

Influence of surgical and postoperative treatment on survival in differentiated thyroid cancer

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Background: The extent of thyroidectomy in patients with differentiated thyroid cancer (DTC) remains controversial. The aim of this study was to identify how surgical technique and postoperative treatments influence survival and locoregional recurrence in DTC.

Methods: A nested case-control study was conducted in a cohort of 5123 patients diagnosed with DTC in Sweden between 1958 and 1987. One matched control subject was selected randomly for each patient who died from DTC. Details regarding surgery and postoperative treatments were obtained from medical records. The effect of treatment on survival was estimated by conditional logistic regression.

Results: Patients not treated surgically had a poorer prognosis, but the risk of death from DTC was not affected by the choice of surgical technique. The extent of surgery influenced survival only in patients with TNM stage III disease. Locoregional recurrence resulted in a fivefold increased risk of death. Postoperative treatment was not associated with improved survival.

Conclusion: In operated patients, the most important prognostic factor was complete removal of the tumour. The extent of removal of remaining thyroid tissue was of prognostic importance in stage III disease only. Adjuvant postoperative treatment did not influence the prognosis favourably.

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Introduction

The prognosis for patients with non-medullary differentiated thyroid cancer (DTC) is excellent, with a 10-year survival rate greater than 90 per cent¹. Survival is influenced by tumour node metastasis (TNM) stage, histopathological findings and completeness of surgery².

The primary treatment for patients with DTC is thyroidectomy, but there is still disagreement regarding the extent of surgery³⁻⁵. This is due mainly to a lack of prospective randomized controlled trials comparing the extent of thyroidectomy and the use of postoperative treatments such as radioactive iodine. Because of the low incidence and favourable prognosis of patients with DTC, an adequate assessment of treatment effects requires multi-institutional collaboration and large study populations. Differences in methodology, patient selection and duration of follow-up, together with low statistical precision because of the small numbers of patients, make it difficult to compare studies and interpret results. Relatively extensive

surgery seems to be associated with lower recurrence and mortality rates³. The question of whether ablative postoperative treatment with radioactive iodine is of any benefit in terms of prognosis is controversial⁶⁻⁹.

In patients with a high risk of locoregional recurrence following a poor response to radioactive iodine, external radiotherapy may improve local control. Traditionally, radiotherapy was given to patients with inoperable, locally advanced disease and to those with distant bone or brain metastases^{10,11}. Chemotherapy is not a standard treatment for DTC, and is usually reserved for patients with severe metastatic disease. There is still no published evidence that chemotherapy improves survival in patients with metastatic thyroid disease^{12,13}.

The authors have shown previously that survival in DTC is strongly determined by TNM stage, subclassification of histopathological findings and completeness of surgery. The aim of this study was to identify how the extent of surgery and postoperative treatments, such as radioactive

iodine, external radiotherapy and chemotherapy, influence survival and locoregional recurrence in patients with DTC.

Patients and methods

All Swedish residents are assigned a unique national registration number that is used to index health registers. Since the nationwide Swedish Cancer Registry (SCR) was established in 1958, it has been mandatory for clinicians, cytologists and pathologists to report detected tumours. In the interval to 1978, the proportion of all thyroid cancers reported to the SCR was estimated as 98 per cent¹⁴; coverage is now considered to be close to 100 per cent¹⁵. The SCR does not register tumours for which the sole source of information is the death certificate. Tumours detected incidentally at autopsy were excluded from the present study.

From 1958 to 1987, when Sweden had 8.4 million inhabitants, 7906 thyroid cancers were reported to the SCR. After excluding 1405 patients (17.8 per cent) with anaplastic and medullary thyroid cancers and 947 (12.0 per cent) with follicular thyroid adenomas, 5554 individuals with DTC remained, of whom 5123 had survived for at least 1 year after diagnosis. Matching of these 5123 patients with the Swedish Causes of Death Register for 1959–1999 identified 693 patients (potential cases) for whom thyroid cancer was reported as the cause of death.

