Chapter 16: Thyroid neoplasms

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Incidence

Malignant tumours of the thyroid gland represent less than 0.5% of all cancers in England and Wales (Young and Addison, 1983). In southern Sweden there are roughly two cases per 100,000 population per annum (Tennval, 1984), and in the USA the equivalent figure is slightly less than four (Third National Cancer Survey, 1971).

It is predominantly a disease of females, the female:male ratio being about 2.5:1.

Aetiology

Radiation

After reviewing all the available evidence, there is little doubt that radiation stands out as the most definite of all possible aetiological factors.

The practice of irradiating the thymus was fashionable in the earlier part of the century, particularly in America, and for a time irradiation of the tubotonsillar lymphoid tissue also enjoyed a passing vogue in the years leading up to and including the Second World War.

After reviewing the histories of such patients, it was concluded that radiation to the head, neck, and thorax in small doses during childhood was liable to induce cancer of the thyroid gland in later life (Winship and Rosvoll, 1961).

Further evidence of the carcinogenic effect of radiation during childhood came from the survivors of the atomic bombs in Japan, 18% of whom developed cancers of the thyroid gland. Most patients were under the age of 10 at the time of exposure, implying that susceptibility to the disease is most pronounced before puberty; furthermore most tumours were of the papillary type, the most common of the differentiated neoplasms (Sampson et al, 1969).

Although the adolescent and adult gland is evidently less at risk, reports of cancers in adults who had previously been irradiated for Hodgkin's disease of the cervical lymph nodes 10-15 years before clearly indicate a continued susceptibility, albeit on a somewhat reduced scale (McDougall et al, 1980). There is also some evidence to suggest that benign nodular disease may in some instances be linked to a history of previous radiation, possibly as much as 35 years previously (Favus et al, 1976).

On the experimental level, Doniach (1953) demonstrated that rats fed on thiouracil and subsequently treated by radiotherapy developed thyroid cancer. This led him to postulate that two factors were necessary for carcinogenesis, namely a high level of thyroid stimulating hormone (TSH), which one would normally expect in the prepubertal subject, and secondly ionizing radiation. The finding that most differentiated thyroid cancers regress if TSH is suppressed by the administration of thyroxine, supports this contention (Crile, 1966).
**Hormonal causes**

Experimental work on rats has shown that excessive production of TSH over prolonged periods, whether induced by the administration of thiouracil, by partial thyroidectomy, or by iodine-deficient diets, may induce benign and malignant tumours (Doniach and Williams, 1962). The addition of a specific carcinogen such as 2-acetylamino-fluorene increases the incidence of cancer (Bielschowsky, 1944).

One should therefore expect a higher incidence of cancer in glands hypertrophied by high levels of TSH over prolonged periods of time, such as in areas where goitre is endemic (Wegelin, 1928). The evidence in support of this is, however, contradictory and the issue unlikely to be resolved by comparing the statistics of one country with those of another. In favour of the view that endemic goitre predisposes to carcinoma is the finding that the predominant pathological type in such areas is the follicular neoplasm, whereas for non-endemic goitre it is more often papillary (Wohner et al, 1966).

**Genetic factors**

Familial medullary carcinoma, as opposed to the sporadic disease, is passed on as an autosomal dominant form of inheritance, with an increased predisposition to other tumours, mainly of neuroectodermal origin, such as phaeochromocytoma, epithelial neuroma, and parathyroid adenoma.

In the north-western coastal area of Norway, which is not particularly noted for endemic goitre and which until quite recently was isolated from the rest of the country, the incidence of differentiated thyroid cancer is high, a fact which has led to the suggestion that this may have resulted from inbreeding over a considerable period of time (Wade, 1975).

**Autoimmune thyroiditis**

Malignant lymphoma is a well-known sequel of Hashimoto's disease but the exact frequency of this change is difficult to assess.

**Classification, pathology and natural history**

Solitary non-functioning nodules of the thyroid gland are either cystic or solid, and the latter are either benign adenomata or cancers. Anything up to 20% of non-functioning solid nodules will prove to be cancerous, although a more common figure is about 10% (Katz and Warren, 1976; Burrow et al, 1978).

For a comprehensive review of the pathology of malignant tumours of the thyroid, the reader can do no better than refer to the paper by Woolner et al (1961), which reviews a very large number of cases collected in a major centre. The two most common cancers, specifically of thyroid tissue origin, are papillary and follicular carcinoma. Because of their distinctive histological features and behaviour, they are sometimes grouped together and referred to collectively as differentiated tumours.
Medullary carcinoma arises from the parafollicular or C cells and is, therefore, not a true thyroid neoplasm, but because of its anatomical location and similarities in behaviour, it is included in all discussion of thyroid neoplasia.

**Papillary carcinoma**

This tumour comprises about 60% of all malignant neoplasms in the larger American series, but figures a little less prominently in European reports. It is the type which most often follows previous irradiation. The histological appearance is one of papillary excrescences together with neoplastic follicles; in most cases encapsulation is absent.

Small papillary tumours not exceeding 1.5 cm in diameter and exhibiting marked desmoplasia and psammoma bodies are referred to as occult carcinomata. By contrast to their bulkier counterparts, they are usually detected by accident or their presence may be suspected when a metastatic node is discovered in the absence of palpable disease at the primary site.

