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Recurrence Rate and Survival in 260 Patients With Oncocytic Thyroid Cancer According to Response to Initial Treatment – A Single-Institution Experience

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: Oncocytic thyroid carcinoma (OTC) is a rare disease. There is little information about risk factors for recurrence. The aim of our retrospective, single-institution study was to investigate the recurrence rate in OTC patients with and without an excellent response after initial treatment according to the 2025 American Thyroid Association guidelines response criteria based on type of initial intervention.

Material/Methods: Altogether, 260 patients with OTC (57 men, 203 women; mean age 60.35 years; range 16-90 years) treated from 1972 to 2024 were included. Initially, regional and distal metastases were diagnosed in 15 (6%) and 25 (10%) patients, respectively. Cox's multivariate regression model was used to identify the risk factors for recurrence.

Results: The follow-up period ranged from 0.1 to 45.2 (median 7.9) years. Recurrence was diagnosed in 39 (17%) of the 235 patients without disease after initial treatment. Locoregional, distant, and combined locoregional and distant recurrence was diagnosed in 18, 14, and 7 patients, respectively. Among 154 patients with an excellent response, recurrence occurred in 6.5%, and among the 81 patients without an excellent response, it occurred in 36% (P<0.001). Independent risk factors for recurrence were: sex (males, hazard ratio (HR)=2.5, 95% CI 1.3-4.8; P=0.009), age (≥55 years, HR=2.7, 95% CI 1.2-5.8; P=0.012), pT stage (pT3 or pT4, HR=1.4, 95% CI 1.0-1.9; P=0.023), and residual tumor after surgery (R1 or R2 residual tumor, HR=1.2, 95% CI 1.07-1.3; P=0.001). The 5-year disease-free survival rate for the entire cohort was 88%, while the 10-year and 20-year disease-free survival rates were 79%, and 74%, respectively.

Conclusions: Recurrence rate in patients with and without an excellent response was 6.5% and 35%, respectively. Recurrence was more common in men, older patients, those with regional metastases, and those with residual tumor after surgery.

Keywords: **Prognosis • Risk Factors • Survival Rate • Thyroid Neoplasms**

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Introduction

Since 2017, the World Health Organization (WHO) has classified oncocytic thyroid carcinoma (OTC) as a distinct subtype of thyroid carcinoma [1,2]. According to the 2022 WHO classification, the term OTC is used in cases of invasive malignant follicular cell neoplasms composed of at least 75% oncocytic cells in which the nuclear features of papillary thyroid carcinoma and high-grade features are absent [3]. OTC is a rare thyroid carcinoma that accounts for 3% to 7% of all malignant thyroid tumors [4].

Since OTC is a very rare disease, it is understandable that very little data have been published in the literature on the length of survival of patients with OTC who have had long-term follow-up. Coca-Pelaz et al [4], in a recent systematic review and meta-analysis, reported that in the last 20 years, there have only been 9 publications on 10-year overall survival and only 7 studies on 10-year disease-free survival in patients with OTC alone. Single-center studies have included from 33 to 239 patients [5-12], while Goffredo et al [13] reported data from the Surveillance, Epidemiology, and End Results (SEER) database about the prognosis of OTC. Apparently, there is a paucity of published data on predictive factors for recurrence in patients with OTC.

The American Thyroid Association (ATA) 2015 guidelines established criteria for assessing treatment efficacy [14]. However, with the new ATA 2025 guidelines redefining estimated risk factors for OTC recurrence [15], the question arises as to what proportion of patients have an excellent response to treatment and whether patients with an excellent response to initial treatment should be monitored in the same way as those with a poorer response. The aim of our retrospective, single-institution study was to determine the recurrence rate in patients with and without an excellent response to initial treatment. Another aim of our study was to determine the frequency and risk factors for recurrence, disease-free survival, disease-specific survival, and overall survival in patients with OTC.

Material and Methods

All 260 patients with OTC (57 men, 203 women; mean age 60.35 years; range 16-90 years) and treated from 1972 to 2024 at the Institute of Oncology Ljubljana (IOL) were included. All of the patients with OTC in Slovenia were treated and had follow-up throughout their lives at the IOL, so our data is actually a nationwide population study.

The institutional Medical Ethics Committee and the Protocol Review Board (ERID-KSOPKR-0082/2020, ERIDEK-0083/2020, ERIDNPVO-0040/2020) approved the study. Our study was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki. In accordance with national legislation, it was not necessary to obtain patient consent, as this was a retrospective data review and the research was approved by the National Ethics Committee and the institution's Protocol Review Board.

An experienced pathologist (Barbara Gazic) reviewed all histological slides. The criteria for the diagnosis of OTC were (1) the presence of at least 75% oncocytic cells without nuclear features of papillary thyroid carcinoma, lacking high-grade features [3], and (2) evidence of invasion through the tumor capsule or into the blood vessels and/or regional metastases and/or distant dissemination.

A chart review was performed and data on patients' clinical characteristics, disease extension, therapy, locoregional and/or distant recurrence, disease-free interval, cause of disease, disease-specific survival, and overall survival were collected. The disease stages were assessed using the tumor, node, metastasis (TNM) clinical classification of the Union for International Cancer Control (UICC) criteria from 2017 [16].

Diagnostic procedures before treatment and during the follow-up period have been described in our previous report [11]. All patients were followed up at the IOL at least once a year. During each follow-up visit, serum thyroglobulin (Tg) levels were measured and appropriate diagnostics were performed if disease progression was suspected based on the increase in Tg levels or the patient's symptoms.

The criteria for excellent or non-excellent response for the initial interventions used in the present study were based on 2025 ATA guidelines [15]. The criteria for an excellent response after total thyroidectomy followed by ablation with radioiodine were: suppressed Tg <0.2 ng/mL, thyroid stimulating hormone (TSH)-stimulated Tg <1 ng/mL, absence of accumulation on radioiodine scan, and negative imaging with neck ultrasound. Patients without an excellent response had structural or functional evidence of disease or a suppressed Tg >1 ng/mL, a stimulated Tg >10 ng/mL, or rising anti-Tg antibody levels [15]. The criteria for an excellent response after total thyroidectomy without ablation with radioiodine were Tg <2.5 ng/mL and negative imaging [15].The criteria for an excellent response after a lobectomy were concentration of Tg <30 ng/mL, anti-Tg antibodies stable or declining in the absence of structural or functional disease confirmed by negative imaging. Patients without an excellent response after a lobectomy had structural or functional evidence of disease or Tg levels of more than or equal to 30 ng/mL, or anti-Tg antibodies rising in the absence of structural or functional disease confirmed by negative imaging.

