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ORIGINAL ARTICLE

Long-term outcome of rare oncocytic papillary (Hürthle cell) thyroid carcinoma following (adjuvant) initial radioiodine therapy

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Abstract

Purpose Oncocytic (Hürthle cell) papillary thyroid carcinoma (OPTC) is a rare variant of the papillary thyroid carcinoma (PTC) which comprises approximately 1 to 11 % of PTC cases. Its clinical course and prognosis have not been comprehensively documented and the clinical outcome remains a controversial issue. Therefore, we investigated the long-term prognosis after thyroidectomy and (adjuvant) initial radioactive iodine therapy (RIT) of OPTC compared to PTC.

Methods A total of 563 patients (47 with OPTC and 516 with PTC) with a median follow-up of 9.9 (0.3; 23.5) years were studied. All patients underwent thyroidectomy followed by (adjuvant) initial RIT. Data on the patients' demographics, pathology, laboratory findings, imaging studies, treatment, and follow-up including recurrence, and disease-specific survival were collected. Cox's multivariate regression model was used to identify independent prognostic factors for survival.

Results OPTC patients were significantly older (55.2 ± 12.3 years) than PTC patients (50.3 ± 13.5) at the time of initial diagnosis (p value 0.016). Initial tumor size was larger in the OPTC group (2.8 ± 1.8 cm for OPTC patients, 1.5 ± 1.2 cm for PTC patients, p value < 0.001). Before matching, OPTC patients presented more often with evidence of disease at the last visit of follow-up (p value 0.046). However, this difference was not observed anymore after matching for risk factors (p value 0.637). Disease-specific survival did not differ significantly. Age (HR, 1.183; 95% CI, 1.097–1.276) was identified as an independent prognostic factor for disease-specific survival. OPTC patients predominantly showed a recurrence of distant metastasis within a shorter time despite being not statistically significant.

Conclusion At initial diagnosis, OPTC shows significant differences in terms of age and initial tumor size compared to PTC. Patients suffering from OPTC present with the same clinical long-term outcome indifferent to PTC after (adjuvant) initial RIT after matching.

Keywords Papillary thyroid cancer · Oncocytic · Oxyphilic papillary thyroid cancer · Hürthle cell carcinoma · Thyroid gland

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Background

The oncocytic variant of papillary thyroid carcinoma (OPTC) is a rare subtype of PTC and comprises approximately 1 to 11 % of PTC cases [1, 2]. As a result of its rare occurrence, only a few studies have directly addressed the prognosis of patients with OPTC in comparison to patients diagnosed with a classic PTC. Moreover, these studies have shown conflicting results regarding patients' clinical outcome. It has been reported that OPTC is a more aggressive and more invasive variant of PTC [3–5]. The poorer outcome has been attributed to the lack of radioactive iodine (RAI) uptake, especially in distant bone and pulmonary metastasis [6, 7]. In contrast to these data, others have suggested that OPTC shows a similar outcome, especially in case of matched risk factors [8, 9]. In this context, male gender, advanced age, advanced TNM stage, extrathyroidal extension, multifocality, and residual tumor after thyroidectomy are considered as risk factors [7, 8, 10–14]. Therefore, we evaluated the long-term clinical outcome of patients presenting with an OPTC in comparison to those with a classic PTC from a larger patient cohort at our center.

Methods

Patients

We retrospectively reviewed patients with a histopathologically confirmed diagnosis of classic PTC or OPTC who underwent (adjuvant) initial radioiodine therapy (RIT) at our institution between 1993 and 2001. Patients with poorly differentiated thyroid cancer, anaplastic, medullary, classical follicular thyroid cancer (FTC), tall cell variants, and other variants of PTC, besides classic and oncocytic, were excluded. Patients with a latency period between surgery and RIT of more than 12 months, patients < 18 years, and patients without follow-up were excluded from the analysis. Patients treated with an initial activity of less than 3000 MBq (81 mCi) radioiodine due to remaining thyroid tissue in ultrasound and/or simultaneously high local uptake in RAI testing were excluded to ensure an adequate thyroidectomy state. For our study, 1090 patients were screened and the final study population included 563 patients (516 classic PTC and 47 OPTC patients). Patients with a classic PTC served as our reference group. TNM staging was based on the AJCC 7th edition in all patients [15].

Treatment

All patients underwent total or near-total thyroidectomy and were referred to our department for RAI. Patients received a cervical ultrasound of the thyroid bed and the cervical lymph node compartment levels I–VI. RIT (mean, 3771 ± 475 MBq I-131) was performed in hypothyroidism after thyroid hormone withdrawal in concordance with German and European recommendations. TSH, free T4, free T3, thyroglobulin (Tg), and Tg recovery were measured prior to administration of radioiodine. If the postoperative, stimulated Tg at the time of first RIT was > 10 ng/ml, Tg was considered to be "out of proportion." This definition is based on a current ATA statement that postoperative Tg values (stimulated or non-stimulated) > 10 ng/mL increase the likelihood of persistent or recurrent disease or distant metastases, of failing initial RAI ablation, and of dying of thyroid cancer [16].

