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Drug Therapy Alternatives in the Treatment of Thyroid Cancer

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Summary

Therapy of thyroid cancers is based on the removal of the primary disease by surgery, replacement of the hormonal deficiencies and subsequent therapy of the recurrent and metastatic disease. The metabolic characteristics of many thyroid tumours mean that radionuclide techniques have been used in the identification of sites of tumour and their subsequent therapy.

Differentiated thyroid cancers, papillary, follicular and mixed papillary follicular, are treated by surgery – usually a total or subtotal thyroidectomy. Postoperatively, patients have thyroxine as a replacement therapy and to suppress thyroid-stimulating hormone production. Radioiodine therapy is often given to ablate the thyroid remnant. This allows (a) adequate follow-up of patients using thyroglobulin measurements and assessment scans as necessary, and (b) further therapy with radioiodine for metastatic disease.

Patients with a short effective half-life of radioiodide may require higher activities or pharmacological methods of prolonging the retention half-times of iodine. The use of chemotherapy in this group of tumours is limited and at best provides palliation. The overall prognosis is good for differentiated thyroid cancer; papillary carcinomas have an 80 to 90% 10-year survival, whereas follicular tumours are associated with a 65 to 75% 10-year survival.

Medullary carcinomas may be sporadic or familial, and some of the latter form part of a multiple endocrine neoplasia syndrome (MEN). Primary treatment is surgery, and total thyroidectomy is usually recommended since tumours are often multifocal. The use of radiolabelled metaiodobenzylguanidine (MIBG) and ^{111}In octreotide as potential therapeutic agents has been explored and may be potentially useful in palliative care. Chemotherapy is of limited benefit. The 10-year survival for medullary carcinomas is 60 to 70%.

Anaplastic tumours of the thyroid are usually aggressive, with a high mortality. Treatment is palliative by surgical debulking; some patients may benefit from local radiotherapy or occasionally chemotherapy.

The use of therapeutic doses of radionuclides is well tolerated, although it may be associated with a variety of mostly transient adverse effects, including gastritis, thyroiditis and sialadenitis. Therapy with high activities of radioiodine require radiation protection precautions. Despite retreatment with radioiodine there appear to be no long term effects on the fertility of patients, and healthy children are born to women receiving this treatment.

^{131}I remains perhaps the most specific cancer therapy available today and has few adverse effects. It is difficult to see any marked improvement being developed for differentiated thyroid cancer, with the possible exception of targeted gene therapy.

The incidence of thyroid cancer is 30 to 40 per million population. Thyroid nodules occur in 5 to 10% of the population, but the chance of having a thyroid cancer in a solitary thyroid nodule is still low in the adult. In children, however, approximately 40% of nodules are cancerous.[1]

Most thyroid cancers arise from the follicular epithelium. 55 to 65% are papillary (including mixed papillary and follicular), 15 to 25% are follicular and 5 to 15% are anaplastic. Hürthle cell and clear cell tumours are derivatives of follicular carcinoma and carry a worse prognosis. The parafollicular cell cancers are called medullary cell cancer and constitute less than 10% of malignant tumours of the thyroid.[2-4] 80% of medullary tumours are sporadic in origin and 20% familial, and these may be part of the syndrome of multiple endocrine neoplasia (MEN) type 2a and (less commonly) type 2b. Rarer tumours of the thyroid arise from the lymphoid or connective tissues, and even less commonly are a result of metastases from other tumours.

There is a wide variation in the malignant potential of these tumours. As a group, papillary carcinomas are the least aggressive, whereas the follicular carcinomas range from the slightly invasive with low metastatic potential to aggressive tumours with poor outcome, and anaplastic tumours are highly malignant.

Features other than the gross histology of the carcinomas have been used to try to predict outcome. These include patient age, size of the primary tumour, extension of tumour to juxtathyroidal structures or distant metastases. More recently, other histological and immunocytochemical features [adenylate cyclase activity, ploidy of the cells, thyroid-stimulating hormone (TSH) receptors, epidermal growth factors, guanyl nucleotide regulating protein (G protein) mutations, ras and other oncogenes] have been used to define outcome.[5]

Primary treatment is by surgery, but there is no common agreement on the 'correct' surgical procedure, which varies from a hemithyroidectomy to total thyroidectomy.[6] Macroscopically involved lymph nodes are resected, but formal block dissection is not recommended. There remains considerable controversy over the best method of follow up for differentiated thyroid cancers and the optimum therapy. These difficulties arise because of the rarity of the tumour, its variable but often good prognosis, and the absence of prospective clinical trials.

Tumour recurrence rather than death is often taken as the end-point in evaluating treatment. A recent review of the cases of carcinoma of the thyroid in Europe shows that, despite an increase in the numbers of patients identified with carcinoma, the mortality rate has not changed over the years (UK figures 0.3 per 100 000 for men and 0.5 for women).[7]

This review describes the various cancers of the thyroid and the medical management strategies which may be employed in addition to the primary surgical therapy.

1. Differentiated Thyroid Cancer

1.1 Staging

The thyroid cancer tumour cell type affects outcome; papillary carcinomas have an 80 to 90% 10-year survival, whereas follicular tumours are associated with a 65 to 75% 10-year survival. These differences are less apparent when allowance is made for patient age and disease stage at first presentation.

Primary tumour size is an important determinant of outcome, and papillary tumours less than 1.5 to 2cm in diameter have low recurrence rates and few instances of metastatic disease.[8-11] Size is a less important factor in follicular cancers where the outcome is less predictable.[12,13] Various predictive factors have been identified and incorporated into classification systems to predict outcome, such as Age, Grade, Extent and Size (AGES)[10] and Age, Metastases, Extent and Size (AMES).[14] This information is of importance in the discussion of prognosis with the patient and in determining choice of therapy.

1.2 Principles of Treatment

The primary form of treatment in differentiated thyroid cancer is surgery.