Most papillary cancers present as discrete hard intrathyroid masses, but additional discrete deposits are found in other parts of the gland in as many as 40% of cases, most of these being microscopical. Whether these smaller deposits represent spread within the gland along lymphatic channels or entirely independent new tumours is impossible to say, but their presence has led some people to believe that papillary cancer is truly multifocal in origin.

The tumour generally grows slowly and is late to break through the capsule of the gland, although lymph node metastasis is not uncommon in many cases. The disease may occur at any age, but it is classically commoner in younger subjects, 42% being under the age of 40 (Woolner et al, 1961).

The ratio of females to males for all papillary cancers in the same study was 2.4:1, but that in cases which had broken through the capsule of the gland was 1.5:1, and in inoperable cases 0.7:1. This suggests that the prognosis may be influenced by the sex of the individual, although other factors also need to be taken into account.

Once the tumour has become extrathyroidal, it attaches itself to neighbouring structures and ultimately becomes invasive. Typically the tumour invades the strap muscles first and although lacking a capsule, it may well provoke the formation of fibrous tissue at its leading edge, thus creating the impression of encapsulation.

Gross invasion of veins is virtually absent, but invasion of the trachea, larynx, oesophagus, and recurrent nerves takes place when the disease has extended far beyond the confines of the gland.

Almost all papillary cancers exhibit a mixed papillary and follicular pattern, in varying proportions. At one end of the spectrum are cases which are wholly papillary, while at the other end the proportion of papillary elements is overshadowed by a predominantly follicular pattern. Even those exhibiting a mainly follicular appearance lack a capsule and behave in a similar way to their papillary counterparts.
Nodal metastasis occurs in as many as 40% of cases (Woolner et al, 1961). Deposits appear classically in the paratracheal nodes, but may present anywhere in the neck, so that lymphadenopathy in the carotid or supraclavicular triangles is common. Bilateral spread to the nodes is found in about 8% of patients.

Pulmonary metastasis is uncommon at presentation, and only affects 4% of all patients, chiefly those in the older group and those with extrathyroidal spread. It often presents as a diffuse coarse miliary infiltrate rather than a series of discrete rounded shadows.

**Follicular carcinoma**

Whereas the mean age for papillary cancer was 42 years in the series of Woolner et al (1961), that for follicular carcinoma was 50. The sex ratio however, was similar at 2.6:1 in favour of females, and the total group comprised 18% of all malignant thyroid neoplasms.

Follicular carcinoma is typically encapsulated and, in those lesions with minimal invasive characteristics it may be mistaken for a follicular adenoma. The extent to which the capsule is invaded, and in particular the veins located within the capsule, provides an indication of the likelihood of metastasis. The term 'micro-angio-invasive' has been coined to describe those tumours with little evidence of venous invasion, and in which the potential for local invasiveness and distant metastasis is consequently low. Gross infiltration of capsular veins is a bad prognostic sign and generally portends distant dissemination of the disease.

Besides this particular feature of follicular cancers, the pathologist may recognize a graduation from a well-differentiated to a poorly differentiated pattern, and this feature may also be used in forecasting the outcome. In some, de-differentiation assumes an even more sinister quality so that the tumour ultimately becomes anaplastic.

Once follicular carcinoma becomes extrathyroidal, the capacity for local invasion becomes more dramatic than in papillary cancer, although the target areas are essentially the same, namely the larynx, trachea, oesophagus and recurrent nerves. Curiously the only structure which defies invasion in both types of neoplasm is the carotid artery. In the case of the larynx and trachea, cartilage is destroyed and intraluminal extension of disease causes airway obstruction and bleeding. Oesophageal invasion is uncommon and late, and usually manifests as an insinuation of the disease between trachea and oesophagus, followed by migration some distance up and down the muscle coat, and between muscle and mucosa. The tumour rarely penetrates the mucosa to enter the lumen of the oesophagus and is unlikely therefore to be recognized by preoperative endoscopy.

Nodal metastasis is uncommon in purely follicular cancers being found in about 4% of the total (Woolner et al, 1961).

Metastases of angio-invasive tumours to bone and viscera are common, and the better differentiated of these may resemble normal thyroid tissue. In the lungs the appearance on X-ray is generally of multiple large rounded shadows and, in the bones, that of osteolytic lesions. The latter in fact may be extremely vascular, to the extent of resembling arteriovenous malformations.
In rare instances, the primary tumour may present as a hyperfunctioning nodule causing some degree of hyperthyroidism.

**Medullary carcinoma**

Medullary carcinoma, comprising between 5 and 10% of thyroid neoplasms, is a tumour of the parafollicular or C cells and, unlike differentiated thyroid neoplasms, is of neuroectodermal origin (Hazard, Hawk and Crile, 1959). It falls into one of two categories, namely the sporadic or the familial hereditary type of disease.

The former is generally seen between the third and seventh decades of life, with women again predominating over men. The latter, which is inherited as an autosomal dominant trait, may appear as early as the second decade, and affects both sexes equally.

