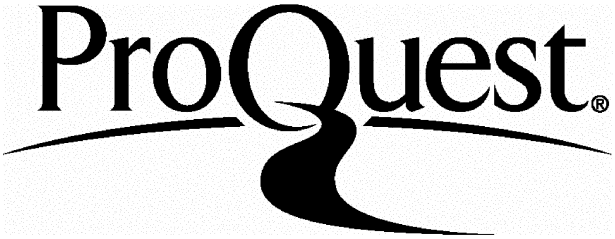
M.D. THESIS

TREATMENT OUTCOME AND RADIOIODINE DOSE-RESPONSE IN DIFFERENTIATED THYROID CARCINOMA

Mary E.A.O'Connell



TREATMENT OUTCOME AND RADIOIODINE DOSE-RESPONSE IN DIFFERENTIATED THYROID CARCINOMA

by

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A thesis submitted to the University of London
for the degree of Doctor of Medicine

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November, 1992.

ABSTRACT

Radioiodine (^{131}I) has been used to treat differentiated thyroid carcinoma for the past fifty years. The activity administered remains empirical and most clinicians prescribe a fixed activity for ablation and therapy based upon experience and likely side effects. This lack of tumour dosimetry contrasts sharply with planning for external beam radiotherapy where precise tumour-dose prescription is mandatory. Estimation of absorbed radiation dose delivered to target tissue has been largely ignored in the past partly beacuse of the difficulty in measuring that part of the target volume which is metabolically active. Where absorbed dose has been estimated there is no consensus as to what absorbed dose should be delivered in order to destroy thyroid remnants and metastatic lesions.

In order to calculate the absorbed radiation dose to those tissues which concentrate radioiodine, three parameters must be determined: the initial activity in the target tissue; the effective half-life of the radioiodine and the mass of tissue. Tumour and normal thyroid absorbed doses have been determined using a dual-headed whole-body scanner with special high-resolution low-sensitivity collimators. Improved accuracy in the estimation of functioning tumour mass has been achieved using positron emission tomography with a low-cost large area multi-wire proportional chamber camera, developed by the Physics Department of the Royal Marsden Hospital in collaboration with the Rutherford Appleton Laboratories.

Dosimetry studies were performed for 54 patients with differentiated thyroid carcinoma (40 papillary, 14 follicular). There were 39 females and 15 males, ages 22 to 79 years. Dose-response graphs have been constructed in order to determine the tumouricidal dose for differentiated thyroid carcinoma metastases and thus enable precise activities of radioiodine to be prescribed in order to maximise tumour kill and minimise morbidity. The clinical data demonstrate that the administration of fixed activities of radioiodine results in a very large range of radiation absorbed dose to residual normal thyroid tissue and metastases of differentiated thyroid carcinoma. Following near-total thyroidectomy and 3.0 GBq ^{131}I, a mean absorbed dose of 349 Gy achieved complete ablation of thyroid remnants in 67% of patients (73% of sites). Patients who had persistent uptake in the thyroid region on subsequent

radioiodine scanning had received a mean absorbed dose of only 80 Gy. Failure to ablate may be attributed to two possible factors: large residua following less than radical surgery and the presence of tumour in association with normal tissue. Radioiodine therapy appears to be most effective in destroying small volumes of tissue after optimum surgical cytoreduction. Moreover, when tumour remains in association with normal tissue, the results here indicate that a much lower concentration of radioiodine can be achieved. For these two groups of patients, higher activities of ^{131}I are indicated.

Successful destruction of cervical node metastases has been accomplished with absorbed doses of 150 Gy following functional neck dissection. Bone metastases, which are generally associated with a poor prognosis, require doses in excess of 100 Gy for eradication but this can be achieved for solitary deposits following initial surgical debulking. Nevertheless, worthwhile palliation may still be achieved with absorbed doses lower than this. However, the clinical data suggest that absorbed doses less than 20 Gy are sub-therapeutic and that alternative therapy should be considered if less than this can be achieved with radioiodine therapy.

The dose-response data explain the spectrum of clinical response to fixed activities of radioiodine. In future they will enable precise prescription of radioiodine to achieve tumouricidal doses whilst avoiding the morbidity, staff hazards and expense of ineffective therapy.

CONTENTS

ACKNOWLEDGEMENTS

I am indebted to Dr C.L.Harmer, Head of the Thyroid Unit and Chief of Radiotherapy Services,for permitting me to report on patients under his care and for continued encouragement and advice. I am especially grateful to Dr M.A.Flower of the Department of Physics, Institute of Cancer Research and Royal Marsden Hospital who initiated and supervised the radioiodine dosimetry studies in the treatment of differentiated thyroid carcinoma. I wish to thank Professor A.Horwich and Professor V.R.McCready for support and guidance. I also wish to thank Dr R.J.Ott, Dr Mary Saunders, Dr S.Webb and Professor G.G.Steel for helpful discussions and criticism.

I am greatly indebted to Mrs B.Cronin, Mrs B.Pratt, Mr J.Mundy and to all staff involved with clinical positron emission tomography (PET) imaging. I am most grateful to Sarah Chittenden for her help with calibration studies for the STARCAM gamma camera analysis. I gratefully acknowledge the assistance of the radiographers of the Nuclear Medicine Department for their helpful co-operation and for performing the STARCAM gamma camera studies (data acquisition only) on patients. I am most grateful to Dr David Cosgrove and Dr Chiara Bossi for performing mass estimates using ultrasound.

I am indebted to Roger A'Hern, Computing Department who performed the statistical analysis for the patient survival data. I thank Sue Jones, Pauline Cummings and Pam Drake of the Medical Records Departments at Fulham and Sutton who helped obtain patient records.

I am indebted to the Research Committee of the Royal Marsden Hospital for supporting me during this project. PET imaging with ^{124}I was made possible by funding from the Cancer Research Campaign.

Finally, I dedicate this work to the memory of my late parents
Drs Patrick J. and Lilian M.O'Connell.

STATEMENT OF ASSISTANCE RECEIVED

All clinical work was carried out at the Royal Marsden Hospital, Sutton during the appointment of the author as Clinical Research Fellow and Honorary Senior Registrar in the Academic Unit of Radiotherapy and Oncology at the Royal Marsden Hospital. All work was performed by the author herself unless otherwise stated.

Clinical positron emission tomography studies (data acquisition only) were carried out by Mrs B.Cronin and Mrs B.Pratt. Patient studies using the whole-body rctilinear scanner (data acquisition and analysis) were performed by Mrs B.Pratt and Mr P.J.Hinton of the Physics Department, Royal Marsden Hospital. Mr .Babich and Mr J.Mundy of the Radiochemical Laboratory, Royal Marsden Hospital were responsible for dispensing and measuring the radiochemical purity of [^{124}I]NaI for patients. Dr Chiara Bossi performed mass estimates of thyroid remnants using ultrasound.

The statistical analysis for Chapters 2 and 3 were performed by Mr R.P.A'Hern, Department of Computing and Information (The Royal Marsden Hospital).

ETHICAL CONSIDERATIONS

All patients taking part in the ^{124}I PET dosimetry studies did so of their own volition and on the understanding that the study did not form part of their treatment.

According to the procedure laid down by the Ethics Committee of the Royal Marsden Hospital, the nature and purpose of the study were explained to the patient in the presence of a witness. Both the witness and the doctor responsible for the study signed a statement that following a full explanation , consent had been freely given. This form was then filed in the patient's case notes.

The following study was approved by the Royal Marsden Hospital Ethics Committee:

Clinical evaluation of positron emission tomography: Protocol No.24.

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(abbreviated titles)

INTRODUCTION

The overall management of thyroid carcinoma is multi-disciplinary embracing surgery, radioiodine, endocrine therapy, external beam radiotherapy and chemotherapy. The Thyroid Unit at the Royal Marsden Hospital was created by Professor V.R. McCready in 1973 when the first "clinic" was held in his office at Sutton together with Dr Spathis and Dr C.L. Harmer. The original patients were referred for treatment of an overactive thyroid, the concept being multi-disciplinary care for an unpredictable disease which required the expertise of a Physician as well as Nuclear Medicine Specialist and a Radiotherapist/Oncologist. Professor Sir David Smithers had pioneered the use of radioiodine in the treatment of thyroid cancer during the 1940's, and treated the first patient in the United Kingdom with radioiodine in 1948 (Walton,1950). Dr Nigel Trott performed the early work on dosimetry in the Department of Physics at Sutton. Mr Greening had previously established a combined clinic at London and a further clinic was later established at St. George's Hospital, Tooting. The Thyroid Unit probably sees more new patients with thyroid cancer than any other centre in the United Kingdom and, because it is such a rare tumour, depends for its success upon the triple referral to these three sites. In addition, there is a large referral from abroad particularly from Malta and long-term follow-up of these patients is maintained with the referring clinician by providing routine serum thyroglobulin assay at the Royal Marsden Hospital.

Owing to the rarity of the disease and its long natural history, there are no randomised controlled prospective trials to evaluate different treatment strategies for differentiated thyroid carcinoma. However, useful information on prognostic factors as a basis for therapeutic decisions can be obtained from retrospective studies. The first part of this MD Thesis was thus to establish a data-base for the Thyroid Unit in order to analyse survival data and determine prognostic factors for 649 patients referred to a single major centre for treatment of differentiated thyroid carcinoma from 1949 to 1991. Survival curve comparisons were performed with the log rank test for univariate analysis and Cox proportional hazard model for multivariate analysis. A stepwise selection procedure with the Cox proportional hazards regression model was used to determine independent prognostic factors in multivariate

analysis. From this, a prognostic index was derived and four risk groups identified which divided patients into good prognostic groups and poor prognostic groups. In future, this prognostic index could be used to identify risk groups and help guide therapeutic decisions. In Chapter 3, the role of external beam radiotherapy is discussed with reference to the clinical results obtained in 113 patients who received radical-dose external beam radiotherapy at the Royal Marsden Hospital.

In the second part of this Thesis, the in vivo dosimetry of radioiodine (^{131}I) ablation of post-operative thyroid remnants and therapy of differentiated metastases are described. Absolute quantitation of absorbed dose has been performed using a dual-headed rectilinear whole-body scanner with special high-resolution low-sensitivity collimators. A major problem with dosimetry studies in the past has always been the estimation of that mass which is metabolically active. This uncertainty in mass may explain the considerable variation in dose estimates for ablation of thyroid remnants given in the literature. Ideally this so-called "functioning mass" should be determined using a radionuclide technique. Where radionuclide techniques have been used, however, there is no consensus as to what absorbed dose should be delivered in order to destroy thyroid remnants and metastases from differentiated thyroid carcinoma. Improved accuracy in the estimation of functioning mass has now been achieved using positron emission tomography (PET) with a low-cost large area PET camera developed at the Royal Marsden Hospital in collaboration with the Rutherford Appleton Laboratories.

The activity of ^{131}I administered has remained largely empirical over the past fifty years and the policy at the Royal Marsden Hospital has been to give a fixed activity of 3.0 GBq ^{131}I for ablation of thyroid remnants following near-total thyroidectomy. In patients with known residual or metastatic tumour a therapy activity 5.5 GBq ^{131}I is given with repeated doses being given every 3 to 6 months until all tumour has been eradicated. This lack of dosimetry for radioiodine treatment contrasts sharply with the delivery of external beam radiotherapy where precise tumour-dose prescription is mandatory. The results of the dosimetry study presented in this Thesis, show evidence of dose-response relationships. The dose-response data explain the varying clinical response observed to fixed activities of radioiodine. In future, it is hoped that such data will enable precise prescription of radioiodine to achieve tumouricidal doses whilst avoiding the potential morbidity, expense and staff hazards of ineffective therapy.

CHAPTER 1

DIFFERENTIATED THYROID CARCINOMA

DIAGNOSIS AND TREATMENT

1.1 NATURAL HISTORY

1.1.1 Incidence

Thyroid cancer is rare, accounting in most countries for about 1% of all cancers. In clinical terms, it accounts for 3.8 to 10 cases per 100,000 per annum (Riccabona,1987). Incidence rates reported vary from 12 to 15 per 100,000 women in the islands of Iceland and Hawaii down to 1 only in the British Isles, in which the incidence is nearly the lowest recorded. These geographical differences are probably caused by environmental or dietary factors rather than by race or heredity. However, the incidence rates rise considerably (6 to 10%) in routine autopsies of patients with no antecedants of thyroid disease (Williams, 1980; Lang et al,1988). In contrast, the figures for mortality (adjusted for age) are not high, ranging from 0.31 to 1.62 cases per 100,000 per annum (Kurihara,1984; Riccabona,1987). This reflects the relatively favourable prognosis of most malignant thyroid neoplasms.

The incidence in women is always higher and the female to male ratio varies from about 1.5:1 to 4:1. There is a steady increase in incidence with age in men but in women there is a substantial incidence in young adults (25 to 35 years old). Data available on changing trends of incidence and mortality are subject to reservation regarding diagnostic criteria but it is probable that mortality is slowly decreasing while incidence is slowly increasing. Indeed, the 3rd National Cancer Survey (1975) showed a 50 percent increased incidence of both papillary and follicular thyroid

carcinoma in the United States between 1973 and 1977 (Beierwaltes, 1986).

1.1.2 Aetiology

Papillary carcinoma occurs more commonly in iodide-rich areas, for example, it is five times as common in thyroidectomy specimens in Iceland as it is in North East Scotland, and a rising incidence has been reported in patients on a high iodine diet (Williams et al, 1977). On the other hand, follicular carcinoma appears to be more common in low iodine endemic goitre areas and is possibly induced when thyrotrophic hormone concentration is high (Thompson et al, 1978).

Although both chemical and dietary goitrogens produce cancer experimentally, it is difficult to assess their possible role in the aetiology of human thyroid cancer. There is no question, however, that goitrogens cause a TSH-induced hyperplasia which may be extreme. A great number of foods, drugs, minerals and chemicals are goitrogenic and with increasing exposure it is quite likely that their role in the production of human thyroid cancer will become both more recognised and more significant.

Anaplastic carcinoma is mainly a disease of the elderly. The aetiology is unknown but there is increasing evidence that it occurs with pre-existing differentiated carcinomas. A substantial proportion of medullary cancer is genetic and malignant thyroid lymphoma occurs more commonly when thyroiditis and thyroid antibodies are prevalent.

Among survivors of the atomic bombing in Hiroshima and Nagasaki, there has been a slightly increased incidence of papillary carcinoma of around 2 to 9 cases per million population per year-rad (Socolow et al, 1963). Therapeutic irradiation of the neck in infants and children for treatment of enlarged thymic glands or other conditions such as tuberculous adenitis (Cade, 1957) or medulloblastoma (Raventos & Duszynski, 1963) has led to a small but significant increased incidence of thyroid carcinoma (Pifer & Hempelmann, 1964). While many of the lesions were papillary adenocarcinoma, other types of thyroid cancer occurred as well. Comparable or even larger doses of irradiation to the thyroid of adults have not significantly increased the cancer incidence. Similarly, large doses of radioiodine to ablate the thyroid, (for example in cardiac patients) have failed to produce cancer of the thyroid.

In experimental tumour induction, hyperplasia of the thyroid epithelium often precedes the development of benign or malignant tumours. There is some evidence from large surgical series that an

association exists between hyperplasia, particularly that of Graves' disease, and neoplasia (Pemberton & Black, 1948; Meissner & Adler, 1958; Olen & Klinck, 1966; Petro & Hardy, 1975; Farr, 1976; Mazzaferri et al, 1977).

Genetically-induced thyroid cancer occurs in the three multiple endocrine adenoma syndromes: with chemodectoma and paraganglioma in Pendred's syndrome (goitre and neurosensory deafness); Gardners syndrome (polyposis coli, osteomas and sebaceous cysts) and in Cowden's disease (multiple harmatoma) (Schottenfeld & Gershmany, 1977). Although non-medullary thyroid carcinoma is not usually considered to be a component of the "multiple endocrine adenoma" syndrome, an association between hyperparathyroidism and papillary carcinoma has been suggested (Meissner & Adler, 1958; Laing et al, 1969; Farr, 1976; Mazzaferri et al, 1977). An increased incidence of second malignancy has been reported in patients with thyroid carcinoma, most commonly breast cancer (Shimoaka et al, 1962; Wyse et al, 1969).

1.1.3 Anatomy

The thyroid gland consists of two lateral lobes connected by an isthmus. In addition a pyramidal lobe extends upward from the isthmus in about 40% of the population. The average weight of the normal adult thyroid is considered to be 25 to 30 g (range 10 to 60 g). Important neighbouring structures include the oesophagus, parathyroid glands, recurrent laryngeal nerves and carotid arteries; all of these may be affected by an enlarged thyroid gland.

The structural unit of the thyroid is the follicle, a closed sac lined with epithelium and containing colloid. Individual follicles are approximately spherical with diameters ranging from 50 to 500 microns. The colloid of the thyroid follicle consists essentially of thyroglobulin, a glycoprotein (molecular weight 660,000) formed on polyribosomes in the endoplasmic reticulum of the follicle cell. The follicle cells trap and incorporate iodide into the thyroglobulin and by secreting various oxidative enzymes bring about the iodination of tyrosine to form thyroid hormone.

1.1.4 Lymphatic Drainage

The lymphatic drainage of the thyroid gland is very rich and more widespread than is commonly realised. The drainage generally runs in superior, lateral and inferior directions, following the branches of the superior thyroid vessels, the inferior thyroid artery and the inferior and middle thyroid veins. The superior pathways drain the upper pole regions as well as the medial aspects of the lobes adjacent to the isthmus and pyramidal lobe when present. These terminate in precricoid and upper and middle jugular lymph nodes. The lateral lymphatic pathways follow the middle and lower jugular chain. The inferior pathways drain into either the pre- and paratracheal nodes or the lower jugular nodes. There is considerable spread in the para- and pre-tracheal spaces extending down into the mediastinum and relating also to the oesophagus and larynx. There are other well known deep and superficial cervical chains and there is also communication with the supraclavicular region laterally and into the sub-mandibular region superiorly.

Less commonly, lymphatic drainage may pass into retropharyngeal nodes, the nodes in the superior mediastinum in the region of the thymus, and in rare instances the submandibular lymph nodes. There is a rich intraglandular lymphatic network with free communication between the two lobes. Lymphatic drainage from one thyroid lobe to nodes on the opposite side of the neck is not infrequent.

1.1.5 Pathology

Most thyroid tumours arise from the epithelial elements of the thyroid gland. Mesenchymal neoplasms are uncommon, malignant lymphoma being the least rare. For the sake of simplicity, thyroid cancer may be subdivided into three histological groups: (i) tumours arising from the thyroid cells ranging from papillary and follicular to anaplastic; (ii) medullary carcinoma arising from the parafollicular C-cells and (iii) primary thyroid lymphoma from the lymphoid series. The WHO classification (Hedinger et al, 1988) is given in Table 1.1. Differentiated thyroid carcinoma refers to papillary and follicular histological types and for the foregoing discussion only brief mention will be made of anaplastic, medullary carcinoma and lymphoma.

Table 1.1

WHO HISTOLOGICAL CLASSIFICATION OF THYROID TUMOURS

Epithelial tumours

Benign
Follicular adenoma
Others

Malignant
Follicular carcinoma
Papillary carcinoma
Medullary carcinoma
(C-cell carcinoma)
Undifferentiated
(anaplastic) carcinoma
Others

Non-epithelial tumours

Malignant lymphomas

Miscellaneous tumours

Secondary tumours

Unclassified tumours

Tumour-like lesions

1.1.6 Papillary Carcinoma

Papillary carcinoma of the thyroid has been defined as a malignant epithelial tumour showing evidence of follicular cell differentiation, typically with papillary and follicular structures as well as characteristic nuclear changes. Less constant features include an invasive growth pattern, psammoma bodies and a fibrous stroma. Many of these tumours lack one or more of the above features.

Papillary carcinoma of the thyroid is characterised by complex branching papillae arranged on a fibrovascular stalk. Typically, the epithelium is single layered, but multi-layering does occur. The tumour cells are cuboidal with a homogeneous cytoplasm surrounding a central ovoid nucleus. The nuclear chromatin is often dispersed in fine grains giving a so- called "ground-glass" appearance. The nuclei of papillary carcinoma cells may show a number of other changes; these include large size, pale staining, irregular outlines with deep grooves, inconspicuous nucleoli and pseudoinclusions resulting from cytoplasmic invaginations. The nuclei often overlap. These nuclear features are important in the recognition of papillary carcinoma by fine-needle aspiration cytology. Although they are helpful in establishing the diagnosis of papillary carcinoma, they are not constant and in many tumours only a minority of cells may show them.

Mitoses are extremely rare. The cytoplasm is usually pale-staining and the cells show immunohistochemical evidence of thyroglobulin production. Squamous metaplasia is sometimes present. About 40% of papillary carcinomas contain laminated, calcified spherules known as psammoma bodies. Psammoma bodies practically never occur in other thyroid lesions. Follicles are almost always present and may be the predominant component; these follicular elements are often irregularly shaped but may be well differentiated. In addition to papillary and follicular structures, solid or trabecular growth patterns may occur. Multiple foci may occur in the same lobe as the primary or less commonly, in both lobes. These are probably due to intraglandular lymphatic spread within the rich intrathyroidal lymph plexus rather than to multi-centric growth. Multi-centricity is said to occur in 10 to 20% of cases. Most papillary tumours contain a mixture of papillary fronds and colloid-filled follicles and since these tumours exhibit the biological behaviour of papillary carcinoma it is now generally agreed that these mixed tumours should be included in the papillary group.

Small papillary tumours (less than 1.5 cm) were formerly termed "occult papillary carcinoma" because the primary lesion is usually (but not always) impalpable. Synonyms included "occult sclerosing carcinoma" and "encapsulated sclerosing tumour". Extensive bulky cervical lymph node metastases occur in about 22% of these occult tumours and spread to regional lymph nodes is common in all groups. Distant metastases on the other hand are infrequent. In the differential diagnosis, it is important to bear in mind the possibility of secondary spread to the thyroid gland and supraclavicular nodes from a papillary carcinoma arising in other organs, notably: colon, ovary and prostate. Immunohistochemical staining with thyroglobulin may help to confirm or refute a diagnosis of primary thyroid carcinoma.

1.1.7 Variants of Papillary Carcinoma

Papillary microcarcinoma is defined as a papillary carcinoma 1.0cm or less in diameter. These microcarcinomas are common in population-based autopsy studies and as incidental findings in carefully examined resected thyroid glands. Although they may be associated with cervical lymph node metastases, the prognosis is excellent and distant metastases exceptionally rare.

Encapsulated variant is a circumscribed or encapsulated tumour variant which is rare. Encapsulated papillary carcinomas may metastasise but have been reported to have an even better prognosis than the more common non-encapsulated tumours. There are no reliable morphological criteria to distinguish those associated with metastases from those that are not. The use of the term "papillary adenoma" is not therefore recommended.

Follicular variant refers to those papillary carcinomas which are composed entirely or almost entirely of follicles. When such tumours are circumscribed their differentiation from follicular carcinomas or adenomas may be difficult. Apart from the absence of papillae these tumours resemble papillary carcinoma in their morphological features as well as their clinical behaviour.

1.1.8 Follicular Carcinoma

Follicular carcinoma of the thyroid may be defined as a malignant epithelial tumour showing evidence of follicular cell differentiation but lacking the diagnostic features of papillary carcinoma. The morphology of

follicular carcinomas is extremely variable, ranging from well-formed follicles containing colloid to a solid, cellular growth pattern. Poorly formed follicles or atypical patterns, for example, cribriform may occur, and coexistence of multiple architectural types is common. The epithelial cells of follicular carcinoma show relatively little pleomorphism and mitoses are infrequent. The cytoplasm usually resembles normal follicles but Askanazy, Hürthle or clear cells may be found, and may even predominate. No papillae should be present. However, neither architectural nor cytological atypicalities are by themselves reliable criteria of malignancy, as these changes may be present in benign neoplasms, most notably atypical adenomas. Mitotic activity has not proved to be a useful indicator of malignancy. There is contraversy as regards the prognostic significance of different histological growth patterns, for example microfollicular or trabecular. A group of uncommon poorly differentiated tumours with distinctive architectural features referred to as *insular* carcinoma is, however, associated with a worse prognosis.

For prognostic purposes, it is important that follicular carcinomas are classified according to their degree of invasiveness. *Minimally invasive (encapsulated)* are grossly encapsulated solitary tumours, often with solid, fleshy, firm cut surfaces. Minimally invasive carcinomas are almost always architecturally and cytologically indistinguishable from adenomas (that is, embryonal, foetal, or atypical) and the diagnosis of malignancy depends entirely upon the demonstration of unequivocal vascular invasion (often with endothelium-covered intravascular tumour masses) and/or invasion that penetrates the full thickness of the capsule. Invasion of one or more vessels within or immediately outside the capsule is present in the vast majority of cases and is a much more reliable criterion than capsular invasion. Examination of multiple blocks through the periphery of all unusually cellular encapsulated thyroid neoplasms is necessary to exclude evidence of invasion. Since the distinction between a minimally invasive follicular carcinoma and a follicular adenoma depends upon vascular or capsular invasion, cytological studies, including aspiration cytology, may not be adequate for diagnosis. *Widely* invasive tumours show widespread infiltration of blood vessels and/or adjacent thyroid tissue and often lack complete encapsulation. In contrast to the minimally invasive tumours, they are rarely a diagnostic problem. Tumours which show extensive microscopic invasion, particularly vascular, should be placed in this catagory even if grossly encapsulated.

Lymph node metastases are uncommon in follicular carcinomas except in the poorly differentiated insular type. Distant metastases occur infrequently with minimally invasive carcinomas but are commonly associated with widely invasive tumours. The most frequent metastatic sites are lung and bone. The histology of metastases often differs from that of the primary neoplasm. Very well-differentiated metastatic carcinomas, indistinguishable from normal thyroid , were formerly termed metastasising adenoma, malignant adenoma or metastasising goitre. The primary thyroid tumour of such cases is nearly always more cellular and less well-differentiated than the metastasis. Immunoperoxidase staining for thyroglobulin is valuable in confirming the thyroid origin of a metastatic tumour.

1.1.9 Variants of Follicular Carcinoma

The *follicular carcinoma, oxyphilic cell type.* Included in the classification of follicular carcinomas are those tumours composed largely or entirely of eosinophilic cells. These tumours were formerly referred to as Hürthle cell carcinomas but are now termed follicular carcinoma, oxyphilic cell type. Carcinomas composed of oxyphilic cells have been shown to take up radioiodine with much less avidity than follicular carcinomas (Fitzgerald et al,1950). The same criteria of malignancy apply to follicular tumours of oxyphilic cells as to those composed of ordinary follicular cells. Oxyphilia per se is not a criterion of malignancy. Oxyphilic cells are characterised by their larger size (compared with ordinary follicular cells) and abundant, eosinophilic cytoplasm which may appear granular and homogeneous. These cells are found in both tumours and a variety of non-neoplastic thyroid conditions including Hashimoto's disease. Most workers regard them as transformed follicular cells although the cause and nature of the change are uncertain. The cytoplasm of the oxyphilic cell contains numerous mitochondria, and is rich in oxidative enzymes and adenosine triphosphatase (Frieman & Kaplan, 1960; Tremblay & Pearse,1960). These tumours have been reviewed by Horn (1954), Gardner (1955) & Hamperl (1962). A rare *clear cell* variant of follicular carcinoma shows similarities of architecture and clinical course to usual follicular carcinomas. These tumours must be distinguished from clear cell adenoma, and metastatic clear cell carcinomas, particularly renal cell carcinoma. Thyroglobulin localisation by immunohistochemistry is of value in the differential diagnosis.

1.1.10 Physiology

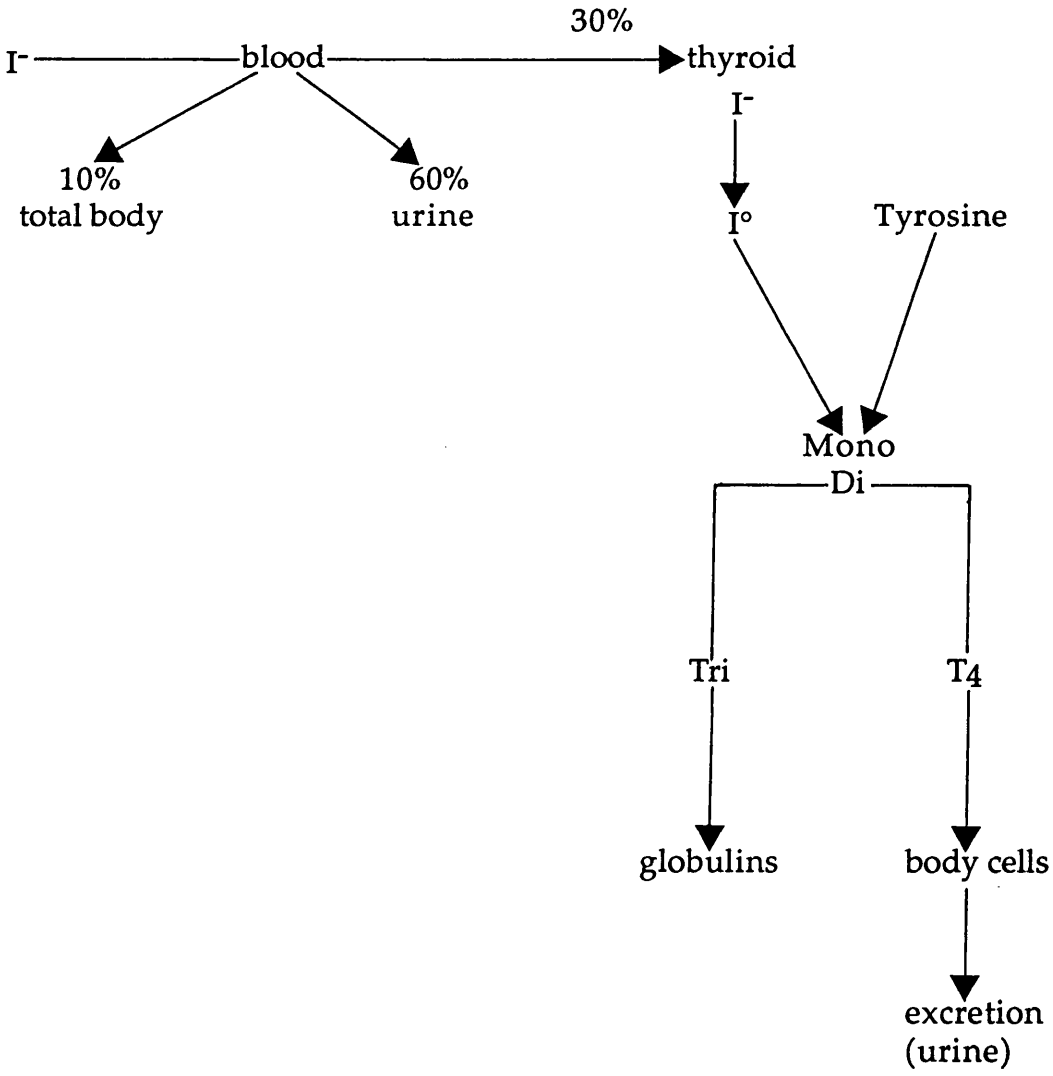
The primary function of the thyroid gland is the secretion of thyroxine (T_4) and 3,3' triiodothyronine (T_3); about 85% of T_3 is produced by mono-iodination of T_4 in tissues other than the thyroid (for example, liver, kidney, muscle). T_3 is metabolically more active than T_4 and, indeed, T_4 may serve as a prohormone requiring conversion to T_3 for expression of its hormonal activity. In the plasma, both T_4 and T_3 are almost entirely bound to thyroxine binding globulin (TBG), albumin and thyroxine-binding pre-albumin. It is the minute concentrations of unbound (free) hormones (less than 0.1% of total T_4 and total T_3) which diffuse to the tissues and exert their hormonal activity. T_4 and T_3 are removed from the plasma by hepatic and renal metabolism, with excretion of the inactive metabolites.

The production of T_4 and T_3 in the thyroid is stimulated by the peptide hormone thyroid stimulating hormone (TSH) which is secreted by the thyrotroph cells of the anterior pituitary. TSH secretion is in turn stimulated by the hypothalamic tripeptide, thyrotrophin releasing hormone (TRH). Production of T_3 and T_4 is normally regulated by a negative feed-back system which maintains the levels of free T_4 and free T_3 in the plasma within enclosed limits. High levels of free hormones suppress TSH secretion by the pituitary, resulting in decreased T_3 and T_4 production and restoration of normal free hormone levels. Conversely, low levels of free hormones increase TSH secretion, and hence thyroid hormone production. Most of the effects of TSH on thyroid function are mediated by 3':5'-cyclic adenosine monophosplate (cAMP) which is generated by adenylate cyclase after the binding of TSH to its receptor. The important point is the role of the pituitary in the control of the thyroid gland and therefore the hormone dependence of thyroid tumours.

1.1.11 Iodine Metabolism

The iodine metabolic pathway in man is shown in Fig. 1.1. The salivary glands, the lactating breast and the stomach all concentrate and secrete iodide at a concentration about thirty times than in plasma. Hormonal protein bound iodine is degraded to iodide in peripheral tissues where it controls metabolism and is also concentrated about six times in the liver. Iodide trapped by the thyroid is rapidly converted via iodinated tyrosines into the two hormones T_4 and T_3 which are stored in thyroglobulin in the colloid.

Figure 1.1: Metabolic Pathways of Iodine



1.2 CLINICAL COURSE

1.2.1 Symptoms, Signs and Presentation

Papillary adenocarcinoma is typically an indolent slow growing tumour and may be discovered as an incidental finding on histological examination in patients undergoing thyroid surgery for reasons other than suspected neoplasm. It may also be suspected as a solitary, cold nodule on radionuclide scanning. A common presentation, especially in young adults, is cervical lymphadenopathy from a small or occult primary. In general, up to 50% of patients with papillary carcinoma have obvious cervical lymph node metastases at surgery (Mazzaferri et al, 1977). However, a higher incidence is reported in some adults (Crile, 1971; Mustard, 1970) and in most children with this disease (Harness et al, 1971; Leichty et al, 1972; Veith, 1964). A thyroid mass is the presenting feature in about 40% of patients (Mazzaferri et al, 1977) which may or may not be preceded by a history of rapid growth. Neck pain, dysphagia and hoarseness are less common presenting symptoms which usually occur in older patients and in those with large primary tumours or extracapsular spread.

Distant metastases on presentation, which are mainly to the lungs, only occur in 5 to 10% of adults (Crile, 1971; Woolner et al, 1961) although there is a higher incidence of 15 to 20% in children (Winship, 1970; Leichty et al, 1972). Follicular carcinoma is less common and tends to occur in older patients. Lymph node metastases are less common and are found in about 28 percent of patients (Halnan, 1982). Distant metastases, especially to bone, are more common and occur in about 14 percent of patients (Table 1.2) in whom they may be the presenting feature. Indeed, symptoms and signs of spinal cord compression due to vertebral secondaries is the first presentation in a significant number of patients. Fixation of the gland is a late feature and more typical of anaplastic carcinoma.

Table 1.2

Frequency of Metastases from Thyroid Cancer
(EORTC, 1978, unpublished data)

Site	Follicular	Papillary
lymph node	28%*	47%
distant	14%	3%
lung	20/47	4/10
bone	29/37	2/10
viscera	4/27	4/10

* of all new tumours in each category

1.2.2 Diagnostic Investigations

A full history should be taken and clinical examination performed. A family history of thyroid or other endocrine disease, previous radiotherapy to the head and neck and any previous thyroid history should be sought. Ultrasound examination of the neck can help to differentiate between solid and cystic areas. Chest X-ray should be obtained to exclude possible mediastinal extension of disease and pulmonary metastases. Computerised tomography (CT) will often show small lung metastases before conventional radiology. Radioiodine or technetium ($^{99}Tc^{m}$) scanning of the neck will show tumours and cysts as "cold areas" but this will only be an additional indication for biopsy or thyroidectomy. Radionuclide bone scans will demonstrate the presence of bone metastases before there is conventional radiological evidence. Radioiodine scanning is discussed further below.

Biochemical tests of thyroid function should be performed including serum thyroid-stimulating hormone (TSH) and thyroglobulin (Tg). Routine full blood count, blood urea, serum calcium and liver function tests should also be obtained.

Table 1.3

TNM Clinical Classification

The following are the procedures for assessment of the T, N and M categories:

T *categories* Physical examination, endoscopy and imaging
N *categories* Physical examination and imaging
M *categories* Physical examination and imaging

Regional Lymph Nodes

The regional lymph nodes are the cervical and upper mediastinal nodes

T Primary Tumour

TX Primary tumour cannot be assessed
T0 No evidence of primary tumour
T1 Tumour 1 cm or less in greatest dimension, limited to the thyroid
T2 Tumour more than 1 cm but not more than 4 cm in greatest dimension, limited to the thyroid
T3 Tumour more than 4 cm in greatest dimension, limited to thyroid
T4 Tumour of any size extending beyond the thyroid capsule

Note: All categories may be subdivided: (a) solitary tumour, (b) multifocal tumour (the largest determines the classification)

N Regional Lymph Nodes

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Regional lymph node metastasis
N1a Metastasis in ipsilateral cervical lymph node(s)
N1b Metastasis in bilateral, midline or contralateral cervical or mediastinal lymph node(s)

M Distant Metastasis

pTNM Pathological Classification

The pT, pN and pM categories correspond to the T, N and M categories

Stage Grouping
Papillary or Follicular

	under 45 years			45 years and over		
Stage I	Any T	Any N	M0	T1	N0	M0
Stage II	Any T	Any N	M1	T2	N0	M0
				T3	N0	M0
Stage III	-			T4	N0	M0
				Any T	N1	M0
Stage IV	-			Any T	Any N	M1

1.2.3 Clinical Classification and Staging

The clinical classification and staging for thyroid carcinoma used will be the TNM system (UICC, 1987). The characteristics of the primary tumour (T category) are determined by clinical examination and, where appropriate, radionuclide scanning and ultrasonic examination (Table 1.3). Similarly there is both clinical and pathological lymph node classification and finally, simple definition of the presence or absence of distant metastases. For the purpose of treatment policy and as a predictor of outcome, cases may be grouped together into a Stage classification.

1.3 ROLE OF SURGERY

1.3.1 Introduction

Histological confirmation of carcinoma is mandatory. Preliminary evidence may be obtained by biopsy. Fine needle aspiration cytology may be performed (Gershengorn et al, 1977; Smeds & Lennquist,1988) and if the nodule or tumour is solid drill biopsy is practicable (Hawk et al, 1966; Wang et al, 1974). In general, however, these methods are of little value if negative and an open biopsy will be preferable. If lymph node metastasis is evident, excision of the whole lymph node will be very helpful. If biopsy has not been performed, frozen section examination per-operatively can be very helpful in deciding on the extend of surgery required.

1.3.2 Thyroidectomy

Surgery remains the definitive initial treatment for differentiated thyroid carcinoma. However, there is no universal agreement as to the extent of surgery required. Some surgeons such as Cady et al (1985),Carcangiu et al (1985), Crile et al (1985), Farrer et al (1980), Schroeder et al (1985), Wanebo et al (1981) advocate thyroid lobectomy including isthmusectomy. Some such as Beahrs (1984), Buckwalter & Thomas (1972), Staunton & Greening (1976) and Saker et al (1980) recommend near total thyroidectomy. Others such as Attie et al (1979), Beirewaltes et al (1982), Clark (1982), Harness & Thompson (1986), Heitz et al (1976), Lennquist (1986), Massin et al (1984), Samaan et al (1983) and Schlumberger et al (1986) advocate total thyroidectomy.

Most surgeons agree, however, that the minimum procedure for unilateral thyroid disease should be lobectomy (Van der Velde et al,1988). If frozen section (which should always be performed) shows malignancy, then

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 recognised at frozen section and paraffin sections are sometimes inconclusive even after five tissue blocks. A recent consensus (Van der Velde et al,1988) agreed that in those cases of so-called "minimal invasive" follicular carcinoma further surgery is unnecessary and the initial (diagnostic) lobectomy can be considered as the definitive procedure. This consensus also defined "occult cancer" as a cancer which is removed incidentally during a thyroidectomy for another problem (for example, multinodular goitre) and is discovered during microscopic examination. Clinical cancers less than 1 cm diameter were defined as "minimal cancers". The consensus view was that no further surgical treatment is necessary for patients with papillary thyroid carcinoma less than 1 cm, confined to the thyroid gland and without signs of metastases.

The arguments in favour of lobectomy are that the operation has a lower morbidity since only one recurrent laryngeal nerve and only two parathyroid glands are at risk. The remaining thyroid tissue can then be ablated with radioiodine. However, the reported incidence of recurrence of malignancy in the opposite lobe after unilateral lobectomy is 2 to 40% (Black et al, 1960; Hirabayashi & Lindsay, 1961; Tollefsen & De Cosse, 1964; Clark et al,1965). There is also some evidence that 15 year survival rates in patients with papillary thyroid carcinoma increase from 78% after lobectomy to 92% after bilateral thyroidectomy (Mazzaferri et al, 1981).

The arguments in favour of near total thyroidectomy are that it has a greater chance of removing microscopic tumour foci but without the attendant morbidity of total thyroidectomy. Microscopic foci are found in the contralateral lobe in 38 to 87% of patients (Clark et al, 1959; Mortensen et al,1955; Black et al,1960; Russell et al,1963; Tollefson & De Cosse, 1964; Meissner & Warren,1969; Shields & Farringer,1987) depending upon the perseverance of the pathologist in studying tissue sections. Whether these foci are truely multicentric sites of neoplasia or intrathyroidal metastases is not certain (Russell et al, 1963). It is also possible that some foci may be anaplastic (0.7% in the Mayo series) and that their removal will therefore avoid progression to aggressive malignancy. There is also evidence that near total thyroidectomy is associated with increased survival (Sarker et al,1980). A smaller absorbed dose of radioiodine is subsequently required to ablate remnant thyroid tissue after near-total thyroidectomy than following lobectomy (O'Connell et al,1992).

True total thyroidectomy results in inevitable hypoparathyroidism if all four parathyroid glands are removed. Rusted et al (1963) found that after total thyroidectomy 11.8% of patients develop permanent hypoparathyroidism requiring life-long calcium or Vitamin D. There is also the additional hazard of bilateral recurrent laryngeal nerve damage resulting in vocal cord paralysis. Radioiodine scanning almost always shows some residual uptake after "total" thyroidectomy (Clark, 1982). Near total thyroidectomy complemented by an ablative dose of radioiodine to eliminate residual thyroid tissue can achieve totalisation of thyroidectomy without producing hypoparathyroidism in most cases. It is therefore suggested that it is sufficient to do a complete lobectomy on the affected side and subtotal on the contralateral side, leaving a tiny residue containing a parathyroid gland. However, in patients with bilateral tumours, metastatic disease or recurrent carcinoma total thyroidectomy is often necessary. When there is extensive central neck disease with tumour extending into surrounding structures, extensive primary operations are required. 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 necessary. When the larynx is extensively involved, surgery will not be curative and treatment with radioiodine and/or external beam radiotherapy is preferable.

1.3.3 Neck Dissection

The role of neck dissection remains controversial. Owing to the very extensive lymphatic drainage of the thyroid to para-oesophageal, supraclavicular, mediastinal and other lymph nodes, true en block removal of cancer arising in the thyroid gland is impossible. Furthermore, the conservative "functional" neck dissection gives as good results as more radical and mutilating operations and removal of the sternocleidomastoid muscle is rarely indicated. There is no evidence that prophylactic lymph node dissection is worthwhile.

It is important to distinguish between lymph node involvement in the central neck (between carotid arteries, from thyroid cartilage to superior mediastinum and down along the tracheo-oesophageal groove) from that in the lateral neck. The influence of lymph node metastases on survival in papillary carcinoma is considered minor (see section 1.8.2). Local excision or "node picking" is therefore considered an acceptable procedure in papillary carcinoma with limited involvement and central neck disease.

Careful examination of the central neck is sufficient to exclude that there are tumour bearing lymph nodes in that area. However, some surgeons remove the lymph nodes and all fatty tissue in the central neck routinely but this is at the risk of devascularisation of the parathyroid glands. There is no need to split the sternum in order to explore the superior mediastinum routinely.

Multiple involvement of lymph nodes in the lateral neck by papillary carcinoma should preferably be treated by modified radical neck dissection, which removes all fatty tissue and lymph nodes with preservation of the sternocleidomastoid muscle, the internal jugular vein and the vagal and spinal accessory nerves. A supra-hyoid dissection is usually unnecessary unless the highest nodes are involved with tumour. The submandibular triangle is not included in the dissection. A modified radical neck dissection can easily be performed, concomitant with or separately from the total thyroidectomy, through an extension of the Kocher's incision with minimum deformity and postoperative morbidity. Modified radical neck dissection is the treatment of choice for lymph node metastases of follicular carcinoma.

1.3.4 Risks and Complications of Radical Neck Dissection

In the early part of the century radical neck dissection was only occasionally performed with reported mortality rates varying from 10 to 14% MacComb,1968). The causes of mortality were listed as pneumonia, haemorrhage and uraemia. As the procedure became more widely used by surgeons limiting their practises to the surgery of the head and neck, the safety of the procedure became established. Martin et al in 1951 reported on 100 radical neck dissections performed for a variety of diseases with no post-operative mortality. They stated that mortality from neck dissection should not exceed 1 to 2%.

The type of incision has caused some problems. Vertical incisions or extensions may cause contractures or form keloid scars and restrict neck mobility, quite apart from cosmetic objections. Multiple incisions or those having angles or trifurcate portions may dehisce or necrose owing to poor blood supply; such wounds may jeopardise exposed carotid arteries. Use of transverse incisions and preferably the single transverse incision avoids these complications (Attie, 1957).

Meticulous haemostasis will avoid post-operative haemorrhage. Serous collections are common following neck dissection; suction under

flaps for a few days minimises the problem. Infection post-operatively is rare unless openings are made into the trachea, larynx or oesophagus. In such cases, antibiotics, temporary tracheostomy and nasogastric feeding are used.

Structures encountered during the procedure may be sacrificed if invaded by tumour. Trauma to the vagus nerve on one side of the neck results in hoarseness due to vocal cord paralysis. Bilateral vagal injury, however, is more serious and in addition to bilateral vocal cord injury cardiac and gastro-intestinal problems may result. Division of the sympathetic trunk causes Horner's syndrome. Phrenic nerve injury causes elevation of the diaphragm on the affected side. Laceration of the carotid artery can usually be repaired-ligation of the internal or common carotid artery can result in hemipareses or even death.

Injury to the thoracic duct, if unrecognised during the operation, can lead to chylous collections in the wound, chylous fistula or chylothorax. Although the leak of chyle will usually close spontaneously, it may persist for many months leading to severe dehydration and inanition due to loss of nutrients. Chylothorax can lead to pulmonary and mediastinal complications. Re-operation and ligature of the thoracic duct or occlusion by suture will relieve the condition.

