraclavicular metastases. Only two were cured at five years. Waagensteen,³⁵ in 1948, used supraclavicular, cervical, and upper anterior mediastinal dissection together with excision of the homolateral internal mammary chain as an extension of the radical mastectomy. However, he likewise found similiarly poor results when supraclavicular metastases were present. In light of the poor results from attempts to eradicate the disease with supraclavicular dissection when these nodes were involved and anatomical evidence which supports that supraclavicular involvement is synonomous with blood stream dissemination, excision of supraclavicular nodes has lost favor in primary therapy of mammary carcinoma.

The internal mammary nodes, likewise are not removed by radical mastectomy. The incidence of metastases to this region is significantly high in patients with localized disease. Somewhat representative studies, which have aided in establishing the percentage of metastases to this area, by Thackray³⁶ and Urban³⁷ have found the incidence to be approximately 25-30%. These studies suggest that many patients who have a radical mastectomy procedure are not receiving a good cancer operation, i.e., one which removes all foci of malignant cells. Also, as judged by anatomical considerations, internal mammary metastases is not the equivalent of disseminated disease. (A few dissenters, e.g., Haagensen³⁸ considered metastatic disease of nodes of the first intercostal space as "beyond surgical cure.") Because the prospects for an operation which attacks this area did not appear so limited, it has received more extensive trial.

In 1951, Urban³⁹ devised an operation which consisted of radical mastectomy in continuity with resection of the mammary chain. This procedure he applied mainly to medial quadrant and central lesions, i.e., primary tumor sites which are shown to be associated with a higher incidence of internal mammary node metastases. The following table illustrates results with this procedure.

TABLE V⁴⁰

250 Primary operable breast cancer Combined procedure - 5-year survival rates		
Nodes	Total	Surviving 5 Years
All clear	112	97 (87%)
(only axilla +)	54	32 (59%)

These results will be compared with Haagensen's results illustrated previously in Table IV, page 20.

It is intended to compare patients selected on the basis of Haagensen's clinical and triple biopsy criteria when they receive the radical vs. the extended radical operation. For the radical mastectomy group, Haagensen's series from 1952-55 is obviously appropriate. To find a comparable series from Urban's group of patients, the following was done

First: The reported cases of all nodes clear and axilla only positive and the number surviving the extended operation were added.

TABLE VI

Group	No.	5-Yr. Surv. No.
All nodes clear	112	97
Only axilla positive	<u>54</u>	<u>32</u>
Total	166	129

Second, Urban reported that 100 cases from the series of 250 patients would have been considered inoperable by Haagensen's clinical and pathological criteria.⁴¹ Of these 100 patients, 84 had internal mammary node invasion. Therefore, only 16 of the "operable by Haagensen" patients could have been in the all nodes clear plus only axilla positive group. Then, I subtracted all 16 patients from this group (these 16 could possibly have apical node involvement or be clinically inoperable). Further, we must consider that of these 16 excluded, some 5-year survivals might be recorded. The proportion surviving is not known; but, from Urban's published work in 1959,⁴² he did report 7 cases inoperable by Haagensen's criteria because of apical node involvement (but no mammary metastases). Of these 7 patients, 4 survived 5 years. Therefore, at least these 4 patients must be subtracted from the 129 survivals. Not knowing the fate of the other 9 patients, I will consider them as all succumbing within 5 years. The comparison can then be made from information shown in the following table.

TABLE VII

Group	No.	5-Yr. Surv. No.
Urban--All nodes clear	112	97
+ only axilla positive	54	32
	<u>166</u>	<u>129</u>
Less 16 patients inoperable by Haagensen criteria	16	
	<u>150</u>	<u>129</u>
Less 4 patients surviving, known to have subclavicular metastases, but no internal mammary node metastases		4
	<u>150</u>	<u>125</u>

From the above table we can see that 83.3% (125 divided by 150) of the patients who would fit Haagensen's criteria of operability survived 5 years as a result of the extended mastectomy procedure. From Table IV we see that an 82.2% 5-year survival rate was obtained from the classical mastectomy. Hence, if the comparison is valid and representative, we see that the application of the super-radical mastectomy would probably not be superior to the conventional operation. More data, of course, is needed to make this a statement of fact.

