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Hürthle Cell (Oxyphilic) Papillary Thyroid Carcinoma: A Variant with More Aggressive Biologic Behavior

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The latest World Health Organization International Classification defines papillary thyroid carcinoma by its "follicular cell differentiation . . . as well as characteristic nuclear changes". However the oxyphilic (Hürthle cell) papillary carcinoma have nuclei which generally resemble the nuclei seen in oxyphilic follicular carcinomas, and such oxyphilic papillary tumors may behave more aggressively than typical papillary cancers. To further characterize these rare tumors, we identified during a 32-year period 22 patients with oxyphilic papillary cancer and compared them with 1,084 patients with typical papillary cancers and 57 patients with oxyphilic follicular cancers treated by the Mayo surgical group during the same time period. Although typical papillary and oxyphilic papillary cancers were comparable with regards to patient age, tumor size and extent, TNM stage, and prognostic score (AGES), there were significant differences. Compared to typical papillary tumors, oxyphilic papillary cancers had fewer neck nodal metastases at primary diagnosis (5% vs 40%, $p < 0.0001$), were more often DNA non-diploid (71% vs 21%, $p < 0.001$), and after 10 postoperative years had higher rates of both tumor recurrence (28% vs 11%, $p < 0.0001$) and cause-specific mortality (1.7% vs 4%, $p < 0.0005$). In these four important respects the oxyphilic papillary cancers more resembled the oxyphilic follicular cancers. For oxyphilic follicular cancers, the frequency of initial neck nodal metastases was 7% (cf 5%); 83% of the oxyphilic follicular tumors were non-diploid (cf 71%), and at 10 years postoperatively the tumor recurrence and cause-specific mortality rates were 28% and 18%, insignificantly different from 28% and 17% seen with the oxyphilic papillary cancers. These results demonstrate that oxyphilic papillary tumors are more similar to oxyphilic follicular than typical papillary cancers, and suggest that in a differentiated follicular cell-derived carcinoma a predominance of oxyphilic cells may be a prognostically more relevant feature than the individual tumor's predominant papillary or follicular morphologic pattern. Perhaps in future Histologic Classifications the World Health Organization should group the oxyphilic papillary cancers with the oxyphilic follicular rather than the typical papillary carcinomas.

In the most recent World Health Organization (WHO) International Histological Classification of Thyroid Tumours, Hedinger and colleagues [1] have defined papillary thyroid carcinoma as "a malignant epithelial tumour showing evidence of follicular cell differentiation, typically with papillary and follicular structures as well as characteristic nuclear changes." It is well recognized that the typical papillary carcinoma characteristically spreads to regional lymph nodes [2, 3], is usually DNA diploid [4–6], and from our experience of more than 1,800 cases, is associated with a 20-year cause-specific mortality rate of only 5-6% [2, 7].

The latest WHO classification [1] recognizes that a small minority of tumors with classical papillary architecture are predominantly or entirely composed of oxyphilic cells. These oxyphilic (Hürthle cell) papillary (OP) cancers have nuclei which resemble those seen in oxyphilic (Hürthle cell) follicular (OF) tumors, and usually do not show the nuclear changes commonly associated with typical papillary cancers. However, according to Hedinger and colleagues [1], in other respects these OP cancers "resemble typical papillary (TP) carcinomas in both morphology and behaviour."

In papillary thyroid carcinoma series published since 1955, the reported frequency of OP cancers has varied from 1% to 11%; 37 such cases were described in five studies (1955–77) comprising 1,058 tumors [8–12]. Although first recognized by histologists more than 36 years ago, no large series with long-term follow-up [13] has to date been reported and, thus, uncertainty still exists with regard to the biologic behavior of this unusual papillary thyroid carcinoma variant. Recent studies from Schröder and coworkers from Germany [14] and Rosai and colleagues [15] in the United States have taken issue with the WHO viewpoint [1] and have suggested that widely invasive OP cancers "behave aggressively" [15] and have a "dismal prognosis" [14].

