Differentiated thyroid carcinoma. Follow-up of 264 patients from one institution for up to 25 years

Gemsenjäger, Ernst; Heitz, Philipp U; Seifert, Burkhardt; Martina, Benedict; Schweizer, Ingrid

Abstract: UNLABELLED The optimum treatment for differentiated thyroid carcinoma (DTC) is still debated. Results obtained using a selective treatment strategy for papillary (PTC) and follicular (FTC) thyroid carcinoma over 25 years in one institution are reported. 149 patients (mean age 46 yrs) had PTC in TNM stages I-IV in 58%, 26%, 15% and 1% respectively. Total thyroidectomy and remnant 131I ablation (43%) were carried out in TNM high-risk patients (stages III and IV) and in low-risk patients (I and II) at risk for a (curable) recurrence (stages pN1 and/or pT4). Hemi- or total thyroidectomy, without radioiodine, was used in 76% of pT1-3 N0 tumours (68%). Central and/or lateral lymphadenectomy was performed in 42% of patients (electively in the last 4 years). The mean follow-up was 7 years. RESULTS 6 patients died of PTC and 8/143 patients treated for cure had a recurrence (6 nodal, 1 contralateral, 1 local). In low-risk patients–including 68% of patients aged ≥ 45 yrs–the cause specific 25-year survival rate was 100%, vs. 62% (at 15 years) (p < 0.0001) in high-risk patients. In stage I and stage II the recurrence-free survival rates at 25 years were 95% and 100% respectively. Risk factors for recurrence were macroscopic (p < 0.0001) but not microscopic local invasion (pT4); stage pN1 (p = 0.0004). Only 1/107 patients initially judged node-negative had a nodal recurrence. FTC (n = 115; mean age 56 yrs; mean follow-up 8 yrs): Cause-related death (n = 8) or serious recurrence (n = 3) occurred in 10/53 grossly invasive FTC, in 1/53 minimally invasive FTC with vascular invasion, and in none of 17 FTC with capsular invasion (CI) alone, under radical treatment (131I) in 75%, 33%, and 12% respectively. 20-year disease-free survival in grossly and in minimally invasive FTC was 78% and 95.5% respectively (p = 0.0007). Patients aged < 45 yrs and patients with minimally invasive FTC with CI alone (all ages) had 100% 20-year disease-free survival vs. 80% (p = 0.013) in the remainder. There was no curable recurrence in FTC. The ratio of grossly invasive FTC decreased (p < 0.0001) during the study period. CONCLUSIONS Risk-0 groups may be defined and selected for a reduced extent of treatment (PTC pT1-3 N0; FTC < 45 yrs, or CI alone). Older (> or = 45 yrs) patients with PTC in stages I and II have an excellent prognosis (risk 0). With selective (therapeutic) lymphadenectomy the risk of nodal recurrence may be very low in node negative tumours, without use of radioiodine. Meticulous lymphadenectomy is indicated in pN1 tumours with nodal recurrences despite 131I (5/36 patients). The technique of capsular dissection for extracapsular total uni- or bilateral thyroidectomy provides excellent oncological and surgical results. A decrease in the incidence of FTC parallels a decrease in endemic goitre in Switzerland.
Gemsenjäger, Ernst; Heitz, Philipp U; Seifert, Burkhardt; Martina, Benedict; Schweizer, Ingrid (2001). Differentiated thyroid carcinoma. Follow-up of 264 patients from one institution for up to 25 years. Swiss Medical Weekly, 131(11-12):157-163.
Differentiated thyroid carcinoma

Follow-up of 264 patients from one institution for up to 25 years

Ernst Gemsenjäger, Philipp U Heitz, Burkhardt Seifert, Benedict Martin, Ingrid Schweizer

a Surgical Clinic, Spital Zollikerberg, Zollikerberg/Zurich, Switzerland
b Department of Pathology, University of Zurich, Switzerland
c Department of Biostatistics, University of Zurich, Switzerland
d Medical Department, Kantonsspital Basel, Switzerland
e Surgical Clinic, Kreisspital Männedorf, Switzerland

