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Current Innovations and Opinions in the Surgical Management of Differentiated Thyroid Carcinoma

Brian Hung-Hin Lang

*Department of Surgery, University of Hong Kong Medical Centre, Queen Mary Hospital,
Hong Kong SAR,
China*

1. Introduction

Over the last decade, surgeons have witnessed dramatic changes in the surgical management of differentiated thyroid carcinoma (DTC). This is not only a result of the introduction of new technologies in surgery but also a result of better understanding of the disease and its behavior. DTC accounts for over 90% of all follicular-cell derived thyroid malignancies and is the commonest primary endocrine-related malignancy. In our locality, its age-adjusted incidence has doubled over the last 20-25 years with a similar trend being observed elsewhere. (Hong Kong Cancer Registry, 2011) Despite this, the cancer-specific mortality remains low with an overall 10-year survival above 90%. (Lang et al., 2007a) However, recurrent or persistent disease after seemingly curative surgery poses a problem for both clinicians and patients. (Mazzaferri et al., 2001) Since surgery remains to play a pivotal role in the overall management of DTC, the primary aim of any new changes would be to further reduce and if possible, to prevent these recurrences or persistent diseases from occurring. Examples of some of these new changes would include: 1. the adoption of new, innovative surgical approaches (i.e. endoscopic, robot-assisted and trans-oral thyroidectomy) in surgical management of DTC in order to reduce the surgical morbidity, shorten hospital stay and enhance patient satisfaction; 2 the use of several surgical adjuncts such as new alternate energy sources (Harmonic scalpel (Ethicon), Sonosurg® (Olympus) and LigaSure™ (Valleylab), intraoperative nerve monitoring (IONM) and quick intraoperative parathyroid hormone assay (IOPTH) 3. the routine adoption of prophylactic central neck dissection (pCND) in DTC during total thyroidectomy. The aims of this review were to examine and evaluate these 3 broad subjects in an evidence-based matter and see if these changes could lead to better patient outcomes when compared to the conventional open thyroidectomy with or without the help of the surgical adjunct(s).

2. Innovative surgical approaches

2.1 Endoscopic thyroidectomy

The application of endoscopic visualization to thyroid surgery has allowed surgeons to perform thyroidectomy through incisions far smaller and less visible than the conventional

Kocher's incision – the so-called “less is more”. In general, these endoscopic techniques attempt to minimize the extent of dissection, improve cosmesis, reduce post-operative pain, shorten hospital stay and hasten postoperative recovery. Michel Gagner was the first surgeon to report the feasibility of endoscopic technique to neck surgery.(Gagner, 1996) He reported a totally endoscopic subtotal parathyroidectomy in a 37 year old man suffering from familial hyperparathyroidism. (Gagner, 1996) Although the endoscopic procedure took over 5 hours, it demonstrated the technical feasibility and safety. Over the turn of the last century, an increasing number of different endoscopic techniques have been described and may be categorized into namely cervical or direct and extracervical or indirect approaches.(Lang, 2010a) The former is considered as truly minimally invasive since the skin incisions are small in the neck with direct access to the thyroid gland. On the other hand, the extracervical approach is considered as an endoscopic instead of minimally invasive approach because incisions are made distant from the neck and so the approach requires more extensive tissue dissections.(Henry, 2008) However, despite its invasiveness, it offers superior early cosmetic outcome because potentially unsightly scars can be hidden and so patients remains “scarless in the neck”. This approach has been adopted more often in Asian countries where remaining “scarless in the neck” after thyroidectomy is a priority for a select group of patients.(Lang & Lo, 2010b)