At our institution more than 1,100 patients underwent primary surgical treatment for papillary thyroid carcinoma during a 32-year period; 983 of these patients were previously evaluated in an earlier study of the OP variant tumor [16]. The aims of the present study were: (1) to better characterize OP thyroid cancers in a larger series with adequate follow-up, (2) to clarify the differences between TP and OP cancers, and (3) to compare and contrast OP with OF cancers.

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Methods

Patients and Follow-Up

During a 32-year period (1940–51 and 1970–89), 1,106 patients with papillary thyroid carcinoma and 57 patients with OF cancer underwent primary surgical treatment at the Mayo Clinic, Rochester, Minnesota. All 1,163 pathologic specimens were carefully examined histologically by one experienced surgical pathologist (JRG) who identified 22 patients with a diagnosis of OP cancer. Details of the 1,163 patients' clinical findings, initial and subsequent surgical therapy, and postoperative courses (locoregional or distant recurrence, cancer-related deaths) were abstracted for inclusion in the computerized Mayo Clinic Thyroid Cancer Database. Death certificates were examined for all patients who died and autopsy reports obtained whenever available. Information about the living patients was obtained by examination at our institution, by correspondence with the patients' home physicians, or by correspondence with the patients themselves or their relatives.

Patients were followed to August 1991, and all deaths from thyroid cancer identified. The mean follow-up period for the 1,163 patients was 12.6 years (range 1–51 years) for a total experience of 14,694 patient-years. Survival to recurrence or death was studied by standard life-table methods, using the Kaplan-Meier method [17] as available on our Statistical Analysis System (SAS) computer software. Significance testing for differences in survival between groups was performed with the log-rank test [18].

DNA Ploidy Determination

DNA ploidy status was determined by a previously reported flow cytometric technique [19] performed on archival paraffin-embedded tissue blocks derived from 17 of the 22 OP cancers, 262 of the 1,084 TP cancers, and 52 of 57 OF cancers. Further details of the nuclear DNA measurements previously performed on TP and OF cancers have recently been published [7, 19–21].

Results

Characteristics of Oxyphilic Papillary Cancers

There were 14 females and 8 males in the group of 22 patients with OP cancer. Median age at diagnosis was 51 years (range 16–80 years). Primary surgical resection consisted of near-total thyroidectomy in 14 (64%) patients and bilateral subtotal resection in 2 patients (Table 1). Five patients initially had a unilateral lobectomy with isthmusectomy, while the final patient (a 79-year old woman with a locally invasive grade 2 tumor) had only a debulking procedure. In 20 (91%) of the 22 procedures, the surgeon reported complete resection of the primary tumor without gross residual disease.

Mean size (maximum diameter) of the resected primary OP tumors was 3.2 cm (range 0.3-13 cm). Eighteen (82%) of the tumors were histologically grade 1 by Broder's classification [7], and 4 tumors were classified as grade 2. Three (14%) patients had extrathyroid involvement at the time of surgical resection, but only 1 (5%) patient had neck nodal metastases.

Table 1. Primary surgery in 1,163 patients with typical papillary, oxyphilic papillary, and oxyphilic follicular thyroid cancers.

Procedure	TP (%) n = 1,084	OP (%) n = 22	OF (%) n = 57
Near-total or total thyroidectomy	75	64	61
Bilateral subtotal lobar resection	8	9	9
Unilateral lobectomy	14	23	28
Complete resection	95	91	91

TP: Typical papillary; OP: Oxyphilic papillary; OF: Oxyphilic follicular; n: Number of patients.

Postoperative TNM stage [7] was I in 11 (50%) patients, II in 9 (41%) patients, and III in 2 (9%) patients.

The 22 patients with OP cancer were followed from 1 to 31 postoperative years; median follow-up was 11 years. Cause-specific mortality rates at 5 years and 10 years were 5% and 17%, respectively. Cumulative occurence rates for locoregional or distant recurrence in the 20 patients with initial complete tumor resection at 5 years and 10 years were 11% and 28%, respectively.

