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Combined treatment and survival of medullary thyroid carcinoma patients

Research Article

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Abstract: The aim of this study is to analyze the impact of combined treatment (thyroidectomy and radiotherapy and radioactive iodine treatment) on patients' long-term survival with medullary thyroid carcinoma. This is a retrospective study of 59 patients treated from 1977 to 2006 for medullary carcinoma at the Institute of Oncology in Vilnius, Lithuania. Survival was estimated by the Kaplan-Meier method. Univariate and multivariate Cox proportional hazard models were used to explore the association of prognostic factors with long-term survival. The survival of MTC patients was 88.0% (95% CI 68.0-88.9), 67.9% (95% CI 52.3-79.4) and 60.5% (95% CI 43.2-74.0), respectively, 5, 10 and 15 years after diagnosis. In survival analysis, only the type of surgery and lymph node involvement were found to be significant prognostic factors. The results of this study suggest that treatment with radioiodine and external beam radiotherapy do not improve significantly the long-term survival of surgically treated MTC patients.

Keywords: *Medullary carcinoma • Thyroidectomy • External beam radiotherapy • ^{131}I radiotherapy*

1. Introduction

Medullary thyroid carcinoma (MTC) is a relatively rare carcinoma, neuroendocrine neoplasm originating from calcitonin secreting C cells in the upper lateral lobes of the gland. Management of MTC remains controversial, despite many advances over the last decades. MTC is classically managed with surgery alone [1,2]. Adjuvant therapies like radiation therapy, chemotherapy and radioiodine therapy have doubtful benefits. Unlike differentiated thyroid cancers, MTC is not iodine-avid and cannot be treated with systemic radioiodine. MTC has garnered a reputation as being resistant to external beam radiotherapy (EBRT); not surprisingly, patterns-of-care data confirm that EBRT is delivered to less than 15% of patients with MTC [3,4]. Limited data exist to substantiate or refute this practice. Available institutional outcomes data, however, do suggest that radioiodine; external radiotherapy improves locoregional disease control in high-risk cases, despite the lack of an impact on overall survival [5-9].

The aim of this retrospective study was to analyze the impact of combined treatment (thyroidectomy and external radiotherapy and radioactive iodine treatment) on long-term patients' survival with MTC.

2. Material and Methods

2.1. Patients

The study group consisted of patients treated at the Institute of Oncology, Vilnius University for MTC between January 1977 and December 2006. We performed a retrospective search of data on all patients who underwent thyroid surgery, and the diagnoses of MTC were all confirmed on the histology of resected specimens. A total of 59 patients were identified. Data on type of surgery, extent of disease and treatment was collected from the medical records. Clinical data of these patients were used for survival analysis.

There were 59 cases - 16 men and 43 women. The mean age of patients was 48.0±13.8 years (median 49;

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Table 1. Demographic and clinical characteristics and treatment options of a study group (n = 59 Patients).

Variable	No. of patients	% of total
Gender		
Male	16	27.1
Female	43	72.9
Age, years (median, 49 years)		
50	30	50.8
>50	29	49.2
Tumor classification		
T_1	5	8.5
T_2	20	33.9
T_3	15	25.4
T_4	19	32.2
Lymph node classification		
N_0	37	62.7
N_1	22	37.3
M status		
M_0	59	100.0
M_1	0	-
Surgery		
Thyroidectomy	37	62.7
Thyroidectomy with lymphadenectomy	22	37.3
Treatment options		
Surgery alone	7	11.9
Surgery& EBRT	19	32.2
Surgery& EBRT &^{131}I	33	55.9

range 15-77 years) (Table 1). There were no differences in male and female mean age, 48.8±16.5 and 47.7±12.9 respectively. Fifty-six patients were classified as sporadic, and 3 patients as familial cases. Patients with familial MTC had not undergone genetic analysis; however, they had first-degree relatives with MTC.

2.2. Treatment

A thyroidectomy was performed on all patient; 22 patients with lymph node metastases underwent cervical lymph node dissection. The type of lymph node dissection for all patients was performed according to the therapeutic strategy for MTC in our Institute. Routine procedure was performed via central node dissection and also modified radical neck dissection at least on the side ipsilateral to the primary lesion, regardless of whether clinically apparent lymph node metastasis was preoperatively detected. Fifty-two patients received postoperative conventional EBRT to median dose of 44 Gy (38-60 Gy), 33 patients received radioactive iodine ^{131}I to median dose of 4.6 GBq (2.6-13.8 GBq), and 7 patients were treated only surgically. EBRT median dose was 44 Gy (38-60 Gy) via extended opposed anterior/posterior fields supplemented by off-cord photon boost after delivery of 45 Gy. Thirty-three patients received radioactive iodine ^{131}I to median dose of 4.6 GBq (2.6-13.8 GBq). Patients were treated with moderate radioiodine doses (1.11-3.7 GBq) and this dosage was repeated every 3-4 months. Radioactive iodine ^{131}I was administered to the hypothyroid patients, 3 to 12 weeks after surgical treatment or external beam radiotherapy. All 59 patients were treated with L-thyroxin and L-thyroxin doses adjusted to keep the TSH in the normal range (0.17-4.05 μIU/ml). The level of serum calcitonin is well known as a prognostic factor on long term MTC patients' survival. Unfortunately, in Institute of Oncology measurement level of serum calcitonin is not routine procedure; thereafter in survival analysis this important prognostic factor was not included.