2.1.1 Cervical / direct approaches

These approaches include the endoscopic lateral cervical approach and the minimally invasive video-assisted thyroidectomy (MIVAT). In the endoscopic lateral cervical approach, two 2.5mm and one 10mm trocars are inserted under direct vision along the anterior border of the sternocleidomastoid muscle on the side of resection. Using endoscopic instruments, the dissection starts from the lateral aspect of the thyroid gland and moves medially with identification of the recurrent laryngeal nerve (RLN), parathyroid glands and skeletonisation of the superior and inferior thyroid vessels.(Palazzo et al., 2006) Excellent visualization of RLN and parathyroid glands is possible with magnification by the endoscope. However, this technique is limited to unilateral thyroid resection and its application in thyroid cancer surgery is restricted to sub-centimeter papillary thyroid carcinoma (PTC) detected by high-resolution ultrasound machines. In contrast, the MIVAT would be preferred if bilateral thyroid resection is necessary because the incision is made in the midline instead of the lateral aspect of the neck. A 2cm incision is made in the middle of the neck about 2cm above the sternal notch. Blunt dissection is then carried out to separate the strap muscle from underlying thyroid lobe. A 5mm 30 degree endoscope is placed inside the 1.5cm wound for lighting and visualization. The procedure is performed under endoscopic view with the operating space maintained by external retraction. This technique was first applied for selected benign thyroid conditions in 2000.(Miccoli et al., 2000) However, with improvement in techniques, MIVAT has become increasingly adopted for low- to intermediate risk DTC.(Miccoli et al., 2009) MIVAT was shown to achieve similar completeness of resection and 5-year survival outcomes as those with low- and intermediate risk PTC undergoing conventional thyroidectomy.(Miccoli et al., 2009; Miccoli et al., 2002; Lombardi et al.,2007a) In addition, it has been shown that a concomitant pCND is technically feasible in MIVAT during initial total thyroidectomy.(Bellantone et al., 2002) Also for patients with low risk PTC with concomitant lateral lymph node metastases, a minimally invasive video-assisted functional lateral neck dissection through a small neck

incision is also technically possible.(Lombardi et al., 2007b) A recent randomized trial comparing conventional thyroidectomy with MIVAT found that the latter was associated with a lower risk of wound infection.(5.3% vs 0.0%, $p<0.05$)(Dionigi et al.,2011)

2.1.2 Extra-cervical / indirect endoscopic approaches

Unlike the cervical approaches, these approaches involve making incisions either in the chest, breast and/or axilla to hide the scars with clothing.(Lang, 2010a) Ikeda et al. first described these approaches by placing three ports in the axilla with low-pressure gas insufflation for maintaining the operating space. Although cosmetic results were excellent, the procedure was technically demanding and time consuming because of unintentional easy gas leakage and frequent interference of the 3 operating surgical instruments in the small available space in the axilla.(Ikeda et al., 2003) Chung et al. modified this technique by making this approach gasless with the space maintained by a specially designed skin-lifting external retractor.(Kang et al.,2009a) In this approach, the procedure began with a 4 to 5cm incision in the axilla and then a subcutaneous space was created from the axilla to the thyroid gland. To avoid the problem of interference of instruments, an additional 5mm port was inserted in the chest area for medial retraction of the thyroid gland. Chung et al. recently reported their experience with this approach after performing 581 cases.(Kang et al., 2009a) Among these patients, 410 patients had low-risk PTC. In their series, concomitant pCND was performed and the rate of lymph node metastasis was 27.3%.(Kang et al., 2009a)

To further increase the degree of angulations and freedom of interference between instruments, a combined axillo-breast approach was developed utilizing 2 circumareolar trocars in the breast and a single trocar in the ipsilateral axilla. This approach was later modified by using bilateral axillary ports to allow better exposure to both sides of the thyroid compartment. This approach is now known as the bilateral axillo-breast approach (BABA). Despite the extensive tissue dissection, when compared with the conventional open approach, BABA has been shown to have similar results in terms of transient hypocalcemia, bleeding, permanent RLN paralysis and length of hospital stay.(Chung et al., 2007) More recently, a Korean group tried to eliminate wounds around the chest or breast areas all together by making incisions in the axilla and post-auricular areas instead. They reported a small series of 10 patients using this approach and 7 underwent bilateral thyroid resection for low-risk PTC. They demonstrated the feasibility of this technique of scarless (in the neck) thyroid surgery.(Lee et al., 2009a)

