Sentinel Lymph Node Biopsy

for Papillary Thyroid Cancer

by

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Dedication

I would like to dedicate my master's thesis to my loving mother and father, for always supporting me throughout all aspects of my life.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

SLN: Sentinel Lymph Node

SLNB: Sentinel Lymph Node Biopsy

WDTC: Well Differentiated Thyroid Cancer

CCND: Central Compartment Neck Dissection

RLN: Recurrent Laryngeal Nerve

PTC: Papillary Thyroid Cancer

Abstract

Objective: To prospectively evaluate the role of sentinel lymph node (SLN) biopsy in the management of well differentiated thyroid carcinoma (WDTC)

Methods: I designed and implemented a SLN biopsy protocol and subsequently performed it on consecutive patients undergoing thyroid surgery. Thyroid nodules were injected with methylene blue dye. A central compartment neck dissection (CCND) was performed. Frozen section analysis of the SLNs was performed.

Results: 157 patients are included in this study. 94 patients had WDTC. Sevently three percent (69/94) of WDTC patients were found to have detectable SLNs. Twenty percent (14/69) of patients with SLNs were found to have central compartment metastases. The sensitivity, specificity, positive predictive value and negative predictive value of our SLN biopsy technique to remove all disease from the central compartment was 92.9%, 100%, 100% and 98.8% respectively ($p < 0.0001$).

Conclusion: This data series suggests that if a patient has SLNs deemed as negative for malignancy on frozen section, the rest of the central compartment is unlikely to have lymph node metastasis.

Résumé

Contexte: Notre objectif est d'évaluer prospectivement le rôle du biopsy ganglion sentinelle dans la gestion du cancer de la thyroïde bien différencié

Méthodes: Nous avons conçu et mis en place un protocole de biopsie du ganglion sentinelle et par la suite effectuées notre protocol sur des patients consécutifs subissant une thyroïdectomie. Les nodules ont été injectés avec du bleu de méthylène. Un dissection du cou central a été effectuée. Examen intra-operatoire des ganglion a été réalisée.

Résultats: 157 patients sont inclus dans cette étude. 94 patients avaient un dissection central du cou. 73% (69/94) des patients ont été trouvés à avoir ganglion détectable. 20% (14/69) des patients atteints de ganglion ont été trouvés à avoir des métastases compartiment central. La sensibilité, spécificité, valeur prédictive positive et valeur prédictive négative de notre technique de biopsie du ganglion sentinelle pour enlever toutes les maladies à partir du compartiment central était de 92,9%, 100%, 100% et 98,8% respectivement (p <0,0001).

Conclusion: Cette série de données volumineux suggère que si un patient a jugé comme négatif intra-operatoire de malignité sur la section gelée, un dissection central peut être preventire.

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Chapter 1: Introduction

The search for occult cervical lymph node metastasis in well-differentiated thyroid cancer (WDTC) is controversial. Given the risks of hypoparathyroidism leading to hypocalcemia, recurrent laryngeal nerve injury, and increased operative time with a central compartment neck dissection (CCND), the routine adoption of prophylactic lymph node dissection has not been accepted by many as standard management in thyroid surgery for WDTC (Henry et al., 1998; Pereira et al., 2005; Shen et al., 2010). Conversely, others feel that the complication rate for CCND is low and that the benefits of CCND outweigh the risks (Anand et al., 2009; Haigh et al., 2000; Keleman et al., 1998; Pelizzo et al., 2001; Pitman et al., 2003; Rettenbacher et al., 2000). As a result of this controversy, sentinel lymph node biopsy (SLNB) may provide an approach that limits surgical morbidity, while addressing the central compartment lymph nodes.

The principle of SLNB and its historical rise in other fields will be the starting point of this introduction. The SLN is defined as the first lymph node in a regional lymphatic basin receiving lymph flow from a primary tumor. For the past seventeen years, SLNB has been an acceptable technique for identifying the presence of metastatic disease for cutaneous melanoma (Morton et al., 1992) and early breast cancer (Giuliano et al., 1994; Krag et al., 1993). Lymphatic mapping with SLN has permitted staging of malignant tumors in an effort to avoid complete nodal dissection

and its associated morbidity. The justification of SLN surgery stems from the plausibility that the pathological status of the sentinel node is predictive of a primary tumor and its potential to metastasize. If the sentinel node is negative, the pathological status of additional lymph nodes is likely to be negative as well. Recently, SLNB techniques have been proposed for other tumor types, including lung, gastrointestinal and gynecologic malignancies (Makar et al., 2001), squamous cell carcinoma of the head and neck [Pitman et al., 2003; Taylor et al., 2001), colorectal cancer (Saha et al., 2000) and thyroid cancer (Pelizzo et al., 2001; Dixon et al., 2000).

To understand the utility of SLNB in thyroid cancer, the cervical lymphatic anatomy will be reviewed. The mechanism of lymphatic tumoral spread in thyroid cancer and the clinical significance of such lymph node metastases will then be discussed. The arguments in favor and against prophylactic CCND will follow thereby providing the context in which the idea of the SLNB shows its advantages in the management of WDTC. The benefits of SLNB over a formal CCND will be discussed with emphasis on the major advantages such as a decreased risk of hypocalcemia, decreased risk to recurrent laryngeal nerve (RLN) injury and decreased operative time. Different techniques of SLN biopsy will then be outlined. A comprehensive review of the literature on the outcomes of sentinel lymph node biopsy in the approach to management of thyroid cancer will then follow. After reviewing the literature, two aspects of WDTC will become evident. First,

there is no clear consensus as to the proper management of clinically and radiologically node negative WDTC. Secondly, SLNB may be the solution to bridging the gap between surgical morbidity and thorough oncological resection of metastatic lymph nodes.

For these two reasons, after reviewing the literature, an institutional SLNB protocol will be specified. Next, a prospective analysis of the utility of our protocol in detecting metastatic thyroid cancer will follow. Then, to highlight the strengths and weaknesses of the technique, a retrospective review of all the patients ever injected at our institution will follow.

Chapter 2: Literature Review

2.1 Sentinel lymph node biopsy as a surgical tool

In the field of oncology, lymph node status is one of the most important prognostic factors and a key element of tumor staging. It is also a guide towards appropriate therapy and is an overall crucial component in the assessment of patients with cancer. The approach to managing metastatic lymph nodes varies from medical treatment to surgery.

2.1.1 The principle

In 1960, Gould (Gould et al.,1960) introduced the concept of the sentinel lymph node. According to him, lymphatic flow is unidirectional, and there is orderly movement of cancer cells from the primary organ to the first lymph node in the chain before spreading to other regional lymph nodes. This first lymph node draining a regional lymphatic basin from a primary tumor is defined as the sentinel lymph node, and its histological status is thought to be representative of the status of the other nodes in the chain. The SLNB technique is most useful when lymph node dissection would be associated with significant morbidity, such as when applied in the inguinal or axillary regions.

2.1.2 The history

In 1992, the technique for lymphatic mapping was first described by Morton (Morton et al., 1992) in patients with melanoma, and was found to be not only simple and practical, but also reliable with a reported false-negative rate of less then 1%. This report introduced modern surgical oncologists to a new surgical technique with a wide range of applications. Subsequently, Giuliano (Giuliano et al., 1994) applied the technique to breast cancer and demonstrated a reliable identification of SLN using a vital blue dye. In the last two decades, SLN biopsy has been validated as an accurate method for assessing regional lymph node status and has gained acceptance as the standard of management for identifying regional lymphatic spread in melanoma and breast cancer. The use of this technique in the management algorithms for thyroid and other solid cancers is under investigation.

2.2 Cervical lymph nodes in thyroid cancer

2.2.1 The anatomy

There are approximately 500 lymph nodes in the body and 200 of these are in the head and neck region (Grodski et al., 2007). Historically, the location of cervical lymphadenopathies has been described in terms of

chains and triangles, but currently, the most used system of nodal mapping anatomically classifies lymph nodes into levels (Sakorafas et al., 2010).