Both types present as a single hard nodule, but in the familial group there is nearly always histological evidence of multicentricity. The tumour is solid and unencapsulated, and grows in sheets or nests surrounded by a hyaline fibrous stroma which stains strongly for amyloid.

The propensity for lymph node metastasis is exhibited by both familial and sporadic types, and as many as 75% of the total eventually develop lymphadenopathy. Like papillary cancer, medullary cancer may spread to any group of cervical lymph nodes, although the emphasis is frequently on the lower deep cervical, supraclavicular, and mediastinal nodes.

The natural tendency of the primary tumour is to enlarge and then to break through the capsule of the thyroid gland, first to attach to adjacent structures, and finally to invade them.

Medullary cancer is characterized by an elevation of the serum calcitonin, which tends to be relatively higher in the familial type of disease. Selective venous catheterization has been used in the past to determine the site of maximum calcitonin concentration in the gland, and is most useful for the detection of the site of any recurrent disease.

Infusion of calcium into the bloodstream, or the ingestion of whisky, are potent stimuli for the release of calcitonin, a fact which is made use of when cases of occult tumours are suspected, or when screening the siblings of a person known to suffer from the disease. The greater the bulk of the disease, both at the primary site and at sites of metastasis, the higher the level of the serum calcitonin.

When the tumour is confined exclusively to the thyroid gland, eradication of the disease should in theory reduce the serum calcitonin level to normal (less than 0.1 ng/mL), but this is seldom achieved even when distant spread is absent.

There is good evidence to suggest that serotonin is secreted by some medullary cancers since flushing, headache, breathlessness, sweating and fainting are experienced by some patients, and both the serum 5-hydroxytryptamine (serotonin) and the urinary 5-hydroxyindoleacetic levels are raised. Prostaglandins and histaminase are also secreted, the concentration of the latter serving as a useful guide to the extent of metastatic disease.
The intractable and severe diarrhoea which is so typical of many cases of medullary carcinoma is almost invariably linked to the presence of gross metastatic disease, mainly in the liver, but its precise cause is not understood. Of the patients 50% or more eventually suffer from this distressing symptom for which there is no specific antidote.

Blood-borne metastases are seen typically in the liver, but may also affect the lungs and the bones, at which site they may cause severe pain.

Other tumours are seen in about 10% of patients with familial medullary carcinoma, namely phaeochromocytoma, mucosal neuroma and parathyroid adenoma. Investigations should therefore include an estimate of the 24-hour urinary catecholamines, the level of vanillylmandelic acid in the blood and the serum calcium.

**Anaplastic carcinoma**

The average age of patients in this group is about 60 years and once again women outnumber men. The tumour only accounts for about 5% of all thyroid neoplasms, and even this may be an overestimate, since many lymphomata were previously mistaken for anaplastic cancer.

Microscopically, the tumour is characterized by large cells with markedly irregular nuclei some of which may take on a bizarre giant appearance, while others assume a spindly look, hence the subdivision into giant-cell or spindle-cell anaplastic carcinoma.

Typically there is a history of a long-standing, but asymptomatic, goitre preceding the sudden and explosive onset of the disease. The clinical course is characterized by rapid growth with pain, early invasion of surrounding structures, and a swift decline. Patients rarely survive for longer than one year after the diagnosis is made.

**Lymphoma**

Whereas anaplastic carcinoma is almost invariably fatal, the outlook in lymphoma is comparatively favourable.

This histology, which may bear some resemblance to anaplastic tumours, is usually distinctive, and there should rarely be any confusion between the two conditions.

The clinical course, however, may be almost as dramatic as anaplastic cancer, in that there is a sudden onset of swelling spreading to adjacent structures and causing acute respiratory embarrassment. Early treatment is essential for the prevention of complications, and this may then be followed by the appropriate investigations for staging the disease.

**Follicular adenoma**

This is a solitary encapsulated ovoid or rounded mass varying in consistency from firm to soft, depending on whether the growth has been the seat of haemorrhage, infarction, cyst formation, fibrosis, or calcification. The architecture of this neoplasm is one of multiple follicles of relatively uniform appearance with compression of the adjacent fibrous
parenchyma. Care must be taken not to overlook a carcinoma, the key being the absence of venous or capsular invasion.

Adenomata may be non-functioning, or may exhibit some degree of activity, varying from slight to hyperactive. True ‘toxic’ adenomata are uncommon: usually a toxic nodule suppresses the remaining parenchyma of a multinodular gland.

The diagnosis is generally made retrospectively when a solitary nodule is removed by a lobectomy.

**Factors influencing prognosis**

The two most important factors influencing prognosis in differentiated thyroid cancer are the age of the patient and the pathology of the tumour.

Most authors agree that survival is inversely related to age and that this effect is most evident from the age of 40 onwards (Staunton and Skeet, 1979).

The relation of the sex of the patient to prognosis is probably less obvious, although Doll (1969) was of the opinion that males with a differentiated thyroid cancer generally fare worse than females, and Crile (1971) concluded that under the age of 40, females unquestionably had a better prognosis.

The histopathological criteria which govern the behaviour of a thyroid neoplasm are also considered to influence prognosis. Papillary carcinoma tends to be slow growing and, although lacking a capsule, provokes a fibrous reaction as the disease becomes extrathyroidal. This may serve to lessen the tendency towards invasion, at least for a while. It would seem also that both occult tumours and papillary cancer induced by exposure to radiation in childhood carry a particularly favourable prognosis.