In addition to analysis of the comparable series of patients, it is also important to investigate the fate of the 100 patients who would have been denied operation in the radical mastectomy group, but who did undergo the extended procedure. Urban⁴³ reported that of the

100 patients, 42% were free of disease at 5 years. Hence, we have evidence to support the most vigorous objection to Haagensen's method of selection, i.e., the fact that potentially salvageable patients are denied cure by limitations of the criteria. It remains to be seen whether the super-radical mastectomy, the radical mastectomy, or an alternative procedure would have the best success in obtaining cure of the inoperable patients by Haagensen selection.

MODIFIED PRIMARY THERAPY

As previously noted, there are those who advocate a less radical approach to primary therapy. The possibilities range from local extirpation of the tumor to a radical mastectomy limited only in the extent that the pectoralis major muscle is preserved. The advantage claimed from any of the modified is fewer post-operative complications and less deformity. The ogre which haunts these procedures is the likelihood of leaving tumor cells behind for later dissemination.

To discuss the subject of conservative vs. radical surgery, I have chosen the therapy which lies midway between radical mastectomy and the least extensive approach, i.e., the simple mastectomy. Due to the insecurity of operating with a surgical attack which does not

remove known deposits of tumor cells, most modified therapies use supplemental radiotherapy. When the latter is used, the question of whether or not the therapy is then less radical than a complete operative approach arises. Taking a non-committal stand on that issue and admitting to the lack of "purity" in the designation, simple mastectomy, I would like to present a published analysis of the subject conservative vs. radical mastectomy.

Miller and Kennedy⁴⁴ compared the results of simple mastectomy to radical mastectomy when the cancer is confined to the breast. From the private practice of Dr. Kennedy, 1927-1952, 48 patients who were clinically operable by Haagensen's criteria serve as the group for radical mastectomy. The quality of radiotherapy, administered post-operatively, was such that it was considered by these authors to bear no influence on survival.⁴⁵ Table VIII shows their results compared with Haagensen's on the basis of Haagensen's clinical classification.

TABLE VIII*

Clinical Findings	Number of Cases	Number Without Axillary Mestasteses	Number With Axillary Mestasteses	5 Year Survivals		
				No.	Percent	
<u>Group A</u>						
Axillary nodes not clinically involved No grave signs	Haagensen**	181	119	62	153	85
	Miller & Kennedy	43			28	65
<u>Group B</u>						
Axillary nodes clinically involved & no signs	Haagensen	107	24	83	64	60
	Miller & Kennedy	24			10	42

Comparison of Kennedy's and Haagensen's results on the basis of Haagensen's method of clinical classification--from Miller and Kennedy⁴⁶

Number surviving without axillary metastases is 104.

The following considerations were made to arrive at the number in Kennedy's group whose nodes were not clinically involved but would have metastases:

1. The per cent in Haagensen's Group A who had microscopically involved nodes was calculated.
 $181 \text{ divided by } 62 = 34\%$
2. Using 34% as the supposed percentage of the Kennedy-Miller Group A patients expected to have positive axillary nodes. Then 43×0.34 or 15 patients in Group A are expected to have microscopic involvement.

To arrive at the number of survivals of these 15 patients with supposed microscopic metastases the following was done.

3. The assumption that the survival of patients with positive nodes would be as good as the Group B survivals was made; therefore, at least 42% survival expected. The number of survivals is then 0.42×15 , or 6 patients.
4. The five-year survival for the simple mastectomy is then as follows; no. of patients with negative nodes--43 minus 15 = 28; no. of survivals of patients with negative nodes--28 minus 6 = 22.

Five year survival rate of patients with disease confined to the breast is 28 divided by 22, or 78%.

Admitting to the limitations of the comparison due to small series size, the difference observed in the results of radical mastectomy (119 divided by 104 = 87%) vs. that from the simple mastectomy, 78%, was interpreted by Miller and Kennedy as evidence for the superiority of the radical mastectomy in disease confined to the breast.

This example of comparative analysis revealed a method, when the number of axillary metastases in simple mastectomy patients is unknown, of assessing results of that procedure in disease confined to the breast. However, if the method is to be used it should be carried out more completely. We must also consider those patients who have clinically involved but microscopically negative nodes. A more complete analysis by this method is undertaken in the following:

1. Of 107 patients, 24, or 22% of Haagensen's Group B, had microscopically negative nodes. The expected number of patients in the Kennedy-Miller Group B category with negative nodes is therefore 0.22×24 , or 5 patients. The total number of patients with disease confined to the breast is actually 28 plus 5, or 33.
2. To determine how many of these 5 patients survived, I considered the survival rate as being 80%, or comparable to the survival rate from Kennedy and Miller. Therefore, the expected number who survived is 4.
3. To determine the survivals of Group A positive node patients.
 - A. Microscopically positive nodes is 24 minus 5, or 19 for Group B.
 - B. Survival of microscopically positive nodes is 19 divided by 6 (10 survivals from Group B minus 4 which had negative nodes), or 31%.
 - C. Number surviving with axillary metastases in Group A is 0.31×15 , or 5 patients.