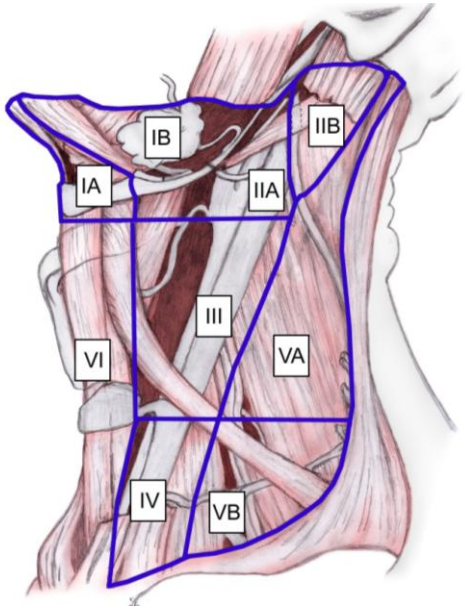

Figure 1. Cervical lymph node levels (from Rugiero, 2008)

Level I is bound by the body of the mandible superiorly, stylohyoid muscle posteriorly, and the anterior belly of the digastric muscle on the contralateral side anteriorly. This level may be divided into level Ia, which refers to the nodes in the submental triangle (bound by the anterior bellies of the digastric muscles and the hyoid bone), and Ib, which refers to the submandibular triangle nodes.

Level II lymph nodes are related to the upper third of the jugular vein, extending from the skull base to the inferior border of the hyoid bone. The anterior border of level II is the stylohyoid muscle, and the posterior border

is the posterior border of the sternocleidomastoid muscle. The spinal accessory nerve, which travels obliquely across this area, is used as a landmark to subdivide this group into IIb, the portion above and behind the nerve, and IIa, the part that lies anteroinferiorly and closer to the internal jugular vein.

Level III nodes are located between the hyoid superiorly and a horizontal plane defined by the inferior border of the cricoid cartilage. The sternohyoid muscle marks the anterior limit of level III, and the posterior border of the sternocleidomastoid muscle is the posterior border.

Level IV refers to the group of nodes related to the lower third of the jugular vein. These nodes are located between the inferior border of the cricoid cartilage and the clavicle, and, like level III, the anterior boundary is the sternohyoid muscle, and the posterior border is the posterior border of the sternocleidomastoid muscle.

Level V refers to the lymph nodes located in the posterior triangle of the neck. These include the spinal accessory, transverse cervical, and supraclavicular group of nodes. Level V is bound anteriorly by the posterior border of the sternocleidomastoid muscle and posteriorly by the anterior border of the trapezius muscle. Level V extends from the apex of the convergence of the sternocleidomastoid and trapezius muscle

superiorly to the clavicle inferiorly as shown below. This level is subdivided by a plane defined by the inferior border of the cricoid cartilage into level Va superiorly and level Vb inferiorly.

Level VI refers to lymph nodes of the anterior, or central, compartment of the neck. Defined by the carotid arteries laterally, the hyoid bone superiorly, and the suprasternal notch inferiorly, it is rich in lymphatics that drain the thyroid gland, subglottic larynx, cervical trachea, hypopharynx, and cervical esophagus. Lymph nodes in this compartment are located in the tracheoesophageal groove (paratracheal nodes), in front of the trachea (pretracheal nodes), around the thyroid gland (parathyroidal nodes), and on the cricothyroid membrane (precricoid or Delphian node). (Rugiero, 2008.)

The thyroid gland contains a dense network of intrathyroidal lymphatics with communication across the isthmus. Lymphatic flow primarily tends to be towards the ipsilateral level VI lymph nodes since thyroid lymphatics usually accompany a venous drainage pattern into the central compartment of the neck (Roh & Kock, 2010). The upper poles, along with the pyramidal lobe and isthmus also drain superiorly toward lymph node levels II/III while the lateral aspect of each lobe drain towards lymph node levels III/IV. The lower pole of the gland drains initially into level VI, and then it goes on to levels IV and VII (Roh & Koch, 2010; Sakorafas et al.,

2010).

2.2.2 Lymph node metastases in well-differentiated thyroid cancer

Papillary thyroid cancer (PTC) is the most common thyroid malignancy. It represents 75% of thyroid malignancy and 90% of well-differentiated thyroid cancers. It spreads predominantly via the lymphatics to the local draining lymph nodes (Balasubramanian & Harrison, 2011). It is generally believed that the central cervical compartment is the primary zone of lymphatic involvement for all thyroid cancers except those located in the upper poles of the thyroid gland from which lymphatic drainage may flow directly into the lateral neck nodes (Henry et al., 1998) In keeping with the theory, Nogychi (Nogychi et al., 1987) in a study of 68 thyroid cancer patients after elective neck dissection, found 78% of nodal metastases in the paratracheal region and 22% in the jugular chain. Many groups have, however, reported that the risk of lymphatic metastases was greatest for the lateral nodal groups (level II, III and IV) **(**Caron et al., 2006; Gimm et al., 1998; Lee et al., 2008; Roh et al., 2007, 2008; Shah et al., 1990) while others have shown comparable rates of involvements in both the cervical and lateral neck compartments (Machens et al., 2002).

Irrespective of location, lymph node metastases are a common finding in PTC. The incidence of lymph node metastases has been reported to be as

high as 90% and the incidence of palpable nodal disease as high as 30%-50% (Dixon et al., 2000; Grodski et al., 2007). Histological evidence of nodal metastases in patients with clinically node negative PTC is approximately 50% (Balasubramanian & Harrison, 2011), but rates anywhere between 25 to 90% have been reported in studies where elective neck dissections were performed on patients without suspicious lymphadenopathy (Cunningham et al., 2010). Interestingly, in a similar group of patients who were observed and did not undergo a neck dissection, the rate of recurrence was only 1.4%, thus questioning the clinical significance of such lymph node metastases. (Kelemen et al., 1998)

2.2.3 Clinical significance of lymph nodes metastases

Most clinical trials confirm that regional nodes are usually the first site of recurrence (Kelemen et al., 1998). In fact, metastases to lymph nodes account for 75% of locoregional recurrence (Grodski et al., 2007). It is estimated that the risk for nodal recurrence is 30% to 50% during a 10 year follow-up for PTC. Others report the overall recurrence rate at 20%, with most of them discovered within 24 months. Of these, 70% are detected through a radioactive iodine whole body scan with only 40% being clinically apparent on ultrasound and clinical exam (Kelemen et al., 1998).

In a series of patients with nodal metastases and a final histological diagnosis of papillary, follicular, or Hürthle cell carcinoma, a recurrence rate of 19% has been recorded vs 2% in patients free of nodal disease (Kelemen et al., 1998). In an age-matched study of patients with differentiated thyroid cancer, recurrences were also more common among patients with nodal involvement (32 vs. 14%) (Grodski et al., 2007). The presence of central node metastases in the lymphadenectomy specimen is therefore an independent predictor of disease free survival, but its actual significance on the overall prognosis remains controversial.

Although PTC lymph node metastases are reported by some to lack clinical significance on outcome of low risk patients, a study among 9904 patients with PTC, found that lymph node metastases, along with other factors predicted poor outcome on multivariate analysis (Podnos et al., 2005). All-cause survival at 14 years was 82% for PTC without lymph node and 79% with lymph node metastases ($p < 0.05$). Another recent study showed that lymph node involvement is an independent risk factor for decreased survival, but only in patients with follicular carcinoma and patients with papillary carcinoma over age 45 years. (Zaydfudim et al., 2008) Multiple metastases and extracapsular nodal extension are other factors that increase the risk of regional recurrence (Leboulleux et al., 2005). However, in an analysis of 5123 patients over a 30-year period,

even when corrected for TNM staging, a significantly higher mortality rate for patients with lymph node involvement has been shown. (Grodski et al., 2007)

Lymphatic spread is associated with increased risk of loco-regional recurrence requiring additional and more complex surgery. This affects patients quality of life not only through the psychological impact of cancer recurrence, but also through increased rates of complications associated with surgery in previously operated necks (Kelemen et al., 1998). Studies have recently shifted focus with regards to the aim of treatment of WDTC, from a focus of mainly on survival to a focus on disease-free status as an endpoint to evaluate the effectiveness of therapy.

2.2.4 Cervical neck dissection in well-differentiated thyroid cancer

While few would argue against a formal therapeutic neck dissection in cases of macroscopic clinically apparent lymph node metastases in patients with WDTC, there is great heterogeneity in the surgical approaches to a clinically and radiologically negative neck. Recommendations in the management of adenopathy associated with PTC are quite varied and include blind nodal sampling, central compartment neck dissection, and modified radical neck dissection (Anand et al., 2009). To eliminate the probability of leaving behind residual

disease, routine total thyroidectomy with cervical lymph node dissection (CLND) would be theoretically the ideal operation. However, such an aggressive surgical approach will represent unnecessary treatment in a large percentage of patients, associated with longer surgical time and an increase in surgical morbidity (Sakorafas et al., 2010). Balancing the risk of increased morbidity from CLND with the benefit of removing the source of potential recurrence creates a controversial and difficult management decision. To help in the decision making process, guidelines for prophylactic CLND have been issued. Unfortunately, they remain vague and unclear with a certain degree of conflicting recommendations. The American Thyroid Association is one of the most respected associations with regards to thyroid management. As can be seen in Figure 2, their guidelines favor elective neck dissection, however the recommendation is vague and allows room for interpretation.