Follicular carcinoma exhibits a greater capacity for invasion, exemplified typically by its tendency to infiltrate the veins which lie in the tumour capsule. The degree of differentiation also has an important bearing on the final outcome, so that the expectations for a poorly differentiated follicular neoplasm must be lower than for a well-differentiated lesion.

In general, follicular tumours have a worse prognosis than purely papillary neoplasms, and papillary tumours with follicular elements are intermediate. Extrathyroidal spread carries a worse prognosis than disease confined to the gland.

Nodal spread of papillary carcinoma apparently does not affect the prognosis adversely.

**Symptoms and signs**

Thyroid neoplasms whether benign or malignant present in the early or intrathyroidal phase as solitary nodules, often of indeterminate consistency. They usually lie in one or other lobe, but occasionally arise in the isthmus of the gland. Even tumours which are eventually
reported by the pathologist to be multicentric generally appear to be uninodular on clinical examination. For the vast majority of patients, the principal concern about which they seek advice is the presence of a swelling.

Attempts to draw conclusions about the nature of the swelling from its consistency are generally unrewarding, for by no means every cancer possesses the hardness of squamous cancers, and in any case the interposition of numerous soft tissue layers between the palpating fingers and the neoplasms makes interpretation of the consistency difficult.

The distinction between benign and malignant in the later stages of the natural history of a thyroid swelling is usually much easier to make because adenomata do not become so overtly extrathyroidal in the way that cancers do. Conversely, large thyroid masses which blend imperceptibly into the adjacent anatomy so that their limits are indeterminate are rarely benign.

Fixation due to escape of the disease from the gland is therefore an important criterion of malignancy, and is evident by the failure of the mass to move up and down with swallowing.

Such is the diffuse extent of extrathyroidal spread in some cases, that the carotid artery may be displaced quite far laterally, or even obscured by the overlying neoplasm so that distal pulsations may be reduced. The close relationship of the cervical sympathetic nerve to the posteromedial aspect of the carotid sheath explains the presence of a Horner's syndrome when spread is as extensive as this.

Displacement of the trachea to the contralateral side does not in itself signify the presence of malignancy, since any large goitre may do this, but compression and narrowing of the trachea leading to wheezing and shortness of breath, especially when the patient lies down, should arouse suspicion of neoplasia.

Haemoptysis on the other hand is a clear indication of an invasive process which has finally broken through into the tracheal lumen, and should leave the clinician in no doubt about the nature of the disease.

Dysphagia is a late phenomenon in the natural history of thyroid cancers, and usually signifies infiltration of the gullet, rather than simple displacement such as occurs when a very bulky goitre comes into contact with the oesophagus.

The laryngeal alae or the cricoid may be infiltrated, and the hypopharynx may be invaded when disease from the posterior aspect of the upper pole of the thyroid attaches itself to the pyriform sinus.

Hoarseness is common in such circumstances, and is later followed by dyspnoea and laryngeal stridor. Indirect laryngoscopy shows an oedematous mucous membrane encroaching on the laryngeal lumen.

Hoarseness is, however, more likely due to paralysis of the vocal cord resulting from infiltration of the recurrent laryngeal nerves by cancerous deposits in its immediate vicinity.
It should be said that vocal cord mobility may be preserved for a long time in the face of obvious invasion of the recurrent nerve.

Lymphadenopathy is most apparent at those sites which are amenable to palpation, but the nodes which are most consistently involved, namely the paratracheal, are deep seated and are therefore rarely palpable.

As nodal disease enlarges, so the likelihood of fixation to the jugular vein and prevertebral fascia increases.

Retrosternal extension, a common feature of large follicular cancers, causes tracheal displacement and narrowing as well as engorgement of the neck and upper chest wall veins. At operation the retrosternal extension, unlike its benign counterpart, is often attached to adjacent structures in the mediastinum such as the pleura, trachea, recurrent nerves, oesophagus and prevertebral fascia.

The pathology of each thyroid nodule largely determines the pattern of symptoms in any given case. Follicular adenomata rarely give rise to any symptoms other than awareness of the presence of a swelling.

In papillary carcinoma, the primary tumour often fails to grow to any significant degree, and may be overshadowed by quite substantial lymphadenopathy.

Follicular and medullary cancers are similar in their behaviour since both diseases tend to be bulkier and to spread more readily. Hence the symptoms are related to the displacement and invasion of structures lying close to the thyroid gland.

Both lymphoma and anaplastic carcinoma are characterized by rapid growth, pain and respiratory obstruction.

Diagnosis

Thyroid scans

Patients undergoing scanning should not have received iodine compounds or thyroid supplements for 4-6 weeks before the procedure, as uptake of tracer is suppressed. The scan is carried out 20-30 minutes after an intravenous dose of technetium-99 or 24 hours after an oral dose of iodine-131 or iodine-123. With technetium either a rectilinear scanner or a gamma camera fitted with a pinhole collimator may be used, but with $^{131}$I the rectilinear scanner is supposedly better.