Differentiated thyroid carcinomas (DTC) are biologically unique tumours. Prognostic classifications serve to segregate a majority of patients with near-zero risk of tumour-related death from a minority at much greater risk [1–8]. Major risk factors are patient’s age, tumour size, grade, extent (invasion) (pT4), metastases (M1), and completeness of resection for papillary (PTC) and follicular (FTC) thyroid carcinoma [9–14]. Several prognostic classification systems based upon these factors (AGES, AMES, MACIS, age-related TNM classification) [1, 2, 5, 13, 15] have proven effective and have led to the development of risk-adapted therapeutic concepts [1–5]. However, the optimum treatment for differentiated thyroid carcinoma (DTC) is still debated. Results obtained using a selective treatment strategy for papillary (PTC) and follicular (FTC) thyroid carcinoma over 25 years in one institution are reported. 149 patients (mean age 46 yrs) had PTC in TNM stages I–IV in 58%, 26%, 15% and 1% respectively. Total thyroidectomy and remnant 131I ablation (43%) were carried out in TNM high-risk patients (stages III and IV) and in low-risk patients (I and II) at risk for a (curable) recurrence (stages pN1 and/or pT4). Hemi- or total thyroidectomy, without radioiodine, was used in 76% of pT1,2 N0 tumours (68%). Central and/or lateral lymphadenectomy was performed in 42% of patients (electively in the last 4 years). The mean follow-up was 7 years. Results: 6 patients died of PTC and 8/143 patients treated for cure had a recurrence (6 nodal, 1 contralateral, 1 local). In low-risk patients – including 68% of patients aged ≥45 yrs – the cause specific 25-year survival rate was 100%, vs. 62% (at 15 years) (p <0.0001) in high-risk patients. In stage I and stage II the recurrence-free survival rates at 25 years were 95% and 100% respectively. Risk factors for recurrence were macroscopic (p <0.0001) but not microscopic local invasion (pT4); stage pN1 (p = 0.0004). Only 1/107 patients initially judged node-negative had a nodal recurrence. FTC (n = 115; mean age 56 yrs; mean follow-up 8 yrs): Cause-related death (n = 8) or serious recurrence (n = 3) occurred in 10/53 grossly invasive FTC, in 1/45 minimally invasive FTC with vascular invasion, and in none of 17 FTC with capsular invasion (CI) alone, under radical treatment (131I) in 75%, 33%, and 12% respectively. 20-year disease-free survival in grossly invasive FTC was 78% and 95.5% respectively (p = 0.0007). Patients aged <45 yrs and patients with minimally invasive FTC with CI alone (all ages) had 100% 20-year disease-free survival vs. 80% (p = 0.013) in the remainder. There was no curable recurrence in FTC. The ratio of grossly invasive FTC decreased (p <0.0001) during the study period.

Conclusions:
– Risk-0 groups may be defined and selected for a reduced extent of treatment (PTC pT1,2 N0; FTC <45 yrs, or CI alone).
– Older (≥45 yrs) patients with PTC in stages I and II have an excellent prognosis (risk 0).
– With selective (therapeutic) lymphadenectomy the risk of nodal recurrence may be very low in node negative tumours, without use of radioiodine. Meticulous lymphadenectomy is indicated in pN1 tumours with nodal recurrences despite 131I (5/36 patients).
– The technique of capsular dissection for extra-capsular total uni- or bilateral thyroidectomy provides excellent oncological and surgical results.
– A decrease in the incidence of FTC parallels a decrease in endemic goitre in Switzerland.

