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Long-term follow-up of patients with medullary carcinoma of the thyroid: a 30-year experience

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Background. The aim of the study was to analyze the impact of combined treatment (thyroidectomy, external beam radiotherapy and radioactive iodine treatment) on the long-term survival of medullary thyroid carcinoma patients.

Methods. This is a retrospective study. In 1977–2006 59 patients (43 female, 16 male, median age 49 years, range 15–77 years) were treated for medullary carcinoma at the Institute of Oncology Vilnius University, of them 56 patients were classified as sporadic and 3 patients as familial cases. Thyroidectomy was performed for all patients; 22 patients with lymph node metastases underwent cervical lymph node dissection; 52 patients received postoperative conventional external beam radiotherapy (EBRT) at a median dose of 44 Gy (38–60 Gy), 33 patients additionally received radioactive iodine ^{131}I (RAI) at a median dose of 4.6 GBq (2.6–13.8 GBq), 7 patients were treated only surgically. All 59 patients were treated with L-thyroxine; the dose was adjusted to keep the TSH in the normal range (0.17–4.05 μIU/ml). The survival was estimated by the Kaplan–Meier method. The statistical difference between the survival curves was determined using the log-rank test.

Results. 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 the survival analysis, only patients' sex and lymph node involvement were found to be significant prognostic factors.

Conclusions. The results of the study suggest that treatment with radioiodine and external beam radiotherapy do not improve significantly the long-term survival of surgically treated MTC patients.

Key words: medullary carcinoma, thyroidectomia, ^{131}J, external beam radiotherapy

INTRODUCTION

Medullary thyroid carcinoma (MTC) is a relatively rare carcinoma. It is a neuroendocrine neoplasm originating from calcitonin-secreting C cells in the upper lateral lobes of the gland. It is an uncommon diagnosis representing 5% to 10% of all thyroid cancers and up to 14% of all thyroid carcinoma-related deaths. MTC is sporadic about 75% and hereditary in 25% of cases (1–5). One fourth of cases are associated with one of the three autosomal dominant hereditary cancer syndromes: multiple endocrine neoplasia type MEN 2A, MEN 2B, and familial non-MEN MTC (6, 7). The genotyping of affected kindred has identified germ line mutations in the RET oncogene, which are now known to be responsible for all hereditary cases (8). Although MTC typically grows slowly, it is lymphotropic and frequently (especially in hereditary cases) presents with multifocal and/or bilateral glandular involvement. Up to 50–80% of patients with a palpable disease have nodal involvement, with the central compartment most commonly affected, followed by the ipsilateral and contralateral cervical nodal chains and superior mediastinum (4, 9).

MTC is classically managed with surgery alone (10, 11). 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; not surprisingly, patterns-of-care data confirm that EBRT is delivered to less than 15% of patients with MTC (2, 12). Limited data exist to substantiate or refute this practice. Available institutional outcomes data do suggest that ra-

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dioactive iodine, external radiotherapy improve locoregional disease control in high risk cases, despite the lack of an impact on overall survival (13–17).

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

MATERIALS AND METHODS

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 of 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 the type of surgery, extent of disease and treatment were collected from the medical records. Clinical data on 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, 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); 56 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.

The clinical characteristics and treatment options of MTC patients are presented in Table 2. Thyroidectomy was performed for all patients; 22 patients with lymph node metastases underwent cervical lymph node dissection; 52 patients received postoperative conventional external beam radiotherapy (EBRT) at a median dose of 44 Gy (38–60 Gy), 33 patients received radioactive iodine ^{131}I at a median dose of 4.6 GBq (2.6–13.8 GBq), 7 patients were treated only surgically.

Fifty-two patients received postoperative conventional external beam radiotherapy (EBRT) at a median dose of 44 Gy (38–60 Gy) via extended opposed anterior / posterior fields supplemented by off-cord photon boost after delivery of 45 Gy; 33 patients received radioactive iodine ^{131}I at a median dose of 4.6 GBq (2.6–13.8 GBq). Radioactive iodine ^{131}I was administered to hypothyroid patients 3–12 weeks after surgical treatment or external beam radiotherapy. Patients were treated with moderate radio iodine doses (1.11–3.7 GBq), and this dosage was repeated every 3–4 months. All 59 patients were treated with L-thyroxine and L-thyroxine doses adjusted to keep the TSH within a normal range (0.17–4.05 μIU/ml).

Statistical analysis

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. Descriptive statistics were used to summarize the study data. The survival was estimated by the Kaplan–Meier method. The statistical difference between the survival curves was determined using the log-rank test. A p-value lower than 0.05 was considered statistically significant.

RESULTS

The mean follow-up time was 9.2 ± 5.7 years (range, 1.5–26.8 years). 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.

