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Prognosis and Morbidity After Total Thyroidectomy for Papillary, Follicular and Medullary Thyroid Cancer

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Abstract—*The prognosis and the morbidity results after total thyroidectomy are reported for* 148 *patients with differentiated thyroid cancer. Ninety-two patients* (62%) *had papillary cancer*, 27 (18%) *had follicular cancer and* 29 (20%) *had medullary cancer. In the latter group*, 16 *patients had no clinical signs of a tumour and underwent total thyroidectomy after elevated calcitonin levels were found in a family screening programme. The mean follow-up period was* 9.7 *years in the present series. The* 5- *and* 10-*year overall survival in the patient group with papillary cancer was* 97% *and* 95% *respectively, in the group with follicular cancer it was* 78% *and* 50% *respectively and in the group with medullary cancer it was* 91% *and* 82% *respectively. Significantly associated with reduced disease-free survival were: extrathyroidal growth* ($P < 0.0001$), *distant metastases at diagnosis* ($P < 0.0001$), *follicular histology* ($P < 0.0001$), *age over* 40 ($P < 0.001$) *and male sex* ($P < 0.05$). *In patients with papillary cancer, recurrences were in most cases located in the neck, while recurrences at distant sites were encountered more frequently in patients with follicular or medullary cancer. Accidental permanent unilateral recurrent laryngeal nerve palsy were registered in* 1.4% *of the nerves at risk; all on the side of the tumour. Permanent hypoparathyroidism was present in* 4% *of the patients.*

INTRODUCTION

FOR DECADES the surgical literature on differentiated thyroid cancer has been dominated by controversies on surgical treatment. In particular, the discussion about the extent of thyroid resection has not yet come to an end. The incidence of differentiated thyroid cancer is low and it generally runs an indolent course [1–4]. This hampers the execution of controlled clinical trials. Most retrospective studies present limited and/or heterogeneous material and thus these studies have limited value in the determination of the optimal surgical treatment for patients with differentiated thyroid cancer. Total thyroidectomy is generally accepted as the best treatment for medullary thyroid cancer. If a surgeon is able to perform total thyroidectomy with a minimal chance of morbidity, it is also considered the optimal treatment for patients with papillary and follicular cancer [5–12]. However, satisfactory results have been reported in patients with papillary and follicular cancer with less extensive procedures than total thyroidectomy [2, 13–25].

In the present study total thyroidectomy as standard treatment in patients with papillary, follicular and medullary thyroid cancer was evaluated retrospectively. Results expressed as disease-free survival and postoperative morbidity were analysed; risk factors for survival were taken into account [1–4, 26–28].

PATIENTS AND METHODS

Patients

Between January 1966 and December 1982 total thyroidectomy was performed in 167 patients with differentiated thyroid cancer in the Leiden University Hospital, either primarily (41%) or after initial surgical treatment elsewhere (59%). Patients whose disease recurred after initial incomplete surgical treatment and before the total thyroidectomy was completed were excluded ($n = 19$) from the analysis. Thus, 148 patients formed the basis of the present analysis. Histological slides were reviewed and classified according to the WHO criteria [29] as previously reported [26]. Staging of the disease was recorded according to the UICC postoperative

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pTNM system [28]. Follow-up ended in July 1987 and was complete in 98% of the patients. The follow-up period ranged from 5 years to 21 years (mean 9.7 years). The 5- and 10-year overall survival in the patient group with papillary cancer was 97% and 95% respectively, in the group with follicular cancer it was 78% and 50% respectively and in the group with medullary cancer it was 91% and 82% respectively.

