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Original article

HÜRTHLE-CELL CARCINOMA OF THE THYROID: CLINICOPATHOLOGIC FEATURES AND SURGICAL OUTCOMES AT A SINGLE INSTITUTION

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Abstract: **Background:** Hürthle cell carcinoma (HCC) is a rare differentiated thyroid malignancy with variable biological behavior. This study evaluates clinicopathologic features, treatment patterns, and long-term outcomes in patients managed at a single tertiary institution.

Methods: We retrospectively reviewed medical records of patients with histologically confirmed HCC between January 2005 and December 2020. Demographics, tumor characteristics, surgical treatment, adjuvant radioactive iodine (RAI) therapy, recurrence, and survival were analyzed. Outcomes were compared with reported retrospective series and discussed in the context of current ATA guidelines.

Results: Forty-eight patients were identified (mean age, 58.7 ± 11.4 years; female-to-male ratio, 2.2:1). Mean tumor size was 38.5 ± 14.2 mm. Minimally invasive disease was present in 29 patients (60.4%), and widely invasive disease in 19 (39.6%). Total thyroidectomy was performed in 36 patients (75%), and lobectomy in 12 (25%). RAI therapy was administered to 30 patients (62.5%), predominantly in widely invasive cases. Median follow-up was 104 months (range, 24–192 months). Recurrence occurred in 8 patients (16.7%), with a median time to relapse of 78 months. Five- and ten-year overall survival (OS) rates were 91.3% and 81.5%, respectively. Disease-specific survival (DSS) was 95.6% at 5 years and 90.2% at 10 years. Ten-year disease-free survival (DFS) was 82.1%.

Conclusions: Our results support existing evidence that minimally invasive HCC carries an excellent prognosis, while widely invasive tumors have a higher risk of recurrence. Long-term follow-up is essential, given the potential for late recurrence. These findings are consistent with current ATA guidelines recommending risk-tailored treatment and surveillance strategies.

Keywords: Hürthle cell carcinoma, thyroid cancer, minimally invasive, widely invasive, recurrence, survival, ATA guidelines.

INTRODUCTION

Hürthle cell carcinoma (HCC) accounts for approximately 3–10% of differentiated thyroid cancers and is characterized by oncocytic cells with abundant granular cytoplasm rich in mitochondria (1, 2). Historically considered a variant of follicular thyroid carcinoma, HCC is now recognized as a distinct clinicopathologic entity in the WHO classification (3). The diagnosis of malignancy requires histologic demonstration of capsular and/or vascular invasion, with classification into minimally and widely invasive subtypes based on the extent of invasion (4). Widely invasive tumors are associated with worse recurrence-free and disease-specific survival rates (5, 6).

Given the rarity of HCC, most outcome data derive from single-institution retrospective series or population registries. Reported recurrence rates range from 8% to 27% (7–12), with disease-specific survival generally exceeding 85% at 10 years in minimally invasive disease but falling to approximately 60% in widely invasive tumors (9, 11). While Oluic et al. (8) and Chiapponi et al. (9) provide foundational recurrence data, more recent investigations by Kim et al. (13) have emphasized the importance of preoperative clinical and radiologic factors in predicting malignancy and long-term outcomes in Hürthle cell neoplasms. Moreover, incorporating contemporary clinical guidelines—notably the 2015 American Thyroid Association (ATA) recommendations for differentiated thyroid

carcinoma management—is essential for framing therapeutic decisions and surveillance strategies in HCC (12).

This study describes the clinicopathologic features, treatment, and long-term outcomes of HCC patients treated at a single tertiary institution over a 16-year period.

Knowledge Gap: While prior studies report 10-year survival rates, data on very late recurrences (> 15 years) remain scarce. Our study provides long-term outcomes with a median follow-up of 104 months, contextualized within recent literature and ATA guideline recommendations.

