INTRODUCTION

Differentiated thyroid carcinoma (DTC) accounts for over 90% of all follicular cell-derived thyroid malignancies and is the commonest primary endocrine-related malignancy. **(Hong Kong Cancer Registry, 2006)**

Despite this, the cancer-specific mortality remains low with an overall 10-year survival above 90%. **(Lang et al., 2007)**

However, recurrent/persistent disease after seemingly curative surgery remains a major cause of patient morbidity and poses a management challenge for clinicians. **(Mazzaferri and Kloos., 2001)**

Furthermore, clinicians have witnessed a paradigm shift in the definition of cure from not dying of the disease to being "completely disease-free" with good quality of life and to, more recently, having undetectable postsurgical stimulated thyroglobulin (Tg) levels. **(Hughes et al., 2010)**

However, despite our best effort, overall 15 to 30% of patients with DTC develop locoregional recurrences after successful initial operation leading to increased patient morbidity. Numerous studies have shown that these recurrences most commonly involve the regional lymph nodes. **(Hay et al., 2002)**

In terms of lymph node metastases, at the time of first presentation, up to 20–30% patients with PTC would have gross involvement and approximately 90% would have microscopic involvement (i.e., micrometastases). Therefore, lymph node metastases in PTC is very common, but it is only over the last 10–15 years that lymph node metastasis is recognized to be associated with a poorer cancer-specific survival. **(D. S. Cooper et al., 2009)**

With better understanding of the lymphatic drainage of the thyroid gland, it is now believed that lymphatic metastasis of DTC tends to occur in the ipsilateral central compartment as the first place for metastasis. From there, it next spreads either to the ipsilateral lateral compartment or contralateral central compartment. **(Moo et al., 2009)**

In attempt to further improve the management of lymph node metastases, the role of prophylactic central neck dissection (pCND) has been extensively studied over the past 5–10 years. For surgeons, pCND has become one of the major research focuses. In year 2006, American Thyroid Association (ATA) published a guideline on management of thyroid cancer and suggested that "pCND should be considered for patients with papillary thyroid cancer". **(Cooper et al., 2006)**

This recommendation was based on the association between lymph node metastasis, recurrence, and survival. It was also based on the assumption that pCND would reduce the risk of recurrence and perhaps improve cancer-specific survival. However, this recommendation was criticized as being vague and imprecise, and it also generated much controversy among the surgical community. In the revised guideline by ATA in 2009, they recommended a much more risk-orientated approach and suggested that "pCND may be performed, especially in patients with advanced primary tumors" and "total thyroidectomy without prophylactic central neck dissection may be appropriated for small (T1 or T2), non-invasive, clinically node negative patients." **(Cooper et al., 2009)**

Low-risk patients have the following characteristics: age younger than 45 years, tumors < 4 cm , absence of distant metastasis , no extra thyroid extension and low grade histology. **(Cooper et al., 2009)**

AIM OF THE WORK

The aim of the work is to revise literatures and conduct meta analysis study trying to answer the question of: is central neck dissection is essential for the treatment of low risk group of lymph node negative patients of differentiated thyroid cancer for better regional control or not.

PATHOLOGY

Thyroid carcinoma is the most common endocrine malignancy, which incidence increased in the last several decades. Papillary thyroid carcinoma (PTC) is the most common histological subtype, accounting for more than 85 % of all cases. The prognosis of PTC is general good, with 10-year survival rate exceeds 95 % and 20-year survival rate exceeds 93 %. **(Brassard et al., 2011)**

A. Papillary Carcinoma :

Papillary carcinoma can occur at any age and rarely has been diagnosed as a congenital tumor. Most tumors are diagnosed in patients in the third to fifth decades of life. Women are affected more frequently than men in ratios of 2: 1 to 4: 1. **(Mazzaferri et al., 2002)**

The gross appearance of papillary thyroid cancer is quite variable. The lesions may appear anywhere within the gland. By definition, typical papillary carcinomas often average 2–3 cm, although lesions may be quite large or subcentimeter in size. The lesions are firm and usually white in color with an invasive appearance. Lesional calcification is a common feature. Owing to the extensive sclerosis, the lesion may grossly resemble a scar, especially in small lesions, which tend to be found in a

subcapsular location in the gland. In addition, cyst formation may be observed. In fact, some lesions may be rarely almost completely cystic making diagnosis difficult**. (Baloch et al., 2002)**