Follow-up

Follow-up examinations were usually performed every 3 months in the first year, every 6 months in the second year after treatment and annually thereafter. At each visit, a cervical ultrasound of the thyroid bed and the cervical lymph node compartments was performed by an experienced nuclear medicine physician. Furthermore, TSH, free T4, free T3, thyroglobulin (Tg), and Tg recovery were measured. A whole-body scintigraphy (WBS) was performed in hypothyroidism after thyroid hormone withdrawal with a mean of 3.9 ± 1.5 months after RAI ablation to evaluate the therapy response. Follow-up additional radiological examinations, such as X-ray of the chest, CT thorax and MRI of the neck, or whole-body FDG-PET scans, were performed in case of suspected tumor recurrence. During follow-up, serum TSH levels were maintained at levels < 0.1 μU/ml until 2013. After 2013, TSH level was reduced to 0.3 to 1.0 μU/ml in patients with no evidence of disease (NED) for more than 5 years and patients with pT1/2, pN0, cM0, and R0. If additional courses of RIT were administered during follow-up, 7400 MBq I-131 were given routinely. Eventually, 3700 MBq and 9200 MBq I-131 were administered depending on the individual decision of the treating physician. In case of recurrent distant disease, 9200 MBq I-131 was given.

Endpoints

The total number of patients with evidence of disease (ED) and no evidence of disease (NED) after initial treatment and at the last visit of follow-up was calculated in each group. NED was defined as Tg under the detection level of each assay, which became more sensitive during follow-up (first control: < 1.6 ng/ml in all patients; last visit of follow-up: < 0.5 ng/ml in 89 %, < 1 ng/ml in 4 %, and < 1.6 ng/ml in 7 %) and no evidence of morphological or functional tumor lesions. Vice versa, ED was defined as Tg level above the available detection rate and/or evidence of morphological or functional tumor lesions. Recurrence rate was determined in M0/Mx patients with complete response in the first follow-up examination, which included unsuspicious

diagnostic RAI WBS and stimulated Tg level under the detection limit < 1.6 ng/ml. Recurrence was assumed if Tg levels increased above the detection limit or if tumor lesions were detected during the second follow-up visit up to the final follow-up visit. Disease-specific survival was defined as the period from the first day of surgery to disease-specific death. Complete remission (CR) was defined as the functional and/or morphological disappearance of all tumor lesions and Tg under the detection level. Partial remission (PR) was assumed if tumor lesions decreased by at least 30 % and if Tg level corresponded. Stable disease (SD) was expected if tumor lesions persisted and Tg level maintained above the normal limit without showing neither a sufficient shrinkage to qualify for PR nor a sufficient increase to qualify for progressive disease (PD). PD was defined as the appearance of one or more new tumor lesions and/or an unequivocal progression of existing tumor lesions (at least a 20 % increase in the sum of the longest diameter of target lesions if morphological imaging was available). Furthermore, presenting with significant differences in baseline characteristics OPTC and PTC patients were matched to exclude influence on survival in a subgroup analysis.

Statistical analysis

IBM SPSS statistics (version 25.0, IBM North America) was used for statistical analysis. Descriptive statistics are reported as mean ± standard deviation. Categorical variables were reported as numbers and percentages. The Kolmogorov-Smirnov test was performed to test normal distribution and comparisons of variables between patients with OPTC and PTC were performed using Student' s *t* test for parametric continuous data, the chi-quadrat-test for binary data, Mann-Whitney *U* test for continuous nonparametric data, and Fisher's exact test for categorical data. The comparison of disease-specific was based on the plotting of the Kaplan-Meier method and the log-rank test. Survival was displayed as mean (95 % CI) as median survival was not reached. Parameters that showed significant influence on disease-specific survival, respectively, in the univariate analysis, were included in the multivariate analysis. Vice versa parameters with p values ≥ 0.5 were not included in the multivariate analysis. The multivariate regression model was applied to analyze prognostic factors associated with disease-related specific survival. Statistical significance was defined as two-tailed p-values < 0.05.

Ethics statement

This retrospective study was approved by the institutional ethics committee (Ethics committee of the Medical Faculty, University Hospital, LMU Munich, Munich, Germany, IRB # 18-768) and has been conducted in accordance with the ethical standards, according to the Declaration of Helsinki, and according to national and international guidelines. The requirement to obtain informed consent was waived due to the retrospective design of this study.

