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Papers

Results of External Beam Radiotherapy in Differentiated Thyroid Carcinoma: a Retrospective Study from the Royal Marsden Hospital

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Between 1969 and 1991, 113 patients with differentiated thyroid carcinoma (follicular and papillary) received radical dose megavoltage external beam radiotherapy. There were 70 females and 43 males, mean age 53 years (range 11–84). Radiotherapy was delivered to both sides of the neck and superior mediastinum, using either megavoltage photons via anterior and posterior portals, delivering a 60 Gy mid-plane dose in 30 fractions and treating daily over 6 weeks (with spinal cord shielding from the posterior field after 40 Gy), or matched 20 MeV and 35 MeV electron beams (to the neck and superior mediastinum, respectively) delivering a 75 Gy applied dose in 30 daily fractions. All patients received suppressive thyroid hormone and 74 received radioiodine. Local recurrence, mostly within field, occurred in 19% of 53 patients with probable and definite residual microscopic disease (both follicular and papillary histologies). For gross residual disease (both follicular and papillary) in 49 patients, complete regression was obtained in 37.5%, partial regression in 25% and no regression in 37.5%. Median follow-up from diagnosis was 49 months (range 3–335). Overall 5-year survival rates were 85% for residual microscopic disease but only 27% for gross disease. 61 patients have died. Nineteen deaths were due to unrelated causes, 15 to distant metastases, 15 to uncontrolled local disease and 12 died with both local and distant tumours.

Key words: external beam radiotherapy, differentiated thyroid carcinoma
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INTRODUCTION

SURGERY REMAINS the definitive initial and potentially curative treatment for differentiated papillary and follicular thyroid carcinoma. In general, the value of external beam radiotherapy (EBRT) in the local control of differentiated thyroid carcinoma has been overlooked partly because many regard these tumours as radioresistant. However, there are three main situations where EBRT may be useful. For residual or recurrent primary tumour or nodal involvement, further surgery should be performed unless precluded by medical reasons. EBRT is then indicated for those patients with residual disease which fails to concentrate radioiodine, and for poorly differentiated tumours which are unlikely to concentrate radioiodine sufficiently to be of therapeutic benefit. For patients with gross inoperable tumour, complete remission may be obtained in a proportion of patients [1]. High-dose EBRT is undoubtedly worthwhile to palliate fungating nodes, bleeding, stridor, dysphagia and superior vena caval obstruction due to progressive tumour [2]. 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 EBRT; evaluation, therefore, relies on retrospective analyses. The purpose of this retrospective study from a major referral centre is to analyse the outcome of patients with differentiated thyroid carcinoma who were given radical dose megavoltage radiotherapy.

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PATIENTS AND METHODS

Patients

From 1969 to 1991, 113 patients with differentiated thyroid carcinoma received radical dose EBRT at the Royal Marsden Hospital (RMH), London and Surrey. The majority of patients were referred from counties in southeast 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 1) indicates an older age group than is found in unselected surgical patients. The male to female ratio was 1:1.6, so the proportion of males was higher than that in an

Table 1. Age and sex distribution by histology

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

Table 2. Histology and grade

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

unselected series. Histology was reviewed in every case by the RMH Department of Histopathology and classified according to World Health Organization criteria [3]. The presence of solid elements was used as a parameter of tumour grading for papillary carcinomas [4, 5]. There were 85 papillary, 24 follicular and four Hürthle cell carcinomas (Table 2). The majority of papillary tumours were well differentiated (62/85), whereas for follicular histology, one half was poorly differentiated (12/24). Distribution by TNM classification [6] at diagnosis is shown in Table 3. TNM stage given is that at initial presentation; many stage T1/2 tumours had been treated by resection enucleation only, and patients with loco-regional recurrence were then referred to RMH for further surgery, where possible, together with EBRT for residual disease. At the time of referral, 53 patients had infiltrating neck masses and 12 had distant metastases. The frequency of follow-up was 3-monthly for the first 2 years, 6-monthly for the next 3 years and thereafter annually. At each follow-up visit, serum thyroglobulin and a chest radiograph were obtained.

Indications for EBRT are shown in Table 4. Among 74 patients given radioiodine, there was failure to concentrate radioiodine in 34 (46%). Other indications for EBRT included poorly differentiated tumours in 21 patients and inoperable tumours in 24 patients, for whom biopsy only was possible. 23 patients had progressive symptomatic disease including stridor, dysphagia, haemoptysis and superior vena caval obstruction. EBRT was also given to patients considered to be at high risk of local recurrence because of advanced age and poorly differentiated tumour, although no residual microscopic disease was apparent in the surgical specimen.

