Hurthle Cell Carcinoma of the Thyroid Gland : Systematic Review and Meta-analysis

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"Hürthle cell carcinoma of the thyroid gland: systematic review and meta-analysis"

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Abstract

Introduction: Hürthle cell carcinoma (HCC) comprises about 5 % of thyroid carcinoma cases. Partly because of its rarity there is much we still need to know about HCC as compared to other histological cancer subtypes.

Methods: We conducted a systematic literature review following PRISMA guidelines and metanalysis, from 2000 to 2020, to investigate the main characteristics of HCC and clarify information concerning tumor behavior and treatment.

Results: Our review included data from 9,638 patients reported in 27 articles over the past 20 years. This tumor occurred more frequently in women (67.5%). The mean age was 57.6 years, and the mean size of the neoplasm at diagnosis was 30 mm. Extrathyroidal extension was common (24%) but lymph node metastasis was not (9%). Total thyroidectomy was the most common surgical approach, with neck dissection usually performed in cases with clinically apparent positive neck nodes. Radioiodine therapy was frequently applied (54%) although there is no consensus about its benefits. The mean 5- and 10-year overall survival was 91 and 76%, respectively.

Conclusion: This review serves to further elucidate the main characteristics of this malignancy. HCC of the thyroid is rare and most often presents with a relatively large nodule, whereas lymph node metastases are rare. Given the rarity of HCC, a consensus on their treatment is needed, as doubts remain concerning the role of specific tumor findings and their influence on management.

Bullet points

1. Hürthle cell carcinoma is a less frequent differentiated thyroid malignancy, of follicular origin, accounting for only about 5% of all thyroid cancers.
2. This type of tumor occurs more frequently in women, at about 60 years of age, and is not usually a large tumor (about 3 cm) when diagnosed.
3. It may exhibit extrathyroidal involvement at diagnosis, but lymphatic metastases are infrequent.
4. The main adverse prognostic factors are male gender, higher age and TNM stage.
5. Increasing knowledge about these tumors is important to elucidate their behavior and to be able to adapt treatments, especially to avoid overtreatment by trying to treat them like other histological types.

1. Introduction

Hürthle cell carcinoma (HCC) is an uncommon differentiated thyroid malignancy, of follicular origin, accounting for only 3% to 7% of all thyroid cancers [1]. Oncocytic cells in the thyroid are often called "Hürthle" cells; but this is a misnomer because they were described in 1898 by Max Askanazy in patients with Graves' disease, and the cells that Karl Hürthle described were the C cells [2]. According to the World Health Organization (WHO) definition, Hürthle (oncocytic) cell tumors are neoplasms that are frequently encapsulated and composed of oncocytic cells [3].

Non-invasive lesions are classified as a Hürthle cell adenomas and lesions with capsular and/or vascular invasion as HCC [3]. HCC is usually a solitary, relatively encapsulated tumor that is composed, by definition, of more than 75% Hürthle cells. Lesions with fewer Hürthle cells are designated thyroid neoplasms with Hürthle (oncocytic) cell features. One or more of the following features is needed to make the diagnosis of HCC: capsular invasion that penetrates the full thickness of the capsule of the tumor in the thyroid gland; spread to adjacent tissue or extrathyroid extension (ETE); vascular invasion; or regional or distant metastases [4]. These hallmarks of HCC can only be definitively seen in resection specimens, not in a fine needle aspiration cytology (FNA) [5]. Hürthle cells can be seen in Hürthle cell adenomas/carcinomas, oncocytic variants of papillary thyroid cancer, Hashimoto thyroiditis, adenomatoid nodules with Hürthle cell metaplasia and nodules arising in a background of Graves' disease [6,7]. The presence of Hürthle cells on FNA in and by itself does not increase the risk of malignancy beyond the Bethesda pathologic category [8].

In the last WHO classification, Hürthle cell tumors were classified separately from follicular neoplasms [3]. Hürthle cell tumor separation from follicular lineage neoplasms is now supported by an understanding of unique genetic underpinning [9,10].

This systematic review and metanalysis includes all articles published about HCC during the last 20 years. The aim was to describe the clinical and pathologic characteristics, along with the prognostic factors of this particular type of thyroid cancer.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

2. Methods

The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) method was used to analyze the literature [11]. The search strategy included articles concerning patients treated for HCC. A PubMed search updated to February 15, 2021 was performed for publications in the English language between 2000 and 2020 using the following search criteria in the title or abstract: “thyroid” coupled with “Hürthle cell neoplasm”, “Hürthle cell tumor”, “Hürthle cell carcinoma”, “Hürthle cell cancer” and “oncocytic cell carcinoma”. The search results were reviewed for eligible studies. When there was information in the abstract addressing HCC, the full text article was searched. This was supplemented with a hand search of the references in relevant review articles and in all retrieved full text articles (Figure 1). Studies were selected if they met the following inclusion criteria: (a) patients treated for thyroid HCC and (b) histological confirmation of HCC, reviewed by a qualified pathologist and following the diagnostic criteria recommended at the time of publication. Studies in which the HCC patients were analyzed as a group with other thyroid carcinoma types were excluded. Articles that only included patients with metastatic or recurrent HCC were also excluded. Case reports were

not included. Some of the study parameters were not available in all studies. All operative procedures that were not total thyroidectomy (including near-total and subtotal thyroidectomy, lobectomy and lumpectomy) were classified as partial thyroidectomy. Total thyroidectomy included all patients whose final treatment was total thyroidectomy, even if they had previously undergone lobectomy. No ethical approval was required.

Data from studies were recorded in an Excel datasheet (Microsoft corp.). We imputed some data not directly available from the studies. Standard deviation was calculated from range data using the formula S.D. = ((((100/(Age(max) – Age (min))*5))– (Age(max)– Age(min)))/(1.96*2)) [12]. Survival information at 5 and 10 years were obtained from Kaplan-Meier graphs using the Engauger Digitizer software version 10.10 (https://github.com/markummitchell/engauge-digitizer). Results were pooled using a meta-analytical approach. All statistical analysis were done with Stata 14.0. METAAN command was used to build forest plots of continuous variables and METAPROP command was used for binomial variables with fixed- effects model.