Keywords: papillary thyroid cancer; follicular thyroid cancer; selective therapy; prognostic TNM classification; capsular dissection; 25-year follow-up

Introduction

Differentiated thyroid carcinomas (DTC) are biologically unique tumours. Prognostic classifications serve to segregate a majority of patients with near-zero risk of tumour-related death from a minority at much greater risk [1–8]. Major risk factors are patient’s age, tumour size, grade, extent (invasion) (pT4), metastases (M1), and completeness of resection for papillary (PTC), and invasiveness for follicular (FTC) thyroid carcinoma [9–14]. Several prognostic classification systems based upon these factors (AGES, AMES, MACIS, age-related TNM classification) [1, 2, 5, 13, 15] have proven effective and have led to the development of risk-adapted therapeutic concepts [1–5]. However, the optimum treatment for differentiated thyroid carcinoma (DTC) is still debated. Results obtained using a selective treatment strategy for papillary (PTC) and follicular (FTC) thyroid carcinoma over 25 years in one institution are reported. 149 patients (mean age 46 yrs) had PTC in TNM stages I–IV in 58%, 26%, 15% and 1% respectively. Total thyroidectomy and remnant 131I ablation (43%) were carried out in TNM high-risk patients (stages III and IV) and in low-risk patients (I and II) at risk for a (curable) recurrence (stages pN1 and/or pT4). Hemi- or total thyroidectomy, without radioiodine, was used in 76% of pT1,2 N0 tumours (68%). Central and/or lateral lymphadenectomy was performed in 42% of patients (electively in the last 4 years). The mean follow-up was 7 years. Results: 6 patients died of PTC and 8/143 patients treated for cure had a recurrence (6 nodal, 1 contralateral, 1 local). In low-risk patients – including 68% of patients aged ≥45 yrs – the cause specific 25-year survival rate was 100%, vs. 62% (at 15 years) (p <0.0001) in high-risk patients. In stage I and stage II the recurrence-free survival rates at 25 years were 95% and 100% respectively. Risk factors for recurrence were macroscopic (p <0.0001) but not microscopic local invasion (pT4); stage pN1 (p = 0.0004). Only 1/107 patients initially judged node-negative had a nodal recurrence. FTC (n = 115; mean age 56 yrs; mean follow-up 8 yrs): Cause-related death (n = 8) or serious recurrence (n = 3) occurred in 10/53 grossly invasive FTC, in 1/45 minimally invasive FTC with vascular invasion, and in none of 17 FTC with capsular invasion (CI) alone, under radical treatment (131I) in 75%, 33%, and 12% respectively. 20-year disease-free survival in grossly invasive FTC was 78% and 95.5% respectively (p = 0.0007). Patients aged <45 yrs and patients with minimally invasive FTC with CI alone (all ages) had 100% 20-year disease-free survival vs. 80% (p = 0.013) in the remainder. There was no curable recurrence in FTC. The ratio of grossly invasive FTC decreased (p <0.0001) during the study period.

Conclusions:
– Risk-0 groups may be defined and selected for a reduced extent of treatment (PTC pT1,2 N0; FTC <45 yrs, or CI alone).
– Older (≥45 yrs) patients with PTC in stages I and II have an excellent prognosis (risk 0).
– With selective (therapeutic) lymphadenectomy the risk of nodal recurrence may be very low in node negative tumours, without use of radioiodine. Meticulous lymphadenectomy is indicated in pN1 tumours with nodal recurrences despite 131I (5/36 patients).
– The technique of capsular dissection for extra-capsular total uni- or bilateral thyroidectomy provides excellent oncological and surgical results.
– A decrease in the incidence of FTC parallels a decrease in endemic goitre in Switzerland.

Keywords: papillary thyroid cancer; follicular thyroid cancer; selective therapy; prognostic TNM classification; capsular dissection; 25-year follow-up
Patients and methods

A total of 264 unselected consecutive patients with DTC were treated and followed up from 1974 to 1999. The records of 166 patients described previously [19] have been updated. Clinical and diagnostic aspects have been reported recently [20]. The patients were operated on by one surgeon (E.G.) or with his assistance. The histopathological assessment was conducted prospectively by one pathologist (Ph.U.H.) and his staff according to the WHO classification [13, 19]. PTC were classified according to the age-related prognostic TNM-classification system [24] (Table 1). Extrathyroidal (pT4) PTC were subdivided into gross invasion based on macroscopic intraoperative evidence (pT4 m), and thyroid capsular penetration as a microscopic finding only (pT4 mi). Follicular carcinomas (FTC) were classified as minimally or grossly invasive [3, 4, 13]; minimally invasive FTC were subdivided into those with vascular invasion (VI), and those with exclusively capsular invasion (CI) [13, 10].