Results

Complete group

Patient characteristics

Patient characteristics are reported in Table 1. Five hundred sixty-three patients (431 female (77 %), 132 male (23 %); mean age 50.7 ± 13.5 years) were included. Of these, 47 patients (8 %) presented with OPTC and 516 (92 %) with classic PTC. One hundred thirty-one patients (23 %) were treated with thyroidectomy and RIT, 289 patients (51 %) with thyroidectomy, lymphadenectomy (LAE); RIT, 28 patients (5 %) with thyroidectomy; RIT, and external radiation therapy (ERT) of the neck, and 115 patients (20 %) with thyroidectomy, LAE, RIT, and ERT of the neck (Fig. 2). RAI therapy with an initial dose of 3771 ± 475 MBq I-131 (102 mCi ± 13 mCi) was performed 49 ± 22 days after surgery in hypothyroidism with TSH > 30 μU/ml. Mean tumor size was 1.6 ± 1.3 cm. Thirty-two patients (6 %) presented with a tumor size greater than 4 cm. Tg out of proportion was seen in 110 patients (20 %) at the time of the first RIT. Multifocality was observed in 136 patients (27 %). TNM classification and tumor grades are presented in Tables 2 and 3.

Outcome analysis

The median follow-up time was 9.9 (0.3; 23.5) years. In the first control after RAI, 407/563 patients (72 %) had NED. Recurrence was observed in 25 patients (6 %). At the last follow-up visit, 516/563 patients (91 %) had NED. Ninety-six patients had died (17 %). Thyroid carcinoma was the cause of death in 15 patients (3 %).

OPTC and classic PTC

Patient characteristics

Dedicated patient characteristics and tumor stages for classic PTC and OPTC are summarized in Tables 1, 2, and 3. OPTC patients were significantly older than those presenting with a classic PTC. Mean tumor size at diagnosis was significantly larger in OPTC patients compared to PTC patients (2.8 ± 1.8 cm versus 1.4 ± 1.2 cm, $p < 0.001$). The OPTC group included significantly more patients with a tumor size above 4 cm. No significant difference was observed regarding gender, mean time between surgery and RAI administration,

Table 1 baseline characteristics at primary presentation

	Total*N* = 563	OPTC*N* = 47 (8 %)	PTC*N* = 516 (92 %)	*p* value
Mean age (years)	50.7 ± 13.5	55.2 ± 12.3	50.3 ± 13.5	*0.016*
> 45 years	377 (67%)	37 (79%)	340 (66%)	0.077
Female	431 (77%)	38 (81%)	393 (76%)	0.59
Mean initial RAI dose (MBq)	3771 ± 475 (102 ± 13 mCi) (IQR, 160)	3798 ± 557 (103 ± 15 mCi) (IQR, 185)	3769 ± 467 (102 ± 13 mCi) (IQR. 160)	0.932
Mean cumulative RAI dose (MBq)	7085 ± 8149 (191 ± 220 mCi) (IQR, 3850)	9236 ± 11110 (250 ± 300 mCi) (IQR, 3768)	6889 ± 7809 (186 ± 211 mCi) (IQR, 3850)	0.344
Median time of follow-up (years)	9.9 (0.3; 23.5)	7.9 (0.3; 23)	9.9 (0.3; 23.5)	0.814
Median time between surgery and RIT (days)	45 (11; 328)	46 (11; 121)	44 (14; 328)	0.658
Mean tumor size (cm)	1.6 ± 1.3 (IQR 1.5)	2.8 ± 1.8 (IQR 2.15)	1.5 ± 1.2 (IQR 1.5)	< *0.001*
Mean tumor size > 4 cm (11 % unknown)	32 (6 %)	8 (20 %)	24 (5 %)	*0.002*
Multifocality (11 % unknown)	136 (27 %)	9 (21 %)	127 (2 8%)	0.375
Tg out of proportion initially	110 (20 %)	12 (26 %)	98 (19 %)	0.336

OPTC, oncocytic (Hürthle cell) papillary thyroid carcinoma; PTC, papillary thyroid carcinoma; MBq, megabecquerel; IQR, interquartile range

initial RAI treatment activity, multifocality, Tg out of proportion at the time of first RIT, and time of follow-up. In both groups, females were affected more frequently (81 % in the OPTC and 76 % in the PTC group). Distant metastases were diagnosed at initial presentation in two patients of the OPTC group (4 %) and in 12 patients of the PTC group (2 %).

Outcome analysis

Outcome after initial treatment—first control In the first control after RIT, 33 OPTC patients (70 %) and 374 PTC patients (73 %) presented with NED (*p* value 0.735). Vice versa, in patients with ED, Tg was above the detection rate (< 1.6 ng/ml) in 9 OPTC patients (19 %) and in 69 PTC patients (13 %, *p* value 0.272). Findings in the thyroid bed or the cervical lymph nodes were documented in 9 % of OPTC patients (2 patients with remnant tissue, 2 patients with lymph nodes) and in 17 % PTC patients (20 patients with remnant tissue, 68 patients with lymph nodes) in the ultrasound (*p* value 0.226). Pathological findings in the diagnostic RAI WBS were found in 9 OPTC patients (19 %) and in 132 PTC patients (26 %, *p* value 0.627).