Unilateral or bilateral pneumothorax has been described following radical neck dissection. Bowden (1950) reviewed a series of 18 cases with two deaths. In only one patient was the pneumothorax due to trauma to the apex of the pleura protruding into the neck wound; in the other patients the probable cause was exposure of the superior mediastinum during a period of respiratory tract obstruction with an increased inspiratory effort. If recognised and treated early (by aspiration or under-water drainage of the pleural cavity) there are no sequelae.

Simultaneous (and rarely non-synchronous) bilateral neck dissection with sacrifice of both internal jugular veins may lead to serious consequences. Insufficient venous drainage of the head and neck may lead to marked oedema and cyanosis causing great discomfort, unsightly swelling and respiratory distress due to laryngeal oedema. Increased cerebro-spinal fluid pressure may lead to lethargy, unusual behaviour and coma. Decreased visual acuity and even sudden permanant blindness have been reported (Torti et al, 1964). Staging the two neck ressections reduces the risk. Preferably, at least one of the internal jugular veins should be preserved. Tracheostomy may be required in bilateral operations.

Elevation of the head to improve drainage, steroids to reduce oedema and spinal tap if rise in cerebro-spinal fluid pressure occurs are important therapeutic measures.

1.3.5 Recurrent and Metastatic Disease

Surgery is important in patients with recurrent neck disease and cure may still be possible. Primary surgery has an important role in the management of metastatic disease especially where bone is involved. Internal fixation of pathological fractures not only offers mechanical stability but also optimum pain relief in conjunction with adjuvant therapy (as discussed below). Decompressive laminectomy is indicated in spinal cord compression especially if this is the first presenting symptom of an otherwise histologically undiagnosed thyroid carcinoma.

1.4 ROLE OF RADIOIODINE THERAPY

1.4.1 Historical Background

The earliest clinical use of radioiodine (^{131}I) in thyroid carcinoma was reported by Hamilton in 1940. In 1942, Keston monitored the uptake of ^{131}I in metastatic carcinoma using a Geiger counter. Subsequent auto-radiographic examinations of thyroid carcinomata (Dobyns & Lennon, 1948; Fitzgerald & Foote, 1949; Marinelli et al, 1947; Rawson et al, 1948) showed that iodine concentration occurs most commonly in well differentiated tumours and particularly if colloid-filled follicles are present. By direct measurement of radioactivity in surgical thyroidectomy specimens, Dobyns & Maloof (1951) found a maximum initial uptake of 0.6% administered radioactivity per gram of tissue for patients with follicular carcinoma and a maximum initial uptake of 0.04% administered ^{131}I per gram of tissue in other types of cancer without follicular components. It has, however, been emphasised repeatedly that uptake is not always correlated with these or other histological structures. The unique avidity of thyroid tissue (whether malignant or benign) for radioiodine provides a method of selective irradiation.

The Royal Marsden Hospital was the first hospital in the United Kingdom to employ ^{131}I in the treatment of thyroid carcinoma (Walton, 1950). It is now generally accepted that radioiodine treatment should be attempted for all patients with well differentiated thyroid carcinoma (papillary or follicular) except, perhaps, those patients with good prognostic

factors as discussed in Chapter 2 (Section 2.8).

1.4.2 Radioiodine ^{131}I

Since normal thyroid tissue almost always takes up iodine more avidly than tumour tissue, it is necessary to ablate the normal thyroid, surgically or by radioiodine, before tumour can be effectively treated. Radioiodine may be used to ablate thyroid remnants following total or near total thyroidectomy and as an alternative to lobectomy in patients who have had a hemithyroidectomy for a solitary nodule which proves to be neoplastic on histological examination. Radioiodine also offers an alternative to surgical resection for patients with inoperable tumour or for those patients who are unfit for surgery. The level of administered activity given by most physicians for the ablation of normal thyroid tissue is in the range 1.0 to 3.0 GBq (Halnan, 1980; Halnan, 1982; Pochin, 1971; Roeslier, 1985). Thereafter, suppressive doses of thyroid hormone are usually administered. The level of activity administered is discussed further in Chapter 7.

If there are adverse features such as incomplete surgical resection of tumour; involved lymph nodes; abnormal chest Xray (for example, mediastinal or paratracheal lymphadenopathy, pulmonary secondaries) further radioiodine therapy is indicated and is usually given at intervals no less than 3 monthly. There is, however, an argument for leaving longer intervals from 6 to 12 months in young patients with papillary carcinoma and pulmonary metastases in whom disease progression is relatively slow.

Quantitative estimates of iodine turnover, such as plasma concentration of radioiodine (PBI) and the role of thyroglobulin in the management of metastatic thyroid carcinoma are discussed below (Section 1.8).

1.4.3 Complications of Radioiodine Ablation

Radiation thyroiditis may occur 3 to 4 days following radioiodine administration and is characterised by pain in the neck often radiating to the ear, pain on swallowing and localised tenderness over the residual thyroid tissue. If one lobe or more is being destroyed the symptoms may be severe and steroids may be required for a few days. Infarction of an entire lobe may occur (Fig.1.2). Transient hyperthyroidism almost certainly occurs if a substantial amount of thyroid tissue is being destroyed but clinically may not be obvious and is often unrecognised. The destruction of thyroid

tissue is accompanied by the release into the circulation of T_3, T_4, thyroglobulin and various degradation products. If serial measurements of thyroid hormones are made the serum levels of T_3 and T_4 can be seen to rise after about 5 or 6 days. If there is clinical evidence of hyperthyroidism, it may be advisable to give a beta blocker such as propranolol which will only be required for a few days as the condition is self-limiting.

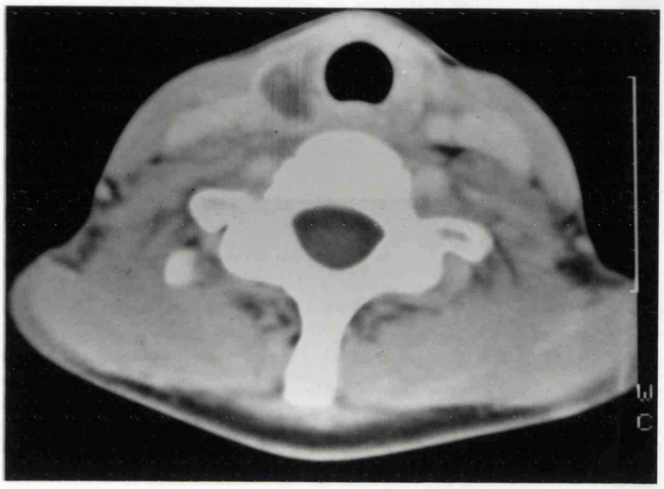


Figure 1.2: *CT scan showing infarction of right thyroid lobe following radioiodine ablation.*

Radiation sialitis is a rare complication (Goolden et al, 1957). It occurs within about 24 hours of radioiodine administration and may affect the parotid or submandibular glands or both. It is most likely to be seen when a large quantity of radioiodine is given to a patient who has very little functioning thyroid tissue. In the absence of any competition from thyroid tissue the salivary glands may concentrate sufficient activity to provoke an inflammatory reaction. Acute sialoadenitis, especially in the parotid, may persist into a chronic phase lasting years. Persistent painful masses may subsequently require surgical intervention.

Oedema of the neck is a relatively uncommon complication which occurs only after a fairly high radiation dose to the thyroid (Hoschl et al, 1965). It differs from radiation thyroiditis in that it is painless and appears within 48 hours of therapy. It is difficult to provide an explanation for this phenomenon. Measurements and calculations of the radiation dose to the

tissues in the vicinity of the thyroid tissue have shown that the oedema cannot be ascribed to a direct effect of radiation on the perithyroid tissues (Goolden et al, 1986). The rapidity of onset, lack of pain and occasional stridor suggest an allergic response rather than a direct radiation effect. The condition responds well to steroids.

1.4.4 Late Effects of Radioiodine Therapy

Bone marrow suppression leading to aplastic anaemia is relatively rare and more likely to occur in patients with extensive bone metastases (Edmonds & Smith, 1986). However, most patients will have some degree of haematological depression and hence the full blood count should always be checked before further radioiodine is administered.

Pulmonary fibrosis has only been reported in patients with diffuse bilateral lung metastases receiving lung uptake greater than 3.7 GBq (Rall et al, 1977).

The incidence of temporary amenorrhea and infertility in the female treated with radioiodine is not significantly different from that of a normal matched population. Fertility in younger male patients, however, may be adversely affected and permanent when cumulative activities exceeding 18.5 GBq are administered. Sperm banking should, therefore, be considered where activities above this level are contemplated. In general, treatment in younger individuals should, therefore, be at the lowest level for effective tumour control. In a 25-year follow-up study of 40 children with thyroid carcinoma treated with a mean total dose of 62.5 GBq ^{131}I, there was no evidence of diminished fertility nor of an abnormal birth history (Beierwalters, 1986).

The carcinogenic hazard of ^{131}I in relation to the treatment of both hyperthyroidism and thyroid carcinoma has been examined in several large follow-up series. There is no doubt that in the past (as it was used) there was an excess of acute leukaemia in patients receiving a total activity in excess of 40 GBq (Pochin, 1959; Edmonds & Smith, 1986). The time interval between death from leukaemia and ^{131}I therapy was short, averaging only 3 years. As regards solid tumours, there is the suggestion of an increased incidence of breast cancer (Pochin, 1959). However, this has not been confirmed by others (for example, Hoffman, 1982) and may be due to a possible association between breast and thyroid disease (Chalstrey & Benjamin, 1966). Hoffman (1982) has shown a slight excess of cancer in organs which concentrate ^{131}I such as salivary glands, digestive tract, kidney and bladder.

For bladder cancer, there was a long latent interval of 14 and 20 years.

The possibility of anaplastic transformation following ^{131}I has been debated. However, Mazzaferri et al (1977) showed that only 50% of the reported patients with papillary and follicular thyroid carcinoma who developed anaplastic cancer had a documented history of previous radioiodine therapy.

1.5 ROLE OF EXTERNAL BEAM RADIOTHERAPY

Although post-operative external beam radiotherapy to the neck is not usually advised (Harmer, 1977; Harmer, 1991) local irradiation may be indicated because of considerable primary tumour or nodal involvement remaining after surgery. This does not preclude the simultaneous administration of an ablative dose of radioiodine which can be followed subsequently by tracer doses for neck and whole body scanning. External beam radiotherapy will also be required for those patients with progressive symptomatic local disease and for those patients with residual tumour post-thyroidectomy who fail to concentrate radioiodine. Other possible indications include high histological grade of tumour.

The primary tumour in the neck and immediate lymphatic drainage make up a U-shaped volume wrapped around the spinal cord. Uniform irradiation of this volume is not easy and the best technique uses high energy electrons from a single anterior field, with wax bolus over the centre to bring the isodoses out in front of, and thereby spare, the vulnerable spinal cord. An applied dose of 75 Gy given in 30 daily fractions is recommended. Megavoltage photon beams can also be used to give similar treatment volumes using opposed anterior and posterior portals. A tumour dose of 60 Gy (median) in 30 fractions (treating all fields daily) over 6 weeks with spinal cord shielding from 40 Gy is recommended (Harmer, 1977).

External beam radiotherapy, using a single direct field or parallel pair technique, is indicated for patients with bone metastases causing spinal cord compression or threatened pathological fracture. Hemibody radiotherapy may also provide prolonged palliation of widespread bone metastases. At this Hospital, a single dose of 8 Gy to the lower hemibody or 6 Gy to the upper hemibody using large anterior and posterior opposed fields is recommended (Hoskin et al, 1989). Pre-hydration and antiemetic therapy with dexamethasone and lorazepam usually prevent nausea and vomiting.

Whole lung radiotherapy giving a midpoint dose of 20 Gy in 15 fractions over three weeks may control lung metastases or bulky mediastinal disease and palliate such distressing symptoms as haemoptysis and stridor in a patient with differentiated carcinoma who fails to concentrate radioiodine.

1.6 ROLE OF ENDOCRINE THERAPY

It is well known that well differentiated tumours are hormone dependent and that in the absence of thyroid stimulating hormone they will atrophy; however, there remains some doubt as to the reliability of this as the sole treatment (Thomas & Burnes, 1961) except in some children with multiple metastases. It is generally agreed that suppressive doses of thyroid hormone should be given to all patients with differentiated tumours in addition to whatever other treatment is indicated. The two main thyroid hormones are sodium-L-thyroxine (0.2 to 0.3 mg average adult daily dose) and sodium-L-triiodothyronine (20 to 120 μg daily dose). Clinical experience shows that administration of thyroxine should be discontinued at 4 weeks and triiodothyronine at 10 to 14 days (owing to the slower metabolism of thyroxine) before radioiodine tests and therapy.

Thyroid stimulating hormone (TSH) may be administered when serum TSH levels are low owing to continued thyroid hormone administration or iodine medication and is effective within hours. Usually 3 to 5 successive daily injections of 10 IU of bovine TSH is recommended, the last injection being given on the day on which radioiodine is to be administered. Generally however, prolonged continuous tumour stimulation by endogenous TSH (secreted because of hypothyroidism) is the best method of ensuring maximum radioiodine uptake.

1.7 ROLE OF CHEMOTHERAPY

Experience with chemotherapy in thyroid carcinoma is limited owing to the rarity of the tumour and also the good response to surgery, radiotherapy, and TSH suppression. Chemotherapy is therefore usually reserved for those 20% of patients with well differentiated papillary or follicular tumours which fail to concentrate radioiodine (Pochin, 1971). Early experience with 5-fluorouracil, nitrogen mustard, cyclophosphamide and actinomycin-D (Gottleib et al, 1972; Rogers et al, 1974) used alone or in combinations showed that thyroid tumours can be chemo-responsive.

Adriamycin has been widely used as a single agent (Gottleib & Stratton-Hill, 1974) with reported response rates of 31 to 45 percent, although complete responses are rare (Shimoako, 1980). Bleomycin is also active (Hirada et al, 1971). The sequential use of etoposide, carboplatin, cis-platinum and methotrexate as single agents has shown that useful responses can be achieved in patients with advanced symptomatic disease and may result in worthwhile palliation and prolongation of survival (Hoskin & Harmer, 1987).

Few attempts have been made at successful combination treatment although Durie et al (1981) reported encouraging results in small numbers of patients using adriamycin, bleomycin, vincristine and melphalan.

1.8 FOLLOW-UP

1.8.1 Introduction

Owing to the long natural history, patients with thyroid carcinoma should be followed up meticulously for life. Biochemical measurement of thyroid hormone and TSH should be performed and the replacement dose of T_4 (or T_3) adjusted as necessary. At each therapy dose full blood count, blood urea, serum calcium and liver function tests should also be performed. Serum assay of thyroglobulin provides a useful marker of residual or metastatic disease (see Section 1.8.2). Chest Xray is particularly cost effective as the lungs are a common site of distant metastases in both papillary and follicular carcinoma. Computerised tomography may, in addition, provide more sensitive documentation of pulmonary metastases. Other radionuclide techniques such as Thallium-201 scanning may improve the detection of metastases (Charkes et al, 1990). Radionuclide bone scanning (using for example technetium-99m labelled diphosphonates) is useful in locating bone metastases. Other scans such as liver ultrasound and CT scanning of the neck in patients with recurrent disease should be performed as clinically indicated. Regular biannual radioiodine whole body scanning has now largely been superseded by serum thyroglobulin assay.

1.8.2 Thyroglobulin

Serum thyroglobulin (Tg) has proved to be of considerable value in the postoperative management and follow-up of differentiated thyroid

carcinoma. It is particularly useful in the presence of suppressive thyroid hormone treatment which not only may reduce the growth rate of the tumour by suppressing TSH, but also reduces the secretion of thyroglobulin by any normal residual thyroid tissue (Ashcraft and Van Herle, 1981). Black and her associates (1981) found that serum thyroglobulin reflected the presence or absence of cancer in 83% of patients not receiving thyroxine and that this concordance improved to 97.5% in patients tested while receiving T_4. It is suggested that monitoring of patients by assay of serum T_g should supplant routine assessment by radioiodine scans of the neck or whole body. This would be of considerable advantage to the patient as thyroid hormone replacement would not require to be withdrawn and render them hypothyroid before radioiodine diagnostic scanning. It is, therefore, proposed that scans should only be performed when the patient's serum thyroglobulin concentration remains greater than 3μg per litre (normal upper limit at this laboratory) or when there is clinical evidence suggesting recurrence.

1.8.3 Protein Bound Radioiodine

After the administration of ^{131}I to a normal individual, the plasma activity rises rapidly to a peak and then falls gradually (Wayne, 1954). This activity should at first be due to the presence of circulating inorganic iodine but after some time, protein bound radioiodine (PBI) should appear. Fourty eight hours after a dose has been given, the PBI should almost always be less than 0.4 per cent of the administered dose per litre of plasma. As only a small amount of T3 and T4 are free in the blood, the PBI effectively represents total circulating thyroid hormones. The euthyroid range is 280 to 640 nmol/l. False low results are due to lowering of thyroid binding globulin by hereditary, androgens or the nephrotic syndrome. False high results are due to iodine contamination, for example X-ray contrast media and expectorants containing potassium iodide: also to pregnancy and oral contraceptives when thyroid binding proteins in the serum are elevated.

When thyroid tumour or metastases are of a type which concentrate radioiodine, the PBI rises steadily and its fall indicates the success of radioiodine therapy as the uptake by tumour or metastasis declines or ceases altogether (Voutilaineum & Virtanen, 1966). Measurement of the PBI is not entirely straight forward, the main problem being that other radioiodinated compounds present interfere with the results. Moreover, the absolute numerical value depends upon the method employed and

therefore varies from laboratory to laboratory.

According to Pochin (1971), following administration of radioiodine, PBI rises to a maximum value at about 4 days from which it then declines more slowly. In any given patient, after thyroid ablation, this maximum PBI concentration should be roughly proportional to the total tumour uptake. Pochin concluded that the plasma PBI concentration on the 6th day of measurement is a good guide to monitor progress of therapy. Furthermore, if normal thyroid tissue has been ablated, any remaining tumour activity is unlikely if the 6th day PBI measurement is less than 0.003 per cent of the administered dose per litre plasma.

1.8.4 Radionuclide (^{131}I) Scanning

Following surgical excision or radioiodine ablation of normal thyroid tissue, the stimulation resulting from high circulating TSH levels causes residual or metastatic tumour to accumulate radioiodine and appear as "hot lesions" on subsequent scanning. Whole-body scanning (using a rectilinear scanner or gamma camera) thus provides a sensitive method for detecting functioning residual tumour in the neck or in distant metastases. The patient should remain off thyroid hormone replacement postoperatively or discontinue T_4 for 4 weeks (or T_3 for 2 weeks) prior to scanning with ^{131}I. The level of endogenous TSH stimulation achieved is important both for detection and treatment. TSH levels should be above 30 mU per litre in order to achieve adequate uptake by tumour (Edmonds et al, 1977).

Scanning of the whole body is essential so that unsuspected metastases may be detected at an early stage. The optimum time for scanning is about 72 hours after the oral administration of radioiodine (Beckerman et al, 1974) when the physiological sites of uptake or excretion (i.e. salivary glands, stomach, kidneys, bladder and colon) have diminished and there is low background activity. However, this may be too early, especially in elderly patients in whom renal function is impaired, resulting in the obscuration of small lesions by high background activity. Occasionally, whole-body scanning following therapy levels of ^{131}I (that is, 1.85 GBq and above) demonstrates lesions not shown by tracer scanning (Preisman & Halpern, 1978).

1.8.5 Enhancement of Tumour Uptake

Various adjunctive methods to improve uptake and visualisation of tumour have been used. These include:

(i) injection of bovine TSH, which is unnecessary when a sufficient endogenous TSH level is achieved and may cause severe allergic complications (Hershmann & Edwards, 1972; Krishnamurthy & Blahd, 1972);
(ii) diuretic therapy which reduces the total pool of stable iodine (Hamburger, 1969);

(iii) low iodine diet to decrease the dilution of radioiodine entering the tumour with stable iodine in the plasma (Hamburger, 1969);
(iv) antithyroid drugs (such as lithium) which utilise the rebound increased uptake shortly after they are discontinued and possibly also block thyroid hormone production by tumour (Rall et al, 1951).

With the possible exception of diuretic therapy and a low iodine diet, these methods probably do not significantly increase the sensitivity of the method and there are no well controlled trials to support their routine use.

CHAPTER 2

RESULTS OF TREATMENT OF

DIFFERENTIATED THYROID CARCINOMA

1949-1991

2.1 INTRODUCTION

Owing to the rarity of the disease and its long natural history, there are no prospective randomised controlled trials to evaluate different treatment strategies for differentiated thyroid carcinoma. However, useful information on prognostic factors as a basis for therapeutic decisions can be obtained from retrospective studies. The purpose of this study was to review the case notes of all patients with differentiated thyroid carcinoma referred to the Royal Marsden Hospital and to analyse the long-term follow-up results; to define prognostic factors and their relative importance as a possible future guide when determining post-operative treatment. A Data Base was established (Appendix A) on which patient details, treatment and follow-up were recorded. The data were then transferred to the main hospital computer (Hewlett Packard). Survival curve comparisons were performed with the log rank test for univariate analysis and Cox proportional hazard model for univariate analysis (Cox, 1972). A stepwise selection procedure with the Cox proportional hazards regression model was used to determine independent prognostic factors in multivariate analysis.

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 those with diploid

tumours (Cohn et al, 1984; Bengtsson et al, 1984). It is not yet clear, however, how this factor will fit in the order of influence on prognosis and further study is required.

2.2 PATIENTS AND METHODS

2.2.1 Patients

The case notes of six hundred and forty nine patients with differentiated thyroid carcinoma treated during the period 1949 to 1991, were reviewed. The majority of patients were referred from counties in South-East England but a substantial number (33%) came from abroad notably Malta, Gibraltar,Turkey and Greece. Hence, no estimate of incidence can be made from these figures. Many of the patients received their initial surgical treatment at other institutions and were subsequently referred to the Royal Marsden Hospital because of loco-regional recurrence or distant metastases.

Table 2.1: Histology and Grade for 649 Patients with Differentiated Thyroid Carcinoma Treated Between 1969-1991.

Histology	Grade	Number
Papillary	1	369
	2	59
	3	30
Follicular	1	98
	2	45
	3	34
Hürthle	1	11
	2	1
	3	2
TOTAL		649

2.2.2 Histology

Histologically, the tumours were classified according to the World Health Organisation (see Section 1.1.5). In most cases, slides were reviewed from these referring hospitals and institutions. Follicular carcinomas were further graded (I to III). There were 458 papillary, 177 follicular and 14 Hürthle cell carcinomas. For the purposes of analysis, the Hürthle cell carcinomas were included with follicular histology. Table 2.1 shows that 80% of papillary tumours were well-differentiated whereas for follicular carcinomas 55 % were well-differentiated and 19 % were poorly differentiated.

2.2.3 Staging

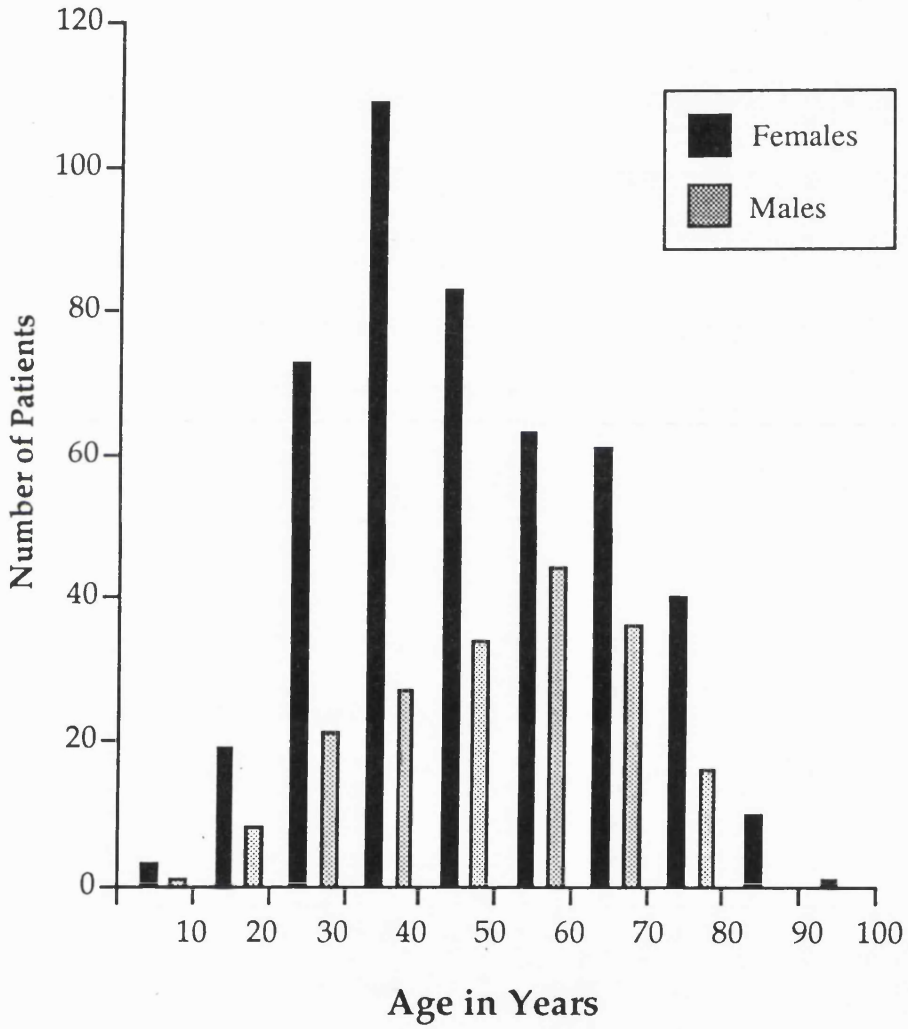
The age and sex of the patient, the presence of distant metastases were determined and patients were staged according to the TNM Classification of Malignant Tumours recommended by the UICC (1987) (Table 2.2). Patients were also catagorised according to the Stage Grouping defined by the UICC (1987).

Table 2.2: TNM Classification at Diagnosis for 649 Patients Treated Between 1949-1991.

Distant Spread	M0			M1			TOTAL
Nodal Status	N0	N1a	N1b	N0	N1a	N1b	
Tx	64	24	7	3	2	1	101
pT1	61	36	6	6	1	1	111
pT2	152	40	18	12	2	4	228
pT3	46	14	7	4		4	75
pT4	59	29	28	5	3	10	134

2.2.3 Follow-up

The frequency of follow-up was three monthly for the first two years, six monthly for the next three years and thereafter annually. At each follow-up visit serum thyroglobulin and chest radiograph were performed (see Fig. 2.2). Median follow-up from diagnosis was 76 months, maximum 514 months.



Figue 2.1: *Age Distribution by Sex for 649 Patients with Differentiated Thyroid Carcinoma Treated Between 1949-1991.*

2.2.2 Clinical Characteristics

There were 462 females and 187 males giving a sex ratio of 2.5 : 1. Fig.2.1 shows the age distribution by sex at presentation for these 649 patients. The median age at presentation was 45 years (range 4-91). For

females the median age at presentation was 43 years (range 4-91) and for males 50 years (range 7-79). The difference in age at presentation was not significantly different for males and females ($p > 0.02$).

2.3 SURGICAL PROCEDURES

Many operations were performed at hospitals allied to the Royal Marsden and from abroad and therefore the initial surgical procedure was not standardised. The following definitions were applied to the type of operation performed on the primary thyroid tumour:

RE resection enucleation

TL total lobectomy
removes all thyroid tissue on one side, exploration of recurrent laryngeal nerve necessary

HT hemi-thyroidectomy
total lobectomy on the affected side together with isthmusectomy

ST subtotal thyroidectomy
leaves a tiny amount of tissue and a complete recurrent laryngeal nerve exploration is not mandatory

NT near-total thyroidectomy
leaves as much tissue behind as needed to protect vital structures on one side (usually 1 to 2 g)
recurrent laryngeal nerve exploration mandatory

TT total thyroidectomy
involves removal of all four parathyroid glands together with exploration of both recurrent laryngeal nerves

The extent of surgery was also recorded as either complete, when the surgeon had removed all macroscopically involved tumour, or incomplete

when obvious tumour was left behind. Neck dissection was catagorised as either modified radical dissection or simple excision of macroscopically involved nodes.

The type of initial operation performed is shown in Table 2.3. In 77 cases, initial surgery was performed at the Royal Marsden Hospital and for the remaining 572 cases initial surgery was performed at other hospitals. At the Royal Marsden Hospital, the policy has been that provided the patient is fit, completion thyroidectomy should be performed in all cases when surgery less than near-total or total thyroidectomy has been performed initially. Radioiodine ablation is then given to destroy any remnants of normal thyroid tissue (see Section 2.5 below). As regards neck dissection, the policy has been that if at initial operation frozen section is positive for metastatic nodes, a modified radical neck dissection is performed in continuity preserving the sternocleidomastoid muscle and spinal accessory nerve.

Table 2.3: Initial Surgical Treatment Performed in 649 Patients with Differentiated Thyroid Carcinoma Between 1949-1991.

			Primary Tumour				Neck Nodes	
Tumour	No. of cases	Biopsy	RE	TL,HT ST	NT	TT	ND	SNE
Papillary	458	37	39	199	82	99	87	91
Follicular	177	9	23	91	23	31	7	16
Hürthle	14	5	2	5				

RE = Resection Enucleation; TL = Total Lobectomy; HT = Hemi-thyroidectomy; ST = Subtotal Thyroidectomy; NT = Near-Total; TT = Total; ND = Neck Dissection; SNE = Simple Node Excision.

2.4 ENDOCRINE THERAPY

In the immediate post-operative period, all patients were reviewed for signs and symptoms of hypocalcaemia and serum calcium monitored. If hypocalcaemia was evident, patients were treated with calcium supplements and Vitamin D. Following thyroidectomy, all patients received thyroid hormone replacement therapy with either T_4 200 μg daily or T_3 60μg daily. Thyroid function was monitored and thyroid hormone replacement adjusted in order to render the patient biochemically euthyroid.

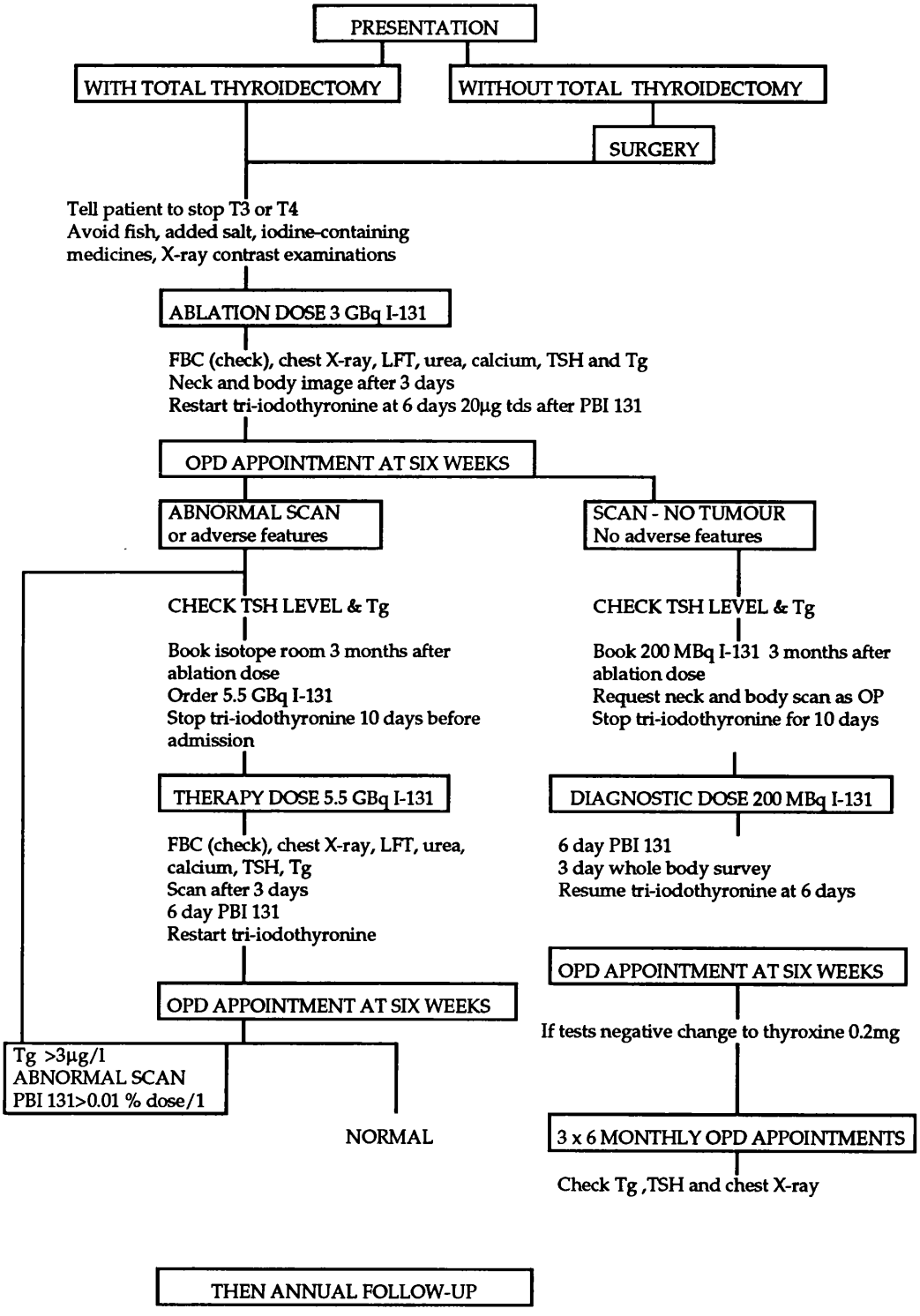
2.5 THYROID REMNANT ABLATION

Thyroid remnant ablation with radioiodine was adopted as Thyroid Unit policy for all patients following initial surgery after 1972 under the care of one consultant and is outlined in Fig. 2.2 . The policy is to give 3.0 GBq ^{131}I for ablation of thyroid remnants following near-total thyroidectomy.

2.6 RADIOIODINE THERAPY

Patients with loco-regional or distant metastases were subsequently treated with a therapy activity of 5.5 GBq ^{131}I at three to six monthly intervals until all traces of uptake were eliminated on subsequent scanning or there was obvious disease progression. At this hospital, there is no upper limit of the cumulative activity of ^{131}I that patients may receive.

Table 2.2: PROTOCOL FOR DIFFERENTIATED THYROID CARCINOMA



2.7 TREATMENT OUTCOME IN 649 PATIENTS WITH DIFFERENTIATED THYROID CARCINOMA

2.7.1 Survival

Survival curves are shown in Figs. 2.3 to 2.12. There was a significant survival advantage for females compared with males (Fig. 2.3, $p < 0.01$). Patients with papillary histology had a significantly better survival than those with follicular carcinoma with 15 year survival rates of 71% and 50% respectively (Fig. 2.4, $p < 0.005$). Survival by histological grade (Fig. 2.5) showed that patients with histological grades I and II (papillary and follicular) had a significantly better survival than those with poorly differentiated tumours (grade III). The importance of age in determining survival is shown in Fig. 2.6 with survival rates at 15 years of 90% for patients less than 40 years of age, falling to 70% for patients 40 to 59 years; 65% for patients 50 to 59 and less than 20% for age 59 and over; these differences are significiant ($p < 0.005$).

Survival by TNM Stage (UICC 1987) for patients less than 45 years (Fig. 2.7) showed that the presence of distant metastases at presentation did not adversely affect outcome whereas for patients over 45 years survival at 15 years for Stage I was 90% contrasted with only 5% for Stage IV patients (Fig. 2.8). For papillary carcinoma, survival by nodal status showed no adverse effect of lymph node involvement on survival (Fig.2.9, $p>0.1$). For follicular histology, however, nodal involvement at diagnosis did adversely effect survival with 15 year survival rates of 50%, 28% and 15% for patients with stages N0, N1a and N1b respectively (Fig.2.10).

The influence of the type of initial surgical procedure on survival is shown in Figs. 2.11 for 649 patients. A total of 105 patients underwent near- total thyroidectomy and these patients had the best long term results with a 75% 15 year survival. Results for patients in whom resection enucleation or biopsy only was performed were much poorer with 35% survival at 15 years. Survival according to era of presentation (Fig. 2.12) shows a significant survival advantage for patients treated after 1972 with 10 year survival rates of 75% for patients treated after 1972 compared with 62% for patients treated from 1949 to 1972. This may be due to presentation at an earlier age or may reflect the routine use of radioiodine ablation adopted as Thyroid Unit policy after 1972.

The indications for and results of external beam radiotherapy in differentiated thyroid carcinoma are presented in Chapter 3.

Figure 2.3: Survival (%) by Sex for 649 Patients with Differentiated Thyroid Carcinoma Treated Between 1949-1991. Table 1 = male (187 cases); Table 2 = female (462 cases).

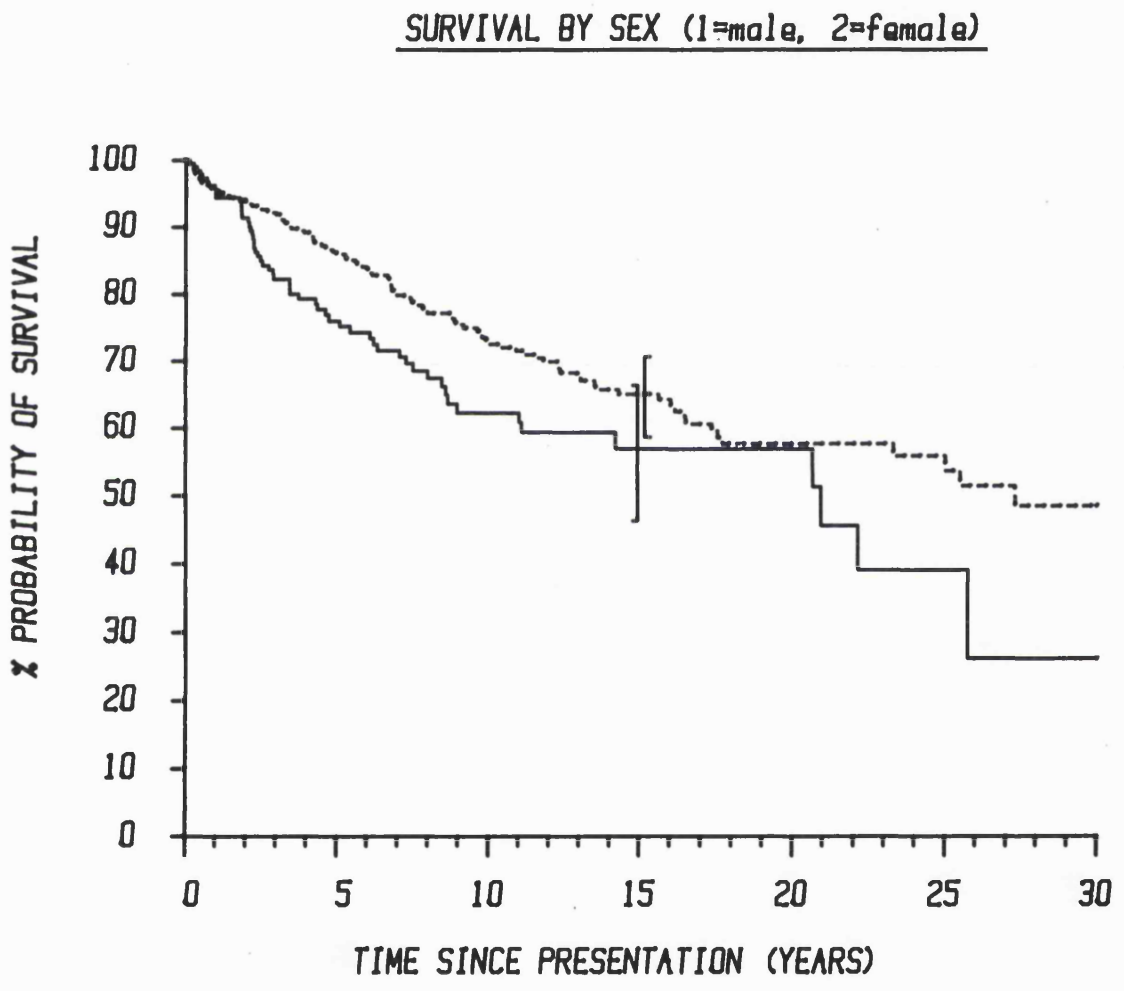


TABLE 1 _____ = 187 Cases (O = 58, E = 43.1).
TABLE 2 _ _ _ _ _ _ = 462 Cases (O = 119, E = 133.9).

Difference is significant (chi-square = 6.78, df. = 1, P < 0.01)

Figure 2.4: Survival (%) by Histology for 649 Patients with Differentiated Thyroid Carcinoma Treated Between 1949-1991. Table 1 = papillary (456 cases); Table 2 = follicular (191 cases including 14 Hürthle cell carcinomas).

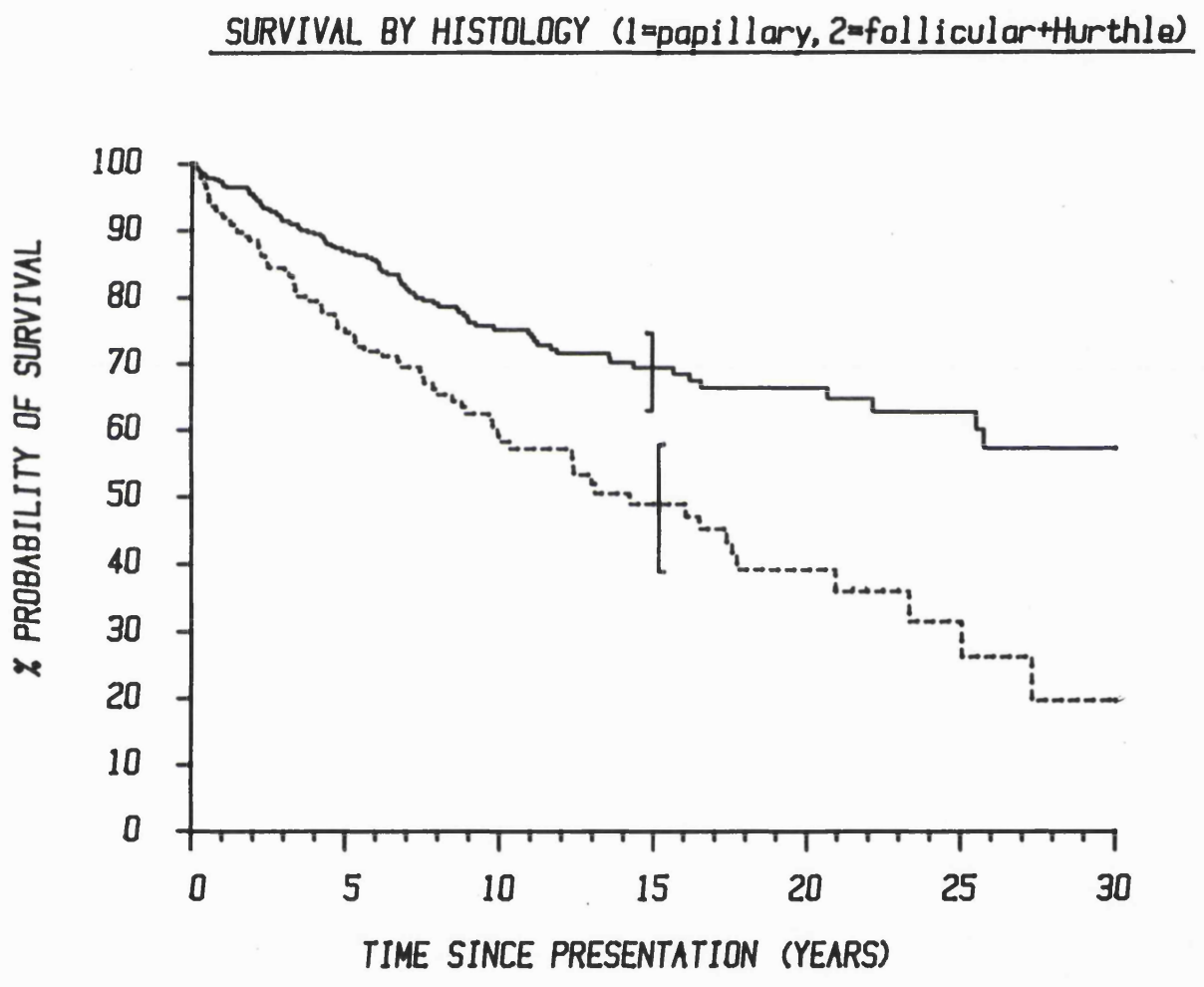


Figure 2.5: Survival (%) by Histological Grade for 649 Patients with Differentiated Thyroid Carcinoma Treated Between 1949-1991. Table 1 = well-differentiated papillary and follicular (459 cases); Table 2 = moderately well differentiated (105 cases); Table 3 = poorly differentiated (66 cases).