The 5-, 10- and 15-year survival rates by demographic and clinical characteristics of MTC patients are shown in Table 3. The 10-year survival was higher in females and in patients younger than 50 years. A better 10-year survival was related to female sex, younger age and smaller tumour size (T). The type of surgery was related to lymph node involvement, thus patients without lymph node involvement undervent only

Table 1. **Demographic characteristics of the study group (n = 59)**

Variable	n	%
Gender		
Male	16	27.1
Female	43	72.9
Age, years (median, 49 years)		
≤50	30	50.8
>50	29	49.2

Table 2. **Clinical characteristics and treatment options of medullary thyroid carcinoma patients (n = 59)**

Variable	n	%
Surgery		
Thyreoidectomy	37	62.7
Thyreoidectomy with lymph node resection	22	37.3
Tumour 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	–
Treatment options		
Surgery alone	7	11.9
Surgery & EBRT*	19	32.2
Surgery & EBRT & ^{131}J	33	55.9

* EBRT – external beam radiotherapy.

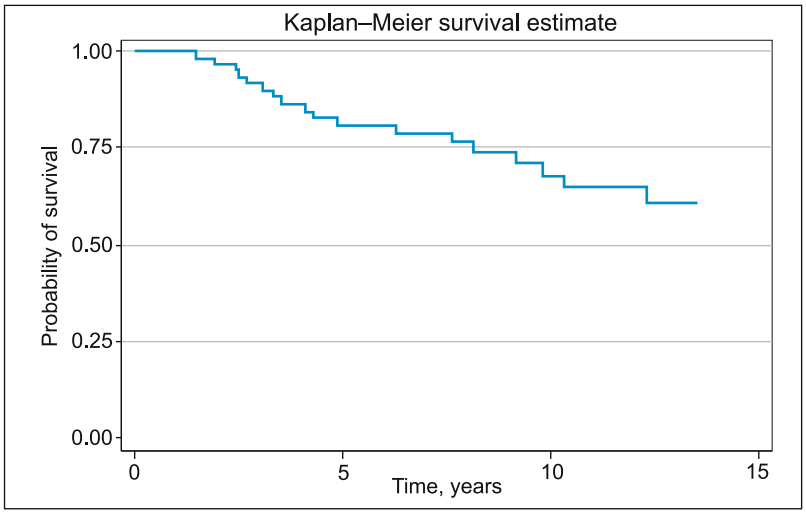

Fig. 1. Kaplan–Meier survival estimate of medullary thyroid carcinoma patients (n = 59)

Table 3. **Long-term survival by demographic and clinical characteristics of MTC patients (n = 59)**

	Survival, %		
	5-year	10-year	15-year
Total	88.0 (68.0–88.9)	67.9 (52.3–79.4)	60.5(43.2–74.0)
Gender			
Male	60.9 (32.7–80.3)	50.8 (22.3–73.6)	38.1 (11.4–65.1)
Female	88.0 (73.5–94.8)	74.5 (55.9–86.1)	68.7 (47.8–82.7)
Age			
≤50	86.0 (66.8–94.5)	71.3 (48.2–85.5)	71.3 (48.2–85.5)
>50	75.9 (55.9–87.7)	64.7 (41.6–80.5)	42.4 (14.6–68.3)
Tumour classification			
T_1	100.0	100.0	100.0
T_2	84.1 (58.3–94.6)	84.1 (58.3–94.6)	56.1 (17.3–82.6)
T_3	73.3 (43.6–89.1)	66.0 (36.5–84.3)	66.0 (36.5–84.3)
T_4	78.0 (51.5–91.1)	18.2 (1–0–53.3)	–
Lymph node classification			
N_0	97.3 (82.3–99.6)	82.3 (62.1–92.4)	72.0 (48.7–86.0)
N_1	52.1 (29.2–70.9)	41.7 (17.5–64.5)	41.7 (17.5–64.5)
Treatment			
Surgery alone	71.4 (25.8–92.0)	71.4 (25.8–92.0)	–
Surgery & EBRT	87.5 (58.6–96.7)	72.9 (32.3–91.6)	72.9 (32.3–91.6)
Surgery & EBRT & ^{131}J	78.8 (60.6–89.3)	65.0 (45.4–79.0)	54.8 (33.7–71.7)

* EBRT – external beam radiotherapy.

thyreoidectomy (N_0) and also had a better survival than patients with lymph node resection (N_1). Survival by the type of treatment did not clearly differ 10 years after diagnosis.

We have evaluated the influence of sex, age, type of surgery, tumour size, lymph node involvement and the type of treatment on long-term survival (Table 4). The Kaplan–Meier survival estimate and log rank test showed the sex and lymph node involvement to be significant prognostic factors for a long-term survival of MTC patients (Figs. 2, 3).