3. Results

Our search criteria identified 1,206 publications. After removal of duplicates and those that did not meet our inclusion criteria, 27 articles were selected (Figure 1) for data review as summarized in Table 1 [13,14,23–32,15,33–39,16–22]. Most papers were excluded because they analyzed HCC patients together with other histologies. Our review included 9,638 patients reported in 27 articles over a period of 20 years (2000–2020). Twenty-six studies reported gender distribution. There were 6,502 females (67.5%) and 3,117 males (32.3%) with a prevalence of female gender of 68% (95% CI 67-69, range 46-85%; Figure 2A). Twenty-three studies reported age data. The mean age at diagnosis was 57.6 years (range, 44.6-66 years). Sixteen studies reported the mean tumor size,

which was 30 mm (range, 25-47 mm; Figure 2B). Eighteen studies reported categorized size: Forty nine percent (95% CI 47%-50%, range 0-64%) of patients had nodules larger than 4 cm. Twenty-one studies reported ETE and the prevalence was 24% (95% CI 23-25%, range 0-64%; Figure 2C). Twenty-four studies reported lymph node metastasis at diagnosis and prevalence was 9% (95% CI 8-9%, range 0-56%; Figure 2D). The type of surgical treatment was reported in 25 studies, where total thyroidectomy was the surgical treatment in 83% of patients (95% CI 82-84%, range 27-100% Figure 2E). Use of radioiodine therapy (RAI) was reported in 22 studies and employed in 54% of patients (95% CI 53-55%, range 8-100% (Figure 2F). Neck dissection was reported by 14 studies and was performed in 29% of patients (95% CI 27-30%, range 4-53%). Less common therapies were reported: radiotherapy, in 8 studies with a frequency of 5% (95% CI 4-6%, range 4-48%), and chemotherapy in 5 studies with a frequency of 1% (95% CI 0-1%, range 3-27%). Treatment data were not available for 63 patients (0.6%). The mean follow-up time was reported by 17 studies and the mean was 60.6 months (range, 10-141). Data about overall survival (OS) and disease-free survival (DFS) at 5 years and 10 years respectively are shown in Table 2. The mean 5-year and 10-year OS rates were 91% (95% CI, 88-94%, Figure 3A) and 76% (95% CI, 70-82%, Figure 3B), respectively. And the mean 5-year and 10-year DFS rates were 87% (95% CI, 80-93%, Figure 3C) and 80% (95% CI, 70-89%, Figure 3D).

4. Discussion

Oncocytic tumors have been found in different organs such as salivary, lacrimal, pituitary, liver, kidney, pancreas, thyroid and parathyroid glands [40]. Oncocytic tumors in the thyroid gland are called Hürthle cell tumors, and they can be benign or malignant, depending on the presence of capsular and/or vascular invasion. Macroscopically**,** HCC usually appears encapsulated and has a mahogany brown color (Figure 4). Necrosis and

hemorrhage may be observed due to its degenerative nature. Sometimes calcification is observed and is more often found in HCC than in Hürthle cell adenoma. Histological diagnosis of HCC is made when on examination, capsular invasion and/or vascular invasion, is demonstrated (Figures 5A, B). Like follicular carcinoma, based on its histology, the tumor is subcategorized as minimally invasive, encapsulated with vascular invasion or widely invasive. Minimally invasive HCC refers to grossly encapsulated tumors with microscopically identifiable foci of capsular invasion. Widely invasive HCC shows extensive capsular and vascular invasion. With increasing extent of vascular invasion, the prognosis gets worse.

HCC is composed of pleomorphic or polygonal large cells with abundant, granular and acidophilic cytoplasm and large nuclei with prominent nucleoli (Figure 5C). It often shows follicular (Figure 5C), trabecular, and/or solid architecture, and rarely shows a predominantly papillary pattern. Poorly-differentiated HCC shows tumor necrosis and/or high rate of mitotic activity (≥ 3/10 high-power field). These lesions have lower iodine avidity and worse prognosis [3].

The genetic profile of HCC differs from papillary thyroid carcinoma and follicular thyroid carcinoma. Molecular pathways that differentiate Hürthle cell adenoma from HCC with wide invasiveness included the PIK3CA-Akt-mTOR and Wnt. HCC shows changes in both nuclear DNA and mitochondrial DNA (mtDNA)[40].

Ganly et al. [9] elucidate recurrent mutations impacting the RTK/RAS/AKT/mTOR pathway, DNA damage/repair, epigenetic modifiers, TERT promoter and the mitochondrial genome in HCC. HCCs also display prevalent chromosome 5 and 7 duplications, loss of heterozygosity, and in-frame gene fusions. The mutational profile was very different, in their study from that of other types of well

differentiated thyroid cancer such as papillary and follicular cancers. There were no BRAF mutations (present in 62% of papillary thyroid cancer) and the frequency of NRAS was much lower than that of follicular thyroid cancer. Genes important in poorly differentiated and anaplastic carcinoma such as TP53, TERT promoter, PTEN, PIK3CA and ATM were identified in the HCC cohort but at a lower frequency (TP53: 7% vs 73%; TERT: 22% vs 73%; ATM: 5% vs 9%; PIK3CA: 0% vs 18%; PTEN: 4% vs 15%). In another study, the TP53 mutation was found in 22% of HCC overall [41].

Widely invasive HCC did have loss of thyroid differentiation as compared to the minimally invasive phenotype, even if lacking the histological features of poorly differentiated thyroid cancer (i.e., presence of mitoses and necrosis). Other molecular differences between minimally invasive HCC and widely invasive HCC could be demonstrated by gene expression analysis. Among these differences, beta-catenin (CTNNB1) was a significant gene set that was enriched. In widely invasive HCC, beta-catenin is involved in regulating vascular invasion [42]. TERT promoter mutations, associated with unfavorable prognosis in various cancers, are found mainly in widely invasive HCCs. However, genetic rearrangements of PAX8/PPAR, RET/PTC, EML4/ALK, and ETV6/NTRK3 are infrequently observed in HCC.

Mitochondrial mutations may play a part as one of many factors leading to tumor development. Somatic missense mutations in GRIM19 have been found in approximately 11% of HCCs [43]. These mutations of the complex I subunit are the only nuclear gene mutations specific to oncocytic tumors reported to date [3]. A distinctive immune-related gene expression profile was found in poorly differentiated HCC, with increased intratumoral lymphocytic infiltration and PDL1 expression and confirmed a more aggressive outcome in this cancer subtype [44].

