

Thyroid Cancer Recurrence

Wally Patching Memorial Lecture, May 15, 2005
given by Irving B. Rosen, M.D.

In 2004, the Board of Directors of the *Canadian Thyroid Cancer Support Group (Thry'vors) Inc.* announced the creation of the annual **Wally Patching Memorial Lecture** to honour one of our most vibrant and determined founding members and to help contribute to his vision of improved Canadian thyroid cancer patient information, support and access to qualified thyroid cancer specialists. The first memorial lecture was given on May 14th, 2005 in Ottawa by Dr. Irving B. Rosen.

Wally was diagnosed with a rare and aggressive variant of papillary thyroid cancer in 1998 at age 58. At the time of his diagnosis, his cancer had already spread beyond his neck and he died in January 2004. Wally often joked that being 'advanced' meant that he had a lot more experience on how to live while battling thyroid cancer. Wally and his wife Diane shared their experiences, strength and vision with Thry'vors members and their determination inspired us all.

Dr. Irving B. Rosen gave the first annual **Wally Patching Memorial Lecture** on the topic of Thyroid Cancer Recurrence. Dr. Rosen is currently an attending surgeon at Mount Sinai Hospital, Toronto, specializing in general, head and neck, and endocrine surgery. He is also Professor of Surgery at the University of Toronto where his research contributions deal predominantly with thyroid cancer, and his specialty is surgical oncology. Dr. Rosen helped to organize the early meetings to form Thry'vors, is a member of our medical advisory panel, and continues to be one of our most determined supporters.

Dr. Rosen kindly agreed to summarize the key points of his Patching lecture, contained in this file.



Diane & Wally Patching

On May 15, 2005 in the city of Ottawa at the Lakeside Hospital, I had the honour of delivering the first **Wally Patching Memorial Lecture** to members of *Canadian Thyroid Cancer Support Group (Thry'vors) Inc.* and the Thyroid Foundation of Canada, both of whom should be complimented on their energy and lay involvement in thyroidology. They show an ongoing interest in education in thyroid disease and in the **Thry'vors** case, they have a special consciousness of malignancies of the thyroid gland. Patricia Sharkey, who is a leading member of the **Thry'vors** and a patient of mine, has requested that I set down some of the points that were delivered at that meeting for publications in the **Thry'vors** newsletter. This I am most pleased and honoured to do.

Mr. Wally Patching was not known to myself in a personal way, but his widow Diane Patching supplied me with biographical information. In 1998 he was diagnosed with thyroid



cancer, and I am unaware of the extent of his initial problem. Five years later when he was aged 63, his wife Diane wrote an account of his illness in the *Thyrobuletin* (a TFC publication). Wally's disease was recognized as metastatic at the onset which proved persistent despite management. Further treatment became futile and unpleasant. Diane Patching stated to me that "even though thyroid cancer is often referred to by physicians as a good cancer or the best one to get, I strongly disagree. No cancer can be deemed good, even thyroid cancer." No one can disagree with those sentiments.