Although a number of factors need to be taken into consideration for the optimum surgical approach, total or near-total thyroidectomy is commonly recommended in patients with tumours more than 1.5cm in diameter.[15-17] Macroscopically abnormal lymph glands are also removed but radical block dissection is not indicated. The importance of preserving parathyroid gland function is well recognised.

Postoperatively, patients are treated with suppressive doses of thyroxine or tri-iodothyronine. This is given for 2 reasons. One is that following total thyroidectomy, thyroid hormone replacement is required. The second is that there is evidence that growth of at least some thyroid tumours is promoted by TSH, and its suppression may reduce this growth. Tumour cells have thyrotropin receptors,[18] suggesting a mediator role for TSH. Also, tumour shrinkage has been seen with thyroxine and tumour recurrence rates increase significantly when thyroid hormone replacement is not given postoperatively,[19,20] although increased survival has not been confirmed.[21]

Thyroxine is normally given at doses sufficient to suppress TSH to low or undetectable levels. This requires higher doses than replacement therapy in hypothyroidism, and average doses of 2.7 μg/kg/day have been recommended.[22] This increased level of thyroxine replacement does not appear to cause significant osteoporosis in premenopausal women, although results of bone mineral density studies in that population suggest there may be significant bone mineral loss after prolonged (9.9 years) high dose treatment.[23]

Postoperative ablation of normal thyroid tissue with radioiodine is common practice but remains a controversial issue.[24,25] Reasons given for this procedure are:

1. Its use is associated with lower rates of tumour recurrence.

2. Ablation of residual normal thyroid tissue increases the specificity of thyroglobulin measurements as a tumour marker for detecting recurrent disease.

3. Radioiodine therapy cannot be provided effectively until after normal thyroid remnants are ablated. This is because normal thyroid tissue is much more efficient at trapping iodine than tumours, even when these are well differentiated.

4. Radioiodine cannot be used in diagnostic scans to identify metastatic sites or tumour recurrences until normal remnants have been ablated.

5. Radioiodine can ablate micrometastases at the time of normal thyroid tissue ablation.

1.3 Iodine Chemistry and Pharmacology

Sodium iodide is normally supplied as a solution or as a capsule for oral administration containing sodium thiosulphate, phosphate buffer and sodium chloride. The solution is colourless and odourless, with no taste. It is volatile, and therefore to prevent risk to staff from inhaling the vapour solutions should be prepared in well ventilated areas. Containers of iodine capsules should also be opened in a ventilated area since ^{131m}Xe gas and volatile ^{131}I is liberated. The ^{131}I is carrier free (in some preparations) with an activity ranging from 0.037 to 7.4 GBq with sodium iodide concentration 0.03 to 40 mg/L at the reference date for therapy. The iodide is present in tracer quantities which will have no effect on unlabelled iodide in the body.

Iodide enters the thyroid follicles as inorganic iodide and is transformed into the thyroid hormones. The individual steps are: (a) active transport of iodide; (b) iodination of tyrosyl residues of thyroglobulin (Tg); (c) coupling of iodotyrosine molecules within Tg to form T_4 and T_3; (d) proteolysis of Tg to release the thyroid hormones; (e) deiodination of the iodotyrosines to reuse the iodide; (f) deiodination of T_4 and T_3 in the thyroid.

Other tissues concentrating iodine include gastric mucosa, salivary glands, mammary gland, choroid plexus, ovaries, placenta and skin. This wide physiological distribution is a potential source of problems with regard to ^{131}I therapy.

The very small chemical amounts given do not have a significant effect in humans. Even those who are sensitive to chemical iodine may be given ^{131}I therapy with safety as 'allergic reactions' have not been recorded.[26] There is a possibility that some patients may react to reducing agents in the preparations but this is an extremely rare occurrence. The effects are produced by the radiation liberated.

After oral administration 90 to 100% of the dose is absorbed, having been completely ionised in the lumen of the gastrointestinal tract. Absorption occurs primarily from the small intestine but may also occur through the stomach[27] and is complete after 3 hours even in nonfasting patients.[28] Iodide enters the extracellular fluid and while most cell membranes are impermeable to it, red blood cells are an exception and the concentration of iodide in these is the same as in plasma. Diffusion of iodide into the extracellular fluid is usually complete by the second hour after oral administration,[28] with a volume of distribution of 18 to 25L.[28,29] Iodide is filtered through the glomerulus and part is reabsorbed through the tubules; the resulting renal clearance of iodide is 0.72 to 3.72 L/h with a gradual fall with increasing age and a decrease with renal failure. In healthy individuals with a thyroid uptake of 25% the urine excretion is approximately 75% of the administered dose over 24 hours; the hyperthyroid patient may retain in excess of 50% of the iodine in the thyroid.

The metabolism of the radioiodine depends on the clinical condition for which it is being given. In patients with carcinoma of the thyroid the ^{131}I is often excreted almost wholly unmetabolised, since in athyreotic patients incorporation into hormone is not possible unless there is functioning tumour present. The proportion that is metabolised will follow the same route as for patients with a functioning thyroid.

Thyroxine is conjugated in the liver with glucuronic acid and sulphonic acid and the clearance is equivalent to approximately 8.5 to 17mg of iodine per day.[30] Thyroxine is excreted into the gastrointestinal tract with the bile. The presence of liver activity on scans of thyroid cancer patients has been thought to indicate the presence of thyroid cancer somewhere in the body since iodine is only concentrated in the liver when it has been organified.[31]

1.4 Ablating Thyroid Remnants

Before ablation, patients must stop any thyroid hormone preparation they are taking (section 1.5).

The activity for ablation varied between 1110 and 5550 MBq (30 and 150 mCi). The ablation success has varied from 5 to 83%[24,32-35] with these low dose regimens. A comparison of 2 regimens (1073 and 3700 MBq) found that the low dose was as effective as the higher.[36] Others found that higher doses of 3700 to 7400 MBq (100 to 200 mCi) were required,[37] particularly when the percentage of iodine uptake in the neck was lower.[38,39] A calculated activity to achieve 30 000 rad has been proposed[39], but the large number of variables in calculating the required activity mean that many prefer an empirical approach. The activity necessary to achieve this dose will depend on the retention half-time and the uptake per gram of tissue. If higher activities of ^{131}I are used, with a high remnant uptake, it may be argued that not only is the thyroid ablated but the micrometastases may also be treated soon after surgery.