Whenever the medical history, physical examination, laboratory findings (elevated Tg above the limit of excellent response),

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and/or radioiodine uptake indicated a recurrence and/or distant metastasis, additional diagnostic work-up was done. This included X-ray, neck ultrasound, neck and chest computed tomography (CT), magnetic resonance imaging (MRI), bone scintigraphy, scintigraphy with (99m)Tc-sestamibi (MIBI), and/or 18-F fluorodeoxyglucose positron emission tomography-computed tomography (18-F FDG PET-CT). From 2002 on, in all patients with Tg >1 ng/mL, the diagnostic work-up included radioiodine scintigraphy and 18-F FDG PET-CT.

Treatment

Surgery is the mainstay of the treatment for OTC. Among surgically treated patients, 88% had primary surgery at the IOL and 12% elsewhere, while all other specific therapies (surgery, radioiodine, external beam radiotherapy (EBRT), chemotherapy, and/or targeted therapy) and follow-ups were conducted at IOL for all patients.

For more than 50 years, the diagnostics and treatment of patients with OTC in the thyroid, regional dissemination and/or distant metastases has not been uniform at the IOL [11,17]. During the last 30 years, our patients were treated according to the ATA guidelines from 1996 and 2015 [18,14] and the European consensus for the management of patients with differentiated thyroid carcinoma [19]. The best surgical treatment for OTC is removal of the entire or nearly entire thyroid gland. All patients received postoperative L-thyroxine therapy in a dose sufficient to suppress TSH. However, since 2015, in patients with minimally invasive OTC, lobectomy is considered an appropriate surgical procedure and replacement therapy with L-thyroxine is sufficient, so that TSH is at the lower limit of the normal values.

Survival

Disease-specific survival was defined as the period from the first day of primary treatment (surgical procedure, chemotherapy, EBRT, or targeted therapy) to death due to OTC or the last follow-up. Overall survival was defined as the period from the first day of primary treatment (surgical procedure, chemotherapy, EBRT, or targeted therapy) to death due to any cause or the last follow-up. Disease-free survival was defined as the period from the first day of primary treatment (surgical procedure, chemotherapy, EBRT, or targeted therapy) to the radiologic or morphologic diagnosis of a recurrence or the last follow-up. Only lymph node metastases were considered regional recurrence. The median duration of the follow-up was 7.9 years (range 0.1-45.2 years).

Statistical Analysis

Descriptive statistics described the entire cohort and separate groups, with frequencies used for categorical variables and median or mean used for continuous variables. Missing data for key variables (eg Tg levels and pathological details) were handled with complete case analysis. Differences between groups were assessed using the Chi-Square or Mann-Whitney U test. Kaplan-Meier curves were constructed to evaluate differences in survival between groups. Factors associated with patient survival were identified by univariate analysis. The Mantel-Cox test was used to compare patient survival. A *P* value of <0.05 was considered statistically significant. Predictive factors for recurrence and prognostic factors for survival were determined by Cox regression. All clinically relevant variables from the univariate analysis with a *P* value <0.1 were included in the multivariate model. Continuous factors were categorized (eg, age <55 years and ≥55 years) and then included in the multivariate model. For statistical analysis, the statistical package PASW 18 (SPSS Inc., Chicago, IL, USA) was used.

Results

The patient characteristics, tumor characteristics, treatment, and outcomes for all 260 patients, and for 235 patients with no evidence of disease after surgery, are presented in **Table 1**. The primary tumors measured 0.4-18 (mean 4.4) cm. Initially, regional and distal metastases were diagnosed in 15 (6%) and 25 (10%) cases, respectively. The mean ages of patients without and with distant metastases were 59 and 69 years, respectively.

Relapse Rate According to Treatment Response

Among 235 patients without distant metastases, the disease recurred in 39 patients during the median follow-up of 6.9 (range 0.1-45.2) years. Locoregional, distant, and both locoregional and distant recurrence were diagnosed in 18, 14, and 7 patients, respectively. The aim of our study was to investigate the recurrence rate in patients with and without an excellent response to initial treatment. Among the 154 patients with an excellent response, recurrence occurred in 6.5%, and among the 81 patients without an excellent response, it occurred in 36% (*P*<0.001). None of the patients with an excellent response died due to OTC, while 24% of the patients without distant metastases and without an excellent response died due to OTC (*P*<0.001).

Disease-Free Survival

Another aim of our study was to determine the frequency and risk factors regarding disease-free survival in patients with OTC. The 5-year, 10-year, and 20-year disease-free survival rates were 88%, 79%, and 74% (**Figure 1**).

Univariate analysis has shown that the duration of disease-free survival was statistically associated with gender, age,

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Table 1. Patients' characteristics, tumor characteristics, treatment, and outcome for all 260 OTC patients and 235 patients with no evidence of disease after surgery.

Factor	Subgroup	All patients N=260 Number (%)	Patients with no evidence of disease after surgery N=235 Number (%)
Age (years)	<55	88 (34)	87 (37)
	≥55	172 (66)	148 (63)
Sex	Female	203 (78)	187 (80)
	Male	57 (22)	48 (20)
Tumor diameter (cm)	0-3.99	127 (49)	124 (53)
	4 or more	133 (51)	111 (47)
pT tumor stage	pTx	3 (1)	1 (0.4)
	pT1	39 (15)	39 (16.6)
	pT2	90 (35)	89 (38)
	pT3	108 (41)	93 (40)
	pT4	20 (8)	13 (5)
N stage	N0	245 (94)	228 (97)
	N1 or N2	15 (6)	7 (3)
M stage	M0	235 (90)	235 (100)
	M1	25 (10)	0 (0)
Subtype of invasiveness	Minimally invasive	104 (40)	83 (35)
	Widely invasive	128 (49)	127 (54)
	Unknown	28 (11)	24 (10)
Thyroid surgical procedure	Total or near-total thyroidectomy	224 (86)	206 (88)
	Lobectomy or less	36 (14)	29 (12)
Residual tumor after surgery	R0	217 (84)	208 (89)
	R1	27 (10)	15 (6)
	R2	16 (6)	12 (5)
Neck dissection	No	249 (96)	229 (97)
	Yes	11 (4)	6 (3)
Radioiodine ablation after surgery	No	30 (12)	27 (12)
	Yes	230 (88)	208 (88)
Therapy with radioiodine	No	226 (87)	168 (71)
	Yes	76 (29)	67 (29)
EBRT to the neck	No	232 (89)	216 (92)
	Yes	28 (11)	19 (8)

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Table 1 continued. Patients' characteristics, tumor characteristics, treatment, and outcome for all 260 OTC patients and 235 patients with no evidence of disease after surgery.