HCC are generally regarded as more aggressive than conventional follicular carcinoma of the thyroid gland [27,39], although this is unclear [15,28]. Their biological behavior is to some degree disputed in the literature perhaps in part due to their infrequent incidence. This review constitutes the most extensive presentation on HCC, as it includes information on 9,638 patients. However, data reporting outcomes was diverse and difficult to analyze. In this review, gathering data only of proven HCC patients, the mean OS at 5 and 10 years was 91% (95% CI, 88-94%) and 76% (95% CI, 70-86%), respectively. Nagar et al. [45] found in their series on 1416 HCC patients during a 35-year period, a significant improvement of HCC survival rates while follicular cell carcinoma survival rates had remained stable (increase in survival at 5 years, 21.7% vs 0.4%; at 10 years, 21.3% vs 5.2%), such that survival rates for the two entities are now comparable, but their data do not explain why HCC survival has improved. Although, they suggest that this is possibly due to the fact that they were considered more aggressive than follicular carcinomas and therefore treatment has been more aggressive, and follow-up has been stricter. Factors that could have influence on prognosis are discussed below.

4.1. Epidemiological features

The preponderance of women in the HCC patient population has been established in the existing literature. In the present review HCC occurred more frequently in women (68% female, with a female-to-male ratio of 2.1). In the earlier HCC reports, female-to-male ratio varied from 1.6 to 4.8 [15,31,33]. However, the study by Goffredo et al. [27] which included 3311 thyroid HCC, stated that, although the female preponderance persists, HCC was less common in women than other differentiated thyroid cancers (68.9% vs 77%, respectively; $P < .001$).

In some studies, male gender implied a worse prognosis [46]. In the study by Haigh et al. [15] (where 70% of patients were women), male gender was associated with a higher risk of mortality (HR, 2.07; 95%CI, 1.52-2.81). This point was not confirmed by Kushchayeva et al. [20].

HCC is reported to be more common between the 6th and 7th decades of life [27,28,30,31]. In the present systematic review, the mean age was 57.6 years. The mean age of Hürthle cell adenoma patients is lower than that of patients with HCC (Hürthle cell adenoma 43.1 vs HCC 51.8 years old) [14]. Increasing age at diagnosis has also been associated with a worse prognosis [14,15,27,28,46].

4.2. Pathological features

Tumor size is an important differentiating and prognostic factor. Chindris et al. [31] found a relationship between tumor size and the risk of recurrence or mortality. Lopez-Penabad et al. [14] found that the HCC group had significantly larger tumors (4.3 cm vs. 2.9 cm) compared with the Hürthle cell adenomas group. Stojadinovic et al. [13], described the median tumor size for widely invasive HCC was significantly larger than that observed for minimally invasive HCC (4.5 vs. 3.0 cm; P = 0.03). Some articles divided tumor size in two groups for analysis (≤4 or >4cm). Nodules with oncocytic follicular cells noted on FNA biopsy were more likely to be carcinomas if they were larger than 4 cm. [40]. In our analysis, 49% of patients had a nodule larger than 4 cm. Stojadinovic et al. [13] found that one of the variables that negatively influenced prognosis was widely shown invasiveness. However, when they compared patients with widely invasive HCC with and without ETE, they found that ETE of disease was in itself associated with a significantly worse relapse-free survival (8-year RFS, 6% vs. 56%; P = .002) and disease-specific survival (8-year DSS, 33% vs. 94%; P = .01). In our review,

the mean size of the HCCs was 30 mm. In 11 of the 20 articles (55%) in which data on tumor size were provided, the mean size was less than 4 cm [13,16,17,22,25–27,29,31,36,39]. The study by Maxwell et al. [17] reported the smallest average tumor size with a mean of 25 mm, although the range varied from 5 to 80 mm, with one third (15/45) having multifocal tumors. They concluded that despite the wide range in tumor size in their study, size had no influence on either risk of recurrence or survival rates. Certainly, small tumors can still be HCCs.

With respect to ETE and its implications, it is logical to suppose that tumors with ETE will have a worse prognosis than those without. This supposition was supported in our review of the literature [14,27,38]. The same holds true for lymph node metastases, both findings imply tumor dissemination, and are associated with a worse prognosis [14,20,27,30] in HCC but not papillary thyroid cancer. Maybe the reason for "lymph node metastasis" portending a worse prognosis was revealed by Bishop et al. [47], who reported that in the majority of cases, there were not true lymphatic metastases but tumor emboli in veins that reimplant along the venous outflow tract as discrete nodules. On microscopic examination, these metastatic nodules were not surrounded by any peripheral cuff of lymphoid tissue or capsule. They were surrounded by a thin zone of compressed elastic fibers of a vascular structure, without a muscular wall, representing distended veins rather than arteries or arterioles. This demonstrates that HCC behaves more like follicular thyroid cancers spreading in a hematogenous fashion primarily. As expected, the presence of distant metastasis has been associated with a worse prognosis [13,15,23].

4.3. Treatment

There is great variability in the treatment chosen for patients with HCC. Surgery alone, from partial to total thyroidectomy is employed with some patients also receiving

a neck dissection and post-surgical RAI treatment. A lobectomy that reveals unifocal HCC between 1 and 4 cm, in the absence of prior head and neck radiation, familial thyroid carcinoma, ETE or lymph node metastasis, can be considered therapeutic [48]. Total thyroidectomy is recommended for all HCCs larger than 4 cm [48]. Outcomes after total or partial thyroidectomy are controversial [15,23], although some studies reported better cancer-specific survival for patients undergoing total thyroidectomy [33]. In our review, the most frequent operation performed was total thyroidectomy with 83% (95% CI, 82-84%) of patients receiving it.

