Prognostic risk factors for rare oncocytic variant in 101 cases of papillary thyroid carcinoma

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Abstract

Objective: Oncocytic variant (OV) is an unusual subtype of papillary thyroid cancer whose histopathologic diagnostic criteria, clinicopathologic features and biological behavior are different and have not been comprehensively studied, characterized in literature. Previous studies present conflicting results upon its prognosis. We investigated demographic and clinicopathologic risk factors affecting its prognosis while presenting our clinical experience. **Subjects and Methods:** This is a retrospective cohort study reviewing 101 patients of OV from an archive of 4500 well-differentiated thyroid cancer patients treated with iodine-131 (^{131}I) between 1991 and 2017. Predefined parameters of age, gender, tumor size (TS), total ^{131}I dose, time to recurrent disease, overall survival, extrathyroidal extension, multifocality, vascular invasion, accompanying other variants, capsular status of thyroid gland, initial cervical lymph node (LN) metastases, preablation stimulated thyroglobulin level, background thyroiditis and stage were evaluated by statistical comparison between metastatic and nonmetastatic groups. **Results:** Seventeen cases (17%) developed metastases/ recurrence, 70% of the recurrences occured before 24 months. Four patients (4%) died during the follow-up. Metastatic sites were usually cervical LN, local recurrence in thyroid bed and lungs. Multivariate analysis revealed stage (IV) and TS were the main parameters impacting recurrence/metastases. In the follow-up, isolated cervical LN metastases were found in 41% of metastatic cases, while 12% had sole recurrence in thyroid bed. Eighty eight percent of the metastatic disease included locoregional (cervical) and/or remote LN. The recurrences were associated with initial thyroid masses greater than 3.5cm in diameter. **Conclusion:** We found that the prognosis of OV is not poor in our series. Stage (IV) and tumor size are the main risk factors in metastatic development.

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Introduction

The most frequent thyroid cancer type is papillary thyroid carcinoma (PTC) and it accounts for approximately 80% of all malignant thyroid tumors. Papillary thyroid carcinoma has a more favorable prognosis than other types of thyroid carcinomas [1]. It contains various described histological variants. Patient demographics, clinicopathologic features, therapy and prognosis of these variants show different significant changes. Some of them represent a relatively indolent clinical course. Variants such as tall cell, columnar cell and diffuse sclerosing have a more aggressive clinical behaviour and less favorable prognosis requiring extensive surgery and ablation therapy with a high dose of radioiodine (^{131}I).

Oncocytic variant (OV) of PTC has been classified by the World Health Organization (WHO) as a unique thyroid neoplasm. Its diagnosis was established on the basis of conventional nuclear criteria in which oncocytic cells compose predominantly more than at least 75% of the entire tumor area [2]. Characteristic morphological features of oncocytic cells are large in size, polygonal-to-square in shape, distinct in cell borders with a dense, eosinophilic, granular cytoplasm of sharp outline [2, 3]. The enlarged nuclei may exhibit typical features of classic PTC. Nuclei in OV ratherly tend to be in an apical orientation and slightly more hyperchromatic, contrary to classic PTC or tall cell variant. Although there is also an abundant eosinophilic cytoplasm in tall cell variant, the cells are markedly taller and wider appearance discriminating from oncocytes.

Oncocytic variant is an unusual malignancy whose histopathologic diagnostic criteria, clinicopathologic features and biological behavior have not been comprehensively studied and characterized in literature. Previous studies present conflicting results upon its prognosis. In this study, we present our clinical experience pertaining to OV. We investigated the demographic and clinicopathologic risk factors effecting its recurrence/metastasis.

Subjects and Methods

This is a retrospective cohort study reviewing cases of OV treated at a tertiary hospital from 1991 to 2017. A hundred and one patients with OV were enrolled from an archive of nearly 4500 well-differentiated thyroid cancer. Oncocytic variant was diagnosed according to basic nuclear criteria that oncocytic cells dominate at least 75% of the total tumor cells with characteristic oncocytic features [2] (Figure 1). These are large, polygonal-to-square shaped cells in a dense, eosinophilic cytoplasm [2, 3]. Patients with a family history of PTC, a previous radiation exposure and a follow-up duration shorter than 18 months were neglected from the study. All cases were treated by total thyroidectomy with adjuvant ^{131}I therapy. Fifty one out of a hundred and one of the patients (50%) underwent lymph node (LN) dissection in the primary surgery and 31/51 of them (61%) had positive nodes.