1.5 Treating Metastases: Practical Issues Concerned with Radioiodine Treatment

Clinical assessment, imaging investigations or thyroglobulin measurements are used prior to radioiodine therapy to confirm disease presence.[5,25] Information as to whether iodine can be used may be based on an assessment with lower doses of radioiodine to try to visualise metastatic disease. The process requires rendering the patient hypothyroid and then administering between 74 and 370 MBq of radioiodine for assessment. Recently, the use of recombinant TSH has been attempted for these assessment studies, but to date this is not as successful as the stoppage of thyroxine and endogenous TSH stimulation.[40]

Thyroxine therapy is stopped 6 weeks before therapy and scanning. Triiodothyronine, which has a shorter biological half-life, can be substituted and then stopped 10 to 14 days before therapy. TSH levels in the serum should be above 30 mIU/L.[41] Various methods have been used to try to enhance tumour uptake of iodine, including reducing body iodine by low iodine diet[41] or diuretics,[42] and the use of lithium to increase the retention times in tumours.[43,44] Individual activities used are normally between 5550 and 7400 MBq (150 and 200 mCi), but higher activities are used for bone metastases. A 6- to 12-month period should be left between therapies to allow time for bone marrow recovery. In the small number of patients who may be expected to receive large cumulative activities, a bone marrow harvest should be considered early in their treatment plan.

Failure of radioiodine therapy may be a result of inadequate concentration of iodine in the tumour, thus delivering less than the required radiation dose to the tumour cells. Radiation doses of greater than 8000 rads to a metastasis are likely to eradicate this tumour,[45,46] but there are major inaccuracies inherent in calculating this figure. One difficulty is in estimating the functioning tumour mass and another lies in measuring the effective half-life of iodine in the tumour. Furthermore, there is evidence that using a tracer activity of ^{131}I to calculate the variables can in itself change tumour uptake and the pharmacokinetics of iodine in subsequent therapy doses – so-called 'thyroid stunning'.[47] The effective half-life of iodine in tumours is a major determinant of dosimetry and therefore, if the patient is known to have a short half-life, a larger dose will need to be administered or tumour retention promoted pharmacologically.[25]

1.6 Adverse Effects and Complications of Radioiodine Therapy

Radioiodine therapy is generally well tolerated by patients. Often the most troublesome adverse effects are those due to hypothyroidism following thyroid hormone withdrawal. The adverse effects of radioiodine are listed in table I. These can be divided into acute and late (immediate or those that occur after days, weeks or months) effects. The most common acute effect is nausea, and occasionally vomiting. This occurs due to the high local gastric radiation dose, can be seen in 50 to 70% of individuals and rarely lasts more than 72 hours.[48] Laxatives may reduce the gastrointestinal dose and the whole-body radiation dose.

Table I. Adverse effects of radioiodine in patients with thyroid cancer

Radiation gastritis
Sialadenitis
Radiation thyroiditis
Radiation cystitis
Reduction in sperm counts/azoospermia
Thyroid storm
Leukaemia
Acute haemorrhage or swelling of cerebral metastases

Radiation thyroiditis can occur between 2 and 4 days after therapy in those with significant thyroid remnants. This can lead to pain and tenderness over the thyroid or referred pain to the ear, neck or teeth, and can result in a transient thyrotoxicosis. Treatment may require simple analgesia, nonsteroidal anti-inflammatory drugs and/or corticosteroids.

Sialadenitis occurs in up to 12 to 30% of patients and is usually associated with pain and swelling; it may subsequently result in a dry mouth and, rarely, loss of taste. It may occur as early as the first day or usually within 3 weeks of the therapy but occasionally later than this, up to 6 months after the treatment. The question as to whether increased saliva flow reduces this effect has not been answered but it is not unreasonable to ask the patient to suck sweets that may promote flow and therefore reduce the radiation dose to the salivary gland.

Perhaps the most serious acute complications occur if there is acute oedema or haemorrhage in the tumour or metastasis. This is a very rare occurrence but can occur if there are central nervous system metastases, or related to the major airway.[5]

Late complications are uncommon but may include damage to the gonads, bone marrow, lungs[5] (it is more likely that the effect on lung function is due to residual tumour than to radiation from the radioiodine) and the induction of other cancers. During the first year after therapy transient ovarian failure has been reported in one-quarter of patients. Men may develop oligospermia proportional to the activity of ^{131}I administered.

Several large series showed no increase in the incidence of second malignancies,[49] although there have been reports of a slightly increased risk of bladder cancer occurring approximately 14 to 20 years after radioiodine, colonic cancer[50] and breast cancer.[51] The reports of leukaemia have in the main been associated with cumulative activities of more than 37 GBq (1 Ci) given to the patient,[52,53] usually over short treatment intervals. No genetic risk has been demonstrated to offspring of treated patients.[54,55]

1.7 Evidence for Improved Outcome with Radioiodine

The exact contribution of radioiodine to treatment outcome is unknown, since there are no prospective controlled studies. Available studies are retrospective, with a mixture of treatment protocols.

There are a number of studies with long periods of follow-up that demonstrate a large reduction in tumour recurrence or metastases after ^{131}I[17,56,57] although survival from the disease may[58] or may not[56] be improved.