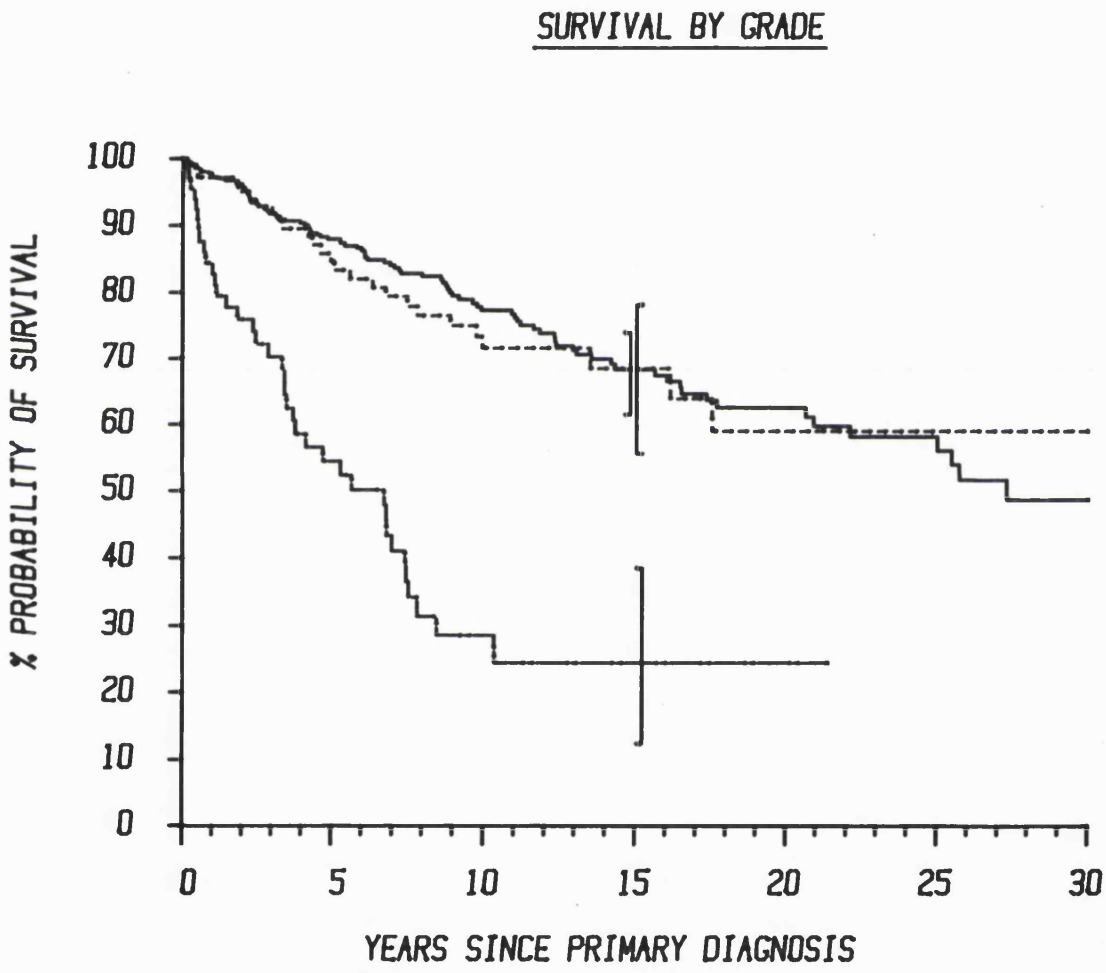


Figure 2.6: Survival (%) by Age for 649 Patients with Differentiated Thyroid Carcinoma Treated Between 1949-1991. Table 1 = age < 40 years (204 cases); Table 2 = age 40-59 (83 cases); Table 3 = ages 50-59 (63 cases); Table 4 = age > 59 (112 cases).

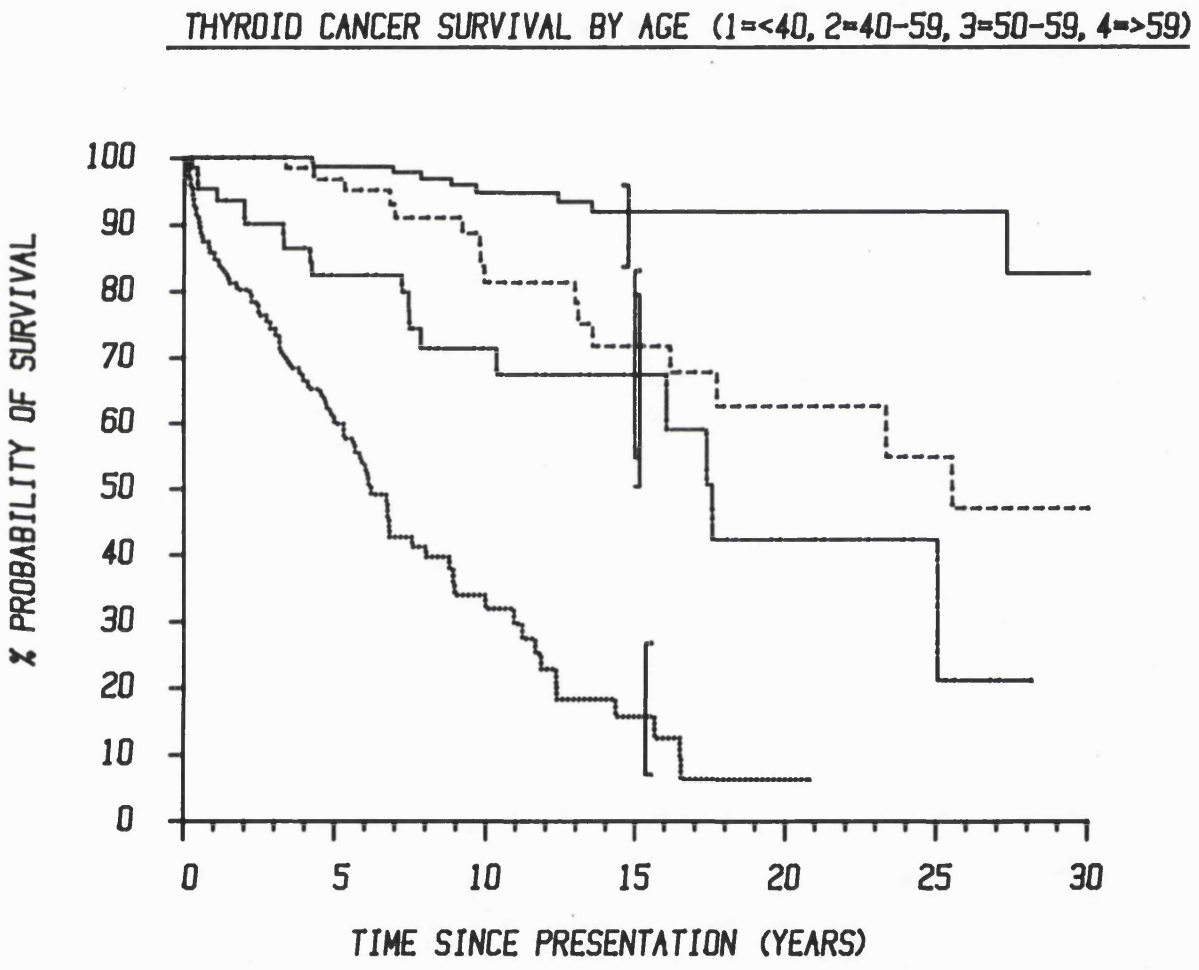


Figure 2.7: Survival (%) by Staging for Patients < 45 Years. Table 1 = Stage I (315 cases); Table 2 = Stage II (16 cases). For Stage Group definition see Table 1.3 (UICC, 1987).

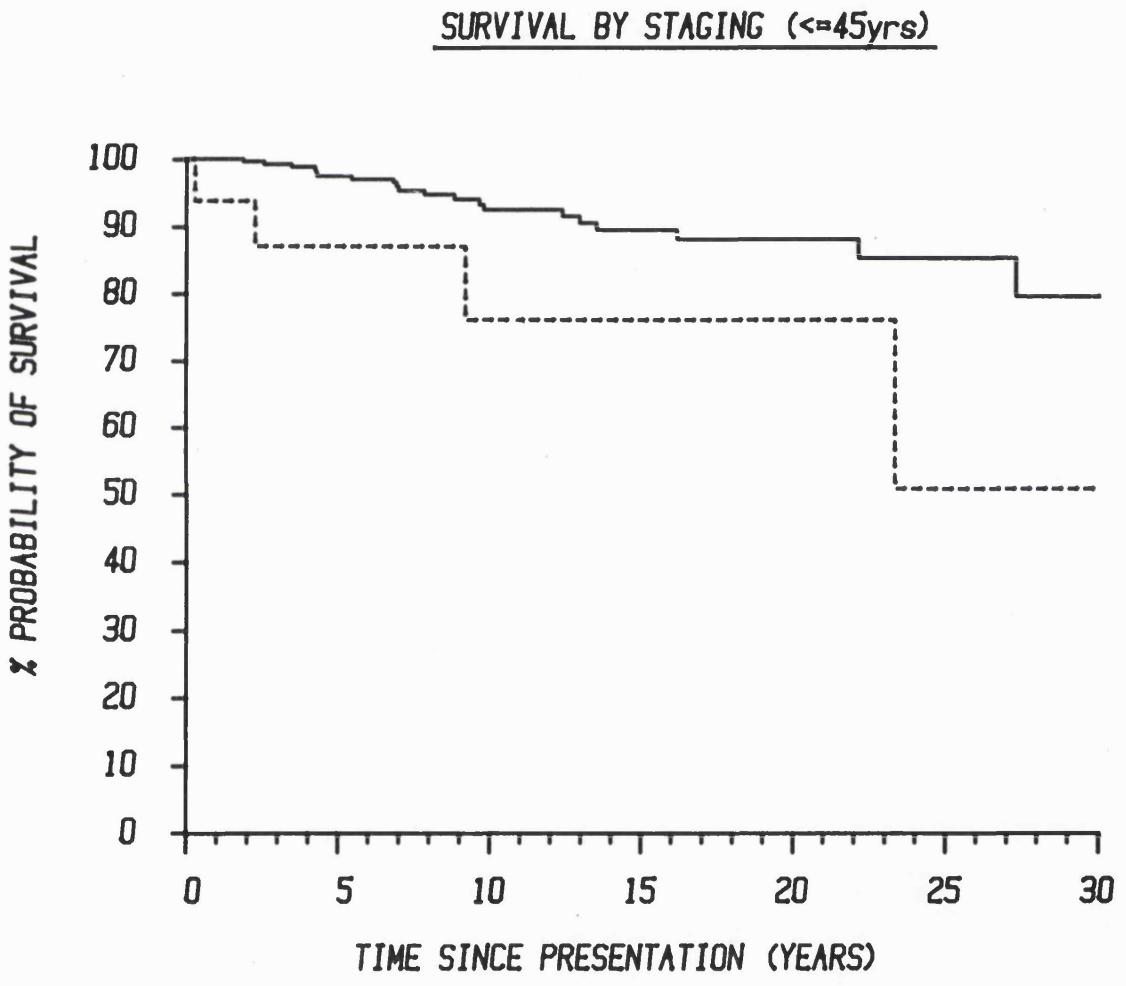


TABLE 1 _____ = 315 Cases (O = 24, E = 25.7).
TABLE 2 _ _ _ _ _ _ = 16 Cases (O = 4, E = 2.3).

Difference is not significant (chi-square = 1.43, df. = 1, P > 0.1)

Figure 2.8: Survival (%) by Staging for Patients > 45 Years. Table 1 = Stage I (345 cases); Table 2 = Stage II (126 cases); Table 3 = Stage III (126 cases); Table 4 = Stage IV (52 cases). For Stage Group definition see Table 1.3 (UICC, 1987).

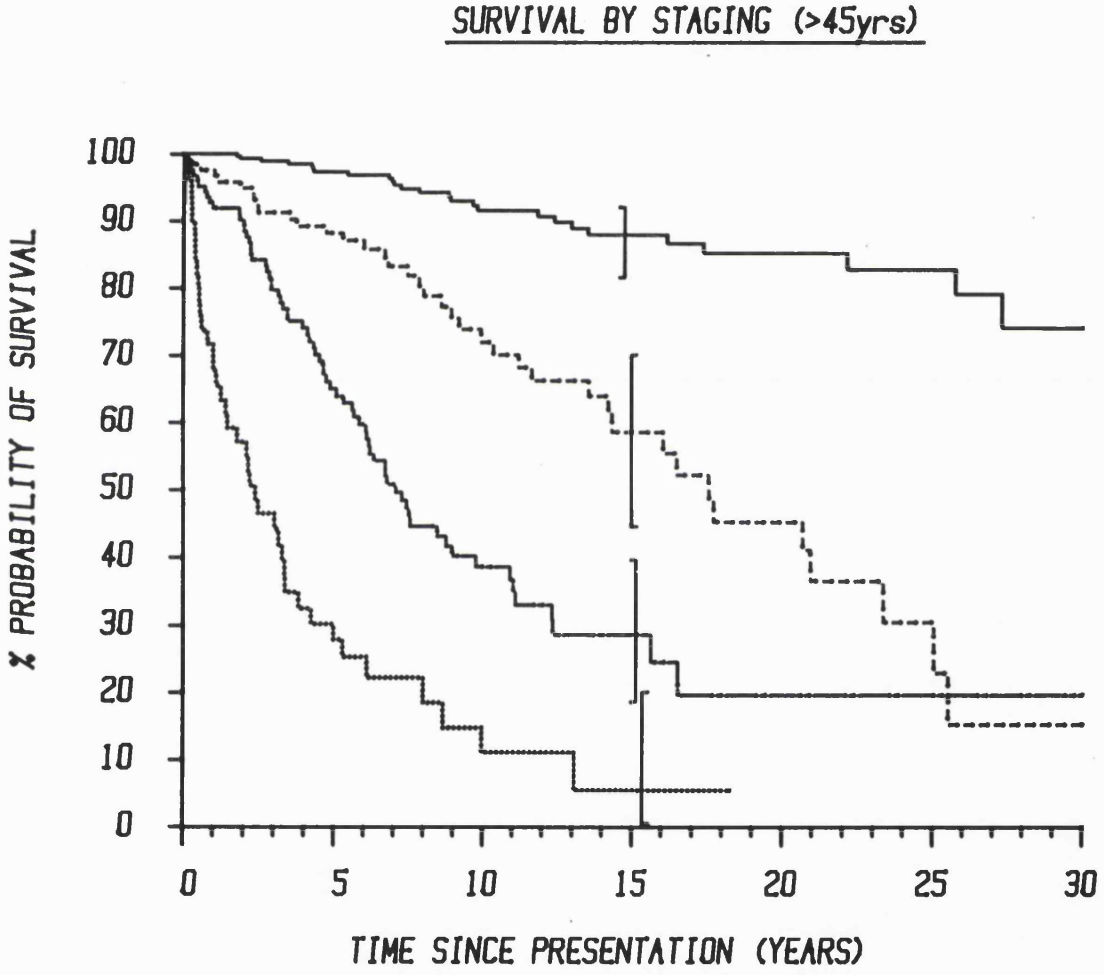


Figure 2.9: Survival (%) by Lymph Node Status for Patients with Papillary Carcinoma. Table 1 = N0 (247 cases); Table 2 = N1a (133 cases); Table 3 = N1b (75 cases). Lymph node status as defined in Table 1.3 (UICC, 1987).

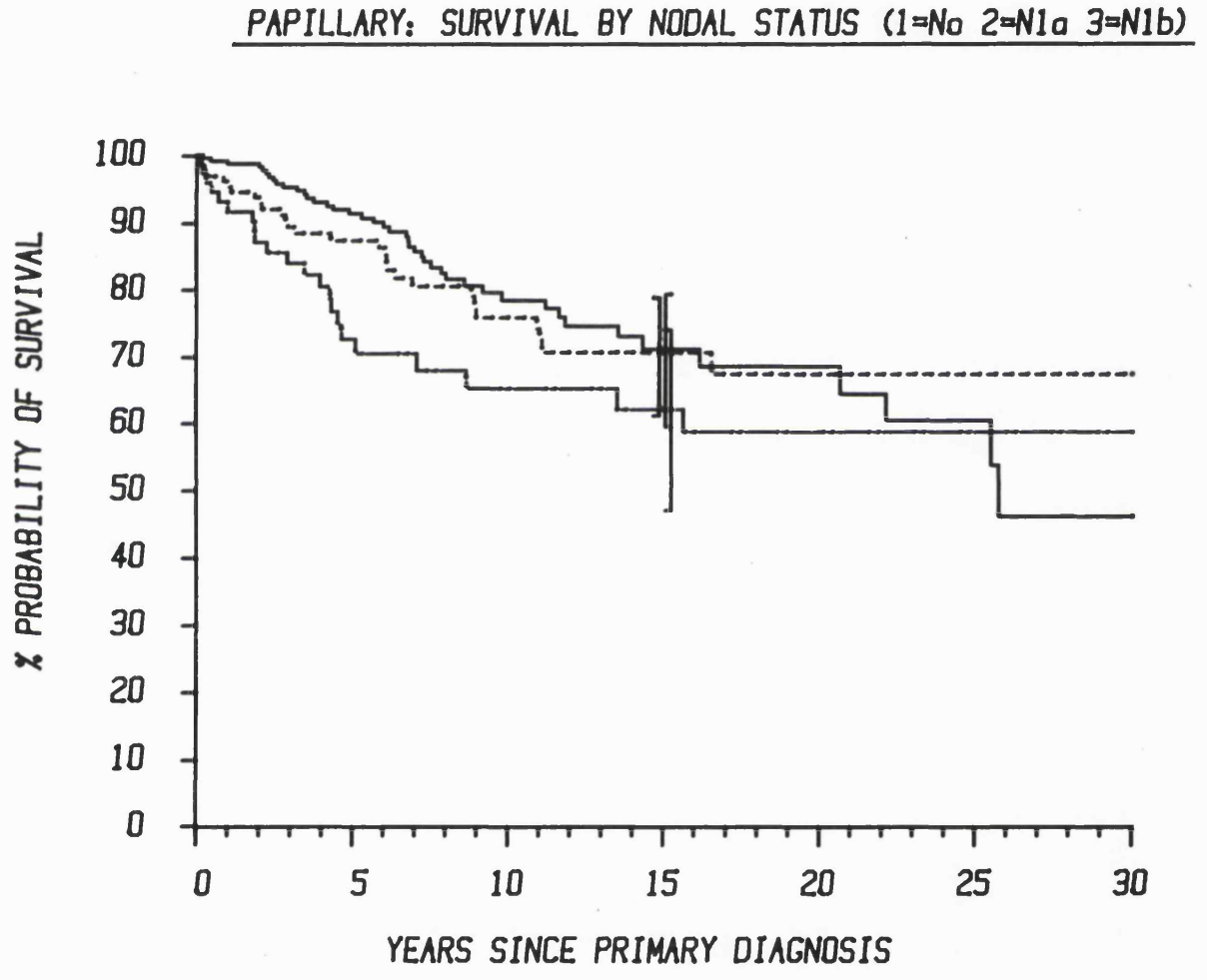


Figure 2.10: Survival (%) by Lymph Node Status for Patients with Follicular Carcinoma. Table 1 = N0 (150 cases); Table 2 = N1a (17 cases); Table 3 = N1b (9 cases). Lymph node status as defined in Table 1.3 (UICC, 1987).

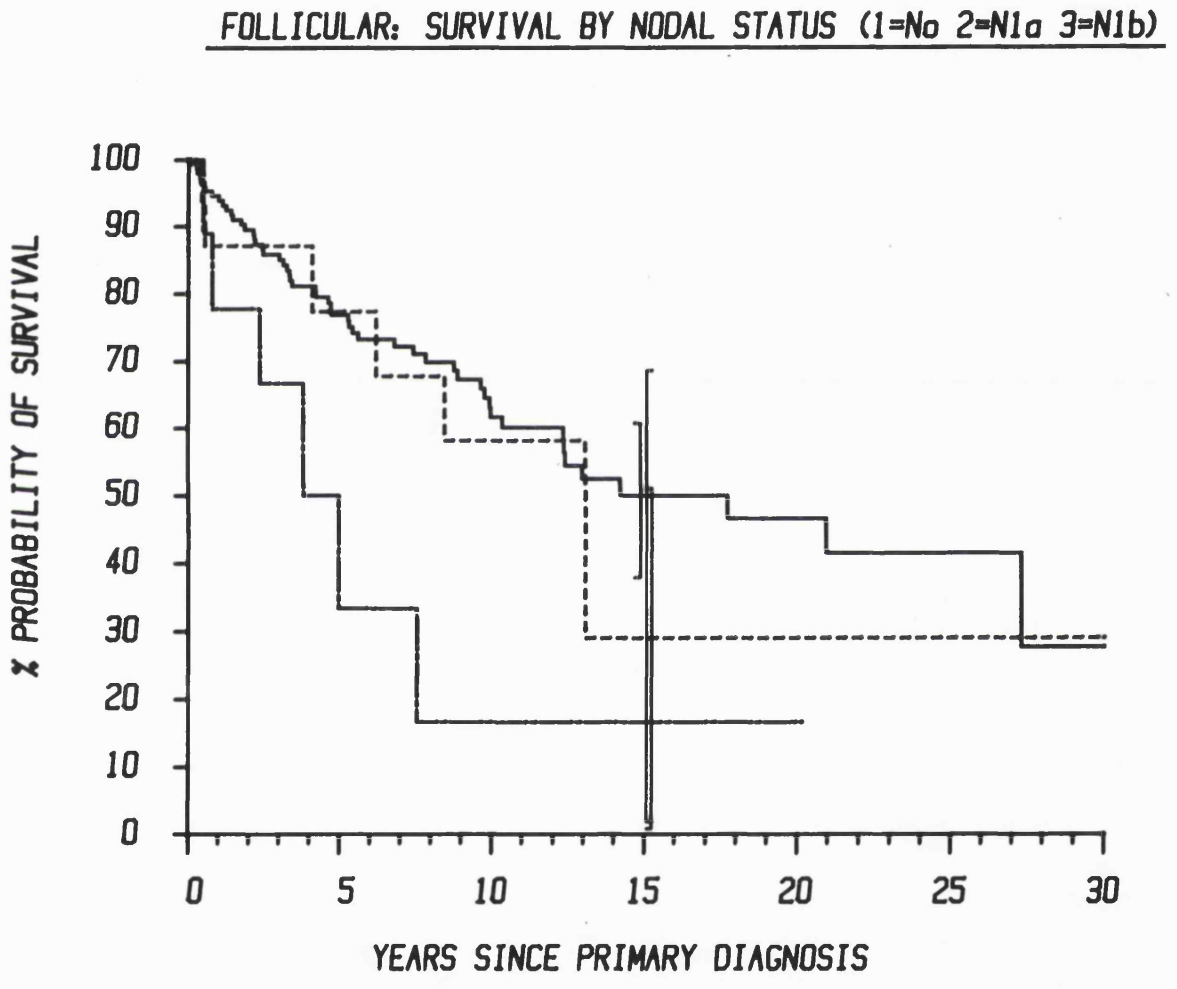


TABLE 1 _____ = 150 Cases (O = 54, E = 57.8).
TABLE 2 _ _ _ _ _ = 17 Cases (O = 6, E = 5.9).
TABLE 3 _____ = 9 Cases (O = 6, E = 2.3).

Difference is significant (chi-square = 6.01, df. = 2, P < 0.05)
Trend test is significant (chi-square = 4.11, P < 0.05)

Figure 2.11: Survival (%) Following Metastasis. Table 1 = patients with lung metastases only (72 cases); Table 2 = patients with other sites of distant metastases (52 cases).

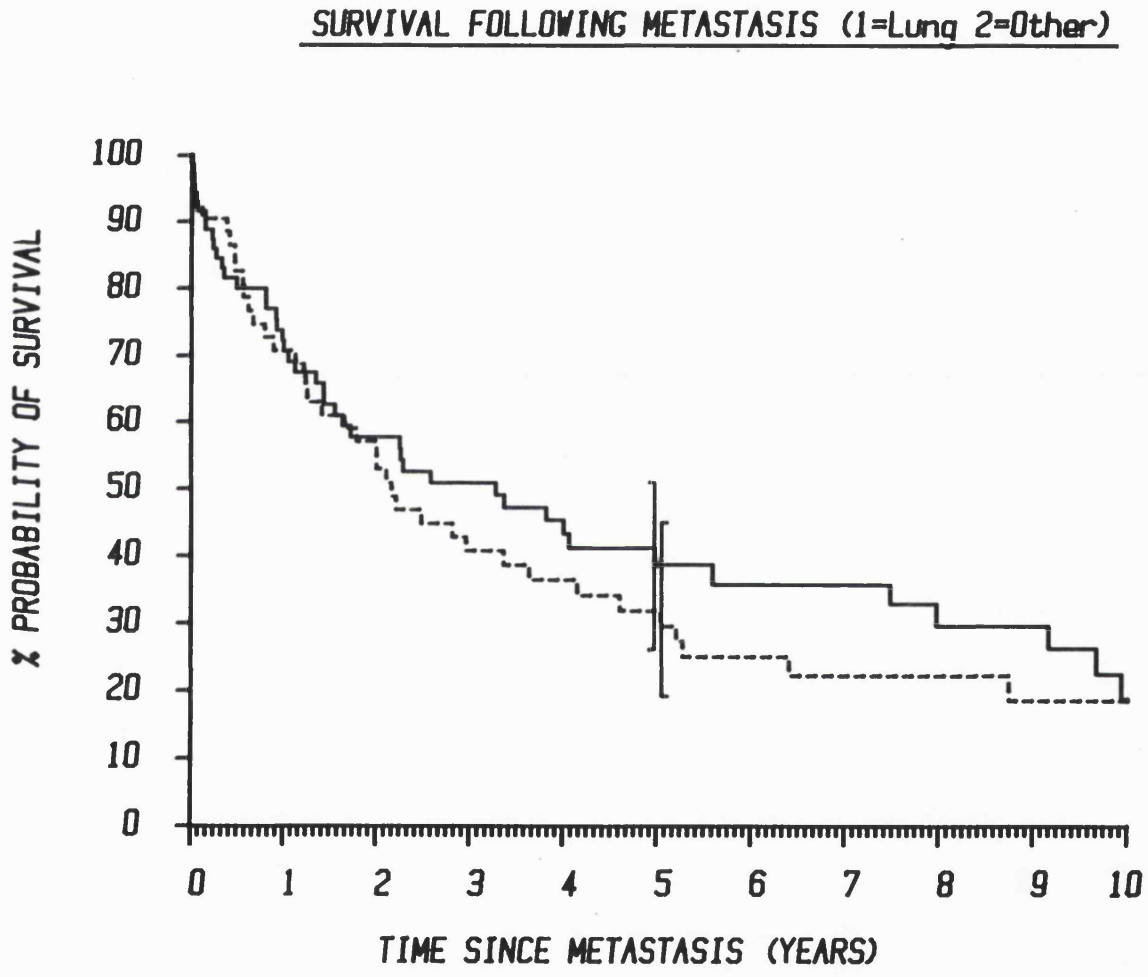


TABLE 1 _____ = 72 Cases (O = 44, E = 48.4).
TABLE 2 _ _ _ _ _ _ _ = 52 Cases (O = 42, E = 37.6).

Difference is not significant (chi-square = 0.91, df. = 1, P > 0.1)

Figure 2.12: Survival (%) by Type of Initial Surgical Procedure for 649 Patients Treated Between 1949-1991. Table 1 = biopsy only or resection enucleation (115 cases); Table 2 = subtotal, total lobectomy or hemi-thyroidectomy (298 cases); Table 3 = near-total thyroidectomy (105 cases); Table 4 = total thyroidectomy (131 cases).

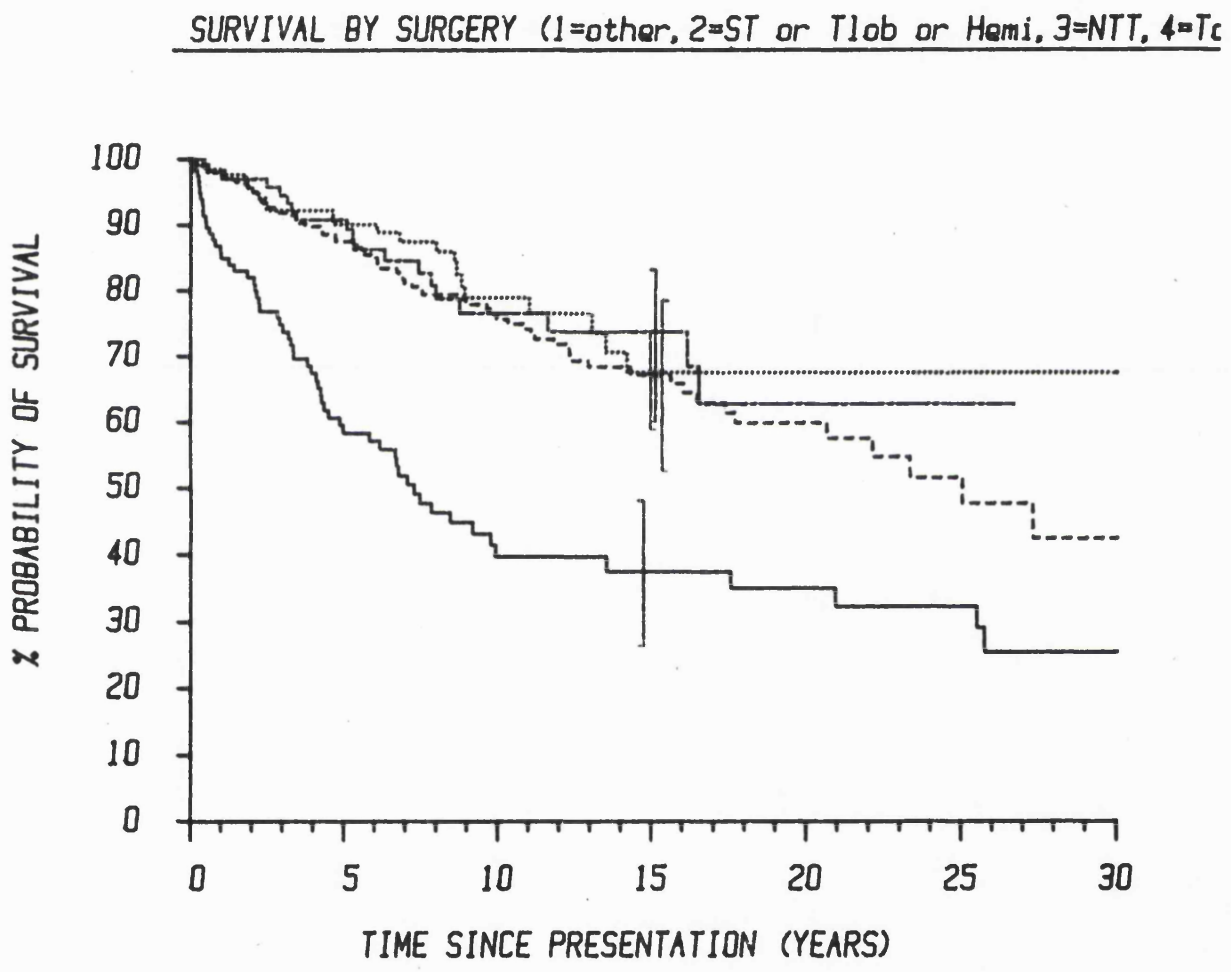


Figure 2.13 *Survival (%) by Era of Presentation. Table 1 = 1949 to 1972 (165 cases); Table 2 = 1972-1991 (484 cases).*

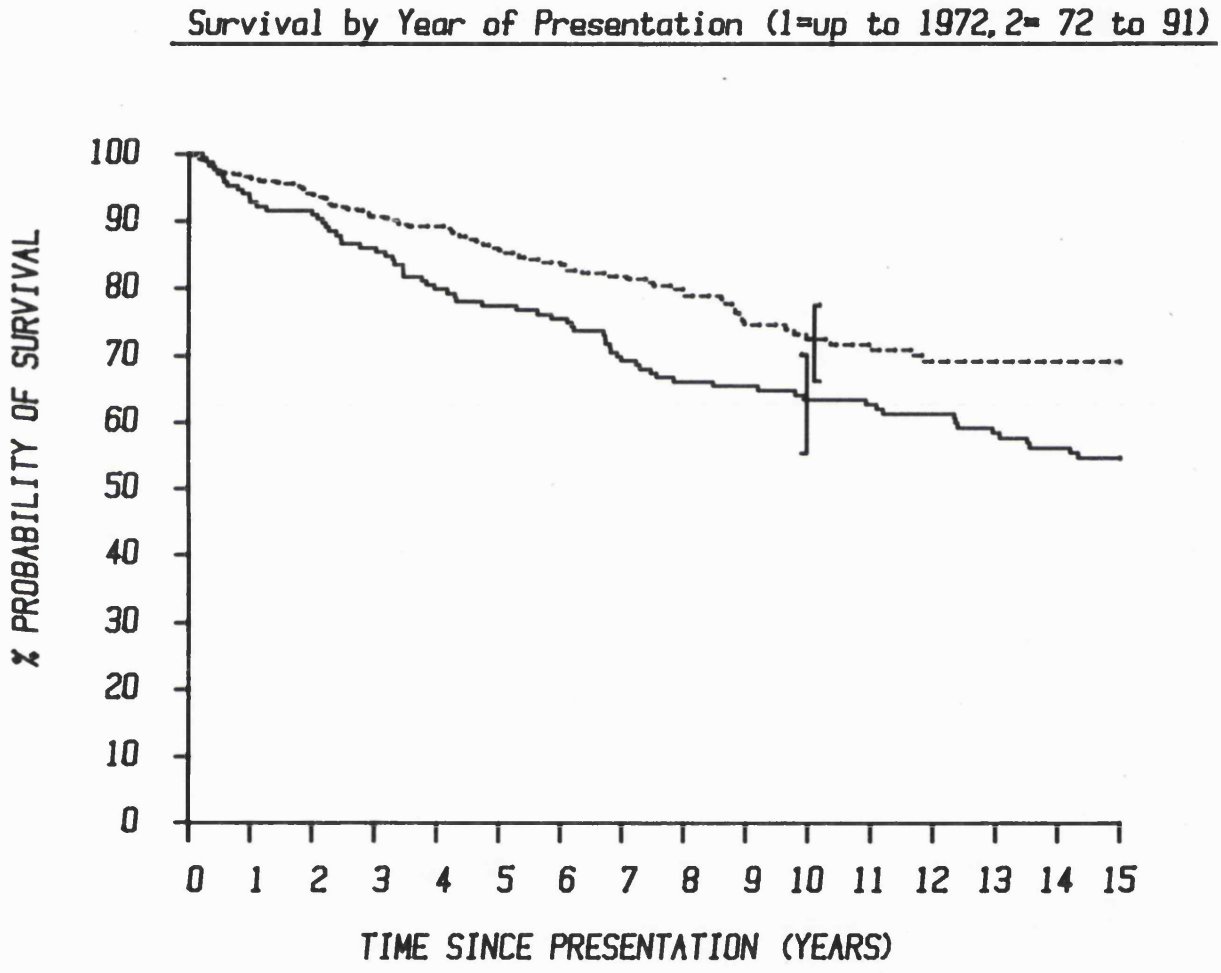


TABLE 1 _____ = 165 Cases (O = 90, E = 72).
TABLE 2 _ _ _ _ _ = 484 Cases (O = 87, E = 105).

Difference is significant (chi-square = 7.56, df. = 1, P < 0.01)
Trend test is significant (chi-square = 7.56, P < 0.01)

2.8 PROGNOSTIC FACTORS IN THYROID CARCINOMA

2.8.1 Results of Univariate Analysis

Table 2.4: Results of Univariate Analysis for Prognostic Factors in 649 Patients Treated Between 1969-1991.

Factor		Hazard Ratio (95% confidence interval)	p-value
Age	<20	1.00	
	20-29	4.80(1.53-15.1)	
	30-39	8.14(2.78-23.8)	*p<0.001
	40-49	19.5(6.71-56.6)	
	50-59	41.8(14.6-119.6)	
	>60	89.2(30.8-258)	
Sex	Male	1.00	p = 0.01
	Female	0.66(0.48-0.90)	
Histology	Papillary	1.00	
	Follicular	2.07(1.54-2.79)	p<0.001
Grade	I	1.00	
	II	1.10(0.71-1.70)	*p<0.001
	III	4.44(3.03-6.49)	
T-Stage	T1	1.00	
	T2	2.02(1.09-3.74)	*p<0.001
	T3	3.37(1.74-6.54)	
	T4	6.10(3.33-11.2)	
Multifocality	Unifocal	1.00	not significant
	Multifocal	0.76(0.50-1.17)	
Lymph Node Status	N0	0.77(0.51-1.15)	
	N1a	0.64(0.40-1.05)	not significant
	N1b	1.00	
Distant Metastases	None	1.00	
	Lung	3.61(2.24-5.83)	p<0.001
	Any	10.64(6.4-17.6)	

*p-value for trend, all other p-values refer to tests for heterogeneity

Survival curve comparisons were made with the log rank test for univariate analysis. Univariate analysis of 8 possible prognostic factors (excluding treatment) demonstrated that age at diagnosis, female sex, pathologic type, T-stage and distant metastases were of statistical significance (Table 2.4). Multifocality (present in 30% of all tumours) proved to be of no prognostic significance. Lymph node status was not associated with a worse prognosis. Patients with pulmonary metastases had a better survival than those with distant metastases at other sites.

2.8.2 Results of Multivariate Analysis

Table 2.5: Results of Multivariate Analysis Using Cox's Regression Model for 649 Patients with Differentiated Thyroid Carcinoma Treated Between 1949-1991.

Variable		Hazard Ratio (95% confidence interval)	p-value
Age	<30	1.00	
	30-39	4.50(1.68-12.0)	
	40-49	14.9 (5.98-37.3)	*p<0.001
	50-59	25.9 (10.5-63.8)	
	>60	34.06 (14.0-83.2)	
Grade	I,II	1.00	
	III	2.81 (1.87-4.22)	*p < 0.01
Stage	T0,T1,T2	1.00	
	T3	1.78 (1.09-2.90)	*p < 0.001
	T4	3.13 (2.11-4.65)	
Metastases	None	1.00	p < 0.001
	Lung only	3.41(1.96-5.94)	
	Other	10.10 (5.59-18.3)	

*p-value for trend, all other p-values refer to tests for heterogeneity

Ranking of prognostic factors by multivariate analysis (Table 2.5) showed that age was the most important factor determining survival followed by histological grade, stage at presentation and the presence of metastases.

2.8.3 Derivation of Risk Groups

In order to minimise the probability of obtaining risk groups that appear spuriously good predictors because the are derived and tested on the same group of patients, it is necessary to divide patients into two groups. A prognostic index can then be derived in one group and tested in the other (independent) group. If it performs well in this second group an overall prognostic index can then be calculated, which can be applied to other studies, by re-deriving the index from all patients.

Patients were split into two approximately equal sized groups on the basis of presentation date. The earlier group was then used to divide the patients into risk groups by deriving a prognostic index based upon the log hazard ratio obtained from multivariate analysis using Cox's regression (Cox, 1972). These risk groups were then tested in the second group of patients. The prognostic index was based on the coefficients for the log hazard ratio derived from Cox's regression. In the first group of patients the score was derived as shown in Table 2. 6 .

Table 2. 6: Derivation of Prognostic Index Based on Log Hazard Ratio Using Cox's Regression.

	Age	Add	Grade	Add	T-stage	Add	Distant Meta-stases	Add
Score=0+	<30	0	I,II	0	T1,2	0	None	0
	30-39	1.5	III	1	T3	0.5	Lung	1
	40-49	2.5			T4	1	Any	2
	50-59	3.5						
	>60	4						

Thus, for a patient age 45 years with a Grade II, T3 tumour and no distant metastases the score would be three:

0+	**Age**	**+2.5**	**Grade**	**+0**	**T-stage**	**+0.5**	**Distant Meta-stases**	**+0**

The score was then used to divide the patients into four risk groups (Table 2.7).

Table 2. 7 : Definition of Risk Groups Using Prognostic Score.

Risk Group	Score
I	0-0.99
II	1-2.99
III	3-3.99
IV	>4

These risk groups were then compared, in the second group of patients, with the groups defined by age alone (the best single predictor). The risk groups were found to be significantly better (chi-square = 16, $p<0.001$). This reinforced the usefulness of this definition of risk groups.

All patients were then used to derive the risk groups; this only resulted in a change in the score contributed by the 50-59 age group (Table 2.9).

Table 2. 8: Re-definition of Prognostic Index Based on Log Hazard Ratio Using Cox's Regression for all Patients.

	Age	Add	Grade	Add	T-stage	Add	Distant Meta-stases	Add
Score=0+	<30	0	I,II	0	T1,2	0	None	0
	30-39	1.5	III	1	T3	0.5	Lung	1
	40-49	2.5			T4	1	Any	2
	50-59	3						
	>60	4						

These four risk groups are shown in Table 2.9. Fig.2.14 shows the survival for these four groups.

Table 2.9: Definition of Risk Groups Using All Patients.

Risk Group	Score	No. of Patients
I	0-0.99	159
II	1-2.99	173
III	3-3.99	76
IV	>4	130

Figure 2.14: Survival (%) for Risk Groups in Differentiated Thyroid Carcinoma as Calculated by Cox's Proportional Hazard Model. Risk Group Definition Shown in Table 2.9. Table 1 = prognostic group I (159 cases); Table 2 = prognostic group II (173 cases); Table 3 = prognostic group III (76 cases); Table 4 = prognostic group IV (130 cases).

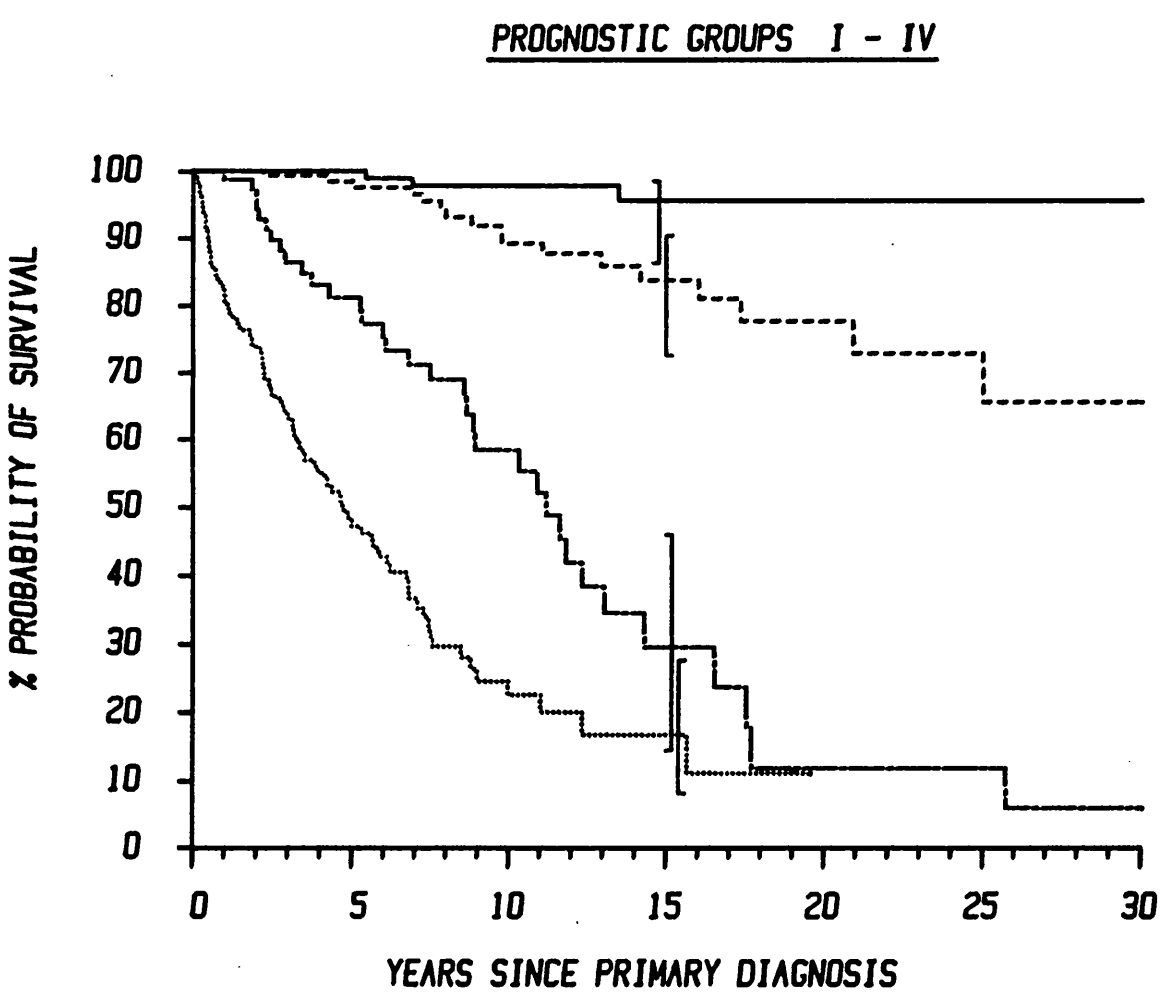


TABLE 1 _____ = 159 Cases (O = 4, E = 48.9).
TABLE 2 ------- = 173 Cases (O = 18, E = 51.4).
TABLE 3 _ _ _ _ = 76 Cases (O = 34, E = 18.8).
TABLE 4 ..... = 130 Cases (O = 84, E = 20.8).

Difference is significant (chi-square = 267.17, df. = 3, P < 0.005)
Trend 231.8

2.8.4 Discussion of 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: patient-related factors such as age and sex; and tumour-related factors including tumour size, extra-thyroidal invasion, nodal involvement, distant metastases, histopathologic type and grade.

In the literature there is a difference of opinion over the relative importance of these factors, particularly the age factor. In univariate studies age has been identified as the single most important risk factor. Many studies have recognised the increasingly adverse effect of advancing age at diagnosis of patients with differentiated thyroid carcinoma (Mazzaferri et al, 1977; Young et al, 1980; Tubiana et al, 1985; Carcangiu et al, 1985; Simpson et al, 1987). The results of the multivariate analysis presented in this Thesis confirm the importance of age as the single most important predictor of outcome. However, other studies such as Bacourt et al, 1986 and Schelfhout et al (1988) have cast some doubt on the importance of age. Differences between univariate and multivariate analyses with regard to the age factor may be explained by the close relationship between the factors age, histological grade and tumour stage (Buckwalter & Thomas, 1972; Bacourt et al, 1986).

Sex is of less prognostic importance; males tend to fare poorly compared with females (Byar et al, 1979; Fourquet et al, 1983; Tubiana et al, 1985; Simpson et al, 1987). The reults of the Royal Marsden study also show a survival advantage for females. Other studies, however, have shown that male sex has no adverse effect on outcome (Wanebo et al, 1981).

In most univariate studies the prognosis of patients with papillary carcinoma has been found to be more favourable than that of patients with follicular histology (Woolner et al, 1961; Franssila , 1973; Samaan et al, 1983; Cady et al , 1985). These findings are confirmed by the results presneted in this Thesis. There are, however, differences in opinion concerning the clinical usefulness of histological grading for papillary and follicular thyroid carcinoma (Carcangiu et al, 1985). Some authors state that the presence of solid elements as a parameter of tumour grade in papillary carcinoma is not related to prognosis (Woolner et al, 1961; Carcangiu et al, 1985). However, other authors have found that the presence of anaplastic foci and of more than 25% solid structures was correlated with poorer survival in patients with papillary carcinoma (Tscholl-Ducommun &

Hedinger, 1982; Sakamoto et al, 1983; Schelfhout et al, 1988). Simpson et al (1987) have found the degree of differentiation to be of prognostic significance for papillary carcinoma but not for follicular carcinomas.