RECOMMENDATION:27*

A. Therapeutic central-compartment (level VI) neck dissection for patients with clinically involved central or lateral neck lymph nodes should accompany total thyroidectomy to provide clearance of disease from the central neck. Recommendation rating: B

B. Prophylactic central-compartment neck dissection (ipsilateral or bilateral) may be performed in patients with papillary thyroid carcinoma with clinically uninvolved central neck lymph nodes, especially for advanced primary tumors (T3 or T4). Recommendation rating: C

C. Near-total or total thyroidectomy without prophylactic central neck dissection may be appropriate for small (T1 or T2), noninvasive, clinically node-negative PTCs and most follicular cancer. Recommendation rating: C

*These recommendations (R27a–c) should be interpreted in light of available surgical expertise. For patients with small, noninvasive, apparently node-negative tumors, the balance of risk and benefit may favor simple near-total thyroidectomy with close intraoperative inspection of the central compartment with compartmental dissection only in the presence of obviously involved lymph nodes. This approach may increase the chance of future locoregional recurrence, but overall this approach may be safer in less experienced surgical hands.

Figure 2: American Thyroid Association Guideline 27

2.2.4.1 Data in favor of prophylactic cervical lymph node dissection

Because of the high rate of occult lymph node metastases, their association with more frequent tumor recurrence, and the limitations of the current imaging modalities to adequately identify these cases pre-operatively, some experts argue in favor of routine prophylactic CLND in cases of WDTC. The British Thyroid Association (BTA) and the American Thyroid Association (ATA) are proponents of the prophylactic CLND (BTA, 2007; Cooper et al., 2009), especially in high risk patients. They maintain that the potential increased morbidity is small in experienced hands and hence a strong argument can be made for routine central CLND in all patients with WDTC and no known preoperative or intra-operative

evidence of nodal involvement. More specifically, the ATA recommends prophylactic CCND for patients with clinically uninvolved lymph nodes, especially for advanced tumors (T3 and T4 disease), and asserts that the CCND may be appropriately omitted for T1 and T2 papillary and follicular thyroid cancers. They also acknowledge that omitting CND for these smaller tumors, ‘‘may increase the chance of locoregional recurrence, but overall may be safer in less experienced surgical hands,’’ to avoid the associated morbidity. This approach to microscopic nodal disease may result in fewer postoperative complications than routine dissection, but may fail to detect lymph node metastases in patients with smaller tumors, and may subject patients with larger tumors who do not have lymph node metastases to unnecessary lymph node resection. In addition, the guidelines allow for interpretation of these recommendations in the light of available surgical expertise at each institution, so that more invasive approaches are only recommended if experienced surgeons are available to carry them out, which is yet another factor contributing to the variability of surgical management.

Besides lower recurrence rates, some authors stat that prophylactic CCND has the advantage of adequate staging, enhancing the effects of radioactive iodine by removing potentially positive lymph nodes while also lowering the postoperative thyroglobulin levels thereby facilitating follow-up. However other authors have refuted this claim. (Grodski et al., 2007;

Sakorafas et al., 2010).

In the discussion about the extent of prophylactic CCND in WDTC, it should be remembered that the impact of the central compartment recurrence differs from that of a lateral compartment LN recurrence. It is generally accepted that lymph node metastases in the visceral compartment of the neck have greater clinical importance than metastases in the lateral neck areas (Henry et al., 1998). Reoperation for recurrence in the lateral compartment can be performed more easily than that for recurrence in the central compartment, where more critical structures (i.e., trachea, recurrent laryngeal nerve, parathyroid glands, great vessels, etc) are located. Since metastases in the central compartment are not uncommon, recurrences in the area are difficult to demonstrate. Also, given that surgery for recurrence in the central compartment may be a complicated procedure, prophylactic CCND during the initial thyroid surgery (usually through the same incision) seems for many to be a reasonable management option (Sakorafas et al., 2010)

2.2.4.2 Data against prophylactic cervical lymph node dissection

The American Association of Clinical Endocrinology, the American Association of Endocrine Surgeons (Cobin et al., 2001) and the NCCN do not recommend routine central CLND, particularly in low-risk patients with

PTC. The argument against prophylactic CLND resides in the added complications associated with the procedure. The possible complications of CCND include hypoparathyroidism leading to hypocalcemia, injury to the recurrent laryngeal nerves, hemorrhage, and seroma (Sakorafas et al., 2010). The morbidity of prophylactic central neck dissection was evaluated in a study of 100 patients who underwent total thyroidectomy of which 50 patients with papillary thyroid cancer and no evidence of macroscopic metastases also had a prophylactic central neck dissection (Henry et al., 1998). In the group that had no neck dissection, there was no permanent hypoparathyroidism, but there were four cases of transient hypoparathyroidism (8%). In the group that underwent the prophylactic procedure, seven patients presented with transient hypoparathyroidism (14%) and two patients (4%) had permanent hypoparathyroidism. The authors concluded that following total thyroidectomy for PTC, prophylactic central neck dissection did not increase recurrent laryngeal nerve morbidity but was responsible for a higher rate of hypoparathyroidism, especially in the early postoperative period (Henry et al., 1998). They attributed the hypoparathyroidism associated with neck dissection to the insufficiency of blood supply generated by the dissection. Similar rates of permanent hypoparathyroidism were reported to be 4.6% (Pereira et al., 2005) with the extent of hypocalcemia correlating with the extent of surgery. A recent study by Mitra showed that total thyroidectomy combined with CCND led to a marked increase in both transient as well as

permanent hypocalcemia (Mitra et al., 2011). These authors therefore concluded that the morbidity of bilateral cervical neck dissection is significant, and one should be cautious of systematically implementing this technique in the absence of gross nodal involvement.

Another factor against routine lymph node dissection is the usefulness of the procedure at preventing recurrence. Recent data has not demonstrated any therapeutic gain in achieving a significant reduction in local recurrence by adding CCND to total thyroidectomy (Zetoune et al., 2010). Despite the high frequency of microscopic lymph node metastases, the recurrence rate in patients with occult nodal disease who did not undergo nodal excision procedures was estimated at a range of 1.4% to 15%, using different patient databases (McHenry et al., 1991; Shen et al., 2010; Takami et al., 2002), while the 5-year mortality rate ranged from 0.9% to 17% (Takami et al., 2002). It therefore appears that for patients undergoing more extensive surgery in presence of a clinically node-negative neck there may be little benefit to prevent recurrence.

2.3 Sentinel lymph nodes biopsy in thyroid cancer

2.3.1 The middle ground in the controversy

The lack of consensus on the matter of prophylactic CLND validates the

need for a modality to accurately predict whether this procedure is necessary. Accordingly, being able to identify those patients who would benefit from nodal dissection before a more extensive procedure is undertaken would improve PTC management (Anand et al., 2009).

Preoperative ultrasound is poor at detecting lymph node metastasis in the central compartment of the neck (Roh & Koch, 2010) while intraoperative palpation and lymph node size assessment are not accurate predictors of lymph node status. (Fukui et al., 2001). In this perspective, the SLN biopsy is theoretically appealing for WDTC since it could detect subclinical lymph node metastases, thereby allowing the formal CCND to be performed only in patients with documented lymph node metastases, thus avoiding the morbidity of CCND in a significant percentage of patients with node-negative disease. In other words, SLN biopsy may be helpful in selecting patients who would benefit from CLND, thus reducing unnecessary surgery and possible morbidity in other patients (Roh & Koch, 2010; Sakorafas et al., 2010).