The largest review of patients by Mazzaferri[59] examined 251 patients treated with surgery (subtotal or total thyroidectomy) and ^{131}I, and 756 patients who were treated with surgery alone. None of these patients had distant metastases. In the radioiodine group there were fewer local and distant recurrences and there were no deaths during the study follow-up of approximately 10 years.[59] These figures confirmed earlier findings showing fewer recurrences in the radioiodine-treated groups.[60,61]

Varma et al.[62] reviewed their patients treated with radioiodine and compared these results with an historical control group. They showed an improved prognosis with radioiodine but the study did not allow for possible changes in management and tumour characteristics with the passage of time. Krishnamurthy and Blahd[58] also showed in a small number of patients that if complete ablation is achieved no serious complications were observed in a mean follow-up period of 8.3 years. These data and a more recent review of a cohort of 1004 patients by Mazzaferri[63] suggest that the use

of radioiodine is effective, especially in large tumours and those with metastatic disease, in reducing the risk of recurrence and death from thyroid cancer. These effects were not apparent in patients with isolated tumours of less than 1.5cm in size that are not metastatic to regional lymph nodes or invasive of the thyroid capsule.

1.8 Other Forms of Therapy

External beam radiotherapy is an important treatment for specific focal complications or those tumours in the neck or bone with a poor response to iodine.[64] Chemotherapy regimens have had limited success in both progression and metastatic disease. Pharmaceuticals that have been tried include: doxorubicin (adriamycin) on its own[65,66] or in combination with melphalan, vincristine and bleomycin,[67] or the use of etoposide, carboplatin and *cis*-platinum.[68] There is little evidence that existing chemotherapy regimens provide anything other than occasional benefit.

2. Medullary Cell Carcinoma

The majority of medullary thyroid cell carcinomas (MTC) are sporadic, with 20% inherited as an autosomal dominant form. The inherited tumour may occur on its own or in association with other endocrine neoplasias and is normally due to mutations in the RET proto-oncogene.[69,70] These are termed MEN type I (parathyroid, pituitary and pancreatic islet tumours), type 2a (parathyroid tumour and phaeochromocytoma) and type 2b (parathyroid tumour, phaeochromocytoma plus mucosal neuromas, marfanoid features); the RET proto-oncogene being associated with familial MTC and MEN types 2a and 2b but not MEN type 1.

The cancer is derived from the parafollicular cell and often has amyloid deposits between cells. Tumours are multifocal in 20% of sporadic cases and 90% of familial. Metastases generally occur in lymph nodes of the neck (50 to 80%) and in the mediastinum. Blood-borne metastases are less common and may be found in the lung, liver and bone.

The tumours are found equally in men and women, the sporadic variety tending to occur in 40- to 50-year-old individuals and the familial variety early, often presenting before the ages of 15 to 30 years, but they can occur at any age. All tumours should be regarded as familial until proven otherwise. Therefore, family screening needs to be undertaken. Other tumours should be excluded and because of the highly individual course, therapy also has to be individualised.

Screening family members for disease has traditionally been by calcitonin measurement, often with stimulation tests, either using calcium infusion[71] or in combination with pentagastrin.[72] More recently, the use of omeprazole has been shown to have a similar effect.[73] Genetic tests are now becoming available and can be used to screen first-degree relatives (i.e. children, brothers, sisters and parents). If the genetic and baseline biochemical tests are negative, the patient is at an extremely low risk of developing disease, and further follow-up is not indicated. When the genetic test is positive for either MEN 2a or the non-MEN associated cancer and the provocative test is positive, then prophylactic thyroidectomy should be considered and a search for associated tumours needs to be undertaken. If the provocative test is negative in a child then annual follow-up until the age of 30 in MEN 2a should be undertaken. In MEN 2b the genetic screening and biochemical testing should be aggressive since the MTC is often aggressive. Patients should have baseline calcitonin and carcinoembryonic antigen (CEA) levels performed.

Imaging can be achieved using a number of methods including ^{201}Tl,[74] pentavalent ^{99m}Tc dimercaptosuccinate (DMSA),[75,76] ^{123}I or ^{131}I metaiodobenzylguanidine (MIBG)[77,78] and octreotide labelled with ^{111}In.[79] These scanning techniques work using different metabolic pathways, and the mechanisms of some of these are not fully characterised. They have variable sensitivities and specificities and are not mutually exclusive. The recommendation should be to perform all tests and use the one with the optimum uptake for follow-up. These tracers can be labelled with therapeutic

radionuclides and therefore the degree of uptake may allow therapy to be predicted (section 2.1). Staging of the tumour will also need standard techniques involving computerised tomography (CT), magnetic resonance imaging (MRI) of the neck and thorax, and bone scanning if appropriate.

2.1 Therapy

Therapy requires complete surgical excision of both lobes of the thyroid and removal of the central lymph nodes. Other macroscopically involved nodes should be removed but radical neck dissection has not been shown to improve prognosis.[80-82] 10-year survival is 60 to 67%.[83,84]

Many patients who have elevated calcitonin levels with a palpable nodule do not normalise their calcitonin levels after resection. The major problem is disease recurrence with compromise of important structures in the neck. The tumour will respond to debulking with repeat surgery. Although postoperative radiotherapy has been suggested by some, most have shown little if any benefit.[83,85,86] Approximately 30% of MTC patients take up ^{131}I-MIBG into the tumour tissue. MIBG is an analogue of guanethidine which is taken up into neuroectodermally derived tumours. The therapy is similar to that described for malignant phaeochromocytoma with repeat treatments at 2- to 8-month intervals. Therapy activities vary between 3.7 and 11.1 GBq of ^{131}I-MIBG dependent on the uptake on a preceding tracer scan and limitation of the calculated bone marrow dose to 2Gy. The agent is administered to patients in suitably shielded rooms and via a shielded infusion system. The infusion is generally over 1-4 hours. The response in MTC is variable, with 50 to 90% deriving symptom relief, although this datum is based on very small numbers of patients from a number of different centres.[87-90]

Singh et al.[91] have prepared ^{186}Re (V) DMSA which has potential as a therapy agent. To date, only one patient has been given the complex, which showed distribution into tumour but also a high uptake in the kidneys which may present as the dose-limiting organ.[92]

The tumour can also be visualised with the radiolabelled octopeptide, somatostatin. This peptide has an inhibitory effect on growth hormone receptors and can inhibit the growth of a number of tumours. Recently, therapy options have been suggested with [^{111}In]octreotide making use of the auger electrons. Patients have developed benefit from these therapies using activities between 2 and 4 GBq per administration. Over a 2-year period of follow-up, no significant adverse effects have been demonstrated.[93,94] The development has continued with the labelling of octreotide using ^{90}Y and ^{161}Tb; these are β emitters with potentially a greater role in therapy. The derivatives may, however, have significant uptake in the pituitary, adrenal, kidney and pancreas if the data from rats translate into human distribution data.[95,96] This will require the careful monitoring of these hormonal axes.