Microscopically, papillary carcinomas share certain features. The neoplastic papillae contain a central core of fibrovascular (occasionally just fibrous) tissue lined by one or occasionally several layers of cells with crowded oval nuclei**. (Baloch et al., 2008)**

The tumors invade lymphatics leading to multifocal lesions and to regional node metastases. Venous invasion rarely occurs and metastases outside the neck are unusual (5–7% of cases). Some data is available suggesting that this finding alone is predictive of a more aggressive behavior. Whether the lymphatic invasion itself causes the 'multifocality' by intraglandular spread and 'take' in distinct foci within the thyroid or whether these foci represent true independent clonal proliferations is still debated. **(Gardner et al., 2000)**

Classical papillary carcinoma is characterized by the formation of papillae and a set of distinctive nuclear features (optically clear appearance, overlapping, pseudoinclusions and nuclear grooves) **(Scopa et al., 1993)**

Psammoma bodies that represent the 'ghosts' of dead papillae are differentiated from dystrophic calcifications by lamellations. True psammoma bodies are formed by focal areas of infarction of the tips of papillae attracting calcium that is deposited on the dying cells. **(Hunt and Barnes, 2003)**

The size of papillary carcinoma is extremely variable with a mean diameter of 2-3 cm. A clinically detected tumor is usually confined to the thyroid, is presented as a fairly well circumscribed or infiltrative neoplasm and has an indolent course. Its mode of spread is most commonly via lymphatics within the thyroid leading to multifocal disease and to cervical node metastases. **(Rosai et al., 1992)**

Indeed, 50% or more of papillary carcinomas have nodal metastases at initial diagnosis. **(Carcangiu et al., 1985)**

Distant metastases of papillary carcinoma to lungs and bones occur in 5–7% of cases. **(Hoie et al., 1988)**

There are several histologic variants of papillary carcinoma, some of which are associated with a more guarded prognosis. **(Sobrinho-Simões., 1995)**

a. Variants of papillary carcinoma

a.1. Papillary microcarcinoma:

The term refers to papillary carcinomas measuring 1cm or less in diameter and replaces the older designation of occult sclerosing carcinoma, also known as nonencapsulated sclerosing tumor and occult papillary carcinoma**. (Rosai et al., 1992)**

Papillary microcarcinomas are frequently detected as incidental findings in autopsy or in surgical specimens and are associated with an excellent prognosis despite occasional regional lymph node metastases. The reported incidence in autopsy material has ranged from 4% to 35.6%. **(Scopa et al., 1995)**

a.2. Encapsulated variant:

The tumor is totally surrounded by a fibrous capsule which may be intact or focally infiltrated by the tumor. These tumors have an exceptionally good prognosis and, although some lesions have shown lymph node involvement, distant metastases or death due to tumor are practically nonexistent. **(LiVolsi, 1992)**

a.3. Follicular variant:

Papillary carcinomas having an exclusive or almost exclusive follicular pattern are designated as a follicular variant

of papillary carcinoma. The biologic behavior of this variant is analogous to that of conventional papillary carcinoma. The metastases may have a mixed papillary and follicular formation. A diffuse or widely invasive form of the follicular variant and macrofollicular variant of papillary carcinoma have also been described. **(Albores-Saavedra et al., 1991)**

a.4. Tall and columnar cell variant:

The main histologic feature of the tall cell variant of papillary carcinoma is the presence of tall cells **(the height being twice the width)**, with an intense eosinophilic cytoplasm, lining well-developed papillae (Figure 1E).