Just before the scan, the patient is given a glass of water to wash away any radionuclide which has found its way into the pharynx in the saliva. Anatomical landmarks, such as the suprasternal notch, are defined on the scan by means of a radioactive marker which is placed on the patient. This is important for the accurate localization of nodules and for confirmation of retrosternal extensions.
Non-functioning solitary nodules, often referred to as 'cold' nodules, appear on the scan as localized areas of diminished or absent tracer uptake, but this does not indicate whether they are cystic and therefore unlikely to be malignant, or solid.

The converse of the 'cold' or non-functioning lesion is the 'hot' nodule, indicative of a biologically active circumscribed area of gland parenchyma. It is rare for such a nodule to be malignant, but exceptionally malignant lesions may be 'hot' on technetium scanning and 'cold' on iodine scan.

There has been no specific radionuclide imaging technique for the demonstration of primary or metastatic medullary cell carcinoma until the recent development of $^{131}$I-meta-iodobenzyl-guanidine (MIBG). Being a guanethidine analogue, it is taken up by chromaffin-containing tissue of neuroectodermal origin, such as phaeochromocytoma, for the imaging of which it was in fact designed. But since medullary carcinoma arises from the parafollicular cells which also originate from the neural crest $^{131}$I-MIBG has been used with some success for the imaging of both primary and metastatic tumours (Clarke, Fogelman and Lazarus, 1986).

**Ultrasound**

This is a valuable complementary investigation to radionuclide imaging since it may distinguish between cystic and solid nodules. Although cancers could conceivably arise in cysts, or alternatively undergo cystic degeneration, such an eventuality is extremely rare and almost all cancers are solid.

The results of ultrasound scanning and the findings at operation are usually in agreement but disparities do occur, such as when a solid nodule has undergone cystic degeneration.

**Radiology**

X-ray of the neck and the thoracic inlet will establish whether there is any displacement or compression of the trachea and will demonstrate the calcification which is sometimes present in papillary cancers.

Barium swallow complements the posteroanterior and lateral plain radiographs and will reveal the presence of oesophageal shift or narrowing.

Chest X-ray is carried out routinely to determine if there are pulmonary metastases, which appear as rounded shadows in follicular carcinoma and as a miliary infiltrate in papillary carcinoma.

**Fine needle aspirate**

Aspiration biopsy cytology is a safe and easy preoperative investigation, but it requires the services of an experienced cytologist for the interpretation of the findings. Unlike larger needles such as the Vim-Silverman which extracts a core of tissue, aspiration with a fine
needle yields a liquid specimen which is smeared on to a slide and may be reported on in minutes.

With such a technique, it is possible to identify papillary and follicular cells as distinct entities, but the distinction between the follicular cells of an adenoma and a carcinoma is very difficult to make.

The simplicity of the technique and the fact that the percentage of false negatives may be as low as 2.2% recommends it as part of the routine work-up of patients with thyroid swellings (Lowhagen et al, 1979).

**Thyroglobulin estimation**

This antibody is detectable in the blood of all patients with thyroid cancer and its level serves as a very sensitive marker of the extent of the disease. Patients who have been treated successfully lose all trace of thyroglobulin in their serum, and those who after a period of quiescence eventually develop a recurrence, once again demonstrate its presence in their blood.

The test is therefore useful for gauging the success or otherwise of treatment.

**Calcitonin estimation**

Calcitonin levels in the blood of patients with medullary carcinoma are abnormally high and, like thyroglobulin, the greater the bulk of the disease, the higher the level.

Unlike thyroglobulin, however, it does not often drop to the normal level of below 0.1 ng/mL in patients who have apparently been treated successfully.

**Other investigations**

Patients suffering from familiar medullary carcinoma may also harbour other neoplasms, such as phaeochromocytoma and parathyroid adenoma.

To rule out the presence of such associated tumours, it is appropriate to estimate the level of vanillylmandelic acid in the blood together with that of the urinary catecholamines over 24 hours and, in addition, the serum calcium.

Patients suspected of metastases from primary follicular or mixed papillary - follicular carcinoma should undergo whole body radioiodine scans after ablation of the thyroid gland.

In the case of medullary carcinoma, scanning is usually carried out with technetium, although (\(^{131}\)I)MIBG may also be used. Because of the expense of this agent, it is generally reserved for the identification of residual or metastatic disease rather than as a primary diagnostic measure.
In its absence, general surveillance of metastatic medullary carcinoma may be carried out with technetium scans to show soft tissue deposits and gallium scans to delineate osseous lesions.

**Principles of treatment**

With the exception of anaplastic carcinoma and lymphoma, the mainstay of treatment for all thyroid neoplasms is surgery. The contentious issue is whether the operation for differentiated lesions should be a partial or a complete removal of the gland, bearing in mind that total thyroidectomy carries a higher morbidity.

The debate hinges on two points, namely whether the more radical of the two procedures improves the prognosis and whether its complication rate is as high as is claimed.

The morbidity of the operation should theoretically be easy enough to assess by reviewing the incidence of parathyroid insufficiency and that of recurrent nerve paralysis in the literature. But as so often happens in large series, there is considerable variability in the clinical material and in the experience of those performing the surgery. If one group of patients has a significantly higher proportion of advanced cases, the morbidity in respect of the parathyroids and the recurrent nerves is bound to be higher.