Treatment

The surgical technique for the total thyroidectomy was comparable to the one described by Thompson *et al.* [5]. Identification of the recurrent laryngeal nerve and parathyroid glands on both sides was standard practice. During the operation the pretracheal lymph nodes were removed *en bloc* with the thyroid. The tracheoesophageal groove was carefully inspected and tissue suspected for cancer was resected. In patients with medullary cancer all tissue in the tracheoesophageal groove was routinely resected. Regional lymph nodes macroscopically suspicious for cancer were removed by local excision. Those patients with extrathyroidal growth or residual uptake of ^{131}I, detected by a postoperative scan, received an ablation dose of ^{131}I. Minimal uptake was present in 58% of the patients, 19% had 3–10% uptake and 5% of the patients had more than 10% uptake. No postoperative scan was performed in 18% of the patients. In the group of patients treated by total thyroidectomy in one session in the University Hospital Leiden ($n = 52$), less than 10% ($n = 5$) had more than 3% ^{131}I uptake on postoperative scan. All the patients received thyroid hormone postoperatively in TSH suppressive doses. All patients underwent indirect laryngoscopy preoperatively as well as postoperatively to test the mobility of the vocal cords. Patients who developed clinical symptoms of hypoparathyroidism and/or definite hypocalcaemia postoperatively were treated with calcium and/or dihydrotachysterol. All patients who required treatment with calcium and/or dihydrotachysterol over 6 months after surgery were considered to have permanent hypoparathyroidism. The function of the parathyroid glands in patients who had normal postoperative levels of serum calcium was not tested. In none of the patients with supposed hypoparathyroidism therapy was actively withdrawn for a period of time.

Statistics

Disease-free survival was calculated after the operation; the following events were used as endpoints: recurrence (after initially successful treatment) or progressive disease. Patients whose disease progressed after initial treatment were considered to have a disease-free survival of less than 1 month. Survival was summarized in Kaplan–Meier curves; differences were compared using the log-rank test [31].

RESULTS

Table 1 shows the distribution of risk factors for prognosis in the 148 patients in relation to the histological diagnosis. The mean age in the group with medullary cancer was 38.1 years, in the group with papillary cancer 45.4 years and in the group with follicular cancer it was 53.6 years. Males and females were almost equally distributed in the group with medullary cancer. In the two other groups the female-to-male ratio was 7:3. Only 4% of the patients with follicular cancer had regional lymph node involvement; a much higher rate was found in the group with papillary and medullary cancer: 40% and 55% respectively. The percentage of patients with distant metastases at diagnosis was highest

Table 1. Population description of 148 patients with differentiated thyroid cancer treated with total thyroidectomy

	Histology							
	Papillary		Follicular		Medullary		Total	
	n	%	*n*	%	*n*	%	*n*	%
Risk factors	92	62%	27	18%	29	20%	148	100%
Mean age (years)	45.4		53.6		38.1		45.8	
Male	26	28%	8	30%	14	48%	48	32%
Female	66	72%	19	70%	15	52%	100	68%
<pT4	71	77%	19	70%	27	93%	117	79%
pT4	21	23%	8	30%	2	7%	31	21%
pN−	55	60%	26	96%	13	45%	94	64%
pN+	37	40%	1	4%	16	55%	54	36%
pM0	86	93%	14	52%	28	97%	128	86%
pM1	6	7%	13	48%	1	3%	20	14%

in the group with follicular cancer: 48% vs. 7% and 3% in the group with papillary and medullary cancer respectively. The advanced stage of patients with follicular cancer resulted in a very poor overall survival rate as mentioned before. There was a relatively large number of young patients with medullary cancer in the present series. This was due to the fact that 19 patients (66%) belonged to three families with hereditary medullary thyroid cancer. Sixteen of these patients had no clinical signs of a tumour and were operated on the basis of elevated calcitonin levels found in a screening programme of these families. As a consequence fewer tumours with extrathyroidal growth (pT4) were encountered in the group with medullary cancer than in the group of patients with papillary or follicular cancer. Three patients with medullary cancer (10%) had a clinically bilateral involvement. Of the other 26 patients, 16 (62%) appeared to have multicentre bilateral cancer at a routine histological examination; 15 belonged to one of the families with MEN II. A bilateral tumour was present in seven patients with follicular cancer, in six of which it had been clinically suspected. In the group with papillary cancer, 86 patients (93%) had a unilateral tumour preoperatively; nine (10%) had microscopic foci in the opposite lobe at routine histological examination. A history of prior neck irradiation was found in 24 out of the 137 patients (in the other 11 patients no mention had been made of neck irradiation). In four of these patients (17%) bilateral cancer was found, which was occult in one.