Data on histopathological findings, growth patterns, tumour differentiation, surgical procedures and findings at follow-up were abstracted from the case records of these 693 patients. A group of three specialists (a cardiologist, an oncologist and an endocrine surgeon) independently evaluated the medical records to confirm DTC as the cause of death. Cause of death was reclassified for 42 patients (6.1 per cent) who died from cardiovascular disease (22), other cancer (11) or thyroid cancer other than DTC (nine). A further 36 potential cases were excluded because the medical records could not be found, and another 14 because the initial diagnosis was made before 1958, leaving a total of 601 cases. A nested case–control study with time from diagnosis as the timescale was generated by randomly sampling one control for each case, matched for age at diagnosis (5-year age groups), sex and 10-year calendar periods of diagnosis. Of the control subjects initially selected, medical records could not be located for 26, and a further 26 had not actually had DTC. A second control was therefore randomly selected for these 52 cases. Because of missing records, a third control had to be randomly selected for three of these cases. Six of the patients were aged over 90 years at diagnosis and had to be

excluded because no matching control could be identified, leaving 595 sets of cases and controls in the analysis.

Histopathology

Two specialists, blinded with respect to case–control status, independently classified histopathological findings based on the histopathology reports. If the report lacked subgroup information, the specimens were re-examined by one experienced pathologist. All tumours were also classified as being well, intermediately or poorly differentiated¹⁶, and restaged according to the 2002 TNM classification¹⁷.

Surgery

The extent of thyroidectomy was classified from the surgeon's report in the case record according to the following definitions. Biopsy refers to the removal of a small piece of tumour for histopathological classification. Resection (lumpectomy) involves removal of the tumour with minimal surrounding thyroid tissue, either unilaterally or bilaterally. Lobectomy (or hemithyroidectomy) refers to removal of the entire lobe, whereas lobectomy and resection also includes resection of the isthmus. Total thyroidectomy (or near-total thyroidectomy) is the extracapsular removal of both lobes and isthmus, leaving no visible thyroid tissue, whereas in subtotal thyroidectomy some thyroid tissue may be left, mainly to avoid damaging the recurrent laryngeal nerve. If repeat surgery was performed within 3 months of the initial operation, this was scored as a single surgical procedure. A record was also made of whether or not the surgeon was aware of the malignant diagnosis before surgery, classified as 'yes', 'no' or 'suspected'.

All information on lymph node surgery was recorded and subclassified according to the surgical and histopathological reports. Node picking refers to an operation in which only grossly affected lymph nodes are removed. Modified (or functional) neck dissection includes removal of all fibrous and fatty tissue including the lymph nodes, but preserves the sternomastoid muscle, internal jugular vein, vagus nerve, spinal accessory nerve and sensory nerves, either unilaterally or bilaterally. Radical neck dissection also includes removal of the latter structures. Central neck dissection includes removal of all lymph nodes pre-tracheally and adjacent to the tumour (all lymph nodes between the carotid arteries).

The completeness of surgical excision was based on information from the surgical and histopathological reports, as well as the presence of metastases. A resection

was regarded as complete even when unaffected thyroid tissue was left in the neck, provided it was considered that the tumour had been completely removed and the resection margins were free from tumour cells.

Postoperative treatment

Radioactive iodine therapy was recorded in terms of the interval between surgery and treatment, the amount of radioactive iodine administered and the number of treatments. External radiotherapy and chemotherapy were recorded whenever administered. Information about postoperative thyroxine suppressive treatment was incomplete, so these data were not included in the statistical analysis.

Locoregional recurrence

Locoregional recurrence was defined as recurrence diagnosed more than 3 months after a successful initial treatment. A second locoregional recurrence was considered only in patients who had undergone curative treatment of the first recurrence.

Statistical analysis

Conditional logistic regression, with matching for age at diagnosis, sex and calendar period, was used to determine odds ratios (ORs) of death from DTC with 95 per cent confidence intervals (c.i.). Univariable analyses were followed by multivariable analysis for various factors, such as histopathological findings, TNM stage, postoperative treatment and type of surgery. Statistical significance at a 95 per cent level was considered when the confidence interval did not include 1.0. Interaction effects were estimated when interactions were suspected from a clinical point of view (for example, more extensive surgery in patients with lymph node metastases or more advanced stage).

