Report of the Consensus Development Conference on the Management of Differentiated Thyroid Cancer in the Netherlands

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A. INTRODUCTION

FOR several decades the management of differentiated thyroid cancer has been controversial. An international symposium was therefore held in Leiden, The Netherlands, 19 and 20 March 1987, to reach a consensus on the management of differentiated (papillary and follicular) thyroid cancer. Various diagnostic and therapeutical approaches and their respective rationales were discussed. On the first day a workshop was held and the discussion was guided by a slide presentation.†† This day was chaired by Dr. B. Cady; comoderators were H.A. Bruining, O.H. Clark, B.M. Goslings, S. Smeds, S. Taylor and C.J.H. van de Velde. The following day the invited speakers shared their different points of view with 160 participants from 13 countries, composed of surgeons, specialists in endocrinology and nuclear medicine and pathologists. Some of these points of view are embodied in the current issue of this Journal elsewhere. The goals of the meeting were to outline general ideas on the management of differentiated thyroid cancer and to set broad guidelines which indicate acceptable and appropriate management.

B. STRATEGIES IN DIAGNOSIS

The main question of this session was: how can patients with thyroid cancer be selected from among patients with nodular enlargement, without operating on all patients? Epidemiological aspects were not discussed in detail, but it was noted that the incidence of anaplastic thyroid cancer is declining to less than 10%. This is probably not the case in areas with iodine deficiency.

Between 80% and 90% of thyroid cancers are either papillary or follicular. The relative proportion of these two tumours is influenced by the level of iodine intake in the population. With normal and high iodine intake 60–70% of all thyroid cancers are papillary (including mixed papillary and follicular types) and approx. 20% are pure follicular tumours.

About 65% of patients who have thyroid cancer present with a single (cold) nodule. In most other cases the nodule is either not solitary because the tumour is advanced, or has developed in a multinodular goitre or the malignant nodule is not cold but indifferent or rarely even hot. About 25% of young patients with papillary cancer present with regional lymph node enlargement, whereas this is unusual in older patients. Children have clinically palpable nodal involvement in the majority of cases. In patients with follicular carcinoma the presence of bone or lung metastases may cause the first symptom. Although the chance of cancer is very small in so-called 'classical multinodular goitre' (CMNG), i.e. a goitre of long duration with little or no progression, which usually occurs in females and is often familial, the possibility of cancer should certainly not only be considered in solitary nodules. A

thyroid gland with multiple discrete nodules has a higher incidence of cancer than CMNG. Differentiated thyroid cancer may occur concomitantly with, and rarely even cause, hyperthyroidism, but is practically never seen in combination with hypothyroidism. Most of the participants believed that thyroid cancer in an irradiated gland behaves similarly to that in non-irradiated glands. The diagnostic evaluation differs, however, because of the multifocal nature of cancer in the irradiated gland and because of the high incidence of cancer in patients who have a thyroid nodule.

The medical history and physical examination are important in raising the suspicion of cancer in case of (for instance) a fixed tumour, the presence of lymph node enlargement, paralysis of a recurrent laryngeal nerve, rapid growth without pain, previous neck irradiation and male sex. Laboratory investigations are not very helpful in the differential diagnosis of nodular goitre. A screening test for thyroid function should be performed in order not to miss an unexpected hyper- or hypothyroidism. The most cost effective test nowadays is a sensitive TSH assay. One should bear in mind that an undetectable TSH level does not rule out the possibility of cancer. An ESR is useful in diagnosing a subacute thyroiditis.

Some tumours can only be diagnosed by thorough histological examination, 'the gold standard' for the diagnosis of thyroid cancer. Different scintigraphic techniques, ultrasonography and fine needle aspiration biopsy (FNA) are being used as screening tests in the selection of patients for surgery. The sensitivity and specificity of these tests determine whether a test is useful in this regard. The predictive value of a test is of course also dependent on the prevalence of cancer, which may vary in different populations. The specificity of technetium and iodine scans is very low (particularly when the more sensitive discrimination level of cold and indifferent versus hot is used). The participants generally felt that these scans contribute very little in the differentiation between benign and malignant tumours in patients with nodular thyroid disease. Thus, in solitary nodules with a prevalence of cancer of approx. 10%, little is gained from a technetium or iodine scan or ultrasonography. The 10 mHz real-time ultrasonography is useful for quantitating the size of the tumour in patients, who will be treated non-operatively. Some additional remarks are necessary. A 201-thallium scan may provide information with an accuracy that is comparable to FNA cytology. It is not yet clear if this information is additional and can be used to discriminate between malignant and benign disease in case of 'suspicious' cytology. The principle of 201-thallium scintigraphy is based on the fact that 201-thallium resides in malignancies longer than in normal thyroid tissue.