The patients were separated into two groups: metastatic/recurrent group and nonmetastatic (complete remission) group. The analyzed parameters included age at initial presentation, gender, tumor size (TS), total ^{131}I treatment dose, time to recurrent disease (disease-free survival: DFS), outcome (overall survival: OS), extrathyroidal extension (ETE), multifocality (MF), vascular invasion (VI), accompanying other variants, capsular status of the thyroid gland (CI: capsule invasion), initial cervical LN metastasis at the beginning preablation cervical LN metastasis (PACLNM), preablation stimulated thyroglobulin level (PAsTg), background thyroiditis and stage. These predefined parameters were evaluated by statistical comparison between these two groups.

Descriptive statistical analyzes were performed. The whole data were analyzed by the Statistical Package for Social Science software (SPSS 15.0, Chicago, IL). Number, percentage, mean, median, standart deviation (SD), minimum (min) and maximum (max) values were used for the description of data analyzes. Accordance of continuous variables to normal distribution was measured with Kolmogorov-Smirnov test. Continuous variables were reported as mean and standard error (SE) with the 95% confidence interval (CI) or median value. Categoric data were suggested in percentages. Mann Whitney-U test was used for continuous variables, Chi square test for categorical variables in the comparisons. Univariate and multivariate analysis with Backward LR Analysis was performed for clarification of risk factors impacting on metastasis. Factors having a P value of <0.2 were processed in multivariate test. Also, predictors with a r value of >0.7 were neglected in an additional correlation analysis. Statistical tests were two-sided with a 5% level of significance. Our institutional ethics committee approved the study.

Results

Mean follow-up duration of patients was 79±37 (median: 65) months (8-292). Mean total administered ^{131}I dose (TAID) to patients was 5846±4033MBq (median: 5550) (1110-37000MBq). Mean time to metastatic development after ablation therapy (disease-free interval) was 20 months (6-56). Mean OS was 120 months (8-292) in dead cases. Seventeen cases (17%) developed metastases/recurrence, 84 cases (83%) lived a disease-free life (total remission). Seventy percent of the recurrences occured before 24 months. Four patients (4%) died during the follow-up. The cause of death in all was diffuse metastases and their complications. Ninety seven patients were alive and 86% of them were well with no evidence of disease.

Mean age (at diagnosis), TS, PAsTg of patients were 45.4± 13.8 years (12-77), 21.6±13.8mm (median: 16) (5-80), 16.8ng/mL (median: 1.6) (0.1-667), respectively. Seventy three percent (n:74) of the patients are female, 27% (n:27) male (female/male ratio:2.74). The tumor is multifocal in 21% of the patients. Confidence interval was positive in 64% of the patients. There was ETE in 22% of the patients. Twenty six percent of the patients were stage VI (+). Thirty percent of the patients

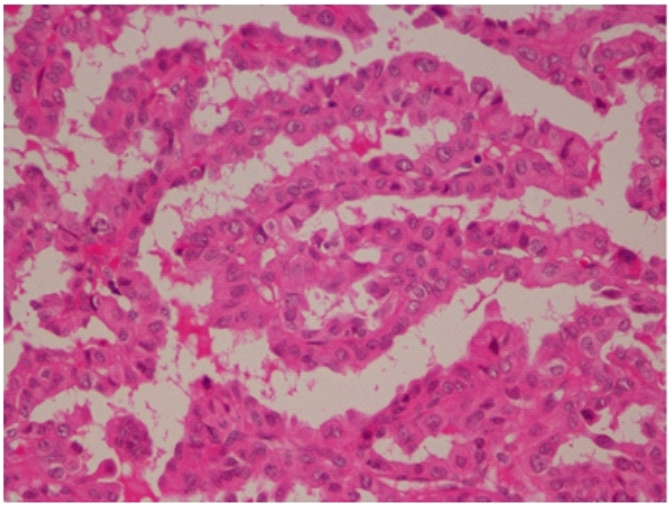

Figure 1. Oncocytic papillary thyroid carcinoma showing thyrocytes with characteristic prominent eosinophylic (pinkish) cytoplasm, and atypical nuclei lining fibrovascular cores (Hematoxylin- Eosin, x40)