The Kaplan–Meier survival estimates by treatment are shown in Fig. 4. The survival differences are evident only in 5-year survival rates: the survival is lowest in the group of patients treated surgically only and highest in the group of thyroidectomy with additional radiotherapy.

Table 4. **Determinants of long-term survival by demographic and clinical characteristics of MTC patients (n = 59)**

Factor	Log rank test
Gender (male, female)	p = 0.0359
Age (≤50; >50)	p = 0.1405
Tumour classification (T_1; T_2; T_3; T_4)	p = 0.1747
Lymph node classification (N_0; N_1)	p = 0.0020
Treatment options (surgery alone; surgery & EBRT*; surgery & EBRT & ^{131}J	p = 0.6372

* EBRT – external beam radiotherapy.

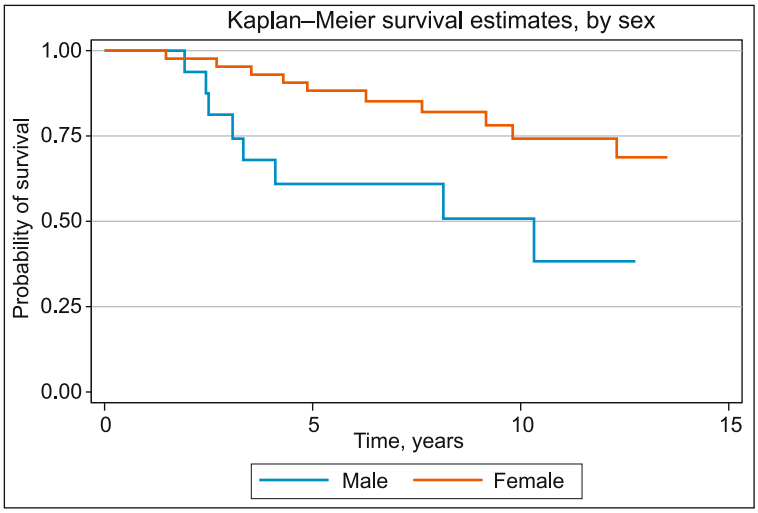

Fig. 2. Kaplan–Meier survival estimates of medullary thyroid carcinoma patients by sex

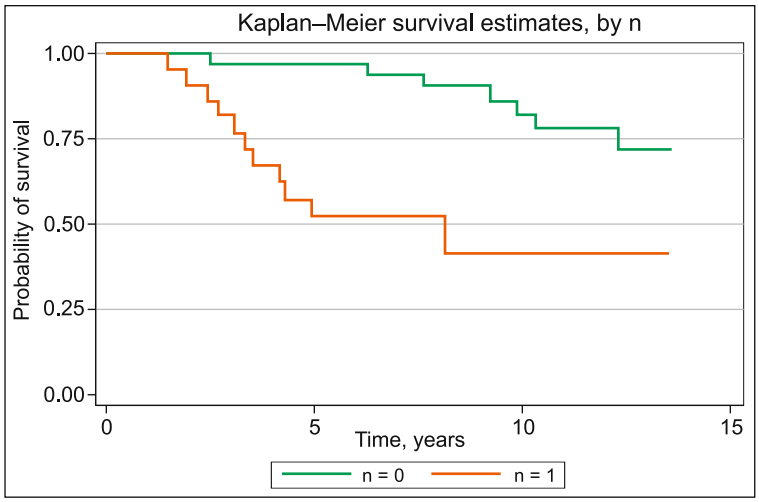

Fig. 3. Kaplan–Meier survival estimates of medullary thyroid carcinoma patients by lymph node involvement. N_0 (0), N_1 (1)

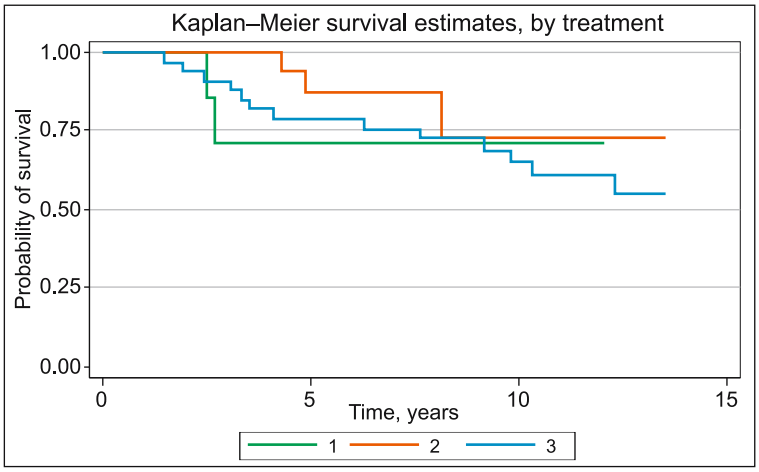

Fig. 4. Kaplan–Meier survival estimates of medullary thyroid carcinoma patients by treatment. Thyroidectomy (1), thyroidectomy, radiotherapy (2), thyroidectomy, radioactive iodine treatment and radiotherapy (3)