Outcome—during follow-up During follow-up, in patients who presented with ED in the first control, one additional course of RIT was performed in 94 patients; > one additional course (2–13 courses) in 32 patients; 1 cycle of RIT and surgical procedures in three patients; > 1 cycle of RIT and surgical procedures in seven patients; RIT, surgery, and ERT in one patient; and consequent TSH suppression in 19 patients

Table 2 TNM classification

TNM classification	Total*N* = 563	OPTC*N* = 47 (8 %)	PTC*N* = 516 (92 %)	*p* value
pTx	29 (5 %)	5 (11 %)	24 (5 %)	*0.015*
pT1a, pT1b	317 (56 %)	18 (38 %)	299 (58%)	(pT1/2 vs. pT3/4;
pT2	64 (11 %)	11 (23 %)	53 (10 %)	*p* value 0.861)
pT3	138 (25%)	13 (28 %)	125 (24 %)	
pT4a	14 (3 %)	0 (0 %)	14 (3 %)	
pT4b	1 (< 1 %)	0 (0 %)	1 (< 1 %)	
pN0	282 (50 %)	22 (47 %)	260 (50 %)	*0.036*
pN1a, pN1b, pN1	122 (22 %)	5 (11 %)	117 (23 %)	
pNx	159 (28 %)	20 (43 %)	139 (27 %)	
cM0/cMx	549 (98 %)	45 (96 %)	504 (98 %)	0.329
cM1	14 (3 %)	2 (4 %)	12 (2 %)	
pR0	352 (63 %)	32 (68 %)	320 (62 %)	0.815
pR1	21 (4 %)	1 (2 %)	20 (4 %)	
pR2	2 (< 1 %)	0 (0 %)	2 (< 1 %)	
pRx	188 (33 %)	14 (30 %)	174 (34 %)	

OPTC, oncocytic (Hürthle cell) papillary thyroid carcinoma; PTC, papillary thyroid carcinoma; T, Tumor; N, nodus; M, metastasis; R, resection; p, histopathologic; c, clinical

Table 3 Tumor stage

Stage	Total*N* = 563	OPTC*N* = 47 (8 %)	PTC*N* = 516 (92 %)	*p* value
I	378 (67 %)	24 (51 %)	354 (69 %)	0.065
II	30 (5 %)	6 (13 %)	24 (5 %)	
III	77 (14 %)	9 (19 %)	68 (13 %)	
III–IVa	7 (1 %)	0 (0 %)	7 (1 %)	
IVa	44 (8 %)	4 (9 %)	40 (8 %)	
IVb	1 (< 1 %)	0 (0 %)	1 (< 1 %)	
IVc	10 (2 %)	2 (4 %)	8 (2 %)	
missing	16 (3 %)	2 (4 %)	14 (3 %)	

OPTC, oncocytic (Hürthle cell) papillary thyroid carcinoma; PTC, papillary thyroid carcinoma

(Fig. 2). OPTC patients with ED in the first control after initial RIT were less often cured during follow-up (*p* value 0.035).

Recurrence during follow-up occurred in 9 % of OPTC patients (3/33) and in 6 % of PTC patients (22/374; *p* value 0.443). One OPTC patient (#93) relapsed only biochemically and was treated with consequent TSH suppression. This patient was cured during follow-up. Two OPTC patients (patients #96, #662) showed biochemical relapse initially. During disease progression, distant metastases of the lung were diagnosed in both patients and were treated with four and five additional courses of RIT, respectively. During treatment, the Tg level remained stable in one patient and increased steadily in the other. In both patients, pulmonary metastases did not show radioiodine avidity. In patient #662, an atypical lung resection was performed after the fifth cycle of RIT treatment. Both patients showed ED in the last follow-up visit and progression of the pulmonary metastases led to death.

Sites of recurrence in PTC patients were lymph nodes (*n* = 3/22), lymph nodes and distant metastases (5/22), and distant metastases (*n* = 3/22). 11/22 PTC patients (50 %) showed biochemical relapse without detectable morphological or functional findings.

Recurrence occurred after a median of 2.8 years in the OPTC group and after a median of 4.0 years in the PTC group, respectively, without being statistically significant. In patients with recurrent disease, 33 % of OPTC patients (1/3) and 55 % of PTC patients (12/22) were treated curatively until the end of follow-up with Tg level under the detection limit and no morphological or functional evidence of metastases (*p* value 0.593). Patients with recurrences are presented in the supplements.

Outcome-Last follow-up visit In the last follow-up visit, OPTC patients presented significantly more often with ED (17 % of OPTC vs. 8 % of PTC patients; *p* value 0.046). In 83 % of OPTC patients (39/47) and in 92 % of PTC patients (477/516), the Tg level was under the detection limit, and no evidence of morphological or functional tumor lesions was diagnosed.

