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PROPHYLACTIC OOPHORECTOMY
IN THE TREATMENT OF BREAST CARCINOMA

by Max Dean

A THESIS

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The College of Medicine in the University of Nebraska
In Partial Fulfillment of Requirements
For the Degree of Doctor of Medicine

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INTRODUCTION

Death from breast carcinoma in a premenopausal patient has directed most physicians who are treating this disease to review their cases and search for a better means of improving the cure rate and extending the survival time of subsequent patients who present with this therapeutic problem.

Advances in surgical technique, improved methods of irradiation therapy, the relatively recent use of new and better understood chemotherapeutic agents, and therapeutic castration have failed to change the mortality rate in breast carcinoma since accurate records have been available. Breast cancer is the leading cause of carcinoma in females. The mortality rate for all females is 27 per 100,000, however, in the 45-50 age group this figure is 45 per 100,000 and there is a linear increase to 113 per 100,000 in the 75-80 age group. (1) The American Cancer Society predicts 29,000 deaths and 67,000 new cases of breast cancer in 1969.

This paper is undertaken as a review of the current concepts in one method of treatment that has long been debated, frequently doubted, and usually supported or condemned with insufficient data. This treatment is prophylactic oophorectomy.

REVIEW OF THE LITERATURE

An English surgeon named Cooper in 1832 was the first to observe clinically and pathologically that there was an increase in size of the tumor premenstrually and diminution after the menopause. However, he apparently did not realize the significance of these changes as he made no proposal as to the causal factors. Therapeutic castration was being done in the late Nineteenth Century and Schinzinger suggested castration in menstruating women who developed this tumor before the malignancy was widespread. He left no report of performing this operation. This was left to Beatson who in 1896 reported improvement following castration in cases of inoperable breast malignancy. (26) Numerous reports of remissions appeared in the literature as various practitioners began to use castration in their armamentarium against recurrent disease, the so-called therapeutic castration. Taylor in 1934 introduced the concept of radiation castration as routine therapy along with radical mastectomy in uncomplicated breast carcinoma in premenopausal women. His basis of therapy was that the decreased ovarian activity would have an inhibitory influence on the development of metastatic deposits. (23) However, in 1939 he reviewed his 17 patients treated by this method and could show no significant difference in longevity from a control group. In this review, Taylor introduced the term "pro-

phylactic castration." (24)

Adair in 1945 and Nathanson in 1951 both felt that the results both pro and con that were being reported for prophylactic castration were from valid, well controlled studies but both concluded that the data they reviewed showed no improvement in longevity when compared to therapeutic castration. (9) (15)

J. Shelton Horsley in 1937 became dissatisfied with the poor results of radical mastectomy in young women and began surgically removing both ovaries in women under forty whenever a radical mastectomy was done for breast malignancy. He based his operations on recent results of experimental work relating estrogens to mammary carcinoma and clinical results showing benefits of castration in advanced disease. This series of patients has been followed and more comment as to long term results will be made later in this paper.

Treves in 1957 reported a series of 152 patients who received prophylactic castration and compared these to a group of 2893 who were treated with radical mastectomy. Even though 84 of these patients were castrated with X-ray and 26 continued to menstruate, his statistics still showed increased longevity and a longer interval before recurrence. In this article, Treves states that immediate cessation of ovarian function is mandatory, however, the

average length of time from mastectomy to castration was 8.7 months in X-ray castrated and 12.2 months in surgically castrated! The degree of tumor involvement was also much greater in the castrated group than in the controls. (25) Even with his rather impressive results this author in a subsequent article in 1958 felt that ovarian ablation should be reserved for patients with metastatic or recurrent disease. (26)

Other studies that have been reported include a study by Huck of 36 patients treated by irradiation sterilization which showed no increased 5 year survival over a matched control group. (7) Siegert reported a difference of 16 months in onset of recurrence in radiation castrated women in a series of 347 treated compared with 260 controls. (21) Smith and Smith showed an increased 5 year survival time in 60 patients undergoing castration, however, 11 of these were postmenopausal and the control group was not matched as to age. (22) Patterson and Russell in a well designed and controlled study to evaluate effects of radiation castration on breast carcinoma showed significant results at three years but not necessarily significant results at five years which suggested to them that although there was no clear-cut long term survival advantage, there was no real disadvantage. (18) M. P. Cole in 1964 reported follow-up results on this series of Patterson and Russell. In 367

cases, 76 had recurrent or inoperable carcinomas. In the 291 cases which were not far advanced, she showed results which although not statistically significant did show a definite trend towards increased survival and increased interval to metastasis. In this follow up, no mention is made as to length of time between mastectomy and castration. It should also be mentioned that these cases were all radiation castration. Even with this not favorable factor, she was able to show a beneficial trend. (2)