Most multivariate studies agree on the importance of tumour stage (represented either by primary tumour extension or the presence of distant metastases) as one of the most important prognostic indicators (Byar et al, 1979; Wanebo et al, 1981; Fourquet et al, 1983; Meybier et al, 1983; Ladurner et al 1985; Tubiana et al, 1985; Bacourt et al, 1986; Kerr et al, 1986; Hannequin et al, 1986; Joensuu et al, 1986; Romme et al, 1986; Tennvall et al, 1986; Simpson et al, 1987; Schelfhout et al, 1988). Extra-thyroidal invasion has proved to be an important prognostic factor (Woolner, 1971; Byar et al, 1979; Cady et al, 1979; Samaan et al, 1983; Carcangiou et al, 1985; Simpson et al, 1987). The results of multivariate analysis presented in this Thesis also confirm this: patients with a large primary tumour (greater than 4 cm) or extension beyond the thyroid gland had worse survival than those with smaller tumours confined to the thyroid; patients with distant metastases at presentation also had a worse survival than those with no distant dissemination but this was of far greater importance for older patients. Although most individuals with distant metastases eventually die of their cancer, survival for many years is well recognised and children and young adults may survive for decades with pulmonary metastases. Indeed growth of both the primary and its metastases may be so slow that calcification and even ossification may occur. The primary and its metastases may remain stationary for long periods of time or even spontaneously regress for a while and then reappear later. Starr (1962) reported a case of pulmonary metastases from papillary carcinoma of the thyroid which regressed after 9 years of observation. Usually, the tumour and its metastases retain the same morphological pattern throughout their history although some may undergo anaplastic transformation. In Simpson's study (1987) distant metastases proved not to be significant for cause-specific survival with papillary carcinoma possibly reflecting this abilitity of young patients to live with pulmonary metastases for many years and also the eradication of lung metastases by radioiodine therapy. In contrast, however, Simpson's study (1988) found that distant metastases were the second most important predictor of survival among patients with follicular carcinoma.

Lymph node involvement appears to be a much weaker prognostic factor for survival. The risk of distant metastases is not necessarily increased. Thus, it differs from other head and neck cancers, where disease

progresses from local involvement to node metastasis when larger and to distant metastasis when neglected. On rare occasions, papillary carcinoma will spread via the blood stream in the absence of nodal involvement. Several studies have not found a reduction of survival when lymph nodes were involved at histologic examination (Woolner, 1971; Samaan et al, 1973; Lacour et al, 1977; Cady et al, 1979; Staunton & Skeet, 1979; Mazzaferri et al, 1977; Young et al, 1980; McConahey et al, 1981;). The results of univariate analysis in this Thesis showed no adverse influence of nodal involvement for differentiated thyroid carcinoma. Indeed, some authors have reported improved survival for patients with nodal involvement. Cady et al (1976) studied 792 patients with differentiated thyroid carcinoma. His study suggested that patients with involved nodes had a better survival than those with negative nodes and survival was proportional to the number of nodes involved. The number of metastatic nodes was inversely proportional to age. In a subsequent paper from the Lahey Clinic (Rossi et al,1986) it was reported that involvement of lymph nodes increased recurrence rates but did not affect survival. Like other authors, they found no difference in survival between patients treated by standard neck dissection and those having modified dissections.

Some authors have reported worse prognosis in patients with nodal involvement when compared to those without nodes. Harwood et al (1978) compared the survival of 50 patients who had negative nodes with 50 who had positive nodes in differentiated thyroid cancer. Twenty-four percent of patients with nodal involvement at initial examination died of thyroid carcinoma whereas only 8% of those without nodes died of the disease. They demonstrated that nodal disease had an adverse effect on prognosis especially in older patients (41% of patients over 40 years with involved nodes died of thyroid carcinoma). Mackenzie (1971) reported a higher incidence of recurrence in patients with nodal disease treated by limited node excision (36%) than those having radical neck dissection. In both groups however, recurrences were successfully treated. Mazzaferri et al (1977) reviewed a series of 576 papillary thyroid carcinomas treated surgically. Of these, 46% had involvement of regional nodes; 233 (40%) of the patients had some form of neck dissection. In their series, there was a slight increase in recurrence and fatality rate in the group having lymph node metastasis, the type and extent of the neck dissection did not seem to affect prognosis. McGregor at al (1985) reported on 77 patients with well-differentiated thyroid carcinoma and proven lymph node metastasis. Of 33

patients with limited nodal involvement (less than 10 nodes) 26 had less than a modified neck dissection; 35% recurred and two died of disease. Of 44 patients with extensive nodal involvement (more than 10 nodes) 24 had limited neck dissections; 50% recurred and six died of disease.

Lymph node metastases are common in young patients and the relatively good prognosis of patients with lymph node involvement may simply reflect the prominent influence of age. When all factors are favourable: for example, a small primary papillary carcinoma not reaching the surface of the gland in a young female, whether or not local lymph nodes are involved, many centres would now agree that radical therapy is not indicated. Indeed, the EORTC (Byar et al, 1979) analysis, supported by the long-standing Mayo clinic survival data, suggests that this good prognostic group (Table 2.10) warrants minimal treatment including adequate surgical excision together with TSH suppression. However, long term assessment is mandatory.

However, other multivariate analyses have shown lymph node involvement to be an important predictor of tumour recurrence (Simpson et al, 1987). It has been suggested that the lack of influence on survival is due to the highly successful management of nodal recurrence by surgery, particularly for papillary carcinoma (Simpson et al, 1987).

Table 2.10: *Minimal Treatment Good Prognosis Group (EORTC, Byar et al, 1979)*

All These Criteria Together
Age <35 years
Papillary or follicular histology
*Primary tumour T_1 or T_2 (not penetrating capsule)
No distant or lymph node metastases

*well differentiated

A limited number of multivariate analyses for differentiated thyroid carcinoma have thus far been published (Franssila, 1975; Byar et al, 1979; Wanebo et al, 1981; Fourquet et al, 1983; Bacourt et al, 1986; Simpson et al, 1987; Schelfhout et al, 1988; Tennvall et al, 1985; Schindler et al, 1991). However, these multivariate studies raise conflicting views particularly as regards the age factor. The different conclusions of these studies may be due to differences in patient selection, staging criteria, treatment and length of follow-up. The conclusions of the multivariate retrospective analysis from a single major referral centre in the United Kingdom described in this Thesis have shown that the prognosis of patients with differentiated thyroid carcinoma can be related by four factors: age, histological grade, T category and distant metastases. All of these prognostic factors and their relative importance should be taken into account when determining treatment.

2.9 LATE COMPLICATIONS

2.9.1 Solid Tumours

The occurrence of 51 second solid tumours found among 649 patients with differentiated thyroid carcinoma followed up to 1991 is shown in Table 2.11. This represents an incidence of 8% and the possible significance will be discussed in detail in a separate publication. Four patients with Hodgkin's lymphoma received mantle radiotherapy which predated the later development of papillary thyroid carcinoma. Previous external beam radiotherapy to the neck is a well recognised aetiological factor for papillary thyroid carcinoma particularly in the young (see section 1.1.2).

2.9.2 Marrow Dysplasia and Leukaemia

Marrow dysplasia was documented in 5 patients (Table 2.12). These patients had no evidence of bone infiltration and had not received external beam radiotherapy. In 4 cases, the haematological complication resolved spontaneously. One patient who developed essential thrombocythaemia required treatment with Busulphan. Six patients with leukaemia were found among the 649 patients in this series. For two patients, leukaemia predated the diagnosis of thyroid carcinoma (see Table 2.13). One patient developed acute myeloid leukaemia 14 years after the diagnosis of thyroid carcinoma; radioiodine had not been given. For the three remaining

patients, two had bone metastases and received supplementary external beam radiotherapy.

Table 2.11: Solid Tumours Found in 649 Patients with Differentiated Thyroid Carcinoma 1949-1991

Carcinoma breast	**10**
Squamous carcinoma lung	**6**
Hodgkin's lymphoma	**4**
Gastrointestinal	
Colorectal	**7**
Stomach	**3**
Gallbladder	**1**
Pancreas	**1**
Genitourinary	
Bladder and renal pelvis	**3**
Prostate	**2**
Gynaecological	
Cervix	**3**
Endometrium	**2**
Ovary	**1**
Head & Neck	
Meningioma	**1**
Parotid	**1**
Nasal cavity	**1**
External auditory meatus	**1**
Parathyroid adenoma	**1**
Hypopharyngeal carcinoma	**1**
Skin	
Basal cell carcinoma	**1**
Melanoma	**1**

Table 2.12 *Marrow Dysplasia in 5 Patients without Metastases and no Supplementary External Beam Radiotherapy.*

Age/Sex	Cumulative ^{131}I	Haematological complication
25M	14GBq over 16 months	thrombocytopenia
38F	18.5GBq over 10 months	thrombocytopenia
66F	14GBq over 75 months	myelodysplasia
82F	20.5GBq over 8 months	pancytopenia
58F	14GBq over 15 months	essential thrombocythaemia

Table 2.13: *Leukaemia in 6 Patients with Differentiated Thyroid Carcinoma followed from 1949 to 1991.*

Age/Sex	Cumulative ^{131}I	Complication	External beam RT	Metastasic sites
66F	45.1GBq over 33 months	preleukaemia	yes	bone
48F	19.88GBq over 33 months	marrow dysplasia preleukaemia	yes	lung bone
35M	1.1GBq ablation	leukaemia	no	no
80M	28.6GBq over 18 months	CLL which predated ^{131}I	no	lung bone
39F	none	AML 14 years after diagnosis of ca.thyroid	no	no
67M	8.5GBq over 4 months	AML which predated ca.thyroid	no	no

2.9.3 Infertility

It is not routine policy at the Royal Marsden Hospital to perform sperm count and motility studies on young male patients undergoing radioiodine therapy although all patients are counselled on possible late sequelae following repeated therapy administration of ^{131}I. Late effects on fertility for females treated at the Royal Marsden Hospital have been reported previously by Brown et al (1984). Among patients treated between 1949 and 1981, two women who received 19.4 GBq and 22.9 GBq ^{131}I subsequently had pregnancies. One had a spontaneous abortion but then had a full-term delivery of a normal girl. The other patient had two normal pregnancies and produced two normal healthy boys. Other studies with long follow-up have found no definite evidence of any decrease in fertility although the radiation dose to the gonads particularly in some males was in the range known to produce impaired spermatogenesis (Speiser et al, 1973; Lushbaugh & Casarett, 1976; Ash, 1980. Handelsman & Turtle (1983) have demonstrated that dose-dependent damage to spermatogenesis (usually transient) may follow high-activity administration of ^{131}I. In another series, among 43 patients treated with radioiodine when age less than 30 years, 8 males fathered 15 normal children and 23 females had 29 live births (Edmonds & Smith, 1986).

Fertility in younger male patients may be adversely affected although this is usually transient. Sperm storage could be offered if repeated therapy ^{131}I administrations are anticipated and treatment, especially in younger individuals should be at the lowest for effective control. Other important ways of achieving this include initial near-total or total thyroidectomy (to reduce the dose of radioiodine required for subsequent ablation) and constant consideration of the surgical alternatives for persistent or recurrent loco-regional disease. Furthermore, the dose-response relationships presented in Chapter 7 of this Thesis could, in the future, form the basis for rational absorbed dose prescription for ^{131}I ablation and therapy to achieve tumouricidal doses and avoid the potential morbidity associated with ineffectual administrations.

CHAPTER 3

RESULTS OF EXTERNAL BEAM RADIOTHERAPY

1969-1991

3.1 INTRODUCTION

3.1.1 Role of External Beam Radiotherapy in Differentiated Thyroid Carcinoma

Surgery remains the definitive initial and potentially curative treatment for differentiated thyroid carcinoma. External beam radiotherapy may, however, be indicated in a number of situations. For residual or recurrent primary tumour or nodal involvement, further surgery should be performed unless there are medical reasons precluding this. External beam radiotherapy is indicated for those patients with residual inoperable disease which fails to concentrate radioiodine and for poorly differentiated tumours which are unlikely to concentrate radioiodine sufficiently to be of therapeutic benefit. External beam radiotherapy will also control such distressing symptoms as fungating nodes, bleeding, stridor, dysphagia and superior vena caval obstruction due to progressive inoperable tumour (Harmer,1977).

Owing to the rarity of the disease, its complex management and long natural history there are no prospective randomised controlled trials to prove the value of external beam radiotherapy; evaluation therefore relies on retrospective analyses. The purpose of this retrospective study from a major referral centre was to analyse the outcome of patients with differentiated thyroid carcinoma who were given megavoltage radiotherapy with curative

intent.

3.2 PATIENTS AND METHODS

3.2.1 Patients

From 1969 to 1991, 113 patients with differentiated thyroid carcinoma received megavoltage external beam radiotherapy with curative intent at the Royal Marsden Hospital (London and Surrey). The majority of patients were referred from counties in South-East England but one third (42/113) came from abroad. There were 70 females and 43 males, ranging in age from 11 to 84 years (mean 53). The age and sex distribution (Table 3.1) indicates an older age group than is found in unselected surgical patients. The male to female ratio was 1:1.4 so the proportion of males was higher than that in unselected

Table 3.1: Age and Sex Distribution by Histology for 113 Patients Receiving External Beam Radiotherapy.

Age (years)	Papillary		Follicular	
	Male	Female	Male	Female
11-19		3		
20-29	3	9		3
30-39	1	10		
40-49	5	3	1	1
50-59	8	11	2	2
60-69	15	4	1	8
70-84	6	7	1	9
TOTAL	38	47	5	23

series. Histology was reviewed in every case by the Department of Histopathology. There were 85 papillary, 24 follicular and 4 Hürthle cell

carcinomas (Table 3.2). The majority of papillary tumours were well differentiated (60/85) whereas for follicular histology one half were poorly differentiated (12/24).

Table 3.2: Histology and Grade for 113 Patients Receiving External Beam Radiotherapy.

Histology	Grade	Number
Papillary	1	62
	2	14
	3	9
Follicular	1	6
	2	6
	3	12
Hürthle	1	4
TOTAL		113

Distribution by TNM Classification (1987) is shown in Table 3.3. At the time of referral, 53 patients had infiltrating neck masses and 12 had distant metastases. The frequency of follow-up was three monthly for the first two years, six monthly for the next three years and thereafter annually. At each follow-up visit serum thyroglobulin and a chest radiograph were obtained. Median follow-up from diagnosis was 49 (3-335) months.

Table 3.3: *TNM Classification at Diagnosis in 113 Patients Receiving External Beam Radiotherapy.*

Distant Spread	M0			M1			TOTAL
Nodal Status	N0	N1a	N1b	N0	N1a	N1b	
Tx	10	3	4				17
pT1	3	2		1			6
pT2	13	4	4	3			24
pT3	6	2	3	0		2	13
pT4	21	8	18	2	1	3	53

3.2.2 Indications for External Beam Radiotherapy

Indications for external beam radiotherapy are given in Table 3.4. Amongst 80 patients given radioiodine there was failure to concentrate radioiodine in 34 (43%). Other indications for external beam radiotherapy included poorly differentiated tumour in 21 patients and inoperable tumour in 24 patients in whom thyroid biopsy only was possible. 23 patients had progressive symptomatic disease causing stridor in 12, dysphagia in 5, haemoptysis in 5 and superior vena caval obstruction in 1 patient. The remaining patients had either microscopic or gross extra-thyroidal infiltration.

Table 3.4: Indications for External Beam Radiotherapy in 113 Patients.

Failure to concentrate radioiodine		**34/80**
Poorly differentiated tumour		**21**
Inoperable tumour		**24**
Microscopic or gross extra-thyroidal infiltration		**11**
Progressive symptoms:	**stridor**	**12**
	dysphagia	**5**
	haemoptysis	**5**
	caval obstruction	**1**
TOTAL		**113**

3.2.3 Surgery

In 101 of the 113 cases, the initial surgery was performed at another hospital (often abroad) and therefore the initial surgical procedure was not standardised (Table 3.5). Biopsy only was performed in 24 patients with locally advanced inoperable tumour at presentation. Resection enucleation was performed in 11 cases and total lobectomy or hemi-thyroidectomy in 17. Subtotal thyroidectomy was performed in 19 patients and near or total thyroidectomy in 42. Modified neck dissection was performed in 17 and simple excision of macroscopically involved nodes in 18 patients. Twenty three patients underwent further surgery at the Royal Marsden Hospital for recurrent loco-regional disease at the time of referral.

Table 3.5: Initial Surgical Treatment in 113 Patients Subsequently Treated with External Beam Radiotherapy.

Nodal dissection	None	Simple nodal excision	Modified neck dissection
Biopsy only	22	1	1
Enucleation	10	1	
Lobectomy or Hemithyroidectomy	13	2	2
Subtotal thyroidectomy	15	2	2
Near total or Total thyroidectomy	+18	12	*12
TOTAL	78	18	17

+ 5 patients also had tracheostomy and 1 had laryngectomy
* 2 patients had bilateal neck dissection and sternal split

3.2.4 External Beam Radiotherapy

The whole of both sides of the neck from the level of the hyoid including the supraclavicular nodes and extending down to the superior mediastinum was irradiated in most cases. One hundred and five cases were treated with megavoltage radiotherapy (^{60}Co photons or 5MV Xrays) via anterior and posterior portals with shielding to the floor of mouth and lungs (Fig.3.1).

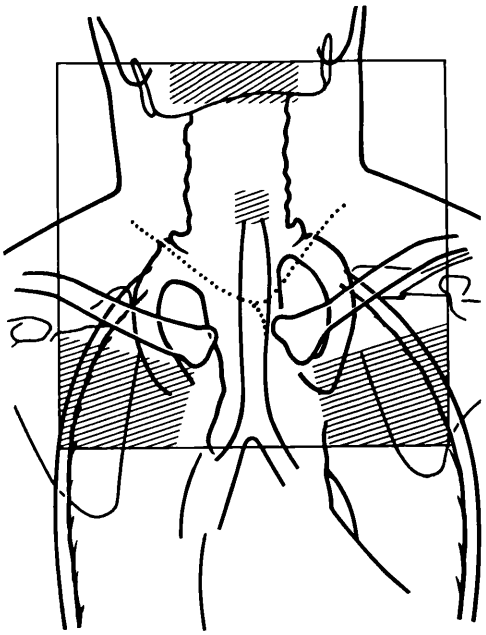


Figure 3.1: Comprehensive anterior field with shielding to floor of mouth and lungs.

The majority received a tumour dose of 60 Gy in 30 daily 2Gy fractions with spinal cord shielding after 40 Gy. Eight patients were treated using a pair of matched 20 MeV and 35 MeV electron beams to the neck and mediastinum respectively with midline wax bolus in the upper field to pull the isodoses anteriorly and so reduce dose to the spinal cord. Fig.3.2 shows a sagittal section in a patient with the resultant 80% isodose curve corresponding exactly to the required tumour volume with a greater depth where it is required in the chest. Fig. 3.3 shows the neck in transverse section with the upper field applied at 20 MeV. By using midline build-up material the 80 % isodose was pulled anteriorly and so lifted off the spinal cord; posterior neck disease was adequately covered with bolus also used at the sides to ensure uniform dosage at depth. Using the electron technique, 75 Gy applied dose was delivered in 30 daily fractions with a minimum tumour dose of 60 Gy to the 80% isodose and a dose of 45 Gy only to the cervical cord.

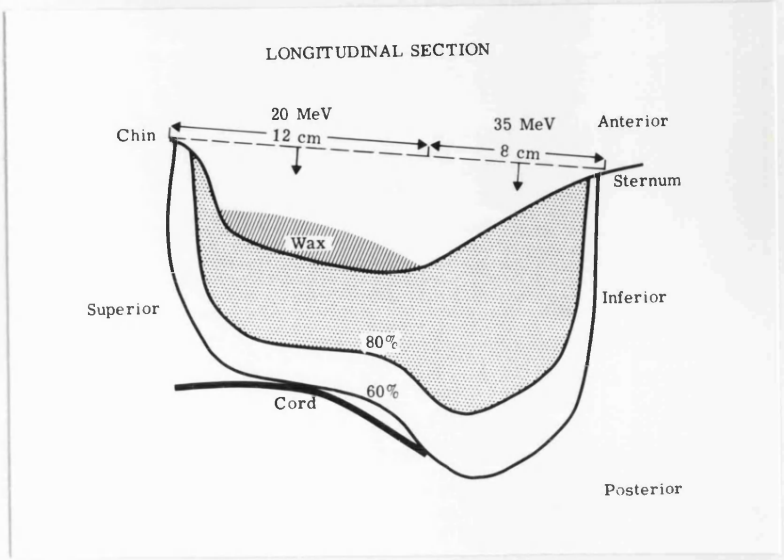


Figure 3.2: *Sagittal section of patient illustrating relationship of 80% isodose to the spinal cord.*

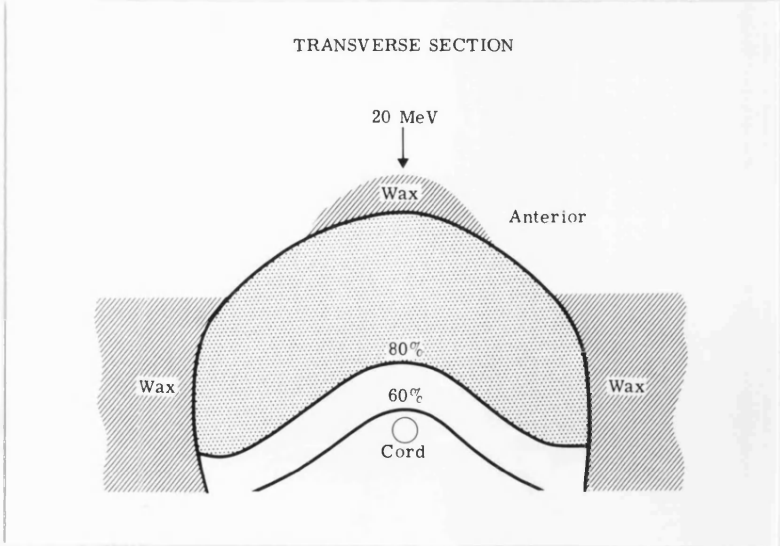


Figure 3.3: *Transverse section of neck with 80% curve lifted anteriorly by build-up.*

3.2.5 Radioiodine

All patients received suppressive thyroid hormone with either thyroxine 0.2 mg daily or tri-iodothyronine 60 μg daily. Eighty patients received radioiodine ^{131}I, although 58 received only 3.0 GBq radioiodine to ablate remnants following their initial surgery. A further 22 patients received therapy administrations in addition for either residual local disease or distant metastases. The total maximum cumulative administered activity was 36 GBq ^{131}I with a mean of 10 GBq.

3.2.6 Analysis

Patients were classified according to the completeness of surgical excision. Patients were identified as having no residual disease if the surgeon stated that all gross tumour was removed and microscopic examination confirmed a good margin of uninvolved tissue. Patients were designated as having probable residual microscopic disease if tumour was close to lines of excision (within 2 mm). They were classified as having definite residual microscopic disease if tumour had been removed by blunt dissection (for example shaved off the trachea, larynx or oesophagus). Patients were described as having gross disease if visible tumour remained either in the thyroid bed or in regional lymph nodes. For the purposes of analysis, 4 patients with well differentiated Hürthle cell carcinoma have been included with the group having follicular histology.

Complete regression was defined as complete disappearance of all clinical and radiographic disease with normalisation of serum thyroglobulin. Partial regression was defined as at least 50% reduction in clinical and/or radiographic disease. No regression included patients in whom there was less than 50% reduction in measurable disease, tumours which were unchanged or those in whom disease progressed.

Data were transferred to the main hospital computer (Hewlett Packard). Survival curve comparisons were performed with the log rank test for univariate analysis and Cox proportional hazard model for multivariate analysis (Cox, 1972). A stepwise selection procedure with the Cox proportional hazards regression model was used to determine independent prognostic factors in multivariate analysis.

3.3 RESULTS

3.3.1 Papillary Thyroid Carcinoma

Only two patients who returned abroad were not seen beyond 3 months follow-up. Three patients with locally advanced inoperable disease died before completion of external beam radiotherapy and are therefore not evaluable for analysis: one death was due to bronchopneumonia and 2 due to local haemorrhage. For papillary carcinoma, local recurrence occurred in 7/43 (16%) of patients with probable or definite residual microscopic disease (Table 3.6).

For patients with gross residual disease and papillary carcinoma response rates were: complete regression 13 (41%), partial regression 7 (22%), no regression 12 (37%) (Table 3.7).

Table 3.6: *Response of Papillary Thyroid Carcinoma to External Beam Radiotherapy-Microscopic Disease.*

Residual microscopic disease	No recurrence	Local recurrence
None	10*	0
Probable	23+	2
Definite	13x	5
TOTAL	46	7

*4 also received radioiodine
+14 also received radioiodine
x11 also received radioiodine

Table 3.7: Response of Papillary Thyroid Carcinoma to External Beam Radiotherapy-Gross Disease.

Response	Complete Regression	Partial Regression	No Regression	Not Known
Radiotherapy	13(41%)	7(22%)	12 (37%)	2
Radioiodine ablation	11	5	10	

3.3.2 Follicular Thyroid Carcinoma

For follicular histology, local recurrence occurred in 4/10 (40%) of patients with probable or definite residual microscopic disease (Table 3.8). For patients with gross residual disease from follicular carcinoma response rates were: complete regression in 5(31%), partial regression in 5 (31%), no regression in 6 (38%) (Table 3.9).

Table 3.8: Response of Follicular Carcinoma to External Beam Radiotherapy-Microscopic Disease.

Residual microscopic disease	No recurrence	Local recurrence
None	1	0
Probable	2*	2*
Definite	4+	2*
TOTAL	7	4

*2 also received radioiodine

+1 also received radioiodine

Table 3.9: Reponse of Follicular Carcinoma to External Beam Radiotherapy-Gross Disease.

Response	Complete Regression	Partial Regression	No Regression	Not Known
Radiotherapy	5(31%)	5(31%)	6(38%)	1
Radioiodine ablation	4	2	5	

3.3.3 Summary of Results

Overall, external beam radiotherapy achieved 79% local control when residual microscopic disease was present and complete regression in 37% of patients with gross disease. Moderate oesophagitis developed in all patients and severe erythema of the skin with telangiectasia occurred following electron beam therapy but there were no significant late sequelae following external beam radiotherapy.

3.3.4 Clinical Case Study

Radical-dose external beam radiotherapy is preferable to mutilating surgery in patients with inoperable disease as illustrated by the following case. This 67 year old Mauritian presented with a 3 month history of swelling of the left side of his neck and dysphagia. Examination revealed a mass displacing the left lobe of thyroid. Computerised tomography (CT) of the neck (Fig.3.4) confirmed a mass arising from the left lobe of thyroid, involving the left sternomastoid muscle and intimately related to adjacent blood vessels. Exploration of the neck was undertaken but only biopsy was possible. Histology showed papillary carcinoma of thyroid roigin. Clinically there was no evidence of lymph node involvement. Chest radiograph showed no evidence of pulmonary metastases. He was treated with external beam radiotherapy via anterior and posterior portals to cover the whole neck and upper mediastinum with a tumour dose of 60 Gy in 30 daily fractions using 6MV Xrays. The spinal cord was shielded after 40 Gy.

On completion of radiotherapy swallowing had markedly improved and the neck was less swollen. A dose of 3.0 GBq ^{131}I was then administered to ablate the remaining normal right thyroid lobe and he was started on tri-iodothyronine 60μg daily. Three months later there was almost complete resolution of the left neck mass. Radioiodine scanning had shown intense uptake into the presumed normal right lobe and therefore two therapy administrations of 5.5 GBq ^{131}I were given at three monthly intervals until no further uptake was seen on scanning. Follow-up CT scan (Fig.3.5) showed possible radiation necrosis of the left thyroid cartilage but no soft tissue mass was demonstated. He remains in clinical remission with normal thyroglobulin levels 3 years after initial therapy.

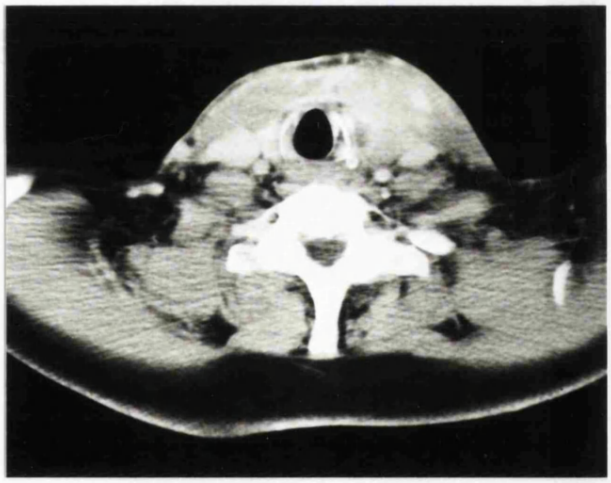


Figure 3.4: *CT scan showing a mass on the left side of neck invading the sternomastoid muscle and inseparable from the vascular sheath with tracheal deviation to the right.*

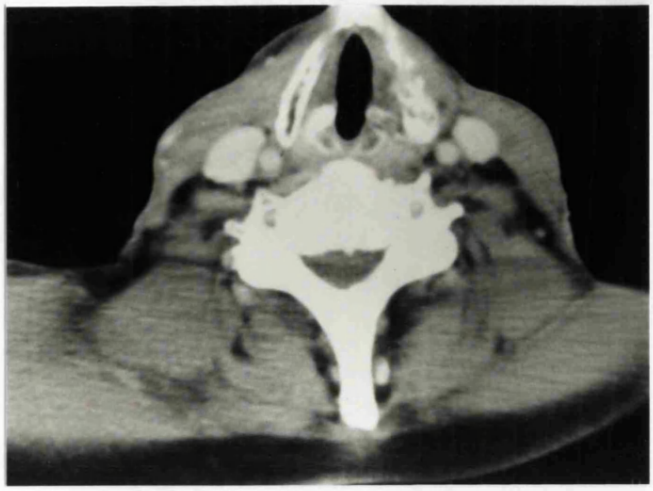


Figure 3.5: CT scan 3 months after radical-dose external beam radiotherapy showing possible radiation necrosis of the left thyroid cartilage but complete resolution of soft tissue mass.

3.4 SURVIVAL AND PROGNOSTIC FACTORS

3.4.1 Survival

Survival curves are shown in Figs. 3.6 to 3.10. Females did not have a significantly better survival than males (Fig. 3.6). Patients with papillary carcinoma had a better rate of survival than those with follicular histology (Fig.3.7, $p<0.005$). This may reflect the fact that 80% of papillary tumours were well differentiated whereas 50% of follicular tumours were poorly differentiated. The important influence of age on survival is shown in Fig. 3.8 with survival rates at 10 years of 81% for patients less than 45 years of age, falling to 36% for patients 45 to 64 and only 6% for age 65 and over; these differences in survival are significiant $p<0.005$. This is in accord with other series showing age to be an important independent prognostic factor in thyroid carcinoma (Simpson et al,1987). There was no significant difference in survival for patients receiving radioiodine in addition to external beam radiotherapy (Fig.3.9). This may be explained by the fact that 43% of patients receiving radioiodine showed no uptake by residual tumour. Fig. 3.10 shows the importance of residual disease in determining survival. Thus patients with no residual microscopic disease had 91% overall survival at 10 years contrasted with only 13% for patients with gross residual disease ($p<0.005$).

Figure 3.6: Survival (%) by Sex for 113 Patients Receiving External Beam Radiotherapy. Table 1 = male (43 cases); Table 2 = female (70 cases).

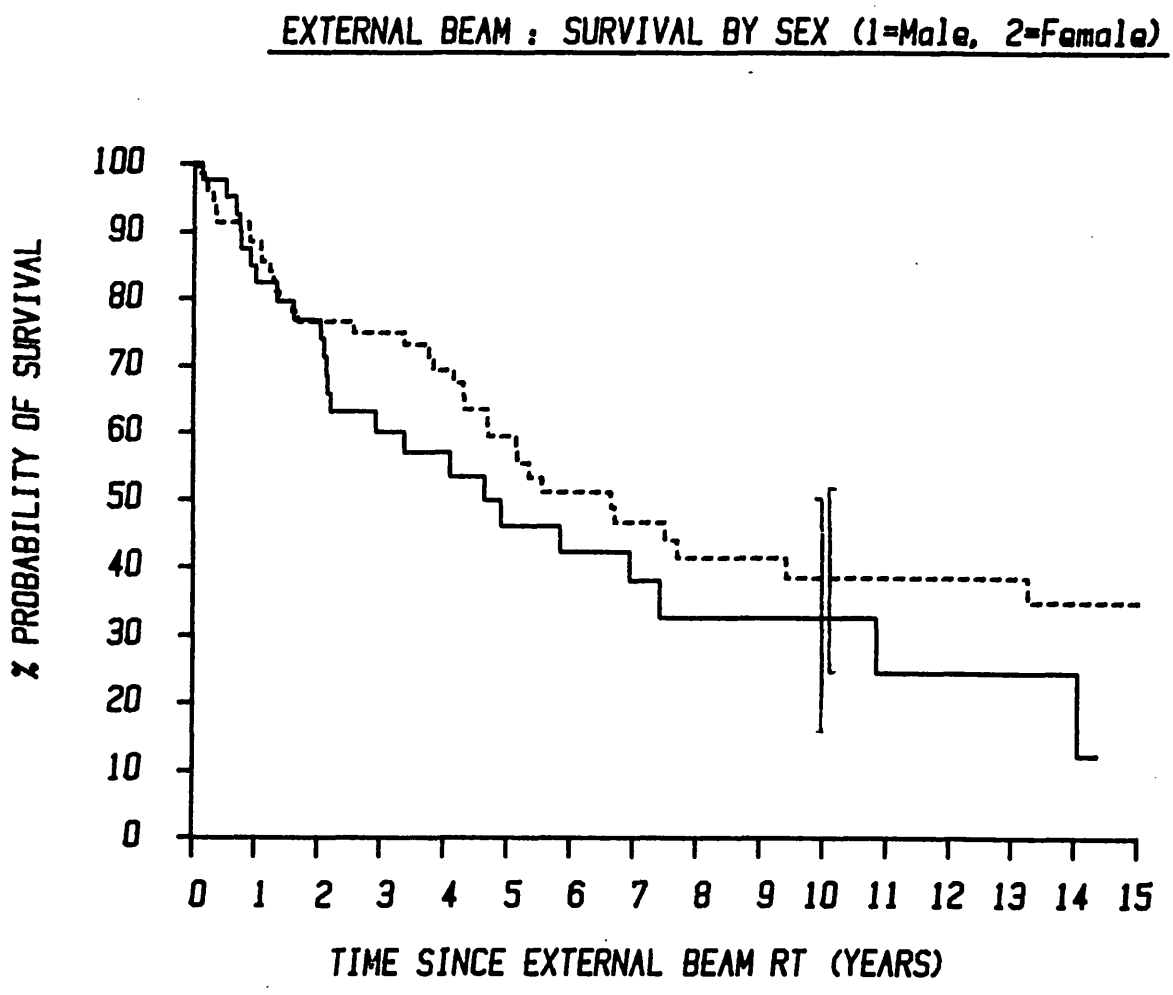


TABLE 1 _____ = 43 Cases (O = 24, E = 19.4).
TABLE 2 _ _ _ _ _ _ = 70 Cases (O = 37, E = 41.6).

Difference is not significant (chi-square = 1.60, df. = 1, P > 0.1)
Trend test is not significant (chi-square = 1.60, P > 0.1)

Figure 3.7: Survival (%) by Histology for 113 Patients Receiving External Beam Radiotherapy. Table 1 = papillary (85 cases); Table 2 = follicular (28 cases).

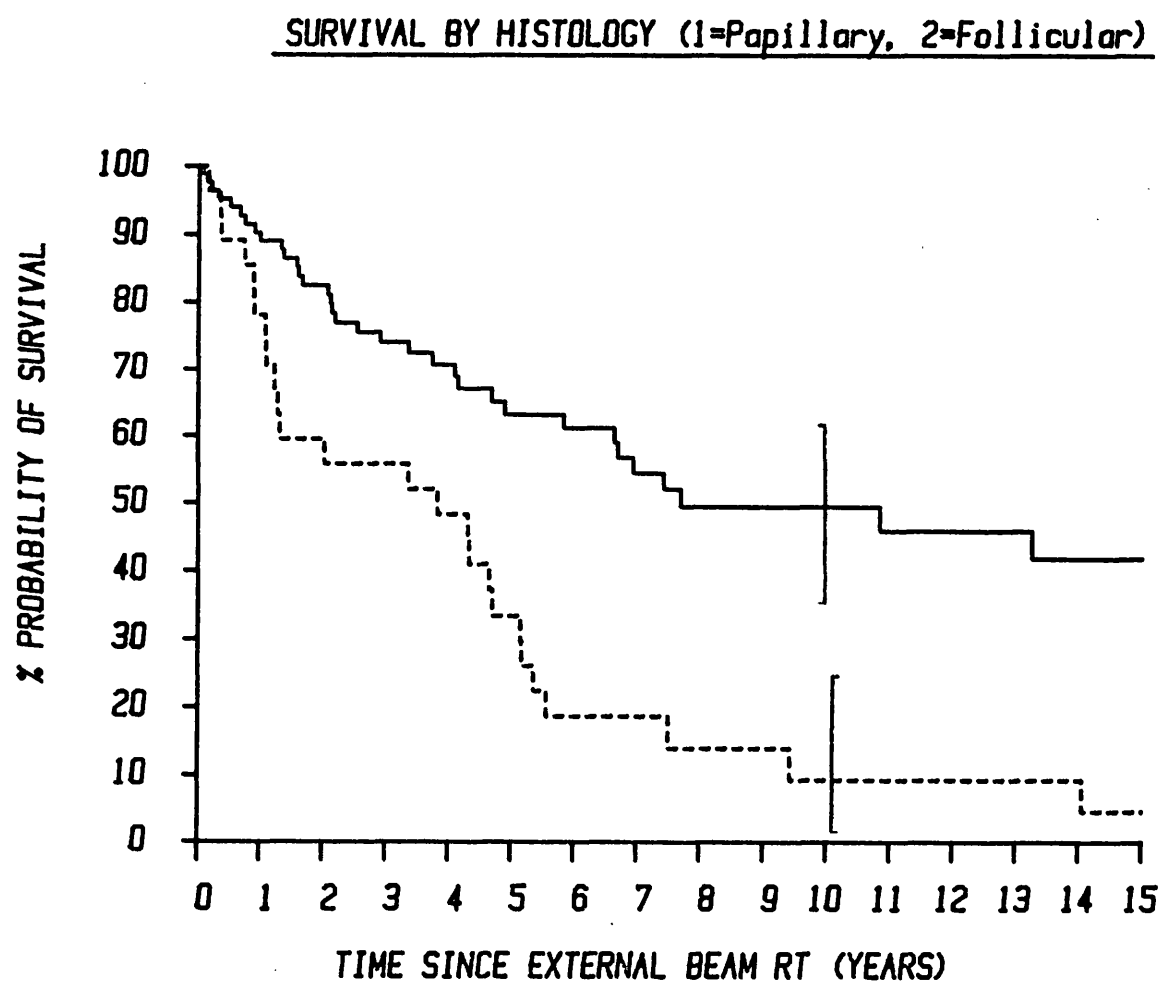


Figure 3.8: Survival (%) by Age for 113 Patients Receiving External Beam Radiotherapy. Table 1 = age < 45 years (35 cases); Table 2 = ages 45-64 (39 cases); Table 3 = age > 65 (39 cases).

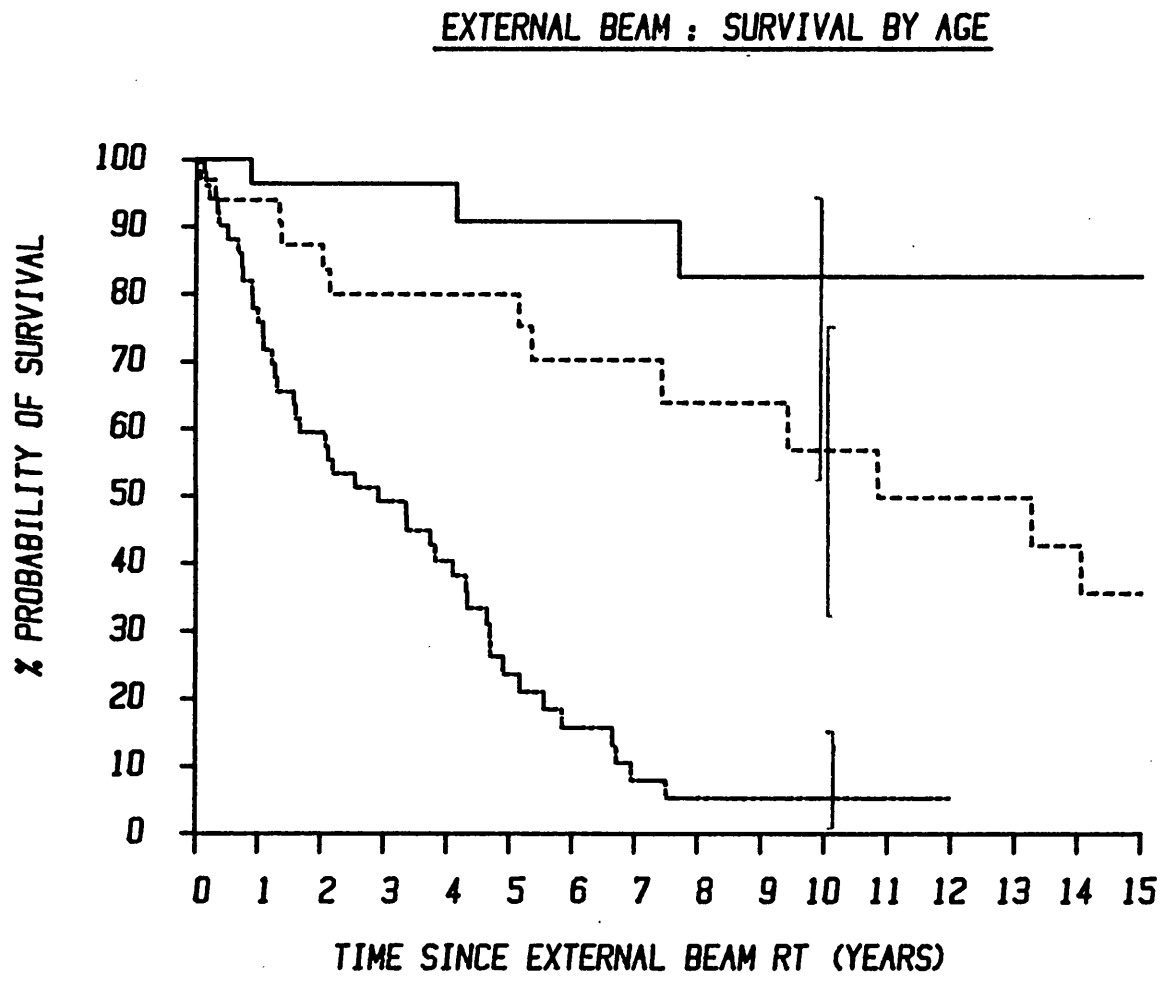


Figure 3.9: Survival (%) by Radioiodine in Addition to External Beam Radiotherapy. Table 1 = radioiodine (74 cases); Table 2 = no radioiodine (39 cases).

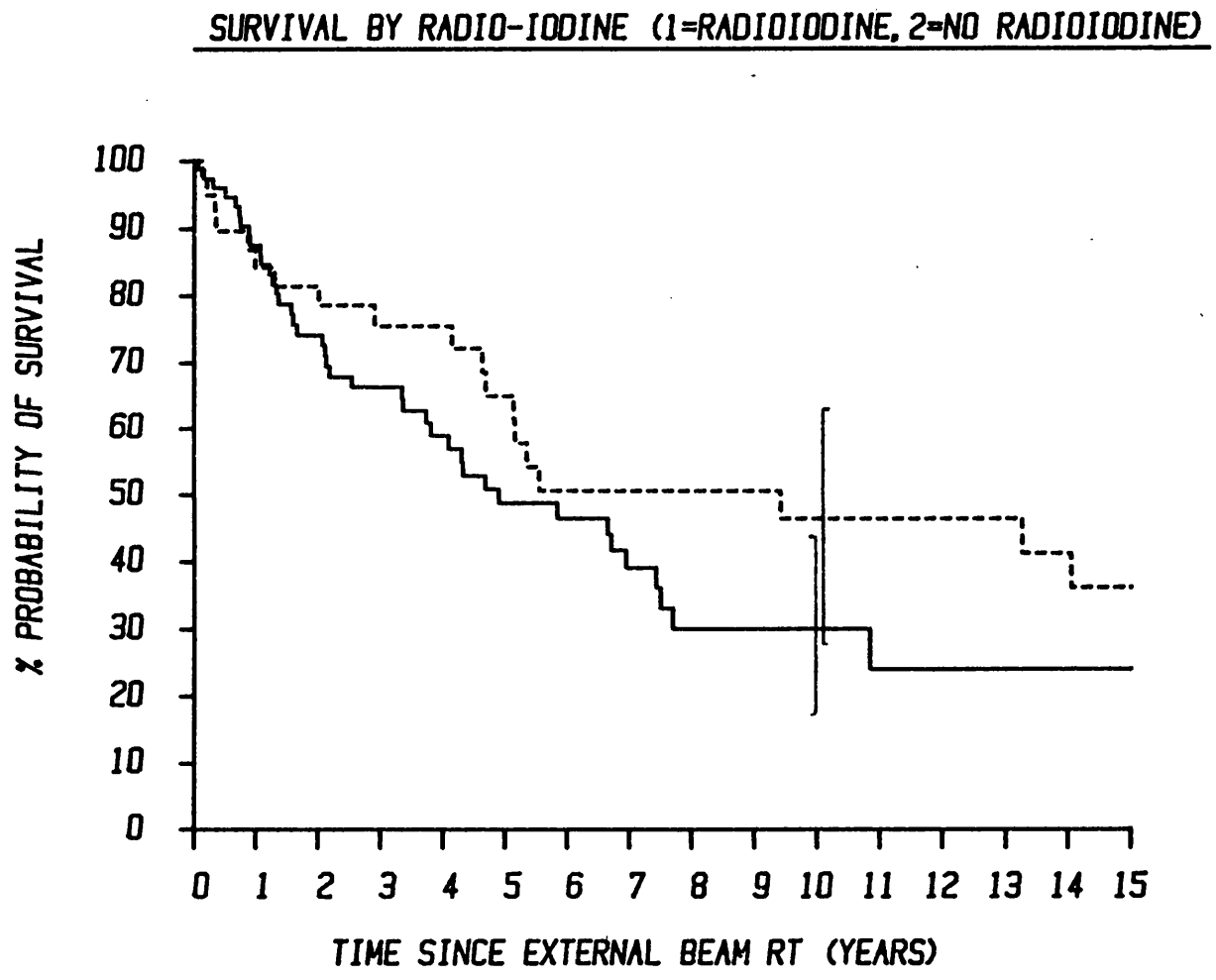


TABLE 1 _____ = 74 Cases (O = 41, E = 35.5).
TABLE 2 _ _ _ _ _ = 39 Cases (O = 20, E = 25.5).

Difference is not significant (chi-square = 2.05, df. = 1, P > 0.1)
Trend test is not significant (chi-square = 2.05, P > 0.1)

Figure 3.10: Survival by (%) Post-operative Disease Status. Table 1 = no residual microscopic disease (11 cases); Table 2 = probable residual microscopic disease (29 cases); Table 3 = definite minimal microscopic disease (24 cases); Table 4 = gross residual disease (49 cases).

