Prognostic factors in differentiated thyroid carcinoma

KEYWORDS: Thyroid Neoplasms; Prognosis

ABSTRACT

High cure rates are achieved after initial treatment of patients who develop differentiated thyroid cancer (DTC) and long-term outcome is usually favorable. However, some patients are at high risk of recurrence and even of death. These patients can be identified at the time of diagnosis by using well-established prognostic factors. The extents of primary operation on thyroid gland and regional lymph nodes, radioactive iodine ablation, as well as other treatment features still remain controversial. The most appropriate initial treatment can be applied and follow-up can be finely tailored. Prognostic factors for DTC are defined as specific features of patients (age, gender), tumors (histology, extent, aneuploidy), and treatment. During the past two decades the great efforts were made to establish the optimal prognostic scoring system that should include the most important prognostic factors for patients with differentiated thyroid carcinoma (DTC). The article reviews the chronology of prognostic scoring systems with their main characteristics in a goal to make easier the decision of adequate initial treatment modalities based on risk groups of patients with DTC.

INTRODUCTION

During the past two decades the great efforts were made to establish the optimal prognostic scoring system that should include the most important prognostic factors for patients with differentiated thyroid carcinoma (DTC). The extents of primary operation on thyroid gland and regional lymph nodes, radioactive iodine ablation, as well as other treatment features are remaining controversial. High cure rates are achieved after initial treatment of patients who develop differentiated thyroid cancer (DTC) and long-term outcome is usually favorable. However, some patients are at high risk of recurrence and even of death. These patients can be identified at the time of diagnosis by using well-established prognostic factors. The most appropriate initial treatment can be applied and follow-up can be finely tailored. Prognostic factors for DTC are defined as specific features of patients (age, gender), tumors (histology, extent, aneuploidy), and treatment (1).

EORTC SYSTEM

In 1979, Bayar and coworkers started a new era by publishing the EORTC prognostic system based on results of European multi-institutional multivariate analysis of prognostic factors in 507 patients with all types of thyroid cancer. They found age, histology type, distant metastases, extrathyroid extension and gender, to be independent prognostic factors for thyroid carcinomas (2).

THE INSTITUTE GUSTAVE ROUSSY (IGR) SYSTEM

It was developed in 1985 in 546 patients with DTC without distant metastases at diagnosis. The system takes into account the two most relevant prognostic factors singled out in the cohort by multivariate analysis: age at diagnosis and the histological type. With these parameters, the authors defined two groups of patients:

- A group with a good prognosis, comprising patients (80%) below 45 years of age at diagnosis and who had a well-differentiated cancer (papillary or follicular) with a 25-year cancer-specific mortality rate of 2% and with mostly curable local recurrences.

- A group with a poor prognosis (25-year cancer-specific mortality rate of 30% and usually incurable local recurrences), comprising patients over 45 years of age or suffering from poorly-differentiated or widely invasive follicular thyroid cancer (2).

In the following years, authors from France (3,4), Scandinavia (5), and the Netherlands (6,7), have criticized EORTC system, on the basis of their results on 1813 patients with thyroid cancer.

THE TNM STAGING SYSTEM (BY THE UICC)

It was introduced in 1987 and reviewed in 1992. Since 1988, it has been recognized as the reference international staging system. In the TNM system, DTC are staged separately from medullary and anaplastic carcinomas. It takes into account the age at diagnosis and is based on three variables: the extent of the primary tumor (T), the presence (N1) or absence (N0) of lymph node metastases and the presence (M1) or absence (M0) of distant metastases. This system defines 4 stages with increasing cancer specific mortality rate at 11.3 years: 1.7%, 15.8%, 30% and 60.9%, respectively (8).

THE AGES AND MACIS SYSTEMS

Hay and coworkers from Mayo Clinic (1987) have suggested new prognostic scoring system, based on results of multivariate analysis on 1938 patients with differentiated thyroid carcinoma (DTC). They defined AGES system (age, tumor grade, local and distant extension, tumor size). They found that 86% of patients (group 1) have low (1%) cancer specific mortality rate, while others
have higher mortality rate (24%, 49% and 93%, respectively) in 25-years followup (9).

