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Prognostic factors in well-differentiated thyroid carcinoma in patients treated and followed in the same Institution

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AIM: *To test the prognostic significant of clinicopathologic factors in patients affected by well-differentiated thyroid carcinoma (WDTC).*
METHODS: *A retrospective review of patients treated for WDTC (thyroidectomy and a radioactive iodine (I131) thyroid ablation) at our Institute with a minimum of 10 years of follow-up was carried out. The unfavourable prognosis at the end of the follow-up was defined as persistence/recurrence of WDTC or death due to the cancer.*
RESULTS: *234 patients (162 female, 72 male), mean age of 47.6±16.6 years, were included in this study (mean follow-up 158.4±34.8 months): 78 (33.4%) subjects had persistence/recurrence of neoplasia while 5 (2.1%) died for cancer. The multivariate regression showed that prognostic factors were old age, size of cancer, detectable thyroglonulin levels six months after metabolic ablation, and DeGroot staging system.*
DISCUSSION: *Our mortality rate is lower (2.1%) than reported in literature (10%): this could be explained by the different pathological classification and treatment. The mortality rate appears higher in patients treated with emitiroidectomy and TSH suppressive therapy than in those with total thyroidectomy and I131 ablation. Even if we have chosen an "aggressive" therapy and our mortality rate is lower, one third of patients have persistence/recurrence of cancer: it seems that tumour recurrence rate better reflects clinical problems related to cancer.*
CONCLUSION: *WDTC has with a good disease-specific survival but a significant recurrence rate. The most important predictors are the old age and the size of lesion. We suggest a radical surgery followed by radiometabolic ablation in all patients with WDTC.*

KEY WORDS: Differentiated thyroid carcinoma, Management, Prognostic markers.

Introduction

Well-differentiated thyroid carcinoma (WDTC) accounts for approximately 90% of all thyroid malignancies [1]. Even if WDTC represents less than 1% of all human cancers [2] and it's considered a slow growing neoplasia with indolent course [3], it's responsible for nearly 70% of all deaths from thyroid tumours [4]. Several publications have investigated the clinical pathological features and molecular biology of WDTC to identify prognostic factors [5-11]. These reports have given conflicting results and the authors believe that it may be due to the different pathological classification and treatment modalities and, above all, to the fact that patients were not always treated in the same way and followed in the same institution.
For this reason, in order to test the prognostic significant of clinicopathologic factors in patients with WDTC we have carried out and reviewed the clinical history of our patients treated with the same modalities and followed in our Institute from 1980.

Material and methods

A retrospective review of patients treated for thyroid can-

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cers at our Institute from 1980 to 2005 was carried out. All patients consecutively treated for WDTC with a minimum of 10 years follow-up were eligible for inclusion in the study.
Patients died for causes not related to thyroid carcinoma were excluded from the study. All the pathological features (histology, size, multifocality, extrathyroidal spread….) were collected from the pathological reports. All the cancers were classified according to the system proposed by DeGroot et al. (stage I: intra-thyroidal; stage II: lymph node involvement; stage III: extra-thyroidal spread; stage IV: distant metastasis) [12].
In all the patients a radioactive iodine (I^{131}) thyroid ablation (30 mCi) was given 4-5 weeks after radical surgery in hypothyroidism. All patients with positive whole body scan (WBS) or negative WBS but with detectable thyroglobulin (Tg) serum levels in absence of antibodies anti-Tg, were treated many times with high doses I^{131} (100 mCi) to normalize WBS and/or thyroglobulin levels. All patients were treated with a to TSH suppressive L-tiroxine sostitutive theraphy according to the TSH sensitivity of our laboratory (IRMA Co Tube 2ª generation; normal range: 0.2-4.0 m IU/L-BIORAD,HERCULES,CA,USA). The clinical follow-up was performed every 6-month for the first 5 years and then yearly. The follow up period was calculated from the end of the primary treatment to the last contact. The occurrence of unfavourable clinical course at the end of the follow-up was defined as persistence and/or recurrence of the disease (elevated serum thyreoglobulin levels and/or positive I^{131} WBS) or death due to thyroid cancer. Thyroglobulin was measured with RIA KRONUS KIT (KRONUS CORP-San Clemente Ca) with a detection limit of 1 µg/l. Anti-Tg antibodies were also measured by radioimmunoassay (Thymune-T, Murex Diagnostics, Dartford, United Kingdom).

