Trans-Sphenoidal Hypophysectomy in the Treatment of Advanced Breast Cancer

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Summary: Trans-sphenoidal hypophysectomy was performed in 19 patients after the failure of antioestrogens and other methods of hormonal manipulation to control advanced breast cancer. Remission of symptoms was obtained in 12 patients (66.6%) for more than six months and in seven patients (36.8%) for more than 12 months. Two patients have survived 53 and 55 months without requiring further treatment.

The results of this study shows that trans-sphenoidal hypophysectomy has a useful role in the treatment of advanced breast cancer and should be considered when planning the treatment.

Introduction

The choice of treatment for advanced breast cancer is confusing and controversial. It is made more difficult by the number of methods available. This wide choice reflects the inability of any one method to control the disease satisfactorily. The most useful innovation in recent years has been the introduction of hormonal receptor assays. Based on the receptor status, hormonal therapy or chemotherapy is used.

Hypophysectomy has proven effective in the management of advaned breast cancer. This is based on the theory that suppression of growth hormone might induce tumour regression over and above that obtained from oestrogen suppression.[1] Trans-sphenoidal hypophysectomy is the operation of choice from the point of patient morbidity and mortality as compared to the trans-frontal route. In unselected cases, the remission rate has been approximately 30–40%.[2] In the receptor positive cases the remission rates have been higher at 50–60%.[3]

In this retrospective study, we present the results in 19 patients who underwent trans-sphenoidal hypophysectomy following the failure of the other methods of hormonal manipulation to control the advanced disease.

Patients and Methods

From 1979 to 1983, 19 patients were referred to the senior author for trans-sphenoidal hypophysectomy. Prior to this, 16 patients had received hormonal therapy (Tamoxifen and/or aminogluthetimide); one patient had received chemotherapy (mitomycin); one patient had received radiotherapy; and one patient had undergone adrenalectomy. The ages of the patients ranged from 39–71 years. All the patients had oestrogen receptor positive tumours.

All the operations were performed by the senior author using microsurgical techniques through a transethmoidal route. The pre-operative work-up included clinical and radiological examinations to exclude nasal and paranasal sinus disease. The operation was performed with hypotensive anaesthesia and under antibiotic and steroid cover. Postoperatively the fluid balance was closely monitored for diabetes inspidus. This was corrected with fluid replacement and the administration of DDAVP whenever necessary.

The stitches and nasal packing were removed at one week and the patients discharged with steroid and thyroxine replacement. The patients were initially reviewed at the ENT and surgical breast clinic. Subsequent reviews were at the breast clinic.

The difficulty in evaluating treatment is the lack of clearly defined evaluable lesions. Several investigators have suggested that a useful parameter for determining objective response, in the absence of specifically measurable lesions, is the length of survival after hypophysectomy.[3] In this study, we define remission as survival for six months or more without requiring any other treatment.

Results

The average duration between the diagnosis of breast cancer and trans-sphenoidal hypophysectomy was 55.8 months. That between evidence of widespread metastases and trans-sphenoidal hypophysectomy was 38.9 months. On average, the operation was performed 10.4 months after the failure of the other methods.

The crude survival after trans-sphenoidal hypophysectomy was 21 months in all cases. Patients with ascites and local recurrence did not do as well as the patients with bony and pleural metastases.

Of the 19 patients 12 (66.6%) survived more than six months without requiring further treatment. Their average duration of their response was 18.3 months. This result compared favourably with that of other authors (Table 1). Of the 12, eleven patients had received tamoxifen and/or aminogluthetimide as the initial treatment. One patient had undergone adrenalectomy (Table 2).

Of the 12 who obtained remission, seven (36.8%) survived more than 12 months without requiring further treatment. Two of them are still alive at the time of reporting. One has survived 53 months and the other 55 months without further treatment. Two other patients had good response to further therapy after hypophysectomy. One survived a further 17 months on progesterone and the other 26 months on Tamoxifen.

The average duration of hospitalisation was 14.6 days. There was no operative mortality and the complications encountered were mild. Two patients had cerebrospinal fluid leak which required repacking. Epistaxis which was easily stopped by nasal packing was encountered in one patient. One other patient developed post-operative lung infection. This resolved with conservative medical treatment. Most of the patients had varying degrees of diabetes insipidus but in none was it severe.

AUTHOR	YEAR	NO. OF PATIENTS	REMISSION RATE	DURATION OF RESPONSE
Pearson et al	1962	343	144 (41.9%)	6 mos.
Kennedy et al	1965	71	39 (55%)	14 mos.
Fracchia et al	1971	100	33 (33%)	–
Van Gilder	1975	50	29 (58%)	–
La Rossa et al	1978	15	7 (46.6%)	10.1 mos.
Pearson et al	1978	28	15 (53.5%)	11 mos.
Kiang et al	1979	12	8 (67%)	12.5 mos.
Lee et al	1982	28	9 (32%)	17.4 mos.
Present series	1985	19	12 (66%)	18.3 mos.