Results

The mean age at diagnosis in the 595 sets of cases and controls was 63.8 years. Some 391 sets were female and 204 sets male, giving a female: male ratio of 1.9:1, compared with a ratio of 3:1 in the entire cohort of patients with DTC during the study period¹. The mean duration of follow-up (that is, survival) for the cases was 6.7 years.

Thyroid surgery

Most patients underwent thyroid surgery (cases 82.7 per cent, controls 92.1 per cent) (*Table 1*). The risk

of death from DTC in patients who had no thyroid surgery was 2.9 times higher than in those who had surgery. After adjusting for all other therapies, such as chemotherapy, radioactive iodine and external radiotherapy, this risk decreased slightly, but remained significant (OR 2.4 (95 per cent c.i. 1.3 to 4.4)). Almost half of the patients had a total thyroidectomy (cases 43.5 per cent, controls 45.9 per cent) (*Table 1*); the risk of death in these patients was similar to that in patients who had another type of thyroid resection, except for subtotal thyroidectomy, which was associated with an increased risk of death from DTC (OR 2.2 (95 per cent c.i. 1.2 to 5.0)). Adjustment for TNM stage did not result in any significant difference, except in patients who had a subtotal thyroidectomy (*Table 1*). In a second step (data not shown), an analysis was undertaken according to grouping by unilateral resection, bilateral resection or total thyroidectomy. In a third step, total thyroidectomy was compared with all surgical procedures. The extent of surgery did not affect mortality in either of these analyses, regardless of whether the different surgical procedures were analysed individually or in subgroups (*Table 1*).

To compare the prognosis for total thyroidectomy with that for other thyroidectomies within each TNM stage, interaction effects between TNM stage and type of surgery were estimated. The surgical procedures were equally distributed for each stage (*Table 2*). Patients with TNM stage III and a subtotal operation had a 50 per cent increased risk of death from DTC compared with those having a total thyroidectomy. For patients with TNM stage I and II tumours, survival was independent of the type of thyroid surgery. For TNM stage IV there was a non-significant decrease in the risk of death from DTC when a subtotal operation was performed (*Table 2*).

The mortality rate from DTC was slightly higher when the surgeon did not know of the cancer diagnosis before surgery (OR 1.7 (95 per cent c.i. 1.0 to 2.8)). When the surgeon had a clinical suspicion of DTC, the risk of death was lower (OR 0.6 (95 per cent c.i. 0.5 to 0.9)). After adjusting for completeness of surgery, TNM stage, histological type and other treatment, these values remained significant (data not shown).

Lymph node surgery was performed in equal proportions of cases (52.1 per cent) and controls (51.4 per cent) (*Table 1*), indicating that the procedure itself was not related to prognosis. A large proportion of operations were node-picking procedures (29.7 per cent of cases, 35.6 per cent of controls). Fifteen patients underwent radical neck dissection. Bilateral modified neck dissection was associated with a significantly poorer prognosis than node picking (OR 4.2 (95 per cent c.i. 1.5 to 11.4)), but adjustment for

Table 1 Influence of type of surgery on survival of patients with differentiated thyroid cancer