Statistical analysis

Comparison of frequency distributions was performed by χ^2 test, with a conventional significance level set at $p<0.05$. Multivariate analysis was done with a stepwise Cox proportional hazard regression model that included all the variables that were statistically significant in the univariate analysis for the development of recurrence and disease-specific survival.
Data were collected by Windows '98 program. All statistics were analysed using SPSS Software, version 11.5 (Chicago, IL).

Results

Two hundred and thirty-four patients (162 female, 72 male), mean age of 47.6±16.6 years (range 10 to 88), with a diagnosis of WDTC were eligible for inclusion in this study.
No patients had previously exposure to ionizing radiation. One hundred ninety-four patients (83%) had a total thyroidectomy in a time while 40 (17%) subjects in a second time, after a partial resection. In these cases the second surgery was performed from two to four weeks after the first. An histological diagnosis of papillary cancer (PTC) was obtained in 168 (71.7%) patients, follicular (FTC) in 54 (23%) and Hurtle cancer (HTC) in 12 (5.3%) patients. All the patients were followed in our Institute and the mean follow-up was 158.4±34.8 months. Overall, 78 (33.4%) subjects had persistence and/or recurrence of neoplasia while 5 (2.1%) patients died from cancer. Table I resumes the statistical significance of all the prognostics factors.

Gender

At time of diagnosis male patients presented nodal involvement significantly more frequent than female (44.4% vs 29%, p=0.005), a difference that disappeared during follow-up (p=0.338).
Among the WTDC patients, 55 (33.9%) female and 28 (38.9%) male subjects had an unfavourable clinical course or died during the follow-up; gender was not a predictor of the outcome (p=0.466).

Age

At time of surgery male patients were younger than female (42.2±18.5 yrs vs 45.6±16.9 yrs, p=0.002). Among the patients with an unfavourable clinical course, 56 (67.8%) subjects were older than 45 years compared to 59 (39.1%) patients free of disease (p<0.001). Also the presence of distal metastasis, in particularly bone metastasis, at diagnosis or developed during follow-up was significantly associated to the patients older than 45 years old (p<0.001).
The patients with age between 10 to 20 yrs old presented, at time of surgery , a significant increase of nodal involvement compared to all the other (24.7% vs 8.5%, p=0.007), but these patients were also associated with a

Table I – *Showed the statistical significance of all the prognostics factors at the end of follow-up.*

	Univariate Analysis	Multivariate Analysis
Gender	NS	NS
Age ≥45 years	p<0.001	p<0.01
Histology (HTC)	p=0.005	NS
Size ≥50 mm	p=0.021	p=0.002
Extra-thyroidal extension	NS	NS
Multifocality	NS	NS
Vascular Invasion	NS	NS
Nodal involvement	NS	NS
Thyreoglobulin	p<0.001	p<0.001
DeGroot staging system	p<0.002	p=0.006