The treatment strategy consisted in a restricted interventional approach in selected low-risk patients [19, 20]. 120/264 (45%) patients underwent total thyroidectomy with radioiodine. Total thyroidectomy (n = 184) was achieved in 62 patients (34%) by completion thyroidectomy, after definitive histological diagnosis. Some patients (7%) refused completion total thyroidectomy or use of radioactive iodine, as proposed by the therapeutic scheme. Up to 1995 lymphadenectomy was performed for macroscopically involved nodes (selective therapeutic lymphadenectomy). From 1996 an elective routine (diagnostic, prophylactic) lymphadenectomy of the central compartment was introduced for pre- or intraoperatively confirmed PTC [25]. Technically complete extracapsular (no subtotal or near total lobar excision was performed by capsular dissection [20, 26, 27] on the side of a suspicious or carcinomatous nodule.

261/264 patients were followed up 0.5–25 years. Mean follow-up was 7 years (median 6) for PTC, and 8 years (median 7) for FTC. 14 patients had died from thyroid carcinoma and 28 from unrelated causes without tumour manifestation. 10 patients had been lost since the last follow-up.

Data analysis

For statistical analyses the programs Stat View 4.51 (Abacus Concepts, Inc.) and SPSS for Macintosh Release 6.1.1 were used. Continuous variables are presented as mean ± standard deviation and were analysed using the Mann-Whitney test. Nominal variables are presented as number of patients (%) and were compared using the chi-square test or Fisher’s exact test when appropriate.

Late results were analysed using the method of Kaplan and Meier.

Survival curves were compared using the log-rank test. The effect of tumour diameter on survival curves was analysed using Cox regression. P-values below 0.05 are considered significant.

Table 1

<table>
<thead>
<tr>
<th>Stage</th>
<th>Age &lt;45 years</th>
<th>Age ≥45 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>pT4a N0 M0</td>
<td>pT4a N0 M0</td>
</tr>
<tr>
<td>II</td>
<td>pT4b N0 M0</td>
<td>pT4b N0 M0</td>
</tr>
<tr>
<td>III</td>
<td>pT1–3 N0 M0</td>
<td>pT1–3 N0 M0</td>
</tr>
<tr>
<td>IV</td>
<td>pT4a N0 M1</td>
<td>pT4a N0 M1</td>
</tr>
</tbody>
</table>

Notations:
- I: pT1–4 N0 M0
- II: pT1–4 N1 M0
- III: pT1–4 N1 M0
- IV: pT1–4 N0 M1

Results

During the study the ratio of PTC increased from 35% to 66% (p = 0.03), whereas that of grossly invasive FTC decreased from 41% to 9% (p <0.0001) [20]. A concomitant benign nodular goitre was more frequent in patients with a grossly invasive FTC than in PTC (45% vs. 18%; p = 0.002); the same was true for nodular goitre with functional autonomy (19% vs. 3%; p = 0.0007) [20].

Papillary carcinoma

Age groups

68/149 patients (46%) were in the young (<45 yrs) and 81 (54%) in the older age group (≥45 yrs). N1-status (27%) was more common in young than in older patients (35% vs. 20%; p = 0.033), and in pT1 than in pT1+; tumours (65% vs. 17%; p <0.0001). A pT4 tumour (21%) was found in 18% of young and 23% of older patients (p = ns); gross extrathyroidal invasion was present in 9%.

M1 status

All patients with haematogenous metastases (7/149; 5%) had extensive nodal disease (pN1), 5
patients had a pT4 tumour. 5/68 (7%) young patients had diffuse pulmonary radioiodine uptake on the post-remnant ablation scan, and in 2/81 older patients (2.5%) pulmonary metastases were seen on preoperative chest radiography.