had initial cervical LN metastases before ablation therapy, 32% associated background thyroiditis. Sixty six per cent of the patients were at stage I (Figure 2), 10% at stage II, 10% at stage III, 14% at stage IV. These values belonging to the groups and their comparisons are briefed in Tables 1-2. Tumor size, PAsTg, TAID, CI, VI, stage, ETE and PACLNM were determined as in-dependent variables for metastatic development in univariate analysis.

There were no significant differences in recurrence rates between men and women (log-rank test, P=0.61), nor between the age strata (less than or more than 45 years of age; log-rank test, P=0.66). Metastatic sites were usually cervical LN, local recurrence in thyroid bed and lungs. Other rare recurrences were seen in supraclavicular and mediastinal LN, remote organs (bones and brain). In the follow-up, isolated cervical LN metastases was found in 41% of metastatic cases, while 12% had sole recurrence in thyroid bed. Eighty eight percent of the metastatic disease included locoregional (cervical) and/or remote LN. The recurrences were associated with initial thyroid masses greater than 3.5cm in diameter (Figure 3). Besides the oncocytic cell variant, there were concomittant other variants such as tall cell (4), classical (11), columnar cell (1) and follicular (1) variant of PTC. Tumor size, total ^{131}I treatment dose, OS, ETE, VI, CI, PACLNM, PasTg and stage appeared as independent risk factors in univariate analysis. Multivariate analysis revealed stage (IV) and TS as the main parameters impacting recurrence/metastases (Tables 3, 4).

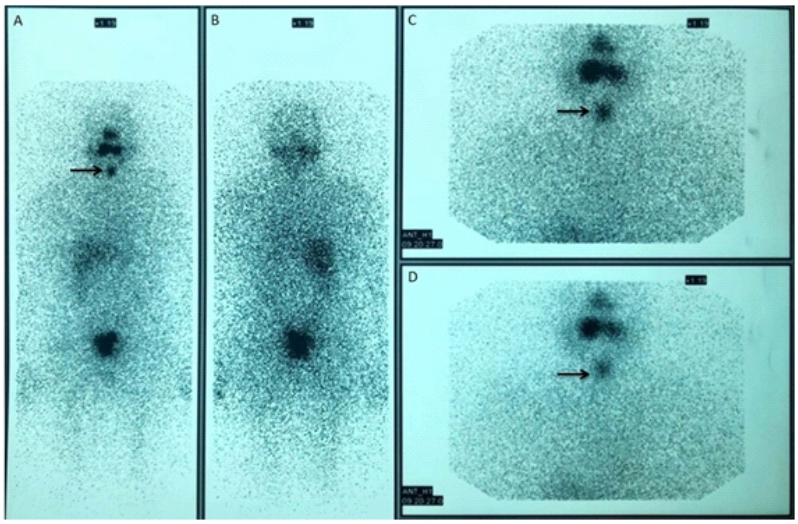

Figure 2. A 31 years old male patient with papillary thyroid cancer of OV had a tumor size of 1.5cm in right lobe, preablation Tg level of 3.69ng/dL (TSH:124.4IU/mL, anti-Tg antibody: <15.0IU/mL) and no lymphovascular invasion or initial metastatic LN. The patient underwent total thyroidectomy followed by a 3700MBq ^{131}I ablation therapy. Anterior (A), posterior (B) RxWBS and anterior spot planar images (C, D) showed focal uptake in the neck consistent with residual thyroid tissue (arrows). Recurrence was not detected during a 78months follow-up.