Still, it is questionable whether it can differentiate between follicular adenomas and carcinomas. At this moment the use of a 201-thallium scan in combination with or instead of FNA seems to be equivocal and more experience is needed. Some participants, particularly those that work in iodine deficient areas, would prefer an iodine scan instead of a thallium scan in patients with a 'suspicious' FNA diagnosis in order to recognize benign hyperfunctioning nodules. The sensitivity of FNA is about 90% when 'malignant' and 'suspicious' diagnoses are both considered as a positive test result. For this discrimination level the specificity is about 70–75% and the positive predictive value for carcinoma in the solitary nodule will consequently be about 30–35%. This means that cancer will be found in one out of three operations instead of one out of ten when all solitary cold nodules are operated on. By performing FNA cytology routinely in any suspicious nodular goitre one also diminishes the chance of missing a carcinoma not presenting as a solitary nodule. However, the sensitivity is lower when multiple nodules are present in the thyroid; behind a large benign nodule a small cancer may be hidden. The determination of malignancy in patients with follicular tumours is very difficult by FNA. The chance of cancer with a 'benign' diagnosis by FNA is approx. only 1%.

There was no consensus of opinion on who should perform the FNA biopsy: the cytopathologist, the endocrinologist or the surgeon. To avoid sampling errors it seems logical to choose the clinician, who is most experienced in palpating thyroid glands. The expertise of the cytopathologist in the difficult field of thyroid cytology is of course of utmost importance and any department that wants to introduce this technique should seek after its own sensitivity and specificity and use FNA on that basis. When an inadequate specimen is obtained the FNA should be repeated.

The participants *unanimously* felt that patients with clinically suspicious tumours should be recommended surgical treatment regardless of the FNA diagnosis. FNA might be useful in clinically suspicious tumours in obtaining additional information, like the type of tumour (e.g. medullary thyroid cancer, metastatic disease, lymphoreticular malignancy). In these cases another diagnostic and therapeutic strategy can be more appropriate. For this purpose immunohistochemistry on cytologic preparations should also be performed. The risk of unnecessary (doctors) delay of treatment in patients whose goitre is clinically suspicious for cancer, but is considered benign because of false-negative FNA, is unacceptable.

Figure 1 shows the proposed strategy for the evaluation of thyroid lesions. It is based on calculations that are applicable in certain countries: a
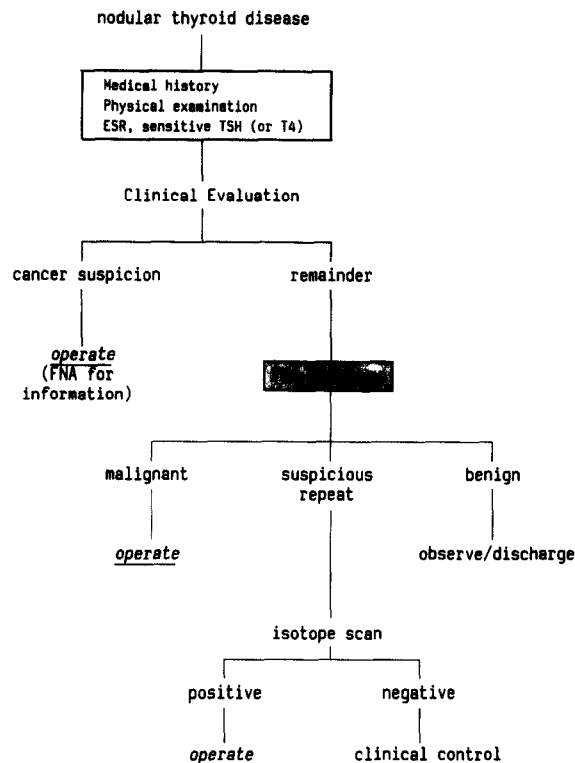
nodular thyroid disease
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┌─────────────────────────┐
│ Medical history         │
│ Physical examination    │
│ ESR, sensitive TSH (or T4) │
└─────────────────────────┘
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|
Clinical Evaluation
|
┌────────────────────┴────────────────────┐
cancer suspicion   remainder
| |
operate
(FNA for
information)
|
┌──────────────┼──────────────┐
malignant   suspicious   benign
               repeat
| |
operate   observe/discharge
               |
           isotope scan
               |
       ┌───────┴───────┐
    positive   negative
       | |
   operate   clinical control

Fig. 1. Diagnostic strategy in nodular thyroid disease.

non-iodine deficient area and advanced medical care. The proposed strategy is also chosen because of its cost effectiveness.