Outcome-End of study At the end of our study, 12 OPTC patients (26 %) and 84 PTC patients (16 %) had died (*p* value 0.108). Thyroid carcinoma was the cause of death in 3 OPTC (6 %) and 12 PTC patients (2 %, *p* value 0.103). The 5-year, 10-year, and 20-year disease-specific survival rates were 100 %, 97 %, and 84 % in patients with OPTC, and 99 %, 98 %, and 95 % in patients with PTC, respectively (Fig. 1a). Mean disease-specific survival was 21.6 years (20.1–23.1) in the OPTC group and 22.9 years (22.5–23.2) in the PTC group (*p* value 0.142). Figure 2 summarizes the outcome of OPTC and PTC patients during the study period.

Age, T-stage, R-stage, M-stage, tumor size, and Tg out of proportion at the time of the first RIT were associated with shorter disease-specific survival in the univariate analysis (Table 4). Age was an independent unfavorable prognostic factor in the multivariate analysis for disease-specific survival.

Subgroup analysis: matched patient group

Patients were matched by age, sex, and TNM classification, R-stage, tumor size, and RAI dose. Two hundred thirty-one patients (185 PTC, 46 OPTC) were included in the matched patient group analysis. After matching, no significant differences in patient outcome could be observed between the two groups. In the first control after RIT, 72 % of the OPTC group and 69 % of the PTC had NED (*p* value 0.858). Sixty-two percent of OPTC patients and 72 % of PTC patients with ED in the first control were treated curatively at the end of follow-up (*p* value 0.511). Recurrence during follow-up was detected in 9 % of the OPTC and 6 % of the PTC patients (*p* value 0.697). At the last follow-up visit, 85 % of OPTC patients and 87 % of PTC patients had NED (*p* value 0.637). The 5-year, 10-year, and 20-year disease-specific survival rate were 100 %, 97 %, and 84 % in patients with OPTC, and 98 %, 97 %, and 90 % in patients with PTC respectively (Fig. 1b). Mean disease-specific survival was 21.6 years (20.1–23.1) in the OPTC group and 22.4 years (21.6–23.1) in the PTC group (*p* value 0.595).

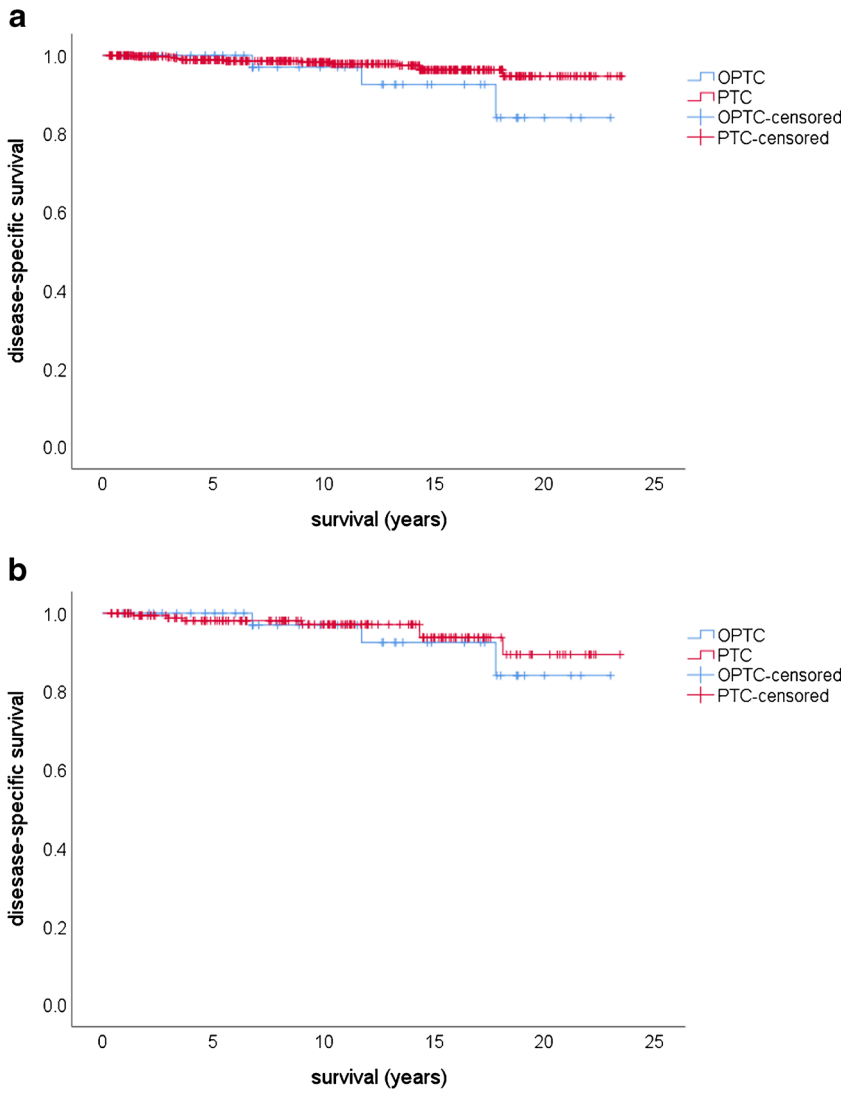

Fig. 1 Disease-specific survival in all patients (**a**) and after matching (**b**). Disease-specific survival did not statistically differ between the two groups before and after matching, although they slightly diverged after 20 years (*p* value 0.142 and 0.595, respectively). OPTC, Hürthle cell (oncocytic) papillary carcinoma; PTC, papillary thyroid carcinoma

