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ORIGINAL ARTICLE

Differentiated thyroid cancer in a Swedish county – long-term results and quality of life

REBECKA R. MALTERLING[1], ROLAND E. ANDERSSON[1], STURE FALKMER[2], URSULA FALKMER[3], EVA NILÉHN[2] & JOHANNES JÄRHULT[1]

[1]*Department of Surgery, Ryhov Hospital, Jönköping, Sweden,* [2]*Department of Pathology, Ryhov Hospital, Jönköping, Sweden and* [3]*Department of Oncology, Ryhov Hospital, Jönköping, Sweden*

Abstract

Background. There is still no complete agreement about the proper treatment of differentiated thyroid cancer (DTC). *Material and methods.* All patients (n=130) with DTC in a defined population, treated with surgery between 1985 and 1999, were carefully followed up (median 13.1 years). Fifty three were operated with subtotal and 77 with total thyroidectomy. Twenty seven percent of the patients in the subtotal group and 56% of those in the total thyroidectomy group had postoperative radioiodine ablation. Thirty nine patients had papillary cancers incidentally detected during surgery for benign disorders (median size 7 (1–30) mm). Living patients answered the Swedish version of the SF-36 health survey. *Results.* Eleven of 106 patients considered tumour-free after primary surgery developed recurrences during follow-up. Fifteen patients (12%) died from DTC but only one within stage I–II (1.2%). No patient below 50 years of age at diagnosis died from DTC. Only three of 29 patients with isolated loco-regional spreading of their disease at the time of diagnosis have died from thyroid cancer. There was no statistically significant difference in the 10 year cancer-specific survival rate between those operated with subtotal or total thyroidectomy – irrespective of stage. Survival rate was significantly better for papillary than for follicular cancer. Mental and physical quality of life among patients treated for DTC were similar to the healthy Swedish population. *Conclusions.* Patients with DTC stage I–II (according to TNM) or low-risk (according to AMES) have an excellent prognosis. Treatment as well as follow-up should not be exaggerated.

Differentiated thyroid cancer, i.e. papillary and/or follicular carcinoma, is a rare disorder in general but one of the most common malignant neoplastic diseases in individuals below 40 years of age [1]. Despite an excellent prognosis with a 10-year-survival rate exceeding 90%, some patients do die of the disease, while some others have to live with sequelae after the initial treatment. The advocated treatment in patients with differentiated thyroid cancer has been total thyroidectomy, postoperative radioiodine remnant ablation and lifelong thyroxine replacement therapy, sometimes rendering the patient subtoxic [2–6]. However, the scientific evidence for such a routinely aggressive approach to these well-differentiated tumours is rather weak and some authors have proposed a more conservative treatment [7,8]. The purpose of the present study was to compare the long-term outcome and the quality of life in patients with papillary and follicular cancers after "aggressive" (total thyroidectomy and frequent radioiodine ablation) or "conservative" (subtotal thyroidectomy and occasional radioiodine ablation) treatment.

Methods

Patients

All patients with differentiated thyroid cancer from the County of Jönköping during the period 1985 to 1999 were identified from the Swedish Cancer Registry and from a registry at the local Department of Pathology, County Hospital Ryhov. All histopathological specimens were re-examined by one of the

Correspondence: Johannes Järhult, Department of Surgery, Ryhov Hospital, S-55185 Jönköping, Sweden. Tel: +46 36 321000. Fax: +46 36 321321. E-mail: johannes.jarhult@lj.se

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article's authors (E.N.). The county had approximately 320 000 inhabitants during the study period.

All hospital files were analysed for details of the surgical technique, radioiodine and thyroxine treatment as well as short- and long-term complications.

The patients were divided into two groups according to the extent of surgery. Those who underwent a total thyroidectomy, either in one session or as a two-step procedure, and those who had a subtotal thyroid resection, implying every operation with a thyroid tissue remnant >1 gram. Completion thyroidectomy was carried out in altogether 30 patients, of whom 28 had a microscopically radical, primary operation. The indication for surgery in these patients was the opinion of the responsible surgeons that complementary thyroidectomy was the golden standard in this situation. Seven of the completion thyroidectomies were performed in patients with incidental cancers.