In 1993, the same authors reviewed their scoring system, excluding tumor grade and including distant metastases, age, completeness of surgery, invasion of extra-thyroidal tissues and size (MACIS). The results of this cohort comprising 1779 patients with papillary thyroid cancer showed that 20-year survival rate was 99%, 89%, 56% and 24%, respectively for increasing scores (10). The value of this scoring system was confirmed in another study by the same authors based on 2512 patients with DTC followed from 1940 till 2000 (11).

THE AMES AND DAMES PROGNOSTIC SYSTEM

The AMES system was created in 1988 by Cadry and Rossi (Lahey Clinic). It is based on combination of age, distant metastases, and extent and tumor size. The AMES system defines a low-risk group (89%) of patients with DTC with mortality rate of 1.8%, and high-risk group (11%) with mortality rate of 46% in 20-year follow-up (12). Paiseka and coworkers have suggested that adding a DNA ploidy to AMES system (DAMES) should increase the predictive value of AMES system (13).

THE MEMORIAL SLOAN-KETTERING CANCER CENTER SYSTEM

In 1992, the authors have suggested that prognostic factors for DTC should be based on those related to patients and those related to tumor features. Besides low-risk (younger than 45 years with low risk tumor) and high-risk group (older than 45 with high risk tumor), they proposed intermediate risk group (younger than 45 with high-risk tumor and older than 45 with low-risk tumor). The long-term cancer specific survival was 99%, 87% and 57% in low-, intermediate-, and high-risk groups of patients (14).

THE OHIO STATE UNIVERSITY SCORING SYSTEM

Back in 1994, Mazzaferri and his group have reported results of multivariate analysis of prognostic factors in DTC based on 1355 patients followed-up for 30 years. The scoring system does not include features related to patients - age at diagnosis and gender. Tumors are staged clinically into 4 categories according to tumors size, the presence or absence of neck lymph node metastases, multifocality, local tumor invasion, and distant metastases. Recurrence and mortality rates are respectively 8% and 0% in group 1 (13% of patients), 31% and 6% in group 2 (70% of patients), 36% and 14% in group 3 (15% of patients), and 62% and 65% in group 4 (2% of patients) (15). Analyzing his own results and the results of similar comparative studies, Mazzaferri brings a critical review on therapy modalities and treatment results in patients with DTC. The age over 40 years at diagnosis, tumor stage (size, multifocality, local invasion, lymph node metastases), initial surgery at least “near” total thyroidectomy, radiiodine ablation are independent prognostic factors for DTC. Aggressive initial therapy gives a chance for complete cure in more than 90% of patients (16).

CONCLUSION

The numerous, mostly retrospective studies, have shown that different prognostic factors have influence on recurrence and mortality rate in patients with DTC. They resulted in prognostic scoring systems that enables choosing adequate treatment modalities, especially extent of primary surgery, based on risk groups of patients.

The opposite opinions on the extent of primary operations have somehow become closer with fact that completeness of surgery is independent prognostic factor in MACIS system after 50 years follow-up. Some studies have shown that multifocality and presence of lymph node metastases are also independent prognostic factors for recurrence and survival rate in patients with PTC. All of these could provide arguments for more radical primary surgery in differentiated thyroid carcinoma.

Nevertheless, experienced surgeon in this field perform these operations with minimal or no morbidity. That is why surgeon is a factor of prognosis both for long-term disease free survival and quality of life (17).

REFERENCES

Can thyroidectomy be performed in secondary thyroid cancer?

**Background:** Secondary thyroid cancer is much less frequent than primary and in the majority of cases represents disseminated disease where operation on thyroid is useless or thyroid tumor is not operable, infiltrating surrounding structures.