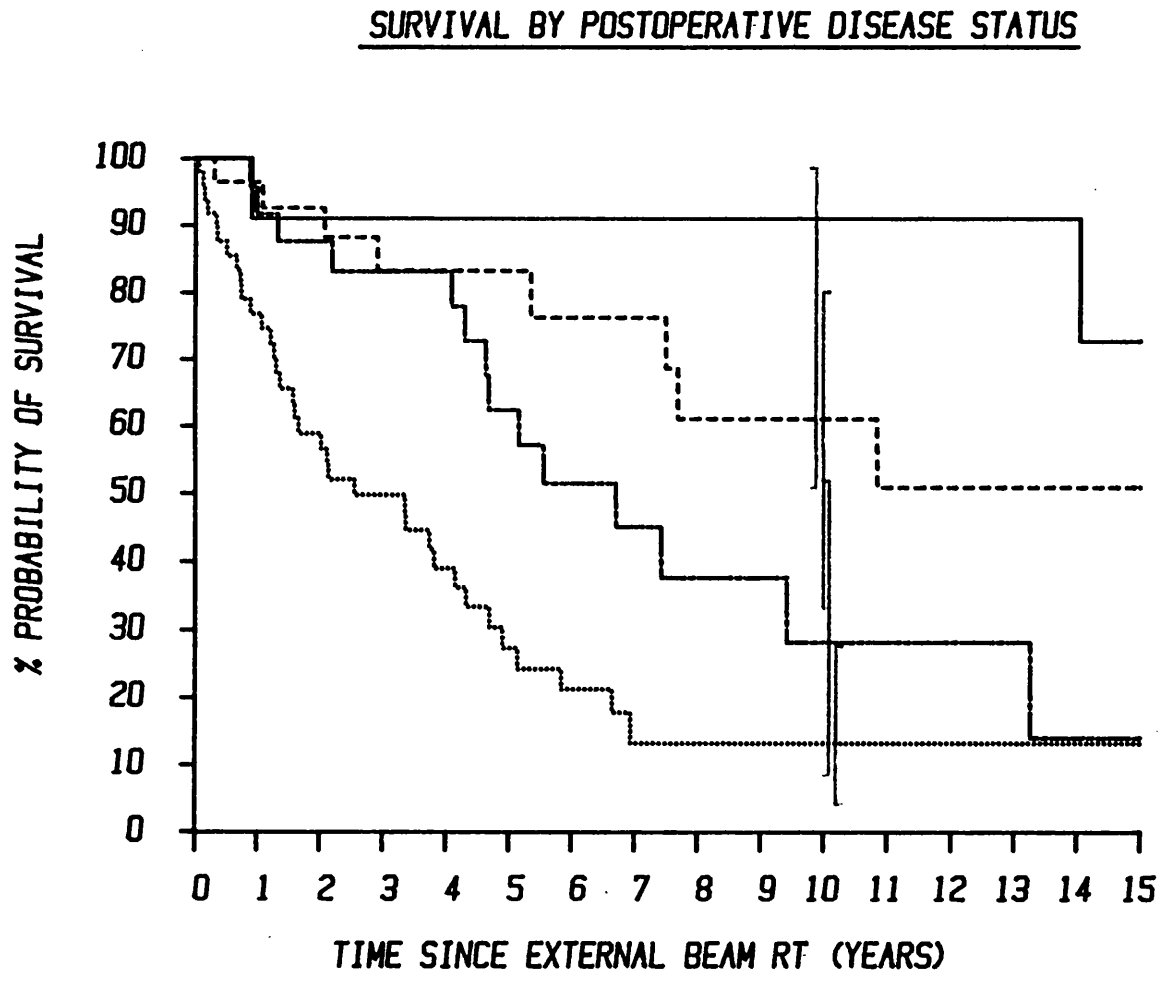


Table 3.8: Present Status of Patients Treated with External Beam Radiotherapy.

Status		Papillary	Follicular
Alive	free of disease	38	2
	local disease	6	
	distant metastases	4	1
	both	1	
	TOTAL	49	3
Dead	local disease	11	4
	metastatic disease	6	9
	both	4	8
	Unrelated cause	16	4
	TOTAL	37	25

Overall 5-year survival rates for probable or definite residual microscopic disease were 85% at 5 years, 60% at 10 years, and 15% at 15 years. For gross disease 5 year survival was only 27% . Sixty two patients have subsequently died: 20 deaths were due to unrelated causes. Fifteen deaths were due to distant metastases, 15 were due to local disease and 12 patients died with both local and distant metastases (Table 3.8).

3.4.2 Prognostic Factors

Table 3.11: Results of Univariate Analysis for Prognostic Factors in 113 Patients Treated with External Beam Radiotherapy between 1969-1991.

Factor		Hazard Ratio (95% confidence interval)	p-value
Age	<40	1.00	
	45-64	3.58(1.68-7.65)	*p<0.001
	>65	7.99(4.25-15.0)	
Post-operative status	No residual	1.00	*p<0.001
	Probable microscopic	2.66(0.78-9.04)	
	Definite microscopic	5.56(2.08-14.9)	
	Gross residual	8.51(4.31-16.8)	
Histology	Papillary	1.00	
	Follicular	2.69(1.45-5.0)	p<0.001
Grade	I	1.00	
	II	1.18(0.60-2.32)	*p<0.05
	III	1.92(0.93-4.0)	
Sex	Female	1.00	not significant
	Male	1.39(0.81-2.38)	

*p-value for trend,all other p-values refer to tests for heterogeneity

Results of univariate analysis for overall survival showed post-operative status, age, histology and degree of differentiation to be of significiant prognostic importance (Table 3.11). Ranking of prognostic factors by multivariate analysis (Table 3.12) showed that post-operative status was the most important factor determining survival followed by age, histology and sex. The importance of post-operative disease status has also been stressed by other series notably that of Simpson et al ,1987.

Table 3.12: *Results of Multivariate Analysis for 113 Patients Treated with External Beam Radiotherapy between 1969-1991.*

Variable		Hazard Ratio (95% confidence interval)	p-value
Post-operative status	No residual	1.00	
	Probable microscopic	1.82(1.32-2.50)	
	Definite microscopic	3.30(2.39-4.54)	*p=0.0001
	Gross residual	5.98(4.34-8.25)	
Age	<45	1.00	
	45-64	2.02(1.33-3.06)	*p=0.0005
	>65	4.08(2.69-6.19)	
Histology	Papillary	1.00	p=0.003
	Follicular	2.00(1.29-3.1)	
Sex	Female	1.00	p=0.05
	Male	1.79(1.00-3.25)	

*p value for trend

3.5 DISCUSSION OF ROLE OF EXTERNAL BEAM RADIOTHERAPY IN THE MANAGEMENT OF DIFFERENTIATED THYROID CARCINOMA

Surgery remains the initial and potentially curative treatment for differentiated thyroid carcinoma. However there is no agreement as to the extent of surgery required, partly because many still regard differentiated thyroid carcinoma as a benign disease. Unfortunately, owing to the rarity of the disease, there have been no prospective randomised controlled trials to address the extent of surgery which is required. The majority of patients in the series reported here who have died did so as a direct result of thyroid carcinoma, stressing that this is not a benign disease. The early series from the Mayo clinic (Woolner et al, 1968) claimed survival of patients with non-invasive thyroid carcinoma to be comparable with that of a normal population. Subsequent re-analysis (Beierwaltes, 1978) using sex and age matched controls showed a steady decline in survival for both occult and intrathyroid carcinomas at 40 years follow-up. There was a marked attrition rate for extra-thyroidal disease. Other reports (Clarke et al, 1966; Buckwalter & Thomas, 1972; Thompson et al, 1973) have stressed the importance of "adequate" surgery and most surgeons now agree that the minimum procedure for unilateral thyroid disease should be lobectomy (Van der Velde et al, 1988). If frozen section (which should always be performed) shows malignancy then total lobectomy (including isthmusectomy) or total thyroidectomy should be completed at the same session. Hirabayashi and Lindsay (1961) found a much higher incidence of local recurrence after partial thyroidectomy (17%) than after total thyroidectomy (2%). Following unilateral lobectomy, Tollefson et al (1972) found a 5 to 7% occurrence rate of clinical carcinoma in the contralateral lobe and a 32 to 58% incidence of carcinoma on histopathological examination. Young et al (1976) found a 15% recurrence rate following lobectomy compared with 9% if total thyroidectomy was performed.

In further support of a more radical initial approach is the high incidence of multifocality especially in papillary carcinoma (Black et al,1960). Microscopic foci are reported in the same or contralateral lobe in 38 to 87% of patients depending upon the perseverance of the pathologist in studying tissue sections (Black et al, 1960; Clark et al, 1965; Meissner & Warren, 1969; Mortensen et al, 1955; Russell et al, 1963; Shields & Farringer, 1977). Some foci may be anaplastic (0.7% in the Mayo series) and removal will therefore avoid progression to aggressive malignancy. Arguments in favour of near or total thyroidectomy include not only a reduction in recurrence rate and improved

overall survival but also optimisation of subsequent radioidine ablation and ability to detect recurrence using thyroglobulin (Black et al, 1987;Powell & Harmer, 1990; Sisson, 1983; Tubiana et al, 1985).

The role of neck dissection remains controversial. Local excision or "node picking" is considered an acceptable procedure in papillary cacinoma with limited involvement and central neck disease. Multiple involvement of lymph nodes in the lateral neck should preferably be treated by modified radical neck dissection with preservation of the sternocleidomastoid muscle. This operation is also the treatment of choice for lymph node metastases from follicular carcinoma.

When tumour involves larynx,trachea,oesophagus, or carotid sheath, complete surgical excision is impossible. Residual tumour will progress ultimately resulting in death by local invasion. External beam radiotherapy may therefore be of benefit and complete regression of gross disease has been achieved in 37% of our patients which is comparable with other series (Mabille,1961; Tubianan et al, 1975; Tubiana et al, 1977; Tubiana, 1981). Radical dose is required as differentiated thyroid carcinoma is relatively radioresistant (Harmer, 1977).

There is evidence that survival rates for incompletely excised tumours may also be improved by radical-dose external beam radiotherapy (Benker,1990; Halnan, 1975; Lenio, 1976; Sheline, 1966; Smedal et al, 1967; Simpson & Carruthers, 1978; Windeyer, 1954). In our series of patients with residual microscopic disease (both probable and definite) survival rates were 80% at 5 years; 60% at 10 years and 40% at 15 years. Local control was achieved in 83% of patients. These survival rates are comparable with those obtained by other large series (Simpson & Carruthers, 1978; Tubiana, 1981).

External beam radiotherapy does not interfere with the simultaneous administration of ablative radioiodine which can be followed by diagnostic doses for neck and whole body scanning. However, at least 20% of all differentiated thyroid carcinomas will fail to concentrate iodine sufficiently to be of therapeutic benefit (Pochin, 1971). Radioiodine alone is unlikely to destroy bulky residual disease unless a very high absorbed dose is achieved. Radioiodine alone is unlikely to achieve significant shrinkage of bulky inoperable local disease. Dosimetry studies described in Chapter 7 using quantitative scanning and positron emission tomography show that at least 100 Gy absorbed dose is required to destroy small remnants of nodal disease and that if absorbed doses less than this are delivered, repeated therapy administrations of ^{131}I are ineffectual. Maxon et al (1992) have shown that a

single radioiodine administration resulting in absorbed doses in excess of 80 Gy achieved destruction of neck nodes in 74% of patients with small volume disease (less than 2g).

Complete surgical extirpation if at all feasible is therefore advocated to achieve cure with subsequent radioiodine ablation and therapy if residual tumour concentrates radioiodine. Inoperable disease usually carries a poor prognosis but radical-dose external beam radiotherapy will palliate distressing local symptoms and a significant proportion of patients may achieve complete regression. In future novel fractionation schedules may improve local control. A pilot study using accelerated fractionation has recently been reported (Huddart et al, 1992). Seven patients with high grade carcinoma received a tumour dose of 60.4 Gy in 32 fractions in 20 to 24 days, treating twice daily, five days per week. A high response rate (4/7 complete clinical resolution) and good relief of local symptoms was seen but its toxicity was unacceptable. A modified regimen is therefore presently being evaluated.

CHAPTER 4

DOSIMETRY OF RADIOIODINE

4.1 INTRODUCTION

4.1.1 Empirical Approach

In the past, the therapeutic use of unsealed radionuclide sources has been mainly empirical. This empirical approach contrasts sharply with the delivery of radical-dose external beam radiotherapy where precise dose prescription is mandatory. Most physicians prescribe a fixed activity of radioiodine for ablation of thyroid remnants (Snyder et al, 1983) and treatment of metastases from differentiated thyroid carcinoma (Pochin, 1971) based upon clinical experience and likely side effects (See Section 1 . 4 . 4). In practice, this means that each individual administration of ^{131}I is limited to about 7.4 GBq (Benua et al, 1962).

4.1.2 Calculated Dose

The Sloane Kettering group has adopted an alternative approach based upon dosimetry calculations required to deliver a maximum blood absorbed dose of 2 Gy. These calculations are derived from tracer kinetic studies (Leeper, 1973). Such dose calculations have enabled the administration of an average single therapy activity of 11.4 GBq ^{131}I (range 2.6 to 24 GBq) (Leeper, 1982). For rapidly progressive disease, activities are increased to give an absorbed blood dose of 3.0 Gy or 5.5 GBq whole-body ^{131}I retention at 48 hours. Rigorous pharmacokinetic studies are required, however, and measurements of blood, urine, whole body and organ activity are performed over 4 days following the administration of a tracer amount of ^{131}I. A possible major difficulty with this approach arises because therapy kinetics may differ from those of tracer studies (Benua, 1962; Hurley et al, 1988; Maxon et al, 1992) . This may lead to an underestimate of absorbed dose of about 20% when tracer kinetics are used

(Hurley et al, 1988; Maxon et al, 1992).

4.1.3 Absolute Quantitation of Absorbed Dose

Accurate absorbed dose calculations are desirable in order to:

(i) evaluate the limiting radiation absorbed dose to normal critical organs;
(ii) monitor the radiation absorbed dose delivered to thyroid remnants and metastases;
(iii) establish dose response relationships for normal thyroid tissue and metastases from differentiated thyroid carcinoma;
(iv) avoid administration of further radioiodine to patients where sub-therapeutic absorbed doses can be predicted and thereby avoid the morbidity of excessive therapy.

In order to calculate the radiation absorbed dose to specific tissues which concentrate radioiodine, three parameters must be determined. These are:

(i) the initial or maximum radioactivity in the target tissue;
(ii) the effective half life of radioiodine in the tissue of interest;
(iii) the functioning mass of the tissue.

At the Royal Marsden Hospital, a protocol has been developed to measure these three parameters using a dual-headed whole-body rectilinear scanner and tomographic imaging (Flower et al, 1989). Details of the rectilinear scanner and the performance of special collimators designed for imaging therapy levels of ^{131}I are described in Chapter 5 of this thesis.

The most difficult problem in quantifying radiation absorbed dose is the measurement of that part of the tumour volume which is metabolically active. Ideally, therefore, a radionuclide technique should be used. In this project, two different techniques have been used to determine this so-called "functioning" mass and are discussed in detail in Chapter 7. A dual-headed rectilinear scanner with specially designed collimators has been used to image therapy activities of ^{131}I and small lesions of about 2 g can be measured (see Section 6.2.1). The introduction of tomographic imaging using tracer ^{124}I and positron emission tomography has further improved the accuracy in the determination of volume (and hence mass). The positron camera is described fully in Section 6.4.

There is no consensus on the absorbed dose which is required to destroy thyroid remnants and metastatic lesions from differentiated thyroid carcinoma. This work has attempted to address the problem and the clinical results (Chapter 7) show that dose-response relationships can be established. In future, it is hoped that this will enable precise prescription of radioiodine therapy and optimum dose scheduling. The methods described can, of course, be equally applied to other forms of systemic therapy.

4.2 ABSORBED DOSE CALCULATION

4.2.1 Definition of Terms

By absorbed dose is meant the amount of energy absorbed from ionising radiation per unit mass of tissue. The parameters required for the calculation of absorbed dose are the biologic distribution data, the physical properties of the radionuclide and the method or schema which combines the biologic and physical data into the absorbed dose estimate. One commonly used schema is that due to the Medical Internal Radiation Dose Committee (MIRD) of the American Society of Nuclear Medicine (Loevinger et al,1989). This schema is based on microcuries and rads rather than units of the modernised metric system known as Le Système International d'Unités (SI units see Appendix B). Data presented in this Thesis are expressed in SI units, however, and data derived from MIRD may be converted into SI units using the following conversion factor:

$$1 \text{ g rad } \mu\text{Ci}^{-1}\text{h}^{-1} = 0.27 \text{ g Gy MBq}^{-1}\text{h}^{-1} \quad (4.1)$$

4.2.2 Concept of Source and Target Organ

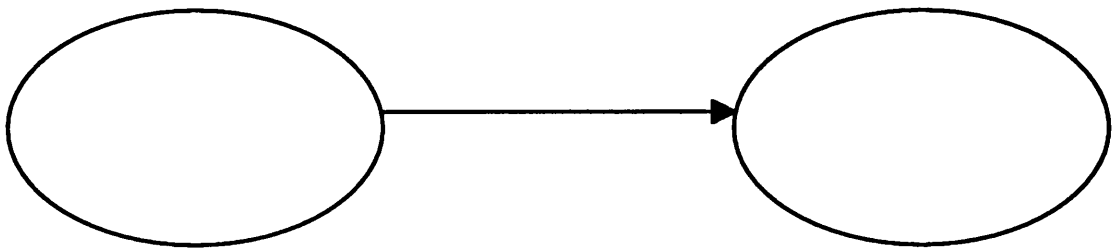
In order to calculate the internal radiation absorbed dose to different organs, the body is considered as a set of source organs (that is, those which have a significant uptake of the radiopharmaceutical) and a set of target organs (that is, those which are irradiated by the source organs). The MIRD defines target organs as any organs or tissues of interest for which the absorbed dose is to be estimated and hence can include normal tissues in addition to tumours. Different configurations of source and target organs can be considered:

(i) target and source organ geometrically separated;

(ii) target and source organ the same organ;

(iii) source within target organ;
(iv) source encompasses target organ.

Figure 4.1: Pair of source and target organs.



4.2.3 MIRD Schema

For each pair of source and target organs (Fig.4.1) the absorbed dose $D_{t \leftarrow s}$ (in Gy) to a target organ (t) from activity in a source organ (s) is calculated from the equation:

$$D_{t \leftarrow s} = \tilde{A}_s \left[\frac{1}{m_t} \sum_i \Delta_i \phi_i \right] \tag{4.2}$$

where:

$\tilde{A}_S$ is the cumulated activity in the source organ (in MBq h);
m_t is the mass of the target organ (in g);
Δ_i is the equilibrium absorbed dose constant for radiation of type i or the mean energy per nuclear disintegration (in g Gy MBq^{-1} h^{-1});
ϕ_i is the absorbed fraction, defined as the fraction of the radiation of type i emitted from the source and absorbed by the target.

The total dose to a single organ arising from radiation emitted by several source organs is the sum of the absorbed doses from each individual source organ.

The cumulated activity, $\tilde{A}_S$, is the total number of radioactive disintegrations which occur in the source organ. This depends upon a

number of factors including activity administered; uptake of radioactivity, retention by and excretion from the organ; and the physical decay of the radionuclide. $\tilde{A}_S$ is equal to the time integral of the activity in the source organ given by:

$$\tilde{A}_s = \int_0^\infty A_s(t)dt \tag{4.3}$$

This is the area under the activity-time curve, $A_S(t)$ for that organ, illustrated graphically in Fig. 4.2.

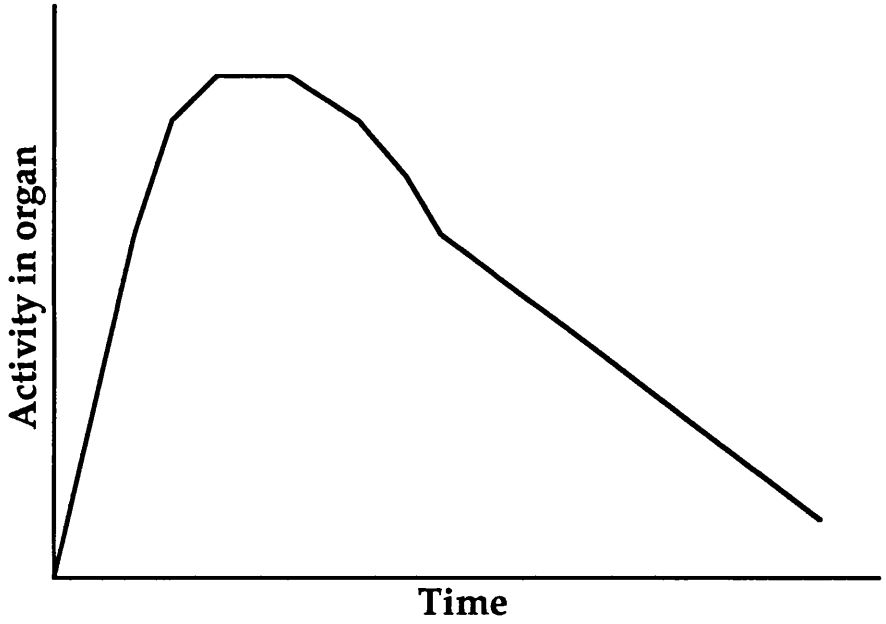


Figure 4.2: Plot of activity in an organ as a function of time.

The radiation energy delivered by a radionuclide in an organ will be totally or partially absorbed in that organ depending upon the type of emission. For a pure beta particle emitter, since the range of the beta particles is small, it can be assumed that all the energy emitted is absorbed in the organ. In this case the absorbed fraction ϕ_i is unity. All particulate radiation, that is electrons (internal conversion electrons and Auger electrons) and positrons can be considered as non-penetrating as their range is of the order of a few millimetres. For gamma emitting radionuclides and electromagnetic radiation above 11 keV there is significant energy loss

from the source organ. For such penetrating radiation the fraction of energy emitted from the radioactivity in one organ (source organ) which is absorbed by a second organ (target organ) must be known. Values for the equilibrium absorbed dose constant, Δ_i , are given in nuclear decay tables for each type of radiation (penetrating and non-penetrating) emitted. Δ_i is given by:

$$\Delta_i = 0.576 n_i \bar{E}_i \tag{4.4}$$

where:

n_i is the mean number of the ith type of radiation emitted per disintegration;

$\bar{E}_i$ is the mean energy of the ith type radiation (in MeV).

For non-penetrating radiation:

ϕ_i = 0 when the target and source organs are geometrically separated;

ϕ_i = 1 when the target and source are the same organ;

ϕ_i= 1/2 at a source/target interface, for example when considering the dose to the bladder wall when the bladder contains radioactive urine.

For penetrating radiation ϕ_i depends upon the geometry of the source/target configuration and varies between zero and unity.

The absorbed dose constant Δ_i is given in standard tables (ICRP Publication 38, 1983) and values for ^{131}I are given in Table 4.3. The quantities Δ_i and ϕ_i are dependent only on the type of radionuclide and the source and target organs. They may be combined to give the mean dose per cumulated activity $S_{t \leftarrow s}$ (in Gy $MBq^{-1}h^{-1}$) :

$$S_{t \leftarrow s} = \frac{1}{m_t} \sum_i \Delta_i \phi_i \tag{4.5}$$

Values of the mean dose per unit cumulated activity (known as S values) have been tabulated for different radionuclides and different source/target configurations. Hence the absorbed dose to a target organ from a single source organ is given by:

$$D_{t \leftarrow s} = \tilde{A}_s S_{t \leftarrow s} \tag{4.6}$$

4.2.4 Determination of Time Interal of the Activity (Ã)

For a single organ the activity-time curve may be represented by a single exponential of the form:

$$A_s(t) = A_0 \exp\left(-0.693\frac{t}{T_e}\right) \tag{4.7}$$

where:

A_0 is the initial activity in the source organ (in MBq) at time 0;
T_e is the effective half-life of the radionuclide in that organ (in h) and is given by:

$$\frac{1}{T_m} = \frac{1}{T_p} + \frac{1}{T_b} \tag{4.8}$$

where T_p and T_b are the physical and biological half-lives respectively. Implicit in equation 3.8 is the assumption that the uptake of ^{131}I into the tissues of interest is rapid and that the wash-out from these tissues follows a single exponential function. The period of initial uptake is usually negligible compared with the half-life of the radionuclide. Substituting equation (4.7) into equation (4.3) gives:

$$\tilde{A}_s = 1.44 T_e A_0 \tag{4.9}$$

Substituting for Ã in equation (4.7) gives:

$$D_{t \leftarrow s} = 1.44 T_e A_0 S_{t \leftarrow s} \tag{4.10}$$

A correction has to be made to the S value for any discrepancy between the mass of the target organ (m_t) and the standard mass (m_s). Combining all constants and correction factors into one constant, the absorbed dose equation can then be written:

$$D = \frac{0.16 T_e A_0}{m} \tag{4.11}$$

where: D is the absorbed dose in Gy;
T_e is the effective half-life in hours;
A_0 is the extrapolated initial activity in MBq;
m is the mass in g.

Equation (4.12) applies to ^{131}I in tissues of dimensions > 5 mm but < 50 mm, and in the situation where the target and source tissues are identical (Schlesinger et al, 1989). All dosimetry calculations are based upon the assumption that radionuclide is distributed uniformly throughout the tissue of interest. This is a reasonable assumption for ^{131}I since the range of beta particles from ^{131}I (mean 2.5 mm) ensures that a reasonably uniform distribution of absorbed dose is achieved despite heterogeneity in the location of the radionuclide.

4.2.5 Measurement of Biologic Distribution Data

In this study, A_0 and T_e were derived from the activity-time curves obtained from sequential quantitative scans using either the rectilinear whole-body scanner (see Section 5.2) or the STARCAM gamma camera (see Section 5.3).

The mass (m) has been estimated by measuring the volume of tissue which concentrates radioiodine and assuming a density of 1 g cm^{-3} This functioning mass was obtained either from the planar images produced by the rectilinear scanner (Section 6.2.1) following ^{131}I therapy or from tomographic images produced by the MUP-PET camera following a tracer amount of ^{124}I (see Section 6.2.2). When scan data were not available, an estimate of anatomical mass has been used. For these cases, the size of thyroid remnants was assessed from images taken in the axial and longitudinal planes using an ACUSON real time scanner with a 5 MHz linear array probe. Computed tomography (CT) and magnetic resonance imaging (MRI) were used to assess the size of pulmonary, soft tissue and bone metastases (Section 6.1.1).

4.3 SELECTION OF RADIONUCLIDES FOR THERAPY

4.3.1 Physical Chararcteristics

Although in theory, both positively (positron) and negatively (beta) charged particles could be employed, in practise only the negatively charged particles are employed. Positrons have a range of 1 to 2 mm in tissue before they annihilate to form a pair of photons. The possibility of using positron-emitters for therapy and simultaneously locating them by annihilation-photon tomography has not yet been explored. In general, beta emissions are most useful in therapy because they dissipate their ionising energy in the small volumes of tissue being treated. Beta particles are emitted in a continuous spectrum of energy up to a maximum and thus have a distribution of ranges. The average energy of an emitted beta particle is approximately one-third of the maximum and the range (which depends upon the particle's energy) is generally of the order of millimetres.

Conversely, radionuclides emitting medium energy gamma rays (80 keV to 200 keV) that escape the target organ are excellent for high-resolution imaging techniques but because of their low radiation dose to the target organ are of little use in therapy. However, many beta particle emitting radionuclides emit gamma photons as well and these photons may be used to locate the distribution of the radionuclide and estimate its concentration. For radionuclides which emit beta particles of high energy only, the accompanying bremsstrahlung can be used to locate the radionuclide in the body.

Alpha particles are energetic helium nuclei (two protons and two neutrons) and because of their mass and charge they interact vigorously with the matter through which they pass , losing energy rapidly and travelling short distances in relatively straight lines. The radiation characteristics of alpha emitters (sharp localisation of radiation, high radiation density, high linear energy transfer (LET)) make them appear attractive for therapy. Owing to their high LET, the tumouricidal effects are much less oxygen dependent than for beta particles. Astatine isotopes (Friedman, 1978) are the only short-lived alpha emitters which can be produced easily from common target materials and have acceptable chemical characteristics. In particular, ^{211}At has a convenient half-life of 7.2 hour and no long-lived radioactive daughters. ^{211}At emits alpha particles with a range of 60 μm and an average energy of 6.8 MeV. Being a halogen, organic molecules can be astatinated by the same techniques by which they

can be iodinated. Hence, one can bind astatine to proteins, enzymes and simple molecules. Although not used as yet for therapy, the potential uses of astatine are currently being explored.

4.3.2 Chemical Considerations

The main chemical considerations for a radionuclide to be useful in therapy depends upon the kinetics and metabolism of the radiochemical under certain pathophysiological conditions. The localisation of the radio-labelled compound is determined primarily by its chemical form and to a lesser extent by its physical state. Ideally, in its administered form (or when metabolised) it should be highly localised in the tissue of interest and with minimum uptake in non-tumour tissue. The biologic behaviour of a radiopharmaceutical depends upon the nature and extent of disease of the patient, the chemical nature of the pharmaceutical and its route of administration.

4.3.3 Specificity

For systemic radionuclide therapy, a high degree of specificity is demanded because of the possible damaging effects of the high level of ionising radiation on normal tissues.

4.3.4 Radionuclides of Iodine for Treatment of Differentiated Thyroid Carcinoma

The radionuclides of iodine established in the diagnosis and therapy of thyroid carcinoma are shown in Table 4.1.

^{123}I is relatively short-lived and the 159 keV gamma ray emission is suitable for diagnostic imaging with conventional gamma cameras. Tomographic imaging can also be accomplished using single photon emission tomography (SPECT). The short half-life and lack of non-penetrating radiation, however, mean that it is not suitable for therapy.

The use of ^{124}I in conjunction with positron emission tomography (PET) to estimate the functioning mass of thyroid remnants and metastases from thyroid carcinoma are fully described in Chapter 6. Its potential use for therapy has not yet been explored owing to expense and availability.

Table 4.1: Radionuclides of iodine used in diagnosis and therapy of thyroid carcinoma.

Radionuclide	Half-life	Main Emission	Application
^{123}I	13 hour	159 keV photons	diagnostic imaging with gamma camera SPECT
^{124}I	4.20 day	511 keV annihilation photons positrons	diagnostic imaging PET potential therapy
^{131}I	8.05 day	192 keV beta (89.8% abundance)	therapy
		364 keV photons (82% abundance)	imaging

Sodium iodide [^{131}I] is the radiopharmaceutical of choice for therapy in differentiated thyroid carcinoma. ^{131}I emits both energetic electrons and gamma rays (Table 4.2). The therapeutic absorbed dose emanates mainly from the beta particle emissions whilst the gamma photons can be used scintigraphically to localise metastatic deposits and to measure the concentration of radioiodine required for absorbed dose calculations (see Section 4.2). Sodium iodide is easily absorbed through the gastrointestinal mucosa into the blood stream, whence it is extracted (trapped) with high efficiency by the thyroid gland and functioning metastases (Section 1.1.6). First incorporated into thyroid hormone precursors, it is stored and concentrated in the thyroid follicles. No other radiopharmaceutical has so far approached its effectiveness, due to the unique avidity of iodide for thyroid tissue.

Table 4.2: Nuclear data for dosimetry calculations for ^{131}I. Data from MIRD,1975.

Nuclear data for the most abundant radiations emitted from ^{131}I			
Radiation	n_i	E_i (MeV)	Δ_i (g Gy MBq^{-1} h^{-1})
Non-penetrating:			
β_1	0.0200	0.0691	0.008
β_3	0.0664	0.0964	0.004
β_5	0.8980	0.1916	0.099
Penetrating:			
γ_4	0.0578	0.2843	0.010
γ_9	0.8201	0.3644	0.172
γ_{12}	0.0653	0.6367	0.023
γ_{14}	0.0173	0.7228	0.007

CHAPTER 5

IN VIVO MEASUREMENT OF RADIOIODINE (^{131}I) UPTAKE: INSTRUMENTATION AND METHODS

5.1 HISTORICAL BACKGROUND

5.1.1 Introduction

In order to calculate the absorbed dose to thyroid remnants and functioning metastases it is necessary to perform sequential measurements of the radioactivity in the area of interest over a period of time (Saunders et al, 1974; Schlesinger et al, 1989). These measurements may be carried out using a conventional imaging system such as a gamma camera (Anger, 1964) or a rectilinear scanner (Mayneord & Newbery, 1952). Quantitative methods for such in vivo measurements have been described by several authors (Fleming, 1979; Myers et al, 1981; Clarke et al, 1982). There are a number of physical problems which require careful investigation for the particular type of instrument used. Firstly, there is the problem of the inevitable loss of sensitivity of a moving detector system as opposed to a stationary one. Calibration of a given detector system must allow for the absorption and scattering of radiation by tissue and for the unknown size and distance from the detector of a source (or sources) in vivo. Corrections for dead-time of the counting system are required when this leads to significiant loss of counts. It may be difficult to identify the edges of an area of interest when there are adjacent background areas with high uptake of radioactivity. Ideally, therefore, the system should have good spatial resolution and a response which is depth independent.

5.1.2 Profile Scanners

The first so called "profile" or linear scanner used for the diagnostic and therapeutic investigation of radioiodine (^{131}I) in thyroid carcinoma was described by Pochin in 1950. The detector consisted of a lead cathode Geiger-Müller tube mounted on a scanning rack above the couch on which the patient lay. The detector performed a single linear movement from head to toe of the patient. By recording the count rates with the counter at different positions, a curve or profile indicating the distribution of radioactivity in the body was constructed. Such profile curves (after correction for background, physical decay and counter dead-time) could be calibrated and analysed further to yield organ uptake as a percentage of the administered dose (Corbett et al, 1956). The author stated that estimates of organ activity were accurate to within 10%.

5.1.3 Whole Body Scanners

With the advent of more sensitive scintillation detectors such as sodium iodide (thallium activated) NaI(Tl) whole body scanning became feasible. This has the advantage of locating metastases more accurately and also distinguishing them from uptake in normal tissues such as salivary glands and stomach. It also makes it possible to estimate the size of individual lesions and therefore the radiation dose to the tumour can be calculated (Scott et al, 1970; Henk et al, 1972; Edmonds et al, 1970).

5.2 DUAL-HEADED RECTILINEAR WHOLE-BODY SCANNER

5.2.1 System Design and Performance Characteristics

The dual-headed rectilinear whole-body scanner used in this study was built in 1965 and is housed in the Low Background Laboratory at the Royal Marsden Hospital, Sutton. The scanner was originally designed for high sensitivity tracer studies (Trott et al, 1973; Saunders et al, 1973; Cottrall et al, 1973). The equipment can be operated as a moving couch whole body counter; as a profile scanner or as a two dimensional rectilinear scanner with a maximum scan area of 184 cm x 82 cm. The upper and lower detectors consist of heavily shielded cylindrical NaI(Tl) scintillation crystals 12.5 cm diameter and 5.0 cm long which can be fitted with different collimators depending upon the energy and activity of the radionuclide used. The upper and lower heads of the scanner are rigidly mounted but both detectors may be raised or lowered by motors within the detector

heads. The scan speed may be varied from 0.42 cm s^{-1} to 1.41 cm s^{-1} depending upon the statistical accuracy required. Obviously, the slower the scan speed the higher the total counts acquired. The couch is a 2 m x 0.91 m perspex sheet fitted to the pallet as shown (Fig. 5.1) and may be moved in both longitudinal and transverse directions.

Figure 5.1: Dual-headed rectilinear whole-body scanner.

Measurements were carried out in the pulse height analysis mode in which counts are accumulated during longitudinal movement and the counter is reset at each step. During the transverse movement no counts are accumulated. Data from the detectors are stored in a micro-computer (which controls the scanner and counting system). The standard scanning conditions used for the clinical studies described in this thesis, unless otherwise stated, were 3 mm scanning step sizes in both the longitudinal and transverse directions and a longitudinal scanning speed of 4.20 mm s^{-1}

5.2.2 High-Resolution Low-Sensitivity Collimators

Special high-resolution low-sensitivity collimators have been designed for quantitative imaging of high activity levels of ^{131}I (Flower et al, 1986; 1989). Two pairs of multihole collimators were used for these studies. The first pair (referred to as 9RH3) each comprised nine 3 mm diameter holes arranged on a square array with focal length 200 mm. This collimator (9RH3) is shown schematically in Fig.5.2 and the actual collimator is shown in Fig.5.3.

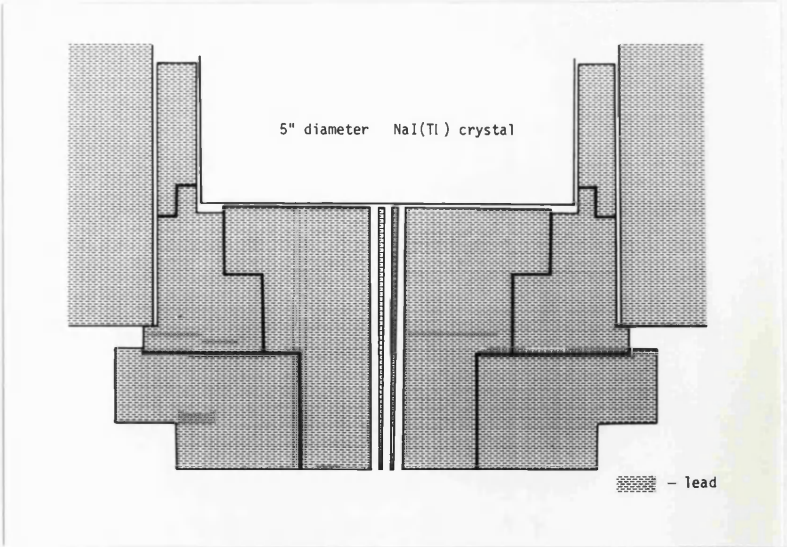


Figure 5.2: *Schematic diagram of nine-hole 3 mm diameter parallel-bore collimator (from Flower et al, 1989).*

The second pair (referred to as 19RH4) each comprised nineteen 4 mm diameter holes arranged on a hexagonal array. The specifications of the collimators were:

(i) penetration and leakage effects to be minimised;
(ii) spatial resolution (in terms of full width at half maximum) (FWHM) of line spread function) to be less than 10 mm;
(iii) quantification of therapy levels of ^{131}I to be possible.

These specifications have been met as follows. The amount of lead surrounding the detectors has been increased to reduce radiation penetration effects and all the lead-lead interfaces were designed to minimise leakage and penetration.

Figure 5.3: *Pair of nine-hole 3mm diameter parallel-bore collimators.*

It has been shown (Hinton, 1988) that a reasonably flat response can be achieved by combining the output of the two opposed detectors geometrically, that is combined counts = [upper detector counts x lower

detector counts] $^{1/2}$. This is known as "isosensitivity" that is, the geometric mean is independent of the depth of the source in tissue (Sharma, 1968).

5.2.3 Spatial Resolution

Profile scans across a line source of ^{131}I were used to evaluate the spatial resolution of the scanner. Spatial resolution was measured in terms of the full width at half maximum (FWHM) of the line spread function as a function of the distance of the line source from the upper detector. Fig. 5.4 shows the variation of resolution with position of the upper detector alone and reveals that the minimum value of the FWHM (7.6 mm for collimator 9RH3, 10 mm for collimator 19RH4) occurs at about 120 mm distance, which is much closer than the focal plane (200 mm).

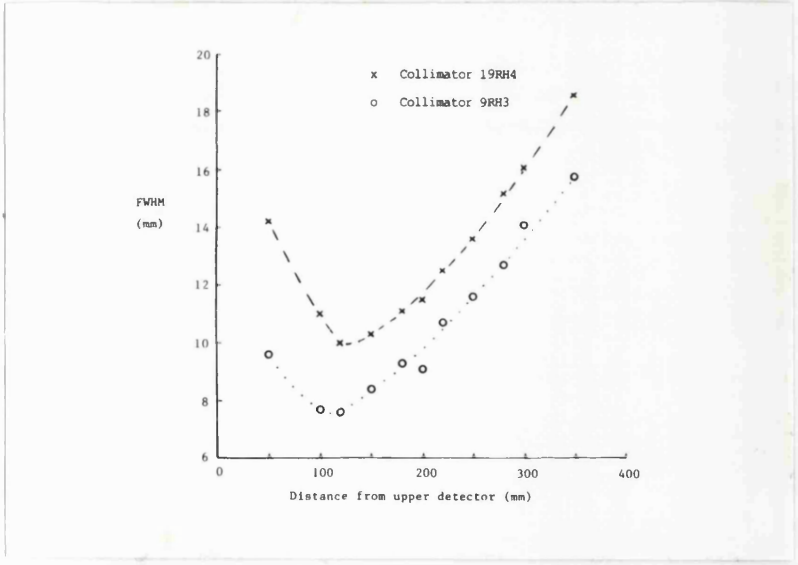


Figure 5.4: *Variation of resolution (FWHM of line spread function in air) with position of upper detector alone for collimators 19RH4 and 9RH3 (Reproduced from Flower et al, 1989).*

This is due to the fact that the collimator holes are focussed towards the focal plane but not tapered towards the focal point. Fig. 5.5 shows the variation of resolution with position when the counts from both detectors positioned 400 mm apart are combined using the geometric mean. This

shows that an "isoresolution" response is achieved over the central 200 mm which is a typical patient thickness. Thus, if patients are positioned centrally between the detectors (400 mm apart) tumours can be imaged with a resolution of 9.0 $\pm$ 0.3 mm.

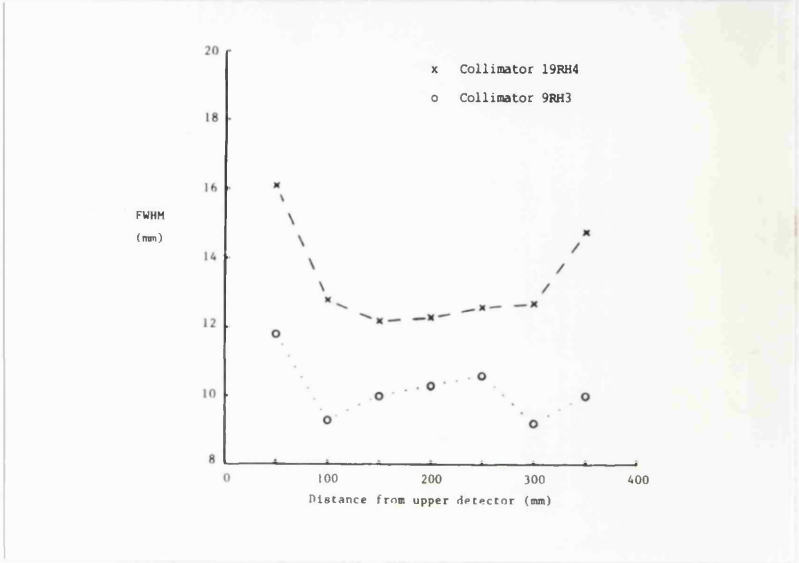


Figure 5.5: *Variation of resolution (FWHM of line spread function in air) when both detectors positioned 400 mm apart; combined geometric output achieves isoresolution. (Reproduced from Flower et al,1989).*

The high resolution of collimator 9RH3 is illustrated in the images of the Picker thyroid phantom (Fig. 5.6) which show that both the 10 mm diameter cold and hot spots in the inferior right and left lobes respectively are well visualised but in addition the 5 mm and 8 mm cold spots in the superior right and left lobes are also distinguishable.

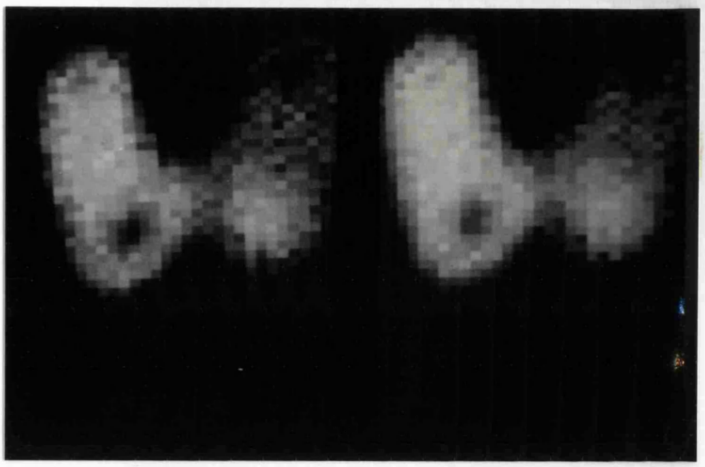


Figure 5.6: Images of Picker thyroid phantom containing ^{131}I for 9RH3 collimator. (From Flower et al, 1989).

5.2.4 Dead-Time Correction

In most detector systems there is a minimum time interval which must separate two events in order that they be recorded as two separate signals. This minimum time is referred to as the dead-time of the counting system. By measuring the dead-time, the true count rate (N_T) can be calculated from the expression:

$$N_T = \frac{N_0}{1 - N_0 \tau} \tag{5.1}$$

where N_0 is the observed count rate. The dead-time (τ) was determined using the method of Knoll, 1979.

5.2.5 Calibration of Scanner

The calibration of the scanner for quantifying the uptake of ^{131}I has been described by Masoomi, 1985. If a collimated source of monochromatic radiation and a suitable detector are separated by a fixed distance and increasing amounts of a uniform absorber are interposed, then the amount

of radiation detected follows a simple exponential fall described mathematically by Beer's Law:

$$C_m = C_0 \exp(-\mu t) \tag{5.2}$$

where

C_0 is the count rate measured with no absorber present;
C_m is the count rate measured with absorber present;
t is the thickness of the absorber;
μ is the linear attenuation coefficient of the absorber.

If the activity of the source is known, then a calibration factor (CF) for the detector can be found:

$$\text{CF} = \frac{\text{Count rate due to source of known activity}}{\text{Activity of source}} \tag{5.3}$$

If a similar source of unknown activity is then used and set up with identical geometry the activity can be found from:

$$\text{Activity} = \frac{\text{Count rate due to source of unknown activity}}{\text{CF}} \tag{5.4}$$

In practice, however, there are a number of physical considerations which must be taken into account when measuring absolute activity in vivo:

(i) the source is not collimated;
(ii) most radionuclides are not monoenergetic but emit gamma rays of several different energies and the absorption of these photons is a function of energy;
(iii) the amount of absorber between the source and detector is unknown (since the source is inside the patient).