Lethal Oxyphilic Papillary Cancers

By the time of latest follow-up 8 (36%) of the 22 patients had died, 4 (18%) patients as a direct consequence of OP cancer. Details of these 4 lethal cases are shown in Table 2. The primary tumor was completely excised in patients 1, 2, and 3, who had unilateral lobectomies performed during 1943–50. The fourth patient who presented in 1986 with disease invading the strap muscles, infiltrating the trachea, and encasing the carotid arteries, had only a debulking procedure performed. Two of the 4 fatal cases developed lung metastases (diagnosed at 4 years and 7 years postoperatively); all 3 of the patients with no gross disease after lobectomy developed locally recurrent disease within 2 to 8 years of diagnosis. Flow cytometry was performed on tumor blocks from patients 3 and 4; neither tumor was DNA diploid (normal). DNA aneuploidy was demonstrable in both primary and locally recurrent tumor from patient 3; the primary tumor in patient 4 was DNA tetraploid/polyploid.

Comparison of Oxyphilic Papillary and Typical Papillary Cancers

Presenting features of OP and TP cancers are compared in Table 3. The patients with OP cancers tended to be older ($p = 0.08$), had on average slightly larger tumors ($p = 0.06$), and were more likely to have higher grade disease ($p = 0.02$), as well as higher AGES [7, 22] prognostic scores ($p = 0.05$). There appeared to be no significant difference in the initial tumor extent, as evidenced by the presence of either extrathyroid invasion or distant metastases. Similarly, postoperative TNM stage [7] was 2 or greater in 50% of OP and 40% of TP cancers, a difference that was not statistically significant ($p = 0.71$).

One striking difference between OP and TP cancers was the frequency of neck nodal metastases at initial surgical procedure (Fig. 1). Only 1 (5%) of the 22 OP tumors metastasized initially to regional nodes. This was in sharp contrast to the frequency

Table 2. Details of four lethal cases of oxyphilic papillary cancer.

Pt. no.	Age (yr)	Tumor size (cm)	Tumor grade	Locally invasive	AGES score	Initial surgery	Local recurrence(s) or persistence (no. of events)	Distant metastases	Year of death (years postop)
1.	44	3.0	1	No	2.82	Lobectomy/isthmusectomy	Yes (2)	Yes, lungs	1951 (8)
2.	51	13.0[a]	2	No	6.15	Lobectomy/isthmusectomy	Yes (1)	Yes, lungs	1953 (7)
3.	50	5.0	1	No	3.50	Lobectomy/isthmusectomy	Yes (3)	No	1980 (30)
4.	79	>5.0	2	Yes	6.95	Debulking procedure	Yes	No	1988 (2)

[a]Weight of thyroid lobe = 710 g.
Postop: Postoperatively.

Table 3. Comparison of AGES variables and TNM stages in 1,163 patients with typical papillary, oxyphilic papillary, and oxyphilic follicular thyroid cancers.

Variable/stage		TP n = 1,084	OP n = 22	OF n = 57
Median age (yr)	(A)	46	51	62[a]
Grade ≥2 (%)	(G)	6[a]	18	46[a]
Extrathyroid (%)	(E)	12	14	7
Distant mets (%)	(E)	1	0	5
Tumor size (cm)	(S)	2.1	3.2	4.0
Median AGES score		2.65	3.11	4.75[a]
TNM stage ≥2 (%)		40	50	79[a]

[a]$p < 0.05$ compared to OP.
TP: Typical papillary; OP: Oxyphilic papillary; OF: Oxyphilic follicular.

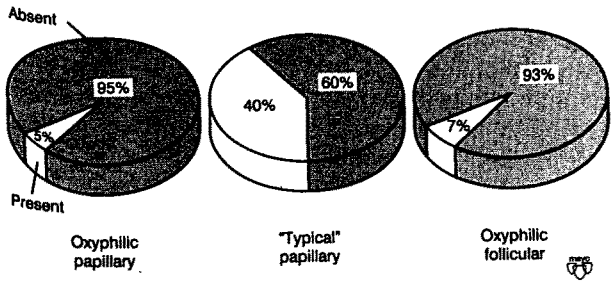

Fig. 1. Frequency of neck nodal metastases at time of initial neck exploration in 22 oxyphilic papillary, 1,084 typical papillary, and 57 oxyphilic follicular thyroid carcinoma patients.