2.2 Robotic-assisted thyroidectomy

The application and feasibility of the endoscopic approach was given a further boost with the availability of various robotic systems such as the da Vinci system (Intuitive Surgical, Sunnyvale, California). Unlike other cancers such as prostate cancer, the initial enthusiasm of using the robot in thyroid cancers was not great because of its relatively high cost, bulkiness of the robotic arm and long operating time. However, since the publication of two large surgical series demonstrating the feasibility and safety of robotic assisted thyroidectomy in DTC, an increasing number of specialized surgical centers worldwide are beginning to accept and perform this procedure. The theoretical advantages of using the robot over the endoscopic approach include the three-dimensional view offer to the

operating surgeon, the flexible robotic instruments with seven degree of freedom and 90° articulation, the increased tactile sensation and the ability to filter any hand tremors.(Kang et al., 2009b) Kang et al. recently reported their experience of 200 robot-assisted total thyroidectomy using the gasless trans-axillary approach for low-risk PTC with concomitant pCND and found excellent short-term results in terms of postoperative pain and patients' satisfaction.(Kang et al., 2009c) This was followed briefly by another report of 338 benign and malignant cases using the same trans-axillary.(Kang et al., 2009d) To date, this group has performed over 1000 cases. A separate Korean group also reported similar results using the da Vinci robot via the BABA technique.(Lee et al., 2009b) Although both techniques have been demonstrated to be feasible and safe, they have been limited to a few high-volume specialized centers. The surgeons performing these operations have had years of operating experience with the endoscopic approach and so the learning curve for a novel, non-endoscopic thyroid surgeon or someone who predominantly perform open thyroid procedures, remains undefined but is likely to be longer than one might think. Furthermore, better comparative studies such as a randomized controlled trial between robotic-assisted and endoscopic thyroidectomy are needed in order to better assess the added patient outcome benefits over the latter approach.

2.3 Endoscopic vs robotic-assisted thyroidectomy via the transaxillary route

Since both approaches actually utilize the same surgical approach (i.e. the transaxillary route), an obvious question would be whether using the robot would have added benefits over the conventional endoscopic operation, perhaps in terms of operating time, complication rate or number of assistants required.(Lang et al., 2011a) Lang et al. first reported a small series of patients who underwent the endoscopic (i.e. without the robot) and the robot-assisted thyroidectomy for mostly benign cases and compared their outcomes. They found that the robotic group was associated with an increased total procedure time and resulted in higher pain score on day 0 than the endoscopic group but the robot was able to eliminate the need of an extra surgical assistant at the time of operation.(Lang & Chow, 2011b) Lee et al. reported a larger series of patients with mostly papillary thyroid microcarcinomas. In their series, the robotic group was associated with shorter operating time, more lymph nodes retrieval and shorter learning curve.(J.Lee, 2011) This was followed by another larger series reported by the same group comparing the two approaches. In this study, they confirmed that the robot assisted thyroidectomy was superior to endoscopic and postulated that the reason for this superiority was because of the limitations of the conventional endoscopic instruments. (S.Lee, 2011) These contradictory findings could be explained by the fact that the first series comprised mainly benign nodular cases and so no pCND was necessary whereas in the latter two series, pCND was performed at the time of the thyroidectomy. Therefore, perhaps more complex surgical procedures might benefit from the robot whereas a straightforward operation such as a hemithyroidectomy or total thyroidectomy, the robot might not be any extra benefits.(Lang et al., 2011a)

2.4 Transoral thyroidectomy

This remains one of the most contentious surgical approaches and one of the most extreme examples of preferring "scarless in the neck" in thyroidectomy. The concept began in 2008 when Witzel et al. presented an experimental "natural orifice surgery" or NOS approach for

thyroidectomy.(Witzel et al.,2008) To minimize the surgical trauma, they presented a transoral access to the thyroid gland using a single port access via an axilloscope. Following this, Wilhelm et al. reported the first 8 cases of transoral thyroidectomy in humans. The incisions were made in the vestibule of the mouth and conventional endoscopic instruments were inserted in the subplatysmal layer, anterior to the thyroid cartilage. However, parathesia of the mental nerve was reported in the first six cases and two unilateral RLN palsies were also noted in two of eight cases. Also there was one patient who developed a minor infection at the vestibular incision 4 weeks after surgery.(Wilhelm & Metzger, 2011) Therefore, at this moment, one could say that this approach is technically feasible but remains experimental and is associated with a higher rate of complications than the conventional open approach.