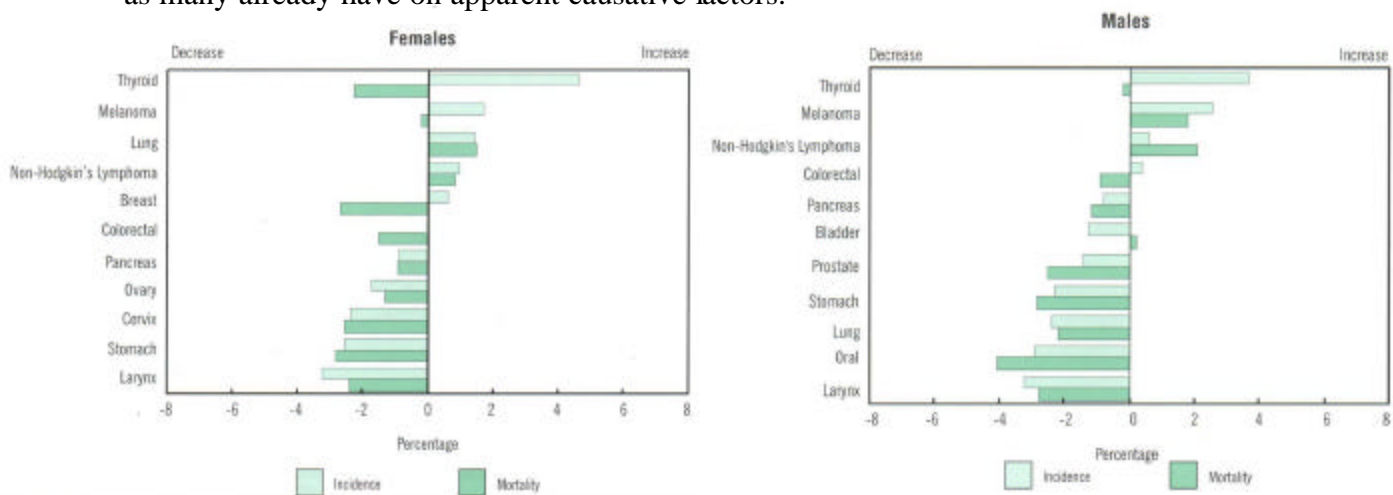
Recurrent cancer then is the hallmark of progressive disease and in itself makes a commentary on what many patients have decried, i.e. the medical doctor's over assurance regarding the "benign" nature of thyroid cancer. It was the recognition that both these features - recurrence

and the undue medical assurance - were germane that made me present these aspects as the main portion of my presentation.

ONCOLOGIC ASPECTS

Thyroid Malignancy

While thyroid nodules occur in about 50% of humans, the frequency of thyroid cancer is rare. An annual incidence of thyroid cancer on a worldwide basis has varied from one-half to 10 per 100,000 of the population. The Canadian Cancer Society statistics have indicated in the last 3 years that thyroid cancer is showing the greatest average annual percentage increase of any cancer in an age standardized incidence for both males and females alike. This increase has been noted world-wide. Why this is taking place is not scientifically clear although one can speculate as many already have on apparent causative factors.



Canadian Cancer Statistics 2004

Since 1945 and the explosion of the first atomic bomb on Hiroshima, the world has had to face up to living with ambient radiation and radioactive materials which make up the so-called nuclear age. The widening availability of radioactive isotopes for diagnostic and therapeutic uses in medicine as well as ongoing atomic power plants, atomic weapon testing and accidents such as the famous Chernobyl disaster that took place 20 years ago in the Soviet Ukraine make up our nuclear age. Nuclear accidents have occurred repeatedly over the decades. Thyroid tumours are especially an example of radiation contamination. Radiation at one time was used for such non-lethal conditions in the head and neck area as acne, eczema, fungus of the scalp, facial hair, blood vessel tumour, tonsillitis, adenoiditis, and tuberculosis adenitis. Radiation causes effects such as growth disturbance in children or radiodermatitis of the facial skin which were unpleasant, but worst, still, radiation caused characteristically thyroid cancer as well as other tumours and malignancies in the head and neck area. This radiogenic induction of thyroid cancer has altered medical practice. Radiation still persists as a factor because of x-ray management of malignancies elsewhere in the body or for those employed in the nuclear industry.

About 30 years ago, ultrasonography came into use in the management of thyroid nodular disease, due largely to the work of the Toronto Mount Sinai Hospital group of physicians. It was