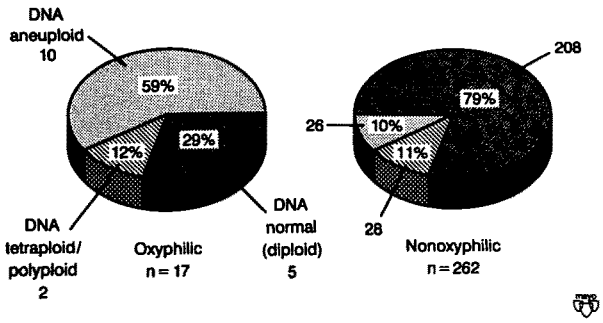

Fig. 2. Distribution of DNA ploidy patterns in 17 oxyphilic papillary and 262 nonoxyphilic (typical papillary) thyroid carcinomas.

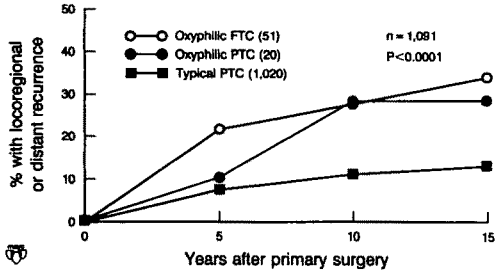

Fig. 3. Cumulative occurrence of either locoregional or distant tumor recurrence in 1,091 oxyphilic follicular, oxyphilic papillary, and typical papillary thyroid cancer patients undergoing potentially curative surgery at the Mayo Clinic for disease confined to the neck. FTC: Follicular thyroid cancer; PTC: Papillary thyroid cancer.

seen in TP cancer, where nodal metastases were found initially in 434 (40%) of 1,084 cases ($p < 0.0001$).

A second major difference between OP and TP cancers related to the frequency of DNA non-diploid tumors (Fig. 2). Of the 17 OP cancers available for DNA ploidy studies, only 5 tumors were DNA diploid (normal); the other 12 (71%) tumors were abnormal (DNA non-diploid). By contrast, TP cancers were usually DNA diploid (79%), and significantly fewer (21%) of the 262 TP tumors analyzed were DNA non-diploid ($p < 0.0001$).

A third significant difference between OP and TP cancers related to both the development of locoregional or distant recurrences (Fig. 3), and the cause-specific mortality rate (Fig. 4). For 1,020 patients with TP cancers who had undergone potentially curative surgery for disease confined to the neck, the recurrence rate at 5 years and 10 years was 8% and 11%, respectively, significantly lower than the comparable rates seen with OP cancer ($p < 0.0001$). Similarly, the cause-specific mortality rate for the 1,084 patients with TP cancers at 5 years and 10 years was 1.5% and 3.6%, significantly lower than the 5% and 17% seen with OP cancers ($p = 0.0005$).

Comparison of Oxyphilic Papillary and Oxyphilic Follicular Cancers

When compared to patients with OP cancers, those 57 patients with OF cancers tended to be older ($p = 0.025$), and had higher grade tumors ($p = 0.024$) at a more advanced TNM stage ($p = 0.020$). Of interest, however, was the fact that the properties which tended to separate the OP from the TP cancers were found to be remarkably similar when OP and OF cancers were compared. Figure 1 illustrates the 7% frequency of neck nodal

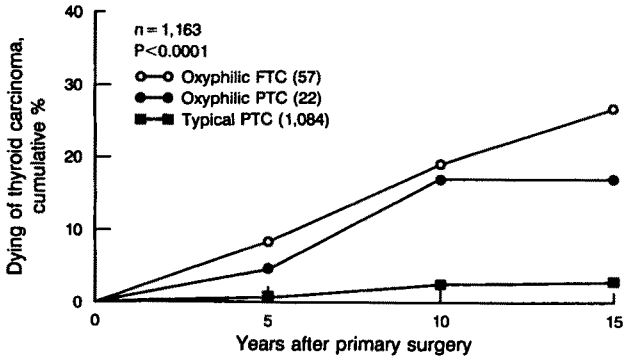

Fig. 4. Cumulative mortality from thyroid carcinoma for 1,084 patients with typical papillary cancer, 22 patients with oxyphilic papillary cancer, and 57 patients with oxyphilic follicular thyroid cancer treated surgically at the Mayo Clinic. FTC: Follicular thyroid cancer; PTC: Papillary thyroid cancer.