3. Use of surgical adjuncts

3.1 IONM

RLN injury is a leading cause of litigation in thyroid surgery.(Ready & Barnes, 1994) To those with this injury, it not only affects the voice quality but also diminishes the overall quality of life because of communication, social and work-related problems.(Smith et al., 1998) Routine RLN identification is considered the standard of care in thyroid surgery. However, with the availability of IONM, the questions are whether this new piece of technology could further reduce the risk of iatrogenic RLN injury in thyroid surgery or thyroid cancer surgery in particular.

Although IONM has been around for over 3 decades, its widespread usage in the surgical practice only dates back 5-10 years. There has been an increased in interest on applying this technique for thyroid surgery because of the introduction of new and user-friendly devices from technological advance.(Chan & Lo, 2006a) Currently, there are two types of IONM systems, namely those with electromyographic (EMG) documentation and those without EMG documentation. The former involves RLN stimulation with registration of the elicited laryngeal muscle activity through endoscopic insertion of electrodes into the vocal fold or with the use of endotracheal surface electrodes. The latter utilizes RLN stimulation with observation of posterior cricoarythenoid muscle contraction or palpation or intraoperative inspection of vocal cord function.(Dralle et al., 2008; Dralle et al., 2004) To date, there is no consensus on which is the best system and the choice depends on the availability of which system in your institution and the operator familiarity or experience. Regardless of which systems, there are potential flaws and pitfalls. In general, the positive predictive value (PPV) is proportionally low with this technology. That means that when a nerve has no signal during stimulation, it does not mean that it is injured. In fact, in our experience, the PPV was only 15% in low-risk thyroid surgery i.e. approximately only 1 out of 9 RLNs with no signals had an actual injury. This might be due to some technical errors such as detachment or displacement of electrodes or poor contact of the probe with the nerve due to inadequate exposure.(Chan & Lo, 2006) Perhaps, direct vagal stimulation could possibly reduce some of these errors but need more unnecessary dissection. Even more intriguing is the fact that this technique is also associated with false negative results, albeit rarely. In our experience, among 271 nerves at risk, 15 (5.5%) ended with RLN palsy but of these, 7 still had a positive IONM signals. Therefore, it seems that IONM might not be able to detect "sub-lethal" injury

to RLN. It is possible that the action potential could be propagated along the neural pathway, as detected by the IONM, but not to the extent of initiating laryngeal muscle contraction during the postoperative period.(Chan, 2006a,2006b) Fortunately, all these injuries would invariably recover.

On the other hand, although the objective of the use of this device is to avoid RLN injury during thyroid surgery, the evidence of supporting its routine use has been weak. The first multicenter study including 29,998 RLNs at risk confirmed that the incidence of RLN palsy was not significantly reduced by the additional use of IONM when routine RLN identification was performed.(Dralle et al., 2004) There were more than 20 publications addressing this issue but majority of these studies were heterogeneous in terms of patients' characteristics (such as primary operations vs reoperations or benign vs malignant goiters), IONM techniques and the extent of resection (i.e. total vs subtotal lobectomy). A recent literature review could not definitely draw confirm conclusions or evidence on the effectiveness of IONM in reducing RLN injury in thyroid surgery.(Dralle et al., 2008) Furthermore, most studies were either case-series with no control group or retrospective studies with inadequate statistical power to demonstrate a difference between those with or without using IONM. In fact, a randomized study utilizing approximately 7,000 patients in each arm of patients undergoing thyroidectomy with or without IONM will be required to have adequate statistical power to show a difference in outcome with reference to RLN paralysis.(Dralle et al., 2004; Dralle et al., 2008) Interestingly though, the first prospective randomized study comparing IONM with routine RLN visualization only was recently published.(Barczynski et al., 2009) In this study, approximately 500 patients were randomized into each arm. The number of patients recruited in each arm was based on the principle of detecting a 2% difference in the incidence of transient RLN injury with a 90% probability at $p<0.05$. This study did demonstrate a statistically significant difference in reducing transient RLN injury when IONM was adopted in comparison with RLN visualization only. However, as expected, the rate of permanent RLN injury was similar in the two study arms because of inadequate statistical power. Nevertheless, despite the inadequate power of most published IONM studies, there seemed to be a trend toward improved RLN protection with the use of this new technology.(Dralle et al. 2008) In addition, the IONM may be of potential benefit for "difficult" cases such as reoperative thyroidectomy, locally advanced thyroid cancers or central neck dissection for cancer recurrence. Perhaps, for the relatively inexperienced surgeons, the IONM might reduce the incidence of RLN injury in difficult cases.