Factor	Subgroup	All patients N=260 Number (%)	Patients with no evidence of disease after surgery N=235 Number (%)
EBRT (any site)	No	220 (85)	214 (91)
	Yes	40 (15)	21 (9)
Chemotherapy	No	240 (92)	226 (96)
	Yes	20 (8)	9 (4)
Targeted therapy	No	248 (95)	230 (98)
	Yes	12 (5)	5 (2)
Recurrence	No	196 (75)	196 (84)
	Yes – locoregional	18 (7)	18 (8)
	Yes – distant	14 (5)	14 (5)
	Yes – locoregional and distant	7 (3)	7 (3)
	Disease present permanently	25 (10)	0 (0)
Outcome	Alive	212 (81)	199 (84)
	Dead of disease	25 (10)	14 (6)
	Dead of other causes	18 (7)	18 (8)
	Lost to follow-up	5 (2)	4 (2)

pT tumor stage – pathological primary tumor stage; pTx – unknown pathological primary tumor stage; N stage – regional lymph node stage; M stage – distant metastasis stage; Minimally invasive – limited vascular invasion (<4 vessels); Widely invasive – ≥4 vessels with vascular invasion; R0 – without any residual tumor after surgery; R1 – microscopic residual tumor after surgery; R2 – macroscopic residual tumor after surgery; Therapy with radioiodine – application of radioiodine therapy after radioiodine ablation od thyroid remnant after surgery; EBRT – external beam radiotherapy.

and residual tumor after thyroid surgery. Multivariate Cox proportional hazards regression has shown that the duration of disease-free survival was statistically associated with sex, age, pT stage, and residual tumor after thyroid surgery (**Table 2, Figure 2**). On multivariate analysis, factors associated with shorter disease-free survival were: male sex (HR=2.5, 95% CI 1.3-4.8; *P*=0.009), age (≥55 years, HR=2.7, 95% CI 1.2-5.8; *P*=0.012), pT stage (pT3 or pT4, HR=1.4, 95% CI 1.0-1.9; *P*=0.023), and residual tumor after surgery (R1 or R2 residual tumor, HR=1.2, 95% CI 1.07-1.3; *P*=0.001). The duration of disease-free survival was not statistically associated with N stage, subtype of invasiveness, thyroid surgery, or radioiodine ablation after surgery.

Disease-Specific Survival

Among 260 patients with OTC, a total of 25 patients died of the disease during the median follow-up of 7.9 years (range 0.1-45.2). Distant metastases, local disease only, or both distant metastases and local disease were a cause of death in 22, 1, and 2 patients, respectively. The 5-year, 10-year, and 20-year disease-specific survival rates were 97%, 92%, and 81% (**Figure 1**).

Univariate and multivariate Cox proportional hazards regression showed that the duration of disease-specific survival was statistically associated with gender, age, and postoperative thyroid tumor remnant (**Table 3, Figure 3**). On multivariate analysis, factors associated with shorter disease-specific survival were: male sex (HR=2.5, 95% CI 1.1-5.6; *P*=0.028), age (≥55 years, HR=6.4, 95% CI 1.4-30.2; *P*=0.019), and residual tumor after surgery (R1 or R2 residual tumor, HR=1.3, 95% CI 1.3-1.4; *P*=0.001). Both univariate and multivariate analyses showed a statistical trend of association between disease-specific survival duration and M stage. The duration of disease-specific survival was not statistically associated with pT stage,

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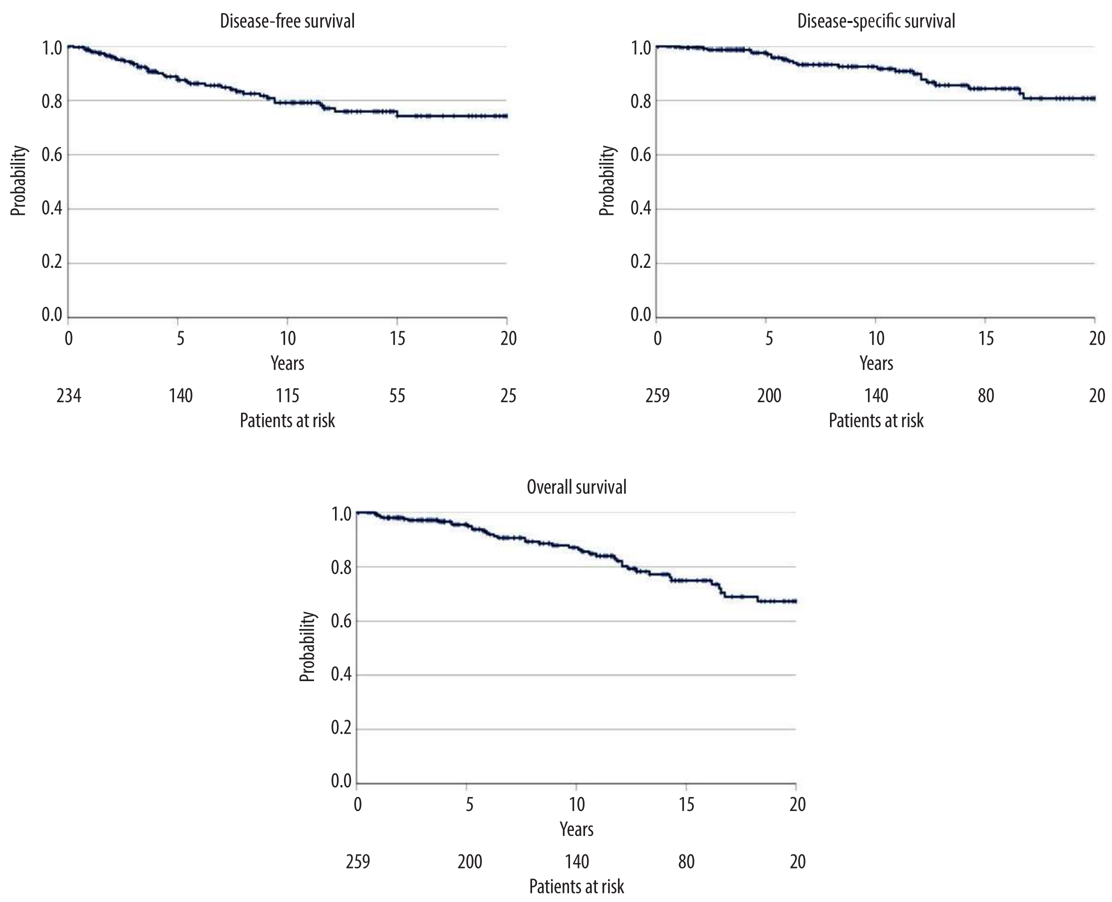

