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The Use of Radioactive Iodine in Thyroid Carcinoma

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Abstract—*The use of radioactive iodine (^{131}I) for the treatment of primary carcinoma of the thyroid and as an alternative to a surgical thyroidectomy in the management of patients with metastatic disease is described. The rationale for using ^{131}I to ablate normal thyroid tissue after a surgical thyroidectomy is considered in relation to the natural history of papillary and follicular tumours and in recognition of the results of such a policy in some recently reported series. It is concluded that ^{131}I ablation is indicated in patients with follicular tumours: and in patients with papillary tumours if they are over the age of 40 or if the tumour contains a substantial follicular component.*

The management of patients undergoing post-operative ^{131}I ablation is outlined and the possible complications of such treatment which include radiation thyroiditis, radiation sialitis, transient hyperthyroidism and oedema of the neck are described.

INTRODUCTION

THE use of radioactive iodine (^{131}I) for treating metastatic disease in thyroid cancer is well established. Such patients, however, form only a small proportion of the total number of patients with malignant disease of the thyroid. Treatment here is fairly well standardized and is described in a number of articles [1–3].

^{131}I may also be used to treat a primary thyroid tumour or to destroy normal thyroid tissue either as a preliminary to treating metastatic disease or post-operatively when the primary thyroid tumour has been resected. The ablation of normal thyroid tissue after thyroidectomy is the main topic discussed in this review but treatment directed towards the primary tumour and ^{131}I ablation as an alternative to a surgical thyroidectomy merit brief consideration.

TREATMENT OF PRIMARY THYROID TUMOUR

The treatment of differentiated thyroid carcinoma is preferably surgical. If, however, the tumour is inoperable in the first place or if surgical removal is known to have been incomplete radiotherapy is usually needed. Most patients will require external irradiation but the possibility that some tumours, in particular the follicular variety, may concentrate iodine should be borne in mind and treatment with ^{131}I should therefore be considered in addition to external irradiation.

The difficulty here is that normal thyroid tissue will almost certainly be present and if the neck is scanned it may not be possible to distinguish uptake of ^{131}I in tumour from that in normal thyroid tissue. The problem can usually be resolved by giving an ablative dose of ^{131}I to destroy all normal thyroid tissue, and carrying out a further investigation 3 months later. If any focal concentration of isotope is seen it can be assumed that this represents functioning tumour rather than normal thyroid tissue, in which case further treatment with ^{131}I is indicated. In the meantime external irradiation can be undertaken and will not interfere with any ^{131}I therapy that may be required subsequently because the maximum dose which can be given by conventional radiotherapy is unlikely to have any significant effect on thyroid function.

ABLATION OF NORMAL THYROID TISSUE AS AN ALTERNATIVE TO SURGICAL RESECTION

Any patient who has a metastasis from a differentiated carcinoma of the thyroid should be considered as a possible candidate for treatment with ^{131}I. Function in tumour tissue can often be demonstrated while the thyroid gland is still *in situ* but it cannot be ruled out until all normal thyroid tissue has been ablated because normal thyroid tissue

invariably concentrates iodine more efficiently than even highly differentiated tumour tissue. A surgical thyroidectomy is the method of choice in this situation but if the patient is considered to be unfit for surgery ^{131}I can be used instead.

ABLATION OF NORMAL THYROID TISSUE AFTER THYROIDECTOMY

^{131}I has been used after a surgical thyroidectomy in those patients in whom functioning thyroid tissue in the neck can be demonstrated after the operation. The purpose of this treatment is to achieve a total thyroidectomy, something which can rarely be achieved by surgery alone. There is, however, no consensus of opinion on whether ^{131}I given in these circumstances is of any benefit over surgery alone in disease which has a relatively good prognosis.