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 5). Hemi-thyroidectomy was defined as total lobectomy on the affected side together with

Table 4. Indications for external beam radiotherapy

	No. of patients
Failure to concentrate radioiodine	34
Poorly differentiated tumour	21
Inoperable tumour	24
Local recurrence	11
Progressive symptoms	
Stridor	12
Dysphagia	5
Haemoptysis	5
Caval obstruction	1

Table 3. TNM classification at diagnosis

		M0	Distant Spread		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

Table 5. Initial surgical treatment

Surgery for primary tumour	Surgery for neck node metastases: 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.

isthmusectomy. Subtotal thyroidectomy was defined as leaving a small remnant of thyroid tissue without exploration of the recurrent laryngeal nerve. 23 patients underwent further surgery at RMH for recurrent locoregional disease at the time of referral.

External beam radiotherapy

Both sides of the neck from the hyoid including the supraclavicular fossae and extending down to the superior mediastinum was irradiated in most cases. 105 cases were treated with megavoltage radiotherapy (^{60}Co photons or 5MV X-rays) via anterior and posterior portals, with shielding to the floor of mouth and sub-apical portions of the lungs. The majority received a tumour dose of 60 Gy in 30 daily 2 Gy fractions treating both fields daily for 6 weeks. The spinal cord was shielded from the posterior field after 40 Gy. 8 patients were treated using a pair of matched 20 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. 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.

Thyroid hormone and radioiodine

All patients received suppressive thyroid hormone with either thyroxine 0.2 mg daily or tri-iodothyronine 60 μg daily. 74 patients received radioiodine ^{131}I; 58 received only 3 GBq to ablate remnants following initial surgery, and 22 received therapy administrations, in addition, for either residual local disease or distant metastases. The maximum cumulative administered activity was 36 GBq ^{131}I with a mean of 10 GBq. At this hospital, no formal limit to the maximum cumulative activity of ^{131}I has ever been adopted.

Analysis

Patients were classified according to the completeness of surgical excision. They 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 the tumour was close to lines of excision (within 2 mm). They were classified as having definite residual microscopic disease if the tumour had been removed by blunt dissection (for example, shaved off the trachea, larynx or oesophagus). Finally, patients were described as having gross disease if visible tumour remained either in the thyroid bed or in regional lymph nodes. For 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 a 50% reduction in clinical and/or radiographic disease. No regression included patients in whom there was less than a 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 hazards model for multivariate analysis [7]. A stepwise selection procedure with the Cox proportional hazards regression model was used to determine independent prognostic factors in multivariate analysis.

RESULTS

Only 2 patients who returned abroad were not seen beyond 3 months of follow-up. For papillary carcinoma, local recurrence occurred in 7/53 (13%) patients with probable or definite residual microscopic disease (Table 6). For patients with gross disease and papillary carcinoma, response rates were complete regression 13 (41%), partial regression 7 (22%) and no regression 12 (37%) (Table 7). For follicular histology, local recurrence occurred in 3/10 (30%) patients with probable or definite residual microscopic disease (Table 8). For patients with gross disease from follicular carcinoma, response rates were complete regression in 5 (31%), partial regression in 5 (31%) and no regression in 6 (38%) (Table 9). Overall, EBRT achieved 81% 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

Table 6. Response of papillary thyroid carcinoma to EBRT microscopic disease

Residual microscopic disease (*n*)	No recurrence	Local recurrence
None (10)	10*	0
Probable (25)	23†	2
Definite (18)	13‡	5
Total (53)	46	7

* 5 also received radioiodine. † Also received radioiodine. ‡ 12 also received radioiodine.

Table 7. Response of papillary thyroid carcinoma to EBRT gross disease

Response	Complete regression	Partial regression	No regression
Radiotherapy	13*(41%)	7†(22%)	12‡(37%)

* 12 also received radioiodine. † 5 also received radioiodine. ‡ 11 also received radioiodine.

Table 8. Response of follicular carcinoma to EBRT microscopic disease

Residual microscopic disease (*n*)	No recurrence	Local recurrence
None (1)	1	0
Probable (4)	2*	2*
Definite (6)	4†	2*
Total (11)	7	4

* 2 also received radioiodine. † 1 also received radioiodine.

erythema of the skin with telangiectasia occurred following electron beam therapy, but there were no significant late sequelae.