Figure 1. Disease-free survival of 235 patients and disease-specific and overall survival in 260 patients with oncocytic thyroid carcinoma.

N stage, subtype of invasiveness, thyroid surgery, or radioiodine ablation after surgery.

Overall Survival

Among 260 patients with OTC, a total of 43 patients died. The cause of death was OTC in 25 patients and other causes in 18 patients. The 5-year overall survival rate was 96%, while 10-year and 20-year overall survival rates were 87% and 67%, respectively (**Figure 1**).

Univariate and multivariate Cox proportional hazards regression showed that the duration of overall survival was statistically associated with age, pT stage, and residual tumor after thyroid surgery (**Table 4, Figure 4**). On multivariate analysis, factors associated with shorter disease-specific survival were: age (≥55 years, HR=6.2, 95% CI 2.2-17.8; *P*=0.001), pT3 or pT4 stage (HR=1.8, 95% CI 1.2-2.5; *P*=0.001), and residual tumor after surgery (R1 or R2 residual tumor, HR=1.2, 95% CI 1.1-1.3; *P*=0.001). Both univariate and multivariate analyses showed a statistical trend of association between overall survival duration and radioiodine ablation of thyroid remnant. The duration of overall survival was not statistically associated with gender, N stage, M stage, subtype of invasiveness, thyroid surgery, or radioiodine ablation after surgery.

Discussion

OTC has only been an independent histopathological entity according to the WHO classification since 2017 [1,2]. Previously, OTC was classified as a subtype of follicular thyroid cancer, and there is a relatively large amount of data in the literature on the survival of combined groups of patients with follicular cancer [20]. However, there is little information in the literature on predictive factors for recurrence, disease-free survival, disease-specific survival, and overall survival of patients who have OTC [20]. Furthermore, to our knowledge, there

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Table 2. Factors associated with the length of disease-free survival after the beginning of oncological therapy by univariate and multivariate Cox proportional hazards regression.

Factor	Univariate				Multivariate*			
	P value	Exp (β)	Exp (β) 95% CI lower	Exp (β) 95% CI upper	*P* value	Exp (β)	Exp (β) 95% CI lower	Exp (β) 95% CI upper
Sex (Female)	**0.012**	**2.545**	**1.226**	**5.283**	**0.009**	**2.455**	**1.250**	**4.822**
Age (<55 years)	**0.007**	**2.927**	**1.348**	**6.355**	**0.012**	**2.694**	**1.242**	**5.844**
pT stage (pT0, pT1 or pT2)	0.071	1.329	0.976	1.810	**0.023**	**1.401**	**1.048**	**1.874**
N stage (N0)	0.216	2.157	0.639	7.281	–	–	–	–
Subtype of invasiveness (minimally invasive)	0.790	0.983	0.864	1.117	–	–	–	–
Residual tumor after thyroid surgery (R0)	**0.008**	**1.149**	**1.037**	**1.272**	**0.001**	**1.173**	**1.072**	**1.285**
Thyroid surgery (lobectomy)	0.746	1.016	0.925	1.115	–	–	–	–
Radioiodine ablation after surgery (no)	0.133	4.622	0.627	34.077	–	–	–	–

* Variables not included in the multivariate model due to lack of significance (*P*>0.10) on univariate analysis. Exp (β) – hazard ratio; CI – confidence interval; pT tumor stage – pathological primary tumor stage; N stage – regional lymph node stage; '–' – variables not in the multivariate model due to lack of significance (*P*>0.10) on univariate analysis, Minimally invasive – limited vascular invasion (<4 vessels); Widely invasive – 4 or more vessels with vascular invasion; R0 – without any residual tumor after surgery.

are no published data in the literature on the frequency of OTC recurrence based on assessment of recurrence risk following an initial response to therapy, as described by Tuttle and colleagues [21]. Since we have information on the course of OTC from one of the largest single-center studies, with a very long follow-up period, covering the entire population of a whole country, we want to contribute highly needed data in this area to the literature, with this paper. The aim of our study was therefore to determine the recurrence rate in patients with and without an excellent response to initial treatment. Among our patients without distant metastases, the disease recurred in only 17% during the median follow-up of 7.9 years. An important finding of our research is that among the patients with an excellent response, OTC recurred in only 6.5%, while among patients without distant metastases at diagnosis and without an excellent response, it recurred in as many as 36% (*P*<0.001).

Furthermore, among our patients with an excellent response to the initial treatment, none died from OTC. This finding could have important therapeutic implications. The ATA guidelines [14] from 2015 recommended long-lasting TSH suppression for patients with non-minimally invasive OTC after a total thyroidectomy and radioiodine ablation. Our results indicate that in case of an excellent response after initial treatment, permanent or very long-lasting TSH suppression is probably not beneficial, especially in older patients with comorbidities (osteoporosis, diabetes, or cardiovascular disease). This finding of ours is in line with ATA guidelines from 2025 [15].

Another aim of our study was to determine the frequency and risk factors for disease-free survival. The 5-year disease-free survival of our patients was 88%, while 10-year and 20-year disease-free survival rates of our patients were 79% and 74%, respectively. This is in line with the disease-free survival intervals reported in the literature [7,8,12,22,23]. Cola-Pelaz et al [4], in a systematic review and meta-analysis, reported that disease-free survival was calculated in 17 studies over a 20-year period, and the mean 5-year and 10-year disease-free survival rates were 87% and 80%, respectively [4]. Independent risk factors for disease-free survival in our patients as shown by a multivariate analysis were: sex, age, pT stage, and residual tumor after thyroid surgery.