The main advantage of an accurate SLN biopsy technique would be the identification of node-negative patients with thyroid cancer in whom an unnecessary prophylactic central node dissection could be avoided (Roh & Koch, 2010). It allows the surgeon to alter the surgical procedure intra-operatively. Completing a CCND at the time of initial surgery can also

potentially avoid the higher complication rates that have been reported with reoperation in the central neck compartment. Another advantage of SLN biopsy is that it may help identify patients who are likely to develop a central compartment recurrence at the time of initial operation. The SLN technique may also permit early detection of patients who may benefit from adjuvant radioactive iodine ablation (Anand et al., 2009; Roh & Koch, 2010). Alternatively, biopsies of SLNs may obviate the need for I^{131} treatment in patients with low-risk thyroid cancers with SLNs that are negative for metastases. Furthermore, malignant Hürthle cell tumors and well-differentiated follicular carcinomas are difficult to identify histologically, and SLNB in such cases may aid in establishing the diagnoses if metastases can be identified in SLNs (Takami et al., 2002).

In summary, the SLN biopsy is an alternative approach that may guide the decision to proceed with formal CCND. For this tool to be truly useful, it needs to accurately identify lymph node metastases, have a low false-negative rate, and be associated with less morbidity than CCND. SLN Biopsy for WDTC has therefore been studied in several settings using different techniques; the sections that follow will review this data.

2.3.2 The technique

Since the introduction of the SLN Biopsy in PTC by Keleman et al. several

variations of the technique have been described. The variability resides mainly in the type of dye or isotope injected, the amount injected, the timing of injection, the site of injection, and the subsequent assessment of the SLN. Table 1 modified from the largest meta-analysis of SLN Biopsy in WDTC, summarizes the techniques used in all the studies performed up to now on this topic (Balasubramanian & Harrison, 2011).

Vital blue dyes are the most frequently injected medium with methylene blue, isosulphan blue, and patent blue V being the most common types. In general, methylene blue is the least expensive and seems to generate less hypersensitivity reactions than other dyes. Isosulfan blue has been shown to be the most reactive, since rosaniline dyes are used in many commercially available products, including cosmetics, paper, and textiles. Patients may be sensitized to isosulfan blue by previous exposure to apparently unrelated compounds. Moderate and severe allergic reactions, including anaphylaxis, have been reported in up to 2% of patients receiving isosulfan blue (Kelley and Holmes, 2011). The blue dye disappears during histologic processing and does not affect histologic analysis (Roh and Koh, 2010).

In terms of radioisotopes, different forms of 99m-Technetium labeled colloids have been used. The SLN in these cases is localized either by a marking on the skin overlying the lymph node; alternatively, it can be localized by radiotracer using a gamma-probe intraoperatively.

Reference	*n*	*Population*	*Dye/Isotope*	*Volume injected (ml)*	*Timing of injection*	*Site*	*Assessment of SLN*
Cunningham et al. 2010	211	PTC	1%isosulphan blue	0.5-2	After mobilization	IT	FS and H
Anand et al. 2009	97	Suspicious and PTC	1% methylene blue	0.2-0.3	Before mobilization	PT	H
Takeyama et al. 2009	37	Suspicious and diagnostic	1% sulphan blue	0.1	Before mobilization	PT	FS and H
Lee et al. 2009	54	DTC	2% methylene blue	0.1-0.5	Before mobilization	PT	FS and H
Bae et al. 2009	11	PTC	2% methylene blue	0.5	After strap muscle retraction	IT	FS and H
Roh and Park, 2008	50	PTC	2% methylene blue	0.2	After strap muscle retraction	PT	FS and H
Wang et al. 2008	25	PTC	2% methylene blue	2-Jan	NA	PT	H
Rubello et al. 2006	153	PTC	0.5% patent blue V	0.25ml/cm	After strap muscle retraction	IT	FS and H
Abdella 2006	30	Benign nodules	1% isosulphan blue	0.5-1	After strap muscle retraction	IT	H
Peparini et al. 2006	9	PTC	2.5% patent blue V	0.1-0.2	NA	PT or IT	NA
Falvo et al. 2006	18	PTC	Methylene blue	0.4	After mobilization	IT	H
Dzodic et al. 2006	40	DTC	1% methylene blue	0.2	After strap muscle retraction	PT	FS and H
Chow et al. 2004	15	PTC	2.5% patent blue V	0.5-1	After strap muscle retraction	IT	H
Takami et al. 2003	68	PTC	1% isosulphan blue	0.3	After strap muscle retraction	PT	FS and H
Tsugawa et al. 2002	38	PTC	1% patent blue VF	0.2-0.5	NA	IT	H
Fukui et al. 2001	22	PTC	2% methylene blue	0.1	After mobilization	PT	FS and H (but not all cases)
Arch-Ferrer et al. 2001	22	PTC	1% isosulphan blue	0.5	After mobilization	IT	H
Catarci et al. 2001	8	Suspicious and PTC	2.5% patent blue V	0.2-0.4	Before mobilization	IT	H
Dixon et al. 2000	40	Suspicious and DTC	Isosulphan blue	0.1-0.7	After strap muscle retraction	IT	FS and H

Kelemen et al. 1998	17	Suspicious and DTC	1% isosulphan blue	0.1-0.8	After strap muscle retraction	IT	FS and H
Lee et al. 2009	43	DTC	99mTc-labelled tin colloid	0.1-0.2	Preop US	IT	FS and H
Boschin et al. 2008	65	PTC	99mTc-labelled nanocolloid	0.1-0.2	Preop US	IT	FS and H
Carcoforo et al. 2007	64	Suspicious and PTC	99mTc-labelled nanocolloid	0.3	Preop US	PT	H
Stoecki et al. 2003	10	Suspicious and DTC	99mTc-labelled sulphur colloid	0.2	Preop US	PT and later IT	H
Catarci et al. 2001	8	Suspicious and PTC	99mTc-labelled colloidal albumin	0.1	Preop US	IT	H

(Adapted from Balasubramanian & Harrison, 2011)

Table 1: Characteristics of studies evaluating sentinel lymph node biopsy in thyroid surgery

Legend: SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy; PTC, papillary thyroid cancer; IT, intratumoral; PT, peritumoral; FS, frozen section; H, histology; DTC, differentiated thyroid cancer; US, ultrasound; NA, data not available.

2.3.3 Review of outcomes

Keleman et al, in 1998, were the first to report the use of SLN biopsy in thyroid cancer. Isosulfan blue dye was injected in 17 patients with thyroid neoplasms and the SLN was identified in 15 patients. SLN detection was missed in 11.8% of patients due to retrosternal localized SLN's, moreover false-negative cases constituted 8%. Haigh & Giuliano in 2000 performed SLN biopsy in 17 cases and identified metastasis in 56% of cases. Notably, a control neck dissection was not carried out in all patients in both of these studies, and as such, positive and negative predictive values could not be determined. In a recent study Cunningham performed a retrospective review of 211 patients and concluded that SLN biopsy is feasible, safe and can identify patients who may benefit from CCND. As in the other previous studies, however, a CCND was not performed on all patients and thus a false negative rate could not be determined (Cunningham et al., 2010).

Given its aim of identifying patients who do not require CCND, the single most critical qualitative descriptor for SLN biopsy is the false-negative rate (FNR). This requires comparison of SLN biopsy to the gold standard for the identification of occult metastases. The gold standard used varies from study to study. Most frequently, a control neck dissection is performed in all cases with its extent going from CCND to a formal modified lateral neck

dissection passing through a localized dissection of non-sentinel lymph nodes above and below the omohyoid (Dzodic, 2006) Another study used I^{131} whole body scan as the gold standard to help define the true-positive and true-negative SLN (Dixon et al., 2008).

Fukui et al conducted a study in 2001 on 22 patients with PTC who underwent a control lateral and central compartment neck dissection. SLN's were found in 21 of 22 patients and the prediction of disease status was accurate in 19 of 21 patients (90%). Two false negatives were reported in this study. Using peritumoral injection of blue dye, Takami et al (2002) reported a 12.5% SLN FNR in a prospective study of 68 patients. Similarly, Roh et al (2007) reported a 22% FNR using peritumoral blue dye in 50 patients. In 2009, Anand et al published the largest prospective series on SLN biopsy to date (N = 98) showing the reliability of SLN biopsy in the management of WDTC. The study showed a sensitivity of 100% that a negative SLN on permanent pathological analysis represents a negative central compartment. The primary goal of the study was to determine if the SLN in WDTC was indeed a sensitive predictor of the status of the central compartment while avoiding the possible confounding affect of frozen section analysis. For this reason frozen section analysis was not performed.