2.3. Statistical Methods

The numeric variables were presented as mean ± SD. The vital status of the study group was assessed as of September 1, 2009, by passive follow-up, using data from the population registry. It was found that 20 (33.9%) of the patients had died. Survival was estimated by the Kaplan–Meier method. Univariate and multivariate Cox proportional hazard models were used to explore the association of prognostic factors with long-term survival. First, univariate analysis was performed and included any potential prognostic factor. Thereafter, only variables with a value of $P < 0.20$ by univariate analysis were introduced in the multivariate Cox proportional hazard model. $P < 0.05$ indicated a significant statistical difference. All statistical analyses were performed using Stata Statistical Software version 11 (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX, USA).

3. Results

The mean follow-up time was 9.2±5.7 years (range 1.5-26.8 years). The overall survival of MTC patients was 88.0% (95% CI 68.0-88.9), 67.9% (95% CI 52.3-79.4) and 60.5% (95% CI 43.2-74.0), respectively, 5, 10 and 15 years after diagnosis.

Results of univariate analysis are shown in Table 2. Better survival was related to female sex, younger patient age, and smaller tumour size and absent lymph node metastases. Univariate analysis demonstrated that the following were significant risk factors for long-term survival: patient sex, lymph node status, and type of surgery. Cervical lymph node metastases and surgery type in our group of patients were correlated variables;

Table 2. Prognostic factors on long term survival of MTC patients (univariate analysis).

Variable	Hazard ratio	95% CI	P
Gender			
Male	1.00	ref	
Female	0.38	0.15-0.97	0.04
Age			
50	1.00	ref	
> 50	2.02	0.78-5.26	0.15
Tumor classification			
T_1-T_2	1.00	ref	
T_3	1.26	0.38-4.17	0.70
T_4	2.83	0.93-8.62	0.07
Lymph node classification			
N_0	1.00	ref	
N_1	4.00	1.56-10.2	0.004
Surgery			
Thyreoidectomy	1.00	ref	
Thyreoidectomy with lymphadenectomy	4.00	1.56-10.2	0.004
EBRT			
no	1.00	ref	
yes	0.75	0.17-3.31	0.71
^{131}I			
no	1.00	ref	
yes	1.39	0.52-3.71	0.51
Treatment			
Surgery alone	1.00	ref	
Surgery& EBRT	0.52	0.09-2.92	0.46
Surgery& EBRT &^{131}J	0.87	0.19-3.93	0.86

therefore, for further analysis we included in the model only surgery type. The remaining variables, such as age, EBRT and ^{131}I application for treatment, were not statistically significant. Age of patient and tumour size was also included in the multivariate analysis, because these variables could be relevant to the final model (P value less than 0.2).

At multivariate statistical analysis (Table 3) the only significant independent prognostic variable influencing survival was surgery type (with or without lymphadenectomy). Patients who underwent major surgery (thyroidectomy with lymphadenectomy) showed a worse prognosis and survival than other patients: this was related to the advanced disease of those patients.

Table 3. Prognostic factors on long term survival of MTC patients (multivariate analysis).

Variable	Hazard ratio	95% CI	P
Surgery			
Thyreoidectomy	1.00	ref	
Thyreoidectomy with lymphadenectomy	3.42	1.19-9.78	0.02

4. Discussion

MTC is a relatively rare carcinoma. Although MTC typically grows slowly, it is lymphotropic and is frequently (especially in hereditary cases) accompanied by multifocal and/or bilateral glandular involvement. Up to 50-80% of patients with palpable disease have nodal involvement, with the central compartment most commonly affected, followed by the ipsilateral and contralateral cervical nodal chains and superior mediastinum. Distant metastasis to various organs can also occur early in the course of the disease [10,11]. The 5, 10 and 15-year survival of MTC patients varies. The overall survival rate of MTC in our study was similar to other studies: 5-year survival rate in our study was 88.0%, in other studies 69.0-97.7%, 10-year survival rates 67.9% and 52.0-91.0%, 15-year survival rates 60.5% and 54.0-85% [5-9].

There are numerous studies on prognostic factors in patients with MTC [5-9,12,13]. In our study we have evaluated the influence of patient sex, age, type of surgery, tumour size, lymph node involvement, and type of treatment on long-term survival. Univariate analysis demonstrated that for long-term survival, patient sex, lymph node status and type of surgery were significant risk factors. At multivariate statistical analysis, the only significant independent prognostic variable influencing survival was surgery type (with or without lymphadenectomy). Our data is in accordance with other studies [5,7,12,13].

In the studied group, postoperative EBRT and radioiodine treatment did not influence overall long-term survival rates of MTC patients. Currently, the role of EBRT in MTC is controversial; however, some evidence suggests that EBRT may improve locoregional disease control in high-risk patients, although an improvement in overall survival has not been established [14-19]. In patients with a macroscopic residual tumour in the neck after incomplete surgery, Schlumberger M et al. [16] advocated EBRT for local disease control. Brierley J et al. [17] reported in a series of MTC patients that the local/regional relapse-free rate between patients that received EBRT and those that did not was no different;

however, in high-risk patients (microscopic residual disease, extra glandular invasion, or lymph node involvement), the local/regional relapse-free rate was 86% at 10 years with postoperative EBRT, and 52% for those with no postoperative EBRT (p=0.049).

The role of postoperative radioiodine treatment, how of EBRT in MTC is controversial. Some studies suggested, that selected patients might benefit from the use of ^{131}I treatment as an adjunct to surgery in medullary thyroid carcinoma [20,21]. However, recent studies do not confirm that radioactive iodine treatment plays a role in the postoperative management of patients with MTC, either as remnant ablation or treatment of residual, recurrent, or metastatic disease [4,22]. The results of our study suggest, too, that EBRT and treatment with radioiodine do not improve significantly the long-term survival of surgically treated MTC patients.

In conclusion, the results of this study suggest that EBRT and treatment with radioiodine do not improve significantly the long-term survival of surgically treated MTC patients.

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