Table 2 shows the disease-free survival. Patients over 60 had significantly more progressive disease than those under 40 ($P < 0.01$). Relatively more patients with progressive disease were found in the group with follicular cancer ($P < 0.001$), in the group with extrathyroidal growth ($P < 0.001$) as well as in the group with distant metastases at diagnosis (pM1) ($P < 0.001$). The 10-year disease-free survival rate was significantly higher in patients with tumour stage <pT4 and in those without distant metastases at diagnosis (both $P< 0.0001$). Patients under 40 ($P < 0.01$), females ($P < 0.05$) and patients with papillary or medullary cancer compared to patients with follicular cancer ($P < 0.0001$ and $P < 0.01$ respectively) had a better 10-year disease-free survival. There was no significant difference in 10-year disease-free survival between patients with or without metastases in regional lymph nodes of patients with papillary or follicular cancer. In the group with medullary cancer, however, four out of the six patients whose disease recurred had nodal involvement.

The first sign of recurrent disease was mainly found in the neck in patients with papillary cancer, whereas in patients with follicular cancer the disease recurred mainly at distant sites: seven vs. two and one vs. five respectively. Two patients with papillary cancer had recurrent disease centrally in the neck; in one patient there was no evidence of disease after treatment for 10 years, after which he died from a cause unrelated to thyroid cancer. In the other patient the disease is now progressive. Three pati-

Table 2. Disease-free survival and localization of recurrent disease related to risk factors in 148 patients with differentiated thyroid treated with total thyroidectomy

	Total		Disease-free period* 1 month†		1 year		5 years		10 years		Recurrence	
	n		*n*		*n*		*n*		*n*			
Risk factors	*n*	%	At risk	%	At risk	%	At risk	%	At risk	%	Neck *n*	Distant *n*
<40 years	56	38%	55	98%	54	96%	52	95%	27	91%	3	1
40–60 years	54	36%	51	94%	45	87%	39	79%	17	75%	3	6
>60 years	38	26%	33	87%	25	68%	20	62%	6	54%	4	4
Male	48	132%	44	92%	37	77%	32	70%	11	62%	5	6
Female	100	68%	95	95%	87	89%	79	86%	39	82%	5	5
Papillary	92	62%	90	98%	82	91%	75	85%	42	85%	7	2
Follicular	27	18%	20	74%	16	63%	13	51%	5	42%	1	5
Medullary	29	20%	29	100%	26	86%	23	86%	3	74%	2	4
<pT4	117	79%	114	98%	105	93%	97	90%	40	84%	7	9
pT4	31	21%	25	81%	19	64%	14	53%	10	53%	3	2
pN−	94	64%	88	94%	81	87%	71	83%	32	79%	5	7
pN+	54	36%	51	94%	43	80%	40	76%	18	72%	5	4
pM0	128	86%	128	100%	116	93%	105	88%	49	84%	10	9
pM1	20	14%	11	55%	8	45%	6	33%	1	17%	0	2

*Differences in 10-year disease-free survival were significant ($P < 0.05$) for all risk factors except for the nodal status.
†Taken as measure for progressive disease.

ents had recurrences laterally in the cervical nodes, which were all treated successfully by modified radical neck dissection. Another patient with papillary cancer had recurrent disease centrally as well as laterally in the neck and he died of the disease. One patient with follicular cancer had a local recurrence, which resulted in a tracheostomy and this patient was treated with external radiation. The patient currently has persistent but stable disease. Two patients with medullary cancer had a recurrence in the neck. In one it was located centrally in the neck and was successfully removed. The other patient developed cervical lymph node metastases which were removed by neck dissection. He died of an unrelated disease 2 years later.

Major postoperative complications are summarized in Table 3. Temporary paresis of the recurrent laryngeal nerve was found in five patients. Permanent paralysis was found in 16 patients. In six patients vocal cord paralysis was present preoperatively. In another six patients the nerve was sacrificed, because of extensive tumour growth. Two of these patients had bilateral permanent paralysis because of extensive tumour growth in both nerves resulting in tracheostomy. Accidental permanent unilateral paralysis of the recurrent laryngeal nerve was registered in four patients (3%): 1.4% of the nerves at risk. In these four patients the tumour was located on the side of the paralysis and in two the tumour was either large or showed extrathyroidal growth. Sixteen patients suffered postoperative hypoparathyroidism, which was temporary in 10 and permanent in six patients (4%). In five of these six patients the surgeon claimed to have identified at least two parathyroid glands. One of the six patients with permanent hypoparathyroidism had a non-radical operation, in one patient an extensive local tumour growth was found and three other patients underwent concomitant lymph node dissections. Two patients suffered from lesions of the accessory nerve after neck dissection. Postoperative bleeding occurred in two patients, complicated by a wound infection in one.