MATERIAL AND METHODS

Study design and setting

A retrospective review was conducted of patients diagnosed with Hürthle cell carcinoma (HCC) between January 2005 and December 2020 at Bin Tayyab Medical Complex (BTMC) Hyderabad, Sindh, Pakistan. Patient inclusion spanned 2005–2020, and follow-up extended through 2024, allowing for updated survival outcomes. This retrospective study was approved by the Institutional Review Board. The requirement for informed consent was waived owing to the retrospective nature of the study and anonymization of patient data.

Inclusion criteria were**:** Histopathologic confirmation of HCC**,** primary surgical management at our institution and minimum follow-up of 24 months.

Exclusion criteria were: Hürthle cell adenoma**,** non-oncocytic thyroid malignancies and incomplete medical records.

Data collection

Patient demographics, presenting symptoms, tumor size, histologic subtype (minimally vs. widely invasive), surgical approach, radioactive iodine (RAI) administration, follow-up duration, recurrence type, and survival status were recorded.

Définitions

***Recurrence*:** Recurrence was defined as the reappearance of Hürthle cell carcinoma after achieving an initial complete response following primary surgical management. Recurrence included locoregional disease (thyroid bed or regional lymph nodes) or distant metastasis (lung, bone, or other sites). All recurrences were confirmed either radiologically (contrast-enhanced CT, MRI, or ultrasound) or histologically via biopsy.

***Overall survival (OS)*:** OS was defined as the time interval from the date of initial thyroid surgery to death from any cause, regardless of disease status. Patients alive at the last follow-up were censored.

Disease-specific survival (DSS): DSS was defined as the time interval from surgery to death caused specifically by Hürthle cell carcinoma. Deaths from unrelated causes were censored at the date of death.

Disease-free survival (DFS): DFS was defined as the time interval from surgery to the first documented recurrence (locoregional or distant) or death attributable to Hürthle cell carcinoma, whichever occurred first. Patients without events were censored at the last follow-up.

Statistical analysis

Kaplan–Meier methods were used to estimate OS, DSS, and DFS. Survival comparisons between subgroups were performed using the log-rank test. Cox proportional hazards regression was applied to evaluate prognostic factors, including age, tumor size, and invasion type. A p-value < 0.05 was considered statistically significant. Statistical analyses were conducted using SPSS version 26.

RESULTS

Patient demographics and tumor characteristics

Forty-eight patients were included. Baseline characteristics are summarized in Table 1. The cohort had a mean age of 58.7 ± 11.4 years and a female predominance (68.8%). Mean tumor size was 38.5 ± 14.2 mm. Minimally invasive Hürthle cell carcinoma was observed in 29 patients (60.4%), and widely invasive disease in 19 patients (39.6%). Vascular invasion was present in 21 patients (43.8%). Widely invasive tum-

Table 1. *Patient demographics and tumor characteristics*

Variable	Total (N = 48)	Minimally Invasive (n = 29)	Widely Invasive (n = 19)	P Value
Female Sex, n (%)	33 (68.8%)	21 (72.4%)	12 (63.2%)	0.49
Tumor Size (mm), Mean ± SD	38.5 ± 14.2	32.1 ± 10.5	48.3 ± 12.8	< 0.001*
Vascular Invasion, n (%)	21 (43.8%)	7 (24.1%)	14 (73.7%)	0.002*

*P value for vascular invasion added to clarify subgroup differences.

ors were associated with significantly larger tumor size and a higher rate of vascular invasion, while patient age and sex did not differ between groups.

Treatment details

Total thyroidectomy was performed in 36 patients (75%), while 12 patients (25%) underwent lobectomy. Radioactive iodine (RAI) therapy was administered to 30 patients (62.5%), predominantly in widely invasive cases (84.2% vs. 48.3% in minimally invasive disease; p = 0.02). A summary of patient and treatment characteristics is provided in Table 2.

Recurrence analysis

Eight patients (16.7%) developed recurrence—locoregional in 5 patients and distant (lung or bone) in 3 patients. The median time to recurrence was 78 months (range, 36–144), illustrating the need for extended follow-up (Table 2). Widely invasive tumors had a 3.8-fold higher risk of recurrence (hazard ratio [HR] = 3.8; p = 0.01). Tumor size > 4 cm and vascular invasion showed non-significant trends toward increased recurrence, suggesting limited statistical power to detect significance.