The use of chemotherapy regimens only produces moderate response but appears to be well tolerated. Combinations of cyclophosphamide, dacarbazine and vincristine or dacarbazine and fluorouracil or bleomycin, doxorubicin and *cis*-platinum have achieved partial responses.[97-99]

The best prognosis is in patients who have tumours found on screening and/or are young women; the non-MEN familial tumours fare the best followed by MEN 2a sporadic disease and MEN 2b. Follow-up can be performed using both calcitonin measurements and CEA levels. The CEA measurements tend to be less variable.

3. Radiation Safety Following Radionuclide Therapy

Patients given therapeutic doses of radiopharmaceuticals provide a potential radiation hazard to members of the staff caring for them, to other patients on the ward, to family and to members of the public. Patients who are to receive radioiodine therapy (either as iodine or MIBG) for cancer of the thyroid generally need to be admitted to hospital for a short period. The issues related to the need for hospital admission are:

1. The patient becomes a radiation source after the administration and therefore presents a possible problem to members of the public and to family members.

2. There is a risk of contamination of the environment. This risk is principally due to loss of radioactivity in the urine but there is also a minor risk from the radioactivity in sweat and saliva.

3. There is a low risk of nausea and vomiting in patients soon after the administration of iodine, which can best be handled in the hospital environment.

Guidance on radiation protection issues varies around the world but a number of countries take an annual dose limit of 1 mSv to children from a treated patient or 5 mSv for a 'carer'. The dose rates from patients have been measured and can be used to provide effective guidance to patients and their families.[100] With basic precautions there should be little risk to others from emitted or contaminant radiation.

3.1 Guidance with Regard to Pregnancy

Guidance on whether the patient can start a family is determined primarily by the patient's likely clinical course and the effects of radiation. Therapy must not be given if the patient is pregnant, and to avoid fetal exposure to radioiodine women are usually advised not to become pregnant for 4 to 6 months following radioiodine therapy. Casara et al.[101] have shown that the incidence of fetal abnormality in patients who produced children after being treated with ^{131}I for differentiated thyroid cancer was similar to that of the general population.

4. Anaplastic Carcinoma of the Thyroid

Anaplastic carcinoma of the thyroid carries a poor prognosis, with most patients dying within 6 to 9 months. The approach to therapy is surgical resection or debulking of disease followed by radiotherapy and/or chemotherapy, with various agents given either as single drug or multiple drug regimens. Agents that have been used include doxorubicin,[102] bleomycin[103] and cisplatin. Occasionally, unresectable tumours become resectable after initial radiotherapy or chemotherapy. Even with these treatment options prognosis is poor, with few long term survivors. These tumours do not concentrate radioiodine and are therefore not suitable for this form of treatment.

5. The Future

Treatment of differentiated thyroid cancer using radioiodine therapy is one of the most specific treatments currently available for any cancer. A major problem is the necessity to render patients hypothyroid before treatment. One potential development is the use of recombinant TSH which might allow circumvention of induced hypothyroidism.

Difficulty arises in tumours which do not take up iodine. The existence of metabolic pathways in thyroid and other endocrine tumours provides the potential for developing novel specific forms of therapy. However, success in this approach will require greater characterisation of these metabolic processes and development of new radiopharmaceuticals to exploit them. Developments in gene therapy have yet to be explored in thyroid cancer.

References

1. Harness JK, Thompson NW, Nishiyama RH. Childhood thyroid cancer. Arch Surg 1971; 102: 278-84
2. Heshmati HM, Gharib H, van Heerden JA, et al. Advances and controversies in the diagnosis and management of medullary thyroid carcinoma. Am J Med 1997; 103: 60-9
3. Marsh DJ, Learoyd DL, Robinson BG. Medullary thyroid carcinoma: recent advances and management update. Thyroid 1995; 5: 407-24
4. Gharib H, McConahey WM, Tiegs RD, et al. Medullary thyroid carcinoma: clinicopathologic features and long-term follow up of 65 patients treated during 1946 through 1970. Mayo Clin Proc 1992; 67: 934-40
5. O'Doherty MJ, Nunan TO, Croft DN. Radionuclides and therapy of thyroid cancer. Nucl Med Commun 1993; 14: 736-55
6. Baldet L, Manderscheid JC, Gluioer D, et al. The management of differentiated thyroid cancer in Europe in 1988: results of an international survey. Acta Endocrinol 1989; 120: 57-62
7. Franceschi S, Boyle P, Maisonneuve P, et al. The epidemiology of thyroid carcinoma. Crit Rev Oncol 1993; 4: 25-52
8. Hubert Jr JP, Kiernan PD, Beahrs OH, et al. Occult papillary carcinoma of the thyroid. Arch Surg 1980; 115: 394-9
9. Hay ID. Papillary thyroid carcinoma. Endocrinol Metab Clin North Am 1990; 19: 545-61
10. Hay ID, Grant CS, Taylor WE, et al. Ipsilateral lobectomy versus bilateral lobar resection in papillary thyroid carcinoma: a