Invasiveness subtype was not an independent prognostic factor for disease-free interval, disease-specific survival, or overall survival in our patient cohort. Stojadinovic et al [24] reported that none of a cohort of 23 patients with minimally invasive OTC developed a recurrence or died of the disease [24]. Similarly, Chindris et al [25] from the Mayo Clinic reported that none of their cohort of 44 patients with minimally invasive histology developed persistent disease, clinical recurrence, or disease-related death. However, in our 83 patients with minimally invasive OTC, 18 of them had a recurrence and, among them, as

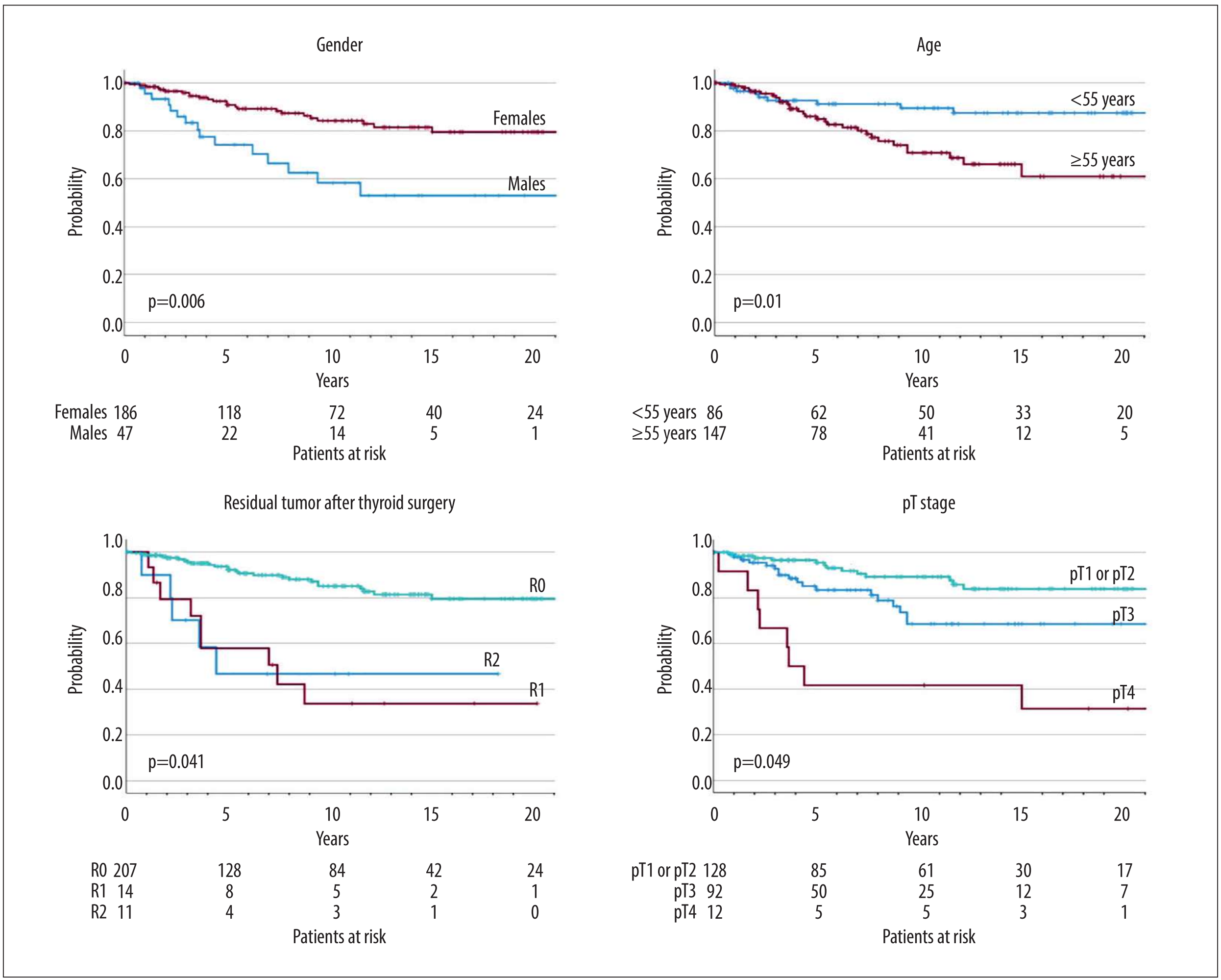

Figure 2. Sex, age, pT stage, and residual tumor after thyroid surgery were independent factors associated with the duration of disease-free survival.

many as 11 developed distant metastases. The reason for the recurrences in our patients with minimal invasion could be that the pathologist was unable to demonstrate the location of extensive vascular or transcapsular invasion in their large tumors despite extensive tumor sampling. As many as 62% of our patients with minimally invasive OTC had a tumor larger than 4 cm, while others reported a >4-cm tumor in only 22% [24] and 20.5% [25] of their patients, respectively. Furthermore, the median age of our patients with minimally invasive OTC was 65 years, while other authors reported 51 years [24] and 61 years [25]. Can the biology of minimally invasive OTCs change with age and tumor diameter? The cause of the altered biology of minimally invasive OTCs seen in patients with older ages and larger tumors could be a change in tumor genes. This hypothesis is supported by the finding of Hellgren et al [26], who reported that patients with minimally invasive follicular carcinoma or OTC and mutated TERT tumors were older, with a median age of 71 years, compared with patients with wild-type tumors with a median age of 57 years (*P*=0.041).

Patient age ≥55 years was an independent prognostic factor for disease-free survival, disease-specific survival, and also overall survival in our patient cohort. Of course, this is quite understandable for overall survival. This is also understandable for disease-specific survival, as age ≥55 years is included in the TNM classification. Our results confirm that the TNM classification is also valid for OTC. Interestingly, age ≥55 years had the highest HR for shorter survival among all independent prognostic factors. For disease-specific survival, the HR was as high as 6.4 (95% CI 1.4-30.2; *P*=0.019). Other authors also reported that patient age was a prognostic factor for disease-specific survival [11,13,27-29]. According to the literature, patients with OTC have 5-year, 10-year, and 20-year disease-specific survival rates of 74% to 97%, 49% to 93%, and 67% to 90%, respectively [12,28-32]. Similarly, the 5-year, 10-year, and 20-year disease-specific survival rates of our patients were 97%, 92%, and 81%, respectively.