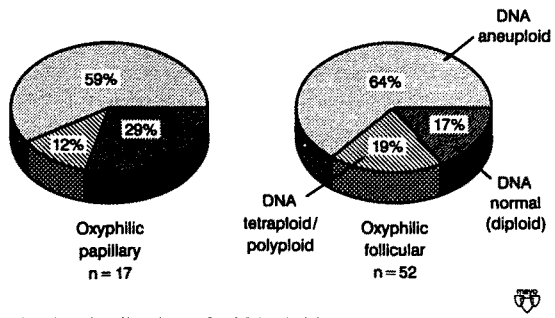

Fig. 5. Distribution of DNA ploidy patterns in 17 oxyphilic papillary and 52 oxyphilic follicular thyroid carcinomas.

metastases, as compared to the 5% found with OP. Figure 5 demonstrates the similarity in DNA ploidy distribution between OP and OF cancers. Of the 52 OF cancers examined, 83% were DNA non-diploid, 64% being DNA aneuploid. Figures 3 and 4 demonstrate the recurrence and mortality rates seen over 15 years with OP, TP, and OF cancers. In neither curve was there any significant difference found between the rates seen with OP cancers and those found with OF cancers. At 10 years the recurrence rate and cause-specific mortality rate for OF cancers were 28% and 18%, not significantly different from the 28% and 17% seen with the OP cancers ($p = 0.6$).

Discussion

The Hürthle cell (oxyphilic) variant of papillary thyroid cancer is a rare thyroid cancer, being found in only 3.5% of 1,058 papillary cancers described from 1955 to 1977 [8–12]. The frequency of this unusual tumor was 2% in the present series of 1,106 patients with papillary thyroid cancer seen for primary treatment at the Mayo Clinic during a 32-year period. This frequency is somewhat lower than the 11% described in 1982 from Switzerland [23] and the 8% found in a German study published in 1987 [14].

In the past the diagnosis of papillary thyroid cancer was based on histological criteria [9–11]. However, in recent years the diagnosis of papillary thyroid cancer has more often been based on cytologic grounds, particularly the characteristic nuclear changes described in the WHO monograph [1]. While the histologic features of OP cancers have been amply illustrated [23–25], the cytologic features have not been emphasized [13, 26]. A recent report by Chen [13] has demonstrated that many features of high diagnostic value for TP, such as "papillary tissue fragments, multilayered clusters, psammoma bodies, metaplastic cytoplasm, characteristic cytoplasmic vacuoles, and nuclear grooves" may be either absent or present only focally in OP cancers. Chen also indicated that intranuclear inclusions, a diagnostic feature of TP tumors, could not be reliably used as an aid for the diagnosis of OP cancers [13].

The WHO monograph [1] concedes that the characteristic nuclear features of TP cancer may not be constant "and in many tumours only a minority of cells may show them." Hedinger and colleagues [1] also state that in OP cancers the nuclei "generally resemble the nuclei seen in other oxyphilic tumours and do not show the nuclear changes commonly associated with papillary carcinoma." In the present study we have clearly demonstrated that in OP cancers the majority of tumors have a nuclear DNA content that is aneuploid, a situation similar to OF cancers and significantly different from the predominantly DNA diploid nuclei of TP cancers. Since we [7, 19–20] and others [4–6, 21] have previously shown that in both TP and OF cancers the presence of DNA aneuploidy has independent prognostic significance, it seems probable that the currently observed high frequency of DNA non-diploid tumors seen in OP cancers may be associated with higher rates of tumor recurrence and cause-specific mortality.

Most recent reports [13, 26] reflect the WHO stance [1] that the biologic behavior of OP cancers appears to be comparable with that of TP carcinomas [13]. In a Swiss study from 1982 it was noted that OP cancers showed "little evidence of nodal and distant metastases" [23]. Although the average follow-up period in the Swiss study was particularly short (2 years and 8 months), Tscholl-Ducommun and Hedinger [23] considered that for OP cancers "the cure rate is high."