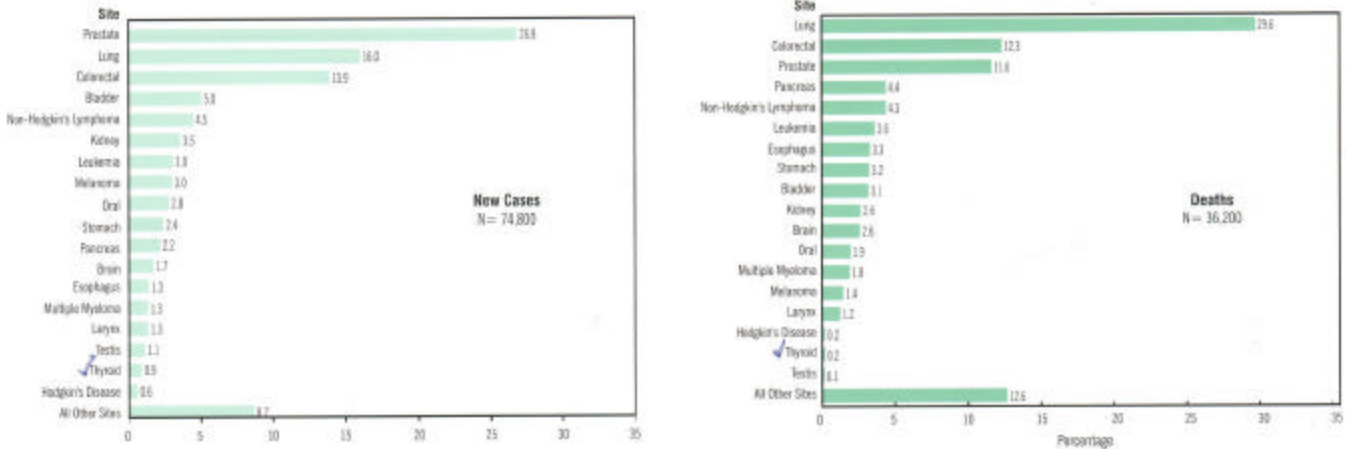
used to discriminate between solid and cystic thyroid lesions with the presumption of a benign nature for the cysts. Experience with ultrasonography demonstrated the frequency of false positives and negatives so that the use of this modality as a strict diagnostic feature for the nature of an underlying thyroid lesion is limited. Nevertheless, its current use has been expanding because patients who present with ill-defined complaints in the head and neck area are referred by their doctors for ultrasonography of the head and neck area which reveals a 50% frequency of thyroid nodular disease. Ninety per cent of these nodules are impalpable but nevertheless they demand diagnostic validation.

Fine needle aspiration biopsy (FNAB) was applied to tumours in the head and neck area primarily by Hayes Martin of the U.S.A. in the 1930s. After the Second World War its application to thyroid nodular disease was advocated by the Scandinavian workers. Twenty years ago its advantage was emphasized to North America by the Toronto Mount Sinai Hospital group who were working with thyroid disease. It has since been widely accepted resulting in unanticipated diagnoses of thyroid malignancy. Prior to FNAB, tumour diagnosis depended on clinical features. The use of nuclear scanning of the thyroid gland is still used, but its implication of a cold scan favouring neoplastic identity is of historical importance since it is not as precise as FNAB in the diagnosis of tumours. FNAB is not perfect since it can only sample a minute portion of a lesion so that repeated aspirations become part of patient management.

All these factors, namely radiation, the use of ultrasound, and the use of fine needle aspiration biopsy have presumably contributed to the increasing frequency of thyroid cancer. Other causes have not to date been defined.