**Methods:** Five case reports of patients operated for secondary thyroid cancer.

**Results:**
- **Case 1:** In male patient aged 64 years, thyroidectomy was done for thyroid solid tumor 5 years after lung lobectomy for bronchogenic planocellular cancer. FNB suspected nonthyroid cancer, histological analysis revealed planocellular cancer (Grimelius staining excluded medullar cancer) and multinodular goiter.
- **Case 2:** In female patient aged 65 years, thyroidectomy was done 4 years after left mastectomy with the history of long standing multinodular toxic goiter. Infiltrate remained in trachea and esophagus, histology revealed breast cancer metastasis in thyroid, confirmed with special mucin I, and estrogen receptor staining with negative thyroglobulin staining.
- **Case 3:** In female patient aged 76 years, thyroidectomy was performed for metastatic lucidocellular kidney cancer in recurrent goiter (with Vimentin staining), a year after nephrectomy and 50 years after first goiter operation.
- **Case 4:** In female patient aged 58 years, thyroidectomy was performed for planocellular infiltration of esophagus into the left thyroid lobe.
- **Case 5:** In female patient aged 77 years, thyroidectomy was done for hemorrhage into thyrotoxic goiter, histology revealed metastasis of planocellular cancer of unknown origin into thyroid.
- **Case 6:** In male patient aged 54 years, thyroidectomy was performed for thyroid metastatic lucidocellular cancer of kidney, 2 years after nephrectomy.

**Conclusion:** Although prognosis of secondary thyroid cancer is poor, in rare cases aggressive surgery with adjuvant therapy may be successful.

Factors influencing successful radioidine therapy of thyroid

**Background:** Well-known fact is that the good surgical treatment, leaving only small residuals of thyroid tissue, is the outmost valid predictive factor of successful ablative radioiodine treatment. Assuming that all patients had state of the art surgical treatment, with this study we tried to evaluate other possible predictive factors of successful radioiodine therapy after total thyroidectomy.

**Methods:** Total of 56 patients (15 males and 41 females; mean age 43.37±13), operated during the year 2001 was evaluated. Due to differentiated carcinoma of the thyroid total thyroidectomy was done in 7 with follicular and in 49 patients with papillary cancer. Forty one patients received ablative $^{131}$I dose (3.7GBq) and fifteen patients received therapeutic dose (5.55GBq) of radioiodine therapy. As possible predictive factors the TNM classification (T1, 6; T2, 17; T3, 4; T4, 28 and 24 with N0; and 32 with N1), the number of foci on whole body scan (WBS), and the serum level of thyroglobulin were statistically evaluated. One year after radioiodine therapy control WBS was done and successful outcome of the therapy was considered to be the WBS without visible accumulation of radioiodine and with low serum level of thyroglobulin.

**Results:** Outcome of ablative radioiodine therapy was considered as successful in 55.4% patients and 44.6% of patients needed additional radioiodine therapies. Only the number of foci and the level of thyroglobulin showed statistically significant (p<0.05) influence on the outcome of applied radioiodine therapy.

**Conclusion:** Significant influence of the thyroglobulin level and number of foci on the WBS in patients with total thyroidectomy could be explained by the fact that there were the signs of minimum thyroid residual tissue, and that there were no microscopic spread of disease.
Background: This study was performed with aim to analyze differentiated thyroid carcinoma (DTC) in patients staged as pathological T4 (pT4), related to the DTC patients staged as pT1-pT3.

Methods: 267 patients staged as pT1-pT4 were treated in a period from 1977 to 2000, and followed until the end of 2001. Out of the total number, 117 patients were staged as pT4, 49 patients as pT3, 78 patients as pT2, and 23 patients as pT1. All patients were treated surgically, by radioiodine and by hormonal therapy; some of them underwent external radiotherapy and/or chemotherapy.