	Cases* (n = 595)	Controls* (n = 595)	Univariable analysis†	Multivariable analysis†
			OR#	OR**
Thyroid surgery				
Yes	492 (82.7)	548 (92.1)	1.0	1.0
No‡¶	103 (17.3)	47 (7.9)	2.9 (1.8, 4.7)	2.8 (1.5, 5.4)
Thyroid procedure				
Total thyroidectomy	259 (43.5)	273 (45.9)	1.0	1.0
Unilateral resection	31 (5.2)	37 (6.2)	0.9 (0.5, 1.5)	1.5 (0.8, 2.9)
Bilateral resection	17 (2.9)	28 (4.7)	0.7 (0.4, 1.3)	0.8 (0.4, 1.7)
Lobectomy	84 (14.1)	121 (20.3)	0.7 (0.5, 1.1)	0.9 (0.6, 1.4)
Lobectomy and resection	68 (11.4)	71 (11.9)	1.0 (0.7, 1.5)	1.2 (0.8, 1.9)
Subtotal thyroidectomy	33 (5.5)	18 (3.0)	2.2 (1.2, 5.0)	2.2 (1.1, 4.6)
Biopsy	23 (3.9)	12 (2.0)	2.4 (1.2, 4.9)	2.3 (1.0, 5.1)
Total thyroidectomy	259 (43.5)	273 (45.9)	1.0	1.0
All subtotal procedures	233 (39.2)	275 (46.2)	0.9 (0.7, 1.2)	0.9 (0.7, 1.2)
Unknown and biopsy‡	27 (4.5)	16 (2.7)	2.6 (1.5, 4.6)	2.6 (1.7, 4.0)
Lymph node surgery§				
Yes	310 (52.1)	306 (51.4)	1.0	1.0
No	249 (41.8)	272 (45.7)	1.0 (0.8, 1.2)	1.1 (0.9, 1.5)

Values in parentheses are *percentages (calculated from the total number of cases and controls, including those with incomplete information) or †95 per cent confidence intervals. Data missing for ‡eight patients and §53 patients; ¶107 never had an operation. Odds ratio (OR) adjusted for #matching variables (age, sex and calendar period) and **tumour node metastasis stage.

Table 2 Influence of type of surgery and tumour node metastasis stage on survival of patients with differentiated thyroid cancer

TNM stage	Total thyroidectomy*	Subtotal procedures*	Odds ratio†
I and II	193 (45.0)	212 (49.4)	1.0 (0.6, 1.5)
III	239 (46.0)	239 (46.0)	1.5 (1.0, 2.3)
IV	89 (42.6)	53 (25.4)	0.5 (0.2, 1.2)
Total	521	504	

Values in parentheses are *percentages (calculated from the total number of cases and controls, including those with incomplete information) or †95 per cent confidence intervals. Data on type of surgery and tumour node metastasis (TNM) stage were missing for eight and 33 patients respectively.

TNM stage eliminated this difference (data not shown). A comparison between node picking and any other kind of neck dissection procedure indicated a significantly better prognosis for patients in the node-picking group, although this difference was also lost after adjustment for TNM stage (data not shown).

Postoperative treatment

External radiotherapy was given to 48.7 per cent of cases, compared with 25.5 per cent of controls. Patients who had radiotherapy were more likely to die from DTC (OR 2.9 (95 per cent c.i. 2.2 to 3.8)). This risk remained after adjustment for TNM stage and other

postoperative treatments (Table 3). Sixty-nine patients with DTC received chemotherapy and for these patients the association with death from DTC was almost six times greater. Adjustment for type of surgery and other treatment modalities reduced this risk, but the difference was still significant (Table 3).

Radioactive iodine was given to more than half of the cases (50.8 per cent) but to only 41.5 per cent of controls. The risk of dying was thus greater when radioactive iodine was given, even after adjusting for TNM stage, completeness of resection and other treatments (Table 3). To determine whether this was due to biased selection, the effect of radioactive iodine was estimated in different models containing interactions of TNM stage, completeness of surgical excision and total *versus* subtotal thyroidectomy (data not shown). No interaction effects were found to explain these results. Neither the radioactive iodine dosage nor the number of treatments was evaluated in this study.

Locoregional recurrence

The number of locoregional recurrences differed greatly between cases (329) and controls (112) (Table 4). Locoregional recurrence was associated with surgical technique and completeness of surgical excision. Adjuvant postoperative treatment and TNM stage did not influence the risk of recurrence. The risk of death from DTC was five

Table 3 Influence of postoperative treatment on survival of patients with differentiated thyroid cancer