A systematic review and meta-analysis of sentinel node biopsy in thyroid

cancer was recently published and looked at all the possible outcomes with the use of this technique (Balasubramanian & Harrison, 2011). Twenty-four studies were included in the analysis and great heterogeneity in techniques, assessment methodology and extent of nodal surgery were noted. The overall detection rate of SLN was 86.3% (blue dye 83.7%, and radioisotope 78.4%). The combined use of blue dye and radioisotope reached a detection rate of 96%. Sentinel lymph nodes with evidence of metastasis were present in 42.9% of patients with PTC and an identified SLN. Following this positive SLN biopsy, 60.5% of patients had additional lymph node metastasis identified on the neck dissection. The FNR of the blue dye technique was 7.7% while the radioisotope technique had a FNR of 16%. The combined FNR was 0%. This meta-analysis also evaluated the methods of assessment of SLN biopsy. It demonstrated that in this context frozen section was not as reliable as permanent pathological analysis since it had a FNR of 12% (i.e. the frozen section was negative but the final histopathology of the same lymph node was positive). However, with the use of intraoperative immunohistochemical staining such as anticytokeratin and antithyroglobulin antibody, additional cases could be adequately identified thereby decreasing the FNR. This analysis concluded that SLN biopsy in thyroid cancer is a promising technique that has the potential to avoid prophylactic lymph node surgery in up to 57% of patients with clinically node-negative thyroid cancer. At this stage the data is still inconsistent and there appears to be a need for a more rigorous

assessment of the SLN biopsy technique in thyroid cancer.

However, with all this data, critical analysis finds that the two largest series are retrospective reviews and the largest prospective study did not include frozen section analysis in there results. This shows that a large prospective analysis that is clinically applicable with the use of frozen section is still needed.

2.3.4 Pitfalls of sentinel lymph node biopsy in papillary thyroid cancer

2.3.4.1 The false-negative rate

As described above, despite the more promising recent studies, FNRs as high as 22% have been reported and remain a serious concern regarding the value of SLN biopsy (Sakorafas et al., 2010). Others have demonstrated that false negative SLN happen even in cases of grossly positive metastatic PTC in the neck and have hypothesized that this is possibly occurring because the normal path of lymphatic drainage was blocked by tumor-laden lymphatics (Dixon et al., 2000). In addition to blockage of lymphatics by tumor, lymphatic disruption during dissection of the thyroid nodule could also explain that an otherwise positive lymph node may be missed.

It is also likely that the extensive lymphatic network in the neck complicates the practical application of the theoretical concept of SLN biopsy in patients with thyroid cancer (Sakorafas et al., 2010). Noguchi et al., in 1987, demonstrated that up to 7% of thyroid metastases appear in the lateral compartment only, bypassing the central lymph nodes, which could explain the false-negative rate in studies limited to examining LNs in the central neck compartment.

Furthermore, the concept of “SLN blind spot” was introduced by some authors to account for some of the false-negative cases. They describe three such cases where a blue node adherent to the substance of the thyroid gland was found ex vivo by the pathologist, and might have not been found intraoperatively because the blue-stained thyroid gland masked the blue tract and blue node (Cunningham et al., 2010).

2.3.4.2 Adverse events related to sentinel node biopsy

In addition to the complications associated with a CCND that can follow a positive SLN biopsy, the procedure of the SLNB has in itself been associated with some adverse events. One study has reported permanent hypoparathyroidism secondary to removal of a parathyroid gland that stained blue (Cunningham et al., 2010). Various dermatologic

manifestations to the blue dye have also been reported. For instance, methylene blue, despite its safety record, has been associated with intense erythema, superficial ulceration, and on one patient a necrotic lesion (Kelley & Holmes 2011). Methylene blue-induced skin necrosis results from oxidation of surrounding tissues causing breakdown of cell membranes and inflammation, as well as a local vasoconstrictive effect due to an inhibitory effect of methylene blue on nitric oxide. No increase in recurrent laryngeal nerve injury rates associated with SLN biopsy have been reported (Roh & Koch, 2010).

2.4 Conclusion of literature review

The management of occult cervical lymph node metastasis in WDTC is controversial. The SLN biopsy is a safe and accurate method for assessing the possible involvement of the cervical lymph nodes by a primary thyroid tumour which allows for intraoperative decision making regarding the extent of neck dissection needed in each case. Despite the promising data, it might be too early to consider the SLN biopsy technique as a standard of care in the management of patients with thyroid cancer. A large prospective series is needed to establish it as an effective technique.

Chapter 3: Rational and Objectives

The search for occult cervical lymph node metastasis in WDTC is controversial. Given the risks of hypoparathyroidism leading to hypocalcemia, recurrent laryngeal nerve injury, and increased operative time with a CCND the routine adoption of prophylactic lymph node dissection has not been accepted by many as a standard of care in thyroid surgery for WDTC.

At our institution, where CCND is routine in WDTC, the largest prospective series on SLN biopsy to date (N = 98) was published showing the reliability of SLN biopsy in the management of WDTC (Anand et al., 2010). The study showed that a negative SLN on permanent pathological analysis represents a negative central compartment (sensitivity = 100%). The primary goal of this original study was to determine if the SLN in WDTC was indeed a sensitive predictor of the status of the central compartment while avoiding the possible confounding effect of frozen section analysis. For this reason frozen section analysis was not performed at that time.

The primary objective of this thesis is to design and implement a SLN biopsy protocol and subsequently perform it on consecutive patients undergoing thyroidectomy to determine whether pathologists can accurately determine the status of the SLN on frozen section analysis

while the patient is still under general anaesthesia. This would allow for direct clinical applicability of SLN biopsy in the management of WDTC.

Also, to date, no studies or case reports have examined the pitfalls of this technique within the context of WDTC. Therefore, following prospective analysis of our data, a retrospective analysis of all failed patients will be performed in an attempt to understand the potential and common errors encountered when employing this technique.

Chapter 4: Materials and Methods

4.1 Patient Selection

Patients were selected from the three McGill University adult teaching hospitals that are part of the McGill University Thyroid Cancer Center in Montreal, Quebec, Canada. Selection criteria included consecutive patients undergoing thyroidectomy for nodules suspicious for WDTC. Exclusion criteria included medullary and anaplastic thyroid cancer, patients with benign disease (chronic thyroditis and Graves disease), previous surgery on the thyroid gland, pregnancy or active breastfeeding, and known local or distant metastasis. The McGill University institutional review board approved the study, and written informed consent was obtained from each patient. Patient recruitment began in June 2009 and ran until May 2010. During this time, one patient was excluded from the study because they did not give informed consent.

4.2 Institutional Protocol

We designed our institutional protocol as described below (Figure 3). Following separation of the strap muscles to expose the thyroid nodule, a total of 2cc of methylene blue are injected in the four quadrants surrounding the tumor, using a tuberculin syringe. Following injection, one

minute is set aside to allow for diffusion of the dye without manipulation of the gland. The lymphatic channels which stain blue (tract of blue dye, Figure 4) are then followed into the central compartment and the associated blue-stained lymph nodes are harvested and sent for frozen section analysis (Figure 5). Thyroidectomy is then performed. When no blue lymph nodes are identified, thyroidectomy is performed. In either case, re-examination of the central compartment is performed after thyroidectomy and all blue nodes are sent for frozen section analysis. All frozen section samples are submitted for permanent analysis following intra-operative assessment. A bilateral CCND is performed on all patients prior to closure of the wound.