Results: We staged 36 male and 81 female patients. pT4: 98 patients with papillary carcinoma (PAP), and 19 patients with follicular (FOL) DTC. In pT4 stage regional metastases (N1) were found in 68 patients, distant metastases (M1) in 21 patients, and disease related lethal outcome occurred in 10 patients. In pT1 stage N1 were present in 21 patients, M1 in 2 patients, and lethal outcome in 2 patients; in pT2 stage N1 was present in 37 patients, M1 in 8 patients, and lethal outcome in 5 patients; in pT3 stage N1 were present in 14 patients, M1 in 11 patients, and lethal outcome in 5 patients. Regional metastases of DTC patients were significantly more frequent in pT4 stage than in DTC patients staged as pT2 and pT3, but they were significantly more frequent in pT1 stage (p<0.001). Distant metastases were significantly more frequent in DTC patients staged as pT4, related to the patients in pT1 and pT2 stage, but statistical difference was not significant to the patients staged as pT3. We did not find any statistical difference in lethal outcome between patients staged as pT4 and patients in pT1, pT2 or pT3 stages. Complete remission after treatment was achieved in 41.5% of pT4 patients, partial remission in 20.8%, unchanged status in 14.2%, exacerbation in 7.6%, disease related lethal outcome was observed in 8.5%, while 5.7% of patients died from concomitant diseases. The survival probability of all pT4 patients at 5 years was 0.904±0.0401, at 10 years 0.84±0.058, at 15 years 0.764±0.09. In pT4 patients with M1 the survival probability was significantly shorter.

Conclusion: DTC patients staged as pT4 had significantly more frequent N1 and M1 than patients staged as pT2-pT3, and more frequent M1 compared to patients in pT1 stage, but patients staged as pT1 had N1 very frequently, because most of them were detected after discovery of N1. Stage pT4 had no significant influence to the lethal outcome, related to patients staged as pT1-pT3. The expected survival in pT4 patients was long, probably as a result of multimodal treatment, including I-131.
Glutathione S-transferase t1 and m1 polymorphisms and risk of thyroid neoplasms

KEYWORDS: Thyroid Neoplasms; Glutathione Transferase; Genotype; Genetic Predisposition to Disease

Background: In order to test the possibility of association between GSTT1 and M1 (glutathione S-transferase) null allele variant, in which the entire gene is absent, and the risk of TCO (thyroid carcinoma with cell oxyphilia), the case-control study was carried out.

Methods: Genotypes for GSTT1 and GSTM1 were determined by multiplex PCR in the DNA from 108 healthy individuals and in DNA from samples of thyroid tumors from 130 patients of the same race and origin as the control group (Caucasian, Italian). The following types of NMTC were analyzed: oxyphilic adenoma (OA), oxyphilic carcinoma (OC), papillary thyroid carcinoma with oxyphilic features (PTCof), follicular adenoma (FA), follicular carcinoma (FC), follicular variant of PTC (fPTC), and classical PTC. Associations between prevalence of particular genotypes and the occurrence of TCO (versus controls) and other subtypes of NMTC were tested. Associations were quantified by calculating OR (odds ratio) with 95% confidence interval. StatGraphics Plus v. 5 software (Manugistics) was used for statistical analysis.

Results: In this study of the association between the GSTT1 and M1 null genotype and the increased risk of TCO, the frequency of GSTT1 null genotype of 19.2% in cases and 15.7% in controls was found, with an adjusted odds ratio (OR) of 1.4 (95% confidence interval (CI), 0.70-2.81), and the frequency of GSTM1 null genotype of 59% in cases with oxyphilic tumors and of 55.6% in controls (OR 1.24; 95% CI, 0.62-2.48).

Conclusion: These results indicate that the GSTT1 and M1 null genotypes do not increase the risk of development of oxyphilic tumors, as well as other types of NMTC that have been included in this study.

Differentiated thyroid carcinomas and regional metastases

KEYWORDS: Thyroid Neoplasms; Carcinoma, Papillary, Follicular; Lymphatic Metastasis

Background: Aim of the study was to determine the frequency of regional - nodal metastases (N1) of differentiated thyroid carcinomas (DTC), to analyze the modes of treatment, course of disease, and outcome.

Methods: In Department of Nuclear Medicine in Sremska Kamenica, 363 DTC patients were treated from 1977 to the end of 2000. Nodal metastases had 182 patients; most of them were followed to the end of 2000. Methods: All patients with N1 were treated surgically (operation of thyroid gland was done in all patients, surgical treatment of lymph nodes in 80.2% of them), afterwards by radioiodine and long-life by hormonal therapy; external beam therapy was applied in 9.9% of patients, chemotherapy in 1.6% of patients. The range of follow-up was from 2 months to 24.2 years, the mean 4.7 years.