Current practice varies between centres. It has been argued that patients with papillary carcinoma of the thyroid derive no benefit from ^{131}I therapy because of the relatively benign nature of this tumour and its slow rate of growth. Support for such an attitude is provided by the study of Woolner [4] who found only 18 deaths from papillary carcinoma in a series of 656 patients followed for up to 40 years. Beierwaltes [2] on the other hand has for many years advocated ^{131}I therapy after surgery for the majority of patients with differentiated tumours claiming that recurrence rates and mortality are thereby reduced. Another report from the same centre confirmed that patients over the age of 40 with well-differentiated thyroid tumours had a significantly lower mortality when treated with ^{131}I after surgery than did a similar group of patients treated by surgery alone [5].

A clinical trial designed to establish the best policy would need large numbers of patients followed up for several decades because the growth rate of differentiated tumours is slow, most patients have a good prognosis and the differences in survival rates would probably be small. No such trials have been instituted. Treatment, therefore, must necessarily be based on the natural history of differentiated tumours and must take into account the results of treatment in some recently reported series.

Natural history

Most differentiated thyroid carcinomas contain both papillary and follicular components. All degrees of transition from one to the other are seen. The term 'mixed papillary and follicular' is still sometimes used and could well be applied to the majority of tumours. Histologically a papillary pattern may be a minor component but, if present, the tumour will tend to behave as a papillary carcinoma and should be classified as such [6]. These tumours are usually slow-growing and the prognosis is good but the outlook for patients over the age of 40 or for those who have large primary tumours or extracapsular extension is less favourable [7]. Age is an important prognostic factor in papillary carcinoma as it is in all types of thyroid tumour [8].

Follicular carcinoma of the thyroid lacks a papillary component. Histologically it is composed in varying amounts of follicular and solid areas. Prognosis depends on the degree of vascular invasiveness and the histological grading of the tumour. Follicular carcinoma affects a slightly older age group and has a worse prognosis than papillary carcinoma. Follicular tumours have been subdivided into well-differentiated and moderately or less well-differentiated sub-groups [9, 10]. Patients with well-differentiated tumours have a survival similar to patients with papillary carcinoma but survival in the less well-differentiated group is significantly worse [11].

The classification described above places emphasis on behaviour and prognosis rather than histological appearances. In this context the designation of tumours as papillary or follicular may be confusing, but it is accepted by WHO [10].

Rationale for post-operative ablation

There are theoretical reasons why a patient with a papillary or follicular carcinoma of the thyroid might fare better if all thyroid tissue were destroyed. First it could be argued that the factors which resulted in the development of a thyroid tumour in the first place will continue to operate in residual normal thyroid tissue even after all apparently diseased tissue has been removed.

Secondly there is the possibility, bearing in mind the multifocal nature of papillary carcinoma, that the residual thyroid tissue might harbour a microscopic focus of disease which will eventually manifest itself as an overt recurrence. In one series of patients with papillary carcinoma 27.4% of recurrences were situated in the residual thyroid tissue [7]. The radiation dose from ^{131}I would be unlikely to have a lethal effect on macroscopic tumour but it might well destroy a focus of microscopic dimensions and it would in any case produce an environment of avascular fibrous tissue which would be an unfavourable milieu for the development of neoplastic thyroid cells.

Thirdly there is the possibility, particularly in the case of follicular tumours, that occult metastases may already be present [12]. Ablation of the thyroid remnant may be necessary both to detect and treat such metastatic disease.

Post-operative use of ^{131}I

A conservative attitude towards the treatment of papillary carcinoma is supported by the fact that mortality is low in this disease. Overall survival, however, is not the most appropriate means of

judging the efficacy of treatment in papillary carcinoma because relapses may occur after a long interval and furthermore there may be another long interval between relapse and death. In one large series only six of 576 patients died of papillary carcinoma of the thyroid during an average follow up of 10-years but in 84 patients (14.6%) cancer recurred and five of these patients eventually died of their disease [7]. Most of the patients in this study who either died or had recurrent disease would have been considered to have been cured of their disease by conventional 10 year survival criteria. In this same series it was noted that patients who had been given ^{131}I after operation had a significantly better prognosis. There were only seven recurrences and only one patient ultimately died of thyroid cancer in the group given ^{131}I and thyroid hormone.

