TREATMENT OF CARCINOMA OF THE THYROID WITH SPECIAL REFERENCE TO USE OF RADIOACTIVE IODINE

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RADIOACTIVE iodine is most effective in the treatment of well differentiated thyroid cancers. Since the majority of differentiated cancers are amenable to surgical cure, radioactive iodine is rarely required in these cases. Unfortunately, it is of no value in the highly malignant cancers in which it is most needed. For these reasons, *the usefulness of I^{131} is limited to the small group of carcinomas of low malignancy which have metastasized or extended beyond the scope of surgical removal.*

Role of I^{131} in the Treatment of Carcinoma of the Thyroid

Few carcinomas of the thyroid concentrate much radioactive iodine until the normal thyroid has been removed or destroyed with I^{131}. As long as the normal thyroid is functioning, its greater avidity for iodine precludes any significant concentration of I^{131} by the tumor tissue. However many differentiated tumors, which before the thyroid was removed took up little or no I^{131}, concentrate it satisfactorily after abolition of the function of the normal thyroid. Slight concentrations of radioactive iodine may occur even in tumors which seem to be quite undifferentiated, but in our experience the only tumors which can be made to concentrate I^{131} in therapeutic quantities are those which are well enough differentiated to have histologically demonstrable colloid. Two such tumors have been encountered in a series of 105 histologically proved cancers of the thyroid seen at the Cleveland Clinic in the past 5 years and, in both cases, pulmonary and cervical metastases have disappeared in response to treatment with I^{131}.

The take-up of radioactive iodine by most low grade carcinomas of the thyroid is irregular and spotty, certain areas concentrating large amounts and others none at all. Since the radiation given off by I^{131} penetrates only 1 to 3 mm. of tissue, a satisfactory uptake of I^{131} by certain parts of a tumor of the thyroid does not assure complete destruction of the entire tumor. Thus, although the functioning areas may take up enough radioactive iodine to destroy themselves, the more undifferentiated areas may receive almost no radiation. Perhaps under the influence of thyrotropic hormones these undifferentiated areas may be converted to functional tissue that concentrates I^{131} and may be destroyed by subsequent treatments, but there can be no assurance that all cells will be destroyed or that sooner or later, after the more differentiated parts of the tumor are destroyed, the undifferentiated portions will not begin

to grow again. For these reasons radioactive iodine therapy should not be relied upon.

During the past 5 years the commonest single type of carcinoma of the thyroid has been the papillary carcinoma, which constitutes 63 per cent of the cases seen at the Cleveland Clinic. The average age of patients with papillary carcinoma of the thyroid is only 34; 39 per cent are under 30 years of age and 19 per cent are under 20. Since many of these cancers occur in young women and girls and since large doses of radioactive iodine are required to destroy cancers of the thyroid, the question of effect of the radiation on menstruation and child bearing arises.

I^{131} usually can be given in divided doses up to 100 mc. without permanent effect on menstruation, but with larger doses there is danger of permanently destroying ovarian functions. Moreover, total and permanent myxedema must be produced if thyroid cancer is to be treated successfully with I^{131}. For these reasons it is clear that in girls or young women I^{131} should be used only as a last resort and should be reserved for those cases in which there are distant metastases or inoperable local recurrences.

X-ray Therapy

Papillary carcinoma of the thyroid is not often sensitive to x-ray therapy and complete primary regression of the tumors has not occurred in any of the cases in which we have employed it. Since radiation increases the technical difficulty of dissection of the nodes of the neck and is of questionable value in the control of papillary carcinoma, x-ray should not be employed except as a final measure when surgery and radioactive iodine have failed.

X-ray therapy has been of little value in the treatment of the more malignant types of thyroid cancer, although occasionally and unpredictably a satisfactory primary regression is observed. Since the more malignant tumors are rarely curable by operation and since they do not concentrate I^{131} roentgen therapy is the only hope and should be given a trial.

Surgery

The best treatment of carcinoma of the thyroid is surgical excision. Fortunately nearly 70 per cent of all cancers of the thyroid are tumors of low malignancy which remain localized in the thyroid or metastasize only locally to the cervical lymph nodes. Even when extensive cervical metastasis is present the prognosis in these cases is excellent, nor does the histologic invasion of blood vessels by tumor cells materially alter the good prognosis in tumors of low malignancy such as the papillary carcinomas.

In approximately 85 per cent of the cases of carcinoma of the thyroid a definite diagnosis can be made prior to operation, and in an additional 10 per cent the diagnosis of carcinoma can be suspected. In the remaining 5 per cent the diagnosis usually can be made in the operating room from the gross appearance of the tumor. It is therefore possible, in almost all cases, to establish or

suspect the diagnosis of carcinoma before the patient leaves the operating room and to perform a primary operation which will be adequate to insure the best possible chance of recovery.

A curative operation for carcinoma of the thyroid entails complete excision of the lobe of the thyroid on the affected side. In cases in which the tumor is multicentric or involves both lobes, all of the thyroid should be removed. Total lobectomy cannot be accomplished safely without identification and dissection of the recurrent laryngeal nerve, and when both lobes are removed great care must be taken to preserve the parathyroids if this can be done without danger of leaving tumor tissue. These operations are tedious and involve extensive anatomic dissection of the important structures of the neck.

The lymph nodes which are involved by metastasis from papillary carcinomas of the thyroid are the group behind the thyroid and along the course of the recurrent nerve, the nodes of the superior mediastinum, and the deep nodes around and behind the carotid sheath. Frequently a midline node just above the thyroid also is involved.