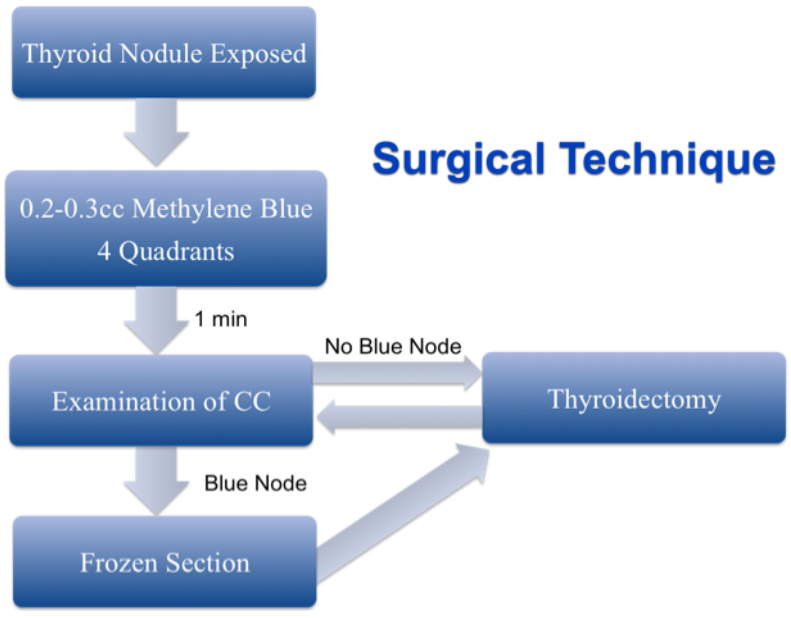

Figure 3: Summary of the McGill Thyroid Injection Protocol

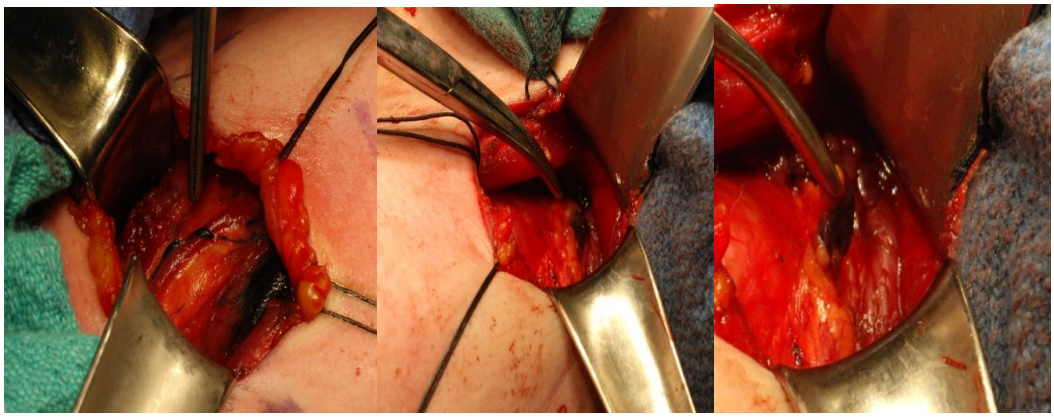

Figure 4: Technique of SLN biopsy. Moments after injection of methylene blue, a tract of blue dye is seen heading towards the central compartment and pooling inside the SLN.

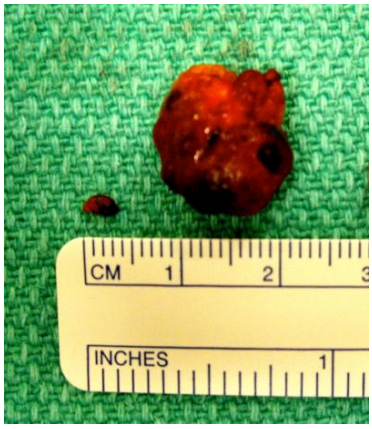

Figure 5: The two lymph nodes above stained blue and were sent for frozen section analysis.

4.3 Samples taken

All patients had their formal CCND and SLN biopsy sent for final pathological analysis. The SLN biopsy was also sent intraoperatively for frozen section analysis. Demographic and pertinent clinicopathological information including age, sex, preoperative risk, preoperative ultrasound, and preoperative fine needle biopsy result was obtained for each patient.

4.4 Statistical analysis

Primary outcome data was placed in 2x2 contingency tables and analysed for sensitivity, specificity, positive predictive value and negative predictive value.

4.5 Pitfalls analysis

Following prospective analysis of the primary outcome data, a retrospective review of the failed patients was performed in an attempt to better understand the weaknesses and pitfalls of the SLN biopsy protocol. For all failed patients a thorough review of the pathology including a discussion with the pathologist was conducted.

Chapter 5: Results

Two hundred and seventy one patients (N=271) were treated with the SLN biopsy institutional protocol. 157 patients underwent frozen section analysis and are included in this analysis (N=157). Demographics of the patients included 128 females and 29 males with a mean age of 48 (SD 13). The distribution of final thyroid pathology is listed in Table 2. Thyroid cancer was found in 94 of 157 patients (60%). There were no observed complications resulting from injection of methylene blue. A blue SLN was identified and sent for frozen section analysis in 69 of the 94 patients (73%) with thyroid cancer. Lymph node metastasis was found in 14 of 69 cancer patients (20%) with detectable SLNs. No patients (0/25) with undetectable SLNs were found to have central compartment metastasis. 12/14 patients with metastatic disease had papillary carcinoma (classical type); the two remaining had papillary thyroid cancers that were < 1cm, but were identified grossly.

Table 2: Distribution of thyroid gland pathology		
Histological subtype		**Total no. of Patients**
Malignant		94
	Papillary Thyroid Carcinoma Classic Type	37
	Follicular Varient of Papillary Thyroid Carcinoma	13
	Oncocytic Varient of Papillary Thyroid Carcinoma	5
	Hurthle Cell Varient of Papillary Thyroid Carcinoma	1
	Papillary Microcarcinoma	35
	Follicular Carcinoma Classic Type	3
Benign		63
		Total: 157

3/157 patients enlisted in the protocol were considered failures or false negatives (1.9%). Out of these three patients, after SLN biopsy we would have left behind malignancy in only one patient if a CCND was not performed. These patients all had benign SLNs based on frozen section while ultimately harboring a malignancy on final pathology.

A detailed discussion of the false negatives follows:

Patient 32: The frozen section could not be assessed without sacrificing the possibility of obtaining a permanent section. SLN biopsy declared “likely negative – crushed node” on frozen section. SLN biopsy was positive for malignancy on permanent section. The CCND was negative for malignancy.

Patient 74: The frozen section could not be assessed without sacrificing the possibility of obtaining a permanent section. SLN declared “likely negative – crushed node” on frozen section. SLN biopsy was positive for malignancy on permanent section. The CCND was negative for malignancy.

Patient 117: Multifocal malignancy. A dominant nodule was present on the right, measuring 4 cm with multiple secondary, smaller nodules. SLN biopsy was benign on frozen section. SLN biopsy was benign on permanent analysis. CCND isolated one lymph node positive for metastatic disease.

Fisher exact test was used to evaluate for any statistically significant associations among SLN metastases and central compartment metastases. Table 3 shows the 2X2 contingency table used for data

analysis. The sensitivity, specificity, positive predictive value and negative predictive value of our SLN biopsy technique to remove all disease from the central compartment were 92.9% (95% CI, 64.2%-99.6%), 100% (95% CI, 94.3%-100%), 100% (95% CI, 71.7%-100%), 98.8% (95% CI, 92.3%-99.9%), respectively ($p < 0.0001$).

Table 3: Fisher Exact 2X2

Contigency Table

	(+) Metastasis	(-) Metastasis	Totals	
(+) SLN / All Mets Removed	13	0	13	PPV = 100%
(-) SLN / Not all Mets Removed	1	80	81	NPV = 98.8%
Totals	14	80	94	
	Sensitivity = 92.9%	Specificity = 100%		

Chapter 6: Discussion

6.1 Clinical significance of results

Our results show that our institutional protocol is effective at detecting the presence of nodal metastasis to the central neck compartment. It is important to highlight that our protocol would have spared a CCND in 144 of the 157 patients enrolled in this study.

6.2 Relation to the literature

The incidence of lymph node metastasis without gross neck adenopathy in WDTC ranges from 27-80%. This large variation is likely the result of variant approaches to management of cervical nodes including blind nodal sampling, "berry picking" of palpable lymph nodes, elective CCND, and modified radical neck dissections. Given the lack of consensus and stark controversy, selected authors have proposed the use of SLN biopsy in patients with clinically occult lymph node metastasis.

Keleman et al were the first to report the use of SLN biopsy for thyroid carcinoma. Isosulfan blue dye was injected in 17 patients with thyroid neoplasms and the SLN was identified in 15 patients. SLN detection was missed in 11.8% of patients due to retrosternal localized SLNs and false-

negative cases constituted 8%. Haigh & Giuliano performed SLN biopsy in 17 cases and identified metastasis in 56% of cases. Notably, a control neck dissection was not carried out in all patients in both of these studies, and as such, positive and negative predictive values could not be determined (Haigh et al., 2000). Fukui et al used methylene blue in 22 patients with papillary thyroid carcinoma. All patients underwent a control lateral and central compartment neck dissection. SLNs were found in 21 of 22 patients and the prediction of disease status was accurate in 19 of 21 patients (90%). Two false negatives were reported in this study (Fukui et al., 2001). In a recent study Cunningham et al performed a retrospective review of 211 patients and concluded that SLN biopsy is feasible, safe, and can identify patients who may benefit from CCND. As in the other previous studies, however, a CCND was not performed on all patients and thus a false negative rate could not be determined.