Another point of controversy regarding the treatment of HCC is whether or not to administer postoperative RAI therapy. Besic et al. [49] investigated the usefulness of RAI in HCC patients noting that metastatic or recurrent HCC showed RAI uptake in 69% of patients; as a consequence, they recommended use of RAI. In contrast, Jillard et al. [32] in their study of RAI in HCC, concluded that current guidelines are inconsistent with regard to the efficacy of RAI for HCC. This fact could explain why nearly 40% of HCC patients did not receive RAI. In our review, RAI was used in 54% of patients (95 CI, 53-55%). Yang et al. [38], in one of the largest reported series on 2799 HCC patients, suggests that RAI therapy is significantly associated with improved OS. However, there was no association between treatment with RAI and disease-specific survival, possibly due to the small number of deaths that were related to HCC. RAI therapy is widely used for adjuvant treatment after total thyroidectomy for the purpose of ablating residual thyroid tissue and thus enabling suspicion of tumor persistence or recurrence by monitoring the thyroglobulin level and/or implementing of RAI whole-body scan [49]. This philosophy is supported by the common practice of sub-total and near-total thyroidectomy, where there is residual thyroid tissue requiring ablation with RAI. However, a true extra capsular total thyroidectomy, considered to be the appropriate

operation for thyroid cancer, leaves no residual thyroid tissue requiring RAI ablation. These patients have postoperative thyroglobulin of < 1, which facilitates follow up with serial thyroglobulin levels. It is well known that the sensitivity of radioiodine scanning is the highest when there is no residual thyroid tissue to compete for iodine uptake, underscoring the importance of total thyroidectomy and radioiodine ablation [50]. However, the need for ablation depends on the completeness of total thyroidectomy.

Because it generally has lower iodine avidity, 18F-FDG PET has been suggested as a more accurate imaging modality for HCC. Studies have shown that 18F-FDG PET has excellent diagnostic accuracy in HCC patients and that intense 18F-FDG uptake in lesions is an indicator of a poor prognosis [51]. This suggests that patients with HCC should undergo 18F-FDG PET as part of their initial postoperative staging study and periodically to screen for occult recurrence, particularly in patients with elevated serum thyroglobulin. On the other hand, elevation of thyroglobulin reflects tumor recurrence, which is likely to be iodine avid, and in such patients a RAI scan may be more informative. Tumor heterogeneity is well known in thyroid cancer, and in some patients some metastatic lesions may be seen on RAI scan, and other lesions on the PET scan. Thus, often both scans may be necessary to assess the full extent of distant metastatic disease.

The role of neck dissection remains a matter of controversy in HCC treatment planning. Guerrero et al. [24] studied this factor in 39 patients with HCC. They found that only, 3 (8%) had lymph node metastasis. All 3 had central compartment nodes affected and one also had lateral nodal metastasis. They found that these patients were older (mean age: 86.7 and 56.4 years, respectively), had larger tumors (mean size: 6 and 4 cm) and were more frequently male (2 of 3). No tumor < 5cm presented with lymph node involvement (3/15 with >5cm cancer had node metastasis, 0/24 with <5cm cancer had

node metastasis). They concluded that older male patients with HCCs greater than 5 cm may benefit from a prophylactic ipsilateral and central neck dissection at the time of primary operation. Oluic et al. [33] found locoregional metastases in 2.5% of their cohort of 239 patients (6 of 78 patients (7.7%) who underwent neck dissection). This finding is similar to the Goffredo et al. [27] study (5.3%), but Sugino et al. [28] noted positive lymph nodes in 21.9% of their patients. In our review, lymph node metastasis was found in 9% of the patients. We feel therefore based on the reported data in the literature that prophylactic central neck dissection is not necessary.

In iodine-resistant or non-avid cases, in patients with disease progression or unresectable disease, there are different approaches that have been used. For patients with non-avid metastases, treatment with tyrosine kinase inhibitors (Sorafenib and Lenvatinib) should be taken into account [52,53]. For sorafenib, results of the phase III DECISION trial led to FDA approval for radioactive-iodine refractory differentiated thyroid cancer, with a median PFS of 10.8 months versus 5.8 months in the placebo arm [54]. In another randomized phase III trial (the SELECT trial), lenvatinib has been shown to increase progression-free survival with 14.7 months compared to a placebo, a 64.8% response rate, and an 87.7% disease control rate in the same indications [55]. External beam radiotherapy can be used to prevent recurrence of advanced tumors and for cases with symptomatic metastases in whom can provide palliative relief [56]. In selected cases, surgical procedure is an useful treatment option for distant metastasis [52]. Chemotherapy can be effective in a neoadjuvant way to decrease size of primary HCC [57]. Lopez-Penabad et al. [14] used chemotherapy for unresectable, progressive or metastatic disease. Thirteen percent of patients received it as a radiosensitizing agent, and the remaining 87% of patients received a full course of treatment. Agents that were used most were doxorubicin alone, doxorubicin plus cisplatin and cisplatin alone.

The rarity of HCC and the variability and heterogeneous data reporting are the limitations of this review.

Conclusions

To our knowledge, this is the largest review of HCC to date. These cancers occur more frequently in women, between the sixth and seventh decades of life, with tumor size at presentation near 3 cm. ETE is not rare at diagnosis but lymph node metastases are uncommon (24% and 9% respectively). The ablation of residual thyroid tissues with RAI in patients who have undergone less than a true extra capsular total thyroidectomy, may improve accuracy of use of thyroglobulin to follow HCC patients for recurrence. It will be important to do further work to standardize the treatment of these tumors to avoid unnecessary overtreatment. The mean OS at 5 and 10 years was 91% and 76%, respectively**.** The main adverse prognostic factors are male gender, higher age and TNM stage. However, our study also realizes the heterogeneity of data and results. Ranges of studies are wide in relation to prognostic factors and outcomes. This is a reflection of differences in inclusion criteria, the period when the sample was collected, and the different therapeutic approaches employed at different centers.

Figure 1: Flow chart showing the study selection process for our PRISMA systematic review.