retrospective analysis of surgical outcome using a novel prognostic scoring system. Surgery 1987; 102: 1088-95
11. Cady B, Sedgwick CE, Meissner WA, et al. Changing clinical, pathologic, therapeutic and survival patterns in differentiated thyroid carcinoma. Ann Surg 1976; 184: 541-53
12. Harness JK, Thompson NW, McLeod MK, et al. Follicular carcinoma of the thyroid gland: trends and treatment. Surgery 1984; 96: 972-8
13. Young RL, Mazzaferri EL, Rahe AJ, et al. Pure follicular thyroid carcinoma: impact of therapy in 214 patients. J Nucl Med 1980; 21: 733-9
14. Cady B, Rossi R. An expanded view of risk group definition in differentiated thyroid carcinoma. Surgery 1988; 104: 947-53
15. McConahey WM, Hay ID, Woolner LB, et al. Papillary thyroid cancer treated at the Mayo Clinic, 1946 through 1970: initial manifestations, pathologic findings, therapy and outcome. Mayo Clin Proc 1986; 61: 978-96
16. Hay ID, Bergstralh EJ, Goellner JR, et al. Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. Surgery 1993; 114: 1050-8
17. Mazzaferri EM, Jhiang SM. Long term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med 1994; 97: 418-28
18. Pujol P, Daures J-P, Nsakal N, et al. Degree of thyrotropin suppression as a prognostic determinant in differentiated thyroid cancer. J Clin Endocrinol Metab 1996; 81: 4318-23
19. Mazzaferri EL. Papillary thyroid carcinoma: factors influencing prognosis and current therapy. Semin Oncol 1987; 14: 315-32
20. Clark OH. TSH suppression in the management of thyroid nodules and thyroid cancer. World J Surg 1981; 5: 39-45
21. Cady B, Cohn K, Rossi RL, et al. The effect of thyroid hormone administration upon survival in patients with differentiated thyroid carcinoma. Surgery 1983; 94: 978-83
22. Bartalena L, Martino E, Pacchiarotti A, et al. Factors affecting suppression of endogenous thyrotropin secretion by thyroxine treatment: retrospective analysis in athyreotic and goitrous patients. J Clin Endocrinol Metab 1987; 64: 849-6
23. Faber J, Galloe AM. Changes in bone mass during prolonged subclinical hyperthyroidism due to L-thyroxine treatment: a meta-analysis. Eur J Endocrinol 1994; 130 (4): 350-6
24. Snyder J, Gorman C, Scanlon P. Thyroid remnant ablation: questionable pursuit of an ill-defined goal. J Nucl Med 1983; 24: 659-65
25. Reynolds JC, Robbins J. The changing role of radioiodine in the management of differentiated thyroid cancer. Seminars Nucl Med 1997; 27: 152-64
26. Graham GD, Burman KD. Radioiodine treatment of Graves' disease: an assessment of potential risks. Ann Intern Med 1986; 105: 900-5
27. Small MD, Bezman A, Longarini AE, et al. Absorption of potassium iodide from gastrointestinal tract. Proc Soc Exp Biol NY 1961; 106: 403-9
28. Keating FR, Albert A. The metabolism of iodine in man as disclosed with the use of radioiodine. Recent Prog Horm Res 1949; 4: 429-31
29. Myant NB, Corbett BD, Honour AJ, et al. Distribution of radioiodide in man. Clin Sci 1950; 9: 421-40
30. Honour AJ, Myant NB, Rolands EN. Secretion of radioiodine in digestive juices and milk in man. Clin Sci 1952; 11: 450-62
31. Chung J-K, Lee YJ, Jeong JM, et al. Clinical significance of hepatic visualisation on iodine-131 whole body scan in patients with thyroid carcinoma. J Nucl Med 1997; 38: 1191-5
32. Kuni CC, Klinensmith WC. Failure of low doses of ^{131}I to ablate residual thyroid tissue following surgery for thyroid cancer. Radiology 1980; 137: 773-4
33. Siddiqui AR, Edmonson J, Wellman HH, et al. Feasibility of low doses of ^{131}I for thyroid ablation in postsurgical patients with thyroid carcinoma. Clin Nucl Med 1981; 6: 158-61
34. Ramacciotti C, Pretorius HT, Line BR, et al. Ablation of nonmalignant thyroid remnants with low doses of radioactive iodine: concise communication. J Nucl Med 1982; 23: 483-9
35. DeGroot LJ, Reilly M. Comparison of 30 and 50 mCi doses of iodine-131 for thyroid ablation. Ann Intern Med 1982; 96: 51-3
36. Johansen K, Woodhouse NJ, Odugbesan O. Comparison of 1073 MBq and 3700 MBq iodine-131 in postoperative ablation of residual thyroid tissue in patients with differentiated thyroid cancer. J Nucl Med 1991; 32: 252-4
37. Beierwaltes WH, Rabbani R, Dunchowski C, et al. An analysis of 'ablation of thyroid remnants' with I-131 in 511 patients from 1947-1984: experience at University of Michigan. J Nucl Med 1984; 25: 1287-92
38. Goolden AW, Davey JB. The ablation of normal thyroid tissue with iodine-131. Br J Radiol 1963; 36: 340-5
39. Maxon HR, Boehringer TA, Drilling J. Low iodine diet in I-131 ablation of thyroid remnants. Clin Nucl Med 1983; 8: 123-6
40. Ladenson PW, Braverman LE, Mazzaferri EL, et al. Comparison of administration of recombinant human thyrotropin with withdrawal of thyroid hormone for radioactive iodine scanning in patients with thyroid carcinoma. N Engl J Med 1997; 337: 888-96
41. Hilts SV, Hellman D, Anderson J, et al. Serial TSH determination after T3 withdrawal or thyroidectomy in the therapy of thyroid carcinoma. J Nucl Med 1979; 20: 928-32
42. Lakshmanan M, Schaffer A, Robbins J, et al. A simplified low iodine diet in I-131 scanning and therapy of thyroid cancer. Clin Nucl Med 1988; 2: 866-8
43. Gershengorn MC, Izumi M, Robbins J, et al. Use of lithium as an adjunct to radioiodine therapy of thyroid carcinoma. J Clin Endocrinol Metab 1976; 42: 105-11
44. Pons F, Carrio I, Estorch M, et al. Lithium as an adjuvant of iodine-131 uptake when treating patients with well-differentiated thyroid carcinoma. Clin Nucl Med 1987; 12: 644-7
45. O'Connell ME, Flower MA, Hinton PJ, et al. Radiation dose assessment in radioiodine therapy: dose response relationships in differentiated thyroid carcinoma using quantitative scanning and PET. Radiother Oncol 1993; 28: 16-26
46. Maxon HR, Thomas SR, Hertzberg VS, et al. Relation between effective radiation dose and outcome of radioiodine therapy for thyroid cancer. N Engl J Med 1983; 309: 937-41
47. Coakley AJ. Thyroid stunning [editorial]. Eur J Nucl Med 1998; 25: 203-4
48. van Norstrand D, Neutze J, Atkins F. Side effects of rational dose iodine-131 therapy for metastatic well-differentiated thyroid carcinoma. J Nucl Med 1986; 27: 1519-27
49. Beierwaltes WH. The treatment of thyroid carcinoma with radioactive iodine. Semin Nucl Med 1978; 8: 79-94
50. de Vathaire F, Schlumberger M, Delisle MJ, et al. Leukaemias and cancers following iodine-131 administration for thyroid cancer. Br J Cancer 1997; 75: 734-9
51. Edmonds CJ, Smith T. The long-term hazards of the treatment of thyroid cancer with radioiodine. Br J Radiol 1986; 59: 45-51
52. Pochin EE. Long-term hazards of radioiodine treatment of thyroid carcinoma. In: Hedinger C, editor. UICC monograph se-