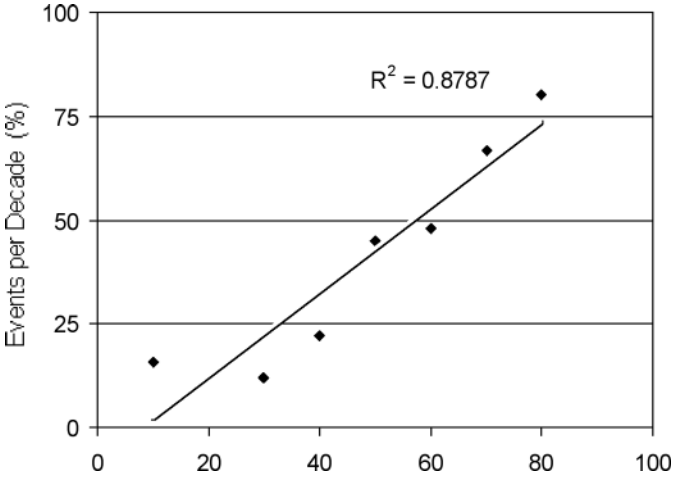

Fig. 1: Tumour recurrence and cancer deaths according to the patient's age at the time of diagnosis.

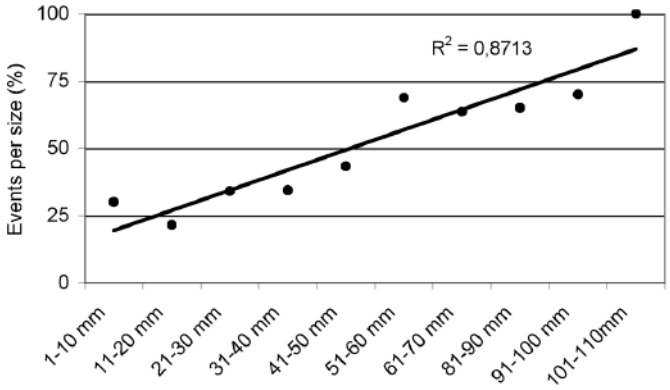

Fig. 2: Tumour recurrence and cancer deaths according to the size of cancer age at the time of diagnosis.

favourable clinical course (72.4% vs 27.6%, p<0.001). Figure 1 shows the correlation between the decades of age and the outcome.

Histology

A histological diagnosis of papillary cancer (PTC) was obtained in 168 (71.7%) patients, follicular (FTC) in 54 (23%) and Hurtle cancer (HTC) in 12 (5.3%) subjects.

PTC was the cancer with the higher prevalence of lymph node involvement at diagnosis and also at follow-up (p<0.001 and p=0.003 respectively). During the follow-up FTC and HTC resulted significantly associated to pulmonary and bone metastasis (p=0.002 and p<0.001, respectively).

Among the 83 patients with an unfavourable clinical course 29.2% were affected by PTC, 50% by FTC and 58.3% by HTC. At univariate analysis only the histological Hurtle cancer was associated with a worse outcome (p=0.005), but this result disappeared at multivariate analysis.

Size

At histological examination the mean diameter of PTC, FTC and HTC were 27.1±17 mm, 45.8±17.9 mm and 30.9±9.3 mm, respectively. Figure 2 shows the correlation between the mean diameter of tumours and the outcome. The presence of nodal involvement at surgery or coming up during the follow-up was not associated to size (p=0.172 and p=0.398, respectively), even not the presence of extracapsular extension of the tumour (p=0.153). Our data showed a strict correlation between the size of cancers and the outcome. In particular cancers with a diameter ≥50 mm were correlated to worse prognosis, independently of histological type (p=0.021).

Extra-thyroidal extension

Forty six (19.7%) patients presented at the histological examination a WDTC with extra-thyroid spread; papillary cancer was the more frequently associated to extra-thyroid extension 34/41 (78 %) than FTC 9/46 (20%) and HCT 1/46 (2%). Our data showed no correlation between extra-thyroid extension and the age of patents or the cancer size (p=0.563, p=0.765, respectively). At time of diagnosis, among the patients with extra-thyroid extension, 16 (34.7%) subjects had nodal involvement, 4 (8.7%) pulmonary metastasis and 2 (4.3%) bone metastasis. No correlation was seen among extra-thyroid spread and the presence of metastasis at time of diagnosis. During the follow-up 16 (34.7%) subjects developed nodal metastasis, 12 (36%) pulmonary and 6 (13%) patients developed bone metastasis, but again these data were not statistically significant (p=0.816, p=0.413, p=0.623).