Radioactive iodine (RAI) administration was associated with a lower risk of recurrence (HR = 0.42; p = 0.04); however, its benefit in minimally invasive HCC remains controversial, given reduced RAI avidity in Hürthle cells and differential treatment allocation favoring widely invasive disease (Table 3).

The results of the multivariate analysis for recurrence are shown in Table 3.

Table 2. *Summary of patient and treatment characteristics*

Characteristic	Value
Sample Size	48 Patients
Mean Age (years)	58.7 ± 11.4
Female: Male Ratio	2.2 : 1
Mean Tumor Size (mm)	38.5 ± 14.2
Histologic Subtype	
Minimally Invasive	29 (60.4%)
Widely Invasive	19 (39.6%)
Surgical Procedure	
Total Thyroidectomy	36 (75%)
Lobectomy	12 (25%)
RAI Therapy Administered	30 (62.5%)
Median Follow-up (months)	
Recurrence Rate	8 (16.7%)
Median Time to Relapse (months)	78 (Range: 36–144)

Survival outcomes

The 5- and 10-year survival rates are detailed in Table 4. Widely invasive disease was associated with significantly lower DFS ($p = 0.01$) and DSS ($p = 0.03$) than minimally invasive disease. The disease-specific survival patterns for the two subtypes are illustrated in Figure 1.

Comparative Analysis

Our outcomes were compared with those from prior studies, as shown in Table 5.

Table 3. *Multivariate Cox regression analysis for recurrence*

Variable	Hazard Ratio (HR)	95% Confidence Interval	P Value
Widely Invasive (vs. Minimally Invasive)	3.8	1.4 -10.2	0.01
Tumor Size > 4 cm	2.1	0.9 – 5.0	0.09
Vascular Invasion	1.7	0.7 – 4.3	0.24
RAI Therapy	0.42	0.18 – 0.98	0.04

HR-hazard ratio. Statistically significant p values ($p < 0.05$) are as follows. An HR > 1.0 indicates a higher risk of recurrence, while an HR < 1.0 indicates a lower risk (protective effect). The 95% confidence interval (CI) shows the precision of the estimate. An interval that does not include 1.0 is considered statistically significant.

Table 4. *Long-term survival outcomes*

Outcome	5-Year Rate (%)	10-Year Rate (%)	15-Year Rate (%)
Overall Survival (OS)	91.3	81.5	76.2
Disease-Specificsurvival (DSS)	95.6	90.2	85.7
Disease-FreeSurvival (DFS)	90.5	82.1	78.4

Notes: *OS: Time from surgery to death from any cause; DSS: Time from surgery to death specifically from Hürthle cell carcinoma; DFS: Time from surgery to first recurrence or death from Hürthle cell carcinoma.*

Table 5. *Comparative analysis with prior studies*

Study	Number of Patients	Recurrence Rate (%)	10-Year Disease-Specific Survival (%)	RAI Use (%)
Our Study	48	16.7	90.2	62.5
Oluic et al (8)	182	12.1	92.5	54
Bešić et al. (10)	89	27.0	88.0	70
Kim et al. (13)	112	15.2	89.8	58

Notes: RAI: Radioactive Iodine therapy.