Tollefsen, Shah and Huvos (1972), for example, quoted an incidence of 21% for hypocalcaemia after total thyroidectomy, whereas that in Mustard's (1970) hands was 12% and that reported by Bartolo, Kay and Talbot (1983) was nil.

Similarly the incidence of permanent recurrent nerve paralysis may be as high as 17% when secondary thyroidectomy is practised (Beahrs and Vandertoll, 1963) or as low as 4.8% after primary total thyroidectomy (Thompson and Harkness, 1970).

The point which is much more difficult to decide is whether total thyroidectomy achieves a higher cure rate than lobectomy in differentiated thyroid cancer. Arguments are marshalled in favour of each, but the truth of the matter is that comparisons between reported series are invalid because of the abundance of variables.

In order to make matters simple, the reasons for and against are discussed, and guidelines for the choice of one of the two options drawn up.

**Papillary carcinoma**

The protagonists of lobectomy argue that the incidence of recurrent disease in the contralateral remaining thyroid lobe is about 4%, in spite of the fact that as many as 40% of cases exhibit signs of multicentricity throughout the gland (Tollefsen and Decosse, 1963; Tollefsen, Shah and Huvos, 1972). It is further suggested that the recurrence rate might have been even lower if the patients had been maintained on thyroxine after operation by virtue of its suppressive effect on TSH (Crile, 1980).

On the other hand, the incidence of recurrence in the contralateral lobe after hemithyroidectomy may be considerably higher: 24% in one series (Rose et al, 1963) and
17% in another (Hirabayashi and Lindsay, 1961). The large difference in the recurrence rate can be explained on the basis of the age factor, since the prognosis of patients over the age of 40 is much worse than that in younger subjects.

There are also some who speculate that some of the recurrences may have been sparked off by the administration of postoperative radioiodine, given with the intention of ablating remaining thyroid tissue after hemithyroidectomy. It has been postulated that this, rather than the inadequacy of the original operation, was responsible for recurrence of disease and that the tumour may also have been transformed from a well-differentiated to an anaplastic lesion in the process (Crile, 1971).

As regards the management of lymph node metastasis, most authors agree that removal of overtly diseased nodes by simple rather than radical dissection suffices in all but the most advanced cases. There is also general agreement that the presence of lymph node metastasis does not make the prognosis any worse.

With all these points in mind, how should one proceed when faced with a case of papillary carcinoma of the thyroid? Patients under the age of 40 with intrathyroidal disease, especially those with a previous history of exposure to radiation, may be managed by hemithyroidectomy with the local removal of any enlarged nodes. The risk of postoperative tetany is nil and that to the recurrent nerve is halved. However, it is vital that the patient is maintained permanently on an adequate dose of thyroxine. If Crile's (1971) comments on the inadvisability of postoperative radioiodine are accepted, a matter which not all are agreed about, this treatment must clearly be withheld.

It would seem that the place for total thyroidectomy is in the management of the older patient, and in all patients who exhibit signs of extrathyroidal escape.

The case for ablating microscopical residues with radioiodine is much stronger in this group in view of the increased likelihood of recurrence if thyroid tissue is allowed to remain. The therapeutic value of such treatment lies both in the eradication of the soil in which microscopical tumour deposits reside and in the effect of the isotope on the tumour cells directly, many of which are derived from mixed papillary and follicular lesions and therefore likely to take up radioiodine.

For those cases with unequivocal papillary tumours which have escaped into the surrounding tissues, the alternative of postoperative external beam radiotherapy may be equally or more effective.

The management of neck nodes does not differ in the more advanced cases, although the need for radical neck dissection as opposed to 'berry picking' may be that much greater. It is mandatory to keep all the patients on thyroxine and to monitor subsequent recurrence by regular scanning and serum thyroglobulin estimations.

**Follicular carcinoma**

Those who support the view that follicular carcinoma with minimal invasion of capsular veins is a relatively benign disease would go on to argue that a hemithyroidectomy
is an adequate procedure for this neoplasm. Such an argument is based on the fact that the potential for spread is small and, consequently, the need for whole body scans to detect metastases after surgery is unnecessary.

However, one can never be certain that a follicular tumour, no matter how benign in appearance, will not metastasize, and since whole body scans for the detection of distant spread are unsuccessful when a significant bulk of normal thyroid tissue remains, the argument in favour of total thyroidectomy would appear to be stronger.

This, together with the fact that follicular carcinoma is seen in an older age group in whom the prognosis is considered to be generally worse, should steer the clinician in the direction of total removal rather than a hemithyroidectomy.

Any residual thyroid tissue or distant deposits which are picked up by a postoperative whole body scan are managed by radioiodine therapy, and hormone therapy is withheld until such treatment is completed.

The propensity for lymph node metastasis in follicular cancer is low, but the principles of their management are the same as for papillary carcinoma.

**Medullary carcinoma**

The prognosis for this tumour is worse than for differentiated tumours. Whereas the presence of lymphadenopathy in papillary neoplasms does not appear to affect the outcome adversely, the same cannot be said of medullary carcinoma. Quite clearly the factors which influence survival are local escape of disease from the gland and malignant lymphadenopathy, both of which herald the appearance of distant spread.