At the end of follow-up 17 (36.9%) patients were free of disease. Our data showed that extra-thyroid extension was not associated to the outcome of thyroid cancer (p=0.814).

Multifocality

Multiple foci of tumour within one lobe or both lobes were present in 51 (21.8%) patients with a prevalence of in PTC 41/234 (80.3%), in FTC 9/51 (19.6%) and HTC 1/51 (0.1%), even if this association had not a statistical significance (p=0.249). At time of surgery 17 (33.3%) patients with multifocality had nodal involvement, 2 (0.3%) subjects bone metastasis and no one had pulmonary metastasis. During follow-up 23 (45%) patients presented nodal involvement while pulmonary and bone metastasis came up in 12 (23.5%) and 10 (19.5%) patients, respectively.

The presence of multifocality resulted a risk factor for developing only nodal involvement during follow-up

(p=0.004). Among the 51 patients with multifocality, 31 (60.7%) were free of disease at the end of follow-up; multifocality was not associated with the outcome of the patients (p=0.527).

Vascular invasion

The vascular invasion at least of one vessel was present in 17 (7.3%) patients. FTC was the only cancer to be significantly associated to vascular invasion 10/17 (59%) (p<0.001). No correlation was found between the presence of vascular invasion and the age of patients or the cancer size (p=0.763, p=0.327, respectively). At surgery time, among patients with vascular invasion, only 1 (0.8%) patient had nodal metastasis, while 3 (21.2%) had bone metastasis. During follow-up 2 (12.4%) subjects had nodal involvement, 3 (21.2%) pulmonary metastasis and 6 (35.2%) patients had bone metastasis. Vascular invasion was strongly associated to the presence of bone metastasis at time of cancer diagnosis (p<0.001). Among the patients with vascular invasion 6 (35.3%) subjects were not free of disease at the end of follow-up. Our data showed that vascular invasion was not correlated to the outcome (p=0.814).

Nodal involvement

At time of surgery 67 (38.6%) patients had nodal involvement, among them, 25 (37.6%) subjects had an unfavourable clinical course at the end of the follow-up. The presence of nodal involvement at time of cancer diagnosis was not correlated to a worse prognosis (p=0.710). During follow-up 58 (24.7%) patients developed nodal metastasis; among them 9 (15.5%) subjects had a worse outcome, but again the development of nodal involvement was not correlated to the prognosis even if with a borderline statistical significance (p=0.063).

Thyroglobulin

Six months after thyroid ablation, 36 (15.4%) patients, in hypothyroidism, had not detectable thyroglobulin serum levels: among them 7 (19.4%) developed nodal involvement and 1 (2.9%) pulmonary metastasis. Eight patients had not detectable thyroglobulin serum levels but they had positive antibodies anti-thyreoglobulin (false negative). Among "false negative" patients, 1 (12.5%) subject developed nodal involvement and 1 (12.5%) pulmonary metastasis. One hundred and ninety patients had detectable thyroglobulin levels: 17/190 (36.8%) developed nodal involvement, 49/190 (25.8%) and 36/190 (18.9%) developed pulmonary and bone metastasis, respectively. At the end of follow-up only 1 (2.8%) patient, among them with not detectable thyroglobulin levels, had a not favourable clinical course, and 1 (12.5%) among the "false negative" cases. Eigthy one (42.6%) subjects, among those with detectable thyroglobulin serum levels, had an unfavorable course.
Our data showed a correlation, with borderline statistical significance, between the presence of thyroglobulin and the developing of nodal involvement (p=0.057). On the contrary, the presence of thyroglobulin serum levels six months after thyroid ablation was strongly associated to a worse prognosis (p<0.001).