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Table 3. Factors associated with the length of disease-specific survival after the beginning of oncological therapy by univariate and multivariate Cox proportional hazards regression.

Factor	Univariate				Multivariate*			
	P value	Exp (β)	Exp (β) 95% CI lower	Exp (β) 95% CI upper	*P* value	Exp (β)	Exp (β) 95% CI lower	Exp (β) 95% CI upper
Sex (Female)	**0.037**	**2.645**	**1.062**	**6.587**	**0.028**	**2.476**	**1.100**	**5.571**
Age (<55 years)	**0.031**	**5.461**	**1.171**	**25.469**	**0.019**	**6.428**	**1.367**	**30.235**
pT stage (pT0, pT1 or pT2)	0.116	1.537	0.899	2.626	–	–	–	–
N stage (N0)	0.458	1.517	0.504	4.564	–	–	–	–
M stage (N0)	0.063	2.531	0.951	6.734	0.061	2.545	0.958	6.758
Subtype of invasiveness (minimally invasive)	0.207	1.096	0.951	1.264	–	–	–	–
Residual tumor after thyroid surgery (R0)	**0.008**	**1.220**	**1.053**	**1.413**	**0.001**	**1.270**	**1.116**	**1.444**
Thyroid surgery (lobectomy)	0.551	1.031	0.933	1.140	–	–	–	–
Radioiodine ablation after surgery (no)	0.532	0.609	0.129	2.885	–	–	–	–

* Variables not included in the multivariate model due to lack of significance (P>0.10) on univariate analysis. Exp (β) – hazard ratio; CI – confidence interval; pT tumor stage – pathological primary tumor stage; '–' – variables not in the multivariate model due to lack of significance (P>0.10) on univariate analysis; N stage – regional lymph node stage; M stage – distant metastasis stage; Minimally invasive – limited vascular invasion (<4 vessels); Widely invasive – 4 or more vessels with vascular invasion; R0 – without any residual tumor after surgery.

M stage has been recognized as a prognostic factor in many studies [5,11,13,24,27,28], but in our patients, M stage had only a statistical trend of association with disease-specific survival. Apparently, other confounding factors had a greater association with survival than M stage in our patients. For example, residual tumor after thyroid surgery was an independent prognostic factor in our patients. Because our patients were operated on by highly experienced thyroid surgeons, residual tumor after surgery essentially also reflects the extent of the disease. Distant metastases were initially diagnosed in 10% of our patients, which is in line with the 4.7% to 18% reported in large studies conducted recently in the United States [5,13,25,31]. Patients can survive for a long time despite having distant metastases. In one of our previous publications, we reported that in patients with distant metastases, the 10-year survival because of OTC was as high as 60% [17]. However, even if it occurs many years later, distant recurrence is a common cause of death in OTC patients. Among our patients who did not have distant metastases at diagnosis and did not have an excellent response to treatment, as many as 24% died later due to distant metastases.

Overall survival is affected by both death from OTC and death from other causes. Altogether, 16% of our patients died: 10% from OTC and 6% from other causes. The 5-year overall survival rate was 96%, while 10-year, and 20-year overall survival rates were 87% and 67%, respectively. Similar overall survival rates have been reported by other authors [4,8,12,29-31]. Our multivariate analysis has shown that the duration of overall survival was statistically associated with age, pT stage, and residual tumor after thyroid surgery. Also, other authors also reported that age is a prognostic factor for overall survival [12,27,29,31]. Other authors reported that additional prognostic factors for overall survival included: sex [27,29], stage of disease [27,29,31], tumor size [27,29], N stage [27,29], M stage [27], treatment with a thyroidectomy [12,27,29,], radioiodine treatment [29], systemic therapy [29], household income [31], and lower tumor grade [31]. Obviously, effective treatment may have an impact on the recurrence of OTC and the survival of patients. Total thyroidectomy is a safe procedure that enables the better detection of recurrent disease and the ablation of any thyroid remnant with radioiodine [14]. We agree with Zhank et al [29] that neck lymphadenectomy should not be performed in all patients with OTC because lymph node metastases are rare.

Our study failed to demonstrate that neither extent of surgical procedure nor radioiodine ablation of the thyroid remnant

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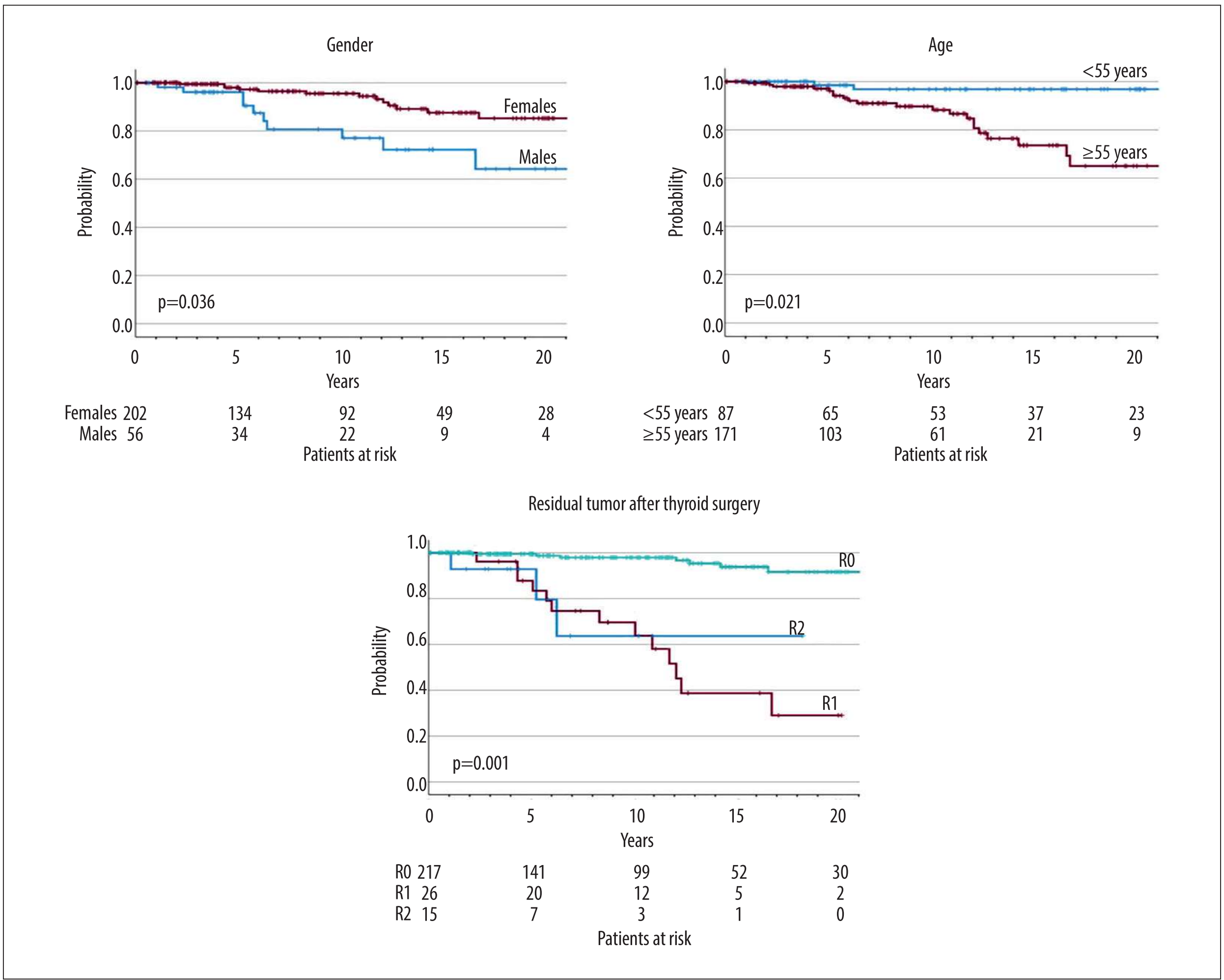