By contrast, in a recent study of 202 patients with papillary thyroid cancer described from the Institute for Pathology in Hamburg, Germany, Schröder and associates [14] demonstrated a "dismal prognosis" for patients with oxyphilic or poorly differentiated tumors. In their Cox model the presence of oxyphilia was an independent predictor of survival and ranked in importance only behind grade of differentiation, patient age, and tumor extent [14]. Similar conclusions were drawn by Barbuto and colleagues [15] who, after studying 3 patients with "widely invasive" OP cancer, suggested that these tumors were more likely than TP cancers to cause cancer-related death and therefore probably should merit more aggressive therapy.

In this study we have demonstrated that OP and TP cancers are similar in regards to patient age, tumor size, presence of extrathyroid invasion or initial distant metastases, TNM stage and median AGES score. We agree with Hedinger and colleagues [1] that OP cancers have atypical nuclei and we have demonstrated from our study that OP cancers are characteristically DNA non-diploid, rarely involve neck nodes at presentation, and result in higher recurrence and cause-specific mortality rates than TP cancers. In these five important respects we consider that OP tumors more resemble OF than TP cancers.

One therefore could reasonably question whether OP cancers should be classified by the WHO in the same category as the less aggressive TP carcinomas [16].

From our results we would suggest that in a differentiated follicular cell-derived thyroid carcinoma a predominance of oxyphilic cells may be a prognostically more relevant feature than the individual tumor's predominant papillary or follicular morphologic pattern. Thus, the similarities observed here between OP and OF tumors may be more readily understood, and the Hürthle cell (oxyphilic) variant of papillary thyroid cancer should be more widely recognized as a tumor variant with a truly more aggressive biologic behavior.

Résumé

La dernière version de la Classification Internatinale de l'OMS définit le cancer papillaire de la thyroïde par rapport à la "différentiation cellulaire folliculaire . . . comme des changements nucléaires caractéristiques". Le cancer papillaire oxyphilique (de cellules de Hürtle) (OP) a des noyaux qui ressemblent aux noyaux généralement vus dans les cancers folliculaires oxyphiliques (OF). Les cancers OP ont une malignité plus élevée que les cancers papillaires typiques. Afin de caractériser ces cancers rares, nous avons identifié 22 patients ayant un cancer OP, observés pendant une période de 32 ans et nous les avons comparés à 1084 patients ayant un cancer TP et à 57 patients ayant un cancer OF traités pendant la même période de temps à la Mayo Clinic. Bien que les cancers TP et OP étaient comparables selon le sexe, la taille et l'étendue tumorales, le stade TMN, et le score AGES, il y avait des différences significatives. Comparées aux tumeurs TP, les cancers OP avaient moins de métastases cervicales (NNM) au moment du diagnostic initial (5% vs 40%, $p < 0.0001$), étaient plus souvent nondiploïdes pour l'ADN (71% vs 21%, $p < 0.001$), et après 10 ans d'évolution, avaient le taux le plus élevé de récidive tumorale (28% vs 11%, $p < 0.001$) et de mortalité spécifique (1.7% vs 4%, $p = 0.0005$). Ainsi, les cancers OP ressemblent beaucoup aux cancers OF. En ce qui concerne les cancers OF, la fréquence de NNM initiale était de 7% (cf 5%); 83% des tumeurs OF étaient du type non-diploïde (cf 71%) et à 10 ans, les taux de récidives tumorales et de mortalité de cause spécifique étaient respectivement de 28% et 18%, très peu différents des taux de 28% et 17% observés avec les cancers OP. Ces résultats démontrent que les tumeurs OP ressemblent plus aux cancers OF, que les cancers TP et suggèrent que dans un cancer folliculaire différencié, la prédominance oxyphilique peut être un facteur pronostique plus important que le caractère papillaire or folliculaire. Peut-être, à l'avenir, les classifications histologiques de l'OMS devrait regrouper les cancers OP avec les cancers OF plutôt qu'avec les cancers TP.