Results: Nodal metastases were detected first, before primary tumor, in 21.9% patients, and simultaneously in 63.2% patients. They appeared subsequently, after detection and initial treatment of primary tumor in 14.8% patients; the incomplete initial therapy in this subgroup of patients was more frequent than complete therapy (p<0.01). Regional metastases N1b were present more frequently than N1a (p<0.001). Distant metastases (M1) in N1 group were discovered in 27.5% of patients; they were more frequent than in NO group of patients (p<0.001). Nodal metastases were found more frequently, after detection and initial treatment of primary tumor in 14.8% patients; the incomplete initial therapy in this subgroup of patients was more frequent than complete therapy (p<0.01). Regional metastases N1b were present more frequently than N1a (p<0.001). Distant metastases (M1) in N1 group were discovered in 27.5% of patients; they were more frequent than in NO group of patients (p<0.001). Nodal metastases were found more frequently in the group of papillary than in the group of follicular carcinoma (p<0.001), and in the men than in the women with DTC (p<0.001). Remission was achieved in 67.7% of patients with N1. Disease related deaths occurred in 15.8% of patients with N1; M1 was cause of deaths in 10.2% of patients, locoregional disease (T4 and/or N1) in 5.9% of patients, and M1 + extended T4 and/or N1 in 0.7% of patients. Late complications of treatment caused the death in 2.1% of patients with N1. The relapses of disease occurred in 31.9% of patients. The survival probability after onset of the nodal disease in N1M0 subgroup was 0.88+/−0.05 after 10 years, and 0.64+/−0.16 after 20 years; the probability of survival was very significantly shorter when M1 were present (p<0.001).

Conclusion: Regional metastases were detected in the half of DTC patients. The detection of N1 was the first indicator of thyroid tumor in about 20% of them. Nodal metastases grew later on after detection and initial treatment of primary tumor in about 15% of patients, mostly as a result of inadequate treatment. The frequency of N1 was greater in patients with papillary type of tumor and in males. The presence of M1 had significant influence on survival of patients with N1.
Surgical treatment for anaplastic thyroid cancer

**Background:** Anaplastic thyroid cancer is relatively rare but extremely aggressive neoplasm. The aim of the present paper was to study the possibility of surgery for anaplastic thyroid cancer.

**Methods:** During 5-year period (from 1998 to 2002) in the Center for endocrine surgery, we found anaplastic thyroid cancer in 65 patients (44 female and 21 male patients), of median age 63 years (range: 37-88 years). Diagnosis was determined on the basis of histological analysis in operated patients or on cytology findings in case of patients who were not operated. Histological analysis confirmed anaplastic transformation of papillary thyroid cancer in 18 cases.

**Results:** In 50% patients we performed only fine needle biopsy, and in 37% patients operative biopsy or tumor reduction. We performed radical surgery, hemithyroidectomy or total thyroidectomy, in 13% patients with anaplastic thyroid cancer. Thyroid goiter was present in 35% patients longer than a year before diagnosis of anaplastic cancer was made.

**Conclusion:** Possibility of surgery for anaplastic thyroid cancer is very limited. In about one third of patients there were longstanding goiter or histological verified dedifferentiation of papillary thyroid cancer. These patients should have been operated before anaplastic transformation.

Galectin-3: a promising marker of thyroid malignancy

**Background:** Galectin-3 is an endogenous beta-galactoside binding lectin implicated in neoplastic transformation and tumor progression. High levels of this lectin have recently been found in malignant thyroid tumors, but not in normal or benign thyroid tissue, suggesting galectin-3 as a promising presurgical marker of thyroid malignancy.

**Methods:** We analyzed immunohistochemically galectin-3 expression in thyroid tissue using a monoclonal antibody. The total of 108 tissue specimens included 55 cases of thyroid carcinoma (30 papillary, 15 follicular, and 10 anaplastic type), 15 samples of follicular adenoma, 15 samples of normal thyroid tissue, and 23 thyroid tissue specimens from human fetuses (16 to 37 weeks of intrauterine life).