4. To determine the percentage of survivals in patients with disease confined to the breast who had simple mastectomy:
 - A. Patients with negative nodes is $28 + 5$, or 33.
 - B. Number surviving is 28 minus the 5 patients in Group A with positive nodes or 23. In addition, we had the 4 patients with negative nodes from Group B expected to survive 5 years. Therefore, total number surviving 5 years with disease confined to the breast is 23 plus 4, or 27.
 - C. The 5 year survival rate of patients with disease confined to the breast who received a mastectomy is 35 divided by 27, or 82%.

An 82% 5-year survival rate is not necessarily inferior to the 87% in Haagensen's group in terms of statistical significance. Furthermore, Haagensen's survival rates represent the best of those reported with radical mastectomy. Unfortunately, others reporting results with radical mastectomy which I reviewed did not state percentages of cure with disease confined to the breast. It is not unlikely, however, that they would average in the range of 80-85%. For example, Butcher,⁴⁶ reported a 76% survival for Group A patients, i.e., 9% less than Haagensen's from Table VIII. It would not be surprising if the 5 year survival from patients without axillary metastases might also be inferior to the 87% of Haagensen's axillary negative patients and might well be comparable to the 82% as calculated above for the Kennedy-Miller series.

Before concluding the analysis of modified vs. radical surgery for carcinoma of the breast, I feel obliged to report my awareness of the obvious objections which would be raised toward the method used for comparison. First, the small series size of the Kennedy-Miller simple mastectomy group precludes the making of any valid statements concerning the effectiveness of that operation as compared to the radical mastectomy. In fact, in analyzing a larger series by Bruce and Trough⁴⁷ where Groups A and B combined totaled 180 patients, by applying the same method of analysis I obtained a survival rate of 77% for disease confined to the breast. Further, I observed that whenever the results of simple mastectomy show increased survival in Group B patients without a comparable increase in Group A, survival for disease confined solely to the breast decreases.

Also, the assumption that 5 year survival for patients with clinically uninvolved by microscopically involved nodes is identical to that of patients which have both clinically and pathologically involved nodes is warranted. It would probably be higher in the first group and correspondingly, the 5 year survival for the axillary negative node group becomes less.

The only conclusion that can be made is that the value of simple mastectomy for limited breast cancer is not established. For all stages, if the results in Table VIII are at all representative, simple mastectomy is probably inferior to the more radical operations.

The question remains as to whether or not simple mastectomy ± radiotherapy deserves more extensive trial. Hicken⁴⁸ has found that 95% of breasts have mammary tissue extending into the axillary tail and occasionally the axilla itself. On these grounds he terms simple mastectomy a "sub-total mastectomy." However, it is not known what per cent of tumors confined to the breast actually harbor malignant cells in this position of the breast beyond the confines of the simple mastectomy operation. Would this percentage, if known, correlate with the percentage of failures, if known, that is produced by using simple mastectomy for disease not involving axillary nodes? I make particular reference to the two "ifs" in the preceding sentence. We know neither of these percentages and any conclusion concerning them would be a presupposition of unproven fact.

I do believe that simple mastectomy, at least for disease confined to the breast, should not be abandoned until further research has established its effectiveness.

This may require preliminary axillary biopsy to establish that the neoplasm is actually confined to the breast. To abandon it on the basis of Hicken's anatomical studies as a theoretical justification, seems unwarranted until we have established that simple mastectomy produces less cures and is an inferior procedure by a cause-effect relationship to the breast tissue, which in 95% of the cases is left unexcised.

SUMMARY

Carcinoma of the breast is reviewed with special focus on the treatment of this disease when it is still localized and definitive cure is deemed obtainable. The facts regarding the frequency of occurrence and the present mortality rate are presented. The the mortality rate has remained stable or was possibly increasing is emphasized.

A broad discussion of the present investigative work is included in the paper to illustrate the various approaches which medical science is using to find answers which will provide improved methods of dealing with this disease. Following this, the question is raised concerning why we are not able to demonstrate positive gains in mammary carcinoma in spite of having the modern

advances in our technology in addition to the increasing fund of knowledge concerning the nature of the disease.