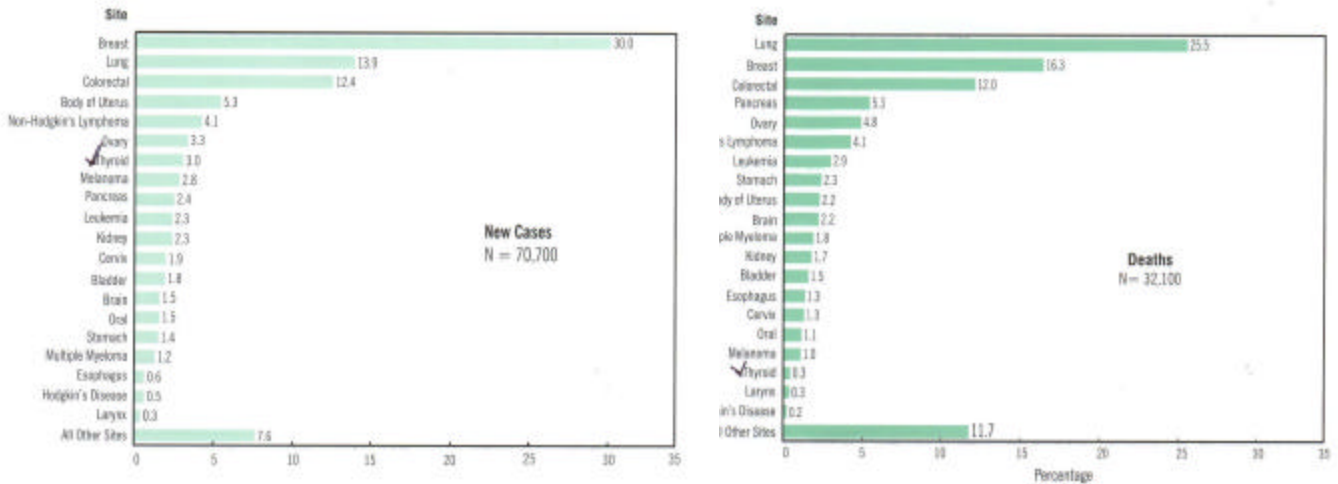
GENERAL ONCOLOGY

When one looks at the Canadian Cancer Society statistics, one has to recognize that thyroid cancer in males makes up 0.9% of all new cancer cases, while prostate at about 27%, lung at 16%, and colorectal cancer at 14% are far more frequent. Thyroid cancer results in .2% of



Thyroid Cancer in Males (2004)

all cancer deaths in males, while lung makes up 30%, colorectal cancer and prostate CA about 12% each of the male mortality. In females, thyroid cancer makes up only 3% of new cancers which is well ahead of such well known entities as melanoma, pancreas, leukemia, or Hodgkin's



Thyroid Cancer in Females (2004)

disease. In females, thyroid cancer makes up 0.3% of all mortalities due to cancer as compared to 26% for lung, 16% for breast or 12% for colorectal cancer.

Cancer curability can also be expressed as 5 year survival figures. Various malignancies can therefore be compared with thyroid cancer. Five year survival rates compiled from various sources can show the 5 year survival for nasopharynx cancer to be at 37 to 50%, ovarian cancer 46%, lung cancer 10 to 14%, colon cancer 50%, renal cancer 9%, breast cancer of the familial type with BRCA diagnosis 21%, pancreas <20%, oral cancer 28%, breast overall 60%, cervix 50 to 70%, prostate 60 to 80%, multiple myeloma 30%, bone 17 to 80%, endometrium or uterus 5 to 95%, bladder 0 to 50%. In comparison, thyroid cancer has a 95% survival rate over a 10 year period of time. It is these factors, i.e. the low frequency of thyroid cancer despite its recent reported increase and its lack of mortality in comparison to other malignant problems that has made physicians take an encouraging attitude when they deal with a patient stricken with thyroid cancer. Physicians are mindful of the terrible dread that will seize a patient's heart and mind at the mere mention of the word cancer, even thyroid cancer. They instinctively hasten to protect that patient from that terrible sense of anxiety by providing reassurance. While a mortality rate of 10% is of comfort to the patient with thyroid CA, it also means that a large number of surviving thyroid cancer patients must be followed for the possibility of recurrence.