Lymph node surgery was either performed as node-picking (n=31) or as unilateral neck dissection (n=13). If the DTC diagnosis was known preoperatively (either at the primary operation or at the completion thyroidectomy), lymph node surgery was carried out if careful bilateral palpation revealed any suspected lymph nodes. Nineteen tumours in stage I–II (23%) and 25 tumours in stage III–IV (51%) had lymph node surgery.

Radioiodine remnant ablation with 4 000 MBq was given to 57 patients (43%): 43 in the group treated with total (74%) and 14 in the group treated with subtotal thyroidectomy (26%). The treatment was decided upon by the responsible surgeon. Most often, radioiodine was given after the detection of a thyroid remnant on a postoperative scintiscan or to patients with stage 3–4 disease.

All patients were classified according to both the TNM-classification and the AMES score.

Follow-up

The patients were followed for 10 years postoperatively at the surgical outpatient departments and by the primary health care system thereafter. The endpoint for follow-up was December 31, 2008, death or emigration, giving a median follow-up of 13.1 (range 0.1–24) years. Hospital and primary health care charts were carefully reviewed and all recurrences and deaths were registered. The cause of death was classified as either due to thyroid cancer or as to other reasons. Complete autopsies were performed only by request from the responsible clinician.

Assessment of quality of life

Quality of life was measured with the Swedish version of the SF-36 health survey (Medical Outcome Study 36-item Short Form Health Status Survey), where the answers can be classified into eight health-status subscales: Physical Functioning, Physical Role Limitations, Bodily Pain, General Health Perception, Vitality, Social Functioning, Emotional Role Limitations, and Mental Health. From these eight scales it is possible to calculate a Physical and a Mental Component Summary.

The quality of life questions of SF-36 were sent to all patients that had been treated for clinically significant cancer and were alive in April 2007 (n=60), of whom 52 responded (87%). Patients with incidental cancers were not incorporated since we could not always found out from their charts if they had been informed about the finding of a cancer in the specimen. The results of SF-36 were compared with age- and sex- matched normal subjects from a large Swedish reference population [9–11].

Statistics

Cancer-free and cancer-specific survival time was measured from the date of resection to the date of recurrence or of death from thyroid cancer, respectively, with patients surviving to at least December 31, 2008, and two patients lost to follow-up being censored in survival analyses. Comparisons of overall survival time between strata of categorical variables were made by the Kaplan-Meier method and log rank test. The χ^2 test or Fishers exact test were used to evaluate the significance of differences in proportions, where appropriate. The level of statistical significance was taken as $p \leq 0.05$ and confidence intervals (CI) were set at 95%.

Since the quality of life questions in SF-36 are composed of alternatives that are ordered in categorical data, the scores in our paper were calculated with a method proposed by Svensson [12]. This method is mathematically and statistically correct compared to the method for computing the scores proposed in the SF-36 manual.

Ethics

The study was approved by the Regional Ethical Committee at Linköping University (M33-07).

Results

Some 134 patients diagnosed with differentiated thyroid cancer between 1985 and 1999 were identified, giving a yearly incidence rate of differentiated thyroid cancer of 2.8 per 100 000 inhabitants, which is similar to that of Sweden as a whole. Four patients were excluded from the study because of inability to undergo surgical intervention.

Table I. Patient characteristics in 130 cases of differentiated thyroid cancer treated with either total thyroidectomy (n=77) or subtotal thyroidecctomy (n=53).