DISCUSSION

Surgery is widely considered as the mainstay in the treatment of differentiated thyroid cancer. The extent of thyroid resection is, however, controversial. Total thyroidectomy seems to be the optimal procedure in the view of many surgeons, but the risk of serious surgical morbidity and the relatively indolent behaviour of the disease have led others to believe in more conservative surgery [2, 13–25]. Total thyroidectomy was standard treatment in our series of patients with differentiated thyroid cancer. The aim of the study was to evaluate treatment results of these patients and to assess the acceptability of total thyroidectomy in terms of postoperative morbidity.

Table 3. Accidental permanent complications after total thyroidectomy in 148 patients with differentiated thyroid cancer

Complication	*n*	%
Recurrent laryngeal nerve palsy	4	3
Hypoparathyroidism	6	4

Although total thyroidectomy is generally accepted as the treatment of choice in medullary thyroid cancer, it is a matter of dispute for all cases of follicular lesions and especially those of the papillary type. The discussion focuses on patients with unilateral papillary cancers or unilateral follicular lesions with minimal capsular and vascular invasion because the prognosis in these patients is quite favourable [1, 2, 15, 32]. Nevertheless, the death rate is not zero and despite the identification of several prognostic factors [1–4, 26–28], it is difficult to predict the clinical course of the disease in the individual patient. The controversies as regards surgical treatment have been kept alive by the absence of prospective studies, so that all data are suspect. The low incidence rate and the usually indolent biological behaviour hampers the collection of such data as survival of patients with differentiated thyroid cancer.

Advocates of routine total thyroidectomy argue that the incidence of multiple tumour foci is high. In MEN II patients medullary thyroid cancer is generally multifocal and bilateral [33, 34], which was confirmed in the present series. In papillary and less frequently in follicular cancer multifocal disease occurs: in 30–80% [7, 11, 35, 36]. In the present study 10% of the patients with clinically unilateral papillary cancer had microscopic foci in the opposite lobe at routine histological examination. Total thyroidectomy, therefore, minimizes the chance of local recurrences which give a less favourable prognosis [27, 35, 37]. Moreover, a residual tumour harbours a risk of dedifferentiation [35, 37, 38] and re-explorations in the neck for recurrent disease carry a substantial risk of surgical morbidity [39–41]. When a persistent or recurrent disease is present, it can be detected more easily by thyroglobulin (Tg) or ^{131}I when all thyroid tissue is removed [42, 43].

Other surgeons advocate a less extensive surgical treatment: total lobectomy on the side of the lesion, isthmectomy and removal of the pyramidal lobe, i.e. hemithyroidectomy [2, 13–25]. This procedure may be performed with a subtotal lobectomy on the contralateral side leaving a small remnant of thyroid tissue in order to ascertain the function of the recurrent laryngeal nerve and the vascularization of the parathyroid glands on at least one side.

These authors object to the routine use of total thyroidectomy for papillary and follicular cancer because it has not been established that this results in higher survival rates. Multiple occult foci are judged biologically insufficient by the 'conservative' group and dedifferentiation of remaining tumour foci is thought to be exceptional [13]. Moreover, they emphasize that a true total removal of all thyroid tissue is seldom reached because postoperative ^{131}I scintigraphy is positive in many patients who underwent a 'total' thyroidectomy [7, 11, 44]. Tg assay and ^{131}I scintigraphy may still be used if normal thyroid tissue is left behind [14, 45]. Some authors even doubt the necessity of total thyroidectomy for large tumours or when there is bilateral involvement [14, 18, 19]. In the series of Rossi *et al.* [14] all the patients who died of a local recurrence originally presented with an extensive local disease, had an irresectable tumour or had distant metastases at initial operation. In their opinion none of these deaths could have been prevented by total thyroidectomy. They concluded that this procedure is not called for in patients with well-differentiated thyroid carcinoma.