FACTORS IN RECURRENCE

Little attention has been paid to recurrent problems in thyroid as a singular topic. Recurrence frequency is said to vary from 5 to 20%. Recurrent disease currently may be more easily diagnosed because of all the diagnostic techniques already mentioned. It is likely that in the past recurrences of a minor nature may have occurred undiagnosed which may not have biologically disturbed the patient as far as survival is concerned. While this is a moot aspect of the problem, it nevertheless deserves recognition. Attitudes towards recurrence may be influenced by the extent of recurrence. Small nodal or thyroid bed recurrent problems may be dealt with expectantly because of the widely acknowledged protean nature of thyroid cancer. My own personal feeling is that while temporization may be acceptable with a patient's debility, advanced age or some other adverse factor, recurrence should be vigorously treated. In Canada we are a resource-challenged medical community in which waiting times are a compelling issue. Resource unavailability may promote an attitude of temporization and conservatism in the face of what seems a less than urgent problem.

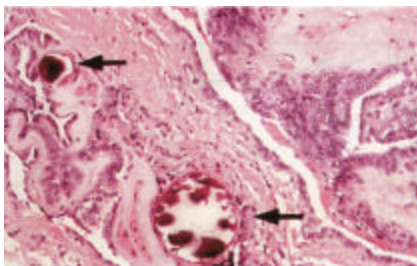
Prognostication of outcome has become an area of academic productivity with particular formulation of risk group classification criteria such as AMES, AGES, TNM, EORTC, MACIS, AJCC as well as individual institutional assessments. These analyses usually are carried out postoperatively and can influence one's attitude regarding postoperative treatment and surveillance. These acronymic criteria have an implication for recurrence and depend usually on patient age, tumour size and behaviour, treatment, and pathology.

The subsequent presentation is based on my experience with over 1000 cases of thyroid malignancy of which 94% were made up of well-differentiated cancers (i.e. papillary or

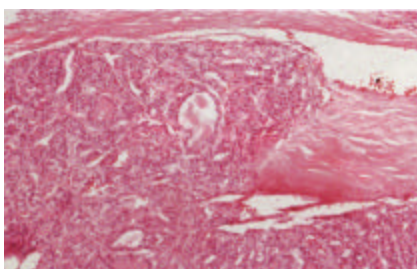
follicular). The recurrence rate in my group of patients comes to approximately a **5% level**, and one-half of these patients were referred after primary treatment elsewhere. The recommendations I make come from this experience, but it should be recognized that variations in attitude occur which make up part of the ongoing controversies that attend thyroid cancer. It is important that patients who have the risk factors cited which have a bearing on recurrence should not feel that the course of their illness is inevitably bad! That is not the case, and examples shall be cited to show the variations that occur in real life.

Recurrence in Dr. Rosen's Patients (1,105 patients, 5% recurrence)	
Sites of Recurrence	%
Primary	34
Node	84
Lung	25
Bone	13
Liver	2
Skin	2
Artery	1
Multiple	27

(1) TYPE OF THYROID CANCER

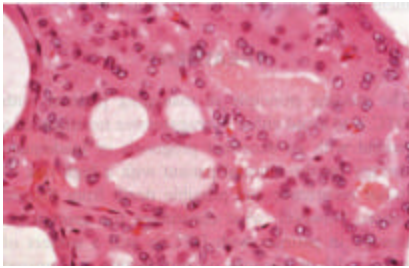


Papillary Cancer



Follicular Cancer

A doctor called a pathologist looks at the thyroid tissue specimen under the microscope and classifies it in various descriptions conforming to accepted standards. Papillary carcinoma, the commonest, has an excellent outcome, but there are infrequent variations such as tall cell, insular, schirrous, and columnar cell variants which have a higher recurrence rate. Follicular thyroid carcinoma, a well-differentiated CA, has a worse outlook than papillary because of its tendency for vascular invasion and systemic metastases. Hürthle cell cancer has a unique appearance being made up of rather large pink-staining cells which has an ambiguous identification as a high risk malignancy. Hürthle cell malignancy, which may not be an entity unto itself but merely a variant of other cancers, emerges as one which also favours the possibility of recurrence. Medullary cancer arises from the parafollicular cells and has a genetic identity and can be associated with other endocrine malignancies which have an overall poorer outlook than the usual Papillary. Anaplastic cancer is the worst malignancy that



Hürthle Cell

occurs usually later in life sometimes in an explosive fashion and is usually incurable and fortunately is decreasing in incidence so it is now viewed as a rare problem. The grade of cancer, i.e. the degree of differentiation, is rarely reported but also influences outlook.