Discussion

PTC is the most common type of thyroid malignancy, accounting for approximately 85 % of all cases [6, 17] with relatively indolent clinical course and favorable prognosis compared to other types of thyroid cancer [18]. Various histopathological variants have been characterized for PTC, including subtypes with inferior prognoses such as the tall cell, Hobnail, columnar cell, and diffuse sclerosing PTC [6]. Up to now, the prognosis of OPTC is discussed controversially. Thus, the aim of our study was to analyze the long-term prognosis of OPTC compared to classic PTC in a large patient cohort treated at our institution. This analysis represents the largest series of OPTC and PTC patients treated at a single center.

In our study, patients with OPTC were significantly older (55.2 ± 12.3 years) compared to patients with classic PTC. This is in line with previously published data suggesting that OPTC manifests more likely in older patients, which is not the case in classic PTC or follicular TC [3, 8, 13]. Furthermore, as previously reported in other studies [8, 13, 19], our data also confirmed that patient's age represents an independent risk factor for disease-specific survival.

Most of the available literature agrees that the mean initial oncocytic tumor size ranges from 25 to 48 mm [10, 14, 20–24]. In our study, OPTC patients presented with a mean tumor size of 2.8 ± 1.8 cm, which is at the lower end of this range. Of note, we only included the papillary oncocytic variant, which may be smaller when compared to the follicular oncocytic variant. Nevertheless, we observed that tumor size was significantly larger in the OPTC group than in the PTC group. Significantly, larger tumor sizes in the oncocytic variants have also been observed by other authors [20]. In the present study, a tumor size of > 4 cm was a risk factor for survival in the univariate but not in the multivariate analysis. However, it is still debatable if tumor size represents a risk factor at all [14, 21]. In contrast, others have shown that tumor size is indeed associated with poorer