**Table 2**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>TNM stage</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>Hemithyroidectomy</td>
<td>26⁶</td>
<td>8</td>
</tr>
<tr>
<td>Total thyroidectomy</td>
<td>32⁳</td>
<td>13</td>
</tr>
<tr>
<td>Total thyroidectomy, ¹³¹I</td>
<td>26⁶</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>84</td>
<td>38</td>
</tr>
</tbody>
</table>

Postoperative events:
- curable recurrences (n = 5), (occurring 1–3 years after primary therapy):
  - contralateral (n = 1) (pT2N0)
  - nodal (n = 4) (1pT1N1, 2pT1N0, stage I; 1pT1N1, stage III)
- deaths (n = 6) (occurring ⁷⁄₈–16 years after primary therapy):
  - (1pT2N0, 3pT1N1, 2pT1N0, M1)
high-risk and in none of the 4 TNM low-risk patients. Thus, there were 5 curable recurrences (Table 2). Only 1/107 nodal recurrence was observed in patients with a primary node negative tumour, vs. 5/36 with a pN1 tumour (p = 0.0004, log-rank test). In 3/83 patients without radical initial therapy a postoperative event occurred (1 death; 2 curable recurrences, 1 contralateral, 1 nodal).

Late results of treatment of PTC are plotted by TNM risk groups in Figure 1. In low-risk patients the cause-specific 25-year survival rate and the disease-free survival rate was 100% and 96.5%, respectively, vs. 62% and 59% (at 15 years) respectively in high-risk patients (p <0.0001). Age ≥45 yrs vs. <45 yrs significantly influenced survival (p = 0.01), but not disease-free and recurrence-free survival (Table 3). Macroscopic (pT4 ma), but not microscopic extrathyroidal invasion was a significant risk factor for outcome in the entire series (p <0.0001), and for recurrence in the low risk (TNM I and II) group (p = 0.0002). Stage pN1 vs. N0 had a significant impact on outcome. Gender, hemithyroidectomy vs. total thyroidectomy, or use vs. non-use of 131I did not influence the results.

**Follicular carcinoma**

The risk-dependent treatment and the late results are shown in Table 4. In minimally invasive FTC 1/62 patient died, from pulmonary metastases from 12 years after total thyroidectomy. 3/53 patients with grossly invasive FTC died 2-7 years after non-curative primary treatment, and 7 further patients developed a serious recurrence leading to death in 4 patients 6-12 years after primary treatment; the remaining 3 patients are living with disease 4-8 years after radical treatment. Patients with an adverse outcome (11/115) were aged 55-80 (mean 71) years.

The disease-free survival for minimally and for grossly invasive FTC are plotted in Figure 2a. Patients aged <45 yrs or those with CI alone had cumulative survival and disease-free survival of 100% (Fig. 2b, Table 5). In univariate risk factor analyses grossly invasive tumour, stage pT4, nodal involvement, and tumour size had an adverse effect on survival and/or disease-free survival (Table 6). The adverse effect of 131I clearly reflects patient selection.

**Surgical morbidity**

One patient, an 83-year-old man (0.4%) died of cardiac failure after operation for a large infiltrating papillary carcinoma. 5/264 patients (1.9%) developed permanent hypoparathyroidism, representing 3% of those with total thyroidectomy. Unilateral recurrent-nerve paralysis developed in 4 patients (1.5%) or in 1% of nerves at risk (n = 407). Seven of the 8 patients with morbidity had a concomitant recurrent benign goitre, completion total thyroidectomy, extensive central nodal involvement, or a grossly invasive FTC respectively.

### Table 3

<table>
<thead>
<tr>
<th>Variable</th>
<th>survival</th>
<th>disease-free survival</th>
<th>recurrence-free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNM high risk vs. low risk</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0025</td>
</tr>
<tr>
<td>Age ≥45 vs. &lt;45</td>
<td>0.01</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Stage T1 vs. T3,4</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.008</td>
</tr>
<tr>
<td>Stage T1, macroscopic vs.</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>T1,4, T4, microscopic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage N1 vs. N0</td>
<td>0.001</td>
<td>&lt;0.0001</td>
<td>0.006</td>
</tr>
<tr>
<td>Stage M1 vs. M0</td>
<td>0.008</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>Ø cm</td>
<td>0.001</td>
<td>0.003</td>
<td>ns</td>
</tr>
</tbody>
</table>