	Cases* (n = 595)	Controls* (n = 595)	Univariable analysis†	Multivariable analysis†	
			OR#	OR**	OR††
External radiation‡					
Yes	290 (48.7)	152 (25.5)	2.9(2.2, 3.8)	2.1(1.6, 2.9)	2.6(1.8, 3.8)
No	252 (42.4)	409 (68.7)	1.0	1.0	1.0
Chemotherapy§					
Yes	58 (9.7)	11 (1.8)	5.7(2.9, 11.2)	5.7(2.7, 12.3)	2.4(1.1, 5.3)
No	470 (79.0)	551 (92.6)	1.0	1.0	1.0
Radioactive iodine¶					
Yes	302 (50.8)	247 (41.5)	1.8(1.4, 2.2)	1.5(1.1, 1.9)	1.4(1.1, 1.8)
No	216 (36.3)	342 (57.5)	1.0	1.0	1.0

Values in parentheses are *percentages (calculated from the total number of cases and controls, including those with incomplete information) or †95 per cent confidence intervals. Data missing for ‡87, §100 and ¶83 patients (included in the analysis). Odds ratio (OR), adjusted for #matching variables (age, sex and calendar period), **tumour node metastasis stage, and ††postoperative treatment, type of thyroid surgery and completeness of surgical excision.

Table 4 Influence of locoregional recurrence on survival of patients with differentiated thyroid cancer

	Cases* (n = 595)	Controls* (n = 595)	Univariable analysis†	Multivariable analysis†		
			OR§	OR¶	OR#	OR**
First LRR‡						
Yes	329 (55.3)	112 (18.8)	5.3 (3.9, 7.1)	4.9 (3.5, 6.9)	4.5 (3.2, 6.2)	5.1 (3.7, 7.0)
No	216 (36.3)	447 (75.1)	1.0	1.0	1.0	1.0
Second LRR						
Yes	121 (20.3)	29 (4.9)	5.4 (3.4, 8.6)	6.0 (3.5, 10.3)	4.9 (2.9, 8.3)	6.1 (3.7, 10.1)
No	329 (55.3)	480 (80.7)	1.0	1.0	1.0	1.0

Values in parentheses are *percentages (calculated from the total number of cases and controls, including those with incomplete information) or †95 per cent confidence intervals. ‡Data missing for 86 patients. Odds ratio (OR), adjusted for §matching variables (age, sex and calendar period), ¶(tumour node metastasis stage, #complete surgical excision and **postoperative treatment (chemotherapy, external radiotherapy and radioactive iodine treatment). LRR, locoregional recurrence.

times greater for patients with locoregional recurrence, and remained after adjusting for initial TNM stage, completeness of surgical excision and postoperative treatment (Table 4). Among patients with a locoregional recurrence, 36.8 per cent of cases and 25.9 per cent of controls had a second locoregional recurrence; the risk of death from DTC was still five times higher (Table 4).

The association between locoregional recurrence and various surgical procedures was modelled separately (Table 5). In patients with locoregional recurrence, the risk of death from DTC was twice as high following a subtotal operation than after a total thyroidectomy (data not shown).

Discussion

In this nested case-control study of the impact of treatment on prognosis for DTC, thyroid surgery itself was found to be important for survival, although the

type of surgical procedure was of minor importance. Lymph node surgery was not related to prognosis. In patients who had less extensive thyroid surgery (subtotal thyroidectomy), the risk of death following locoregional recurrence was greater than that in patients who had a total thyroidectomy. Postoperative treatment (radioactive iodine, external radiotherapy or chemotherapy) was not associated with improved survival.

The data retrieved for both cases and controls included histopathological and surgical reports, clinical variables and reports on the accuracy of the cause of death. This enabled an adjustment for most of the factors that potentially influence prognosis. Information was obtained from case records, treatment charts and histopathological reports in a blinded fashion, making differential misclassification of exposure unlikely.