These problems have been solved as follows. The detectors are collimated. A single channel analyser is used to select radiation from one photopeak

only. By using two opposed detectors, a combined output can be obtained which is independent of the depth of the source within the patient (vide supra, Section 5.2.2). The above situation describes the rectilinear scanner operating in static mode. When used in scanning mode, the counts become a function of the x-y co-ordinates of the scanner so that activity is measured in units of counts s^{-1} cm^{-2} . Calibration scans have been performed using sources of different size positioned within tissue-equivalent material to simulate the scanning conditions of the patient. The standard scanning conditions (unless otherwise stated) were 3 mm scanning step sizes in both the longitudinal and transverse directions and a longitudinal scanning speed of 4.2 mm s^{-1}. The standard calibration factor used throughout the clinical patient studies was 400 counts cm^{-2} MBq^{-1} (Hinton, 1988) with these standard scanning conditions.

5.2.6 Image Quantitation

Quantitative imaging was achieved via isosensitive scanning as described above. The relative area sensitivities for the two different collimators (9RH3 and 19RH4) are shown in Table 5.1 (Flower et al, 1989). The counting rates refer to the geometric mean combining counting rates for the upper and lower detectors and to an area source (of internal dimensions 52 mm x 82 mm x 10 mm) positioned within a 200 mm thick tissue equivalent phantom. These results show that the 19RH4 collimator was about seven times as sensitive as the 9RH3 collimators. The sensitivity of the collimators is such that a reading above background level indicates the presence of a therapeutic amount of ^{131}I for carcinoma of the thyroid.

Collimator	Area sensitivity cps per MBq/cm^2
9RH3	12.1 ± 0.5
19RH4	82.5 ± 3.5

Table 5.1: *Relative area sensitivities for 9RH3 and 19RH4 collimators. (From Flower et al, 1989)*

5.2.7 Determination of Activity and Effective Half-Life

The uptake of ^{131}I in thyroid remnants and metastatic lesions is determined by comparing the counts in the appropriate region of the patient's scan with the counts in the calibration scan. A 45% contour was found to be most useful for boundary delineation, especially when lesions were surrounded by a high level of background. Corrections were made for background activity and for patient thickness where necessary. By performing sequential quantitative scans (for example on days 3, 4 and 7) following the administration of ^{131}I, activity-time curves for each region of interest were produced. By fitting the data and extrapolating to the time of administration, the initial activity, A_o in the tissue and the effective half-life, T_e were determined.

5.2.8 Illustrative Quantitative Scans

The quantitative scans of a patient with papillary carcinoma receiving an ablation 3.0 GBq ^{131}I administration following near-total thyroidectomy are now illustrated. The whole-body scan at 1.1 days using the rectilinear scanner with 6 mm pixels is shown in Fig. 5.7. Fig.5.8 shows the neck scan at 3 days using the high-resolution, low-sensitivity collimator (9RH3) and 3 mm pixels.

***Figure** 5.7: Whole body scan at 1.1 days using dual-headed rectilinear scanner and 6 mm pixels following near-total thyroidectomy and ablation 3.0GBq ^{131}I.*

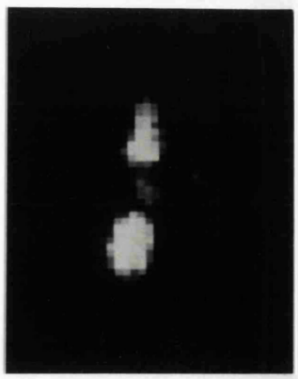


***Figure** 5.8: Neck scan at 3 days using high-resolution low-sensitivity collimators 9RH3 and 3mm pixels.*

(Images reproduced from Flower et al, 1989).

The images show three areas of increased activity in the neck corresponding to three thyroid remnants following surgery. The mass of each thyroid remnant in the neck was obtained from the planar images produced by the scanner as described in Chapter 6. The cross-sectional area of each remnant was estimated from the number of pixels within that region of interest used to outline the remnant. The volume of each remnant was then estimated from the cross-sectional area by assuming tissue density of 1 g cm^{-3} and that for a cross-sectional area a cm^2 the mass (m) in g is given by:

$$m = a^{3/2} \tag{5.5}$$

The estimated sizes of each of these three remnants were 25 mm x 8mm for regions 1 and 2 and 12 mm x 6 mm for region 3. The estimated masses of these remnants were 2.8, 2.8 and 0.6 g respectively assuming that the density of tissue is 1 g cm^{-3} and that each lesion can be approximated to a cube of side a cm. Activity-time curves of activity (logarithmic scale) in the whole body and in three regions of interest (1,2,3) in the neck plotted as a function of time (linear scale) are demonstrated in Fig. 5.9. The average effective half-life for the three regions considered together was 30 hour. Using these data, the dose to the neck was estimated to be 400 Gy. Three months later, no activity was found in the neck or elsewhere following 5.5 GBq ^{131}I. Thus, the earlier ablation had successfully ablated residual (normal) thyroid remnants.

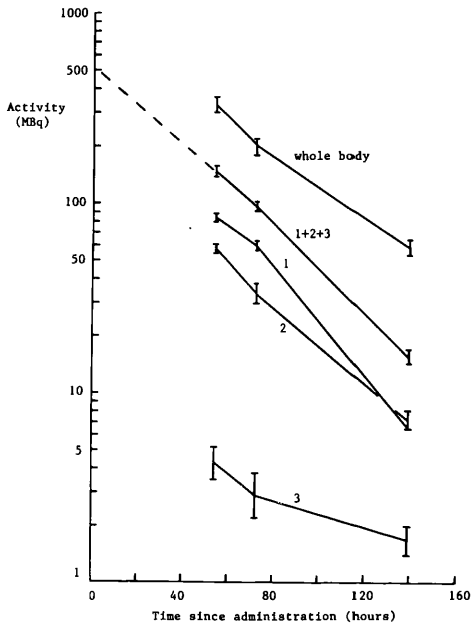


Figure 5.9: Activity-time curves showing activity (logarithmic scale on vertical axis) in the whole body and 3 regions of interest in the neck plotted as a function of time. (Reproduced from Flower et al, 1989).

5.3 STARCAM GAMMA CAMERA

5.3.1. Introduction

The feasibility of using equipment such as gamma cameras (which are more widely available in Nuclear Medicine Departments) for ^{131}I dosimetry scanning was investigated. The design of the gamma camera has been optimised for producing high quality images using the 140 keV photons from $^{99}Tc^{m}$ and is less suitable for quantitative imaging of ^{131}I for which the two main photon energies are 364 keV (with 81.2% abundance) and 637 keV(with 7.2% abundance) (ICRP, 1983). The septal penetration of scattered photons from the 637 keV gamma rays and partial absorption of the 637 keV photons in the thin crystal make this system less ideal than the rectilinear scanner described above and careful calibration and correction factors are required.

Organ uptake was determined by comparing counts in the static images of each area of interest with the counts recorded from imaging a standard phantom containing a known activity of ^{131}I. Counts recorded in both anterior and posterior views of the same region were combined to give the geometric mean which was calculated from the equation:

$$\mathbf{Counts_{GM} = [Anterior\ counts \times Posterior\ counts]^{1/2}} \tag{5.6}$$

Corrections for background activity and for attenuation were necessary and also corrections for camera dead-time when this resulted in a significant loss of counts in the patient images.

5.3.2. STARCAM Gamma Camera

Dosimetry measurements were performed using an IGE STARCAM 400 ATC gamma camera (Fig. 5.10). This camera has a 400 mm diameter NaI(Tl) crystal which is 9 mm thick. A high-energy parallel-hole collimator was used for imaging ^{131}I. The energy peak was set at 364 keV with a window width of 12% with the window offset +1%. Anterior and posterior views were acquired into 128 x 128 matrices with no zoom. For ablation studies static views of the neck were obtained following 3.0 GBq ^{131}I; views of the chest, abdomen or pelvis were obtained following therapy with 5.5 GBq ^{131}I if metastatic lesions were suspected. Static acquisitions were obtained at 24, 48, 72 and 120 hours following ^{131}I administration. Patient thickness in each region of interest (that is neck for thyroid ablation or chest for lung metastases and so on) was also recorded.

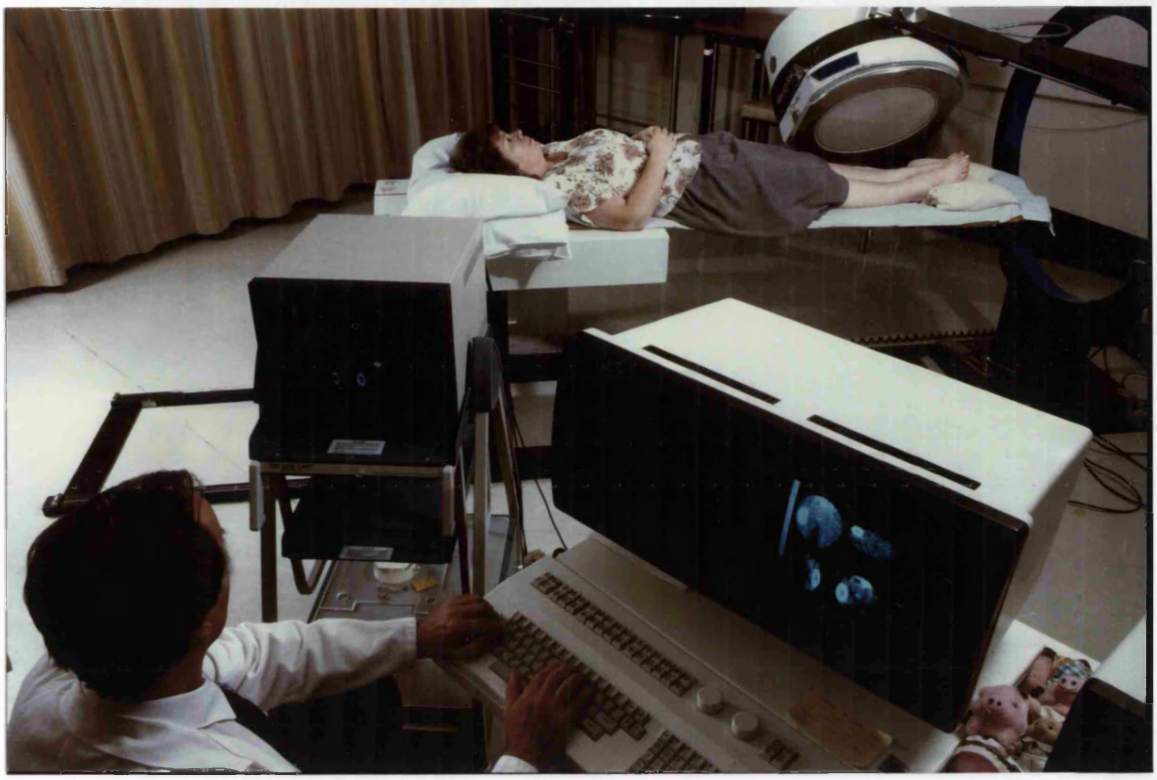


Figure 5.10: STARCAM gamma camera.

5.3.3 Correction for Dead-time

A point source of ^{131}I with sufficient activity so that the count density in the image of the point source was approximately the same as that in the image of the patient was prepared. The point source was placed in the field of view of the camera at the side of the patient during each static acquisition. Additional anterior and posterior static acquisitions were then performed with the point source alone. The counts within a small region of interest positioned over the image of the point source (C_1 with the patient in the field of view and C_2 without the patient in the field of view) were recorded. The dead-time correction was given by the ratio C_2/C_1 . The dead-time correction was remeasured for each new patient image. In subsequent analyses of patient images the counts within the region of interest were multiplied by the corresponding ratio C_2/C_1. If the ratio was less than 1.05 then the dead-time correction was ignored for the later scans of the patient.

5.3.4 Image Processing

Region of interest analysis was performed on static acquisitions in order to determine activity-time curves for each organ of interest. From these curves the initial activity A_0 and effective half-time T_e were determined for each site for subsequent dosimetry calculations as described in Chapter 4. Corrections were made for background activity and also for camera dead-time as described above (section 5.3.3). Scans taken 72 hours following therapy with 5.5 GBq ^{131}I for a patient with bone and pulmonary metastases are shown below. Fig. 5.11 shows the posterior view of the upper chest and right humerus with regions of interest superimposed upon a soft tissue deposit arising in a rib and in two lytic lesions in the right upper arm.

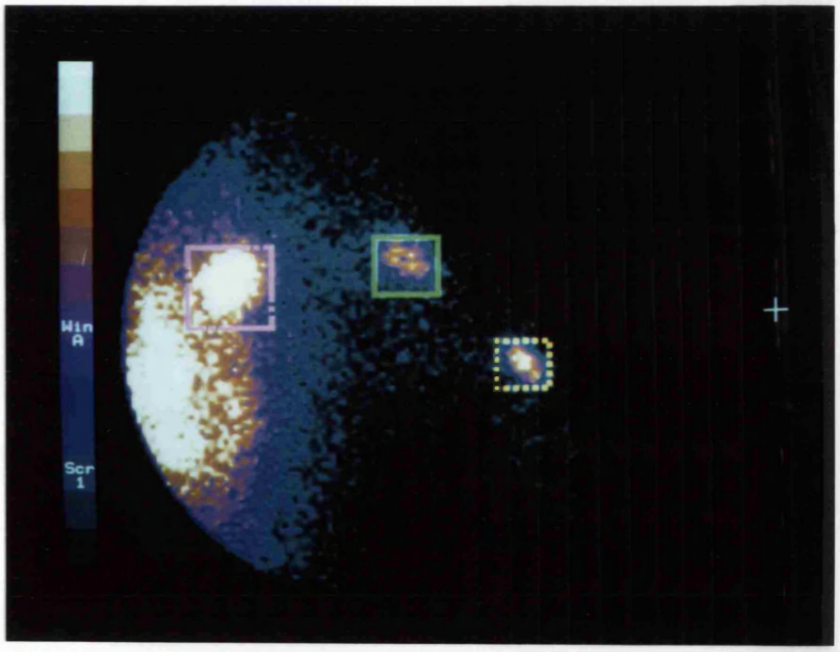


Figure 5.11: *Posterior view upper chest and right humerus following therapy 5.5 GBq ^{131}I for patient with bone and pulmonary metastases.*

Fig. 5.12 shows the anterior view of the pelvis for the same patient with regions of interest superimposed upon a bone deposit in the lower lumbar spine and a further deposit in the right upper femur. This scan also shows that by 72 hours most of the activity in the bladder and bowel had cleared.

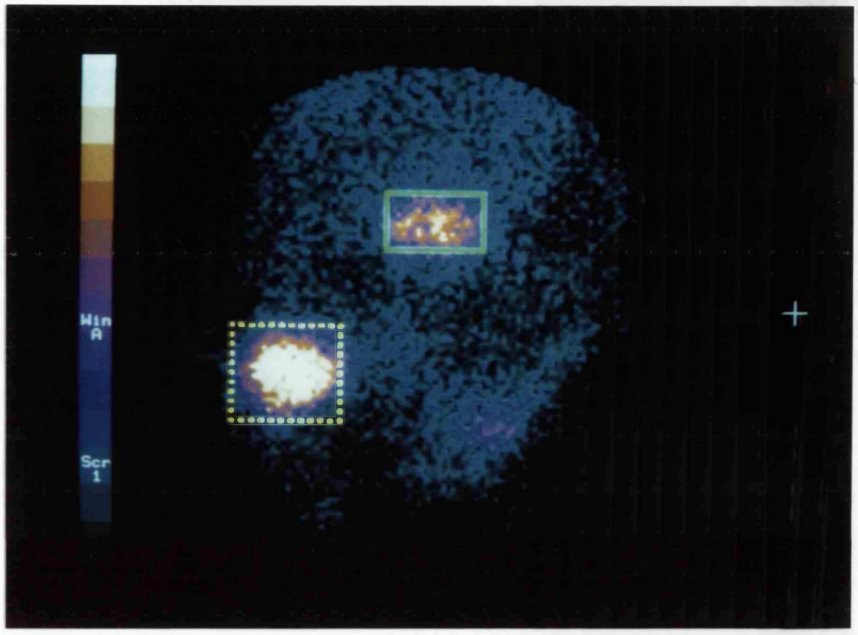


Figure 5.12: *Anterior view pelvis following 5.5 GBq ^{131}I showing regions of interest superimposed upon lytic deposits in lumbar spine and right upper femur.*

5.3.5 Calibration of Gamma Camera

For neck dosimetry studies a 15 ml glass vial containing a known activity of ^{131}I in 5 ml was placed inside a solid perspex neck phantom 12.6 cm diameter. With the gamma camera face upwards the calibration source (within the perspex neck phantom) was placed on the collimator surface.

Static acquisitions of the calibration phantom using an imaging time of 300 seconds were made with the phantom first resting on the collimator surface and then repeated with a variable air gap between the camera and anterior aspect of the phantom. With the phantom then placed on the couch and the camera face touching the underside of the couch static acquisitions were obtained using imaging times of 300 seconds. Acquisitions were then repeated for a range of varying air gaps between the neck phantom and couch (Fig. 5.13).

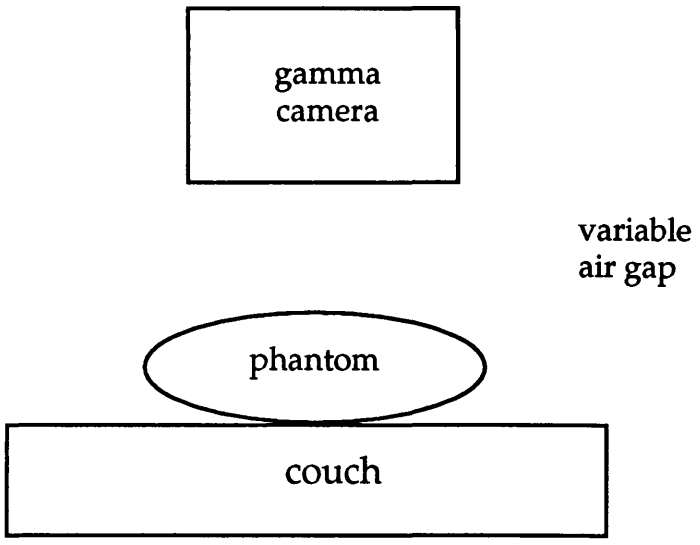


Figure 5.13: *Acquisition set up for calibration factors for STARCAM gamma camera: phantom resting on couch, variable air gap between camera and anterior phantom.*

From these measurements calibration factors were derived for the range of geometries actually used for patient studies (Table 5.2). For lesions outside the neck, calibration factors were derived using larger calibration phantoms with geometrical configurations to closely mimic that of the patient acquisition.

Table 5.2: *Calibration factors for ^{131}I dosimetry using STARCAM gamma camera.*

Acquisition set up	Air gap (cm)	Calibration Factor (cps MBq^{-1})
Camera face touching underside of couch; variable air gap between neck phantom and couch	0	13.56
	2	12.89
	4	12.28
	6	11.80
	8	11.49
Phantom resting on couch; variable air gap between camera and anterior phantom	0	57.13
	2	50.77
	4	45.53
	6	42.24
	8	39.37
	10	37.18

5.3.6 Region of Interest Analysis

As described above, a region of interest was drawn around the thyroid remnant in the neck (anterior view) using the grey scale in the image display to find the 20% (of the maximum count in the thyroid) contour. The total counts within this 20% contour was recorded $C_{ant,thyroid}$ and the area $A_{ant,thyroid}$ of the region of interest. Similarly, the total counts in the posterior view of the thyroid $C_{post,thyroid}$ was recorded together with the area $A_{post,thyroid}$. Area corrected background subtraction was then performed to obtain $C'_{ant,thyroid}$ and $C'_{post,thyroid}$ representing true counts due to the thyroid lesion alone in identical anterior and posterior areas. Thus:

$$C'_{ant,thyroid} = C_{ant,thyroid} - C_{ant,bg}\left[\frac{A_{ant,thyroid}}{A_{ant,bg}}\right] \tag{5.7}$$

and

$$C'_{post,thyroid} = C_{post,thyroid} - C_{post,bg}\left[\frac{A_{post,thyroid}}{A_{post,bg}}\right] \tag{5.8}$$

where:
$C_{ant,thyroid}$ is the recorded anterior counts due to thyroid;
$C_{ant,bg}$ is the counts for the background region;
$C'_{ant,thyroid}$ is the true anterior counts due to thyroid;
$C_{post,thyroid}$ is the recorded posterior counts due to thyroid;
$C'_{post,thyroid}$ is the true posterior counts due to thyroid;
$A_{ant,thyroid}$ is the area for the anterior thyroid region of interest;
$A_{ant,bg}$ is the area for the anterior background region;
$A_{post,thyroid}$ is the area for the posterior thyroid region of interest;
$A_{post,bg}$ is the area for the posterior background region.

The geometric mean was then calculated using the formula:

$$C_{GM} = \left[C'_{ant,thyroid} \times C'_{post,thyroid}\right]^{1/2} \tag{5.9}$$

The geometric mean was converted to counts per second and the activity (MBq) in the thyroid remnant was then calculated from:

$$\text{Activity in thyroid} = \frac{C_{GM}}{CF} \times \exp\left[\mu\left(\frac{D}{2} - 6.3\right)\right] \tag{5.10}$$

where: μ is the linear attenuation coeficcient for 364 keV (0.11 cm^{-1});
D is the patient neck thickness in cm;
diameter of perspex calibration phantom is 12.6 cm;
CF is the calibration factor (cps MBq^{-1});

and the calibration factor is chosen from Table 5.2 to be appropriate for the patient acquisition geometry.

5.4 RELATIVE MERITS OF RECTILINEAR SCANNER VERSUS GAMMA CAMERA

The advantages of the rectilinear scanner over the gamma camera may be summarised briefly as follows:

(i) rectilinear scanners do not suffer from non-uniformity or non-linearity. Corrections for these effects may be performed in modern gamma cameras whose design has been optimised for imaging $^{99}Tc^{m}$ although other radionuclides may be used;

(ii) the 5 cm thick NaI(Tl) crystals of the rectilinear scanner are more suited to the high energy 364 keV photons from ^{131}I than the gamma camera which has a crystal thickness of 9 mm and has been optimised for $^{99}Tc^{m}$ 140 keV imaging.

Calculated photopeak detector efficiencies for 360 keV photons are shown in Table 5.3 (Anger & Davies,1964);

Crystal thickness m m	Photopeak efficiency %
9	22
12.7	30
50.0	82

Table 5.3: Calculated photopeak efficiencies for 360 keV photons.

(iii) with dual-headed detecting systems and focussed collimators; isoresolution and isosensitive scanning can be performed (vide supra, section 5.2.2); however dual-headed gamma camera systems are also available;

(iv) an isoresolution of approximately 1 cm can be achieved using focussing collimators over a patient thickness of 20 cm which is better than that attainable with a single head gamma camera at 10 cm depth at ^{131}I photon energies; typically 1.8 cm resolution;

(v) heavy lead collimation can be used when therapeutic amounts (up to 5.5 GBq) of ^{131}I are being imaged.

The disadvantages of a rectilinear scanner include:

(i) patient motion is less of a problem with the gamma camera as the effects are averaged whereas for a rectilinear scanner activity may be completely missed;

(ii) the small area of crystal used by a rectilinear scanner means that very inefficient use is made of the available photons;

(iii) for a rectilinear scanner, pixel size is chosen with reference to the area to be scanned in order to limit the total scan time to about 30 minutes which is the maximum usually acceptable to the patient.

CHAPTER 6

ESTIMATION OF FUNCTIONING MASS USING POSITRON EMISSION TOMOGRAPHY

6.1 INTRODUCTION

6.1.1 Anatomical Mass Estimation

In the past, the major problem in dosimetry calculations has always been the accurate estimation of the mass of thyroid tissue and of metastatic lesions which concentrate radioiodine. This uncertainty in mass may explain the ten-fold variation in dose estimates for ablation of thyroid remnants quoted in the literature and summarised in Table 6.1 (Goolden, 1963; Doniach, 1974; Maxon, 1981, 1992; Becker, 1982). Palpation and calliper measurements have been used but this is obviously subject to very large errors.

Residual mass following surgery has also been estimated simply from interpretation of the surgical findings (Goolden et al,1963; Snyder et al, 1983; Maxon et al, 1981). For example, following hemi-thyroidectomy it has been assumed that the residual thyroid mass was 15g (Goolden et al, 1963). Maxon and colleagues (1981,1992) estimated the surface area of the thyroid remnant from planar rectilinear scan images but estimated the depth of tissue from the surgical procedure and hence derived an estimate of volume.

Table 6.1: Absorbed dose estimates for ablation of thyroid remnants.

Author	Dose Estimate (Gy)	Method of Measuring Mass
Goolden (1963)	300	palpation,surgical procedure
Maxon (1981;1992)	300-500	surface area from planar images from rectilinear scanner, depth from surgical procedure
Becker (1982)	750-1000	tracer scan

Plain radiographs may be used to estimate tumour size of suitable lesions such as well-defined pulmonary metastases and bone deposits. Two perpendicular diameters (X,Y) after correction for film magnificiation are required. The third dimension Z may be obtained from a lateral view. Volume can then be calculated from:

$$\text{Volume} = \frac{4\pi}{3} x \left[\frac{XxYxZ}{8} \right] \qquad (6.1)$$

Where lateral views are not evaluable, an approximation for Z may be obtained from the mean of the other two dimensions.

Both X-ray computed tomography (CT) and magnetic resonance imaging (MRI) have excellent spatial resolution and may provide precise measurement of anatomical volume. For CT scanning the spatial resolution which can now be achieved is 0.5 mm in the transaxial slices and 1.5 mm in the axial direction. For MRI scanning the spatial resolution achievable is 1 mm in the transaxial slices and 4 mm in the axial direction. CT and MRI are particularly useful for determining the volume of soft tissue masses in the chest and abdomen where normal activity in the radioiodine excretory pathways (that is stomach, liver, gut and bladder) may otherwise obscure uptake in overlying lesions. However, small soft tissue

masses in the thyroid bed are not easily defined, particularly in the presence of artefacts arising from surgical clips and small residua are difficult to distinguish from post-operative fibrous tissue.

The use of high resolution ultrasound in the diagnosis of thyroid disease is well established. Using a 10 MHz probe lesions such as solitary nodules within the thyroid gland of the order of 2 mm may be identified (Simeone et al, 1982). Since ultrasound is widely available, relatively inexpensive and convenient for the patient its use to estimate the mass of thyroid remnants and neck nodal metastases would appear very attractive. However, accurate measurement of thyroid volumes and particularly post-surgical remnants is not without considerable difficulty. Problems include thickening in the skin of the scar post-operatively, the presence of surgical clips (which may produce small acoustic shadows) and difficulty in determining tumour/thyroid margins. Accuracy may be improved by taking closely spaced slices. Measurements in the axial and longitudinal planes are required from which volume could be estimated using equation (6.1).

6.1.2 Concept of Functioning Mass

In order to calculate the absorbed dose to thyroid remnants and metastases which concentrate radioiodine, it is necessary to measure that mass of tissue which is metabolically active. This so-called "functioning" mass will in general differ from the anatomical mass especially if the radionuclide is not uniformly distributed throughout the region of interest. Thus, if the radionuclide is not uniformly distributed this will lead to an overestimate of mass and consequent underestimate of absorbed dose. Ideally, therefore, the functioning volume (and hence mass) should be estimated using a radionuclide technique with inherently good spatial resolution and tomographic capability. For the clinical dosimetry studies described in Chapter 7 of this Thesis, two radionuclide techniques have been used to estimate functioning mass:

(i) planar imaging of therapy ^{131}I using the rectilinear scanner with low-sensitivity high-resolution collimators

and

(ii) positron emission tomography using a multi-wire proportional counter camera following tracer ^{124}I.

The rectilinear scanner and special collimators are described fully in Chapter 5. The clinical multi-wire proportional chamber positron camera (MUP-PET) is described below (section 6.3). Other possible radionuclide techniques which may be used are now briefly summarised.

6.1.3 Radionuclide Techniques

In general, radionuclides used for therapy have poor imaging characteristics. The main emitted gamma rays (364 keV) of ^{131}I may be used for imaging using a high energy collimator. However, even if the collimator is designed to have < 5% penetration at this energy, higher energy photons at 637 and 723 keV will penetrate through the collimator and shielding. As discussed above (Section 5.3.1) calculated photopeak efficiencies for 364 keV photons depend upon the crystal thickness so that for a typical gamma camera with thickness 12.7 mm the efficiency is only 30% and for the STARCAM gamma camera with crystal thickness 9 mm used for the studies reported here the efficiency is only 22%. Spatial resolution is only 10 mm at 5 cm depth. Planar imaging may be used to assess the cross-sectional area of a lesion and a lateral scan is then required to estimate depth. However, such planar methods cannot give accurate estimates of volume when there is significant activity in overlying or adjacent tissues which concentrate radioiodine.

6.1.4 Single Photon Emission Tomography

Single photon emission tomography (SPECT) by providing three dimensional data could give a direct means of assessing volume (and hence mass) and overcome the problem of overlying activity in adjacent tissues. High energy collimators are required for ^{131}I but there are considerable problems owing to septal penetration; scatter from the collimator; low detection efficiency and shield leakage. This leads to poor spatial resolution as defined by the full width half maximum (FWHM) of the reconstructed line spread function; for ^{131}I using 20 cm radius of rotation the FWHM is 34 mm. Images tend to be dominated by noise and image contrast is low. Spatial resolution may be improved by using extended collimators as described by Green et al, 1990. Alternatively, tracer ^{123}I could be used as its lower energy (159 keV) is particularly suitable for imaging with the gamma

camera. Typical values for detection efficiency and spatial resolution are 91% (for a 12.7 mm thick crystal) and 5 mm at 5cm depth respectively. Photon emissions can be efficiently collimated using a low energy collimator (< 5% penetration at 180 keV). Owing to the short physical half-life and minimum of non-penetrating emissions, however, ^{123}I is not suitable for therapy.

6.2 DETERMINATION OF FUNCTIONING MASS

6.2.1 Mass Determination from Planar Images using Rectilinear Scanner

The functioning mass of tissues which concentrate radioiodine was determined either from planar images from the rectilinear scanner or from tomographic images using tracer ^{124}I and the MUP-PET camera (section 6.3). The mass was estimated by measuring the volume of tissue concentrating radioiodine and assuming a density of 1 g cm^{-3}. Using data from the rectilinear scanner, a thresholding technique was used to estimate the cross-sectional area of the region of interest. A threshold of 45% of the maximum count in the region of interest was used. Pixels within this threshold value were counted and converted to area by multiplying by the pixel area. The volume of the region of interest (in cm^3) was then estimated from the cross-sectional area (a in cm^2) by assuming that the mass (m) in g is given by:

$$m = a^{3/2} \tag{6.2}$$

This assumes that the region of interest is equivalent to a cube of side a. The above method was validated by scanning several sources of different shapes and sizes and at different depths in tissue equivalent material (Hinton, 1988). Errors associated with the determination of tissue mass have been assessed (Hinton,1988) and are discussed below (Section 6.4).

6.2.2 Mass Determination from 3D Tomograms

A technique with inherently high spatial resolution such as positron emission tomography should provide a more accurate determination of functioning volume than two dimensional planar imaging. Using the MUP-PET camera, a method to extract the measurement of functioning

volume from the digitised cube of reconstruction data has been developed (Webb et al, 1985). A simple thresholding technique was used which assumes that all pixel values above a certain threshold (a percentage of the maximum pixel value) represent the tissue which concentrates the radioiodine. The amount of smoothing and the value of the threshold have been determined from phantoms containing ^{68}Ga and ^{124}I of known volume (Oghabian, 1987). It was found that a 38% threshold gave an accurate estimate of volume for a large range of volumes scanned.

6.3 MUP-PET POSITRON CAMERA

6.3.1 Introduction

The clinical multi-wire proportional chamber positron camera (MUP-PET) has been developed and built through a collaboration between the Royal Marsden Hospital and the Institute of Cancer Research at Sutton and the Rutherford Appleton Laboratory at Chiltern (Bateman et al, 1984). PET enables improved accuracy over planar imaging in the determination of the volume (and hence mass) of radioiodine concentrating lesions since it is derived from high-resolution three dimensional data rather than a two dimensional projection with similar (or worse) resolution. The use of PET in the measurement of radiation dose to the thyroid of patients undergoing radioiodine therapy for thyrotoxicosis (Ott et al, 1987) and for planning ^{131}I-mIBG therapy for patients with neural crest tumours (Ott et al, 1991; Ott et al, 1992) have already been described.

The sodium iodide (Na ^{124}I) used for PET imaging of patients was obtained from the Nuffield Cyclotron at Birmingham and purified in the Medical Physics Department at Manchester University and also from the Cycloton Unit at the King Faisal Research Institute, Saudi Arabia (Lambrecht et al, 1988). Carrier-free ^{124}I was produced using the $^{124}Te(d,n)^{124}I$ reaction. Radionuclide purity exceeded 99.5% at 48 hour after irradiation (Lambrecht et al, 1988).

6.3.2 The Detector System

The MUP-PET camera has been described in detail elsewhere (Ott et al, 1988). The camera (Fig. 6.1) consists of two large area 60 cm x 30 cm multi-wire proportional chambers mounted diametrically opposite each other on a gantry with a separation of 87 cm between the detector faces. The gantry rotates back and forth continuously through 180° about the patient couch

every 50 seconds during a study in order to achieve the angular sampling necessary for reconstruction. Tomographic images of positron emitting radionuclide distributions are obtained by back projection of acquired data and deconvolution with the system point spread function in Fourier space.

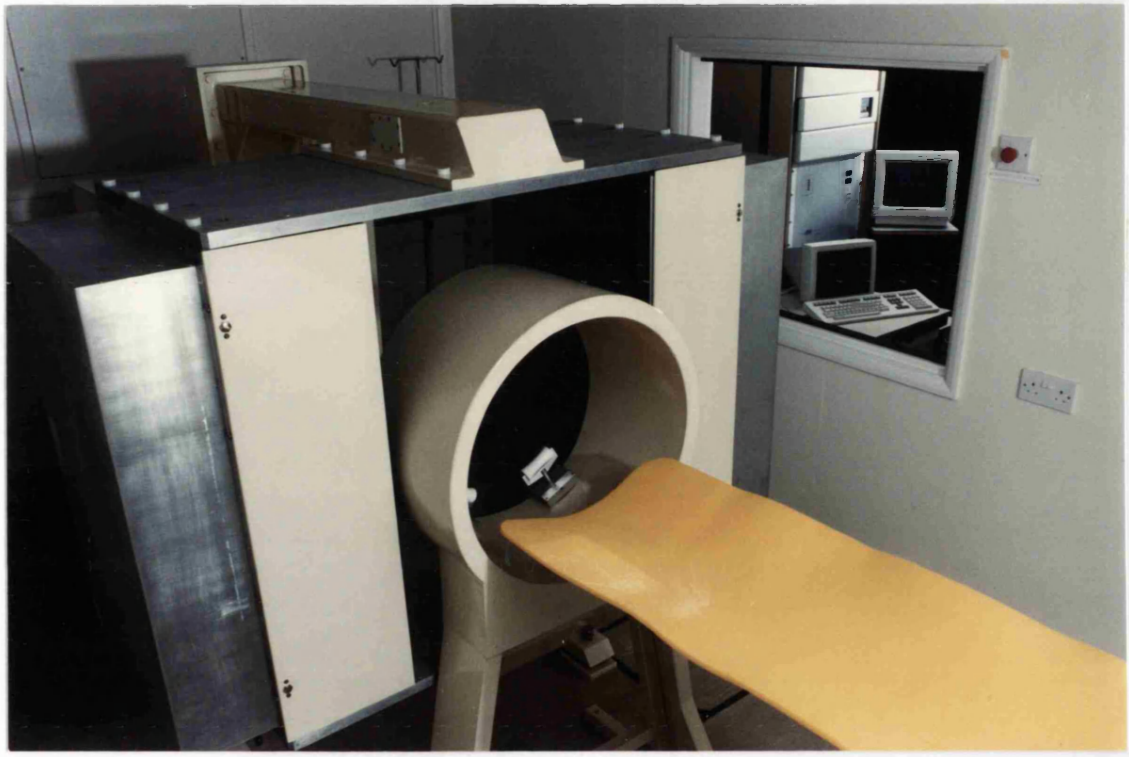


Figure 6.1: MUP-PET positron camera : the two detectors rotate through 180^{o} about the patient couch.

6.3.3 System Performance

The performance parameters of the MUP-PET system have been described previously (Ott et al, 1988; Marsden et al, 1989). The minimum reconstructed spatial resolution is 6 mm full width at half maximum (FWHM) in all directions. For experimental and phantom studies, the positron-emitting radionuclide gallium-68 (^{68}Ga) was obtained from an in-house generator. This has the advantage of being readily available and has a short 1.14 hour half-life which therefore minimises protection problems and staff hazards. Imaging qualities are better than for ^{124}I because only 3%

of emissions from ^{68}Ga produce gamma rays compared with 82% for ^{124}I (see Table 6.2). Gamma rays contribute singles events which degrade image quality by both increasing system dead-time and the rate of accidental coincidences.

Radio-nuclide	Half-life	Production	Main decay routes	Mean positron energy (MeV)
^{68}Ga	1.14 hour	generator	511 (p^+/e^-,88%) 1077 (γ,3%)	0.836
^{124}I	4.18 day	cyclotron	511 (p^+/e^-,16%) 511 (p^+/e^-,16%) 603 (γ,61%) 723 (γ,10%) 1691 (γ,11%)	0.686 0.974

Table 6.2: Comparison of physical characteristics of the positron emitters ^{68}Ga and ^{124}I.

The reconstructed spatial resolution in air was measured for different values of cut-off frequency (W) for the three commonly used pixel sizes (2,4 and 6mm) using a line source filled with ^{68}Ga. Fig.6.2 illustrates that spatial resolution is best at higher cut-off frequencies.

This resolution data permits some theoretical predictions to be made as regards optimising the choice of the cut-off frequency for data reconstruction in order to detect small lesions. Table 6.3 shows the spatial resolution using 2, 4 and 6 mm pixels (commonly used for scanning) expressed as full width half maximum. Raising the FWHM to the power three thus gives an indication of the error on the volume estimate. This predicts that in order to detect very small volumes with a high level of accuracy, high cut-off frequencies are required.

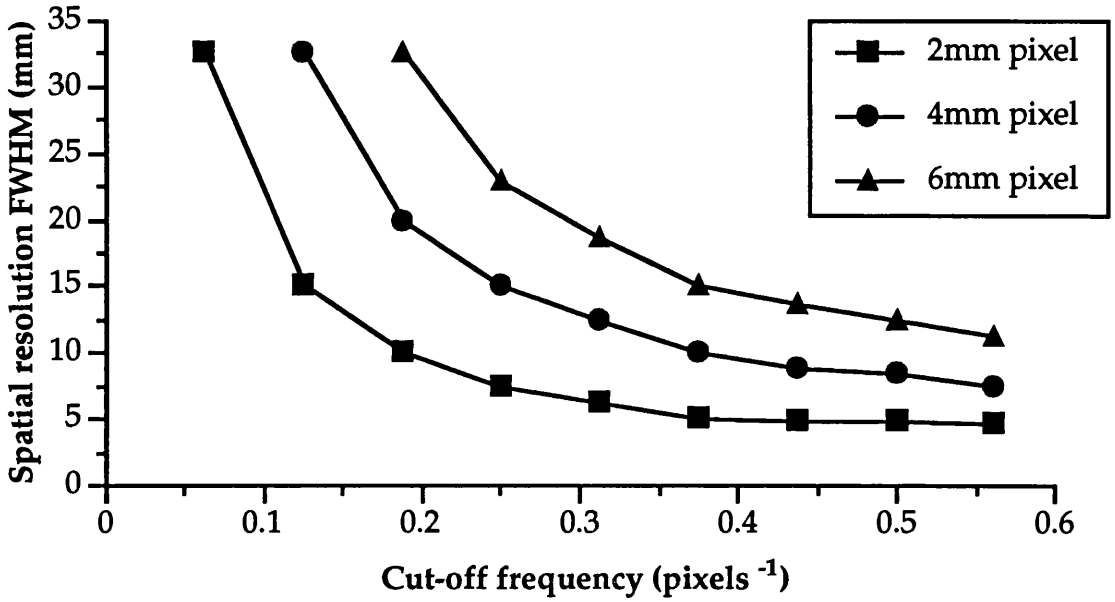


Figure 6.2: Spatial resolution for line source in air containing ^{68}Ga as a function of pixel size and Hanning filter cut-off frequency . (Hanning filter cut-off frequency = 64/W pixels $^{-1}$).

Pixel size (mm)	W value	Resolution FWHM (mm)	Uncertainty on volume estimate (cm^3)
2	12	10	1
	16	7.5	0.4
	20	6.25	0.2
	24	5	0.1
4	12	20	8
	16	15	3.4
	20	12	1.7
	24	10	1
6	12	32	32.8
	16	22	10.6
	20	18	5.8
	24	15	3.4
	28	13.75	2.6
	32	12.5	2.0
	36	11	1.3

Table 6.3: Theoretical prediction of uncertainty on volume estimates using MUP-PET as a function of W value for 2, 4 and 6 mm pixels.

6.3.4 Patient Studies

The volume (and hence mass) of thyroid remnants and functioning metastases were obtained from the PET tomographic images. PET scanning was performed 24 hours after the oral administration of ^{124}I and immediately before the administration of ^{131}I. Patients received 50 MBq ^{124}I prior to an ablation dose of 3 GBq ^{131}I. Those requiring subsequent therapeutic levels of radioiodine to treat residual tissue or metastases received 100 to 200 MBq ^{124}I since their avidity for radioiodine is considerably less than that of normal residual thyroid tissue. PET images (on a 64 x 64 matrix) were obtained using 3 or 4 mm pixels for the neck and 6 mm pixels for any body regions where metastatic lesions were expected. Acquisition times were typically 20 to 30 minutes per view and total counts acquired ranged from l00k to 500k. The spatial resolution achieved with these count densities was approximately 10 mm for neck imaging and about 20 mm for torso imaging.

6.3.5 Experimental Determination of Volume Error Using 38% Threshold

For the clinical dosimetry studies described in this Thesis, volumes were calculated using a 38% threshold as had been previously found to be satisfactory for the determination of thyroid mass for patients with thyrotoxicosis (Ott et al, 1987). Radioiodine uptake in thyrotoxic glands may be up to one hundred times that observed in thyroid carcinoma giving a high signal to noise ratio. The volume of thyroid tissue for these patients is of the order of 25 to 30 g. For patients with thyroid carcinoma, the scanning conditions are much less favourable; post-thyroidectomy residua are typically of the order of 2 g and when tumour is present the uptake per gram can be expected to be of the order of 0.1 to 0.001 percent per gram only (Schlesinger et al, 1989). Scanning conditions are therefore less ideal and volume estimates subject to greater errors.

The error associated with the thresholding technique described above as applied to small thyroid remnants and metastatic lesions with low uptake per gram was investigated as follows. Spherical and cylindrical phantoms of measured volume containing a known activity of ^{68}Ga were scanned in a neck phantom of tissue-equivalent material. 5×10^5 coincidence events were acquired. These datasets were reconstructed into 64^3 images using different reconstruction filter cut-offs. No correction was made for attenuation or scatter. Reconstructions were performed for the

three different pixel dimensions commonly used (namely 3, 4 and 6mm) in scanning the neck and torso. The volume of the phantom was determined using a 38% threshold as described by Webb et al, 1985. This volume was then compared with the true volume and the percentage error in the volume estimate calculated. Results for three different pixel sizes are illustrated graphically in Figs.6.3, 6.4 and 6.5 and given in Tables 6.4, 6.5 and 6.6.

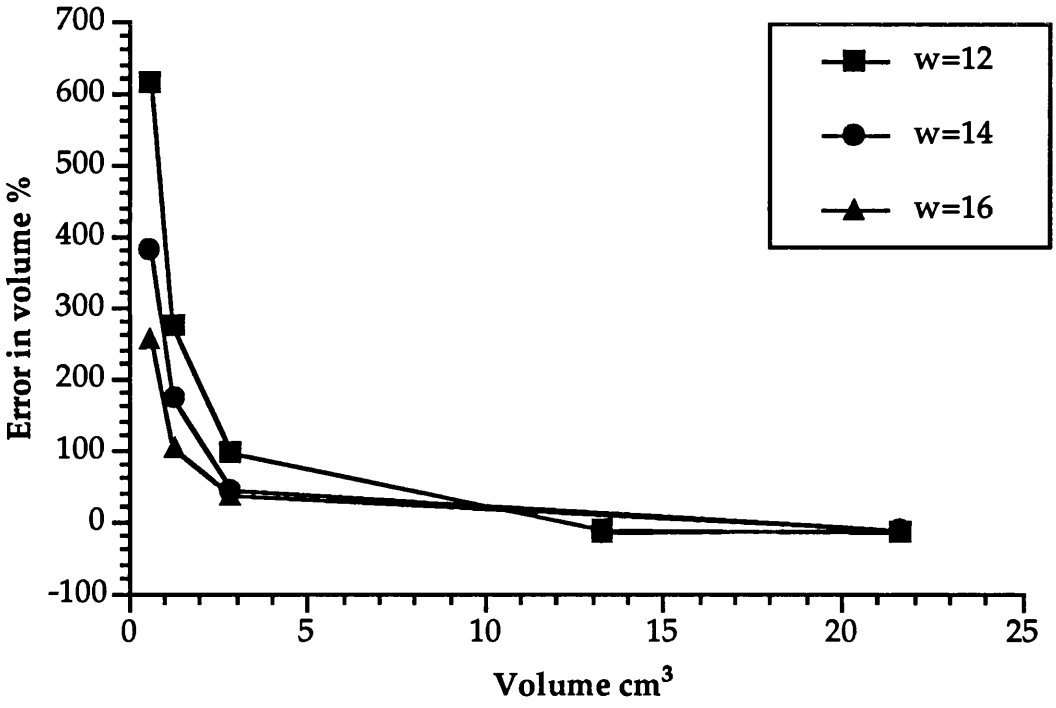


Figure 6:3: Error in volume estimate for 3 mm pixels.