Rannaes in a series of 66 patients felt that although their results were not necessarily statistically significant, they believed that there was a trend toward increased survival and delay in recurrence of disease. (19)

E. F. Lewison who has been a frequent contributor to the literature feels that the decision between prophylactic and therapeutic castration is "The Doctor's Dilemma!" He personally favors prophylactic castration by surgical means in women under age forty with stage II disease and by irradiation in women over forty with stage II disease. For all other patients he reserves castration only for therapeutic means. (12) He has never given his personal series in the articles which were reviewed for this paper and apparently bases his therapy primarily on his own literature review in 1962 which has been widely quoted by other authors. His conclusion from this review

comparing prophylactic and therapeutic castration was that there is a "well defined trend toward a prolonged life expectancy and an improved survival rate" in patients treated with prophylactic castration. (11)

Rosenberg and Uhlmann in 1959 reported their results with 78 castrated and 122 non-castrated females, all of whom had no signs of metastasis at the time of their mastectomy. Five year survival was used as a basis for comparing the efficacy of castration. Fifty-seven percent of the castrated females and thirty-three percent of the non-castrated group survived 5 years. From these observations, the authors advocated prophylactic castration in all women with carcinoma of the breast who exhibited signs of ovarian function. (20)

Kennedy, Mielke, and Fortuny published in 1964 what they felt to be the first studies comparing the relative values of prophylactic castration and therapeutic castration. The senior author had written several previous articles and in each had stressed that the studies which were being followed dogmatically as guidelines to therapy were inadequate. Using 2,908 cases of breast carcinoma, they culled 119 who had had a prophylactic castration and 177 who had had a therapeutic castration. These groups were equal in all factors except that there were more patients undergoing therapeutic castration who had more widespread disease.

Therefore, two comparisons were made in this study, one between total groups and one between patients with equal involvement. In comparing the groups with equal involvement, these authors concluded: 1. That prophylactic castration delayed the onset of recurrent disease. 2. That the interval from recurrence to death was less in the prophylactic castrated group. 3. That the interval from initial tumor therapy to death was not statistically different in the two groups with equal involvement. (9) Kennedy has used this data in other articles as a basis for his method of treatment. He has written that since castration can serve as a very valuable guide to the hormonal responsiveness of a tumor and, hence, responsiveness to further hormonal ablation treatment, it should be done only therapeutically. (8) Kennedy has also stressed that the term "prophylactic" castration is a misnomer as it does not prevent recurrence of disease. Hence, he favors use of the terms "early" and "late" castration when referring to initial and recurrent therapy.

As previously mentioned in this paper, probably the first series of patients receiving adequate follow-up was begun by Horsley in 1937. (6) In 1962, J. S. Horsley, III, and G. W. Horsley reported follow-up on this series. Sixty-eight cases of adenocarcinoma were treated and followed. Overall survival rates at 5 and 10 years were 71% and 47%

respectively. These studies did not have a control group and 17 patients received X-ray therapy.

Roar Nissen-Meyer reported in 1967 the results of breast cancer treatment at the Norwegian Radium Hospital in two different series of patients. The first group was treated from 1932 to 1951 by radical mastectomy and post-operative radiation. The second series was treated from 1957 to 1967 by the same methods with the addition of prophylactic castration. A 59% survival rate was obtained in the first series and a 72% rate in the second series. Meyer wisely analyzed the survival curves and found that the first four years showed a divergency of the survival rate curves in favor of the castrated group but after five years the curves converged. He concluded that prophylactic castration did not change the overall survival rate but did prolong survival time. He also did steroid excretion studies on his patients and found that the ovaries may continue to produce hormones for up to ten years after the menopause. Also noted in this series was no difference in the survival of patients castrated by surgery or by irradiation. (16)

STUDIES OF HORMONE RELATIONSHIPS

It is not within the scope of this paper to extensively review the literature concerned solely with hormone studies which do not have clinical trials of therapy.

In 1919 Loeb reported the prevention of mammary cancer in female mice of a special strain by castration before the age of six months. (13) Lacassagne was the first to report the carcinogenic effect of estrogens on breasts of special strains of mice. (10) It has been argued that these mice are specially inbred and will develop carcinoma even if left alone and also, the doses of estrogens used to produce breast tumors were astronomical. Investigators have been unable to produce carcinogenic changes in monkeys with estrogenic compounds. (28)

There have been no prospective studies on this problem in humans, however, one notes that with the marked increase in estrogen usage in the past thirty years there has been only one type of carcinoma that has had an increase in incidence, that of breast carcinoma ~~in males~~ treated with estrogens for prostatic carcinoma. (17) Many studies have actually shown a "protective effect" of estrogen therapy, particularly in osteoporotic females who have shown less than the predicted number of cancers following prolonged estrogen therapy. (14) There is little doubt, however,

that hormone therapy does promote the growth of cancer of the breast already present. (29)

CASE STUDIES

As a part of this thesis, the cases of breast carcinoma treated by radical mastectomy and prophylactic oophorectomy at the University of Nebraska, Clarkson Memorial and Methodist Hospitals were tabulated for a nationwide study by Dr. Wilson of the University of Texas Medical School. This data was taken from the medical records and is presented below. All patients were menstruating at the time of oophorectomy. One patient had duct cell carcinoma, the remainder being adenocarcinoma. All tumors were less than four centimeters in diameter.