Samaan *et al.* [13] have analysed the results of treatment in 706 patients with differentiated thyroid tumours treated at the M.D. Anderson Hospital. The tumours were divided into papillary, follicular and mixed types. The latter group would according to the WHO classification be designated as having papillary tumours. The frequency of recurrence was significantly less in those patients who were given an ablative dose of ^{131}I after thyroidectomy. When the patients were subdivided into histological types the advantage was seen to apply to the patients with follicular and mixed tumours. Thus there was an indication for giving ^{131}I to those patients with papillary carcinoma whose tumours contained a significant follicular component. Analysis of the results at the M.D. Anderson Hospital also showed, as have other studies [8,11], that age and sex are important prognostic factors. Women under the age of 40 have a better prognosis than men and those over the age of 40.

Similar conclusions were reached by Young *et al.* [14] who noted that the lowest recurrence rate in a group of patients with follicular carcinoma was found in those patients who had had a total thyroidectomy and ^{131}I therapy.

Indications for ablation

There is a good case for ablating any residual thyroid tissue in patients with follicular tumours because these tumours are potentially functioning and some of them may already have metastasized by the time the patient seeks medical advice. There is, furthermore, convincing evidence from some reported series that this approach improves prognosis.

The arguments in favour of ablation for patients with papillary tumours are less cogent. Prognosis for these patients, provided they are under the age of 40, is good but the recurrence rate is not insignificant and recurrences when they do occur are likely to be located in the remaining thyroid tissue. It would seem reasonable to recommend ^{131}I ablation for those patients over the age of 40 and to consider it for those patients whose tumours contain a substantial follicular component [15].

Young patients with papillary tumours showing little or no follicular structure probably require no treatment other than surgery. Most if not all of them will be maintained on thyroxine because the remaining thyroid tissue will be incapable of producing an adequate supply of thyroid hormone. It has been generally accepted that this should be a suppressive dose because some differentiated tumours are known to be hormone-dependent and are believed to respond to suppression with thyroid hormone. A recent report from the Lahey Clinic, however, throws some doubt on this concept: the administration of thyroid hormone did not affect survival in a large series of patients with differentiated thyroid carcinoma [16].

Management

The treatment of differentiated tumours of the thyroid is primarily by surgery. Most patients have either a sub-total or a total thyroidectomy but occasionally a hemithyroidectomy is carried out. Even in those patients who have had a radical operation a post-operative thyroid scan will usually show functioning thyroid tissue in the neck.

It is advisable to wait at least 3 weeks after surgery before instituting tests. These must include a scan of the neck to find out how much thyroid tissue remains and a measurement of thyroid uptake. If the scan confirms the presence of residual thyroid tissue and the uptake is 1% or more, it is usually possible to destroy the remnant with ^{131}I. If there is only a small amount of residual thyroid tissue a low uptake can be expected and it is unlikely that it can be increased by endogenous or exogenous TSH stimulation but if on the other hand there is one lobe remaining and the uptake is less than 20% it can usually be increased either by giving an injection of bovine TSH (5 units) or by putting the patient on a blocking dose of an antithyroid drug such as methimazole or carbimazole for 4 weeks in which case the thyroid tissue will be subjected to endogenous TSH stimulation. The latter procedure is preferable because the stimulation is continuous and the timing is less critical. The antithyroid drug has to be discontinued 48 h before giving a test or therapeutic dose of ^{131}I. If TSH is used it should be given 24 h before giving the test dose of ^{131}I and again 24 h before the therapeutic dose.

The activity given can be empirical in which case 3.0 GBq will usually suffice or it can be calculated so as to give a radiation dose of at least 50,000 cGy which is sufficient to ablate normal thyroid tissue [17]. To achieve this dose an initial concentration

of 37 MBq of ^{131}I per gram of thyroid tissue is required. The above dosage considerations apply to destruction of the whole gland or at least one whole lobe. If it is intended to ablate a small remnant in a patient who has had most of the gland removed surgically due allowance must be made for the shortened biological half-life of ^{131}I in the residual thyroid tissue. Paradoxically the smaller the amount of thyroid tissue remaining the more difficult it becomes to destroy it with ^{131}I.