(2) EXTENT OF CANCER

The extensiveness of a malignancy and its relationship can also be a signal for anticipated post-treatment problems. A cancer that invades outside of the thyroid gland involving strap or esophageal muscles, nerve, or the windpipe or trachea has an increased tendency for recurrence. Where a tumour is greater than 3 to 4 cm. in size, then one can anticipate increased tendency for recurrence. Microcarcinoma which is under 1 cm. in diameter has not a dissimilar frequency of recurrence as the larger forms, but is distinctly unassociated with a lethal outcome. Where cancer occurs in more than one site, namely multifocal disease (MFD), one does anticipate the possibility of increased recurrence although that has not been our own experience. MFD supports the strong partisans of total thyroidectomy. Where cancer has travelled to lymph nodes particularly in the lateral neck, this is generally thought to show a higher recurrence but is reported to be unassociated with lethality which is rather peculiar since recurrence is a factor in a lethal outcome. The frequency of metastatic microcarcinoma of regional nodes occurs frequently in papillary cancer, but no consensual support for active surgical treatment has been settled -- which is testimony to its low lethality. Once cancer travels to more distant sites such as bone, lung, skin or liver, which is **infrequent**, then one can anticipate a much more challenging problem in response to treatment and total control.

(3) PATIENT FACTORS

Age is considered to be the most significant risk factor for recurrence which increases along with mortality linearly particularly after age 40, 45, 50 or 60 years depending on different reported analyses. Age appears to favour less differentiated forms of malignancy, less tolerance of extensive disease. If there is, as well, patient ill health, avoidance of more extensive operative procedure occurs. The male gender has been reported to be an independent poor risk factor in some series but not in all. It is generally conceded that while females may be affected by more thyroid nodular disease than males, that the frequency of cancer is higher in males and appears to be somewhat more serious in the male case. Again, this has not been our experience.

Thyroiditis occurs as an inflammation of the thyroid gland and its relationship to malignancy has been studied. Thyroiditis may give rise infrequently to a lymphoma of the thyroid gland which represents a pathological subtype which has a greater recurrence rate. Usually thyroiditis is unassociated with an adverse outcome in thyroid malignancy, and indeed in our experience was associated with a better outcome.

Invasion of blood vessels by thyroid cancer can usually occur without any dire outcome particularly in papillary cancer but in follicular cancer or the greater suspect pathological subtypes can signal recurrent outcome.

(4) TREATMENT FACTORS

While much controversy has prevailed regarding extent of surgery, it currently appears that complete tumour resection (total or near-total thyroidectomy) predicts a more favourable outcome especially if there is contralateral nodularity and permits the use of adjuvant radioactive iodine (RAI) treatment. RAI is frequently given in a tumour-destructive dose, and much evidence shows that this is superior in control to not giving RAI particularly in high-risk patients and which usually has little in the way of serious side effects. Where spread to neck lymph nodes exists in an obvious way, removal in a block, the so-called modified neck dissection is required. Failure to do this gives rise to recurrence and treatment failure.

DETECTION OF RECURRENCE

Recurrence can take place years after the initial treatment, and while it may be understandable in retrospect in view of the various factors cited, one must recognize that the human response to treatment may be quite successfully individual, in defiance of risk factors that have a ring of "scientific" authority. Several examples will be cited subsequently.

CASE 1 - Adverse Tumour Factors

A 60 year old female was seen 37 years after partial thyroidectomy and modified neck dissection for a lateralized 6 cm. extensive papillary carcinoma and secondary nodal cancer that was radiation-induced. There was no evidence of recurrent disease by examination and imaging on follow-up.