A potential weakness of the study was the incomplete information and missing data in some of the case reports. Because the information about prescribed peroral

Table 5 Interaction model showing the estimated effect of locoregional recurrence after total and subtotal thyroidectomy on survival

	LRR		No LRR		Univariable analysis	Multivariable analysis		
	CSE	No CSE	CSE	No CSE	OR†	OR‡	OR§	OR¶
Total thyroidectomy	98	84	242	58	6.0(3.7, 9.6)	5.9(3.5, 9.8)	4.8(2.9, 7.8)	6.2(3.8, 10.2)
All subtotal procedures	94	111	194	77	8.6(5.4, 13.8)	6.7(4.1, 11.0)	7.5(4.5, 12.4)	7.9(4.8, 13.0)
Unknown	2	39	5	71	0.7(0.3, 1.5)	0.6(0.2, 1.8)	0.6(0.2, 1.5)	0.6(0.2, 1.4)
Total*	194	234	441	206				

Values in parentheses are 95 per cent confidence intervals. *Data missing for 115 patients. Odds ratio (OR), adjusted for †matching variables (age, sex and calendar period), ‡tumour node metastasis stage, §complete surgical excision and ¶postoperative treatments (chemotherapy, external radiotherapy and radioactive iodine therapy), LRR, locoregional recurrence; CSE, complete surgical excision.

medicine taken by patients was incomplete, the effect of postoperative thyroxine treatment could not be evaluated. However, the missing data on thyroxine were distributed equally. There was considerable variation in the quality of medical records and surgical reports over the study period and between different hospitals, which could have influenced the results. However, there was no reason to believe that possible misclassifications might be distributed unevenly between cases and controls. A non-differential misclassification would, in any case, bias the results towards the null. This means that the differences between cases and controls will, if anything, be underestimated.

Based on the results of this study, the authors recommend that more extensive thyroid surgery would improve survival in patients with stage III disease. Survival was not influenced by surgical technique for patients with stage I, II and IV disease. A crucial factor was the completeness of tumour excision^{5,18}. In several patients, complete removal of the tumour was not possible because of extensive growth, but the beneficial effect of complete resection was evident even in patients with stage I or II disease. The risks and benefits of total thyroidectomy^{4,19} should be considered when deciding on appropriate treatment. Compared with total thyroidectomy, a subtotal procedure was twice as likely to be followed by locoregional recurrence. The correlation of locoregional recurrence and incomplete tumour removal with a worse prognosis would appear to favour total thyroidectomy. Even after adjustment, the prognosis of DTC was significantly improved when the surgeon suspected cancer, possibly because he or she was then more meticulous in removing tissue.

Alternative procedures for lymph node surgery (such as lymph node picking, modified and radical neck dissections) did not differ significantly in their effects on survival. A previous study² highlighted the importance of lymph node metastases when assessing mortality risk in patients with DTC, especially those with papillary thyroid cancer (PTC). Surgery that includes removal of lymph nodes appears to be

rational, at least in patients with PTC. The identification of metastases is of prognostic importance, and their removal may improve survival.

No improvement in survival was found in patients who received external radiotherapy or chemotherapy, even after adjusting for TNM stage, completeness of surgical excision, type of thyroid surgery and postoperative treatment. This may be an instance of reverse causality, as radiotherapy and chemotherapy tend to be reserved as palliative measures for patients with large, or even irresectable, tumours or disease spread. This association implies that TNM stage does not completely capture the aggressiveness of the tumour.

Radioactive iodine was given after surgery to nearly half of the patients in this study, but was associated with poorer survival, even in those with early-stage tumours. Thus, radioactive iodine appeared unable to compensate for other risk factors, such as incomplete tumour removal or lymph node metastases. Any positive effects of radioactive iodine have focused mainly on disease-free survival²⁰.

The diagnosis of locoregional recurrence resulted in a fivefold increased risk of death from DTC. The performance of less extensive surgery in patients with TNM stage III disease significantly increased the mortality risk. Patients in whom less extensive thyroid and lymph node surgery was performed tended to have more locoregional recurrences and incomplete surgical excision. In the long term this would be likely to increase the mortality rate from DTC.

Provided the primary tumour can be removed radically, this study does not provide strong evidence that extensive surgery or postoperative treatment modalities benefit the survival of patients with DTC. However, as locoregional recurrence is associated with a significantly greater risk of death in patients with DTC, individualized therapy aimed at minimizing the risk of recurrence must be considered the treatment of choice. The lack of prospective randomized studies continues to make it difficult to determine the optimal treatment for patients with DTC.

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