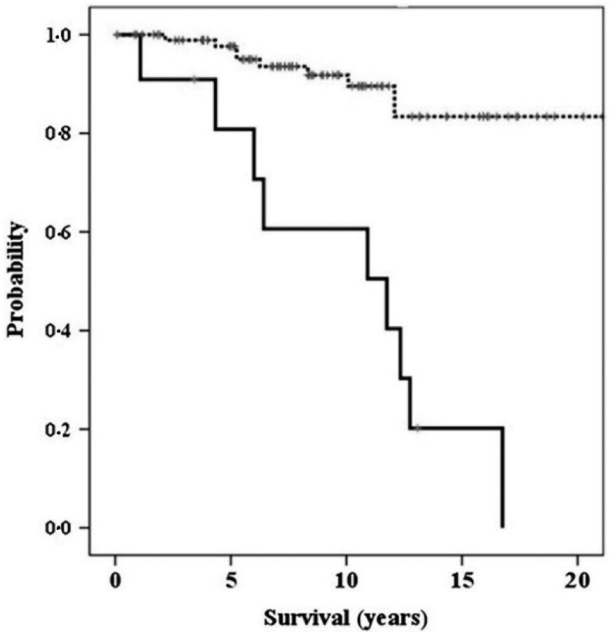

Figure 1. *Disease-specific survival by histologic subtype*
(Image: Kaplan-Meier curve showing two lines, one for minimally invasive HCC with high survival probability, and one for widely invasive HCC with lower survival probability over time.)

DISCUSSION

This study reinforces prior reports that minimally invasive HCC has an excellent prognosis, with rare disease-specific mortality and low recurrence rates (7, 8). Widely invasive disease was associated with higher recurrence and reduced survival, which is consistent with previously published findings (10-year DSS 88%, recurrence 27%) (10) and Oluic et al. (DSS 92.5%, recurrence 12.1%) (8). The mean tumor size in our cohort (38.5 mm) aligns with prior studies, where larger tumors (> 4 cm) have been linked to worse outcomes (5, 10). Our recurrence rate (16.7%) is intermediate between low (12.1% (8) and high (27% (10) published rates, possibly reflecting our higher proportion of widely invasive cases. Late recurrences occurred, emphasizing the need for long-term surveillance—findings echoed by other series reporting relapses beyond 10 years (7, 10).

Incorporation of ATA Guidelines: The 2015 ATA guidelines recommend risk-adapted management for differentiated thyroid carcinoma, including HCC, emphasizing extent of invasion as a key prognostic factor influencing surgical extent, use of RAI, and surveillance intensity (12). Our findings align with these guidelines, supporting more aggressive management and RAI use in widely invasive tumors, while highlighting uncertainty about RAI benefit in minimally invasive disease due to lower RAI avidity of oncocytic cells. The protective association of RAI seen in our analysis may primarily reflect its use among high-risk patients, underscoring the need for further research into selective RAI benefit in minimal disease.

While total thyroidectomy and RAI remain standard for widely invasive tumors, their role in minimally invasive disease remains debated (11, 12). Strengths of this study include detailed histologic classification and a long median follow-up (> 8 years). Limitations include retrospective design, small sample size, and single-center setting.

This single-institution study provides further evidence supporting prior reports that minimally invasive HCC typically has an excellent prognosis, characterized by rare disease-specific mortality and low recurrence rates. Conversely, consistent with findings from other retrospective series, widely invasive tumors are associated with higher recurrence rates and decreased survival (8,10). The mean tumor size observed in our cohort (38.5 mm) is consistent with the literature, which often links larger tumors (exceeding 4 cm) to poorer outcomes. Our observed recurrence rate of 16.7% falls within the intermediate range of published rates, which vary from a low of 12.1% to a high of 27% (Table 6).

Table 6. *Comparison with literature*

Study	Recurrence rate	10-year| DSS
Our study	16.7%	90.2%
Oluic et al[8]	12.1%	92.5%
Besic et al[10]	27%	88%

This variation may partly be attributed to the higher proportion of widely invasive cases included in our study cohort. A critical finding was the occurrence of late recurrences, with a median time to recurrence of 78 months. This observation strongly emphasizes the necessity of long-term surveillance for HCC patients, a finding echoed by other series reporting relapses occurring beyond 10 years. While total thyroidectomy and radioactive iodine (RAI) therapy are considered standard treatments for widely invasive tumors, their precise role and benefit in minimally invasive HCC remain a subject of debate. This debate is further complicated by the potentially reduced avidity of Hürthle cells to RAI.