6.3 Significance of this research

To date, no large series has been able to prospectively suggest implementing the technique into clinical practice. Careful review of the literature shows that the largest sample studies were retrospective, had small sample sizes, and did not include frozen section analysis (Table 4). For this reason, our institution sought to prospectively evaluate the concept of SLN biopsy in WDTC in two distinct phases. Our first report

aimed to determine if the status of the SLN was able to determine the status of the remaining central compartment. Frozen section analysis was initially not reported on to avoid a confounding variable and to fully understand the primary echelon lymphatic drainage of WDTC. The study was able to state that if the SLN was negative for metastasis on permanent pathological analysis, then the remaining central compartment was also free of metastasis and a formal CCND could be avoided. This thesis is the link between the first study and serves to formally evaluate the application of frozen section analysis in SLN biopsy in WDTC. We have shown that our protocol is both highly sensitive and specific for determining the status of the central compartment.

The most clinically significant contribution to the patient would be to spare recurrence, future surgery, possibly improve survival and finally increase the likelihood that all malignant lymphadenopathy is removed while sparing unnecessary surgery, however this can not be directly extrapolated from the data obtained. This data only shows that the SLN protocol presented is accurate at detecting the presence of central compartment metastasis.

6.4 Problems encountered

Our institutional protocol has some drawbacks, as demonstrated by three of the patients. In the cases of patients 32 and 74, the initial intraoperative pathology report, based on the frozen section, came back as benign. The pathologist on service had labeled the sample as a crushed node, and based on gross examination, deemed it likely negative. It was not examined under the same guidelines as the other frozen sections in an attempt to spare sample for permanent section, which has been previously shown to be a strong predictor (3). While frozen section analysis does not demand a specifically trained head and neck pathologist, the SLN biopsy technique may warrant the use of one. Given that lymph nodes harboring metastatic disease can be as small as 3 mm, the problem of a “crushed node” or a sample small enough that it may sacrifice permanent section is not uncommon (3). Formal experience in this setting may help the pathologist better guide surgical decisions regarding CCND.

With respect to patient 117, multifocal disease was present. The dominant nodule was addressed by the protocol as delineated above. The SLNs that were sent for frozen section were free of malignancy, and this result was corroborated by permanent section. Unfortunately, the CCND revealed a lymph node that was malignant, thus corresponding to a failure of the protocol. While only speculative at this point, we hypothesized that while the dominant nodule may have been malignant, a non-dominant nodule also harboring disease that was not injected with methylene blue may

have been the source of metastasis. In this study, we only injected the primary or dominant nodule, and while it may not be feasible to inject all nodules, future studies may be necessary to develop an approach to multifocal disease.

To date, there have not been, to our knowledge, any case reports or retrospective studies assessing the common pitfalls or sources of error in the SLN biopsy technique for WDTC. Some literature has extended speculative comments as to sources of false negatives, varying from direct spread to the lateral compartment of metastatic disease, or adherence of the sentinel node to the thyroid itself (thus preventing detection as a separate blue entity) (Kelemen et al., 1998; Cunningham et al., 2010). In our study, these potential drawbacks were encountered.

From experience, we have noted that during injection, spillage of the dye may cause problems in identification of the SLN, recurrent laryngeal nerve and parathyroid glands. This can, however, be easily overcome by slow intratumoral or peritumoral dye injection and immediate blotting of spillage at the injection site.

Another limitation of this study was that the benefits of sparing a patient from a CCND was not evaluated as all patients underwent CCND. For this reason comparing the added cost of intra operative frozen section with the

potential cost saving from sparing a CCND could not be done and a formal cost benefit analysis was not performed. Moreover, sparing a CCND on a patient may also have the benefit of decreasing operative time and decreasing the incidence of postoperative hypoparathyroidism and recurrent laryngeal nerve injury.

6.5 Injection material

No complication occurred with injection of methylene blue in this study. Methylene blue dye was selected over radionucleotide injection followed by gamma probe as our goal was to utilize and evaluate a technique that is reliable, economical, and easily executable while minimizing additional surgical time. The complete SLN protocol adds less than 5 minutes of operative time. The results establish the efficacy of this technique and illustrate there is no additional need of a radionucleotide tracer that is more time consuming and costly.

Chapter 7: Conclusion

Implementing a new screening tool to detect the presence of lymph node metastases into clinical practice requires certain features to be present. It must be highly sensitive. If the SLN is negative then the surgeon will be confident that no disease remains in the central compartment. The screening test must also lead to a benefit for the patient. This protocol has a sensitivity of 93% and a negative predictive value of 98.8% for removing all metastases from the central compartment. This is a significant finding that will change the current practice of performing CCND on patients with WDTC. Certain pitfalls still need to be addressed, including developing a protocol for patients with multiple thyroid tumors. Also, randomized controlled clinical trials are necessary to determine whether occult nodal metastases play a clinically significant role in quality of life surveys, as well as long-term survival and disease-free survival in patients with WDTC.

Statement of Originality

To my knowledge, this is the largest prospective series to date examining the sensitivity, negative predictive value and logistics of SLN biopsy in WDTC. The findings support the use of our protocol to minimize operative time and potential complications related to CCND.

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Appendix I: Consent forms

CONSENT FORM

SENTINEL LYMPH NODE BIOPSY IN PAPILLARY THYROID CANCER

Investigators: Dr. Keith Richardson**,** Dr Richard Payne, Dr Michael Hier, Dr Martin Black, Dr Michael Tamilia, Dr Louise Rochon, Dr Roger Tabah, Dr Olga Gologan, Dr Jack Howe, Dr Sumeet Anand

Introduction

Thyroid cancer annually affects thousands of individuals throughout North America, however unlike other cancers, thyroid cancer is almost always curable. The most common types of thyroid cancer, known as papillary, follicular or mixed papillary and follicular forms are the most curable with 5 and 10 year survival rates in excess of 95%.

The most effective form of treatment for thyroid cancer is surgical excision. There is a growing body of literature based on long-term follow-up advocating removing as much of the thyroid gland as possible. This assertive form of management will reduce the chance for recurrence and optimize subsequent non-surgical measures such as radioactive iodine

therapy. In about 30% of patients, the cancer may spread from the thyroid gland to nearby lymph glands in the neck. In these instances, the lymph glands should be removed by an operation called a neck dissection. The extent of the removal partially depends on the number of nodes affected by the cancer. The current best treatment calls for a total thyroidectomy and total lymph node dissection.

The sentinel lymph node is defined as the first lymph node in a regional lymphatic basin to receive flow from a tumour. A technique of identifying these nodes by locally injecting a safe, coloured dye is the standard of treatment for skin melanoma and early breast cancer. This technique has also been used in gynecologic, head and neck, colorectal and thyroid cancer. Identifying the specific nodes involved in a tumour can help avoid additional dissection.

Purpose of the study

At McGill we aim to further understand the benefits of sentinel lymph gland identification for the treatment of papillary thyroid cancer. The reason for this study is to understand tumour spread in this disease, which may ultimately help improve the treatment of papillary thyroid cancer. The current standard of practice at many leading thyroid cancer centers worldwide, including the McGill University Health Center, calls for

complete removal of the thyroid gland and all lymph nodes draining the thyroid gland.

Study Procedure

All patients will have the entire thyroid gland and associated lymph glands removed. Lymph glands identified by a methylene blue dye as well as those not identified will be analyzed in the same manner by a trained surgical pathologist. There are no additional costs or compensation for participation. Injection of the dye will add a maximum of up to 1 to 2 minutes to the surgery. We aim to enroll one hundred patients in this study.

Benefits

The patient will not receive any additional benefit from being either included or excluded from this study. Regardless of whether the patient is involved in the study, the care will be of the same high standards.

Risks

The risks associated with thyroid cancer surgery are extremely rare in the hands of an experienced surgeon. Removal of the thyroid gland and

associated lymph glands slightly increases the risk of a transient deficiency in calcium by the temporary injury of nearby parathyroid glands. The potential for damage to the recurrent laryngeal nerve that controls the vocal cords is also rare. In less than 1-2% of patients, methylene blue dye may cause an allergic reaction. In extremely rare instances, methylene blue dye has caused temporary tattooing or ulceration of internal tissues.