	Total thyroidectomy n=77	Subtotal thyroidectomy n=53	p-value
Sex:			
Women	56 (73%)	36 (68%)	
Men	21 (27%)	17 (32%)	p=0.56
Median age (years):	55 (range 17–86)	61 (range 14–88)	
Type of cancer:			
FTC	25 (32%)	15 (28%)	
PTC	52 (68%)	38 (72%)	p=0.70
Accidental cancer:	11 (15%)	28 (53%)	p<0.001
Lymph node surgery:	35 (45%)	9 (17%)	p<0.001
Lymph node metastases:	26/35	4/9	p=0.12
Distant metastases:	5 (6%)	2 (4%)	p=0.7
Microscopic clear margins:	62 (81%)	47 (89%)	p=0.23
TNM-stage:			
1	31 (40%)	31 (58%)	
2	14 (18%)	5 (9%)	
3	22 (29%)	11 (21%)	
4	10 (13%)	6 (11%)	p=0.21
AMES-score:			
Low-risk	57 (74%)	40 (75%)	
High-risk	20 (26%)	13 (25%)	p=1

PTC= Papillary thyroid cancer; FTC=Follicular thyroid cancer.

The characteristics of the patients are presented in Table I. There were 92 women and 38 men, resulting in a female/male ratio of 2.4:1. Altogether, 77 patients (59%) underwent a total thyroidectomy and 53 patients (41%) had a subtotal operation.

In all, no less than 39 of the patients (30%) had a PTC which was accidentally detected at the time of surgery due to a preoperative benign thyroid or parathyroid disorder. Median size of these incidental cancers was 7 mm (range 1–30) and 15 had a diameter >10 mm. Four had lymph gland metastases. Incidental cancers were significantly more common among patients undergoing subtotal thyroidectomy. Similarly, lymph node surgery was performed significantly less often in this group. Apart from these two variables, all other patient characteristics were not significantly different between the two groups.

Cancer multifocality was detected in 16% of specimens.

Altogether 81 patients (62%) belonged to stage I–II and 49 patients (38%) to stage III–IV according to the TNM-classification. Ninety seven patients (75%) were considered as low-risk and 33 patients (25%) as high risk according to the AMES score.

Short-term outcome (Table II)

One hundred and six patients were considered disease-free after primary treatment (microscopic clear margins and no distant metastases).

The frequency of permanent hypoparathyroidism was significantly higher after total than after subtotal thyroidectomy, whereas the rate of permanent recurrent laryngeal nerve palsy was similar in the two groups.

Fifty six percent of the patients with total thyroidectomy had radioiodine remnant ablation compared to 27% in the subtotal group ($p < 0.001$). The difference was due to a much more frequent radioiodine treatment in stage I–II in the total than in the subtotal group (58 and 14% of the patients, respectively ($p < 0.001$)). In stage III–IV, radioiodine was given to 53% of the patients in each group.

Table II. Comparison of short-term outcome after total and subtotal thyroidectomy for differentiated thyroid cancer.

	Total thyroidectomy n=77	Subtotal thyroidectomy n=53	p-value
Considered tumour-free:	60 (78%)	46 (87%)	p=0.25
Complications of surgery:			
Recurrent laryngeal nerve palsy	4 (5%)	4 (8%)	p=0.72
Permanent hypopara-thyroidism	8 (10%)	0 (0%)	p=0.02
Radioiodine treatment:	43 (56%)	14 (27%)	p<0.001

Long-term outcome (Table III and Figure 1)

One hundred and twenty eight of the operated patients were followed to the established endpoints, whereas two patients were lost to follow-up after two and 17 years, respectively, due to emigration.

Eleven of the 106 patients (10%) who were considered tumour-free after primary surgery developed recurrences (local and/or distant) during the follow-up period.

Fifty one patients died, 15 of whom due to their thyroid cancer. Figure 1 shows Kaplan-Meier curves of cancer specific survival in the two groups according to the AMES classification. There was no statistically significant difference in the 10 year cancer-specific survival rate between the two groups irrespective of stage. It is clear that those who died from thyroid cancer belonged to the AMES high-risk group (or to TNM stages III–IV) and that the extent of surgery did not influence outcome significantly.

No patient under the age of 50 at the time of diagnosis was found to have died from thyroid cancer.

Only three of the 29 patients (10%) with isolated loco-regional spreading of their disease at time of diagnosis have died from thyroid cancer. Three of the seven patients with distant metastases at diagnosis are still alive.