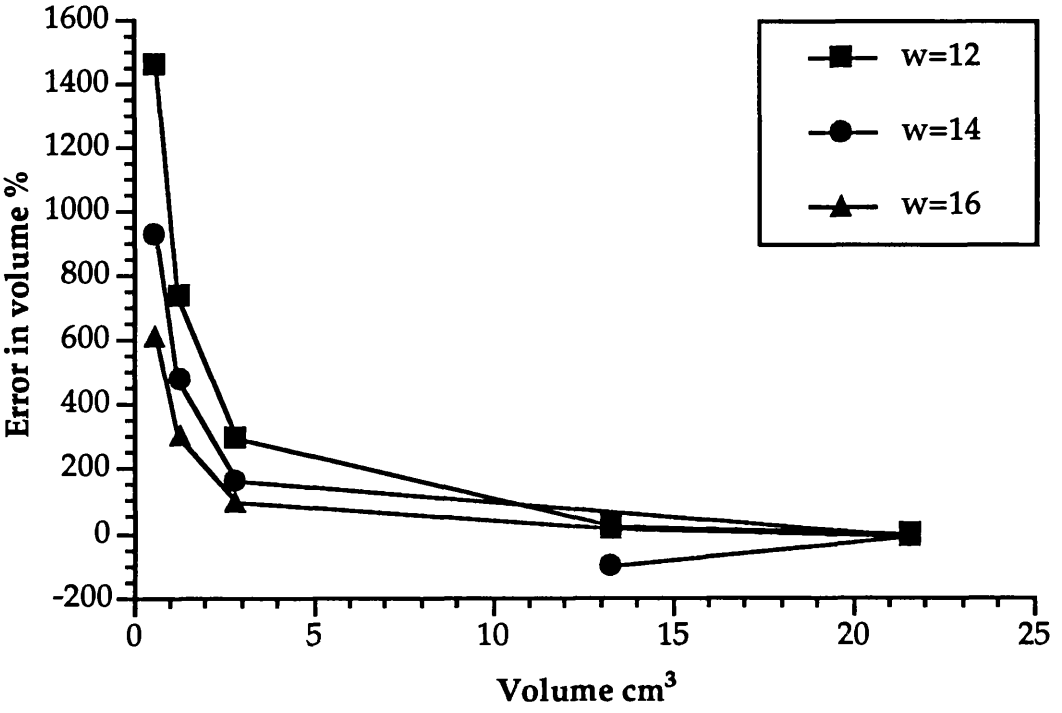


Figure 6.4: Error in volume estimate for 4 mm pixels.

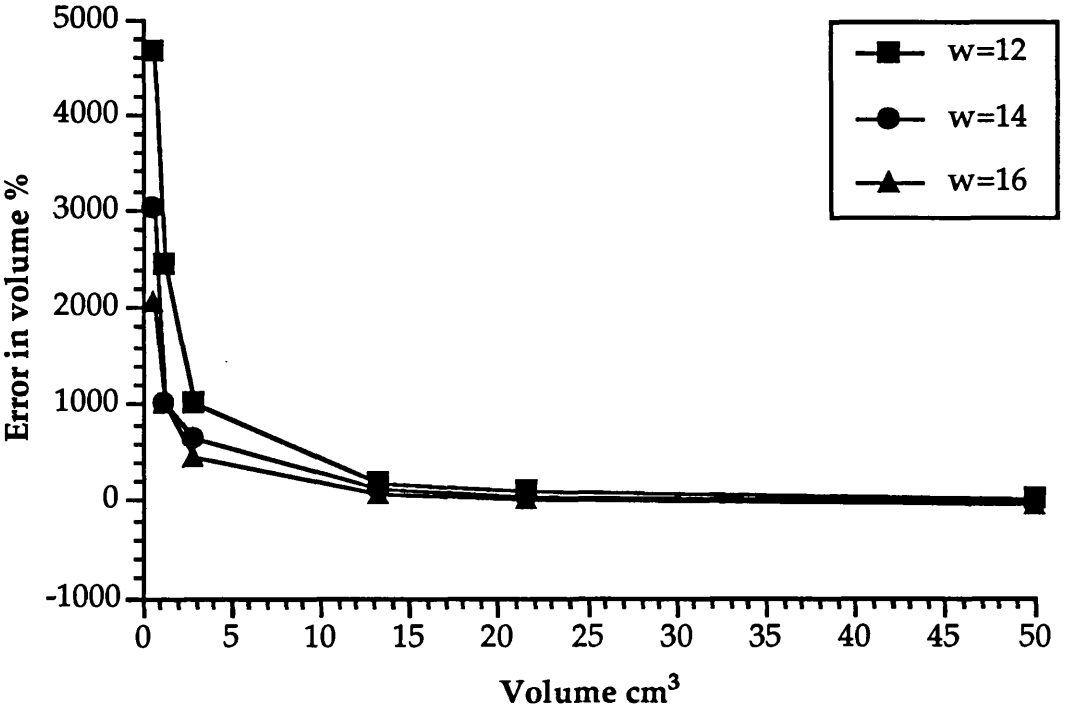


Figure 6.5: Error in volume estimate for 6 mm pixels.

Table 6.4: *Volume estimation for small cylinders containing ^{68}Ga placed in tissue equivalent neck phantom. Total counts acquired 5 x 10^5 back projected into 3mm voxels at different cut-off frequencies (W). No attenuation or scatter correction.*

Cut-off Frequency (W)	True Volume (cm^3)	Threshold at True Volume (%)	Volume at 38% Threshold (cm^3)	Absolute Error (cm^3)	Error in Volume (%)
12	0.62	78	4.43	+3.81	+615
	1.25	70	4.67	+3.42	+274
	2.86	56	5.59	+2.73	+95
	13.28	34	11.64	-1.64	-12
	21.6	32	18.09	-3.51	-16
14	0.62	72	2.97	+2.35	+379
	1.25	64	3.43	+2.18	+174
	2.86	48	4.10	+1.24	+43
	13.28	32	11.15	-2.13	-16
	21.6	34	18.95	-2.65	-13
16	0.62	66	2.19	+1.57	+253
	1.25	58	2.54	+1.29	+103
	2.86	42	3.32	_0.46	+37
	13.28	32	11.02	-2.26	-17
	21.6	32	18.85	-2.75	-13
18	0.62	60	1.57	+0.95	+153
	1.25	52	1.97	+0.72	+58
	2.86	38	2.97	+0.11	+4
	13.28	30	10.99	-2.29	-17
	21.6	30	17.47	-4.13	-19

Table 6.5: Volume estimation for small cylinders containing ^{68}Ga placed in tissue equivalent neck phantom. Total counts acquired 5 x 10^5 back projected into 4mm voxels at different cut-off frequencies (W). No attenuation or scatter correction.

Cut-off Frequency (W)	True Volume (cm^3)	Threshold at True Volume (%)	Volume at 38% Threshold (cm^3)	Absolute Error (cm^3)	Error in Volume (%)
12	0.62	86	9.66	+9.04	+1458
	1.25	80	10.43	+9.18	+734
	2.86	70	11.39	+8.53	+298
	13.28	42	15.87	+2.59	+19.52
	21.6	38	21.38	-0.22	-1
14	0.62	84	6.34	+5.72	+923
	1.25	76	7.17	+5.92	+474
	2.86	64	7.55	+4.69	+164
	13.28	38	-0.35	-2.72	-103
	21.6	34	18.56	-3.04	-14
16	0.62	78	4.42	3.8	+613
	1.25	72	4.99	3.74	+299
	2.86	58	5.70	2.84	+99
	13.28	34	11.84	-1.44	+12.16
	21.6	34	18.11	-3.49	-16
18	0.62	76	2.88	2.26	+365
	1.25	64	3.84	2.59	+207
	2.86	52	4.29	1.43	+50
	13.28	32	11.20	-2.08	-18.57
	21.6	34	18.56	-3.04	-14

Table 6.6: *Volume estimation for small cylinders containing ^{68}Ga placed in tisue equivalent neck phantom. Total counts acquired 5 x 10^5 back projected into 6mm voxels at different cut-off frequencies (W). No attenuation or scatter correction.*

Cut-off Frequency (W)	True Volume (cm^3)	Threshold at True Volume (%)	Volume at 38% Threshold (cm^3)	Absolute Error (cm^3)	Error in Volume (%)
12	0.65	94	30.89	+20.24	+4652
	1.36	92	34.56	+33.2	+2441
	2.96	86	32.4	+29.44	+995
	13.28	64	38.66	+25.38	+191
	21.58	54	40.82	+19.24	+89
	50	38	51.62	+1.62	+3.24
14	0.65	92	20.30	+19.65	+3023
	1.36	90	15.12	+13.76	+1018
	2.96	84	22.03	+19.07	+644
	13.28	56	27.86	+14.58	+110
	21.58	46	28.51	+693	+32
	50	32	39.31	-10.69	-21
16	0.65	88	14.04	+13.39	+2060
	1.36	88	15.12	+13.76	+1018
	2.96	80	16.63	+13.67	+462
	13.28	50	21.38	+8.1	+61
	21.58	40	22.03	+0.45	+2
	50	26	32.62	-17.38	-35
18	0.65	86	9.50	+8.85	+1362
	1.36	84	10.37	+9.01	+663
	2.96	72	11.88	+8.92	+301
	13.28	46	16.63	+3.35	+25
	21.58	34	17.71	-3.87	-18
	50	24	28.94	-21.06	-42

6.4 DISCUSSION OF ERRORS

6.4.1 Rectilinear Scanner

Phantom studies have shown that provided the total phantom thickness and the source depth used in the calibration scan are not greatly different from those encountered in the clinical situation, the estimate of activity localised in a lesion is accurate to within ± 10%. In addition, the depth of the source can be accurately determined to within 10 mm and the system response is isosensitive to ± 4%. By comparing the area within the 45% contour to the known dimensions, the apparent scan dimensions are approximately correct for sources of at least 2 cm^3 volume. However, using these criteria, errors in the estimate of source volume can still be typically around 30% owing to the uncertainty in source thickness and this increases to more than 100% for sources with dimensions less than 10 mm.

6.4.2 MUP-PET

The introduction of PET imaging has reduced the error on the volume estimate to about 4% for all volumes in the range 20 to 70 cm^3 and to around 10% for volumes down to 2 cm^3. In general, both algorithms used for the determination of mass result in an over estimate of the volume (which in turn will lead to an underestimate of the radiation dose) especially for lesions less than 2 cm^3 when both systems are limited by their spatial resolution.

6.4.3 Additional Errors

An additional source of error in the estimate of absorbed radiation dose is associated with the assumptions made concerning the uptake and washout of the ^{131}I in the tumour. If the maximum uptake in fact occurs at 24 hours there will be about a 12% over-estimate on the radiation dose caused by extrapolating the data back to the time of administration. However, this error is compensated by the larger underestimate of the dose which can occur as a result of overestimating the tumour mass.

Other errors are due to poor contrast and low sensitivity. For PET scanning (as shown in Section 6.3.5) errors on the volume estimation can be minimised by using large W values. However, for visual inspection of reconstructed data low W values give a more aesthetically pleasing image. Hence, it is recommended that reconstructions be performed using two W values: low W for visual inspection only and high W for volume

determination. The error in volume estimation could also be reduced by using smaller pixel size (see Tables 6.4, 6.5 and 6.6). Obviously, higher administered activities of ^{124}I for the patient tracer studies would increase the total count rates and improve image contrast.

CHAPTER 7

RADIOIODINE DOSE-RESPONSE CLINICAL RESULTS

7.1 PATIENTS AND METHODS

7.1.1 Patients

This Chapter describes the results of dosimetry studies in 54 patients with differentiated thyroid carcinoma receiving oral radioiodine for ablation of thyroid remnants following thyroidectomy and therapy for loco-regional and distant metastases. Patients ranged in age from 22 to 79 years (mean 49 years). There were 39 females and 15 males. Histologically, there were 40 papillary and 14 follicular carcinomas. The histology for all patients was reviewed by the Department fof Histology, Royal Marsden Hospital. Following surgery, all patients undergoing thyroid ablation were routinely given an oral administration of 3.0 GBq [^{131}I]NaI. Thyroid hormone replacement with thyroxine (T_4) or tri-iodothyronine (T_3) was then instituted. Those patients with metastatic disease were subsequently treated with 5.5 GBq [^{131}I]NaI after thyroid hormone had been stopped for 10 days (T_3) or 3 to 4 weeks (T_4).

7.1.2 Follow-Up

At each therapy administration the full blood count, blood urea, serum calcium, liver function tests, thyroid-stimulating hormone (TSH), thyroglobulin (T_g) and chest Xray were performed. Following each radioiodine administration, a whole-body scan was carried out on the third day in order to demonstrate any areas of concentration of ^{131}I; a quantitative estimate of radioiodine turnover was made by measuring the plasma concentration of protein bound radioiodine (PBI) at 6 days. If the whole-body scan showed significant uptake of ^{131}I in the neck or in distant metastases, especially if the plasma T_g exceeded 3 μg per litre (upper limit of normal in this laboratory) and the 6-day PBI was greater than 0.01% of the administered dose per litre (upper limit of normal in this laboratory), a further therapy administration was given at an interval of 3 to 4 months.

Treatment was continued until there was no uptake of ^{131}I on the scan or until there was clear evidence of tumour progression despite repeated therapies. At this hospital, no formal limit of the maximum cumulative activity of ^{131}I has been adopted.

7.1.3 Dosimetry Scans

Dosimetry calculations were performed on 84 sites in 54 patients using equation (4.9) in Chapter 4. Scans of the neck (for ablation studies) and the torso (for subsequent therapy scans) were performed and used to provide images for subsequent dosimetry estimates. By performing sequential quantitative scans (for example, on days 3, 4 and 7) following administration of radioiodine, activity-time curves for each region of interest were produced. By fitting the data and extrapolating back to the time of administration, the initial activity, A_o in the target tissue and the effective half-life, T_e were determined as described in Chapter 5. Quantitative scanning was performed using the dual-headed rectilinear scanner as described in Section 5.2 or the STARCAM gamma camera described in Section 5.3.

7.1.4 Estimation of Mass

The volume, and hence mass, was obtained either from the planar images produced by the scanner or from the tomographic images produced by the positron camera. When [^{124}I]NaI was not available an estimate of mass was made from ultrasound examination using an Acuson real time scanner with a 5 MHz linear array probe. For bone and soft tissue metastatic deposits, particularly in the pelvis where overlying liver, bowel and bladder concentration of radioiodine obscured uptake in lesions of interest, the mass was obtained from computed tomography (CT) or magnetic resonance scanning (MRI).

7.1.5 PET Studies

PET studies were performed on sixteen of the 54 patients studied. Between 50 and 200 MBq [^{124}I]NaI was given orally to patients 24 hours prior to the administration of the 3.0 GBq or 5.5 GBq [^{131}I]NaI. PET scanning was performed immediately prior to the ^{131}I administration. PET images (on a 64 x 64 matrix) were obtained using 3 or 4 mm pixels for the neck and 6 mm pixels for any body regions where metastatic lesions were expected.

7.2 ABLATION OF THYROID REMNANTS

7.2.1 Dose-Response Relationship

Dose-response data for 42 patients (63 sites) following thyroidectomy and ablation of thyroid remnants with 3.0 GBq ^{131}I are shown in Fig. 7.1.

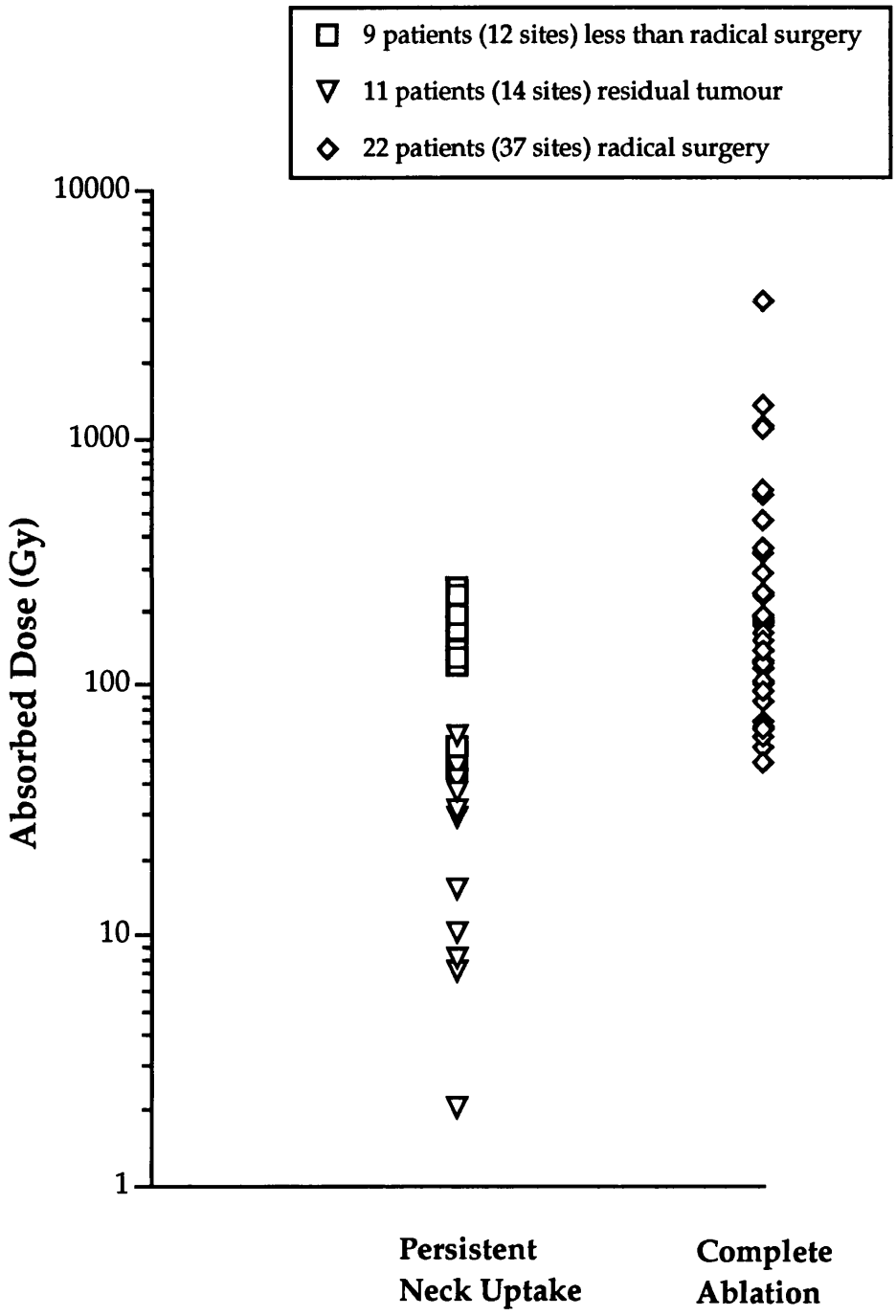


Figure 7.1: Plot of dose estimates (using logarithmic scale on vertical axis) for 42 patients following thyroidectomy and ablation with 3.0 GBq ^{131}I.

The absorbed doses received, for a fixed activity of radioiodine administered, ranged from 2 to 3500Gy. The absorbed dose in Gray is plotted using a logarithmic scale on the vertical axis.

On the horizontal axis, the first column (designated persistent neck uptake) shows those patients in whom 3.0 GBq ^{131}I failed to erase evidence of functioning thyroid tissue on a subsequent radioiodine scan.

The second column (designated complete ablation, symbol ◊) shows those patients in whom there was no evidence of functioning thyroid tissue on a subsequent scan.

7.2.2 Complete Ablation Near-total Surgery

All patients (with only two exceptions) who achieved complete ablation of thyroid remnants had received near-total thyroidectomy. The mean absorbed dose (complete ablation) was 349 Gy with a median absorbed dose of 170 Gy. There has been no evidence of loco-regional recurrence in this group of patients successfully ablated at a mean follow-up of 40 months (range 19-66).

The clinical data is presented in two groups: those patients who had dosimetry studies performed with the rectilinear scanner with longer follow-up and those whose dosimetry studies were performed using the STARCAM gamma camera with a shorter follow-up.

One patient (FC , Table 7.1) developed bone metastases at 15 months follow-up and was treated with therapy radioiodine and is now in clinical remission.

Dosimetry data obtained using the rectilinear scanner are shown for 12 patients (23 sites) in Table 7.2.

Table 7.1: *Clinical data on 12 patients achieving complete ablation of thyroid remnants following near-total thyroidectomy and 3.0 GBq ^{131}I. Quantitative scanning using dual-headed rectilinear scanner.*

Patient	Age/Sex	Histology	TNM stage at presentation	Follow-up (months)
SA	43F	papillary	T1(a)N_0M_0	41
CB	24F	papillary	T2(a)N_0M_0	58
DB	31M	papillary	T1(b)$N_{1a}M_0$	49
DC	65F	papillary	T2(a)N_0M_0	66
MC	61F	follicular	T3(a)N_0M_0	52
*FC	76F	follicular	T2(a)N_0M_0	49
EH	30F	papillary	T1(b)N_0M_0	65
GP	54F	papillary	T4(b)$N_{1a}M_0$	49
PS	40F	papillary	TxN_0M_0	54
JS	39F	follicular	T2(a)N_0M_0	58
JW	51M	papillary	T4(a)$N_{1a}M_0$	45
CY	38F	papillary	T1(a)N_0M_0	45

TNM= UICC International Union Against Cancer (Geneva,1987)
*bone metastases at 15 months, now CR

Table 7.2: *Dosimetry data on 12 patients (23 sites) achieving complete ablation of thyroid remnants following near-total thyroidectomy and 3.0 GBq ^{131}I. Quantitative scanning using dual-headed rectilinear scanner and mass from scanner or PET.*

Patient	A_0 (MBq)	T_e (h)	m (g)	Dose (Gy)	% uptake per g	TSH m U/l
*SA	550	163	4.1	3500	4.4	not available
	167	117	2.3	1359	2.3	
*CB	91	89	2.3	56	0.13	> 100
DB	51	174	2.3	617	0.74	> 100
	13	108	2.4	94	0.18	
*DC	255	15	3.2	191	2.95	45
MC	78	28	3.5	100	0.74	7.2
	300	24	3.4	340	2.9	
+FC	460	148	9.7	1123	1.58	48
EH	44	40	2.4	116	0.61	
	126	34	1.7	285	2.47	> 70
	135	24	2.7	192	1.67	
	160	24	1.7	361	3.14	
GP	21	42	2.3	61	0.3	37
	11	58	2.1	49	0.17	
PS	68	29	2.1	150	1.08	> 70
*JS	50	40	2.6	123	0.64	
	60	40	2.4	160	0.83	> 70
	60	40	2.1	183	0.95	
JW	22	80	1.6	176	0.46	
	31	86	3.1	138	0.33	> 100
	18	68	2.8	70	0.21	
CY	95	35	3.2	172	1.02	61

*I-124 PET study
+less than radical surgery initially

Table 7.3 shows clinical data and Table 7.4 shows the dosimetry data for 10 patients (14 sites) obtained from quantitative scanning using the STARCAM gamma camera; mass was estimated from ultrasound measurements or PET. For patients in the first column of Fig. 7.1, the mean absorbed dose was only 88 Gy (median absorbed dose 45 Gy). The mean absorbed dose for patients achieving complete ablation compared with those with persistent neck uptake were significantly different (student's t test, $p<0.01$). The failures can be attributed to two possible factors: size of the residual thyroid and the presence of tumour in association with normal tissue.

Table 7.3: *Clinical data on 10 patients achieving complete ablation of thyroid remnants following near-total thyroidectomy and 3.0 GBq ^{131}I; quantitative scanning using STARCAM gamma camera.*

Patient	Age/Sex	Histology	TNM stage at presentation	Follow-up (months)
MC	62M	follicular	T2(a)N_0M_0	19
AK	25M	papillary	T2(a)$N_{1a}M_0$	42
GM	32F	papillary	T2(a)N_0M_0	22
MP	60F	papillary	T2(a)$N_{1b}M_0$	19
SR	25F	papillary	T2(b)N_0M_0	24
MS	43F	papillary	T2(b)N_0M_0	21
SS	31F	papillary	T2(a)N_0M_0	23
CT	30M	papillary	T1(b)$N_{1b}M_0$	25
KV	24F	papillary	T1(a)N_0M_0	20
PW	54F	papillary	T2(b)$N_{1a}M_0$	23

TNM= UICC International Union Against Cancer (Geneva,1987)

Table 7.4: *Dosimetry data on 10 patients (14 sites) achieving complete ablation of thyroid remnants following near-total thyroidectomy and 3.0 GBq ^{131}I. Quantitative scans using STARCAM gamma camera; mass from ultrasound or PET.*

Patient	A_0 (MBq)	T_e (h)	m (g)	Dose (Gy)	% uptake per g	TSH m U/l
*MC	20	216	3	230	0.23	> 100
AK	94	198	5	595	0.60	not available
GM	38 35	47 47	1.8 1.8	162 149	0.72 0.78	not available
MP	235	48	2.9	622	2.74	76
SR	41 38	29 29	1 1	189 187	1.37 1.36	> 100
+MS	600	41	16	237	1.25	3.8
SS	30 11	58 48	2 1	138 85	0.53 0.39	> 100
*CT	81	31	6	67	0.45	> 100
KV	1.3 8.6	90 96	2 2	94 66	0.20 0.14	> 100
PW	96	60	2	461	1.6	99

* I-124 PET study
+less than radical surgery initially

7.2.3 Persistent Neck Uptake Less than Radical Surgery

Patients at the top of the first column of Fig. 7.1 (with symbol □) , who were referred from other hospitals in the UK and abroad, initially received less than radical surgery; clinical data for these patients is given in Table 7.5.

Table 7.5: Clinical data on 9 patients following less than radical surgery and radioiodine ablation in whom 3.0 GBq ^{131}I failed to erase evidence of functioning thyroid tissue on subsequent scanning.

Patient	Age/Sex	Histology	TNM stage at presentation	Total ^{131}I activity administered (GBq)	Follow-up
JB	26 M	papillary	T1(b) $N_{1b}M_0$	30.5	NED
RB	73 M	papillary	$T4N_{1b}M_0$	+14	Died carcinoma colon
DH	79 F	follicular	$T3(a)N_0M_{bone}$	8.5	Died IHD
LH	28 F	papillary	$T2(a)N_0M_0$	8.5	NED
SH	24 M	papillary	$T2(b)N_1 M_0$	13.5	NED
FM	77 M	papillary	$T4N_0M_0$	+14	NED
SR	27 F	follicular	$T1(a)N_0M_0$	8.5	NED
A W	74 F	papillary	$T4N_0M_0$	19.3	Died bone metastases
LW	35 F	papillary	$T2(a)\ N_0M_0$	14.5	NED

+ Following 60Gy in 30 fractions over 6 weeks external beam radiotherapy
NED = no evidence of disease
IHD = ischaemia heart disease
TNM = UICC International Union Against Cancer (Geneva, 1987)

The mean estimated residual mass was 12 g (median 11 g) for this group (Table 7.6). All patients subsequently received further radioiodine therapy. Three patients were referred to this hospital with neck node metastases which had not been resected at the time of ablation. Two of these patients received further surgery (after receiving ^{131}I ablation) and one patient received radical external beam radiotherapy (see section 7.2.5) in addition in an attempt to render the neck disease-free.

Table 7.6: *Dosimetry data for 9 patients (12 sites) after 3.0 GBq ^{131}I with large residual thyroid remnants and persistent thyroid uptake on subsequent radioiodine scanning.*

Patient	A_o (MBq)	T_e (h)	m (g)	Dose (Gy)	% uptake per g	TSH m U/l
*JB	61 42 25	127 55 55	11 8 4	136 45 56	0.18 0.15 0.19	> 100
*RB	215	120	25	165	0.29	0.7
DH	180	75	R11	193	0.54	4.4
LH	320 145	72 72	U15 U10	246 167	1.01 0.46	2.5
*SH	260	50	9	231	0.96	45
FM	118	150	R13	230	0.31	not available
SR	400	28	R15	119	0.89	1.9
AW	270	51	R17	127	0.52	0.7
*LW	303	43	11	190	0.92	7.1

*I-124 PET study
C = CT scan
U = Ultrasound
R = Rectilinear scanner

7.2.4 Persistent Neck Uptake Near-total Surgery

The lower group of 11 patients (represented by symbol inverted Δ) in the first column of Fig.7.1 had undergone a near-total thyroidectomy initially; clinical data for these patients is shown in Table 7.7. Dosimetry data in Table 7.8 shows that the mean residual mass was 4.9 g (median 2.5g). Despite a mean TSH of 57 mU/l the percentage uptakes per gram were relatively low (mean=0.09, median=0.08) and are within the ranges observed for deposits of thyroid carcinoma, following thyroidectomy (Blahd, 1979; Pochin, 1971; Roeslier, 1985). The rapid clearance half-lives (mean T_e = 75 h, median T_e = 55 h) were also in the range observed for thyroid carcinoma metastases (Koral, 1982; Maxon, 1983; Pochin, 1973; Roeslier, 1985). This confirmed the presence of tumour in association with normal thyroid tissue as evidenced by examination of the surgical and histopathological findings for these patients.

Table 7.7: Clinical data on 11 patients following near-total thyroidectomy in whom ablation with 3.0 GBq ^{131}I failed to erase thyroid remnants on subsequent radioiodine scanning.

Patient	Age/Sex	Histology	TNM stage at presentation	Total ^{131}I activity administered (GBq)	Follow-up
CB	69F	papillary	T2(b) N_oM_o	8.5	Residual tumour
MB	44 F	papillary	T1(a)$N_{1a}M_o$	9.2	NED
JF	30 F	papillary	T4N_oM_o	13	NED
CH	65 F	papillary	TxN_{1b} M_{lung}	3	Died IHD
GK	65 M	follicular	T2(a)N_oM_o	8.5	NED
JO	79 F	papillary	T3(a)$N_{1a}M_o$	14.5	Died IHD
AR	70 M	follicular	T3(b)$N_{1a}M_o$	14.0	NED
IR	59 M	follicular	T2(a)$N_{1b}M_{lung}$	8.5	Progressive lung metastases
IW	69F	papillary	T4(b)N1aM_o	8.5	NED
W W	67 M	papillary	T4$N_{1a}M_{lung}$	8.5	Died AML
JZ	64 F	follicular	T4N_oM_o	19.5	NED

NED = No evidence of disease
IHD = Ischaemia heart disease
AML = Acute myeloid leukaemia which predated ^{131}I
TNM = UICC International Union Against Cancer (Geneva, 1987)

Table 7.8: Dosimetry data for 11 patients (14 sites) with tumour in association with normal tissue following near-total thyroidectomy and ablation with 3.0 GBq ^{131}I.

Patient	A_o (MBq)	T_e (hour)	m (g)	Dose (Gy)	% uptake per g	TSH m U/l
CB	3	82	U1	40	0.1	76
MB	15 5 7	40 45 72	R2.1 R2.4 R2.7	46 15 29	0.24 0.07 0.08	96
JF	38	28	R4.3	40	0.15	>100
CH	52 16	55 58	C15 C10	31 15	0.12 0.05	1.5
GK	3	102	U1	41	0.10	>100
*JO	30	180	6	7	0.14	not available
AR	2	50	R2.5	7	0.03	not available
IR	3	17	U4	2	0.025	99
IW	4	120	U2	61	0.11	>100
*WW	5	24	2	10	0.05	51
JZ	19	180	R14	37	0.04	0.4

*I-124 PET study
C = CT scan
U = Ultrasound
R = Rectilinear scanner

7.2.5 Clinical Case Study RB

This 73 year old man presented with massive confluent neck adenopathy in continuity with tumour arising in the right lobe of the thyroid. Biopsy only was performed, since he was deemed inoperable, and histology showed papillary carcinoma. The patient developed marked dysphagia and CT scans taken at the level of the thyroid and thoracic inlet (Fig.7.2 and 7.3 respectively) showed tumour encircling the trachea. He was treated with radical external beam radiotherapy in order to achieve rapid shrinkage of the nodes. The neck and mediastinum were treated using 6 MV photons from a linear accelerator and anterior and posterior portals to a median dose of 50 Gy in 25 daily fractions (treating both fields daily) over five weeks (shielding the spine posteriorly from 40 Gy) followed by a further 10 Gy boost to the nodes.

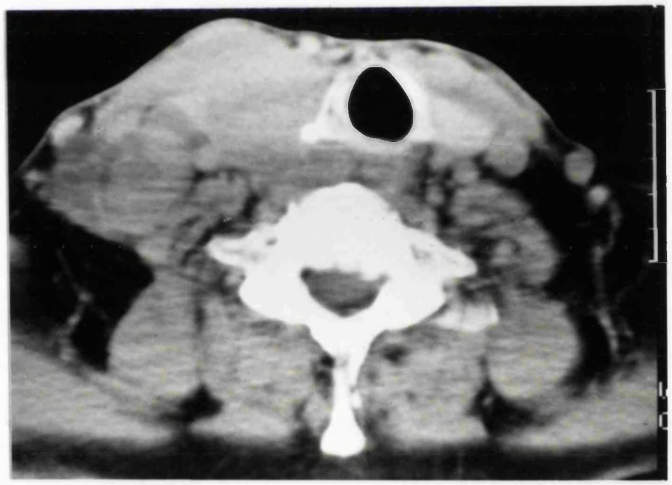


Figure 7.2: *CT scan at level of thyroid for patient RB showing massive confluent neck lymphadenopathy.*

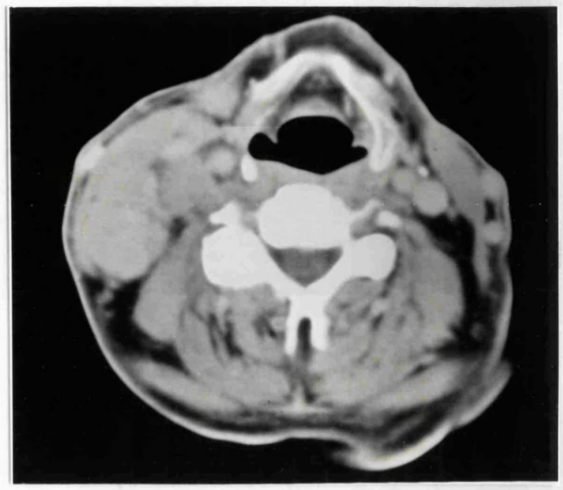


Figure 7.3: *CT scan at level of thoracic inlet showing tumour encircling the trachea.*

Radioiodine therapy was then given over a six-month period in order to ablate the residual thyroid. Fig. 6.4 shows the summed coronal images of the thyroid following 50MBq [^{124}I]NaI given prior to his first ^{131}I treatment. Three dimensional shaded surface images, posterior and right posterior oblique views are shown in Fig.7.5 and 7.6 respectively.

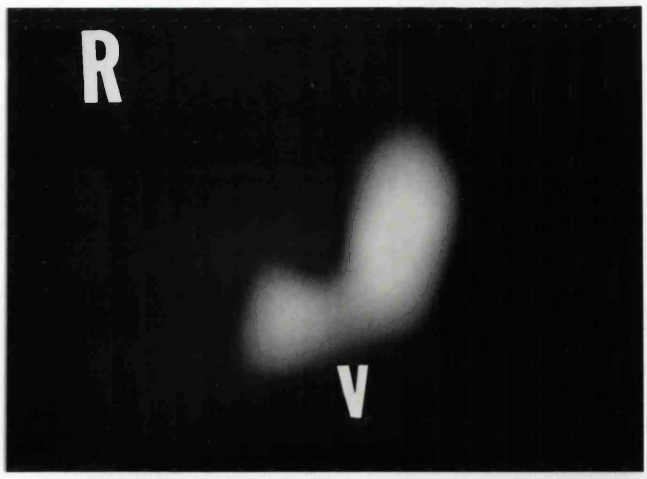


Figure 7.4: *PET scan at 24 hours post 50MBq ^{124}I for RB showing summed coronal images.*

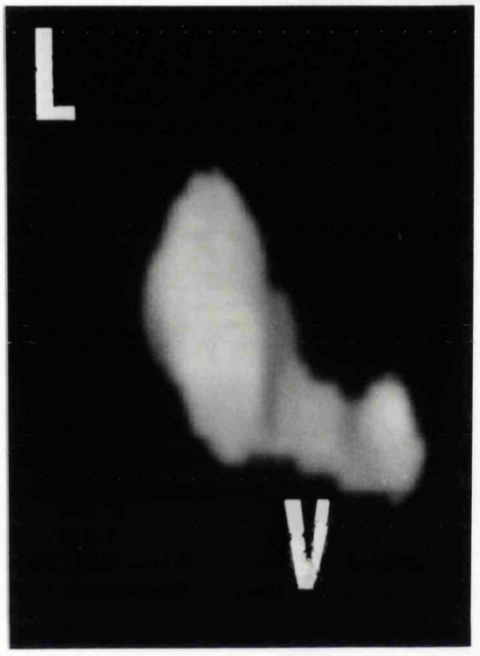


Figure 7.5: 3D surface shaded image right posterior view.

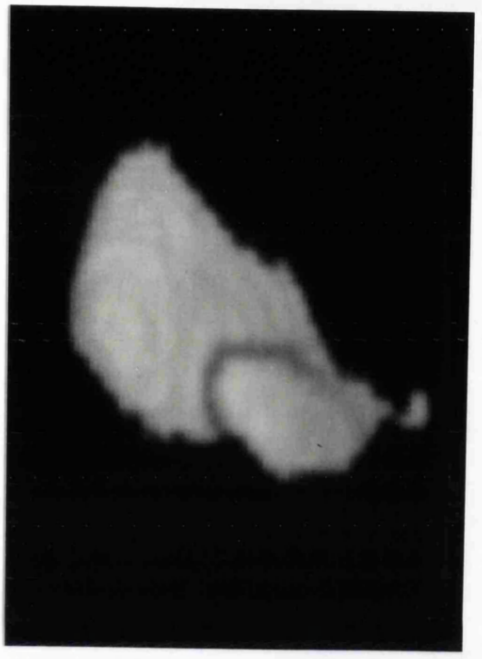


Figure 7.6: 3D surface shaded image posterior oblique view.

Table 7.9 shows the absorbed doses received by the thyroid at each ^{131}I administration; there was no uptake into the previously involved lymph nodes. These data show that as the biological half-life of sequential radioioidine therapies decreases, lower absorbed doses are delivered as a result. The initial TSH value was low as the patient had a functioning left lobe of thyroid, most of the right lobe being replaced by tumour as shown in Figures 7.4, 7.5 and 7.6.

Table 7.9: Dosimetry data for patient RB following ablation and two subsequent therapy administrations of ^{131}I for residual thyroid gland. Initial therapy comprised biopsy of involved nodes and external beam radiotherapy (60Gy/30 fractions/6 weeks) to neck and upper mediastinum.

Activity ^{131}I administered (GBq)	A_o (MBq)	T_e (h)	m (g)	Dose (Gy)	% uptake per g	TSH m U/l
3.0 ablation	215	120	25	165	0.29	0.7
5.5(1st therapy)	294	21	23	43	0.23	> 100
5.5(2nd therapy)	27	34	20	7	0.02	39

Before further therapy could be given, however, the patient succumbed and died of a coexisting rectal carcinoma. Interestingly, his thyroglobulin levels remained negative throughout. Post-mortem examination confirmed extensive residual lymphadenopathy in the neck and a partly necrotic tumour occupying the upper pole of the right lobe of the thyroid.

7.2.6 Summary of Results and Discussion

The clinical results reported here demonstrate that the absorbed dose delivered, following a fixed 3.0 GBq activity of ^{131}I, varies considerably from patient to patient. From the results presented here, if only those patients who had near-total thyroidectomy initially are considered, then the administration of 3.0 GBq ^{131}I eliminated all traces of post-operative thyroid remnants in 67% of patients (73% of sites). A dose-response relationship is evident and complete ablation was achieved with absorbed doses in excess

of 60 Gy for those patients with no residual tumour tissue. The mean absorbed dose for the group of patients successfully ablated was 349 Gy.

Snyder and colleagues (1983) were unable to confirm a dose-response relationship for ^{131}I ablation of thyroid remnants but the only parameter measured was the 24 hour radioiodine uptake in the thyroid remnant. This 24 hour uptake was taken to be the initial uptake. An effective half-life of 5 days was assumed for all patients. Masses were assumed based upon the surgical procedure. Maxon et al (1981; 1992) have proposed a radiation absorbed dose threshold of 300 Gy for ablation of thyroid remnants, based on diagnostic kinetic studies after the oral administration of 74 MBq ^{131}I. Area of interest analysis of conjugate view gamma camera images provided activity time data from which the initial uptake and effective half-life were determined. Mass was calculated from estimation of remnant thickness (determined from surgical operative notes) together with the surface area based on anterior rectilinear scans of the neck. A single administration of ^{131}I (range 0.9 to 16.65 GBq) calculated to deliver 300 Gy resulted in successful ablation in 84% of patients. Therapy and tracer kinetics may differ, however, leading to an underestimate of absorbed dose of about 20% (Hurley et al,1988; Maxon et al,1992). Animal data have shown a direct correlation between initial dose and subsequent rate of discharge of ^{131}I from the thyroid gland owing to follicular cell necrosis (Doniach, 1974). Our data, based on absolute quantitation of absorbed dose following therapy ^{131}I, suggest a lower threshold of the order of 100 Gy.

It also appears that the larger the residual gland, the more likely is the persistence of function following ^{131}I ablation. Radioiodine therapy is thus most effective in controlling small volumes of tumour; this is in accord with Fletcher's fundamental postulates of radiotherapy (Fletcher, 1978). Evidence from other studies (Sisson, 1983) also supports a correlation between the size of remnant and ease of ablation. Maxon et al (1992) have reported successful ablation of 96% foci of residua when the residual remnant was less than 2g. Hence, at least near-total thyroidectomy together with complete excision of macroscopic nodal disease should be performed initially if ablation is part of the therapeutic protocol. Where lobectomy or partial thyroidectomy has been performed, further surgery (that is, completion thyroidectomy) is recommended before commencing radioiodine therapy.

When residual tumour is present, the percentage uptake per gram is much lower than for normal thyroid tissue and the biological half-life is

also reduced (Table 7.10). The data presented in this Thesis suggest that an initial ^{131}I activity in excess of 3.0 GBq is therefore required to deliver an absorbed dose of 100 Gy.

Tissue type	Percentage uptake per gram		Biological half-life (days)	
Normal	1 -3.5	[Goolden,1963]		
	1 -2	[Halnan,1982]	90	[Halnan,1964]
	0.5 -2.3	[Satterlee,1983]	120	[ICRP,1979]
Thyroid cancer metastases	0.5	[Blahd,1979]		
			1.8-2.0	[Koral,1982]
			2.5-5.6	[Maxon,1983]
	0.06-0.3	[Pochin,1971]	4.0	[Pochin,1971]
	<0.25	[Roeslier,1985]	2.3	[Roeslier,1985]

Table 7.10: Ranges of percentage uptakes per gram and biological half-lives in normal thyroid and in thyroid cancer metastases. Note that most of the data are from different sources and that variabilties in each are thus uncorrelated. (Data taken from Schlesinger et al, 1989).

Optimal uptake of ^{131}I requires that serum TSH should exceed 30 mU/l (Edmonds et al, 1977) and post-operative administration of radioiodine ideally should be delayed for at least 6 weeks to achieve this. Alternatively, TSH may be administered (Section 1.6)

7.3 NECK NODE METASTASES

7.3. Dose-response relationship

Clinical data for seven patients with metastatic neck nodes are shown in Table 7.11. Dosimetry data are shown in Table 7.12. Only one of these patients (MK) (Table 7.10) has achieved a complete remission of nodal disease to date (minimum follow-up 30 months) following a single therapy administration of radioiodine. A second patient (SH) required further completion thyroidectomy and functional neck dissection to achieve complete remission and is discussed in detail below (Section 7.3.2).

Table 7.11: *Clinical data on 7 patients with lymph node metastases.*

Patient	Age/Sex	Histology	TNM stage at presentation	Total ^{131}I activity administered (GBq)	Follow-up
TB	59 M	papillary	$T1N_{1b}M_{lung}$	19.5	Died with brain metastases
SH	24 M	papillary	$T2(b)N_{1b}M_0$	13.5	NED
SJ	22 F	papillary	$T4N_{1b}M_0$	8.7	External beam radiotherapy to neck
MK	52 F	papillary	$T1N_{1b}M_0$	8.5	NED
SK	31 F	papillary	$T3(a)N_{1a}M_0$	36	Lung metastases
GP	32 F	papillary	$T4N_{1a}$ M_0	8.5	Raised T_g
A W	74 F	papillary	$T4N_0M_0$	19.3	Died progressive disease

NED = No evidence of disease

Table 7.12: Dosimetry data for 7 patients (10 sites) with lymph node metastases.

Patient	^{131}I	A_0 (MBq)	T_e (h)	m (g)	Dose (Gy)	% uptake per g	TSH mU/l	Response
TB	ablation	51	24	^{C}28	7	0.006	> 100	PNU
	1st therapy	21	20	28	3	0.016	> 100	PNU
	3rd therapy	5.4	20	28	2	0.004	94	PNU
*SH	ablation	78	50	5.2	35	0.5	45	PNU
	1st therapy	5.1	84	2.7	25	0.03	> 100	PNU
	2ndtherapy	7.6	32	3.3	12	0.05	> 100	CR
SJ	1st therapy	34	34	^{R}5.8	32	0.11	not available	PNU
MK	1st therapy	36 60	17 65	^{U}1 2	97 311	0.67 0.56	not available	CR
SK	ablation	10	94	^{R}6.4	24	0.05	not available	PNU
	2ndtherapy	2.6	60	2	12	0.02		PNU
	3rd therapy	5.9	45	5.7	7.5	0.02		PNU
*GP	1st therapy	3 2.6	40 40	2.2 2.7	9 6	0.02 0.02	37	PNU
	3rd therapy	7.6 7.6	19 14	^{R}6.8 6.7	3 3	0.02 0.02		PNU
A W	1st therapy	5.8 7.5	34 50	^{U}5.3 4	6 15	0.02 0.03	0.7	PNU

* I-124 PET study
C = CT scan
U = Ultrasound
R = Rectilinear scanner
CR = Complete response
PNU = Persistent neck uptake

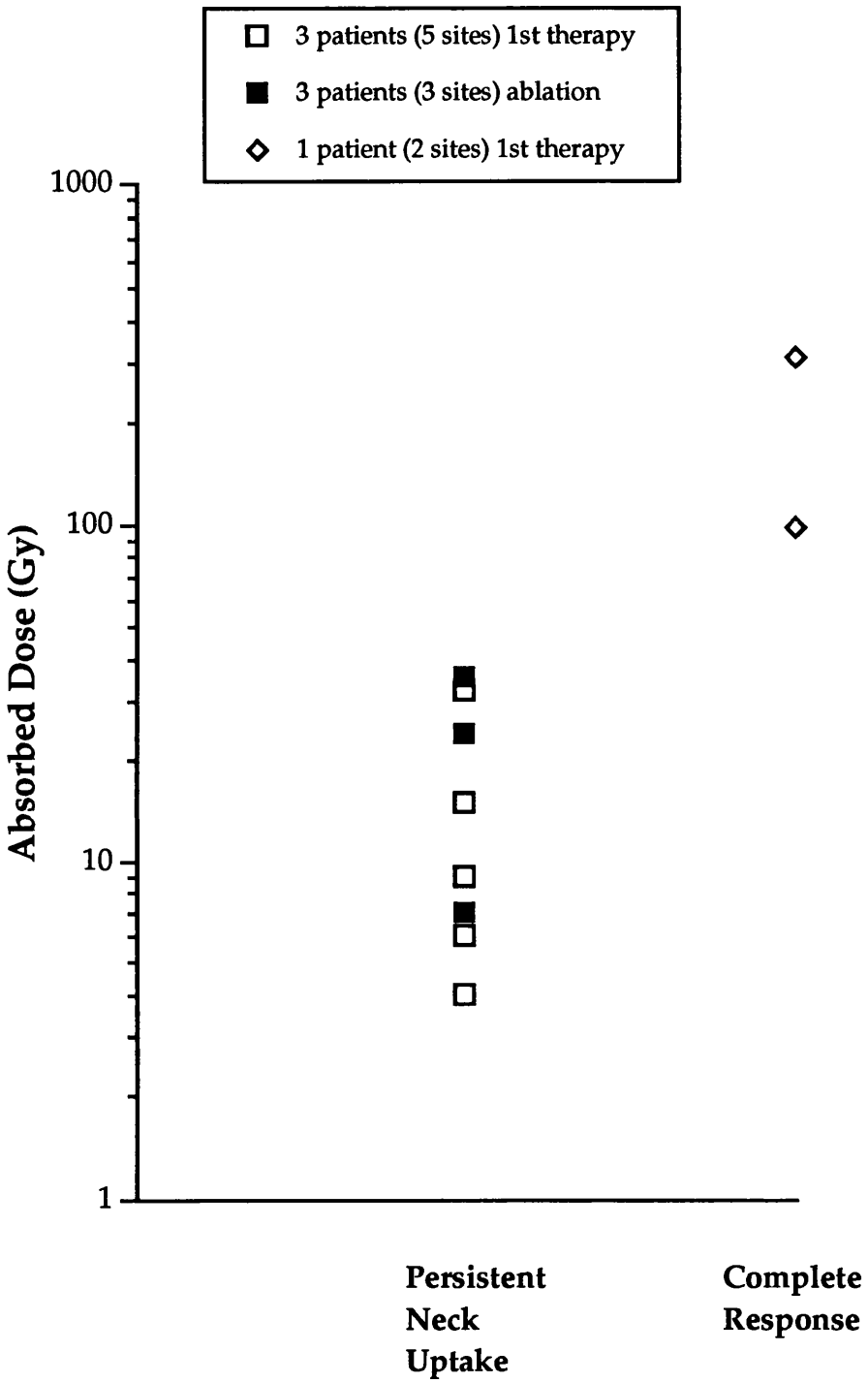


Figure 7.7: Dose-response for patients with metastatic neck nodes. Plot of absorbed dose estimates (using a logarithmic scale on vertical axis) for 7 patients with neck nodal metastases undergoing ^{131}I therapy .