Figure 3. Sex, age, and residual tumor after thyroid surgery were independent factors for the duration of disease-specific survival.

was an independent prognostic factor for survival. This may be due to the relatively small number of patients in our patient subgroups. Whether radioiodine has a therapeutic benefit in OTC patients remains controversial [33]. An analysis of the SEER database of 2279 patients with OTC who underwent total thyroidectomy showed that radioiodine therapy was not associated with disease-specific survival [32]. However, a retrospective analysis of the National Cancer Database showed improved overall survival after radioiodine therapy for OTC patients with N1/M1 disease or T2-T4 tumors with any N/M disease [34]. Mortality after radioiodine therapy was reduced by 30% [34]. Furthermore, radioiodine therapy reduces noncancer death risks in OTC [29]. In our study, which included a relatively small number of patients, we found only a statistical trend toward longer overall survival with radioiodine ablation of thyroid remnants.

Locoregional disease control was achieved in almost all of our patients. Only 3 patients died of locoregional or both locoregional and distant metastases. In our patients with locally advanced OTC, the multimodal treatment approach was effective despite the fact that 20 patients had stage T4 tumors, and as many as 16 had only R2 tumor resection. We believe that in patients with locoregionally advanced differentiated thyroid cancer, EBRT and chemotherapy are essential components of effective locoregional disease control. Our current results regarding OTC treatment confirm the observation from the Memorial Sloan-Kettering Cancer Center showing that locoregional disease recurred after 10 years in 56% of patients who had just undergone surgery and in only 23% after postoperative EBRT [35]. The need for postoperative EBRT and chemotherapy is likely to change as treatment options with everolimus, sorafenib, nintedanib, lenvatinib, and panitumumab have been reported for progressive OTC [36]. For example, a published case report found that lenvatinib treatment for inoperable OTC effectively reduced the tumor size for a long period of time [37].

A limitation of our observational study is that it is a report from a single institution that included only 260 patients. An

Table 4. Factors associated with the length of overall survival after the beginning of oncological therapy by univariate and multivariate Cox proportional hazards regression.

Factor	Univariate				Multivariate*			
	P value	Exp (β)	Exp (β) 95% CI lower	Exp (β) 95% CI upper	*P* value	Exp (β)	Exp (β) 95% CI lower	Exp (β) 95% CI upper
Sex (Female)	0.130	1.719	0.852	3.469	–	–	–	–
Age (<55 years)	**0.001**	**6.149**	**2.100**	**18.008**	**0.001**	**6.202**	**2.162**	**17.788**
pT stage (pT0, pT1 or pT2)	**0.007**	**1.658**	**1.145**	**2.399**	**0.001**	**1.761**	**1.244**	**2.495**
N stage (N0)	0.872	1.083	0.412	2.850	–	–	–	–
M stage (N0)	0.569	1.276	0.552	2.950	–	–	–	–
Subtype of invasiveness (minimally invasive)	0.251	1.064	0.957	1.183	–	–	–	–
Residual tumor after thyroid surgery (R0)	**0.013**	**1.143**	**1.028**	**1.271**	**0.001**	**1.160**	**1.064**	**1.265**
Thyroid surgery (lobectomy)	0.481	1.028	0.952	1.110	–	–	–	–
Radioiodine ablation after surgery (no)	0.057	0.431	0.181	1.026	0.076	0.465	0.200	1.083

* Variables not included in the multivariate model due to lack of significance (*P*>0.10) on univariate analysis, Exp (β) – hazard ratio; CI – confidence interval; pT tumor stage – pathological primary tumor stage; N stage – regional lymph node stage; '–' – variables not in the multivariate model due to lack of significance (*P*>0.10) on univariate analysis; M stage – distant metastasis stage; Minimally invasive – limited vascular invasion (<4 vessels); Widely invasive – 4 or more vessels with vascular invasion; R0 – without any residual tumor after surgery.

additional drawback of our study is that our pathologists did not have the entire tumor available in 12% of patients, therefore they were not able to determine whether the tumor was of the widely invasive subtype. Pathologists were also unable to determine this with certainty in very large tumors that were operated on at our institution. The presence of this factor could significantly affect the results of the multivariate proportional hazards regression. Based on our research, it is not possible to conclude whether treatment is related to the length of patients' lives, as our research was not randomized. Furthermore, our cohort of patients is too small to assess the effect of treatment on disease course and survival. Because our study reports on the treatment of patients over a 50-year period, patient management has changed over this period. The patients included in our study until 2015 had almost all received suppressive hormone treatment with thyroid hormones for many years, so our data on the frequency of relapses cannot speak about how frequent relapses would be if patients had been taking hormones in replacement doses throughout this time. Similarly, based on our data, we cannot draw conclusions on the effect of thyroid remnant ablation with radioiodine on the frequency of disease recurrence. A significant limitation of our study is that the number of patients included was small and only a small proportion of patients relapsed or died from cancer. The fact that a small proportion of patients relapsed or died from cancer is actually very good. It speaks in favor of a favorable prognosis for most appropriately treated patients with OTC.