### Table 4

<table>
<thead>
<tr>
<th>Treatment</th>
<th>minimally invasive (n = 62)</th>
<th>grossly invasive (n = 53)</th>
<th>total (n = 115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemi thyroidectomy</td>
<td>10/17 (88%)</td>
<td>26/41 (67%)</td>
<td>41/115 (50%)</td>
</tr>
<tr>
<td>Postoperative events (n = 11): deaths (n = 8):</td>
<td>1 death; 6 deaths; serious recurrence (n = 3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td>45</td>
<td>53</td>
</tr>
<tr>
<td>Total thyroidectomy, 131I</td>
<td>2/17 (12%)</td>
<td>15/43 (33%)</td>
<td>40/115 (75%)</td>
</tr>
<tr>
<td>Postoperative events (n = 11): deaths (n = 8):</td>
<td>1 death; 6 deaths; serious recurrence (n = 3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Discussion

This study has the advantages of precise prospective documentation and uniform conditions with respect to surgery and pathology. The duration of follow-up was relatively short, due to an increasing number of annually referred patients. However, though late deaths may occur [9], curable recurrences and those heralding an unfavourable course are seen most frequently during the first 5–10 years [5, 9, 21, 22] – 1–8 years in our 16/255 patients with primary therapy for cure.

During the 25-year period the proportion of FTC decreased significantly, from 65% to 34% of all DTC, due to a decrease in grossly invasive FTC. Therefore, PTC became the most frequent tumour. For the 30-year period 1944–1973 a decrease in FTC from 52% to 38% was found in a series of 550 pathological specimens of thyroid carcinoma in Switzerland [28]. These data reflect a continuous decrease in the incidence of FTC, which parallels a decrease in the prevalence of simple goitre [29] and of its toxic nodular variant [30] over decades in Switzerland.

Our results confirm that the prognostic classification of FTC on the basis of invasiveness is valid. The outcome was unfavourable in 10/62 patients with grossly invasive FTC, in 1/45 minimally invasive FTC with VI, and in none of the 17 minimally invasive FTC with CI alone. The cause-specific disease-free survival rates at 20 years were 78% for grossly invasive and 95.5% for minimally invasive FTC (p = 0.0007). In agreement with De Groot et al. [9], no curable recurrence was observed in FTC. No adverse outcome was noted in young (<45 yrs) patients and – independently of the patient’s age – in tumours with CI alone (mean age 54 yrs). Nodal involvement (3.5%) was clinically and intraoperatively obvious, and no metachronous nodal disease occurred. Routine lymphadenectomy is therefore not indicated in FTC [1, 4, 12, 14]. Multifocal and contralateral involvement (7%) was grossly evident and led to total thyroidectomy. Our results are in agreement with studies where subgroups without deaths [9, 10] or with near 100% survival rates [11, 31] were noted, or in which thyroidectomy vs. total thyroidectomy did not adversely influence survival or recurrence [11, 12].

In definable patients without risk of systemic disease complete removal of the local tumour tissue by total primary hemithyroidectomy or total thyroidectomy is essential, whereas remnant ablation does not appear rational. Follicular neoplasia (as evidenced by high cellularity on fine needle aspiration biopsy) [32] should be treated by diagnostic primary hemithyroidectomy, avoiding ipsilateral reoperation with its increased morbidity and potentially incomplete local tumour excision [20, 22].