ries. Vol. 12: thyroid cancer. Berlin: Springer-Verlag, 1969; 293-304
53. Brincker H, Hansen HS, Andersen AP. Induction of leukaemia by 131I treatment of thyroid carcinoma. Br J Cancer 1973; 28: 232-7
54. Sarkar SD, Bejerwaltes WH, Gill SP, et al. Subsequent fertility and birth histories of children and adolescents treated with 131I for thyroid cancer. J Nucl Med 1976; 17: 460-4
55. Safa AM, Schumacher OP, Rodriguez-Antunez A. Longterm follow up results in children and adolescents treated with radioactive iodine (^{131}I) for hyperthyroidism. N Engl J Med 1975; 292: 167-71
56. Massin JP, Savoie JC, Garnier H, et al. Pulmonary metastases in differentiated thyroid carcinoma: study of 58 cases with implications for the primary tumour treatment. Cancer 1984; 53: 982-2
57. Samaan NA, Schultz PN, Haynie TP, et al. Pulmonary metastasis of differentiated thyroid carcinoma: treatment results in 101 patients. J Clin Endocrinol Metab 1985; 65: 376-80
58. Krishnamurthy GT, Blahd WH. Radioiodine I131 therapy in the management of thyroid carcinoma: a prospective study. Cancer 1977; 40: 195-202
59. Mazzaferri EL. Controversies in the management of differentiated thyroid carcinoma [abstract]. Endocrine Society 42nd Annual Postgraduate Endocrine Assembly syllabus; 1990; 167
60. Mazzaferri EL, Young RL, Oertel JE, et al. Papillary thyroid carcinoma: the impact of therapy in 576 patients. Medicine 1977; 56: 171-95
61. Mazzaferri EL, Young RL. Papillary thyroid carcinoma: a 10 year follow-up report of the impact of therapy in 576 patients. Am J Med 1981; 70: 511-8
62. Varma VM, Berjerwaltes WH, Nofal MM, et al. Treatment of thyroid cancer: death rates after surgery and after surgery followed by sodium iodine I-131. JAMA 1970; 214: 1437-42
63. Mazzaferri EL. Thyroid remnant 131I ablation for papillary and follicular thyroid carcinoma. Thyroid 1997; 7: 265-71
64. Tubiana M. External radiotherapy and radioiodine in the treatment of thyroid cancer. World J Surg 1981; 5: 75-84
65. Shimaoka K, Schoenfield D, Dewys WD, et al. A randomised trial of doxorubicin versus doxorubicin plus cis-platinum in patients with advanced thyroid carcinoma. Cancer 1985; 56: 2155-60
66. Gottlieb JA, Hill CS. Chemotherapy of thyroid cancer with adriamycin. N Engl J Med 1974; 290: 193-7
67. Durie BG, Hellman D, Woolfenden JM. High risk thyroid cancer: prolonged survival with early multimodality therapy. Cancer Clinical Trials 1981; 4: 67-73
68. Hoskin PJ, Harmer C. Chemotherapy for thyroid cancer. Radiother Oncol 1987; 10: 187-94
69. Donis-Keller H. The RET proto-oncogene and cancer. J Intern Med 1995; 238: 319-25
70. Mulligan LM, Ponder BAJ. Genetic basis of endocrine disease: multiple endocrine neoplasia type 2. J Clin Endocrinol Metab 1995; 80: 1989-95
71. Sizemore GW, Go VLW. Stimulation tests for diagnosis of medullary thyroid carcinoma. Mayo Clin Proc 1975; 50: 53-6
72. Wells SA, Dilley WG, Farndon JA, et al. Early diagnosis and treatment of medullary thyroid carcinoma. Arch Intern Med 1985; 145: 1245-52
73. Erdogan MF, Gullu S, Baskal N, et al. Omeprazole: calcitonin stimulation test for the diagnosis and follow up and family screening in medullary thyroid carcinoma. J Clin Endocrinol Metab 1997; 82: 897-9
74. Hoefnagel CA, Delprat CC, Zanin D, et al. New radionuclide tracers for the diagnosis and therapy of medullary thyroid carcinoma. Clin Nucl Med 1988; 13: 159-65
75. Ohta H, Yamamoto K, Endo K, et al. A new imaging agent for medullary carcinoma of the thyroid. J Nucl Med 1984; 25: 323-5
76. Clarke SEM, Lazrus CR, Wraight P, et al. Pentavalent [99mTc] DMSA, [131I] MIBG and [99mTc] MDP – an evaluation of three imaging techniques in patients with medullary carcinoma of the thyroid. J Nucl Med 1988; 29: 33-8
77. Endo K, Shiomi K, Kasagi K, et al. Imaging of medullary thyroid cancer with 131I-MIBG. Lancet 1984; II: 233
78. Connell JMC, Hilditch TE, Elliot A, et al. ^{131}I MIBG and medullary carcinoma of the thyroid. Lancet 1984; II: 1273-4
79. Krenning EP, Lamberts SWJ, Reubi JC, et al. Somatostatin receptor imaging in medullary thyroid carcinoma [abstract]. Thyroid 1991; 1 Suppl. 1: S64
80. Chong GC, Beahrs OH, Sizemore GW, et al. Medullary carcinoma of the thyroid gland. Cancer 1975; 35: 695-704
81. Russell CF, van Heerden JA, Sizemore GW, et al. The surgical management of medullary thyroid carcinoma. Ann Surg 1983; 197: 42-8
82. Dralle H, Scheumann GFW, Proye C, et al. The value of lymph node dissection in hereditary medullary thyroid carcinoma: a retrospective, European, multicentre study. J Intern Med 1995; 238: 357-61
83. Saad MF, Ordonez NG, Rashid RK, et al. Medullary carcinoma of the thyroid: a study of the clinical features and prognostic factors in 161 patients. Medicine 1984; 63: 319-41
84. Sizemore WF. Medullary cancer of the thyroid gland. Semin Oncol 1987; 14: 306-14
85. Samaan NA, Schultz PN, Hickey RC. Medullary thyroid carcinoma: prognosis of familial versus sporadic disease and the role of radiotherapy. J Clin Endocrinol Metab 1988; 67: 801-5
86. Nguyen TD, Chassard JL, Lagarde P, et al. Results of postoperative radiation therapy in medullary carcinoma of the thyroid: a retrospective study by the French Federation of Cancer Institutes – the Radiotherapy Cooperative Group. Radiother Oncol 1992; 23: 1-5
87. Clarke SEM. ^{131}I metaiodobenzylguanidine therapy in medullary thyroid cancer: Guy's Hospital experience. J Nucl Med Biol 1991; 35: 323-6
88. Troncone L, Rufini V, Maussier ML, et al. The role of ^{131}I metaiodobenzylguanidine in the treatment of medullary thyroid cancer: results in five cases. J Nucl Med Biol 1991; 35: 327-31
89. Schwartz C, Delisle M-J. Results of ^{131}I metaiodobenzylguanidine therapy administered to two patients with medullary carcinoma of the thyroid. J Nucl Med Biol 1991; 35: 332-3
90. Hoefnagel CA, Delprat CC, Valdes Amos RA. Role of ^{131}I MIBG therapy in medullary carcinoma. J Nucl Med Biol 1991; 35: 334-6
91. Singh J, Reghebi K, Lazarus CR, et al. Studies on the preparation and isomeric composition of 186Re- and 188Re-pentavalent rhenium dimercaptosuccinic acid complex. Nucl Med Commun 1993; 14: 197-203
92. Allen SJ, Blake GM, McKeeney DB, et al. A new radiopharmaceutical, 186Re-V-DMSA, for therapy of medullary carcinoma of the thyroid. Eur J Nucl Med 1990; 16: 432
93. Krenning EP, Krooj PPM, Pauwels S, et al. Somatostatin receptor scintigraphy and radionuclide therapy. Digestion 1996; 57: 57-61