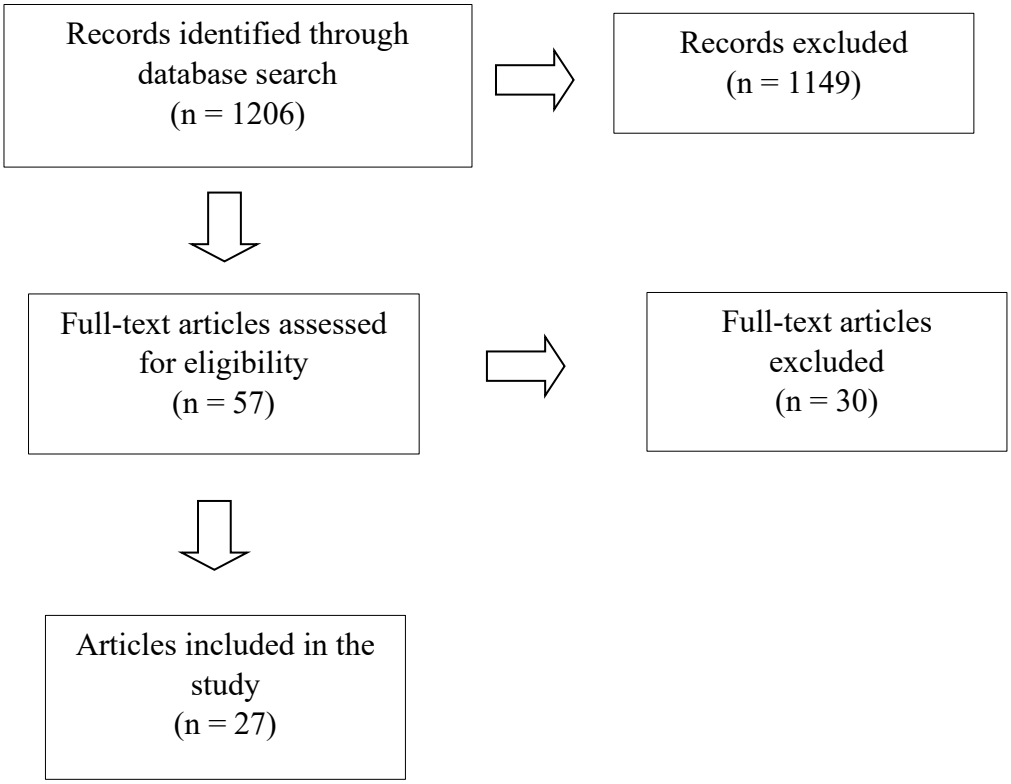

Figure 2: Forest-plots showing the distribution in the reviewed articles by gender (A), tumor size (B), extrathyroidal extension (C), lymph node metastasis (D), treatment with total thyroidectomy (E), and treatment with radioactive iodine.

Figure 3: Forest-plots showing the 5-year overall survival (A), 10-year overall survival (B), 5-year disease-free survival (C), and 10-year disease-free survival (D) reported in the reviewed articles.

Figure 4: Gross findings of the Hürthle cell tumor. The tumor is encapsulated with mahogany brown color. The entire capsule should be examined on microscope looking for capsular and/or vascular invasion.

Figure 5: Histological images of HCCs. (A: HESX10) HCC is diagnosed in cases where a Hürthle cell tumor shows capsular invasion, and/or (B: HESX5) vascular invasion. (C: HESX10) HCC is composed of polygonal large cells with abundant granular and acidophilic cytoplasm. HCC cells have large nuclei with prominent nucleoli. (HES: Hematoxylin and eosin stain).

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Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

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Conflict of interest

All authors Andrés Coca-Pelaz, Juan P. Rodrigo, Jatin P. Shah, Alvaro Sanabria, Abir Al-Ghuzlan, Carl E. Silver, Ashok R. Shaha, Peter Angelos, Dana M. Hartl, Antti A. Mäkitie, Kerry D. Olsen, Randall P. Owen, Gregory W. Randolph, Ricard Simó, Ralph P. Tufano, Luiz P. Kowalski, Mark E. Zafereo, Alessandra Rinaldo, Alfio Ferlito declare no personal, financial, commercial, or academic conflicts of interest.

Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions

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-English editing: Carl E. Silver.

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Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Table 1: HCC articles published between 2000-2020.

Author Year [Ref]	**Number of cases (Sex)**	**Mean age + SD (years)**	**Mean nodule size +- SD, mm**	**ETE**	**LNM**	**Type of surgery**	**RAI**	**Other adjuvant treatment (RT/CT)**	**Median follow-up, months (range)**	**Outcome**
Stojadinovic et al. 2002 [13]	56 (34F/22M)	*56+-20.3	37.5	19	7	17 TT 39 PT	NA	NA	96	DSS 8y: Low risk 100% High risk 58%
Lopez-Penabad et al. 2003 [14]	89 (60F/29M)	51.8	43	35	22	42 TT 47 PT 33 ND	64	43 RT 24 CT	128.4	*OS 5y 86% OS 10y 61% DFS 5y 79 DFS 10y 61
Haigh and Urbach 2005 [15]	172 (105F/67M)	NA	NA	110	29	138 TT 34 PT	56	NA	*112.8+-35.6	OS 10y 73% *OS 5y 93% OS 10y 85%
Ghossein et al. 2006 [16]	50 (29F/21M)	*52+-17.3	32	2	1	29 TT 21 PT	17	NA	*35.9 +-47.8	DFS: 3y 85% 5y 76%

Maxwell et al. 2006 [17]	45 (34F/11M)	*57 +-12.5	*25+-17.5	9	25	41 TT 4 PT 22 ND	39	2 RT	*94 +- 65.6	DSS 5y 96%
Ozlem Küçük et al. 2006 [18]	13 (6F/7M)	48.4+-11.9	NA	3	3	12 TT 1 PT 3 ND	13	NA	85	*OS 5y 100% DFS 5y 92%
Ahmed et al. 2008 [19]	17 (11F/6M)	*44.6 +-12.2	44.3+-6.6	17 NA	3	14 TT 3 PT 9 ND	14	2 RT	*63.4 +- 47.6	NA
Kushchayeva et al. 2008 [20]	33 (23F/10M)	*55.2 +-13.9	NA	8	1	30 TT 3 PT	22	6 RT 2 CT	*66 +- 57.6	DFS 5y 64.7% DFS 10y 40.5% CSM 10y 51%
Zhang et al. 2008 [21]	9 (5F/4M)	66+-6	45+-7.1	9 NA	9 NA	8 TT 1 PT	6	NA	*10 +- 35.1	OS 100%
Barnabei et al. 2009 [22]	19 (19 NA)	*49.3 +-12.5	25.8 +-11.3	19 NA	1	19 TT 1 ND	NA	NA	*62 +- 80.7	DFS 5y 94%
Mills et al. 2009 [23]	62 (38F/24M)	59+-16.5	NA	12	11	32 TT 19 PT	27	14 RT	*58 +- 159.7	OS: 10y 64%