DATE OF MASTECTOMY	AXILLARY NODES	DATE OF OOPHORECTOMY	SURVIVAL STATUS	RECURRENCE
5/12/61	+	6/26/61	Alive 10/3/68	NO (30)
6/20/58	-	6/20/58	Alive 3/31/69	NO (40)
5/31/57	+	9/29/57	Dec'd 11/21/59	YES (44)
9/3/59	-	2/22/60	Alive 9/12/68	YES (47)
2/16/54	+	3/12/54	Dec'd 3/4/59	YES (43)
1/28/59	+	2/10/59	Dec'd 3/28/63	YES (39)
12/13/66	+	1/17/67	Alive 4/1/69	NO (44)
2/8/68	+	2/26/68	Alive 11/7/68	NO (47)

Numbers in () indicate age at mastectomy.

From these few cases one can readily see how important it is to pool the case material from many institutions so as to give physicians an answer in a relatively short time.

DISCUSSION

In reviewing the articles on prophylactic versus therapeutic oophorectomy one is impressed by most writers' pleas for good prospective studies on this perplexing problem. Two studies are currently in progress, the Surgical Breast Adjuvant Study and the University of Texas Medical School Study. To be of significant value these will need to be very long term studies as is well stressed in recent literature the continuing mortality after the usual five or ten year studies.

One aspect of prophylactic castration that is generally agreed upon is the time of oophorectomy. It should be done as soon after the radical mastectomy as the patient's condition will allow. G. W. Horsley has in the past performed the oophorectomy while an assistant was closing the mastectomy incision. (5) This is certainly feasible if the patient's condition is stable and may even carry a lesser morbidity with only one anesthetic and post-operative period.

There is a principle of gynecological surgery that one should almost always remove the uterus when performing a bilateral oophorectomy. Only one article was found which stressed this point. (27) A personal communication with members of the Gynecology Staff of the University of

Nebraska offered agreement and two reasons: 1. This removes with little added morbidity and no added mortality a now useless and frequent neoplasm producing organ.

2. If estrogen chemotherapy is given to the patient at a later date, how will one manage the troublesome bleeding which will occur? Whether a hysterectomy is performed is presently left up to the surgeon performing the oophorectomy. If he feels comfortable in performing a hysterectomy and if he feels there will be no increased morbidity, it should probably be done.

Whether irradiation castration is as effective as surgical castration is certainly debatable. The more recent articles have stressed that all of their patients have stopped menstruating, however, there is always a period of time following irradiation that the ovaries continue to function and some patients will menstruate for several months. Therefore, it would seem that if one desires immediate cessation of ovarian function, surgical castration is the method of choice.

Some authors have discussed the psychological aspects of castrating a young female. These certainly are important and should not be forgotten in the conversations between the physician and the patient preoperatively and during follow-up. There should be very few, if any, instances where if prophylactic oophorectomy would be of

benefit it would be deferred because of the patient's psychological make-up.

The University of Nebraska Hospital is quite active in reappraising the methods of treating breast cancer. We are participating in the Surgical Breast Adjuvant Study. In early 1967 prophylactic castration was not being recommended by some members of the Department of Oncology since it was postulated by Dr. B. J. Kennedy that if a prophylactic castration is performed it will be difficult to tell if the breast tumor is hormonally dependent. Dr. Kennedy also believes that if one compares prophylactic with therapeutic castration, there is no improvement in total survival time. Some members of the University's Surgery and Oncology Departments now feel that there is a delay in recurrence if surgical prophylactic castration is performed and survival time can be increased if chemotherapy is started at the time of recurrence. Because of the University's involvement with the Breast Adjuvant Program, each premenopausal patient with carcinoma of the breast is given a prophylactic castration according to instructions from the Study headquarters at Rosewell Park Hospital, Buffalo, New York. This method is used so that no bias is shown as to which premenopausal patient will be castrated. This is a more

accurate method in order to compare the effects of prophylactic oophorectomy.

No matter what the outcome of future studies on breast cancer, one must always keep the paramount thought in mind that a high degree of suspicion and early diagnosis still affords the best chance of cure in this disease.

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