Strengths of this study include its detailed histologic classification of HCC into minimally and widely invasive subtypes and a long median follow-up period of over 8 years.

Limitations

This study is limited by its single-center retrospective design and small sample size, which may restrict statistical power and generalizability. Larger multicenter prospective studies, as advocated by the ATA, are needed to refine prognostic models and therapeutic guidelines.

CONCLUSION

In conclusion, Hürthle cell carcinoma demonstrates favorable outcomes in its minimally invasive form, with high survival rates and low recurrence. Conversely, widely invasive tumors are associated with a significantly higher risk of recurrence and decreased survival. The potential for late recurrence, as evidenced by our data and illustrated in the survival curves (Figure 1), necessitates prolonged and diligent long-term follow-up for all HCC patients. To further refine current treatment algorithms and establish more definitive guidelines, larger-scale multicenter prospective studies are urgently needed.

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Data Availability Statement: Requests to access the datasets should be directed to the corresponding author.

Note: Artificial intelligence was not utilized as a tool in this study.

Sažetak

HÜRTHLE-CELL KARCINOM ŠTITASTE ŽLEZDE: KLINIČKO-PATOLOŠKE KARAKTERISTIKE I HIRURŠKI ISHODI U JEDNOJ USTANOVI

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Uvod: Hürthle-cell karcinom (HCC) predstavlja redak maligni tumor štitaste žlezde sa promenljivim biološkim ponašanjem. Ova studija procenjuje kliničko-patološke karakteristike, obrasce lečenja i dugoročne ishode kod pacijenata lečenih u jednoj tercijarnoj ustanovi.

Metode: Retrospektivno su pregledani medicinski kartoni pacijenata sa histološki potvrđenim Hürthle-cell karcinomom (HCC) u periodu od januara 2005. dodecembra 2020. godine. Analizirani su demografski podaci, karakteristike tumora, hirurško lečenje, adjuvantna terapija radioaktivnim jodom (RAI), recidivi i preživljavanje. Ishodi su upoređeni sa podacima iz prethodnih retrospektivnih serija i diskutovani u kontekstu važećih smernica Američkog udruženja za štitastu žlezdu (ATA).

Rezultati: Identifikovano je 48 pacijenata (prosečna starost 58,7 ± 11,4 godina; odnos žena i muškaraca 2,2:1). Prosečna veličina tumora bila je 38,5 ± 14,2 mm. Minimalno invazivna bolest registrovana je kod 29 pacijenata (60,4%), dok je široko invazivna bolest bila prisutna kod 19 pacijenata (39,6%). Totalna tireoidektomija izvršena je kod 36 pacijenata (75%), a lobektomija kod 12 pacijenata (25%). RAI terapija primenjena je kod 30 pacijenata (62,5%), uglavnom u slučajevima ši-

roko invazivnog tumora. Medijana praćenja bila je 104 meseca (opseg 24–192 meseca). Recidiv se javio kod 8 pacijenata (16,7%), sa medijanom vremena do relapsa od 78 meseci. Petogodišnje i desetogodišnje ukupno preživljavanje (OS) iznosilo je 91,3% i 81,5%, respektivno. Preživljavanje specifično za bolest (DSS) bilo je 95,6% na 5 godina i 90,2% na 10 godina. Desetogodišnje preživljavanje bez bolesti (DFS) iznosilo je 82,1%.

Zaključak: Naši rezultati potvrđuju postojeće dokaze da minimalno invazivni Hürthle-cell karcinom (HCC) ima odličnu prognozu, dok široko invazivni tumori nose veći rizik od recidiva. Dugoročno praćenje je od suštinskog značaja zbog potencijala za kasni recidiv. Ovi nalazi su u skladu sa važećim smernicama Američkog udruženja za štitastu žlezdu (ATA), koje preporučuju lečenje i nadzor prilagođen riziku.

Ključne reči: Hürthle-cell karcinom, karcinom štitaste žlezde, minimalno invazivno, široko invazivno, recidiv, preživljavanje, ATA smernice.

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