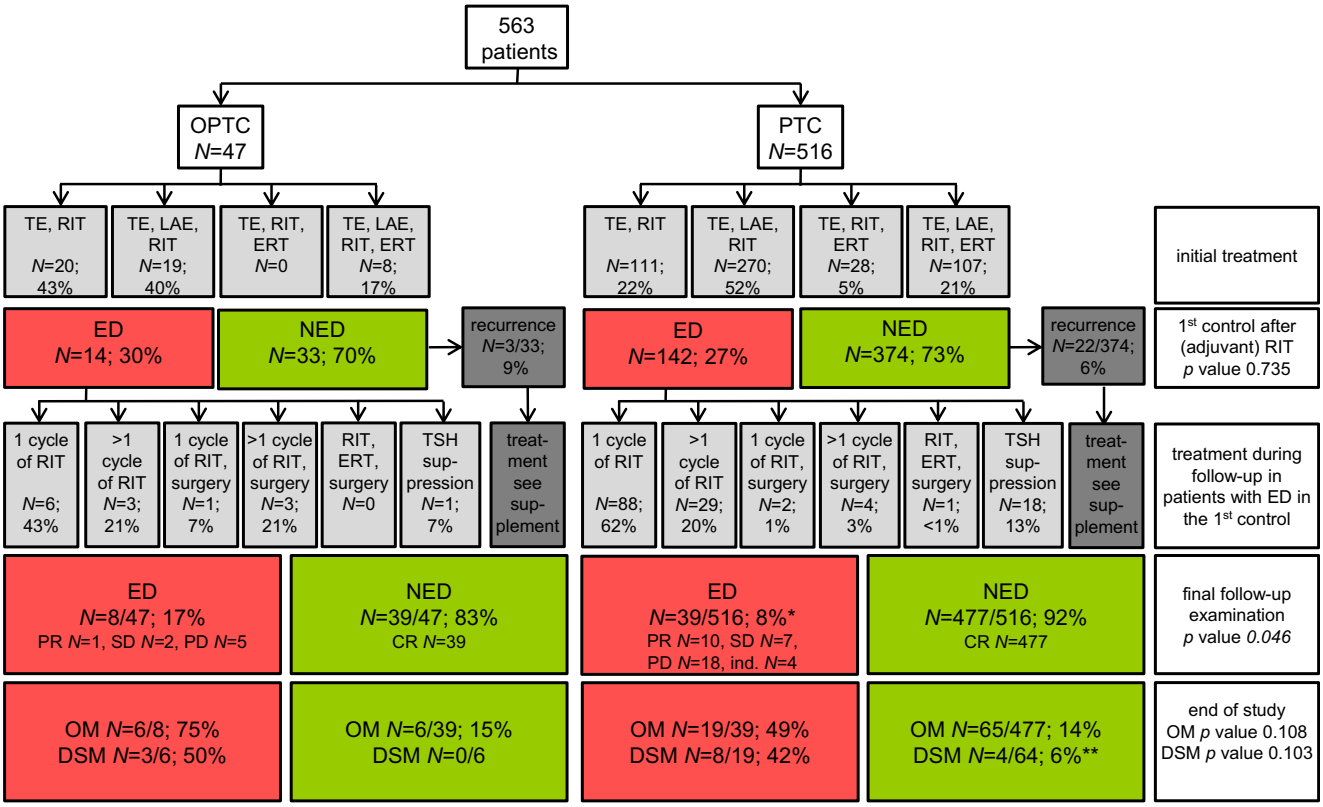

Fig. 2 OPTC, oncocytic (Hürthle cell) papillary thyroid carcinoma; PTC, papillary thyroid carcinoma; TE, thyroidectomy; LAE, lymphadenectomy; RIT, radioactive iodine therapy; ERT, external radiation therapy; ED, evidence of disease; NED, no evidence of disease; OM, overall mortality; DSM: disease specific mortality; n, number of patients; CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease; ind., indeterminate. A single asterisk indicates four patients with NED in the 1 control (#15, 971, 982, 995) had ED in the last control due to more sensitive diagnostic work-up during follow-up. Double asterisks indicate four patients (#555, 715, 729, 925) with NED in the last follow-up visit died disease-related according to the tumor register

prognosis [23]. Furthermore, we identified postoperative stimulated Tg out of proportion as a risk factor in the univariate analysis. Indeed, it has been described before that high postoperative stimulated Tg values of > 10–30 ng/ml are also associated with poorer survival [16, 25–27]. Contemporary studies have recorded gender [10, 11], T- [8, 12, 13], N- [8, 12, 13], and M-stage [8, 13], multifocality [7, 13], surgeon's experience [14], and the presence of other malignancies [14] as further risk factors in the multivariate analysis. However, these studies partly included patients with follicular oncocytic variants, limiting their transferability to OPTC patients. In our study, T- and N-stage, R-margin status, and tumor size proved to be independent risk factors only in the univariate but not in the multivariate analysis.

In our study, the recurrence rate was 9 % in the OPTC group. Compared to other publications, our recurrence rate is quite low. In another study, relapse was found to be 14 % [19]. Our lower recurrence rate might be attributed to the multimodal treatment approach with total or near-total thyroidectomy along with (adjuvant) initial RIT. We have excluded patients treated only with lobectomy or without use of RIT, which is very likely to have an impact on patients' outcome. Additionally, Grogan et al. stated that recurrence can occur even after 30 years [28], implying that we might have missed some relapses because of a too short follow-up time of median 10 years. Finally, in most studies, recurrence is not clearly defined. In contrast to our study, some authors defined progression of existing disease as recurrence [28], which consequently creates different outcomes. In our study, the rate of recurrence did not statistically differ between OPTC and classic PTC patients. This is contrary to a recently published study with 142 PTC patients of whom 65 patients had oncocytic changes which involved less than 75 % of a tumor [5]. They found that patients with oncocytic changes presented with a higher recurrence rate (31 % vs. 12 %, respectively; p value = 0.005), suggesting that the presence of oncocytic change is a negative prognostic factor. However, in their study, 63 % were treated with lobectomy and only 50 % were treated with RIT, limiting comparison. Indeed, RIT may confer a survival benefit when used for ablation therapy, but not when residual disease is present [7]. In our study, the pattern of recurrence seemed to be somewhat different in OPTC and classic PTC. While OPTC patients most often suffered from distant metastases, classic PTC patients presented with both lymph node and distant metastases. Of

Table 4 Risk factors for disease-specific mortality

Covariate	Level	Disease-specific survival			
		Univariate analysis		multivariate analysis	
		HR (95% CI)	*p* value	HR (95% CI)	*p* value
Gender	Female	Ref			
	Male	0.476 (0.172–1.312)	0.151		
Age (years)	Mean	1.203 (1.134–1.277)	*< 0.001*	1.183 (1.097–1.276)	*< 0.001*
Histology	OPTC	Ref			
	PTC	0.632 (0.355–1.192)	0.156		
T-stage	T1	Ref		Ref	
	> T1	20.504 (2.695–155.997)	*0.004*	4.903 (0.541–44.434)	0.157
N- stage	N0, Nx	Ref			
	N1, N2	2.524 (0.898–7.094)	0.079		
M-stage	M0, Mx	Ref			
	M1	2.436 (1.154–5.143)	*0.019*	2.458 (0.912–6.620)	0.075
R-stage	R0, Rx	Ref		Ref	
	R1, R2	4.907 (1.091–22.067)	*0.038*	1.419 (0.157–12.818)	0.755
Tumor size	≤ 4 cm			Ref	
	> 4 cm	10.516 (2.714–40.748)	*0.001*	2.588 (0.522–12.836)	0.244
Multifocality	No				
	Yes	1.328 (0.4–4.414)	0.643		
Tg out of proportion	No	Ref			
	Yes	4.61 (1.67–12.728)	*0.003*	1.791 (0.386–8.317)	0.457