										20y 37% 30y 20% DFS: 10y 43% 20y 17% 30y 9%
Guerrero et al. 2010 [24]	39 (23F/16M)	58.7+-15.9	NA	39 NA	3	39 TT 3 ND	NA	NA	NA	NA
Pisanu et al. 2010 [25]	28 (23F/5M)	*49.6 +-9.5	30 +-3	1	3	28 TT 3 ND	28	NA	*141 +-31.2	DSS 5y 96% DFS 5y 89.3%
Kutun et al. 2011 [26]	23 (15F/8M)	*51 +-10.7	29+-17.6	9	23 NA	19 TT 4 PT 1 ND	21	NA	*49 +-59.2	NA
Goffredo et al. 2013 [27]	3311 (2281F/1030M)	57.6+-0.3	36.1+-22.1	476	172	2480 TT 689 PT 142 No surgery	1486	142 RT	NA	OS 10y 82.1% *DFS 10y 92.3% DSM 5.9%

Sugino et al. 2013 [28]	73 (48F/25M)	58	NA	5	73 NA	20 TT 53 PT	6	NA	58	OS: 10y 93.1% 15y 92% 20y 83.5%
Kim et al. 2014 [29]	80 (62F/18M)	49+-14	34+18	23	0	45 TT 35 PT	38	NA	72	*DFS 5y 98% DFS 10y 98%
Petric et al. 2014 [30]	108 (82F/26M)	*62 +-15.6	*40+-42.7	24	8	77 TT 31 PT 9 ND	87	23 RT 16 CT	*105 +- 85.3	DSS: 5y 96% 10y 88% 20y 67% DFS: 5y 78% 10y 68% 20y 65%
Chindris et al. 2015 [31]	173 (93F/80M)	*62+-15.3	*35+-45.5	173 NA	16	70 TT 101 PT 2 No surgery 73 ND	148	NA	*69.8 +- 101.7	OS 5y 85%

Jillard et al. 2016 [32]	1909 (1220F/689M)	*58.4+-16.1	*45.6+-33.3	1909 NA	599	1909 TT	1162	NA	NA	OS RAI: 5y 88.9% 10y 74.4% OS no RAI: 5y 83.1% 10y 65%
Oluic et al. 2017 [33]	239 (187F/52M)	54.3+-13.7	*41.8+-39.0	33	6	160 TT 76 PT 3 No surgery 78 ND	65	NA	*89.5 +- 58.9	OS: 5y 89.4% 10y 77.2% 20y 61.9% CSS: 5y 94.6% 10y 92.5% 20y 87.5% DFI: 5y 91.1% 10y 86.2% 20y 68.5%

Zavitsanos et al. 2017 [34]	16 (11F/5M)	*57 +-11.9	NA	1	1	16 TT 3 ND	16	NA	*72 +- 27.3	OS and CSS 92% DFS 5y 65%
Ernaga Lorea et al. 2018 [35]	77 (55F/22M)	57.3+-13.8	40.1+-17.8	2	2	77 TT	NA	NA	160.8	DFS: 5y 92.9% 10y 86.1% 20y 78.7%
Amouri et al. 2019 [36]	20 (17F/3M)	*54.5+-8.6	*37.5+-8.9	0	0	20 TT	20	NA	*49 +- 48.6	OS 5y 90%
Santana et al. 2019 [37]	52 (43F/9M)	57.2+-14.5	47.4+-25.7	3	5	NA	NA	NA	NA	NA
Yang et al. 2019 [38]	2799 (1938F/861M)	NA	NA	1131	141	2040 TT 668 PT 91 No surgery 822 ND	1529	15 CT	*64.8 (0- 144)	NA
Wenter et al. 2021 [39]	126 (59F/74M)	*57.8 +-1.36	30 +-(21- 45)	8	5	126 TT 47 ND	126	6 RT 4 CT	*88.8 +- 24.2	DFS: 5y 92% 10y 91% 20y 89%

										OS: 5y 92% 10y 75% 20y 67% DSS: 5y 95% 10y 87% 20y 84%
Total	9638 (6502F/3117M/ 19NA)	55.4	35.4	1914	1064	7508 TT 1829 PT 982 ND 238 No surgery 63 NA	4990 RAI	238 RT 61 CT	*76.3 (10- 160.8)	

CSM: Cancer specific mortality, CSS: Cancer specific survival, CT: Chemotherapy, DFI: Disease free interval, DFS: Disease free survival, DSS: Disease specific survival, DSM: Disease specific mortality, ETE: Extrathyroidal extension, HCC: Hürthle cell carcinoma, LNM: Lymph node metastasis, NA: Not available, ND: Neck dissection, OS: Overall survival, PT: Partial thyroidectomy, RAI: Radioactive iodine treatment, RT: Radiotherapy, TT: Total thyroidectomy. *Imputed data.

Table 2: Pooled results for overall and disease-free survival at 5 and 10 years.

	OS 5 years % (95% CI), range	**OS 10 years % (95% CI), range**	**DFS 5 years % (95% CI), range**	**DFS 10 years % (95% CI), range**
Number of studies reporting data	9	7	14	9
	91% (89-93) 85-100%	81% (80-82) 61-93%	91% (89-93) 63-98%	91% (90-92) 39-98%

OS: Overall survival, DFS: Disease free survival.