In the columnar cell variant, there is a marked nuclear stratification and the cytoplasm is clear, sometimes with subnuclear vacuolization**. (Rosai et al., 1992)**

Both the tall cell and columnar cell variant are said to be more aggressive than classical papillary carcinomas. **(Johnson et al., 1988)**

However, recent studies suggest that the clinical behavior of these rare types of papillary carcinoma depends on tumor size, extrathyroidal invasion and distant metastases. **(Nishiyama, 2000)**

a.5. Diffuse sclerosing variant:

This is an unusual form of papillary carcinoma first described by Vickery et al, who noticed that it more frequently affects children and is associated with a poor prognosis. **(Vickery et al., 1985)**

This tumor is characterized by diffuse involvement of one or two lobes and clinically may be misdiagnosed as Hashimoto.s thyroiditis. Its hallmark, microscopically, is the presence of widespread intrathyroid lymphatic permeation by numerous neoplastic micropapillae. **(Rosai et al., 1992)**

a.6. Other variants:

Variants such as solid variant, clear cell and oxyphilic variant, papillary carcinoma with lipomatous stroma, Warthin.s-like tumor or with nodular fasciitis-like stroma and cribriform papillary carcinoma have been reported, but they are too few in number for an adequate assessment of their prognostic implication. **(Baloch and LiVolsi., 2002)**

The term solid and/or trabecular variant is used when a NOS papillary carcinoma has a solid and/or trabecular pattern throughout the tumor. **(Rosai et al., 1992)**

B. Follicular Carcinoma :

Most authors agree that only follicular tumors that exhibit vascular and/or capsular invasion should be regarded as follicular carcinomas. **(Franssila et al., 1985)**

Depending on the degree of their invasiveness, follicular carcinomas have been divided into two major categories: minimally invasive or encapsulated (the most common), and widely invasive. The frequency of follicular carcinoma among thyroid malignancies ranges from 5-10% in non-iodine-deficient areas to 30-40% in iodine-deficient areas. Macroscopically, follicular carcinomas do not differ appreciably from follicular adenomas. The fibrous capsule surrounding the tumor tends to be thicker and more irregular than in adenomas. **(Rosai et al., 1992)**

Minimally invasive follicular carcinoma is an encapsulated tumor showing capsular and/or vascular invasion only on microscopic evaluation, while the widely invasive neoplasm shows lack of complete encapsulation, extensive areas of invasion to the adjacent thyroid tissue and/or widespread blood vessels infiltration. **(Rosai et al., 1992)**

Immunohistochemistry, morphometry, ploidy analysis, cytogenetic and oncogene markers have failed to provide

reliable information concerning the distinction between follicular carcinoma and follicular adenoma.

The current diagnostic criteria for malignancy are still the histologic assessment of true capsular infiltration (the tumor must penetrate the entire thickness of the capsule) and/or invasion of blood vessels in or beyond the capsule (Figure 1B). **(Sobrinho-Simões, 1995)**

It is apparent that minimally invasive follicular tumors cannot be accurately diagnosed by fine needle aspiration (FNA) cytology since the crucial diagnostic criteria are missing. **(Rosai et al., 1992)**

Similar problems exist in evaluating such lesions by frozen section. **(Scopa et al., 2001)**

Malignant thyroid tumors composed exclusively or predominately (over 75%) of oncocytes (Hürthle cell tumors) share some similarities with follicular carcinomas as regards the clinical presentation, the architectural features and the degree of invasiveness, and therefore should be considered as a variant of follicular carcinoma. **(Rosai et al., 1992)**

However, some authors have suggested that the morphologic features and natural history of these tumors are

distinctive enough that they be considered as a separate entity. **(Pappoti et al., 1996)**