Since the metastases of papillary carcinoma in the cervical lymph nodes remain localized for long periods of time and do not tend to invade muscle or adjacent structures, it is not necessary to remove the sternomastoid muscle or to perform mutilating block dissection of the neck on young girls with papillary carcinoma. On the other hand, operations in which the primary tumor or its metastases are cut into or removed incompletely may disseminate and implant the tumor in such a way that the tumor becomes invasive and radical operations are necessary involving sacrifice of muscle and other important structures. Since secondary operations done in the presence of scar tissue and invasive tumor are always more difficult than the primary procedure, and are attended by a diminished rate of cure, it is most important to eradicate the tumor completely in the area of the neck operated upon and to avoid doing partial and incomplete surgery that might necessitate repetition. Eradication can be accomplished satisfactorily and without mutilation by one or more carefully planned procedures in which the involved groups of nodes are removed completely. No harm will be done if nodes which were not palpable at the time of the first operation appear at a later date contralaterally or in a triangle of the neck which has not been operated upon before because these nodes can be removed cleanly during a secondary procedure without altering the good prognosis.

Results of Surgery in Treatment of Carcinoma of the Thyroid

In a consecutive series of 28 papillary carcinomas of the thyroid in which the first operation was performed in accordance with the principles stated, all but one of the patients are alive, well and apparently free of recurrence for from 3 to 14 years after operation. One patient died 2 years after operation of causes unrelated to the thyroid and without evidence of recurrence. In contrast to these excellent results, all 14 of the patients with undifferentiated carcinomas and sarcomas either are dead of their disease or had experienced

hopeless recurrences when last seen. This experience emphasizes the futility of our methods of treating the highly malignant tumors of the thyroid and suggests that efforts be intensified in attacking tumors of low malignancy in order to reduce the death rate.

Treatment of Discrete Adenomas of the Thyroid

The highly malignant tumors of the thyroid grow with great rapidity, cause distress within a few months of the time they are first noted and almost without exception are diagnosed clinically before operation. Despite the fact that the majority of these patients are operated upon within 3 months of the time the tumor was first noticed, the majority are hopelessly inoperable and all have proved to be incurable.

Despite the fact that most patients with low grade (papillary) carcinomas delay operation for 1 to 10 (averaging 5) years[1] from the time the tumor is first noticed, the results of carefully planned conservative surgical procedures have been excellent. The prognosis in these cases appears to be more closely related to the type of operation performed than to the duration of the disease.

Since many of these low grade cancers enlarge slowly or not at all, they are apt to be confused with benign adenomas. A fairly high percentage of all firm, solitary tumors of the thyroid, especially in young people, prove to be carcinomas, and for this reason suspicious nodules of the thyroid should be removed completely, preferably by total lobectomy, so that secondary operations, x-ray therapy and radioactive iodine will not be required. At the time of the thyroid operation, the retrothyroid area, the midline, the superior mediastinum and the lower part of the carotid sheath should be explored for metastases. If none are felt it is not necessary to do a prophylactic dissection, but if nodes are palpable the involved groups should be removed completely with their surrounding envelope of fatty and areolar tissue. The patient should then be followed closely for at least 5 years, and if any further nodules develop these should be removed.

Our failure to cure the highly malignant cancers by any means now at our disposal, and the fact that 80 per cent of these highly malignant cancers arise in patients who were not aware of any pre-existing abnormality of the thyroid,[1] force us to adopt, for the present, a pessimistic attitude toward this type of carcinoma. However there is little excuse for a high incidence of recurrence of the low grade cancers, almost all of which are curable by an adequate primary operation.

If all operations for discrete adenomas of the thyroid were performed in such a way that an existing carcinoma might be cured, there would be fewer recurrences of low grade cancers and the mortality rate of carcinoma of the thyroid would be lowered significantly.

Summary

1. Radioactive iodine is least effective in the undifferentiated and highly malignant types of carcinoma of the thyroid in which it is most needed.

2. Radioactive iodine is most effective in well differentiated, colloid forming carcinomas of low malignancy, the majority of which are amenable to cure by surgical removal.

3. The usefulness of I^{131} in the treatment of carcinoma of the thyroid is limited to the small group of carcinomas of low malignancy which have metastasized or extended beyond the scope of surgical removal.

4. Roentgen therapy is of little value in the well differentiated carcinomas of low malignancy and should not be given prophylactically to prevent the recurrence of tumors which apparently have been excised completely.

5. In undifferentiated cancers of high malignancy neither operation nor treatment with radioactive iodine are of much value. Although not often effective, roentgen therapy should be given a trial.

6. Even the most radical operations performed within a few weeks or months of the onset of undifferentiated carcinomas of the thyroid have failed consistently to effect cures.

7. Papillary carcinomas which are of a low order of malignancy and which, fortunately, are the most common type of carcinoma of the thyroid, are almost always amenable to surgical cure provided the initial operation on the thyroid is thorough and complete.

8. Since it is clinically impossible to distinguish between a benign, solitary adenoma and a low grade carcinoma of the thyroid, discrete adenomas should be removed completely by excising the entire lobe on the affected side.

9. Thorough and complete removal of thyroid carcinomas and their regional metastases is the safest and most dependable treatment now available.

10. Inoperable recurrences or metastases of well differentiated, colloid-forming cancers of the thyroid may be amenable to control by I^{131}.

Reference

1. Crile, George, Jr.: Factors influencing prevention and cure of cancer of thyroid. Surg., Gynec. and Obst. **91**:210 (Aug.) 1950.