DISCUSSION

Medullary thyroid carcinoma (MTC) is a relatively rare carcinoma. Although MTC typically grows slowly, it is lymphotropic and frequently (especially in hereditary cases) presents with multifocal and/or bilateral glandular involvement. Up to 50–80% of patients with a palpable disease have nodal involvement, with the central compartment most commonly affected, followedby the ipsilateral and contralateral cervical nodal chains and superior mediastinum. Distant metastases to various organs can also occur early in the course of the disease (4, 9). The 5-, 10-, 15-year disease-specific survival of MTC varies. The overall survival rate of MTC in our study was similar to that in other studies: the 5-year survival rate 88.0%, in other studies 69.0–97.7%, 10-year survival rate –67.9% and 52.0–91.0%, 15-year survival rate 60.5% and 54.0–85%, respectively (13–17).

There are numerous studies on prognostic factors in patients with MTC (5, 7, 13–17). In our study, we have evaluated the influence of sex, age, tumour size, lymph node involvement, and the type of treatment on long-term survival. The Kaplan–Meier survival estimate and log rank test showed the patient's sex and lymph node involvement to be significant prognostic factors for the long-term survival of MTC patients. Our data are in agreement with other studies (5, 7, 13, 15).

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 (3, 20–25). In patients with macroscopic residual tumour, in the neck after incomplete surgery, Schlumberger et al. (21) advocated EBRT for local disease control. Brierley et al. (22) reported in a series of MTC patients that the local/regional relapse-free rate between patients that received EBRT and those that did not did not differ; however, in high-risk patients (microscopic residual disease, extraglandular 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 and EBRT in MTC is controversial. Hellman et al. and Deftos et al. considered

the possibility that radioactive iodine (RAI) uptake acts via a "bystander effect" (18, 19). However, recent studies do not confirm that RAI treatment plays a role in the postoperative management of patients with MTC, either as remnant ablation or treatment of residual, recurrent, or metastatic disease (12, 26). The results of our study suggest, too, that external beam radiotherapy and treatment with radioiodine do not improve significantly the long-term survival of surgically treated MTC patients.

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ILGALAIKĖ MEDULINIU SKYDLIAUKĖS VĖŽIU SERGANČIŲJŲ STEBĖSENA: 30 METŲ PATIRTIS

S a n t r a u k a

Tikslas. Ištirti meduliniu skydliaukės vėžiu sergančiųjų sudėtinio gydymo metodo (tiroidektomija + išorinis spindulinis gydymas + jodo radioterapija) poveikį išgyvenamumui.

Tyrimo medžiaga ir metodai. Ištirti 59 pacientai (43 moterys, 16 vyrai, amžiaus vidurkis 49 m.), sergantys meduliniu skydliaukės vėžiu ir gydyti 1977–2006 m. Vilniaus universiteto Onkologijos institute. Sporadinis skydliaukės vėžys nustatytas 56 pacientams, 3 pacientams – šeiminis medulinis vėžys. Visiems tiriamiesiems atliktos tiroidektomijos. Dvidešimt dviem pacientams (iš 59) nustatytos metastazės kaklo limfmazgiuose ir atliktos limfonodulioektomijos. Po operacijos 52 tiriamieji gydyti konvenciniu išoriniu spinduliniu gydymu vidutine 44 Gy (38–60 Gy) doze, 33 pacientai – jodo radioterapija ^{131}J vidutine 4,6 GBq (2,6–13,8) doze. Septyni pacientai gydyti tik chirurginiu metodu. Tiriamiesiems skirta pakaitinė tiroksino (TSH-0,17–4,05 μIU/ml) hormonoterapija. Ligonių išgyvenamumas analizuotas Kaplano-Mejerio metodu, išgyvenamumo kreivių statistiniai skirtumai įvertinti *long-rank* testu.

Rezultatai. Taikant šį skydliaukės medulinio vėžio gydymą (tiroidektomija + išorinis spindulinis gydymas + jodo radioterapija), nustatytas 5, 10, 15 metų išgyvenamumas (atitinkamai 88,0 %, 67,9 %, 60,5 %).

Išvados. Sergantiesiems meduliniu skydliaukės vėžiu (VUOI) buvo taikytas sudėtinis gydymas (tiroidektomija + išorinis spindulinis gydymas + jodo radioterapija). Tyrimo rezultatai atskleidė, kad išorinis pooperacinis spindulinis gydymas ir jodo radioterapija ženkliai nepailgino ligonių išgyvenamumo.

Raktažodžiai: medulinė karcinoma, tiroidektomija, ^{131}J, radioterapija