For PTC the multivariate age-related TNM classification [24] proved to be valuable for defining low-risk (stages I and II) and high-risk (stages III and IV) patients, with significantly different rates of survival (100% vs. 62% at 15 years; p <0.0001), disease-free survival (97% vs. 59%; p <0.0001), and recurrence-free survival (i.e. after primary treatment for cure) (96.5% vs. 80%; p = 0.0025). Treatment strategy was radical treatment in high-risk patients and in those low-risk patients at risk for curable recurrence (N1 or T4 status) [4, 5, 14, 21, 23, 25, 33]. Our results confirm the impact of age on survival: young (<45 yrs) patients had a mortality rate of 0% in spite of stage T4 in 18%, N1 in 35%, and M1 in 7%. The same tumour characteristics determine a much less favourable outcome in older, i.e. high-risk patients. However, in the absence of these characteristics, i.e. in pT1, N0, M0 tumours, older patients belong to the low-risk category and have an excellent prognosis, with no deaths and even with no instance of a curable recurrence in our study. Stages I and II did not have a significantly different prognosis, thus confirming the data of Hundahl et al. [8]. These authors mention the "opportunity for simplifying the current TNM prognostic system further". Our results indicate that a reduced scale of treatment may be adequate for pT1, N0 tumours, independently of the patient’s age. In this subset (66% of all PTC) no death occurred, and there was only 1/36 contralateral recurrence after hemithyroidectomy and only 1/107 nodal recurrence in patients without

Table 5

<table>
<thead>
<tr>
<th>Survival</th>
<th>minimally invasive</th>
<th>grossly invasive</th>
<th>CI alone or patients &lt;45 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 yr</td>
<td>100% (35)</td>
<td>96% (42)</td>
<td>100% (27)</td>
</tr>
<tr>
<td>10 yr</td>
<td>100% (15)</td>
<td>85% (29)</td>
<td>100% (11)</td>
</tr>
<tr>
<td>20 yr</td>
<td>92% (4)</td>
<td>81% (3)</td>
<td>100% (3)</td>
</tr>
</tbody>
</table>

Table 6

<table>
<thead>
<tr>
<th>Risk factors in FTC by univariate analysis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>T1 vs. T1,1</td>
</tr>
<tr>
<td>N1 vs. N0</td>
</tr>
<tr>
<td>Ø cm</td>
</tr>
<tr>
<td>Use of 131I vs. no 131I</td>
</tr>
<tr>
<td>Hemithyroidectomy vs. total thyroidectomy</td>
</tr>
</tbody>
</table>
initial nodal involvement (though 80% had no lymphadenectomy, and 74% had no 131I). After hemithyroidectomy, contralateral recurrences were noted in 4% [6], and in 14% [5, 33] of low-risk patients; several authors report very low rates (0.9%–3%) [18, 21, 33] of nodal recurrence in patients who were initially node-negative without use of radioiodine. In pT1–3 N0 tumours it has not been shown that 131I ablation offers any advantage in improving the already excellent results [16, 19].

On the other hand, radioiodine does not prevent nodal recurrence in patients with initial node disease [5, 21, 22, 34, 35]. In low-risk patients with primary lymph node metastases 131I is also indicated for detection and treatment of diffuse pulmonary metastases. Extensive nodal disease is a marker for disseminated pulmonary disease [21, 22, 36], which was detected in 5 (7%) of our young patients (21% of those with initial nodal disease) on the post-ablation scan (none of these patients developed a recurrence). In rare, anecdotal low-risk patients with PTC a fatal outcome was reported [37, 38]. These patients had gross invasive nodal disease [38, 39].

The question arises how radical lymphadenectomy is to be performed for detection of (occult) nodal disease, adequate staging, and stage-dependent treatment. Interestingly, no significant increase in node positivity, and no influence on therapeutic results were observed in our series with routine vs. selective lymphadenectomy [25]. In one report routine lymphadenectomy resulted in a high incidence of N1 status (82%) and to improvement of survival and recurrence [35]. More radical lymphadenectomy may itself improve therapeutic results by stage migration [40]: occult N1 tumours are eliminated from the N0 group, and N1 groups are enlarged with more favourable tumours with only occult nodal disease (Will Rogers phenomenon) [40, 41]. In sum, the impact of elective (prophylactic) node dissection on outcome remains uncertain [25].

In some apparently intrathyroidal tumours the pathologist may document penetration of the thyroid capsule. We classified these tumours as stage pT4. Woolner et al. [3, 4] classified only tumours with gross capsular infiltration as “extrathyroidal” (10%; 9% in our series), without however detracting from the excellent outcome in the “intrathyroidal” and “occult” (i.e. pT1,0) categories. Accordingly, in our patients only macroscopic, but not microscopic penetration significantly influenced outcome. Special therapeutic measures such as external percutaneous irradiation are not warranted on the basis of microscopic penetration only.