**Results:** The results showed galectin-3 expression in 20/30 papillary carcinomas, 11/15 follicular carcinomas, 10/10 anaplastic carcinomas, and 4/15 follicular adenomas. Thyroid follicular cells in normal adult and fetal tissue were negative.

**Conclusions:** These results further confirm that galectin-3 expression is a feature of malignant thyroid cells, and that immunohistochemical detection of galectin-3 could be useful in thyroid carcinoma diagnostics. The absence of galectin-3 in thyroid cells during fetal development suggests that galectin-3 is expressed de novo during malignant transformation of thyroid epithelium, thus it should not be considered an oncofetal antigen.
Incidence of difficult intubation in thyroid gland surgery

Background: Difficult intubation (DI) occurs in 1% to 3% in general population, and unsuccessful intubation in 0.04%. DI may cause a lot of undesirable effects during prolonged intubation period, including lethal outcome. The aim of the study was to establish the incidence of DI in thyroid gland surgery and to compare the incidence of DI to predicted DI due to different DI screening tests.

Methods: Prospective study included 2000 patients which underwent thyroid gland surgery in Center for endocrine gland surgery, Clinical Center of Serbia, Belgrade, during 1999-2001. 436 of them were thyroid carcinoma, 525 were nodal goiter, 671 polynodal goiter and 368 hyperthyreosis; 1705 female, 295 men, average age 48.1 year. According to ASA classification (American Society of Anaesthesiologist's classification for correlation between co-existing diseases and perioperative complications) there were 886 ASA I, 901 ASA II and 213 ASA III. We used Mallampathi classes, Wilson criteria and Cormack-Lehane (CL) criteria to predict DI, and CL criteria to define DI. The complications during DI were analyzed and the ratio of DI to predicted DI was established.

Results: There were 110 DI - 84 women, 26 men. Considering diagnosis there were 24, PS 42, H 22. ASA III were 9.38%, ASAII 5.77, ASA I 4.28%. There were 3 unsuccessful intubations. Complications during DI were noted in 32 patients. Ratio between expected DI and actual DI, and unexpected DI and DI were: 12.77% failed positive and 0.45% failed negative results.

Conclusion: Incidence of DI in thyroid gland surgery is twice more in men than in women. Screening tests for prediction DI showed higher specificity than sensitivity.

Combined chemotherapy and irradiation in anaplastic thyroid carcinoma

Background: Anaplastic thyroid carcinoma (ATC) is a very rare and extremely aggressive cancer; patient's death usually occurs rapidly after diagnosis, with a mean survival of six months in the majority of individual research series. Treatment of ATC ranges from surgery, radiotherapy, chemotherapy, or a combination of these regimes. Yet, the optimal sequence of treatment modalities has not been established.

Methods: From 1997 to 2002 six consecutive patients with a histological diagnosis of ATC were treated with combined chemotherapy and irradiation at our Clinic for Oncology, Clinical Center Niš. Five of these patients were females and 1 male, aged between 28 and 71 years (mean age: 57 years). None of them had distant metastases at the time of diagnosis. Extrathyroid extension was present in 3 patients, with invasion into skin and hypoderm. Treatment consisted of doxorubicin 60 mg/m² plus cisplatin 60 mg/m² every three weeks. Total doses ranged between 158-375 mg/m² for doxorubicin and 183-380 mg/m² for cisplatin. External beam radiation to the neck was administered, at a daily dose of 1.2 Gy, up to total doses ranging between 45-60 Gy.

Results: One patient achieved a complete response (CR) and one patient achieved a partial response (PR). Three patients had stable disease. One patient with CR progressed during follow-up and died 18 months from bone and brain metastases. The treatment was moderately well tolerated, although all patients experienced some mild form of toxicity; neutropenia occurred in all patients, but none of them required hospital admission. Median survival was 8 months (range: 4-18 months).

Conclusion: We concluded that the present regimen produces meaningful responses for patients with localized ATC. A randomized study is needed to determine the effect on survival.