The subject of primary therapy for breast cancer is discussed in this paper from a comparative analytical viewpoint. It is purely a literature review. The obstacles faced in achieving the goal of finding like series for comparison are indicated, e.g., different methods of patient selection and disparity of series size. The fact that many forms of therapy are omitted is because the results reported did not lend themselves readily to meaningful analysis.

The analysis of primary therapy is attempted by examining the results of three major forms of therapy--the super-radical, radical, and the simple mastectomy.

The works of Haagensen and associates receives extensive discussion and is used as the basis of comparison of radical mastectomy against the other two forms of primary therapy. Special treatment is also given to his clinical and pathological criteria of operability. The works of Haagensen were chosen because his reported series were particularly amenable to statistical comparison with other forms of therapy. Because the authors who report their series usually include only the patients receiving their respective

treatment, I exclude those patients who are considered to be unsalvageable by primary therapy; I was not able to report comparative absolute survival rates. In view of this, the comparisons made were of two forms of therapy applied to a stage of disease where both therapies could be considered adequate on the basis that the tissue involved with tumor cells would theoretically be completely excised by both procedures. Therefore, the super-radical was compared to the radical mastectomy in series constructed where the disease involved only the breast and axilla. Likewise, the comparison of simple to radical mastectomy was applied to cases which had disease confined to the breast. In the latter, to obtain a series representing no neoplastic involvement of the axilla certain tenuous assumptions were made which precluded asserting any conclusive statements.

CONCLUSIONS

After considering the findings in the present study of carcinoma of the breast, I would like to list the following conclusions derived from my study.

1. No evidence is available to indicate, in terms of lives saved from disease, that the prognosis for carcinoma has improved in the last 40 years.

2. There are no results to indicate that any one therapy is the most superior, although radical mastectomy is still the most favored treatment for the localized disease.

3. Extending the radical mastectomy by the addition of supra-clavicular node dissection does not gain a significant percentage of cures to warrant its use in the extended operation.

4. Supraclavicular node metastases appears to be synonymous with dissemination of disease beyond hope of cure by surgery. The presence of metastases in these nodes should be contraindication to operation.

5. Extending the radical mastectomy by removal of the internal mammary nodes does show promise in those cases inoperable, by Haagensen's criteria, on the basis of internal mammary or apical node invasion.

6. Parasternal node dissection does not appear to improve results on these cases considered operable by Haagensen's clinical and pathological criteria.

7. The relationship of apical axillary node involvement to cure rate deserves further clarification. When these nodes are involved and all other signs make a patient operable by Haagensen's criteria, it should be challenged by other workers to prove that patients can be cured by radical mastectomy.

8. The procedure of triple biopsy should be re-evaluated. The reasons for this is as follows.

- A. It offers great advantage, when results of a therapy are reported, of making valid comparisons with other forms of therapy.
- B. It gives precise knowledge of the status of node groups known to affect prognosis and thus the establishing of indications or contraindications may become more precise and objective. Then the disparity of different therapist's criteria for operability may be resolved.
- C. It may influence the choice of procedure so that the appropriate therapy is instituted with advantage of offering the least debilitating form of therapy without sacrificing the chance of cure.

9. The role of the more conservative forms of therapy must be elucidated. This will require preliminary biopsy of at least the axillary nodes if the success of a modified procedure is to be determined for the stage of the disease for which the extent of the procedure is considered adequate. Findings of positive nodes in a procedure which does not include their removal will avoid the kind of statistical method as illustrated in this paper in which determining presence of axillary metastases is suspected rather than proven.

10. At present, for disease localized to the breast, no conclusions can be made as to the inferiority, or or equality of simple mastectomy as compared to more radical procedures.

11. It would be informative, if pathological exam of breast tissue, considered to be unexcised by simple mastectomy, were made from specimens obtained by radical mastectomy. More solid theoretical ground, pertaining to simple mastectomy in cases with no axillary node involvement, could then be established.

12. The role of supplemental radiotherapy, and the question of pre-operative vs. post-operative administration needs further clarification.

13. Whenever possible, all patients seen with carcinoma of the breast should be reported, rather than only those patients receiving the particular form of therapy. In this way, we have a means of viewing the success of a procedure not only by its results when applied but also as to its reflection in the over-all survival rate.

FOOTNOTES

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