De Groot staging system

According to DeGroot's stadiation, 121 (51.7%) patients were classified in stage 1, 56 (23.9%) in stage 2, 45 (19.2%) in stage 3 and 12 (5.2%) in stage 4. At the end of the follow-up 36 (29.8%) patients from stage 1, 18 (32.1%), 19 (42.2%) and 10 (83.3%) patients from stage 2, 3, 4 respectively, had an unfavourable clinical course. Our data showed that Degroot's stadiation was strongly correlated to the outcome of the patients (p=0.006).

Discussion

WDTC is considered a slow growing neoplasia with an indolent course [3], even if its mortality rate has been reported to be 10% approximately [4-6,12-15]. Our data, on the contrary showed a mortality rate of 2.1%. The authors believe that this difference could be explained by the different pathological classification and treatment modalities of the thyroid cancers. In fact, in literature it appears that the mortality rate is higher in all the patients treated with emitiroidectomy and followed only by a TSH suppressive therapy than in those treated with total thyroidectomy and a I^{131} ablation, as reported by Schumberger and recently by Sherman [16,17]. Even if we have chosen an "aggressive" therapy and our mortality rate is lower it is important to underline that approximately one third of patients have persistence or recurrence of cancers; this could show that tumour recurrence rate better reflects clinical problems related to cancer. In literature the role of gender as predictor of outcome is still matter of discussion. In the majority of studies, men have a worse prognosis than women [5,6,15,18,19]. However, some large studies have failed to show any correlation between patient gender and prognosis [5,6]; and also our study shows that gender is not a predictor of outcome. We found also a statistical higher prevalence of nodal involvement in men than in women at time of diagnosis (p=0.005), difference that disappeared during the follow-up. Age at tumour diagnosis has been found to be an important prognostic factor in WDTC [3,5,13,20]; also our study showed a linear increase in cancer recurrence and death related to the patient age, especially after 45 yrs of age (p<0.01, OR=2). Older patients presented distant metastasis, in particular a bone involvement, at diagnosis and/or developed them during the follow-up more often than young people (p<0.001). As already

shown, adolescents have an excellent prognosis even presence of extensive local disease and distant metastasis [3]. In agreement with literature data, our patients with age between 10 to 20 yrs old presented a significant increase of nodal metastasis at time of diagnosis (p=0.007), but they also showed a favourable clinical course (p<0.001).

Many studies reported a worse prognosis in patients affected by HTC and FTC than in those affected by papillary carcinoma [21-25]. In our series, we found that patients affected by HCT and FTC presented a higher number of distant metastasis at diagnosis or during follow-up than those affected by papillary cancer (p=0.025, p=0.001 respectively) but no correlation at multivariate analysis was found between histotypes and prognosis.

Interestingly, we found that all the tumours (independently from the histotype) with diameter greater than 50 mm had the worst prognosis at multivariate analysis (p=0.002, OR=2). Large tumours (40 mm or more) are associated with extra-thyroid spread [3,19,26], but it's unclear from the published studies, if the tumour extension rather than the size is the factor affecting the prognosis [3,20,27,28]. We have clearly demonstrated that extra-thyroid extension is not associated with the outcome of thyroid cancer, and moreover, our data have shown no correlation between extra-thyroid spread and the cancer size (p=0.765).

It's known that papillary carcinoma is frequently multifocal [29-34]. Recently, Shattuck et al. have demonstrated that tumour foci in multifocal papillary cancer are monoclonal suggesting that these lesions are indeed carcinomas that can grow and spread [35]. This evidence supports that all the patients with papillary carcinoma must be submitted to a total thyroidectomy and also to a radiometabolic I^{131} ablation, in order to limit the number of recurrences and deaths [35]. As reported by Schumberger and recently by Sherman, the presence of multifocality in patients treated in an " aggressive" way such as in our patients, was associated with the outcome [16,17]. Also our data showed that the majority of patients with papillary carcinoma presented multiple foci of neoplasia (80.3%), but in our study the presence of multifocality is not correlated with the prognosis.