OPTC, Hürthle cell (oncocytic) papillary carcinoma; PTC, papillary thyroid carcinoma; T, tumor, N, nodus; M, metastasis; *R*, resection; HR, hazard ratio; CI, confidence interval

note, we could not observe a relevant RAI uptake of distant pulmonary metastases in OPTC patients. In this context, it has been reported that only a minority of patients with distant metastasis showed positive I^{131} RAI uptake which contributes to a worse prognosis [7]. However, Jillaed et al. have demonstrated the association of improved survival in Hürthle cell carcinoma patients who were treated with RIT [29]. The effect of RIT in OPTC patients with recurrent distant metastases has to be clarified in further studies. Differences in metastases might have influenced the outcome in these patients, such as only one of three OPTC patients (33 %) and 12 of 22 PTC patients (55 %) with recurrences were treated curatively at the end of follow-up. Moreover, the time of recurrence was shorter in the OPTC group, despite being not statistically significant. However, studies in larger series of OPTC patients are needed to analyze the differences in the recurrence pattern and the impact of relapse on poor prognosis.

At the last visit during follow-up, OPTC patients presented more often with ED (OPTC 17 % vs. PTC 8 %, *p* value 0.046). However, this difference was not observed after matching for influential factors. At the end of our study, 26 % of the OPTC patients and 16 % of the PTC patients had died. Thyroid carcinoma was the cause of death in 6 % of OPTC patients and in 2 % of PTC patients. The disease-specific mortality rate did not differ significantly between OPTC and PTC patients. Disease-specific survival curves slightly separated after 20 years; however, this was not statistically relevant. A recent study by Liu et al. also confirmed that disease-specific mortality and overall mortality rates of patients with OPTC were similar to patients with PTC [8]: After they matched for influential factors (age, gender, TNM stage, multifocality, extension, and radiation treatment), the disease-specific prognosis for patients with OPTC was still similar and the overall mortality was even significantly better compared to those with classic PTC [8]. Recently, Carr et al. also concluded in a small patient cohort of 21 matched patients that oncocytic papillary variant may not represent a more aggressive variant of PTC [9]. In our study, the 5-year, 10-year, and 20-year disease-specific survival rates were 100 %, 97 %, and 84 % in OPTC patients. To our knowledge, survival rates of oncocytic papillary carcinoma have not been published yet. Even though Liu et al. presented survival curves for a 10-year period, the authors did not specify absolute rates [8]. However, in studies including follicular variants of oncocytic TC, a 10-year disease-specific survival ranged from 49 to 93 % [7, 14, 20, 21, 30, 31]. Compared to these studies, our 10-year survival rate focusing on papillary

oncocytic variant only is higher. Further studies are needed to evaluate the prognosis of not an only papillary variant but also a follicular variant of thyroid carcinoma in comparison to their correspondent classic version (PTC/FTC). It is also mandatory to distinguish between the different variants of oncocytic thyroid cancer in future studies.

Limitations

A limitation arises from the retrospective study design; due to the retrospective design and the relatively long follow-up the diagnostic work-up of our patient cohort was limited at the time of diagnosis and improved significantly over time (e.g., no SPECT). As a consequence, reliable differentiation between RAI uptake in the thyroid bed and cervical lymph nodes was not possible in all cases. Nowadays, high-sensitivity Tg assays are available which improves the early detection of recurrence. Furthermore, due to the long follow-up, histological tissues or slides were not available anymore. Therefore, we were only able to review original pathology reports from the referring hospital.

Conclusion

Our study represents the largest series of OPTC and PTC patients treated at a single center. Based on the results of the present study, we could demonstrate that after matching, the long-term prognosis of the rare Hürthle cell papillary carcinoma is similar to classic PTC, although OPTC presents with a higher patient age and tumor size at time of diagnosis. OPTC recurrence is rare after adequate surgical treatment and subsequent (adjuvant) initial RIT. The indifferent clinical outcome of OPTC and PTC patients suggests that adjuvant RIT is effective in OPTC patients. However, its role in metastatic OPTC patients has to be clarified in further studies. Our results indicate that OPTC and PTC patients without metastases could possibly undergo a comparable follow-up.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was authorized by the local ethics committee (Ethics committee of the Medical Faculty, University Hospital, LMU Munich, Munich, Germany, IRB 18-768) in accordance with the ICH Guideline for Good Clinical Practice (GCP) and the Declaration of Helsinki.

Informed consent The requirement to obtain informed consent was waived by the local ethics committee due to the retrospective design of this study.

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