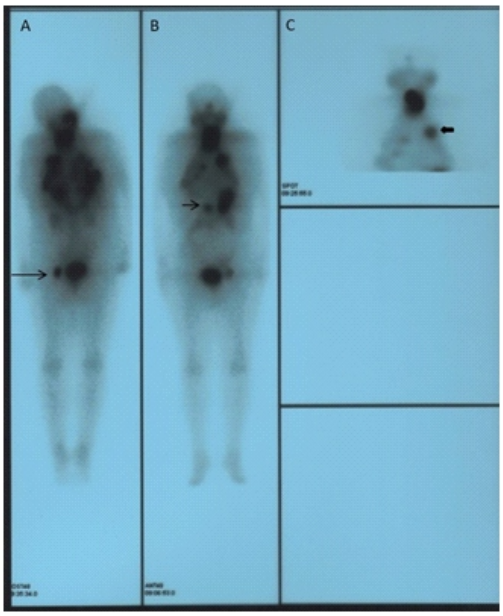

Figure 3. A 71 years old female patient with papillary thyroid cancer of OV had a tumor size of 4.2cm in left lobe, preablation Tg level of 120ng/dL (TSH:195IU/mL, anti-Tg anti-body: <10.0IU/mL), positive lymphovascular invasion and 13 initial metastatic LN. The patient underwent total thyroidectomy + central/left neck lymph node dissection fol-lowed by a 7400MBq ^{131}I ablation therapy. Anterior (A), posterior (B) RxWBS and anterior spot planar image (C) showed bilateral multiple lung (thick arrow), T12 vertebrae (short thin arrow) and left iliac bone (long thin arrow) metastases. The patient died 29 months later.

Table 1. *Comparison of metastatic/recurrent and non metastatic patients with oncocytic variant by age, tumor size, PAsTg, total administered ^{131}I dose, overall survival time.*

Variables	Metastatic/recurrent group Mean±SD or (MV)	Nonmetastatic group Mean±SD or (MV)	P value
Age (years)	48.7±14	44.7±12	0.15
Tumor size (mm)	32.7±14	19.4±9.5	0.001
PAsTg (ng/ml)	85.4 (13.3)	2.95 (1)	<0.001
TAID (mCi)	364 (300)	116±34	0.001
OS (months)	81 (63)	79 (67)	0.71

PAsTg: preablation stimulated Tg level just before the treatment, TAID: total administered ^{131}I dose MV: median value, OS: overall survival

Table 2*. Comparison of metastatic/recurrent and nonmetastatic groups by categorical variables.*

Variables		Metastatic/ recurrent group		Nonmetastatic group		P value	
		n	%	n	%		
Sex	male	8	47	19	23	0.07	
	female	9	53	65	77		
Multifocality	1 focus	12	71	67	80	0.52	
	2 or over	5	29	17	20		
Capsule invasion	exist	16	98	47	56	0.001	
	nonexist	1	2	37	44		
Extrathyroidal extension	exist	12	70	11	13	<0.001	
	nonexist	5	30	73	87		
Vascular invasion	exist	10	59	16	19	0.002	
	nonexist	7	41	68	81		
PACLNM	exist	13	76	18	22	<0.001	
	nonexist	4	24	66	78		
Stage	I	4	23	63	75	0.001	
	II	1	6	9	11		
	III	1	6	9	11		
	IV	11	65	3	3		

(continued)

Mortality	present	4	23.5	-	0	0.001
	none	13	76.5	84	100	
Concomittant other variants	Classic	1	1/17*	10	10/84*	0.73
	Tall cell	1	1/17*	3	3/84*	
Background thyroiditis	present	4	23.5	28	33	0.58
	none	13	76.5	56	67	

*PACLNM: preablation cervical lymph node metastasis *incidence in its own group*

Table 3. *Multiple Logistic Regression Analysis denoting the metastatic potential of oncocytic variant of papillary thyroid cancer. Factors having r value greater than 0.7 were excluded in correlation test.*