94. Stolz B, Smith-Jones PM, Albert R, et al. Somatostatin analogues for somatostatin-receptor-mediated radiotherapy of cancer. Digestion 1996; 57: 17-21
95. de Jong M, Bakker WH, Krenning EP, et al. Yttrium-90 and indium-111 labelling, receptor binding and biodistribution of [DOTA0, D-Phe1, Tyr3] octreotide, a promising somatostatin analogue for radionuclide therapy. Eur J Nucl Med 1997; 24: 368-71
96. de Jong M, Breeman WAP, Bernard BF, et al. Evaluation *in vitro* and in rats of 161Tb-DTPA-octreotide, a somatostatin analogue with potential for intraoperative scanning and radiotherapy. Eur J Nucl Med 1995; 22: 608-16
97. di Bartalemeo M, Bajetta E, Bochicchio AM, et al. A phase II trial of dacarbazine, fluorouracil and epirubicin in patients with neuroendocrine tumours: a study by the Italian Trials in Medical Oncology (I.T.M.O.) group. Ann Oncol 1995; 6: 77-9
98. Wu LT, Averbuch SD, Ball DW, et al. Treatment of advanced medullary thyroid carcinoma with a combination of cyclophosphamide, vincristine and dacarbazine. Cancer 1994; 73: 432-6
99. Orlandi F, Caraci P, Berruti A, et al. Chemotherapy with dacarbazine and 5-fluorouracil in advanced medullary thyroid cancer. Ann Oncol 1994; 5: 763-5
100. Barrington SF, Kettle A, O'Doherty MJ, et al. Radiation dose rates from patients receiving 131-I therapy for carcinoma of the thyroid. Eur J Nucl Med 1996; 23: 123-30
101. Casara D, Rubello D, Saladini G, et al. Pregnancy after high doses of ^{131}I in differentiated thyroid cancer: potential risks and recommendations. Eur J Nucl Med 1993; 20: 192-4
102. Kim JH, Leeper RD. Treatment of anaplastic giant and spindle cell carcinoma of the thyroid gland with a combination of adriamycin and radiation therapy: a new approach. Cancer 1983; 52: 954-7
103. Samaan NA, Ordonez NG. Uncommon types of thyroid cancer. Endocinol Metab Clin North Am 1990; 19: 637-48

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