Dose response data are plotted in Fig.7.7. The absorbed dose in Gray delivered to nodes following the first radioiodine administration when nodal uptake was visualised is plotted using a logarithmic scale on the vertical axs. On the horizontal axis, the first column (designated persistent neck uptake) shows those patients who had persistent nodal uptake on subsequent radioiodine scanning. In addition there was either persistence or progression of nodal disease clinically and radiographically together with raised thyroglobulin. The second column (designated complete response) shows absorbed dose estimates for one patient with two nodal sites who achieved complete remission following near-total thyroidectomy, functional neck dissection and a single therapy administration of radioiodine.

7.3.2 Clinical Case Study SH

Patient (SH), who was referred following left thyroid lobectomy for papillary carcinoma, had developed neck nodal metastases by the time he

Figure 7.8: *Summed coronal PET images post 55MBq ^{124}I showing marked uptake in a chain of nodes on right side of the neck and intense uptake in residual left thyroid lobe.*

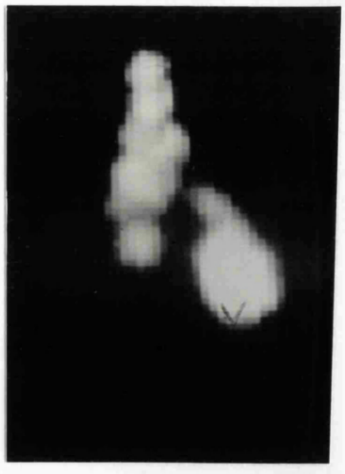


Figure 7.9: *Anterior scan of neck post 3.0GBq ^{131}I using rectilinear scanner.*

was reviewed at this hospital. A PET study was performed following the oral administration of 55 MBq ^{124}I. Fig. 7.8 shows the summed coronal images of the neck demonstrating marked uptake in a chain of nodes on the right side of the neck and intense uptake into the residual left thyroid lobe.

Following ablation with 3.0 GBq ^{131}I, dosimetry studies showed that the remaining left thyroid lobe received an absorbed dose of 230 Gy with 35 Gy to the chain of involved nodes. Fig.7.9 shows the anterior neck scan using the rectilinear scanner following ablation. On review six weeks later, the lymph nodes had progressed and a functional neck dissection and completion thyroidectomy were performed. Histological examination of the residual thyroid was negative and that of the lymph nodes removed confirmed papillary carcinoma. Two subsequent ^{131}I therapy administrations were given at 8 and 12 months post-operatively. The lymph node residuum received an absorbed dose of 25 Gy and 12 Gy at the first and second therapy administrations respectively (Fig.7.10) He remains disease-free with normal thyroglobulin levels at 42 months follow-up.

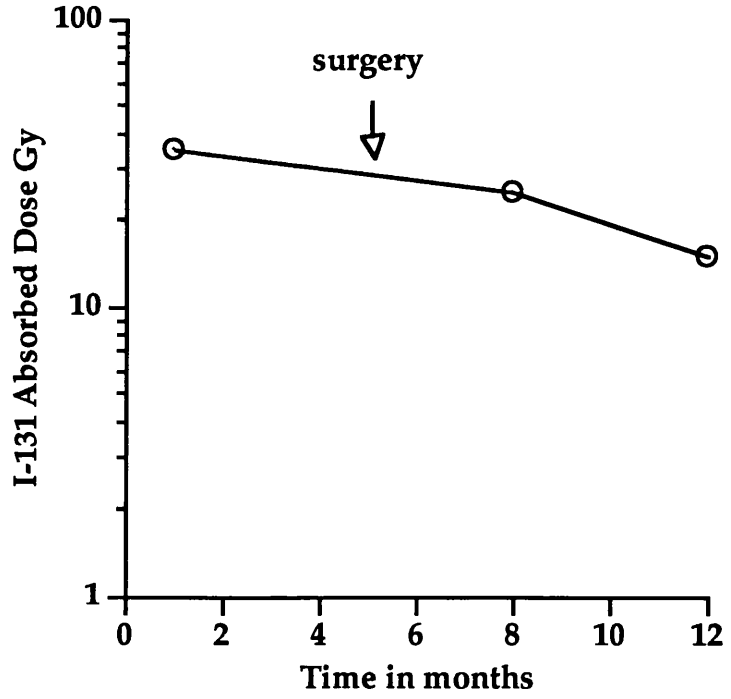


Figure 7.10: Plot of absorbed dose estimates (using a logarithmic scale on vertical axis) to neck nodes for patient SH undergoing thyroid abalation with 3.0 GBq ^{131}I followed by functional neck dissection and two further therapies (each of 5.5 GBq) at three months interval.

7.3.3 Discussion of Results

For the remaining patients in this group repeated therapy administrations were administered. One patient (SJ) underwent further neck dissection for bulky nodal disease and radical external beam radiotherapy was also given. Two patients (TB and AW) have subsequently died with progressive disseminated metastases and one patient (SK) has developed pulmonary metastases. Although the number of patients so far studied is small, the importance of initial surgical cytoreduction is again apparent.

7.4 BONE METASTASES

7.4.1 Dose-Response Relationship

Dose-response data for six patients with bone metastases are shown in Fig. 7.11. The absorbed dose in Gray is plotted using a logarithmic scale on the vertical axis. On the horizontal axis, the first column (designated persistent disease) shows those patients in whom the therapy administration failed to eradicate uptake on a subsequent scan. The second column (designated complete remission) shows two patients who remarkably have had complete symptomatic, clinical and radiographic remission of small solitary bone metastases to date. The mean absorbed dose for the group with persistent disease was only 20 Gy. In general, patients with bone metastases have a poor prognosis (Brown et al, 1984) and those who are iodine-negative fare very badly. Clinical data are shown in Table 6.13 and dosimetry and follow-up data are shown in Table 7.14.

Table 7.13: Clinical data for 5 patients with bone metastases.

Patient	*Age/Sex	Histology	TNM stage at presentation	Thyroid ablation with ^{131}I at presentation
EB	67 F	follicular	$T1(a)N_0M_{bone}$	Yes
CD	57 F	papillary	$T2(b)N_{1b}M_0$	No
CH	47 F	follicular	$T1(a)\ N_0\ M_{lung}$	Yes
AS	59 F	follicular	$T3(a)N_0M_0$	No
EW	68 F	follicular	$TxN_{1a}M_0$	No

* at time of dosimetry study

TNM =UICC International Union Against Cancer (Geneva, 1987)

Table 7.14: Dosimetry data and follow up for 5 patients (11 sites) with bone metastases undergoing therapy with ^{131}I.

Patient	^{131}I	Site	A_o (MBq)	T_e (h)	m (g)	Dose (Gy)	% uptake per g	TSH m U/l	Response
*EB	1st therapy	L1	12	170	3.2	102	0.08	NA	CR at 5 years
CD	1st therapy at recurrence	Sacrum	32	25	X10	307	0.06	NA	CR at 1 year
CH	1st therapy at recurrence	Sacrum	20	59	M8	24	0.05	48	PR
AS	1st therapy at recurrence	Ilium Femur	15	40	C8	12	0.04	92	stable disease
EW	1st therapy	Ilium	190	29	X25	35	0.14	>100	PR
		L4	38	42	X10	26	0.07		
	2nd therapy	Rt rib	27	45	C30	9	0.02	69	PR
		Lt rib	44	46	C27	12	0.03		
		Arm	28	62	X17	16	0.03		
		Arm	18	62	X11	16	0.03		
		Ilium	90	62	C66	14	0.03		
	3rd therapy	Rt rib	33	60	C30	10	0.02	NA	stable disease
		Lt rib	50	60	C27	18	0.03		stable disease
		Ilium	150	60	C66	22	0.04		

*I-124 PET study
C = CT scan
M = Magnetic Resonance Scan
X = Plain radiograph

NA=Not available
CR = Complete response
PR = Partial response

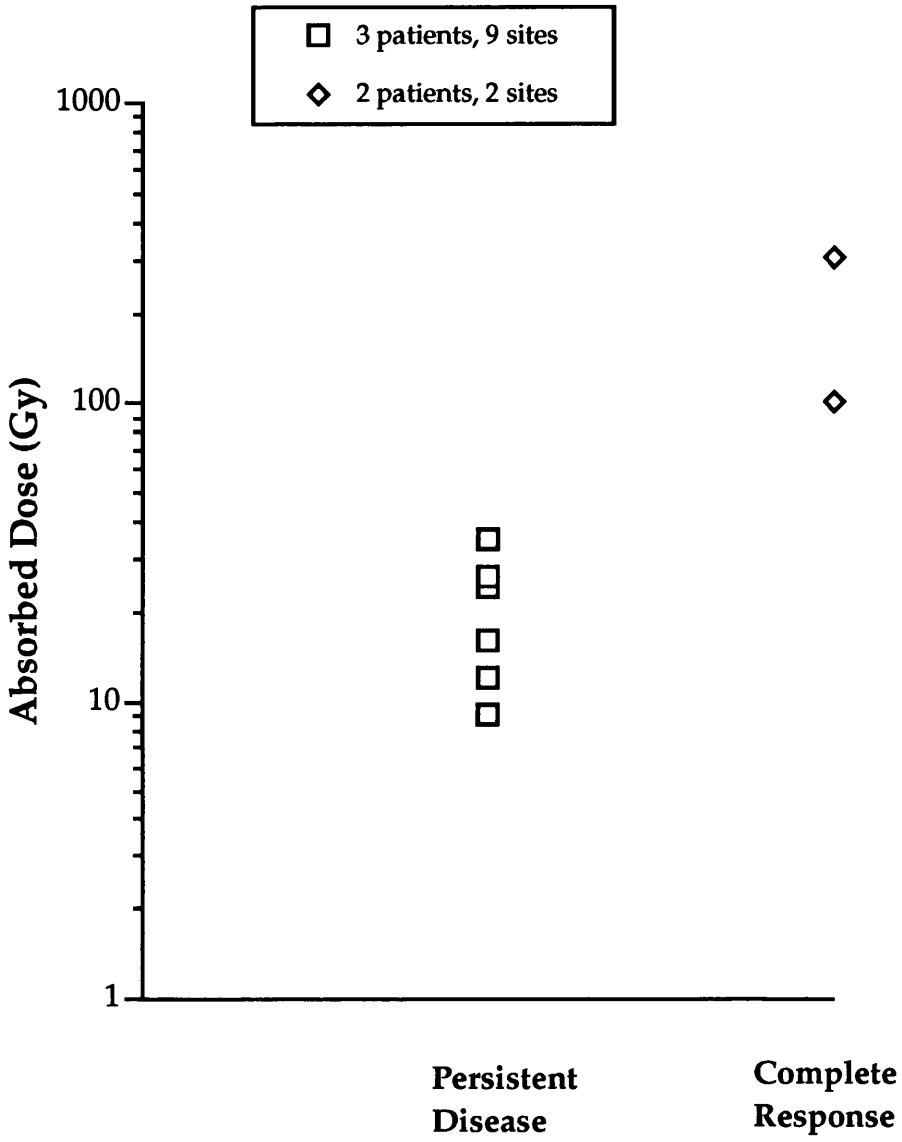


Figure 7.11: *Plot of dose estimates (using logarithmic scale on vertical axis) for 5 patients with bone metastases following first therapy administration with 5.5 GBq* ^{131}I.

7.4.2 Clinical Case Study EB

This 68 year old lady presented with spinal cord compression due to a lytic deposit in the first lumbar vertebra (Fig.7.12). Decompressive laminectomy was performed and histology showed a well differentiated follicular carcinoma of thyroid origin. Staging investigations showed no

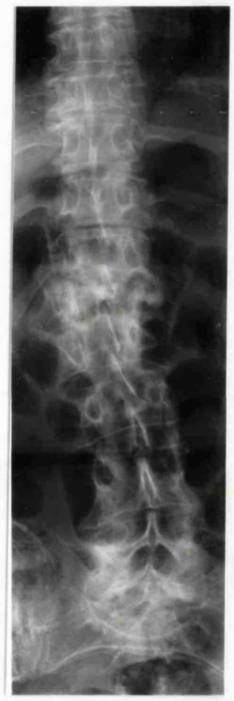


Figure 7.12: *Plain radiograph showing lytic destruction of L1.*

evidence of other metastases and so near-total thyroidectomy was performed in order to facilitate uptake of radioiodine into her solitary bone metastasis. At her first 5.5 GBq ^{131}I therapy administration, this metastatic lesion received an absorbed dose of 100 Gy. No uptake of radioiodine was seen in the spine on a follow-up therapy scan three months later and she remains disease-free with normal levels of thyroglobulin at follow-up for over three years. This case illustrates that a high absorbed dose is required in order to achieve a complete response.

7.4.3 Clinical Case Study EW

However, a partial response has achieved worthwhile palliation of bone pain in another patient (EW) with widespread dissemination of lung and bone metastases. Fig.7.13 shows the whole-body scan at 72 hours following her first therapy 5.5 GBq ^{131}I using the STARCAM gamma camera and illustrates metastases throughout the lungs, two rib lesions and two further lesions in the lumbar spine and right side of pelvis. Dosimetry studies showed that bone deposits in the lumbar spine and pelvis received absorbed doses of 35 Gy and 25 Gy respectively. Scans showing region of interest analysis were presented in Chapter 5 (Fig.5.11 and 5.12). Dose estimates for rib lesions and right humerus at subsequent therapy administrations were given in Table 7.12.

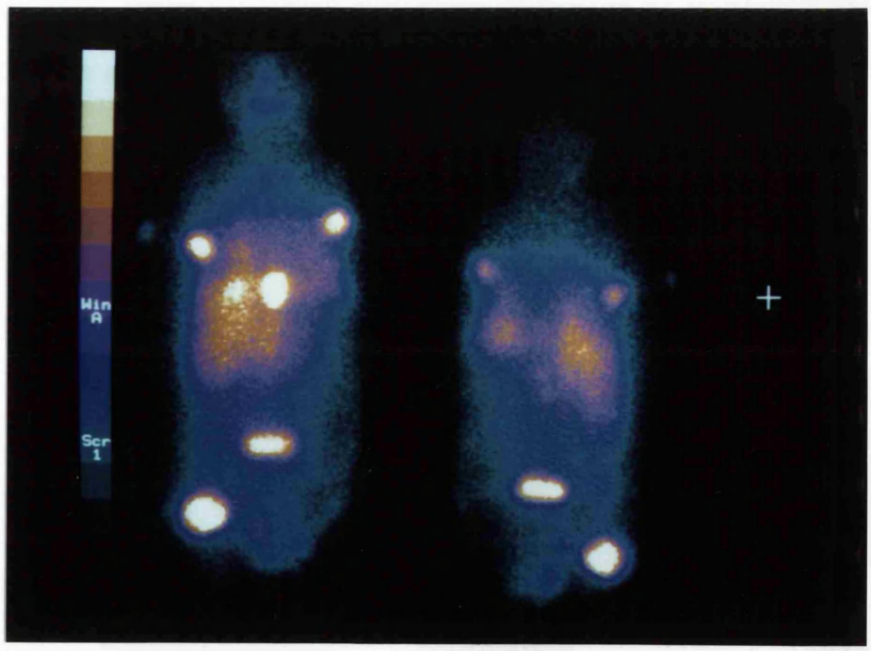


Figure 7.13: *Whole-body scans anterior and posterior views at 72 hours following therapy 5.5 GBq ^{131}I for patient EW using STARCAM gamma camera showing metastases throughout both lungs, ribs, lumbar spine and bony pelvis.*

These absorbed doses are of the same order of magnitude as those delivered with palliative intent by external beam radiotherapy, for example 20 Gy in 5 fractions over one week or 30 Gy in 10 fractions delivered over two weeks. Fig.7.14 shows lytic deposits in the right humerus and a soft tissue mass in the right lateral chest.

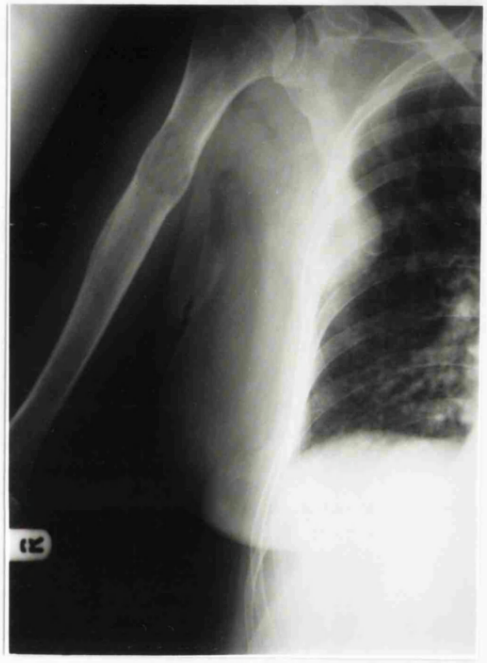


Figure 7.14: *Antero-posterior radiograph showing lytic deposits in right humerus and soft tissue metastasis in right lateral chest.*

Fig.7.15 is the CT scan showing two soft tissue masses arising from ribs bilaterally. The anatomical masses of these lesions were derived from the CT tomograms. Fig.7.16 shows the large lytic deposit in L4. Fig.7.17 shows the corresponding CT tomogram demonstrating the extent of the associated soft tissue mass. Fig.7.18 shows an expanding lytic deposit in the right side of pelvis and Fig.7.19 shows the corresponding CT tomogram. The masses of these lesions were derived from serial CT tomograms. At her follow-up assessment three months later, she was pain-free and thyroglobulin levels were considerably reduced from over 7000 μg/l initially (upper limit of normal 3 μg/l) down to 600 μg/l. This objective response has been maintained at 18 months follow-up.

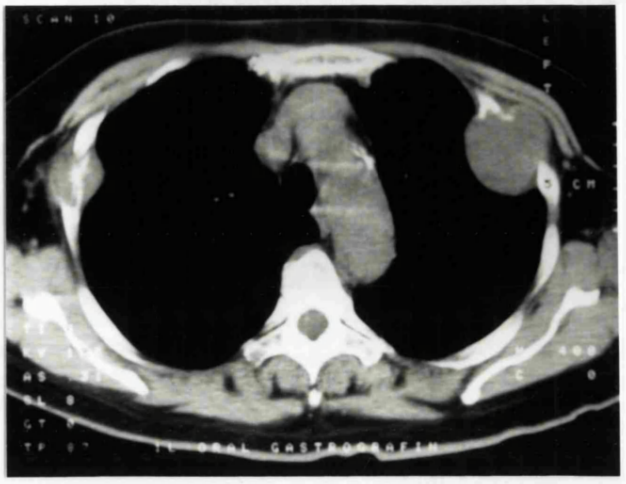


Figure 7.15: CT scan showing bilateral expanding rib lesions with associated soft tissue masses.

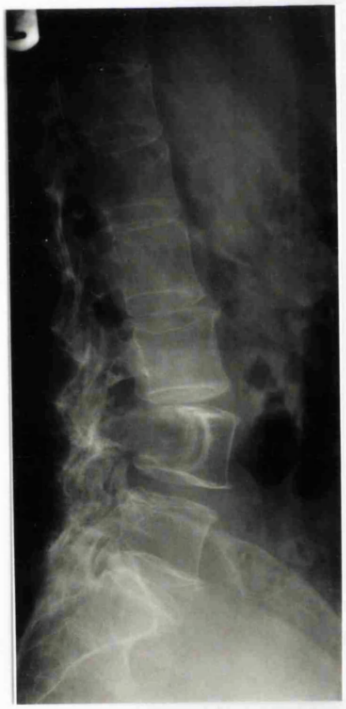


Figure 7.16: Plain radiograph showing lytic deposit in L4.

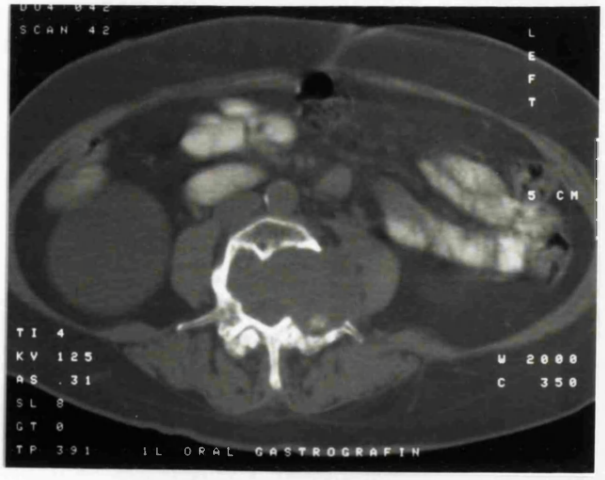


Figure 7.17: CT scan showing expanding lesion in L4.

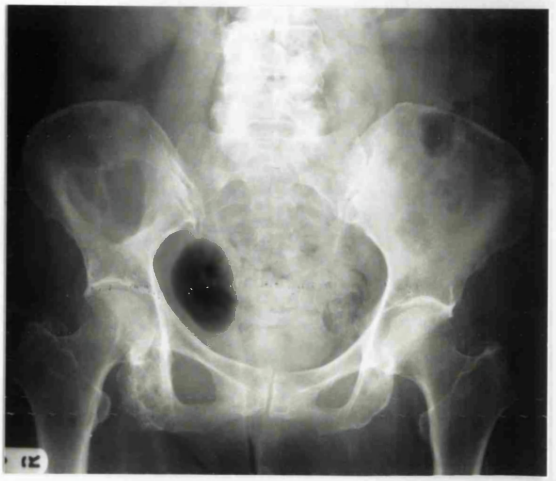


Figure 7.18: *Plain antero-posterior radiograph showing lytic lesion in right hemi-pelvis.*

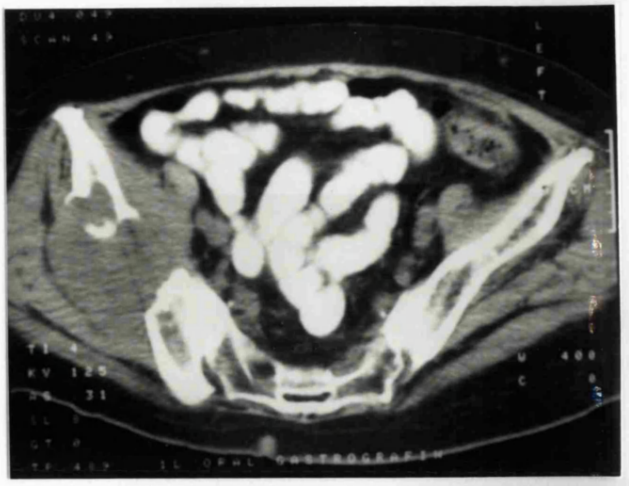


Figure 7.19: *CT scan showing expanding lesion in right hemi-pelvis.*

7.4.4 Discussion of Results

The data presented here suggest that successful destruction of bone and soft tissue metastases requires absorbed doses in excess of 100 Gy. It is not possible to demonstrate any influence of histology or grade on the small series of patients studied to date.

Maxon et al (1983; 1992) recommend that at least 80 Gy should be delivered to lymph node metastases and that alternative therapy for other metastatic sites should be considered if less than 35 Gy is achieved with radioiodine therapy. A single ^{131}I administration calculated to deliver at least 80 Gy successfully treated 74% of patients with nodal metastases. The mean administered activity was 5.8 GBq (range 1.08-9.11 GBq ^{131}I). No information on acute or late side effects resulting from such large single administrations is offered. These dose estimates were based upon quantitative studies following administration of a diagnostic 74 MBq activity of ^{131}I. Such tracer kinetics may differ from those following a therapy administration and firm conclusions should be interpreted with caution. Hadjieva et al (1985) compared the radiation doses predicted from diagnostic studies with those delivered following therapy administrations and found that the actual dose delivered was reduced owing to a shortened effective half-time. Hurley & Becker (1988) found that the measured dose delivered was 80% of that predicted from tracer kinetics owing to a more rapid release of ^{131}I following therapy.

There is also increasing evidence that a suboptimal radiation dose decreases the biological half-life of subsequent radiation doses and thereby decreases the chance of curing the patient. The data presented in this Thesis support this finding.

7.5 LUNG METASTASES

7.5.1 Problems with Quantitation

There are a number of problems associated with absorbed dose calculations for micronodular pulmonary metastases. Such micronodular deposits are frequently only detected by ^{131}I scanning following thyroid ablation and are too small to be imaged by CT scanning or plain radiography. The individual size of such small deposits (of the order of a few millimetres or less) cannot be estimated by radionuclide imaging owing to the limitations in the resolution of detector systems.

7.5.2 Problems with Dosimetry

For very small tumours a large proportion of the total dose from beta particles emitted within the tumour may be deposited in the surrounding tissues. Fig. 7.20 shows the relationship between the ratio of the average beta dose in a sphere to the dose in an infinite volume containing the same radioactive concentration. This data applies to single spheres containing ^{131}I. If there is a neighbouring sphere there will be sphere-to-sphere crossfire which also has to be taken into account in dosimetry calculations.

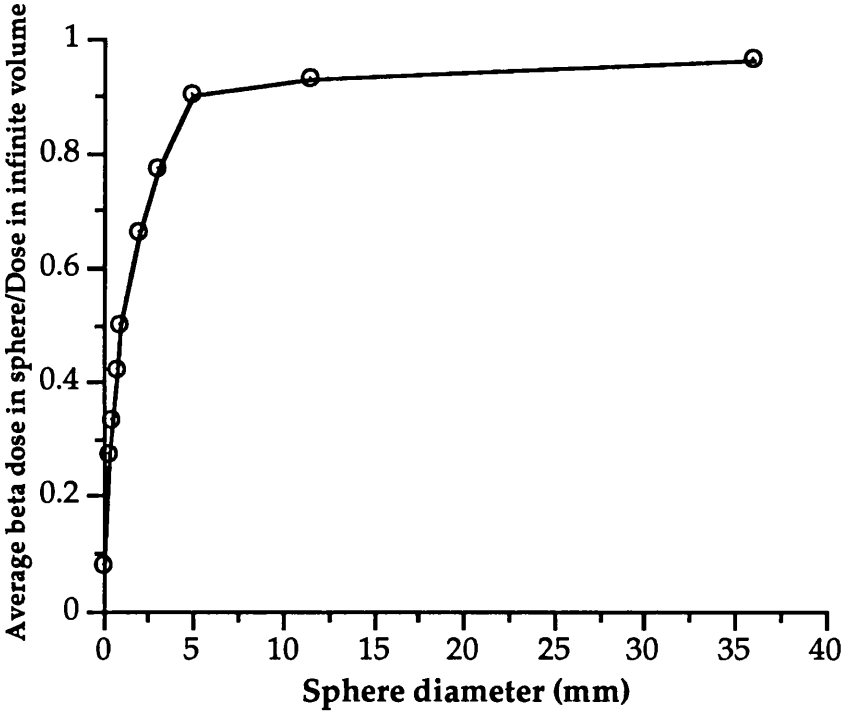


Figure 7.20: Graph of the ratio of the average beta dose in a sphere to the dose in an infinite volume containing the same radioactive concentration. (Data takne from Malone,1975).

7.5.3 Clinical Example

In clinical practise, small micronodular pulmonary metastases are successfully treated with ^{131}I. The explanation for this may be that the reduction in absorbed fraction of beta particle energy is more than compensated for by the very small mass of each individual deposit, since absorbed dose is inversely proportional to mass (Equation (4.9)). Fig. 7.21 shows the antero-posterior gamma camera scintigram for a patient with

occult bilateral pulmonary metastases from well-differentiated follicular thyroid carcinoma. Staging chest Xray was negative and the pulmonary metastases only became evident following ablation of all normal thyroid tissue. This patient received two 5.5 GBq ^{131}I therapy administrations over a six month period and achieved complete remission. She remained disease-free for over thirty years follow-up.

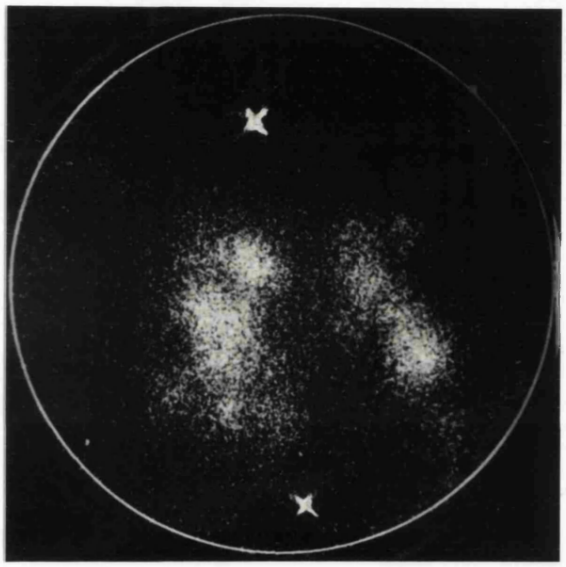


Figure 7.21: *Antero-posterior gamma camera scintigram of chest following therapy with 5.5 GBq ^{131}I showing bilateral uptake in the lungs due to multiple micronodular metastases.*

7.6 OVERVIEW AND DISCUSSION OF RESULTS

After 50 years, the management of differentiated thyroid carcinoma using ^{131}I remains controversial. Debate continues as to the rationale for ablation of normal thyroid tissue in patients from whom thyroid cancer has been resected (Sisson, 1983). Intensive initial therapy has, however, the advantages of not only improved disease-free survival but also allows greater ease of detection of disease at follow-up using serial thyroglobulin and radioiodine scanning (Varma et al, 1970; Tubiana et al, 1985; Black et al, 1987; Powell & Harmer, 1990).

Arguments have also been made for prescribing lower activities of ^{131}I at ablation. McCowen et al (1985) were the first to advocate the use of 1.1 GBq ^{131}I for the ablation of uptake in 'normal' thyroid gland remnants following thyroidectomy. However, 39% of their patients did not respond to this treatment and required an additional 3.7 GBq ^{131}I. It may be assumed that these patients had malignancy in thyroid remnants previously judged to be unaffected. Snyder et al (1983) reported that 1.1 GBq ^{131}I eliminated all traces of post-operative normal thyroid remnants in 61% of 69 patients, but left another 20% with a minimal residuum which was considered insignificant. However, as many as three administrations of 1.1 GBq ^{131}I failed to erase evidence of functioning thyroid cells in four patients. These failures may have been related to the size of the remnant. Using 0.96 to 1.1 GBq, DeGroot & Reilly (1982) destroyed thyroid remnants in 83% of 18 patients. This greater ease of ablation may have been achieved by treating only small amounts of tissue. However, Kline & Klingensmith (1980) and Siddiqui et al (1981) who followed their patients for longer periods of time in order to evaluate the ablative effects of 1.1 GBq ^{131}I in normal remnants, found that a second administration was required in 12 out of 13 and 16 out of 17 patients respectively.

Beierwaltes (1986) on the other hand, advocates the use of higher atcivities of between 3.7 and 7.4 GBq ^{131}I and has achieved ablation of thyroid remnant uptake in 87% of 267 patients. Higher activities may also provide "adjuvant" therapy for patients with occult metastases. Indeed, the New York Memorial Sloane Kettering Group use considerably higher activities than those of the Thyroid Unit at this Hospital. The prescribed activity is based upon dosimetry calculations required to deliver a maximum blood absorbed dose of 2 Gy (Leeper, 1982). Such dose calculations have enabled the administration of an average single therapy activity of 11.4 GBq ^{131}I (range 2.6 to 24 GBq) without encountering permanent bone marrow suppression or pulmonary fibrosis. Leukaemia resulting from ^{131}I therapy has not been reported from the Memorial Hospital over a 22 year period inspite of total activities exceeding 37 GBq in a number of patients. This is possibly due to the limitation of ^{131}I administration to once per annum. For rapidly progressive disease, activities have been increased to give an absorbed blood dose of 3.0 Gy or 5.5 GBq whole-body ^{131}I retention at 48 hours. However, as well as possible increased toxicity, a major difficulty with this approach arises because therapy kinetics frequently differ from those of tracer studies (Benua et al,

1962; Doniach, 1974; Hurley et al, 1988; Maxon et al, 1992) as discussed in section 7.2.6. Animal studies have shown that there is a steady increase in discharge rate from the thyroid gland proportional to the initial activity of ^{131}I administered up to a threshold beyond which there was a sudden massive discharge of ^{131}I due to massive follicular cell necrosis (Doniach, 1974). Similar biological considerations probably apply to man so that tracer kinetics cannot be assumed to predict those following therapy administrations of radioiodine.

As accurate data on radioiodine dosimetry becomes available, these difficulties may now be resolved. The clinical data reported here show that when near-total thyroidectomy has been perfomed an absorbed dose in excess of 60 Gy will ablate normal thyroid remnants in 75% of patients. It also appears that the larger the residual gland, the more likely is the persistence of function following a single ablation administration. Evidence from other studies (Sisson, 1983; Maxon et al, 1992) also supports a correlation between the size of remnant and ease of ablation. Moreover, the efficacy of radioiodine in controlling microscopic disease and small volumes of tumour is a fundamental postulate of radiotherapy (Fletcher, 1978). The radiation dose thresholds recommended in this Thesis and also by others (Maxon et al, 1992) are consistent with theoretical predictions made by Britton et al (1991) assuming that the sterilising dose of radiation required is proportional to the logarithm of the tumour cell number (Wheldon, 1986). Britton et al (1991) have demonstrated a relationship between tumour size, cell content, weight and sterilising dose of radiation For a tumour 1 cm diameter containing 10^9 cells of approximate weight 0.3 g it is estimated that an absorbed dose of 40 Gy is required for sterilisation whereas for a 3 cm diameter tumour containg 10^{12} cells and weighing 15 g a dose of 60 Gy would be required.

Hence, at least near-total thyroidectomy together with complete excision of macroscopic nodal disease should be performed initially if ablation is part of the therapeutic protocol. Where lobectomy or partial thyroidectomy has been performed, further surgery (that is completion thyroidectomy) is recommended before commencing radioiodine therapy. When residual tumour is present, these data also suggest that a higher initial activity should be given in order to deliver an absorbed dose of at least 100 Gy.

Successful destruction of nodal disease has been achieved with absorbed doses in excess of 150 Gy following optimal surgical cytoreduction.

Bone metastases, which are generally associated with a poor prognosis (Brown et al, 1984), require high dose for eradication and this has been achieved following surgery where the deposit was solitary and the tumour well-differentiated. Worthwhile palliation may still be achieved however, with lower absorbed doses. Our data suggest that absorbed doses less than 20 Gy are subtherapeutic. Maxon et al (1983; 1992) recommended that at least 80 Gy should be delivered to metastatic neck nodes and that alternative therapy should be sought if less than 35 Gy to other metastatic sites was achieved with radioiodine therapy. These dose estimates were based upon quantitative studies following administration of a diagnostic 74 MBq activity of ^{131}I. Such tracer studies may differ from those following a therapy administration (as discussed above) and firm conclusions should be interpreted with caution.

There is also increasing evidence that a suboptimal radiation dose decreases the biological half-life of subsequent radioidine adminstrations and thereby compromises the chance of curing the patient (Rawson et al, 1951; Henk et al, 1972; Beierwaltes, 1986). Our data support this finding.

The dosimetry calculations, presented in this thesis, assume uniform distribution of ^{131}I in the target tissue. This is a reasonable assumption since the range of the beta particles from ^{131}I (mean range 2.5 mm) ensures that a reasonably uniform distribution of dose is achieved despite heterogeneity in the location of the radionuclide. Unlike external beam radiotherapy, radionuclides deliver continual or protracted radiation at relatively low dose-rates which decrease exponentially at a rate depending upon the effective half-life of the radionuclide. Since the cell survival fraction curve is exponential, as much radiation is required to reduce a cell population from 10^{10} to 10^{9} cells as is required to reduce it from 10^{2} to 10^{1} cells. Repair during the period of protraction may spare normal cells relative to tumour cells. Hypoxia may also play a role. The core of a large tumour often has a relatively impaired blood supply compared with the periphery. This may limit access of the radionuclide. Also, central cystic necrosis tends to occur in tumours exceeding 3 cm diameter (Thomlinson & Gray, 1955). Tumour that is less well oxygenated is less radiosensitive (Wright & Howard-Flanders, 1957).

Enhancement of tumour uptake of radioiodine using diuretic therapy, injection of TSH, low iodine diet and antithyroid drugs for example (see section 1.7.5) have so far failed. Endogenous TSH stimulation

is important and TSH levels should be above 30 mU per litre to achieve optimum uptake by tumour (Edmonds et al, 1977).

Alternative strategies using radionuclides other than ^{131}I have not yet been explored. Owing to the high linear energy transfer of alpha particle emitters, the tumouricidal effects are much less oxygen dependent than for beta particles. The alpha particle emitting halogen astatine (^{211}At) has theoretical advantages but toxicity to normal tissues such as bladder and bowel and economic constraints have so far precluded its clinical use. Nevertheless investigations as a potential α-endoradiotherapeutic agent in a human thyroid tumour xenograft model in nude mice are promising and may allow a tumouricidal dose to be delivered to undifferentiated thyroid carcinoma which fails to concentrate radioiodine (Brown et al, 1992).

In future, ^{131}I administrations should be scheduled in such a way as to maximise the effects of divided doses in relation to the metabolic activity and growth rate of thyroid carcinoma. The activity prescribed should be determined for each individual patient on the basis of residual gland size, uptake and clearance half-time of radioiodine. An initial tracer study could be performed to determine the therapeutic activity required to deliver a pre-determined absorbed dose, provided account is taken of possible discrepancies between therapy and tracer kinetics. Dose-response relationships must be taken into account in judging the activity of ^{131}I to be prescribed; in determining the frequency and interval between doses; and in withholding further radioiodine treatment when a subtherapeutic outcome can be predicted thus minimising late morbidity, staff hazards and unnecessary expense.

CONCLUSIONS

1. The administration of fixed activities of radioiodine (^{131}I) results in a very large variation in radiation absorbed dose to thyroid remnants at ablation and metastases from differentiated thyroid carcinoma.

2. When near-total thyroidectomy had been performed, the administration of 3.0 GBq ^{131}I was found to ablate thyroid remnants in 67% of patients (73% of sites) when a mean absorbed dose of 349 Gy was delivered.

3. Large residual remnants demand a higher absorbed dose (since absorbed dose is inversely proportional to mass) and therefore higher administered activity is recommended.

4. When tumour remains in association with normal thyroid tissue, the percent uptake per unit mass is low and hence a higher activity (than 3.0 GBq ^{131}I) is also required.

5. Absorbed doses in excess of 100 Gy were required to eradicate metastases. Although in general patients with bone metastases have a poor prognosis, long remission was possible for solitary deposits when initial surgical bedulking was performed.

6. Very high absorbed doses can be achieved in the therapy of micronodular pulmonary metastases; the fraction of beta particle energy absorbed is reduced but is more than compensated for by the small size and hence mass. This may explain their more favourable response to ^{131}I therapy and better prognosis.

APPENDIX A: THYROID CARCINOMA DATA BASE

1. Presentation and Staging

Name: Mr/Mrs/Miss..... Hosp No:.....

GP: ..... Consultant: .....

D.o.B: ...../...../..... Sex: M / F Nationality: UK/OTHER .....

Referred by..... Reference Number: .....

Family History of Thyroid Disease:

.....
.....
.....
.....

Previous Thyroid History:

.....
.....
.....
.....

Previous Thyroid Treatment:

.....
.....
.....
.....

Previous Neck Irradiation:

.....
.....
.....
.....

SYMPTOMS: Thyroid swelling / Lymph node enlargement / Pain / Dysphagia / Stridor / Hoarse Voice / Other (specify)

SURGERY	DATE	WHERE
Biopsy Only		
Resection enucleation		
Lobectomy		
Hemithyroidectomy		
Subtotal thyroidectomy		
Completion thyroidectomy		
Near total thyroidectomy		
Total thyroidectomy		
Neck dissection		
Simple nodal exision		
Other (specify) eg laminectomy		

Histology..... Grade.....

RMH Review YES / NO Pathologist.....

Size of Primary:

Clinical.....cm /Path.....cm / US or Scan.....cm

Extracapsular Extension YES / NO Unifocal YES / NO Multifocal YES / NO

Lymphatic Invasion YES / NO Vascular Invasion YES / NO Capsular Invasion YES / NO

Thyroid Parenchyma: Multinodular Goitre / Thyroiditis / Normal / Other (specify)

TNM STAGE AT PRESENTATION

Tx ☐ T0 ☐ T1 ☐ T2 ☐ T3 ☐ T4 ☐

Nx ☐ N0 ☐ N1a ☐ N1b ☐

UF ☐ MF ☐

Metastases YES / NO Lung ☐ Date ...../...../.....

Bone ☐ Date ...../...../.....

Other (specify below)

..... Date ...../...../.....

..... Date ...../...../.....

..... Date ...../...../.....

..... Date ...../...../.....

T1 = < 1cm
T2 = 1.4cm
T3 = > 4cm
T4 = invading beyond capsule

N1a = ipsilateral cervical
N1b = Bilateral; midline; contralateral cervical; upper mediastinal

UF = unifocal
MF = multifocal

2. Treatment

Radioiodine

Ablation YES / NO Activity..... Date.....

Therapy YES / NO Activity..... Date.....

....

....

....

....

....

Cumulative Dose.....GBq

If Present, did metastases take up I-131? YES / NO

If Metastases were Present, was Tg Elevated? YES / NO

External Beam Radiotherapy

NECK? Primary ☐ Nodes ☐ Mediastinum ☐

Total Dose (Gy) ☐☐ Energy.....

Time (days) ☐☐ Fields.....

METS? Lung ☐ Bone ☐ Other (specify) ☐

.....

Total Dose (Gy) ☐☐ Energy.....

Time (days) ☐☐ Fields.....

Chemotherapy

YES / NO If YES specify:.....
.....
.....
.....

3. **Follow Up**

Recurrence YES / NO If YES - Thyroid Bed ☐ Date...../...../.....

Neck nodes ☐ Date...../...../.....

Distant mets ☐ Date...../...../.....

External Beam Radiotherapy

NECK? Primary ☐ Nodes ☐ Mediastinum ☐

Total Dose (Gy) ☐☐ Energy.....

Time (days) ☐☐ Fields.....

METS? Lung ☐ Bone ☐ Other (specify) ☐

.....

Total Dose (Gy) ☐☐ Energy.....

Time (days) ☐☐ Fields.....

Radioiodine

YES / NO If YES - Activity..... Date.....
Activity..... Date.....

Chemotherapy

YES / NO If YES Specify.....
.....

Treatment Response

I-131 ☐ CR ☐ PR ☐ NR ☐ NK ☐

Ext beam RxT ☐ CR ☐ PR ☐ NR ☐ NK ☐

Chemotherapy ☐ CR ☐ PR ☐ NR ☐ NK ☐

CR = Complete disappearance of all measurable disease
PR = At least 50% reduction of measurable disease
NR = No response / progressive disease / or < 50% reduction of measurable disease
NK = Not known

Leukaemia or Marrow Dysplasia? YES / NO If YES - Date...../...../.....

Second Malignancy? YES / NO If YES - Specify.....
Date.....

Hypocalcaemia YES / NO If YES - Date...../...../.....

Anaplastic Transformation? YES / NO If YES - Date...../...../.....

Last seen ..... Number of years follow-up .....

Deceased YES / NO Date ..... Post Mortem YES / NO

Cause of Death

DISEASE .....
OTHER (Specify) .....

Site of Disease

Local: Thyroid Bed ☐
Lymph nodes ☐

Distant: Lung ☐
Bone ☐
Other ☐

APPENDIX B:

Table of SI Units

Physical Quantity	Text Symbol	SI Unit	Symbol
Activity	A	becquerel	Bq
Cumulated activity	$\tilde{A}$	becquerel-second	Bq-s
Absorbed dose	D	gray	Gy
Mean dose per unit cumulated activity	S	gray / becquerel-second	Gy / Bq-s
Mean energy emitted per nuclear transition	Δ	gray-kilogram / becquerel-second	Gy kg / Bq-s
Energy per particle	E	joule electron volt	J eV
Specific absorbed fraction	Φ	reciprocal kilogram	kg^{-1}
Mass of organ	m	kilogram	kg
Physical half-life	T_p	second	s
Biological half-life	T_b	second	s
Effective half-life	T_e	second	s
Physical decay constant	λ	reciprocal second	s^{-1}

Commonly Used Prefixes for SI Units

Factor	Prefix	Symbol
10^{12}	tera	T
10^{9}	giga	G
10^{6}	mega	M
10^{3}	kilo	k
10^{-3}	milli	m
10^{-6}	micro	μ

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FIRST PRIZE AWARDED

The paper entitled:

" Radiation dose assessment in radioiodine therapy. Dose-response relationships in differentiated thyroid carcinoma using quantitative scanning and PET "

was awarded first prize of the ESTRO-VARIAN Clinical Research Award,1991.