In the present study the results of total thyroidectomy as the standard treatment in a consecutive series of 148 patients with papillary, follicular and medullary thyroid cancer are reported. Most patients come from the same part of the country, which resulted in an almost complete follow-up (98%). We chose to use disease-free survival rate in the evaluation of the results, because the mean follow-up period was relatively short for overall survival: 9.7 years [3, 4, 14, 15]. Risk factors for survival as identified by others also appeared to be important in the present study [1–4, 26–28]. Advanced age, male sex, follicular subtype, extrathyroidal tumour growth and especially the presence of distant metastases at diagnosis were significantly associated with impaired disease-free survival. As seen by other authors [2, 21, 46], a tumour recurred mostly in the neck in the patients with papillary cancer, whereas the tumour recurred more frequently at distant sites in the patients with follicular or medullary cancer. The disease-free survival in the group with follicular cancer was low, which can be attributed to the fact that almost half the patients had distant metastases at the time of diagnosis. Over 25% of the patients with follicular thyroid cancer did not reach a disease-free status. The 10-year disease-free survival was high in the group with medullary cancer. This was probably caused by the fact that 66% of the patients belonged to families with hereditary thyroid cancer; 84% of these patients had no clinical signs of thyroid malignancy and cancer was detected by elevated serum calcitonin levels [47]. The issue of regional lymph node metastases has been described elsewhere [48, 49].

The main objection to the routine use of total thyroidectomy is the higher incidence of accidental palsy of the recurrent laryngeal nerve and permanent hypoparathyroidism. In experienced hands these complications occur after total thyroidectomy in less than 2% of the patients [6–9, 11, 12], and Clark *et al.* [7, 8] concur that, if these complications occur not just incidentally, total thyroidectomy should not be performed on a routine base. Permanent recurrent laryngeal nerve palsy generally occurs in less than 2% of the patients. Higher rates of recurrent laryngeal nerve palsies after total thyroidectomy have also been reported ranging from 3% to 11% of the patients [11, 17, 50]. When looking at the number of nerves at risk, which is relevant in the comparison of unilateral with bilateral procedures, a percentage of 2–7% is not uncommon [22, 41, 51]. In the present study 1.4% of the recurrent laryngeal nerves at risk was permanently damaged by accident. Foster found an incidence of 8% permanent hypoparathyroidism after total thyroidectomy for thyroid cancer in an extensive study, in which 24,108 thyroid operations were reported [52]. We recorded permanent hypoparathyroidism in 4%, mostly occurring in patients with extensive tumour growth in the neck or in patients who underwent concomitant neck dissection. In studies where only a limited number of patients underwent total thyroidectomy, the incidence of permanent hypoparathyroidism is higher: 6–29% [16, 17, 23–25, 35, 51]. The parathyroid glands are especially at risk when a resection of paratracheal lymph nodes is performed [10, 40, 44, 48, 49, 53]. Some authors have shown that the incidence of postoperative morbidity decreases when surgeons have acquired more experience with the total thyroidectomy [6, 12, 54]. Recently, further efforts have been made to reduce the complication rate to a minimum. When a recurrent laryngeal nerve is surrounded by tumour and still functioning, an attempt is made to save the nerve. Mass clamping of the vessels of the superior pole of the thyroid lobe is avoided in order to save the external branch of the superior laryngeal nerve [5, 55]. In the dissection of the thyroid, magnification techniques and bipolar coagulation are nowadays used in order to minimize unwanted lesions to surrounding tissues [8, 54]. When the vascularization of a parathyroid is thought to be impaired, the gland is removed, sliced and autotransplanted in the sternocleidomastoid muscle [56, 57]. Postoperative morbidity is expected to decrease in our hospital because of these refinements.

Most patients with differentiated thyroid cancer will do well and a small percentage will die whatever treatment is applied. Between these extremes, there is a number of patients who will benefit from more extensive treatment. In the present study no

comparison was made between different treatment regimens. Total thyroidectomy can be performed with a minimal complication rate and therefore, we continue to believe that this operation followed by ^{131}I ablation, if necessary, is the optimal treatment for clinical papillary, follicular, medullary thyroid cancer and occult medullary thyroid cancer detected by elevated serum calcitonin levels. Less than total thyroidectomy, i.e. hemithyroidectomy, is acceptable when postoperative hypoparathyroidism can be prevented in a patient with a small unilateral intracapsular papillary or follicular carcinoma [58].

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