After ablation it is convenient to maintain the patient on triiodothyronine (T3) which may be started in a dose of 30–40 μg daily 7–10 days after the ablation dose. T3 is preferable to thyroxine (T4) in this situation because it has a considerably shorter biological half-life and serum TSH will therefore rise more quickly after discontinuation of T3 than after stopping T4. An assessment may be made 2–3 months after ablation. A test dose of ^{131}I (180 MBq) is given 10–14 days after stopping T3 by which time the patient is likely to be clinically hypothyroid with a level of serum TSH in excess of 25 mu/l. A blood sample may be taken to confirm this and at the same time to measure serum thyroglobulin (Tg) which, in the absence of any normal thyroid or tumour tissue, should be low. The absence of any functioning thyroid tissue in the neck is best confirmed by doing a scan. Quantitative measurements are not appropriate in these circumstances. At the same time a whole body scan is done in order to find out whether there is any evidence of metastatic disease. In an athyroidal patient such a scan normally shows concentration of ^{131}I in the mouth or submandibular salivary glands, in the stomach and in the bladder. There may occasionally be some activity in the large bowel. If there is no functioning thyroid tissue in the neck and no abnormal concentration of activity elsewhere the patient is started on a maintenance dose of thyroxine. If the neck scan shows residual thyroid tissue or if the whole body scan shows evidence of metastatic disease further treatment will be required.

Complications of ^{131}I ablation

It is doubtful whether complete destruction of thyroid tissue can be achieved without producing radiation thyroiditis. It usually starts 3 or 4 days after the therapeutic dose has been given and is characterized by pain in the neck often radiating to the ear, pain on swallowing and localized tenderness over the residual thyroid tissue. If a small amount of thyroid tissue is being destroyed the symptoms are usually trivial and require no treatment other than a simple analgesic. If one lobe or more is being destroyed the symptoms may be severe and corticosteroids may be required for a few days.

Transient hyperthyroidism almost certainly occurs if a substantial amount of thyroid tissue is being destroyed but clinically it may not be obvious and it is often unrecognized. The destruction of thyroid tissue is accompanied by the release into the circulation of T3, T4, thyroglobulin and various degradation products. If serial measurements of thyroid hormones are made the serum levels of T3 and T4 can be seen to rise after about 5 or 6 days. If there is clinical evidence of hyperthyroidism it may be advisable to give a β-blocker such as propranolol which will only be required for a few days because the condition is self-limiting.

Radiation sialitis is a rare complication [18]. It occurs within about 24 h of the therapeutic dose and it may affect the parotid or submandibular glands or both. It is most likely to be seen when a large quantity of ^{131}I is given to a patient who has very little functioning thyroid tissue. In the absence of any competition from thyroid tissue the salivary glands may concentrate sufficient activity to provoke an inflammatory reaction.

Oedema of the neck is a relatively uncommon complication which occurs only after a fairly high radiation dose to the thyroid [19]. It differs from radiation thyroiditis in that it is painless and appears within 48 h of treatment. It is difficult to provide an explanation for this phenomenon. Measurements and calculation of the radiation dose to the tissues in the vicinity of the thyroid have shown that the oedema cannot be ascribed to a direct effect of radiation on the perithyroidal tissues [20]. The rapidity of onset, lack of pain and occasional stridor suggest an allergic response rather than a direct radiation effect. The condition responds well to treatment with a corticosteroid.

Follow up

Although as previously mentioned the value of a suppressive dose of thyroid hormone in patients with differentiated thyroid tumours is debatable, it is nevertheless common practice to maintain these patients on such a dose and most of them in fact receive 200 μg of thyroxine daily. On this dose serum T4 values will be above the upper limit of the normal range, serum T3 will be normal and serum TSH will be suppressed.

Measurement of serum Tg may be done at appropriate intervals. This test has the advantage that thyroxine need not be discontinued [21]. There is no need to repeat neck or whole body scans unless there is reason to suspect that the patient has recurrent or metastatic disease.

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