Table 1 : Reported Cases

Table 2 : Responders

PATIENT	AGE	INTITIAL TREATM.	SITE OF METASTASES	DURATION OF RESPONSE (mos.)	SURVIVAL (mos.)	POST-HYPO-TREATM.
1	57	AMG	Bone	8		Nil
2	69	TAH	Bone Marrow	10	10	Nil
3	65	AMG	Bone	27	44	Progesterone
4	39	AMG	Bone	12	17	Chemotherapy
5	41	AMG	Bone	29	29	Nil
6	66	AMG	Bone	48	53	Nil
7	64	TAH	Bone	–	6	Nil
8	47	AMG	Bone, skin pleural effusion	26	55	Nil
9	71	TAH	Bone, pleural effusion	8	15	TAM and DXT
10	56	AMG	Pleural effusion	14	40	TAM
11	44	adrenal-lectomy	Pleural effusion	12	13	Nil
12	57	TAM	Ascites	8	10	Nil

TAM = Tamoxifen, TAH = Tamoxifen, aminogluthetimide, hydrocortisone AMG = aminoglutehtimide, DXT = Rdaiotherapy

Discussion

Hypophysectomy in the management of advanced breast cancer was originally based on the theory that the procedure suppressed oestrogen production by abolishing gonadotrophic and adrenotrophic hormones. It is now thought that other pituitary hormones may also play a part in stimulating tumour growth.[4] To explain the remissions induced by hypophysectomy after antioestrogen failure, Pearsen et al[1] suggests that tumour regression in these patients might have been induced by the suppression of both growth hormone and prolactin. Other possibilities, such as the suppression of insulin secretion by hypophysectomy, cannot be ruled out as an explanation for the hypophysectomy-induced remissions after the failure of antioestrogen treatment.[5]

The presence or absence of oestrogen receptors in the tumour is an established method to determine whether the tumour is amenable to hormonal manipulation. Unfortunately, receptor positivity does not guarantee response to hormonal therapy. The 'clinically free' interval (the duration from diagnosis to recurrence or metastases) and the site of metastases are also unreliable prognostic parameters, and it is difficult to preselect the patients who would respond to hypophysectomy. Fracchia et al[6] however, reported better results in their patients with metastases in the pleura, lung and bone than those with metastases in the soft tissue or skin of the breast. Our results are in agreement with this observation.

The remission rates after hypophysectomy and adrenalectomy are not significantly different. However, Ray and Pearson[2] have demonstrated that the survival time after hypophysectomy is longer than after adrenalectomy (after adrenalectomy, median 15 months; after hypophysectomy, median 23 months). In the same study the operative mortality for adrenalectomy was 4% while that of hypophysectomy was less than 1%. In a prospective, randomised study comparing adrenalectomy and hypophysectomy, Hayward et al[4] reported better response for hypophysectomy.

The introduction of tamoxifen and aminogluthetimide has changed the complex 'cascade' of hormonal manipulation.[7] The growing use of these drugs has meant the less use for endocrine ablative operations. Although tamoxifen has few significant side-effects[8] and is well tolerated, aminogluthetimide is more toxic[9]. Indeed several patients in these series were referred for trans-sphenoidal hypophysectomy because of their inability to tolerate the side-effects of one or the other of these two drugs.

In comparing the effectiveness of tamoxifen and hypophysectomy in treating breast cancer in a randomised trial, Kiang[10] found no difference in the rate and duration of response obtained with the two modalities. When the patients failed to respond or relapse, the therapy was crossed over. Their results showed that tamoxifen was effective in the post-hypophysectomy phase and the sequence of hypophysectomy followed by tamoxifen in the hormone dependent breast cancer, is preferrable to achieve a maximal control of the disease.

In another study by Pearson[1], eight of 28 patients obtained remissions from hypophysectomy after initial tamoxifen treatment. Of the 12 patients who obtained remissions in this study, 11 were also initially treated with tamoxifen and/or aminogluthetimide. These results show that hypophysectomy can induce remission after antioestrogen treatment failure, suggesting that other hormonal factors may play a role in stimulating tumour growth. Pearson reports the detection of prolactin receptors in 51% of human breast cancers, both in oestrogen receptor-positive and receptor-negative tumours. From their study however, it seems unlikely that it will be useful in predicting response to antioestrogen treatment. Whether prolactin receptors will be useful in predicting response to hypophysectomy after antioestrogen treatment remains to be determined.

The choice of treatment in advaned breast cancer does not lie between one hormonal treatment and another. Many patients will respond to one or all of the treatments available, and the clinician needs to be able to select the appro-

priate sequence of treatment. The aim should be maximal tumour response for as long as possible and with the minimal side-effects. Our results, and those of others, show that remissions can be induced by hypophysectomy after anti-oestrogen treatment 'failures'. These remissions result in pain relief and longer survival. Trans-sphenoidal hypophysectomy is a modality of treatment that is associated with a low mortality and morbidity in expert hands and is worthwhile considering when planning the treatment regime in patients with advanced breast cancer.

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