Variable (Referans)	Exp (B)	95% CI for Exp (B) Lower-Upper	P value
Age	1.02	0.92-1.14	0.61
Sex (female)	0.52	0.02-11.06	0.66
Tumor size	1.15	1.00-1.33	0.04
Multifocality	0.41	0.03-5.37	0.50
Vascular invasion	0.57	0.03-10.09	0.70
Initial LN metastasis	8.52	0.47-154.17	0.14
Stage (I-II)	1.45	0.06-31.14	0.81
Stage (I-III)	0.00	0.00-	0.99
Stage (I-IV)	41.03	1.96-858.45	0.01
Preablation Tg	1.12	0.92-1.37	0.24
Other histologic variant	0.40	0.00-26.08	0.66
Background thyroiditis	0.48	0.05-6.31	0.68

LN: Lymph node

Table 4. *Risk evaluation with Logistical Regression Analysis in metastatic/recurrent oncocytic variant of papillary thyroid cancer (including factors having P value lesser than 0.2 by univariate analysis).*

Variable (Referans)	Exp (B)	95% CI for Exp(B) Lower-Upper	P value
Sex (female)	0.57	0.03-10.05	0.70
Tumor size	1.14	0.99-1.31	0.05
Vascular invasion	0.71	0.05-8.84	0.79
Initial LN metastasis	6.51	0.52-81.26	0.14
Stage (I-II)	1.47	0.08-26.28	0.79
Stage (I-III)	0.00	0.000-	0.99
Stage (I-IV)	39.36	3.03-510.58	0.01
Preablation Tg	1.13	0.95-1.35	0.15

LN: Lymph node

Discussion

Oncocytic variant is not a common tumor. Although the frequency of OV is variable depending on different studies, it has been reported to fluctuate between 1%-11% of all PTC [3]. Its incidence was 2.3% in our DTC patient population and this is in congruence with the literature. It is more common in older women than classic PTC and the mean age of patients swarms roughly around 65 years [2]. Most of our cases were female (female/male ratio: 2.74), but mean age of them (45 years) was clearly younger than the majority of other series. Our finding can be partially explained by the meticulous screening of them searching for OV cases. However, there was no statistically significant difference in the distribution of

between genders in our study.

Oncocytic change is defined as cellular enlargement characterized by an abundant eosinophilic granular cytoplasm caused by an accumulation of altered mitochondria [4]. The accumulation of mitochondria and development of oncocytic tumor may be caused by either an alteration of the mitochondrial DNA or nuclear DNA encoding mitochondrial enzymes primarly or a secondary response to autoimmune thyroid disease [5, 6]. The mitochondria containing deleted and/or mutated mitochondrial DNA proliferate more than the normal ones resulting in a progressive increase in the percentage of abnormal mitochondria [4]. Oncocytic change itself and thus OV are accepted as poor prognostic factors in PTC by many authors [7]. The presence of oncocytic change even in less than 75% of the tumour area has been suggested to be significant on the prognosis of PTC [7].

Oncocytes or oxyphilic cells in the thyroid gland are often called Hürthle cells [8]. They are morphologically different, originate from the follicular epithelium and occur in a range of pathological conditions including nodular goiter, atrophic glands of the elderly, Hashimoto's thyroiditis, benign and malignant neoplasms of the thyroid gland [3, 9]. Oncocytic variant is characterized by complex branching papillae in which the predominant cells are oncocytes that cover thin fibrovascular cores [3]. The nuclei exhibit the characteristics of classic PTC or they may instead resemble the pleomorphic nuclei of Hürthle cells which are large, hyperchromatic and pleomorphic [3]. There is ample pathologic evidence that all thyroid carcinomas have an oncocytic component [8].