Total thyroidectomy is the treatment of choice in all cases, be they sporadic or familial, and this includes members of a family who have raised calcitonin levels but who do not show signs of overt disease on clinical examination or on scanning.

Lymph node deposits are generally more diffusely spread than in differentiated thyroid cancer and the surgical clearance must, therefore, be more ambitious, to include the upper mediastinum as well as the cervical nodes.

The question as to whether or not external beam radiotherapy is useful in the control of local disease has not been addressed adequately so far, but there is no reason to suppose that it may not be helpful in management of postoperative microscopical residues.

**Anaplastic carcinoma**

This disease advances with such rapidity that very few cases are suitable for surgical excision. Those early cases which prove to be suitable for total thyroidectomy should receive postoperative radiotherapy to control local disease, even if distant metastases have already appeared.
Inoperable disease which threatens to cause respiratory obstruction should be managed by uncapping the trachea to avert imminent asphyxiation, followed by irradiation. The operation also yields a sample of tissue for histology.

**Lymphoma**

Resection of the isthmus for the purpose of averting or relieving respiratory embarrassment should be followed by immediate radiotherapy with the expectation of rapid recovery. During treatment the patient is fully investigated for the purpose of staging the disease and deciding whether chemotherapy will be required or not.

**Flow chart for thyroid cancer**

Thyroid swelling (Technetium scan) --> Cold solitary nodule (Ultrasound scan) --> Solid nodule (Aspiration cytology; Thyroglobulin estimation; Open biopsy and frozen section; CT scan; Calcitonin estimation) --> Carcinoma:
- Pure papillary
  - Intrathyroidal under age of 40 --> Hemithyroidectomy + thyroxine
  - Extrathyroidal --> Total thyroidectomy + DXT + thyroxine
  - Intrathyroidal over 40 --> Total thyroidectomy + thyroxine
- Mixed papillary/follicular --> Total thyroidectomy + radiiodine + thyroxine
- Follicular --> Total thyroidectomy + radiiodine + thyroxine
- Medullary --> Total thyroidectomy +/- DXT + thyroxine
- Lymphoma + anaplastic --> DXT +/- Chemotherapy.

**Surgery**

Most solitary nodules of the thyroid gland are removed by partial thyroidectomy and the diagnosis in the majority of cases proves to be benign, the commonest diagnosis being follicular adenoma.

The diagnosis of differentiated thyroid cancer is therefore frequently arrived at by accident following lobectomy for a supposedly benign solid nodule. After consideration of all the relevant factors, a decision must then be made as to whether the treatment thus far has been adequate or whether the contralateral thyroid lobe should also be removed.

Some surgeons, however, favour the operation of subtotal thyroidectomy as an alternative to total removal, the aim being to leave a sliver of normal thyroid tissue to protect the recurrent nerve and two parathyroids on the side of least disease.

It is not popular with others, however, because it leaves very little scope for the safe removal of the remaining thyroid tissue in the event of subsequent local recurrence at that site.

The operation generally referred to as lobectomy entails the removal of the dissected lobe, usually with some part of the thyroid isthmus, and is therefore in essence a hemithyroidectomy.
A description of this procedure follows and, as total thyroidectomy is simply a double hemithyroidectomy, it will not be discussed.

**Lobectomy**

With the anaesthetized patient in the supine position, and the head and neck fully extended, a collar incision is made from one side of the neck to the other above the hollow of the suprasternal notch.

To facilitate access to the upper pole of the gland, the incision should not be too low and by setting it above the hollow between the two sternal heads of the sternomastoid muscles, a bow-string effect in the scar can be avoided.

It is deepened down to the deep cervical fascia but, thereafter, access to the gland may be obtained in one of two ways.

For the beginner and in cases of a large goitre, division of the deep cervical fascia transversely with ligation of the anterior jugular veins followed by division of the strap muscles in the same axis is the easier option.

The alternative is to divide the deep cervical fascia vertically in the midline and then to free the deep surface of the strap muscles from the underlying gland, retracting the straps in the process. Access by this method is usually a little more restricted and is more suitable for smaller goitres.

Once the thyroid gland has been sufficiently exposed by lateral retraction of the strap muscles, the lobe is displaced medially and forwards by the assistant, and the common carotid artery identified and then retracted laterally.

The object is to create enough space between the carotid and the gland for the identification and isolation of the inferior thyroid artery, which should be divided as far away from the gland as possible to avoid the recurrent laryngeal nerve. The artery is in fact an important surgical landmark because of its intimate relationship to the recurrent laryngeal nerve, and provides an accurate indication of the depth at which the nerve should be sought. Where the artery enters the gland is one of two points at which the thyroid lobe is tethered posteriorly, the other being the ligament of Berry. Hence division of the artery facilitates the forward and medial mobilization of the thyroid lobe.

An attempt is now made to find the recurrent nerve below the inferior thyroid artery and at a corresponding depth. It lies in loose fibroareolar tissue and can be felt as a cord even before it comes into view.