Our study confirms that it is possible to select patients with FTC or PTC who require radical therapy, and those in whom technically correct hemithyroidectomy or total thyroidectomy without remnant ablation provides a virtually perfect prognosis. In PTC prognostic classification systems may accurately segregate low and high risk for death, but TNM stages I and II engulf an inhomogeneous population with respect to recurrence; N1 and/or T4 status are indicators for radical therapy in young patients with PTC. For clinical PTC without nodes we prefer total to hemithyroidectomy, to eliminate the problem of potential contralateral recurrence. However, some patients feel invalidated by loss of a vital organ and prefer hemithyroidectomy with acceptance of low risk of curable contralateral recurrence. We also favour routine (prophylactic) central lymph node dissection [1, 20, 21, 33], but the possible advantages should not be compromised by damage to the parathyroids or recurrent laryngeal nerves. In 0-risk patients cure of disease should not be compromised by postoperative iatrogenic disease (exogenous hyperthyroidism for TSH suppression) or excessive follow-up measures [1, 2, 6, 14, 23].

Are the surgeon’s tactics and technique prognostic factors [37]? Capsular dissection [26, 27, 42], with fine preparatory technique is essential (a) for low morbidity in thyroid surgery [43], and (b) for oncological adequacy [20]. The technique was first used by Kocher [44, 45], who deliberately opposed it to a less subtle and anatomically different operative practice [44]; hence variance in operative technique is still of concern [27, 46]. Incomplete tumour resection may result in a fatal outcome even in low-risk patients [37, 47].

Correspondence:
Professor E. Gemsenjäger
Surgical Clinic
Spital Zollikerberg
CH-8125 Zollikerberg/Zurich
Switzerland
What Swiss Medical Weekly has to offer:

- SMW’s impact factor has been steadily rising, to the current 1.537
- Open access to the publication via the Internet, therefore wide audience and impact
- Rapid listing in Medline
- LinkOut-button from PubMed with link to the full text website http://www.smw.ch (direct link from each SMW record in PubMed)
- No-nonsense submission – you submit a single copy of your manuscript by e-mail attachment
- Peer review based on a broad spectrum of international academic referees
- Assistance of our professional statistician for every article with statistical analyses
- Fast peer review, by e-mail exchange with the referees
- Prompt decisions based on weekly conferences of the Editorial Board
- Prompt notification on the status of your manuscript by e-mail
- Professional English copy editing
- No page charges and attractive colour offprints at no extra cost

Editorial Board
Prof. Jean-Michel Dayer, Geneva
Prof. Peter Gehr, Berne
Prof. André P. Perruchoud, Basel
Prof. Andreas Schaffner, Zurich
(Editor in chief)
Prof. Werner Straub, Berne
Prof. Ludwig von Segesser, Lausanne

International Advisory Committee
Prof. K. E. Juhani Airaksinen, Turku, Finland
Prof. Anthony Bayes de Luna, Barcelona, Spain
Prof. Hubert E. Blum, Freiburg, Germany
Prof. Walter E. Haefeli, Heidelberg, Germany
Prof. Nino Kuenzli, Los Angeles, USA
Prof. René Lutter, Amsterdam, The Netherlands
Prof. Claude Martin, Marseille, France
Prof. Josef Patsch, Innsbruck, Austria
Prof. Luigi Tavazzi, Pavia, Italy

We evaluate manuscripts of broad clinical interest from all specialities, including experimental medicine and clinical investigation.

We look forward to receiving your paper!

Guidelines for authors:
http://www.smw.ch/set_authors.html

Impact factor Swiss Medical Weekly

All manuscripts should be sent in electronic form, to:
EMH Swiss Medical Publishers Ltd.
SMW Editorial Secretariat
Farnburgerstrasse 8
CH-4132 Muttenz

Manuscripts: submission@smw.ch
Letters to the editor: letters@smw.ch
Editorial Board: red@smw.ch
Internet: http://www.smw.ch