Radical dose EBRT is preferable to mutilating surgery in patients with inoperable disease as illustrated by the following case. A 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 replacing the left lobe of thyroid. Computerised tomography (CT) of the neck (Figure 1) confirmed a mass arising from the left lobe of thyroid, involving the left sternomastoid muscle and inseparable from the vascular sheath with tracheal deviation to the right. Exploration of the neck was undertaken, but only biopsy was possible. Histology showed papillary carcinoma of thyroid origin. Clinically, there was no lymph node involvement. Chest radiograph showed no pulmonary metastases. He was treated with EBRT via anterior and posterior fields to cover the whole neck and upper mediastinum with a tumour dose of 60 Gy in 30 daily fractions using 6 MV X-rays. The spinal cord was shielded from the posterior field after 40 Gy. On completion of radiotherapy, swallowing had markedly improved and the neck was less swollen. A dose of 3 GBq ^{131}I was then administered to ablate the normal right lobe and he was started on tri-iodothyronine 60 μg daily. Three months later, there was almost complete resolution of the left neck mass. Radioiodine scanning had shown intense uptake into the normal right lobe and, therefore, two therapy administrations of 5.5 GBq ^{131}I followed at 3-monthly intervals, but there was no localisation within the tumour. Three months later, CT scan (Figure 2) showed residual tumour damage of the left thyroid cartilage, but no soft tissue mass was demonstrated. He remains in clinical

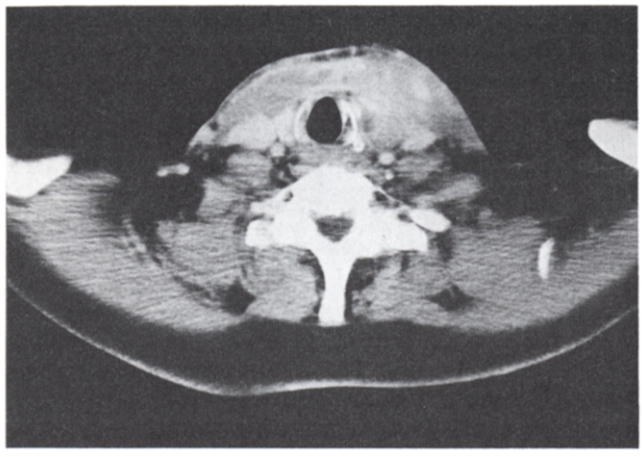

Figure 1. Computed tomography scan showing a mass on the left side of the neck invading sternomastoid muscle and inseparable from the vascular sheath with tracheal deviation to the right.

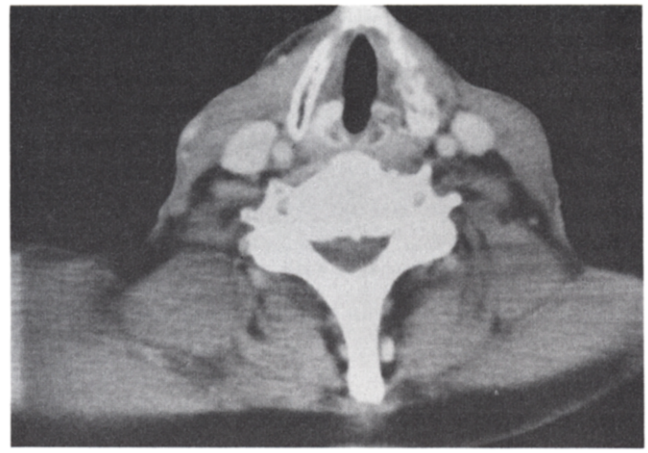

Figure 2. Computed tomography scan at a slightly higher level 3 months after radical dose external beam radiotherapy showing previous tumour damage of the left thyroid cartilage and complete resolution of soft tissue mass.

Table 9. Response of follicular carcinoma to EBRT gross disease

Response	Complete regression	Partial regression	No regression	Not known
Radiotherapy	5*(31%)	5†(31%)	6‡(38%)	1

* 4 also received radioiodine. † 2 also received radioiodine. ‡ 5 also received radioiodine.