The relevance of vascular invasion in WDTC is already a matter of discussion [28]. Gardner et al. showed that this feature was associated to a worse prognosis [36]; on the contrary our data showed a strict correlation only between vascular invasion and the presence of bone metastasis at time of diagnosis (p<0.001), but again this parameter was not associated with prognosis.

The rate of nodal involvement in papillary carcinoma has been reported to range from 47% to more than 80% [37]; many authors have suggested that nodal involvement is an adverse prognostic factor, whereas other have found it to be of no prognostic significance [5,6,8,9,39-42]. As we expected, lymph node metastasis were more frequent in papillary cancer than in the other tumour histotypes. Our data showed that nodal recurrence was not an independent predictor of prognosis (p=0.073).

In 1990, DeGroot et al., developed a clinical class staging system based on disease extent [12]; its simplicity and relative prognostic accuracy lends it popular support, and it continues to be used in staging patients with WDTC. Multivariate analisys indicated that this score system was well correlated to the outcome of the patients (p=0.006, OR=3.1).

As it is known, well-differentiated thyroid carcinomas express thyroglobulin; therefore it is routinely detected in the follow up of these cancers, after a radical treatment [28]. It has been reported that the detection of serum thyroglobulin in withdrawing L-tiroxine therapy patients or after TSH stimulation during follow-up is a strong indicator of persistence and/or recurrence of disease [43]. Our data indicated that the detection of serum thyroglobulyn levels at six months after thyroid ablation is a strong indicator of prognosis (p<0.001, OR=15.3) independently of the presence or not of imaging indicating persistence or recurrence of disease.

Conclusion

Our data, obtained from patients treated with the same modalities (total thyroidectomy followed by radiometabolic ablation) and followed in the same Institution, have clearly demonstrated that WDTC has a lower mortality rate than previously reported; however the choice of an "aggressive therapy" has not reduced the frequency of persistence or recurrence of cancer. Patients older than 45 years or presenting detectable thyroglobulin levels at six months after radiometabolic ablation are those with the worst prognosis.

Riassunto

OBIETTIVO: Valutare il significato prognostico delle caratteristiche clinico-patologiche in pazienti con carcinoma ben differenziato della tiroide (WDTC).

MATERIALE DI STUDIO: Sono stati analizzati retrospettivamente pazienti trattati per WDTC (tiroidectomia totale e radioablazione del residuo con I^{131} (30mCi)) e seguiti presso il nostro Istituto da almeno 10 anni. Al termine del follow-up i pazienti deceduti o con persistenza di malattia sono stati classificati come non guariti.

RISULTATI: 234 pazienti arruolati (162 femmine, 72 maschi) con età media di 47.6±16.6 anni e follow-up di 158.4±34.8 mesi: 78 (33.4%) presentavano persistenza di malattia, mentre 5 (2.1%) sono deceduti per WDTC. All'analisi statistica sono risultati predittivi di malignità l'eta avanzata, le dimensioni della neoplasia, tireoglobulina dosabile sei mesi dopo radioablazione e la classificazione neoplastica secondo DeGroot.

DISCUSSIONE: L'indice di mortalità del nostro studio è inferiore (2.1%) a quanto riportato in letteratura (10%):

questo può essere spiegato in base alla differente stadiazione del WTDC ed al differente approccio terapeutico. La mortalità è risultata maggiore in pazienti trattati con emitiroidectomia e terapia soppressiva che in pazienti sottoposti a tiroidectomia totale e radioablazione. Pur avendo adottato una terapia "aggressiva" ed ottenuto un livello di mortalità inferiore, un terzo dei pazienti ha presento persistenza/recidiva di malattia: la persistenza di malattia sembra quindi riflettere meglio l'andamento clinico della malattia.

CONCLUSIONE: WDTC presenta un'ottima sopravvivenza anche se un'elevata probabilità di recidiva/persistenza di malattia. Fattori prognostici negativi sono l'età avanzata e le dimensioni del tumore. Suggeriamo sempre un approccio chirurgico radicale seguito da terapia radioablativa in tutti i WDTC.

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