Because OTC is a rare disease and patients have favorable prognosis, it is highly unlikely that a randomized multicenter study of the effect of treatment on the frequency of disease recurrence will be possible. It is still unknown which patients should not be treated with total thyroidectomy and which should not have radioactive iodine ablation of the thyroid remnant. Our findings suggest that OTC patients who achieve an excellent response represent a low-risk subgroup for whom de-escalation of intensive long-term monitoring and avoidance of long-term aggressive TSH suppression might be safe. In contrast, patients without an excellent response represent a high-risk group that requires vigilant monitoring and, in the event of distant metastases, appropriate treatment. Hopefully, other researchers with large enough patient series with long-term follow-up will perform a similar analysis and confirm our findings. It would be even better if data on treatment and recurrence were collected prospectively from multiple centers. This could help clarify the questions of: "What are the risk factors for recurrence and patient survival?" and "What is the optimal treatment and follow-up for individual patients?".

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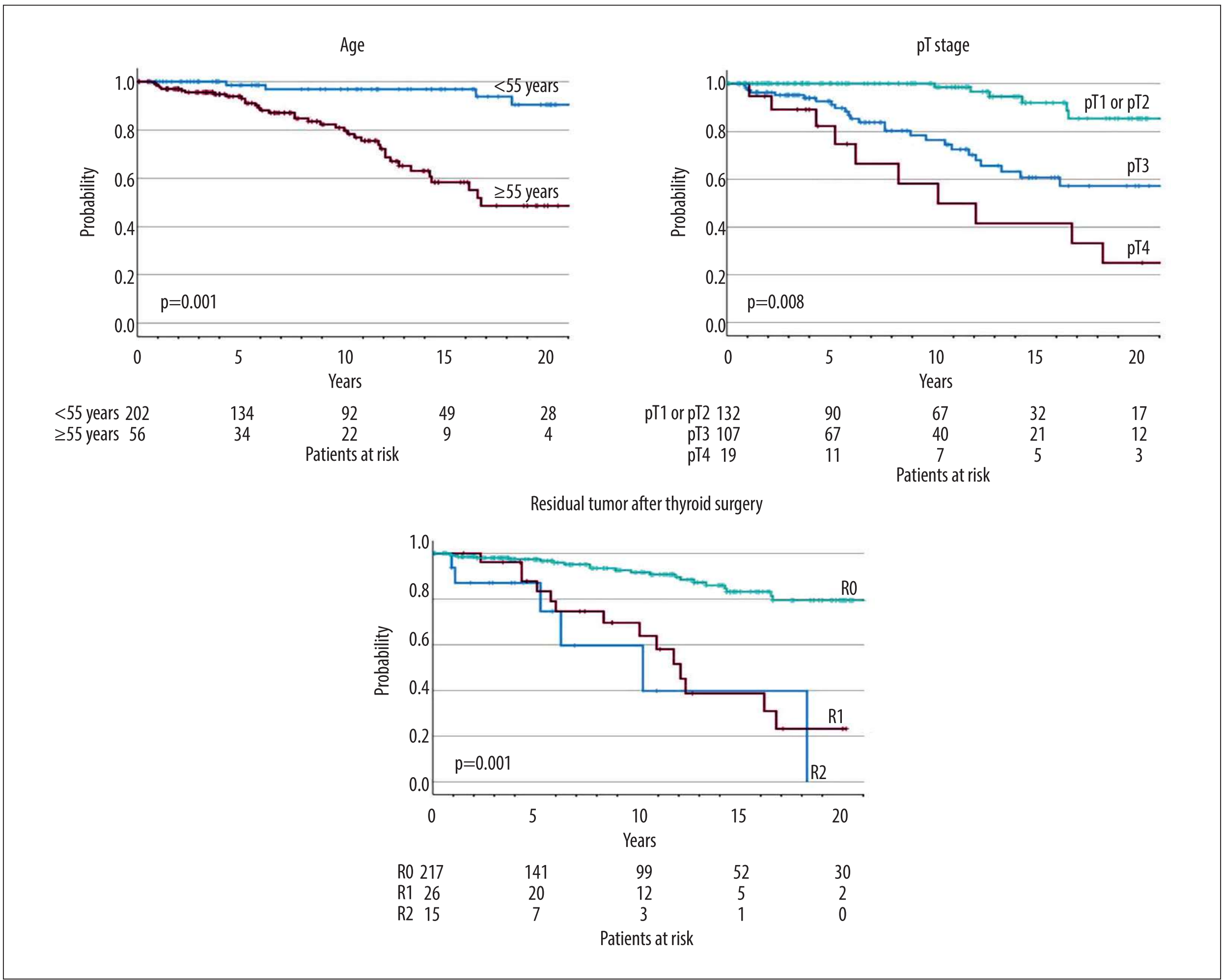

Figure 4. Patient age, pT stage, and residual tumor after thyroid surgery were independent factors for the duration of overall survival as shown by a multivariate analysis.

Conclusions

Recurrence was diagnosed in 17% of patients with OTC. Locoregional, distant, and both locoregional and distant recurrence were diagnosed in 8%, 6%, and 3% of patients, respectively. The recurrence rates in patients with and without an excellent response were 6.5% and 35%, respectively. Our findings suggest that patients with OTC who achieve an excellent response represent a low-risk subgroup for whom de-escalation of intensive long-term follow-up and avoidance of prolonged aggressive TSH suppression may be safe. Conversely, patients without an excellent response constitute a high-risk group requiring vigilant surveillance. Furthermore, we confirm that established clinicopathological factors – male sex, pT3 or pT4 tumor stage, and most significantly, the presence of residual tumor (R2 resection) – are independent prognosticators for recurrence and disease-free survival, reinforcing the paramount importance of complete surgical resection. Advanced age is an important risk factor for shorter disease-specific and overall survival. This study firmly integrates OTC into the modern paradigm of response-adaptive management for differentiated thyroid cancer.

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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