Twenty five percent of the tumors are associated with concomitant thyroiditis [10]. Nearly one third of our patients suffered underlying background thyroiditis too. But we didn't find it as a risk parameter for recurrence both in univariate and multivariate analysis (P=0.58, P=0.68, respectively). In the present series, multifocal disease was found in roundly 35% of the patients. Beckner et al. (1995) reported a lower rate of multifocality in OV (14.7%) [11]. Our multifocality rate was 21%. Asa SL (2004) described CI, VI and TS as poor prognostic factors [2]. Beckner et al. (1995) reported that average age was 44 years, female/male ratio 3.9, mean TS 2.3cm, 91% CI-positive, 18% had initial LN metastasis, 4 recurrences and one death in his study of 34 cases [11]. Gross et al. (2009) declared cervical LN involvement was seen in 43.5%, average age 49 years, 30% had initial LN metastases, mean time to recurrence 69 months, associated thyroiditis rate 43%, multifocality rate 34%, most of the recurrences occured in tumors greater than 2cm and took place earlier than 30 months; found ETE-TS and initial LN metastases as risk parameters in their study of 23 patients with OV [1]. Gross et al. (2009) also found a high incidence of ETE and CI in OV than classic variant. They allege that OV is more locally invasive than classic PTC and this may be responsible for the increased malign potential, but their cure rate came out similar to other cases without OV [1]. We detected ETE and CI as important factors in univariate analysis in our study. Further studies are necessary in order to clarify the prognostic factors and their impact on metastatic development of OV.

Stage and TS appeared as significant risk factors for recurrence and prognosis with multivariate analysis from our study (P=0.01 and P=0.04, respectively). Although there was not a specific report for OV, many researchers found TS and stage independent risk factors in PTC. Choi et al. (2019) reported that TS and stage were prognostic factors on multivariate analysis in their large meta-analysis of 16057 patients with DTC between 1978-2011 [12]. According to our findings, 65% of the metastatic patients were at stage IV and stage IV had a 40% increased recurrence rate when compared with stage I. Fifhty three percent of cases with TS greater than 3.5cm had recurrence.

The studies about the clinicopathologic features and clinical behavior of OV are very rare and the present ones give confusing results. Oncocytic variant and PTC with oncocytic change are associated with a higher recurrence rate and shorter DFS [7]. Some authors have declared that this variant has a clinical behavior similar to that of classic PTC [11,13,14]. On the other hand, others agree that the oncocytic papillary tumors have a more invasive and aggressive course than does classic PTC with higher rates of tumor recurrence and disease-specific mortality [15]. This aggressiveness of OV may be attributed to the inclusion of other accompanying savage variants like tall cell. Nevertheless, we didn't find other accompanying variants (tall cell and classic variant) as a risk factor for recurrence in our study. The discrepancies between the studies may partially be related to lack of precise histologic criteria used to define OV. The prognosis of patients with OV was in other studies similar to that of patients with classic PTC, provided that the ages of the patients and the stages of the tumors were comparable [8,16]. It has been asserted that the only negative aspect of OV which is its lesser ability to trapiodine renders it less responsive to radioactive iodine [4, 8]. However, our long-term findings do not support this notion. Our experience unveils some little-known aspects of this variant. First of all, its prognosis is very favorable contrary to the previous assumptions. Most of the authors consider it a form between tall cell and classic variants according to pathologic features and tumoral behaviour. We think that prognosis is similar to that of classic variant, at least not poorer than that. According to our findings, OV is not refractory to RAI and many patients responded to only one dose of 3700MBq with favorable survival. Recurrence rates about papillary thyroid cancers alternating between 15%-20% have been declared in different series [17,18]. Seventeen percent of our patients developed metastasis/recurrence and 4% died.

Advantages and Limitations

Our patient population of 101 patients with OV was large when compared with other studies. Besides, the follow-up period was long enough with a fine surveilance for prognosis estimation. It was better to evaluate the prognosis of OV by comparing it with other similar variants, especially tall cell and classic ones in a stage-matched and age-matched form. This is the main limitation of our study. Oncocytic variant has RET/PTC rearrangements and BRAF mutations with similar frequency as non-oncocytic PTC [19, 20]. Furthermore, cytogenetic features would be investigated. But these were not performed due to lack of enough data.

In conclusion, we found that the prognosis of OV was not poor in our series. Stage (IV) and tumor size at presentation

were shown to be the main risk factors for metastatic development.

The authors declare that they have no conflicts of interest.

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