Figures

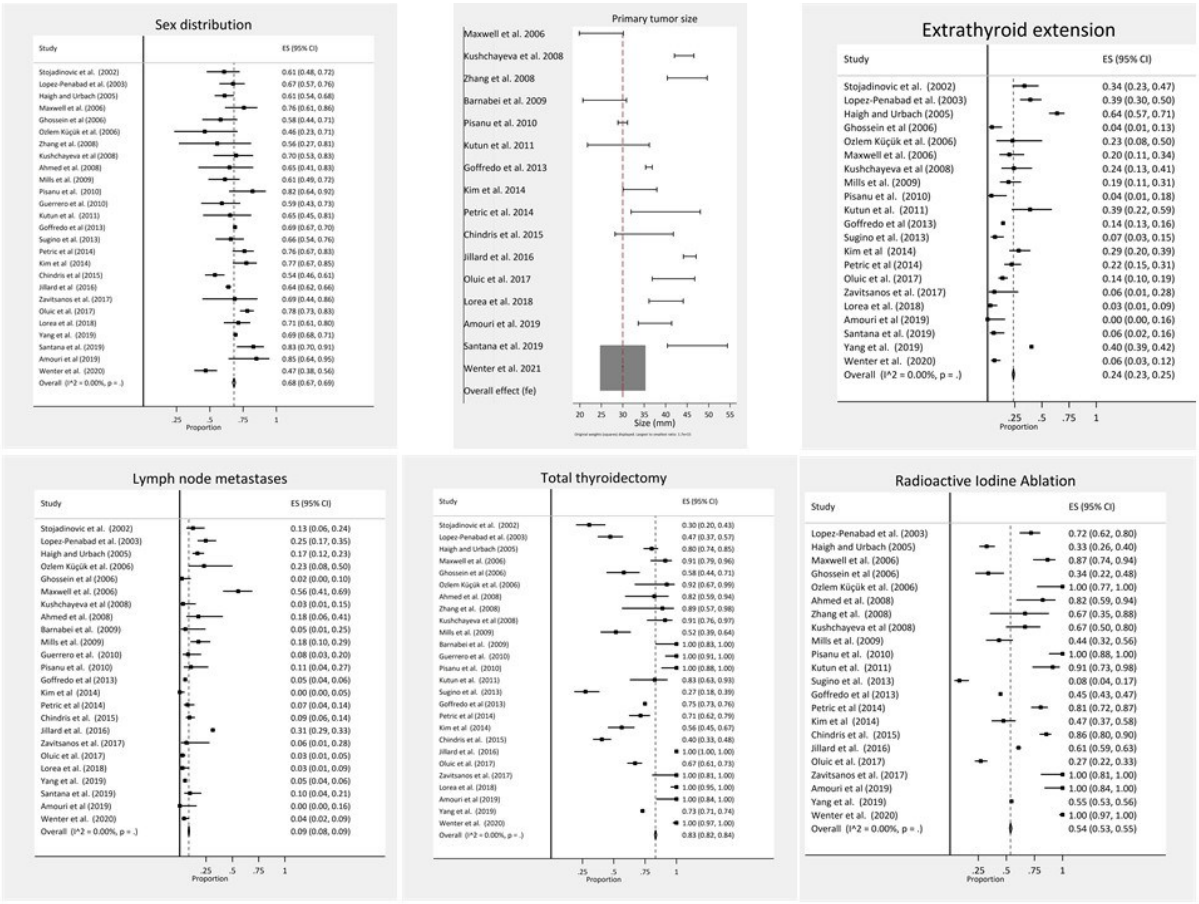

Figure 2

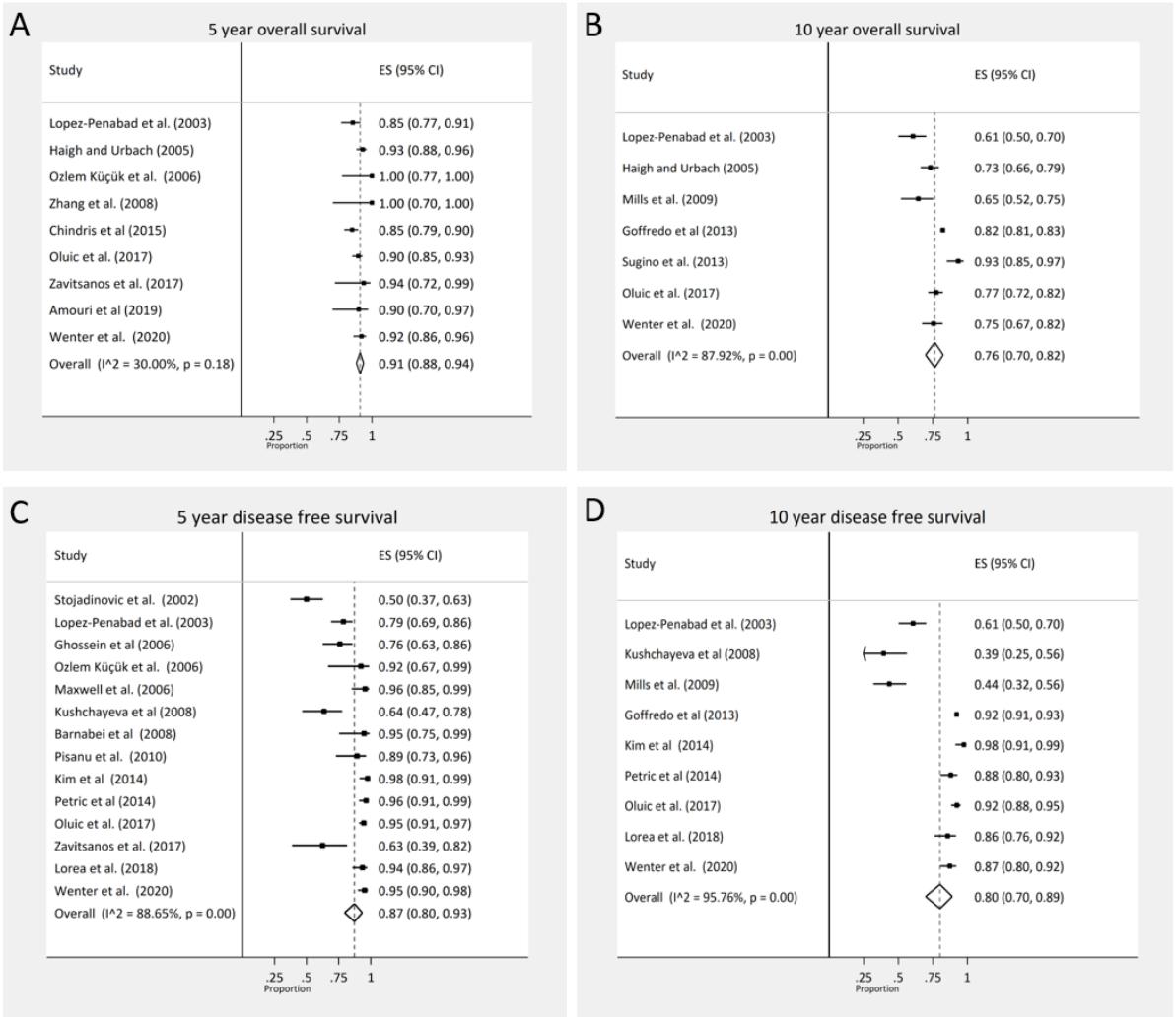
A
5 year overall survival
Study
ES (95% CI)
Lopez-Penabad et al. (2003) 0.85 (0.77, 0.91)
Haigh and Urbach (2005) 0.93 (0.88, 0.96)
Ozlem Küçük et al. (2006) 1.00 (0.77, 1.00)
Zhang et al. (2008) 1.00 (0.70, 1.00)
Chindris et al (2015) 0.85 (0.79, 0.90)
Oluic et al. (2017) 0.90 (0.85, 0.93)
Zavitsanos et al. (2017) 0.94 (0.72, 0.99)
Amouri et al (2019) 0.90 (0.70, 0.97)
Wenter et al. (2020) 0.92 (0.86, 0.96)
Overall (I^2 = 30.00%, p = 0.18) 0.91 (0.88, 0.94)
.25 .5 .75 1
Proportion
B
10 year overall survival
Study
ES (95% CI)
Lopez-Penabad et al. (2003) 0.61 (0.50, 0.70)
Haigh and Urbach (2005) 0.73 (0.66, 0.79)
Mills et al. (2009) 0.65 (0.52, 0.75)
Goffredo et al (2013) 0.82 (0.81, 0.83)
Sugino et al. (2013) 0.93 (0.85, 0.97)
Oluic et al. (2017) 0.77 (0.72, 0.82)
Wenter et al. (2020) 0.75 (0.67, 0.82)
Overall (I^2 = 87.92%, p = 0.00) 0.76 (0.70, 0.82)
.25 .5 .75 1
Proportion
C
5 year disease free survival
Study
ES (95% CI)
Stojadinovic et al. (2002) 0.50 (0.37, 0.63)
Lopez-Penabad et al. (2003) 0.79 (0.69, 0.86)