CASE 2 - Inadequate Surgery

A 50 year old woman was seen 31 years after partial thyroidectomy and modified neck dissection in which the opposite lobe was free of disease. At the time of her follow-up visit, there was evidence of extensive nodular disease of the remaining lobe and she required completion thyroidectomy for presumptive recurrence.

CASE 3 - Age Factors

An 85 year old woman was seen 31 years after a near-total thyroidectomy and modified neck dissection for a 10 cm. primary lesion with extrathyroidal invasion. At the time of her most recent visit, she was completely free of any recurrent problem with excellent voice and in good health.

CASE 4 - Systemic Metastatic Disease

A 50 year old male presented with hoarseness and thyroid cancer. At surgery, nodal metastases were adherent to the recurrent nerve and were dissected away along with total thyroidectomy. Post-op he showed a lung secondary which responded to RAI. He has been well, in good voice and cancer free for 4 years.

All these 4 cases taken from personal experience demonstrate the variation in response that can occur. Cases 3 and 4 in particular show patients who had a set of adverse biological factors, but by their own individual response to treatment showed a good outcome. Partial thyroidectomy at one time was historically highly acceptable and is still favoured in some centres as indicated for a localized lesion. While it can be effective as in Case 1, it does put the patient at risk for recurrence in the contralateral lobe, particularly where nodularity in some form already exists.

Recurrence of course can occur in various forms. Twenty per cent of recurrences occur in the thyroid bed itself; about 60 to 70% of neck recurrences affect lymph node tissue. Involvement of soft tissue such as the aerodigestive tract accounts for 10% of neck recurrences, and while infrequent, metastases to bone and lung also occur.

Post-primary treatment surveillance is important, requiring a thorough physical examination of the head and neck area to exclude local and nodal recurrence. This should be supplemented on an annual basis by ultrasonographic examination of the head and neck area. Where abnormal nodularity is felt to be present, then ultrasonographic FNAB should be carried out before any invasive procedure is contemplated. Where the patient has had some adverse problem such as pathology or extent of malignancy as a clinical behaviour that is aggressive, ultrasound should be supplemented by CT or MRI studies of both the head and neck and lung areas.

Thyroid tissue is the only source of circulating thyroglobulin (a thyroid hormone precursor), and while thyroglobulin may be elevated in conditions of benign thyroid disorder, its elevation on a sequential follow-up basis for cancer following total thyroidectomy is viewed as indicating recurrent cancer. Thyroglobulin levels are not increased in medullary or anaplastic thyroid cancer. The thyroglobulin therefore should be undetectable, generally less than 2 nanograms per millilitre. Where there is a concern for recurrence and thyroglobulin remains normal while taking thyroid hormone replacement, the clinician may consider the withdrawal of thyroid hormone to precipitate an elevation of thyroid stimulating hormone level which would provoke a thyroglobulin elevation as evidence of underlying recurrent thyroid malignancy.

Thyroid hormone replacement is mandatory where a near-total thyroidectomy has been carried out. Where a partial thyroidectomy has been carried out, thyroid hormone discourages the emergence of recurrent cancer. If the patient is taking thyroid hormone, then to establish whether the patient has a thyroglobulin elevation or to even administer radioactive iodine, thyroid hormone must be withdrawn which then produces a state of thyroid hypofunction which is highly uncomfortable for the patient. This can be overcome with the use of recombinant thyrotropin or Thyrogen. Taking recombinant TSH (rhTSH) stimulates radioiodine uptake in normal and abnormal residual thyroid tissue and can stimulate the production of thyroglobulin by both normal and abnormal thyroid tissue and does ensure greater comfort while all these manoeuvres are carried out. At the present time there is a fee for the purchase of rhTSH or Thyrogen which most insurance companies will permit at least on an annual basis. The use of Thyrogen has been highly accepted, and its precise incorporation in a paradigm of surveillance is yet to be determined.