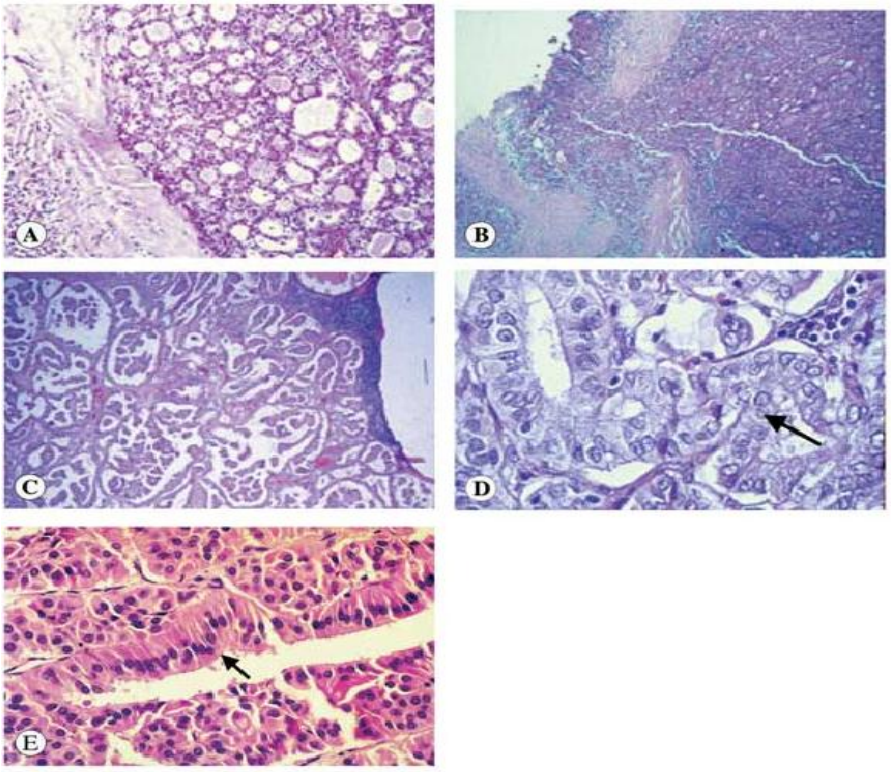

Fig. (1): Histology of Thyroid Tumors. *A.* Follicular adenoma: note the sharp separation of a follicular tumor from the surrounding tissue by a uniform fibrous capsule. *B.* Follicular carcinoma with capsular penetration. *C.* Papillary carcinoma metastatic to a lymph node: typical appearance of papillary carcinoma with complex and branching papillae. *D.* Higher magnification showing optical clear, overlapping and grooved (arrow) nuclei. *E.* Tall cell variant papillary carcinoma, lined by tall cells (arrow)

Incidence of metastatic disease to regional lymph nodes

Metastatic disease to regional lymph nodes is common in patients with papillary thyroid cancer. Palpable nodal disease is

present in approximately 5 to 10 percent of patients with papillary thyroid cancer; a preoperative neck ultrasound can detect lymph node disease in up to 30 percent of patients Standard histologic techniques (hematoxylin and eosin stain) typically reveal positive lymph nodes in 20 to 50 percent of patients undergoing an elective node dissection for papillary thyroid cancer. **(Kim et al., 2008)**

However, after immunohistochemical evaluation (ie, cytokeratin stain), up to 90 percent of patients will have microscopic metastatic disease. It appears that many patients have microscopic regional lymph node disease that never becomes clinically apparent. **(Qubain et al., 2002)**

In contrast, less than 5 percent of patients with follicular thyroid cancer develop nodal metastatic disease; the hematogenous rather than the lymphatic route is the primary pathway for metastasis. **(Zaydfudim et al., 2008)**

Significance of lymph node involvement

The prognosis of differentiated thyroid cancer remains excellent even in patients with lymph node involvement (>90 percent 10-year survival). **(Wada et al., 2007)**

However, metastatic disease to regional lymph nodes at the time of presentation does appear to increase the risk of

cervical recurrence, especially when macroscopic, but does not appear to have a significant impact on overall survival. **(Smith et al., 2012)**

Lymph node involvement in papillary thyroid cancer can be macroscopic (identified on preoperative imaging or intraoperative inspection) or microscopic (identified on pathologic review only). Cervical lymph node metastasis from papillary thyroid cancer is associated with several well-described factors including multifocality, extrathyroidal extension, larger tumor size, younger age, aggressive variants, and the presence of BRAF mutation. **(Howell et al., 2013)**

Macroscopic lymph node involvement is associated with a high rate of local recurrence (10 to 42 percent). **(Randolph et al., 2012)**

Biologic behavior and clinical significance of cervical lymph node metastases

Cervical recurrence occurs in up to 20% of patients with low-risk PTC and up to 60% of those with high- risk disease. **(Mazzeferri and Jhiang, 1994).**

Prognosis for the development of loco-regional recurrences combined in a variety of prognostic algorithms ***(Table 1)*****. (Hay et al., 1993)**