On the right side it passes obliquely from lateral to medial as it approaches the inferior thyroid artery, but thereafter it lies in the tracheo-oesophageal groove. The nerve either passes deep to, or superficial to, or between the terminal branches of the inferior thyroid artery, this last arrangement being the most common finding on the right.
On the left side, the nerve lies in the tracheo-oesophageal groove throughout its entire passage, and crosses behind the artery more often than in front of it or between its branches.

After identifying the nerve, attention is turned to the inferior thyroid veins which are isolated and ligated in turn, and then to the superior thyroid vascular pedicle which is divided as close to the gland as possible to avoid the external laryngeal nerve.

Once all the principal vascular channels have been secured, the surgeon can mobilize the thyroid lobe off the recurrent laryngeal nerve. This is done by releasing the extension of the surgical capsule which passes back from the posteromedial surface of the thyroid lobe to the prevertebral fascia, working from below upwards and dividing this fascial attachment in a plane just superficial to the nerve. The point of greatest adherence between the nerve and the thyroid gland is in the condensation of the surgical capsule which tethers the thyroid lobe to the trachea and to the prevertebral fascia, namely the ligament of Berry. This is the area where the nerve is at most risk since forward traction on the gland pulls the nerve anteriorly with it.

During the process of freeing the thyroid gland from its posterior attachments and from the nerve, every effort should be made to find the two parathyroid glands. The upper is generally found on the posteromedial border of the thyroid lobe, at the level of the pharyngo-oesophageal junction. It is nearly always placed alongside a pad of fat which is separate from the gland, and its feeding vessel is the upper branch of the inferior thyroid artery.

The lower is usually found a short distance from the lower pole of the thyroid and is more anteriorly and medially placed than the upper parathyroid, and therefore closer to the trachea. It too is attached to a pad of fat and is nourished by the inferior thyroid artery by way of its lower branch. Both parathyroids appear as flat, brown, pear-shaped structures, with one sharp edge, and are freely mobile when displaced. They are extremely vulnerable and must be handled very gently.

Once the thyroid lobe is freed from the side of the trachea, it is lifted forwards and medially to mobilize the isthmus of the gland, which is then transected just beyond the midline. After suturing the cut edge of the remaining isthmus with catgut the wound is drained and closed in layers.

Postoperative management

After a total thyroidectomy the serum calcium is estimated daily to detect hypocalcaemia, but if signs of tetany appear, calcium gluconate is given by mouth or, if a rapid effect is required, by intravenous injection. At a later stage the degree of hypocalcaemia is reviewed and a decision taken as to the need for vitamin D₃ supplements.

Patients who undergo lobectomy are prescribed thyroxine in a dosage between 0.1 and 0.3 mg daily, and the effectiveness of suppression of TSH output assessed later, by injecting TRH and estimating the level of TSH in the blood; those who are maximally suppressed by an effective dose of thyroxine will not show a rise of TSH.
By contrast, patients who have undergone total thyroidectomy and who are likely to receive radioiodine are denied replacement therapy for 3-6 weeks to allow their TSH levels to rise before ablating any residual thyroid tissue with radioiodine. It is usual to scan the patient immediately before the administration of the isotope to show the site and extent of the remaining thyroid tissue.

Once ablation with the isotope has been carried out, thyroxine is prescribed long term and is only discontinued for short periods before future diagnostic scans, at which time the serum thyroglobulin is also estimated. The need for repeat treatment with radioiodine is judged on the findings of each scan.

### Complications

Recurrent nerve paralysis is an unlikely complication after lobectomy or total thyroidectomy when disease is purely intrathyroidal. It is generally due to excessive traction, rough handling, coagulating vessels to close together, or catching the nerve in a ligature.

Paralysis is likely when disease has escaped from the gland and abuts against the nerve or when a cancerous paratracheal node is stuck to it. Attempts to peel neoplastic tissue off the nerve sheath are unrewarding; they contribute little to clearance of the disease, and they are likely to paralyse a nerve which hitherto may have been functioning.

Under such circumstances a decision has to be made as to whether or not to dissect out the contralateral nerve, in view of the probability that the nerve on the diseased side is likely to be non-functional.

Unilateral nerve paralysis may require a vocal cord augmentation procedure, either by the injection of Teflon or by the insertion of cartilage strips in the paraglottic space (Shaheen, 1984). Bilateral nerve paralysis is managed by immediate tracheostomy, and later if desired by a partial corpectomy and arytenoidectomy using the carbon dioxide laser (Shaheen, 1984).

External laryngeal nerve palsy is also more likely to occur when disease is extrathyroidal and, if present on its own, is expressed by the patient as a limitation in the register of the voice or an inability to sing. In conjunction with a unilateral recurrent nerve palsy, it manifests as a weak, breathy voice, and with a bilateral recurrent nerve palsy, as a severely compromised airway, although slightly less so than when a bilateral recurrent paralysis exists on its own.

Preservation of at least two parathyroids is necessary for the prevention of tetany, and care should be taken during a total thyroidectomy to identify as many of the glandules as possible. Finding them is never easy, but attention to the finer points of surgical anatomy and the use of the operating microscope generally yield dividends. If no glandule is found during the operation, the excised specimen should be inspected carefully and any parathyroid tissue which is considered to be free of disease is re-implanted into the patient. The value of such a manoeuvre is still the subject of debate, but nothing is lost by attempting it.