Alternative Methods

The alternative management to participation in this study is to undergo removal of the additional lymph glands without the use of the identifying methylene blue dye. Treatment by each method is a respected option for care; the same lymph node groups will be removed independent of participation in the study.

Subjects Rights

Participation in this study is entirely voluntary. It is the right of the patient to:

1) Ask questions at any time

2) Refuse to participate in the study without penalty or loss of benefits to which the subject is otherwise entitled

Confidentiality

The information collected in this study will be kept completely confidential and the patient shall remain anonymous. There will be no way to identify the patients from the results of this study or in the publication of any scientific paper. Research data will be available only to the above listed members of our research team. Data will be stored on a password-protected computer and discarded following the completion of this study. This consent form will be placed in your medical records. Patient's research data or files may be reviewed by representatives from the Research Ethics Board to ensure their protection.

Questions and Contact Information

The participant, or participant's family or representative, may contact Dr Keith Richardson at 514 406-7864 or Dr Richard Payne at 514 340-8246 for any questions or in the event of any side effects.

A Patient Representative (ombudsman) is available to you and your family, in case you have any questions regarding your rights as a study participant. The Patient Representative can be reached at (514) 340-8222 local 5833 at the Jewish General Hospital, at (514) 934-1934 local 35655

at the Royal Victoria Hospital, or at (514) 934-1934 local 43806 at the Montreal General Hospital.

Consent

The study has been explained to me and my questions have been answered to my satisfaction. I have read the contents of this consent form and agree to participate in this study. I do not waive my legal rights by signing this consent form. I will receive a copy of this consent form for my records.

_____

Patient's name Signature of the patient

Date_____

_____

Investigator/delegate name Signature of investigator/delegate

Date_____

FORMULAIRE DE CONSENTEMENT

BIOPSIE DU GANGLION LYMPHATIQUE SENTINELLE POUR LE CANCER PAPILLAIRE DE LA THYROÏDE

Chercheurs : Dr Keith Richardson**,** Dr Richard Payne, Dr Michael Hier, Dr Martin Black, Dr Michael Tamilia, Dr Louise Rochon, Dr Roger Tabah, Dr Olga Gologan, Dr Jack Howe, Dr Sumeet Anand

Introduction

Le cancer de la glande thyroïde affecte des milliers de Nord-Américains chaque année. Cependant, à la différence des autres types de cancer, le cancer de la glande thyroïde est pratiquement toujours guérissable. Les types de cancer thyroïdien les plus répandus, de formes papillaire, folliculaire ou papillaire et folliculaire combinée, sont les types les plus susceptibles d'être soignés avec un taux de survie de 5 à 10 ans dans plus de 95 % des cas.

Le traitement le plus efficace du cancer thyroïdien est l'excision chirurgicale. Un nombre croissant d'études basées sur le suivi à long terme préconise de retirer la plus grande partie possible de la glande thyroïde. Cette forme de traitement réduit les risques de rechute et

optimise les traitements non chirurgicaux subséquents, telle la radiothérapie à l'iode. Chez près de 30 % des patients, le cancer peut s'étendre de la glande thyroïde aux ganglions lymphatiques avoisinants dans le cou. Dans ce cas, il faut retirer les ganglions lymphatiques par une opération appelée dissection du cou. L'ampleur du retrait dépend du nombre de ganglions affectés par le cancer. Le meilleur traitement à ce jour consiste en une thiroïdectomie totale ainsi que le retrait des ganglions lymphatiques.

Le ganglion lymphatique sentinelle est le premier ganglion du bassin lymphatique local qui reçoit l'écoulement d'une tumeur. Il existe une technique afin d'identifier ces ganglions : elle consiste à injecter une teinture inoffensive, comme c'est le cas au cours du traitement normal du mélanome cutané ou du traitement précoce du cancer du sein. Cette technique est aussi employée dans le traitement gynécologique ainsi que dans le dépistage de cancers du cou ou de la tête, du cancer colorectal et du cancer de la thyroïde. L'identification des ganglions spécifiques impliqués dans une tumeur permet d'éviter des ablations supplémentaires.

Objet de l'étude

Au Centre universitaire de santé McGill nous cherchons à mieux comprendre les bienfaits de l'identification du ganglion lymphatique

sentinelle dans le cas du traitement du cancer papillaire de la thyroïde. Le but de cette étude consiste à comprendre comment une tumeur se propage dans le cas de cette maladie, ce qui permettra éventuellement d'améliorer le traitement du cancer papillaire thyroïdien. Les pratiques actuelles utilisées par les plus importants centres de traitement du cancer thyroïdien, dont fait partie le Centre universitaire de santé McGill, ont recours au retrait complet de la thyroïde et des ganglions lymphatiques qui drainent la thyroïde.

Déroulement de l'étude

Tous les patients se feront retirer la glande thyroïde ainsi que les ganglions lymphatiques associés. Un pathologiste spécialisé procédera à l'analyse des ganglions marqués par la teinture de bleu de méthylène ainsi que ceux qui n'ont pas été marqués. La participation à l'étude n'entraîne aucuns frais additionnels ni compensation. L'injection de la teinture ajoutera une à deux minutes à la durée de la chirurgie. Nous cherchons à recruter 100 patients pour cette étude.

Indemnités

Le patient ne recevra aucune indemnité additionnelle, qu'il soit admis à cette étude ou qu'il en soit exclu. Le patient recevra la même qualité de soins, qu'il participe à cette étude ou non.

Risques

Les risques associés à une opération dans le cas d'un cancer de la thyroïde sont rares lorsqu'un chirurgien expert procède à l'intervention. Le retrait de la glande thyroïde et des ganglions associés accroît légèrement les risques momentanés de carence en calcium suite à l'endommagement temporaire des glandes parathyroïdes avoisinantes. L'endommagement possible du nerf laryngé récurrent qui contrôle les cordes vocales est rare. Chez moins de 1 à 2 % des patients, le bleu de méthylène peut causer une réaction allergique. Il est extrêmement rare que la teinture au bleu de méthylène cause une coloration ou une ulcération temporaire des tissus internes.

Méthodes alternatives

Le traitement alternatif à la participation consiste en l'ablation des glandes lymphatiques additionnelles sans le recours à la teinture au bleu de méthylène. L'une ou l'autre des méthodes constitue un traitement

acceptable; le même groupe de ganglions sera retiré, indépendamment de la participation du patient à l'étude.

Droits du patient

La participation à cette étude se fait sur une base volontaire. Le patient a le droit :

1) de poser des questions à tout moment;

2) de refuser de participer à l'étude sans être pénalisé ou encourir de perte de quelque indemnité à laquelle il avait droit autrement.

Confidentialité

Les informations rassemblées au cours de cette étude sont strictement confidentielles et l'anonymat du patient est préservé. Il ne sera possible en aucune façon d'identifier les patients à partir des résultats de cette étude ou de la publication de tout article scientifique. Les données de la recherche ne seront disponibles qu'aux membres inscrits de l'équipe de recherche. Les données seront conservées sur ordinateur et protégées par un mot de passe, puis supprimées une fois l'étude complétée. Ce formulaire de consentement sera conservé dans votre dossier médical.

Les données concernant les patients peuvent être consultées par le Comité d'éthique de la recherche dans le but d'en assurer la protection.

Questions et informations

Les participants, les membres de la famille de participants ou leurs représentants peuvent s'adresser à Dr Keith Richardson au 514-406-7864 ou à Dr Richard Payne au 514-340-8246 pour toute question relative aux effets secondaires.

Un représentant du patient (Commissaire aux plaintes et à la qualité) est aussi disponible pour vous ou votre famille si vous souhaitez obtenir des informations au sujet de vos droits à titre de participant à cette étude. Il est possible de rejoindre un représentant au 514-340-8222, poste 5833 à l'Hôpital Général Juif, au 514-934-1934, poste 35655 à l'Hôpital Royal Victoria ou au 514-934-1934, poste 43806 à l'Hôpital Général de Montréal.

Consentement

On m'a informé au sujet de cette étude et on a répondu à mes questions de façon satisfaisante. J'ai lu le contenu de ce formulaire de consentement et je consens à participer à cette étude. Je ne renonce à

aucun droit légal en signant ce formulaire de consentement. J'obtiendrai une copie de consentement pour mes dossiers personnels.

_____

Nom du patient Signature du patient Date

_____

Nom du chercheur/délégué Signature du chercheur/délégué Date