C. STRATEGIES IN TREATMENT

I. Surgery of the thyroid

Minimal procedure. Hemithyroidectomy (total lobectomy + isthmectomy) was generally accepted and recommended as the minimal operative diagnostic procedure for unilateral thyroid disease. Because hemithyroidectomy in average hands can result in morbidity and because most thyroid nodules are benign, one may locally resect small anterior nodules or nodules in the isthmus; vital structures should thus not be more exposed to risk at a possible secondary operation, since they were not exposed at the initial operation. If the frozen section, which should be performed in these cases, shows malignancy, the total lobectomy or total thyroidectomy should be completed in the same session. However, a follicular carcinoma with minimal capsular and/or vascular invasion is often not recognized at frozen section and paraffin sections are sometimes inconclusive even after five tissue blocks. Most participants felt that in those cases of so called 'minimal invasive' follicular cancer further surgery is unnecessary and the initial (diagnostic) lobectomy can be considered as the definitive procedure.

Occult cancer. In the literature the term 'occult cancer' is often not defined. In this symposium 'occult' was defined as a cancer that is removed incidentally during a thyroidectomy for another problem and is discovered during microscopic examination (e.g. after subtotal thyroidectomy for hyperthyroidism or surgery for CMNG with local symptoms). Clinical cancers less than 1 cm in diameter were defined as 'minimal cancers'. The group accepted that no further surgical treatment is necessary for patients with papillary thyroid cancers less than 1 cm in diameter, confined to the thyroid gland and without signs of metastases.

Technical aspects. In the literature there are no definitions with regard to the extent of thyroid surgery: what is a total lobectomy/thyroidectomy (TL/TT), a near-total lobectomy/thyroidectomy (NTL/NTT), a subtotal lobectomy/thyroidectomy (STL/STT). During the workshop the following definitions were maintained: TL: removes all thyroid tissue on one side; NTL: leaves as much tissue behind as needed to protect vital structures on one side, usually 1 to 2 g; STL: leaves at least a thumbtop amount of thyroid tissue and a complete recurrent nerve exploration is not mandatory (in contrast with the two previously mentioned procedures). The participants agreed that there is no advantage in doing a NTT over a TT; NTT does not carry a lower morbidity than TT. Only if thyroid tissue grows under the recurrent nerve or when it is necessary to leave a little tissue to protect the parathyroids should a NTT be performed.

With regard to the preference for a TT, two additional aspects were discussed:

1. [131]I therapy: When ^{131}I is considered for postoperative scanning or therapy, more extensive surgery is desirable, but not always required. The attending nuclear medicine physicians accepted less than total thyroidectomy for the use of [131]I. Dr. Goolden even felt that it is easier to destroy an entire thyroid lobe than a small remnant. Generally it was accepted that NTT and STT are sufficient, and TT is not needed, when ^{131}I ablation therapy for a thyroid remnant is given. However, subsequent ^{131}I therapy might be needed to ablate possible micrometastases or to treat clinically evident metastases.

2. Follow-up and the use of thyroglobulin (Tg) measurements: Most of the participants agreed that TT is desirable for the use of Tg in the detection of recurrent disease, but certainly not necessary. Serum Tg levels should be undetectable after TT, unless there is persistent or recurrent disease. Tg levels are detectable in patients who have had partial thyroid resections, but the somewhat higher discrimination level for

recurrent disease does not impede the timely detection of recurrent disease.

Conclusion. The argument suggesting that TT must be done in order to use Tg or ^{131}I did not seem to be accepted by many of the participants during the symposium. The only remaining reason to perform TT (and to give ^{131}I) is to remove all possible tumour foci. The question whether this leads to better survival is not resolved by the studies now available. TT (or NTT and STT + [131]I) increases the sensitivity and specificity of the Tg measurements and of ^{131}I total body scan: recurrent disease can be detected earlier and this may improve the outcome for the patient.

If at the time of operation the excised lobe contains a malignancy and if the surgeon is familiar with the TT, most participants felt that a TT is the optimal operation. When the thyroid malignancy is discovered after the operation, it is only necessary to reoperate when the tumour is over 1 cm in size, at the margin, invasive or has local or distant metastases. The definite histology should be available within a week after the first operation, because after this period the risk of surgical morbidity in a second operation is higher. It was *uniformly accepted* that TT is desirable, but not required, for many patients. The morbidity determines the procedure and a surgeon should not feel pressed to do a TT, when uncomfortable with this procedure and when the tumour is limited.