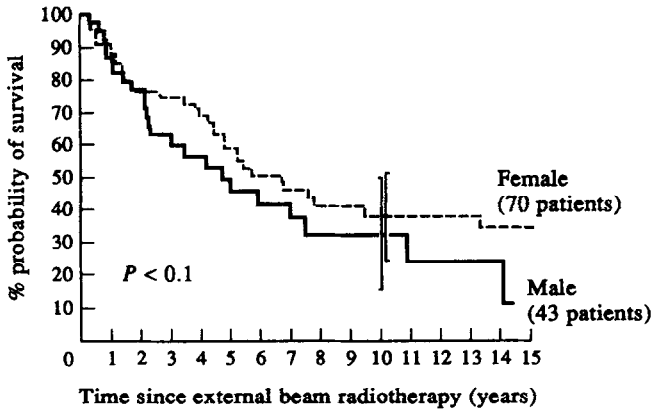

Figure 3. Survival (%) by sex for 113 patients receiving external beam radiotherapy.

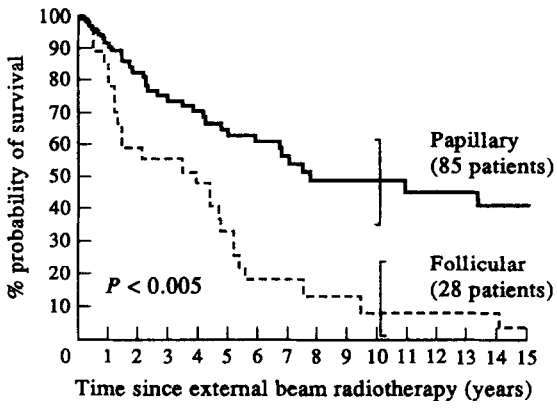

Figure 4. Survival (%) by histology for 113 patients receiving external beam radiotherapy.

remission at 4 years follow-up with an unrecordable thyroglobulin level.

Survival

Survival curves are shown in Figures 3–7. Females did not have a significantly better survival than males (Figure 3). Patients with papillary carcinoma had a better rate of survival than those with follicular histology (Figure 4, $P < 0.005$). This may reflect the fact that 70% of papillary tumours were well differentiated

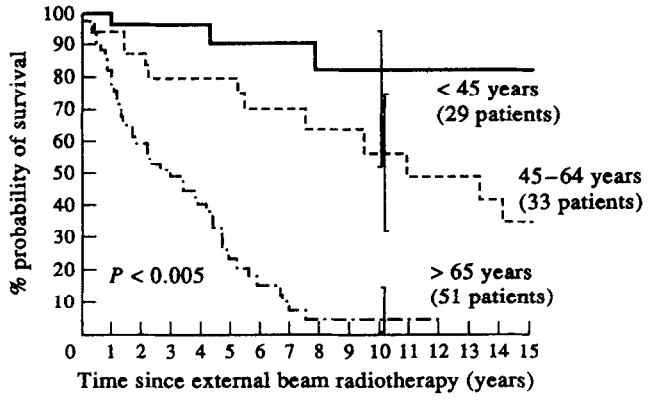

Figure 5. Survival (%) by age for 113 patients receiving external beam radiotherapy.

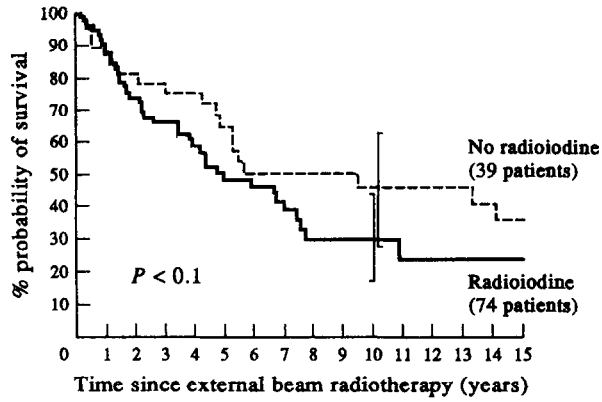

Figure 6. Survival (%) by radioiodine in addition to external beam radiotherapy.

whereas 50% of follicular tumours were poorly differentiated. The important influence of age on survival is shown in Figure 5, with an 81% survival rate at 10 years for patients less than 45 years of age, falling to 36% for patients aged 45–64 years and only 6% for patients aged 65 and over; these differences in survival are significant ($P < 0.005$). There was no significant difference in survival for patients receiving radioiodine in addition to EBRT (Figure 6). This may be explained by the fact that 43% of patients receiving ^{131}I showed no uptake by residual tumour. Figure 7 shows the importance of residual disease in determining survival: patients with no residual microscopic disease had 91% overall survival at 10 years contrasting with only 13% for patients with gross residual disease ($P < 0.005$).