Six of the 11 patients who developed recurrence of thyroid cancer during follow-up have died from their malignancy.

None of the 39 patients with accidentally detected PTC has died of thyroid cancer.

Survival rate was significantly better for PTC than FTC. Thus, the 10-year cancer-specific survival rate was 95% for PTC and 77% for FTC ($p < 0.001$).

Three patients, who were initially classified as follicular adenomas and treated only with lobectomy, latterly developed bone metastases. Histopathological re-assessment of the specimen showed FTC and the tumours were classified as TNM stage III and high-risk according to the AMES score. All three died from their cancer.

Table III. Comparison of long-term outcome after total and subtotal thyroidectomy for differentiated thyroid cancer.

	Total thyroidectomy n=77	Subtotal thyroidectomy n=53	p-value
Considered tumour-free after primary surgery:	60	46	0.25
Recurrences:	5/60 (8%)	6/46 (13%)	0.530
Cumulated recurrence at:			
5-year	3%	11%	
10-year	7%	14%	0.363
Mortality in thyroid cancer:	8/77 (10%)	7/53 (13%)	0.781
Cumulated cancer-specific survival:			
5-year	92%	92%	
10-year	91%	90%	
15-year	91%	84%	0.567
Thyroxine substitution:	77 (100%)	36 (68%)	<0.001

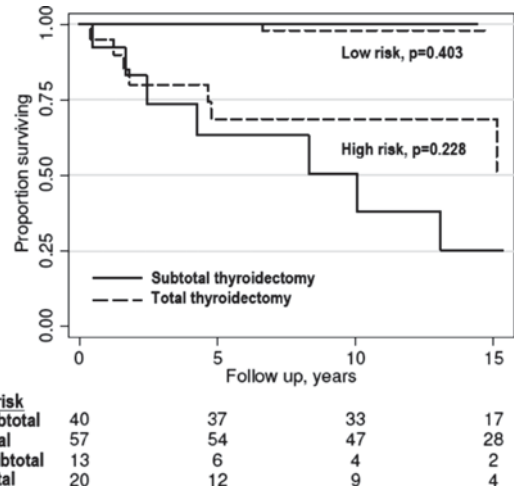

Figure 1. Comparison of disease-specific survival rate after total and subtotal thyroidectomy according to AMES low-risk or high-risk score.

Quality of life

The SF-36 questionnaire was answered by 52/59 patients (88%). Their median age was 61 years and 14 (8–22) years had passed since the primary operation. Seven of them lived with a permanent complication after surgery, four with recurrent nerve palsy, three with hypocalcemia and three had an active thyroid cancer. Another five patients had had a cancer recurrence but were seemingly free from cancer at the time of the questionnaire request.

The different components of mental and physical health according to the SF-36 questionnaire among the thyroid cancer patients are depicted in Figure 2. For comparison, the corresponding values from an age- and sex-matched Swedish reference population are also shown.

There were only some small, insignificant differences between the thyroid cancer group and the healthy Swedish population. Similarly, there were no significant changes in any parameter between patients treated with total or subtotal thyroidectomy.

Discussion

In this study we have carefully analysed the short- and long-term outcomes and the patients' assessments of their quality of life in relation to the mode of treatment in patients with differentiated thyroid cancer in a Swedish county. In accordance with some other