II. *Lymph node surgery*

It is well known that most patients with differentiated thyroid cancer, especially of the papillary type, have lymph node metastases to some extent at diagnosis. Dr. Noguchi (Japan) showed that up to 90% of the patients with papillary carcinoma had at least microscopical lymph node metastases at diagnosis. Despite this finding, it is generally accepted in the literature that there is no place for routine prophylactic neck dissection for patients with papillary thyroid cancer and the classical radical neck dissection has been replaced by a modified version. One should distinguish between the lymph node involvement in the central neck (between carotid arteries, from thyroid cartilage to superior mediastinum and down along the tracheoesophageal groove) from that in the lateral neck. None of the participants felt the need to split the sternum to explore the superior anterior mediastinum routinely. Some surgeons remove the lymph nodes and all fatty tissue in the central neck routinely at the risk of devascularization of the parathyroids (central neck dissection is especially important for patients with medullary thyroid cancer). Most participants felt that careful examination of the central neck is sufficient to exclude that there are tumour contain-

ing lymph nodes in that area. The influence of lymph node metastases of papillary carcinoma on survival is minor. There is no need for *en bloc* dissection, because lymph node metastases of differentiated thyroid cancer rarely implant in the surgical field and seldom extend beyond the lymph node capsule, in contrast with squamous cell carcinomas of the head and neck. Multiple involvement of lymph nodes in the lateral neck should preferably be treated by modified radical neck dissection, which removes all fatty tissue and lymph nodes with preservation (when permitted by tumour growth) of the sternocleidomastoid muscle, the internal jugular vein and the vagal and spinal accessory nerve. A suprahyoid dissection is usually unnecessary unless the highest nodes are involved with tumour. The submanidubular triangle is not included in the dissection. A modified radical neck dissection can easily be done, concomittant with or separately from the total thyroidectomy, through an extension of the Kocher's incision with minimum cosmetic deformity or postoperative morbidity.

Conclusion.

● In case of lymph node metastases of follicular carcinoma a modified radical neck dissection is the treatment of choice.

● Local excision or node picking is an acceptable procedure in cases of papillary cancer with limited involvement and central neck disease, but a modified radical neck dissection should be done if there is clinical involvement of the lateral cervical lymph nodes.

III. *Extensive procedures*

When there is extensive central neck disease with tumour extending into the surrounding structures, extensive primary operations are recommended. Resection of a small part of the oesophagus or a tracheal ring in order to remove all tumour is occasionally advisable. Laryngectomy at the primary operation is not recommended. When the larynx is extensively involved, surgery will not be curative and treatment with ^{131}I or external irradiation therapy is preferable. Eventually, as a secondary procedure, a laryngectomy is rarely indicated.

IV. *Additional* [131]I *treatment*

Follicular as well as papillary cancers show a great variability in ^{131}I uptake, but in principle both types are amenable to ^{131}I treatment. After a postoperative ^{131}I scan for identification of remaining thyroid tissue, ^{131}I is used therapeutically to ablate remaining normal or neoplastic thyroid tissue and to detect and treat distant metastases. Although the routine use of ^{131}I for these purposes is a safe

procedure, not all participants felt that ^{131}I is needed in all patients. It was agreed that an ablation dose of ^{131}I is also useful for the early detection of occult distant metastases, which are more common in follicular carcinoma than in papillary carcinoma. It is well known that the presence of distant metastases impairs prognosis. Four independent variables determine the usefulness of ^{131}I therapy: functional activity of the tumour, age of the patient, size of the metastases and histological type. Patients with clinically occult metastases (i.e. only visible after high dose ^{131}I) have a better prognosis than those with macro-metastases when treated with ^{131}I. Young patients can be successfully treated with ^{131}I in the majority of cases, but the success rate is lower in older patients. If the metastases in the latter show uptake of the isotope, it is still useful to treat these patients with ^{131}I. Well differentiated tumours do take up more ^{131}I than less differentiated subtypes.

It was concluded, that ^{131}I treatment following thyroidectomy may be curative when there are microscopic metastases and is often only palliative for patients with macro metastases. It is more effective in young patients. It should therefore be given to all patients with follicular carcinoma and also to patients with advanced papillary cancer.