Resumen

La última clasificación internacional de la Organización Mundial de la Salud define el carcinoma papilar de la glándula tiroides en términos de su "diferenciación en células foliculares . . . así como sus alteraciones nucleares características". Sin embargo, el carcinoma papilar oxifílico (PO) (de células de Hürthle) exhibe núcleos celulares similares a los que se observan en los carcinomas foliculares oxifílicos (FO), y tales tumores no pueden comportarse en forma más agresiva que los cánceres papilares típicos (PT). Con el propósito de caracterizar mejor estos raros tumores, identificamos 22 pacientes con cáncer PO en un periodo de 32 años, y los comparamos con 1.084 pacientes con cánceres PT y 57 pacientes con cánceres FO tratados por el grupo quirúrgico de la Clínica Mayo en el mismo periodo. Aunque los pacientes con cánceres PT y FO aparecieron comparables respecto a edad, tamaño y extensión del tumor, estadificación TPN y puntaje AGES, se encontraron diferencias significativas. Comparados con los tumores PT, los cánceres PO exhibieron menos metástasis ganglionares en el cuello en el momento del diagnóstico primario (5% vs 40%, $p < 0.0001$), aparecieron más frecuentemente como DNA no-diploides (71% vs 21%, $p < 0.001$) y luego de 10 años postoperatorios presentaron mayores tasas de recurrencia (28% vs 11%, $p < 0.0001$) y de mortalidad de causa específica (1.7% vs 4%, $p = 0.0005$). En cuanto a estas cuatro características, los cánceres PO se asemejaron más a los cánceres FO. Para los cánceres FO, la frecuencia inicial de metástasis ganglionares en el cuello fue de 7% (CF 5%); 83% de los tumores FO aparecieron no-diploides (cf 71%) y a los 10 años la tasa de recurrencia tumoral y la rata de mortalidad por causa específica fueron 28% y 18%, insignificativamente diferente del 28% y 17% observados en los cánceres PO. Estos resultados demuestran que los tumores PO se asemejan más a los FO que los cánceres PT, y sugieren que en un carcinoma diferenciado derivado de las células foliculares la prevalencia de las células oxifílicas puede representar una característica con mayor valor pronóstico que el patrón morfológico de predominio papilar o folicular. Tal vez las futuras clasificaciones histológicas la OMS deban agrupar los cánceres PO con los FO en vez de hacerlo con los carcinomas PT.

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Invited Commentary

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This paper by Herrera and colleagues is an important contribution to our understanding of the behaviour of a small but significant variant of papillary thyroid carcinoma, the Hurthle cell or oxyphil (OP) variant. As the authors point out, the latest World Health Organization (WHO) International Classification of thyroid carcinoma, as well as a number of reference texts, regard oxyphil papillary carcinoma simply as a histological variant with identical morphology and behavior to typical papillary carcinoma. The data presented in this paper emphasize the more aggressive biological behavior of these tumors.

It must be appreciated that it is not just a significant increase in cause-specific mortality associated with the OP variant that has been documented in this study. More aggressive behavior is seen across the spectrum of the disease process, including an increased rate of local tumor recurrence, higher tumor grade, and a higher rate of tumor aneuploidy.

It is important to note however that all the documented cause-specific deaths in the group of patients with OP carcinoma occurred in individuals in whom relatively limited surgical procedures had been undertaken. Three of the 4 patients had only a unilateral lobectomy performed, while the fourth had debulking of a locally advanced tumor. If the recognized propensity of typical papillary carcinoma to contralateral and multifocal disease is also a factor in the OP variant, then the high rate of early local recurrent or persistent disease may well be expected. While it is unlikely that any treatment modality would have significantly altered the prognosis of a 79 year old with locally advanced differentiated thyroid carcinoma of any morphologic type, it is interesting to speculate that more aggressive treatment of the three younger patients who simply had a lobectomy, i.e., with total thyroidectomy and radioiodine ablation, may well have made a significant difference to their survival.

The authors draw an important comparison between the OP variant of papillary carcinoma and the Hürthle cell variant of follicular thyroid tumors (which are now generally accepted as a more aggressive variant of that histologic form of thyroid neoplasm). I fully support their contention that in differentiated follicular cell-derived thyroid carcinoma, a predominence of oxyphilic cells is prognostically a more relevant feature than the tumor's predominant morphologic pattern (papillary or follicular). Indeed it may well be that Hurthle cell neoplasms should be considered as a separate entity within differentiated thyroid