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%. 61 patients have subsequently died: 19 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 disease and distant metastases (Table 10).

Results of univariate analysis for overall survival showed postoperative status, age, histology and degree of differentiation to be of significant prognostic importance (Table 11). Ranking of prognostic factors of multivariate analysis (Table 12) showed that postoperative status was the most important factor determining survival followed by age, histology and sex.

DISCUSSION

Although surgery remains the initial and potentially curative treatment for differentiated thyroid carcinoma, local invasion of

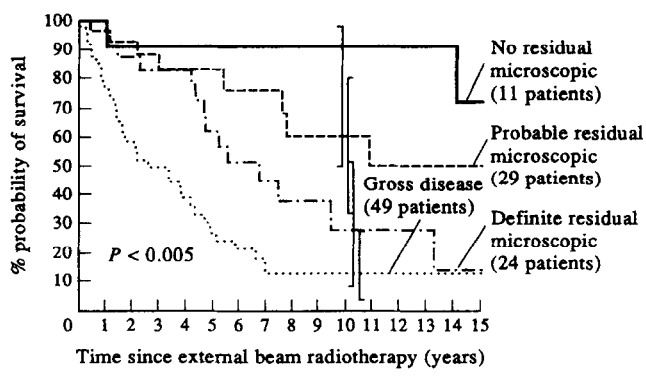

Figure 7. Survival (%) by postoperative disease status.

Table 10. Present status of patients treated with EBRT

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	15	4
Total	36	25

structures such as the larynx, trachea, pharynx, carotid sheath and cervical oesophagus prohibits complete removal. Residual tumour will progress, ultimately resulting in death by local invasion. External beam radiotherapy may, therefore, be of benefit. Radical dose is required as differentiated thyroid carcinoma is relatively radioresistant [2]. Regression is often slow, but in our series of patients was maximal by about 3 months. For gross disease, radical dose EBRT achieved a response in over 60% of patients described in this study with complete regression of gross disease in 37%. This is comparable with other series [1, 8–10]. There is evidence that survival rates for incompletely excised tumours may also be improved by radical dose EBRT [11–17]. In our series of patients with residual microscopic disease (both probable and definite), local control was achieved in 81%. Survival rates were 80% at 5 years, 60% at 10 years and 40% at 15 years. These survival rates are comparable with those obtained in other large series [1, 16].

Multivariate analysis has shown that independent prognostic factors are age, residual postoperative tumour, follicular histology and male sex. The prognostic significance of age has been demonstrated in a number of other series [18–28]. The importance of postoperative disease status has also been stressed by other series, notably that of Simpson and colleagues [16, 27]. A more radical approach, using combined treatment with EBRT and ablative radioiodine together with suppressive thyroid hormone should therefore be considered for those patients with poor prognostic factors.

Table 11. Results of univariate analysis for prognostic factors

Factor	Hazard ratio (95% confidence interval)	*P* value
Age (years)		
< 45	1.00	
45–64	3.58(1.68–7.65)	* $P < 0.001$
> 65	7.99(4.25–15.0)	
Postoperative 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	Non-significant
Male	1.39(0.81–2.38)	

* *P* value for trend, other *P* value refers to tests for heterogeity.

Table 12. Results of multivariate analysis

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 (years)		
< 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.

External beam radiotherapy does not prevent the simultaneous administration of radioiodine, although ^{131}I should be given first whenever possible as uptake may be diminished after EBRT and, if there is good uptake by the tumour, EBRT may become unnecessary. However, 20% of differentiated thyroid carcinomas fail to concentrate iodine sufficiently to be of therapeutic benefit [30]. Furthermore, ^{131}I alone is unlikely to destroy bulky residual disease unless a very high absorbed dose is achieved. Dosimetry studies at the RMH using quantitative scanning and positron emission tomography have shown 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, therapeutic administration is ineffectual [31]. Maxon and colleagues [32] 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 2 g).

Complete surgical extirpation, if at all feasible, is therefore advocated to achieve cure with subsequent radioiodine ablation; ^{131}I therapy should follow if the residual tumour concentrates radioiodine. Absorbed doses less than 100 Gy are unlikely to sterilise the tumour [31, 32]. Radical dose EBRT should then be considered. Inoperable disease usually carries a poor prognosis, but radical dose EBRT will palliate distressing local symptoms, and a significant proportion of patients may achieve complete regression with prolonged survival. In the future, novel fractionation schedules may further improve local control [33].

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