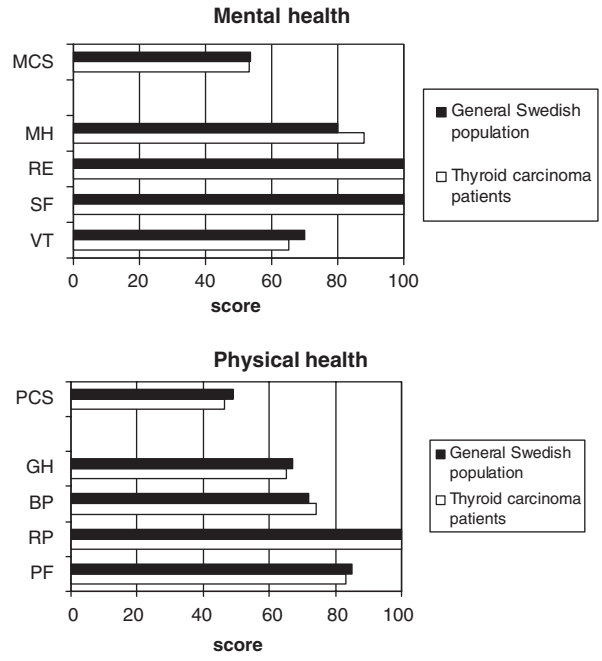

Figure 2. Comparison of long-term quality of life between patients treated for differentiated thyroid cancer and a Swedish reference population.

authors we find no difference in outcome between total and subtotal thyroid resection [7,8] and the addition of radioiodine ablation does not seem to change the chance of cure. Evidently, the prognosis of differentiated thyroid cancer is excellent in TNM stage I–II or AMES low-risk group even with a conservative surgical approach whereas the cure rate is clearly lower in TNM stage III–IV or AMES high-risk group irrespective of the extent of surgery. Probably, as pointed out by Ihre-Lundgren and her colleagues, the crucial factor is to remove the carcinoma with clear margins at the initial operation [13]. Our results also suggest that FTC behaves more aggressively than PTC in terms of more recurrences and a higher mortality. In addition to finding that aggressive treatment of differentiated thyroid carcinomas does not seem to improve survival rate in differentiated thyroid cancer TNM stage I–II or AMES low-risk group, extensive surgery also entails more complications, particularly in terms of permanent hypoparathyroidism. It has also been shown that radioiodine ablation leads to unwanted side effects (sialoadenitis, stomatitis, lacrimal gland injury, lacrimal duct obstruction) which may influence the patient for a long period of time [14]. Furthermore, treatment with thyroxine in high doses – advocated as a means of lowering the risk of recurrence – can have deleterious cardiovascular effects in the long run [15–17].

Several previous investigations have demonstrated that multifocal cancer growth is a very common finding in PTC [18–20]. We were not able to confirm this since multifocal growth was seen in only 16%. This difference most certainly reflects a more careful histo-pathologic examination of the "normal" lobe in the former studies. However, this finding was not shown to have any impact on recurrence or survival [20].

In our study, there was a tendency, although not statistically significant, that subtotal thyroid surgery had a less favourable outcome in high-risk carcinomas (as classified by the AMES and TNM scores) than total thyroidectomy. However, this difference was caused by three patients initially classified as follicular adenomas – and consequently treated with hemithyroidectomy – who later on developed distant metastases and died from their follicular carcinomas. It is unclear whether another primary treatment – had these misdiagnoses not occurred – had changed the outcome of their disease.

Previous studies have shown a decreased quality of life in patients treated for thyroid carcinoma [21,22]. We find a slightly reduced vitality-score in our study, but there is no statistical significant difference between the treated group and a reference group. Neither do we find any differences in quality of life depending on intervention procedure. If that is due to the fact that many years have passed since the treatment, or if the SF-36 questionnaire cannot capture the differences in a correct way, we do not know.

The small population cohort is both the strength and the weakness of our study. The relatively small number of patients has made it possible to perform a very careful follow-up with a minimal number of drop-outs, but it is then of course more challenging to interpret the statistical results. However, our conclusion is that the majority of patients with differentiated thyroid cancer have a moderate disease form with an excellent prognosis, this being collaborated by findings in two large studies with more than five thousand patients in each [7,8]. We therefore believe that the treatment of differentiated thyroid cancer can be individualised to a higher degree than is today's practice. Subtotal thyroid resection without postoperative radioiodine ablation seems to be an adequate treatment not only in low-risk, node-negative papillary cancers <10 mm (as advocated in modern guidelines) but also in most other patients with DTC stage I–II. Both the TNM staging system and the AMES score are useful tools in predicting prognosis and in helping select the correct level of treatment and follow-up strategy.

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