V. Prognostic factors

The role of prognostic factors in guiding therapeutic decisions is becoming more important in this field of oncology as in others. Several prognostic factors have been identified: the patient-related factors age and sex; and the tumour-related factors tumour stage and histological (sub) type. In the literature there is a difference of opinion over the relative importance of these factors, especially in the age factor. Most participants agreed that there is not much difference in survival between the sexes, but some studies suggest men have a worse prognosis. In univariate studies age is the most single important risk factor. However, in recent multivariate analyses the importance of age as a prognostic factor is declining and the general thought among the participants of the workshop was that stage of disease and marked histological atypia now appear to be more important factors than age and sex. Nevertheless, because tumour stage is related to age, there is a worse prognosis with increasing age. The older the patient at the time of diagnosis, the sooner he dies of thyroid cancer. Children in their first decade also have a worse prognosis than older children and young adults.

Generally the participants felt that treatment on the basis of prognostic factors, especially the patient related factors, should be handled with care (only five participants treated their younger patients more conservatively). If one treats younger patients more

conservatively than older patients, one undertreats some of the younger patients. Differentiated thyroid cancer should be considered as a potentially lethal disease, also in young patients.

The influence of aneuploidy of DNA on survival is an interesting area of research and several studies have shown that patients with aneuploid tumours have a worse prognosis than patients with diploid tumours. It is not yet clear how this factor will fit in the order of influence on prognosis; further study is necessary.

VI. Therapeutic guidelines

Before the guidelines for therapy were determined it was stated that about 80% of the patients with differentiated thyroid cancer will do well, regardless of what therapeutic activity is undertaken. Another 5% die whatever effort is employed. Only 15% will be helped with more aggressive treatment, which is optimal only if it can be done without consistent harm to the patient.

General agreement existed on the *acceptable* approach:

● Hemithyroidectomy in case of:

(a) Papillary cancer, well-differentiated, confined to one lobe, without extrathyroidal growth, no or only lymph node metastases on the side of the tumour (peroperative examination) and no distant metastases; irrespective of age.

(b) Follicular cancer, well-differentiated, confined to one lobe, minimal capsular invasion, no lymph node metastases (peroperative examination) and no distant metastases.

● Total thyroidectomy + ^{131}I ablation in all other cases.

When a surgeon is familiar with the technique of TT and is able to perform the procedure without morbidity, some patients appear to receive additional benefit from this operation. When such experienced surgeons are available, TT may be the *optimal* rather than the occasional or *acceptable* operation. A surgeon should never feel compelled to do a TT when it will result in morbidity. In such cases a NTT or lesser procedure should be performed and the remnant ablated with ^{131}I. Postoperative treatment to suppress serum TSH levels is useful after any type of thyroid resection for differentiated (papillary and follicular) thyroid carcinomas.

When the participants were questioned about what thyroid surgery they preferred:

±25% recommended hemithyroidectomy for papillary thyroid cancer between 0.1 cm and 2.5 cm in diameter.

±75% preferred a total thyroidectomy when the tumour was more than 1 cm in diameter.

The lymph node surgery and the indications of

[131]I were uniformly accepted as stated in the paragraph concerning the subjects in this report.

D. CONCLUDING REMARKS

Differentiated thyroid cancer does not lend itself to strict management guidelines. Little harm results from hemithyroidectomy for unilateral papillary and follicular thyroid cancers and hypoparathyroidism is avoided. Surgeons inexperienced with total thyroid resection should not feel pressed to perform this procedure, since in such circumstances there will be a high complication rate with minimal improvement in survival. The majority of the participants felt that in experienced hands total TT is the optimal procedure. Especially Dr. Cady disagreed with the routine use of total thyroidectomy and additional ^{131}I treatment. Postoperative hypoparathyroidism in young patients is probably much worse than leaving microscopic thyroid cancer since the latter can be successfully treated with [131]I. Even the strong proponents of routine TT stated at this meeting that, in cases of low grade cancers when there is minimal capsular invasion, they do not perform a TT in all patients. Moreover, they do not hesitate to leave some thyroid tissue behind, when they are concerned about the blood supply to a parathyroid gland. They prefer to use ^{131}I to ablate the residual thyroid tissue in these patients to clean the area (parathyroid glands that have an impaired vascularization should be autotransplanted). Cooperation between the surgeon and the pathologist is very important for proper selective treatment of patients with differentiated thyroid cancer.

Until a prospective randomized trial is done, there will continue to be controversy concerning the most appropriate treatment of patients with differentiated thyroid cancer.

SUGGESTED FURTHER READING

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