Ghossein et al (2006) 0.76 (0.63, 0.86)
Ozlem Küçük et al. (2006) 0.92 (0.67, 0.99)
Maxwell et al. (2006) 0.96 (0.85, 0.99)
Kushchayeva et al (2008) 0.64 (0.47, 0.78)
Barnabei et al (2008) 0.95 (0.75, 0.99)
Pisanu et al. (2010) 0.89 (0.73, 0.96)
Kim et al (2014) 0.98 (0.91, 0.99)
Petric et al (2014) 0.96 (0.91, 0.99)
Oluic et al. (2017) 0.95 (0.91, 0.97)
Zavitsanos et al. (2017) 0.63 (0.39, 0.82)
Lorea et al. (2018) 0.94 (0.86, 0.97)
Wenter et al. (2020) 0.95 (0.90, 0.98)
Overall (I^2 = 88.65%, p = 0.00) 0.87 (0.80, 0.93)
.25 .5 .75 1
Proportion
D
10 year disease free survival
Study
ES (95% CI)
Lopez-Penabad et al. (2003) 0.61 (0.50, 0.70)
Kushchayeva et al (2008) 0.39 (0.25, 0.56)
Mills et al. (2009) 0.44 (0.32, 0.56)
Goffredo et al (2013) 0.92 (0.91, 0.93)
Kim et al (2014) 0.98 (0.91, 0.99)
Petric et al (2014) 0.88 (0.80, 0.93)
Oluic et al. (2017) 0.92 (0.88, 0.95)
Lorea et al. (2018) 0.86 (0.76, 0.92)
Wenter et al. (2020) 0.87 (0.80, 0.92)
Overall (I^2 = 95.76%, p = 0.00) 0.80 (0.70, 0.89)
.25 .5 .75 1
Proportion

Figure 3

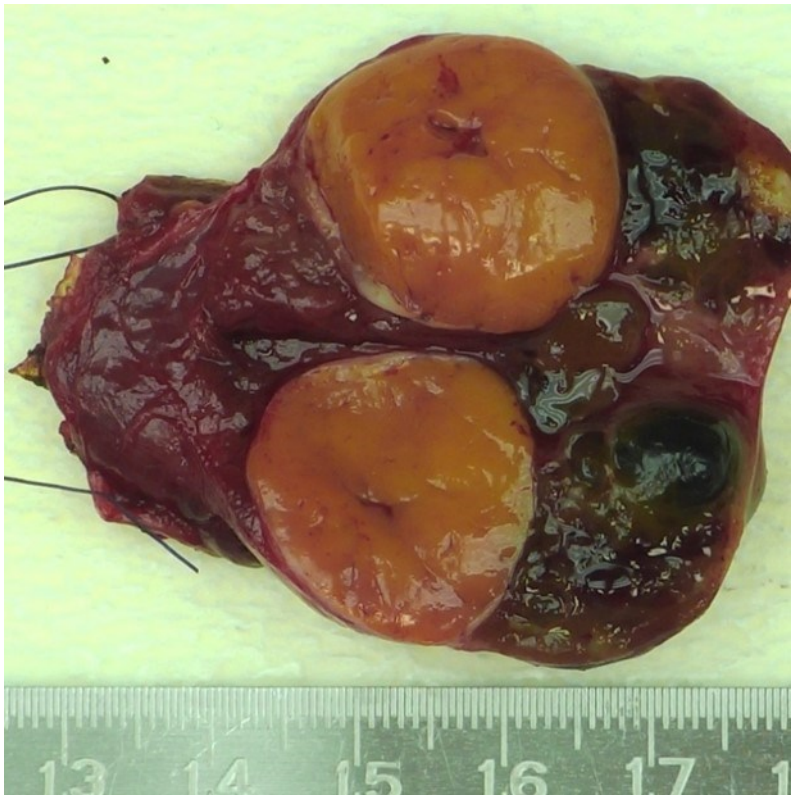

Figure 5