Whole body scanning (WBS) is performed using 2 to 5 mCi of radioactive iodine in which the TSH has been elevated. The identification of radioiodine hungry tumour tissue identifies recurrent malignancy and permits its appropriate management. If there is any amount of normal thyroid tissue still remaining in the neck, then the TSH level will not be sufficiently high to permit radioiodine uptake by tumour or its uptake in the neck will prevent proper visualization of recurrence. Chest x-ray is carried out on an annual basis to possibly detect disease. Surveillance should be annual, perhaps biannually, with imaging being done annually. It may be that in the future sophisticated biological measures will provide an insight into possible recurrent situations.

MANAGEMENT OF RECURRENCE

(1) Surgery is frequently used for the management of recurrent disease particularly where it affects the contralateral lobe, thyroid bed or spread to neck nodes, and such recurrences usually are responsive and have a good outlook following treatment. Surgery can even be applied to metastatic sites such as bone and lung. These situations may be individualized. Here the primary lesion is usually controlled, and a secondary lesion of bone which is persistent presents a risk for pathological fracture, or severe pain, or where a lung lesion is solitary and not diffuse, which is unusual.

(2) Radioactive iodine is often used as adjuvant to a surgical procedure for recurrence providing that the patient has not had an excessive past dosage. Where there is evidence of recurrent disease as manifested by elevation of thyroglobulin (without demonstrable recurrence) or where the patient is in ill health and cannot tolerate surgical intervention or where there is diffuse secondary cancer involving bone or lung, then radioactive iodine may be the only effective treatment available.

(3) External radiation is infrequent and is reserved for the primary area for those malignancies that are inadequately removed, or have a poor pathological risk factor, or as adjuvant to primary recurrence removal, or in palliating diffuse metastatic symptomatic disease.

While the incidence of recurrence is remarkably low in thyroid cancer, there is no question that recurrence when it occurs must be taken seriously. Recurrence stereotypically affects the older patient with more aggressive cell type of tumour, and while outcome of any recurrence is not as good as the primary case, survival after treatment for recurrence is prolonged. Patients may have more than one episode of recurrence which demands appropriate management with the possibility of good control.

CONCLUSION

Patients may resent medical over-reassurance regarding the nature of thyroid cancer but it must still be recognized that thyroid cancer is indeed the "best type" of malignancy to have. If one looks at the other malignancies that affect mankind, thyroid cancer is a shining example in contrast because of excellent response to reasonable management. There is no other malignancy that can approximate the outcome of thyroid cancer. This does not mean that patient's concerns, questions and anxieties should be dismissed or treated in a cavalier fashion nor should one assume an overly pessimistic attitude when dealing with thyroid CA and its subsequent problems.

Surveillance should be set up on a periodic basis following the initial treatment and should be on a lifetime basis.

Duration of time after primary treatment before recurrences may be prolonged before their appearance and may be prolonged after their treatment. Surveillance and appropriate progressive interventions promotes excellent outcome. The results of recurrent treatment as a rule is well tolerated and does not incur some of the morbidity that one may see in the way of serious cosmetic derangement such as mastectomy, or profound deformities such as operations for oral cancer or malignancies of bone. Recurrence is an unwelcome but invariable feature of malignancy, but the treatment of thyroid cancer either primary or recurrent is highly effective and compatible with lengthy survival.

Thyroid cancer patients who are concerned with the quality of care must band together (as in the Thy'vors and Thyroid Foundation of Canada). They must be prepared to do volunteer work in counselling new patients in the positive aspects of thyroid cancer as well as the precaution in ongoing care. They should be advocates for innovations. They must address the problem of fundraising which is important in supporting innovative basic science research as well as improving the quality of Canadian networking. They must be prepared to present the patient's case to political figures and influential health figures. They must be prepared to raise the

consciousness of the Canadian public and medical profession to the concerns and needs of their own thyroid CA situation. I am conscious that Dr. Bob Volpé, known to so many, regrettably passed away unexpectedly just before the **Wally Patching Memorial Lecture**. There is no question that he always was a proud advocate for the cause of a better tomorrow for the thyroid cancer patient.