3.2 IOPTH (intraoperative parathyroid hormone) for predicting post-thyroidectomy hypoparathyroidism

Hypoparathyroidism is a common complication after bilateral thyroid resections or total thyroidectomy. Up to 30% of patients after total thyroidectomy develop temporary hypoparathyroidism.(Pattou et al.,1998) There are many identifiable risk factors leading to postoperative hypoparathyroidism including thyroidectomy for thyrotoxicosis and thyroid cancer, thyroid reoperations, reduced stores of vitamin D, increased extent of thyroid resection and need of concomitant pCND.(McHenry et al., 1994;Abboud et al. 2002) Patients undergoing thyroidectomy for thyroid cancer are particularly prone to hypoparathyroidism because they often need a more complete thyroid resection together with neck dissection. In

fact, total thyroidectomy and pCND is increasingly being performed for DTC to achieve lower recurrences, better disease-free survival and enhanced postoperative athyroglobulinemia.(Roh et al. 2007; Lang et al., 2011c) However, it has been shown that up to 60% of patients after pCND could develop transient hypocalcemia secondary to the frequent occurrence of unintentional or incidental parathyroidectomy.(Pereira et al.,2005) Therefore, in the presence of such a high incidence of postoperative hypoparathyroidism, the need of routine postoperative inpatient calcium monitoring remains questionable after thyroid cancer surgery while the early routine administration of oral calcium and/or vitamin D supplements seems to be relevant and can facilitate the early discharge from hospital shortly after surgery without developing unpleasant hypocalcemic symptoms.(Grodski & Serpell,2008) In fact, a recent randomized study supported this strategy because routine administration of oral calcium was shown to markedly reduce the severity and symptoms of hypocalcemia.(Roh et al.,2009) However, the adoption of this strategy could lead to over-treatment in patients who do not have hypocalcaemia leading to rebound hypercalcemia and increased medication costs. On the other hand, this strategy might lead to inadequate treatment in patients with severe symptomatic hypocalcaemia as oral calcium alone may not fully correct the hypocalcemia and so vitamin D supplements is indicated in such situation.(Lo,2003)

On the other hand, in-patient serial close monitoring of serum calcium is recommended after total thyroidectomy because most symptomatic hypocalcemia occurs around 24-28 hours after surgery.(Pfleiderer et al.,2009) A 24-hour or longer hospital stay is invariably required. Therefore, efforts are made to shorten hospital stays, decrease biochemical blood tests and reduce hospital costs by adopting other strategies to achieve early prediction of post-thyroidectomy hypocalcemia. With the availability of IOPTH and wide application in patients undergoing minimally invasive parathyroidectomy to predict postoperative cure, this new surgical adjunct has been applied to thyroid surgery to monitor parathyroid function and to predict the occurrence of postoperative normocalcaemia or hypocalcaemia. In our early prospective study of using IOPTH in predicting hypocalcemia in 100 consecutive patients (including 33 patients with DTC) who underwent either total or completion thyroidectomy, we found that a normal level of IOPTH at 10mins or a level less than 75% decline in IOPTH at 10 mins after excision of thyroid gland accurately identified normocalcemia.(Lo et al.,2002) It was suggested that intraoperative or early postoperative parathyroid hormone assay might be a sensitive tool to confirm postoperative normocalcaemia and identify patients at-risk of developing postoperative hypocalcaemia. Since then, up to 30 different investigators have published their results of using various different IOPTH assays in predicting hypocalcemia after total thyroidectomy. The IOPTH levels and their rate of decline at various time points after surgery could be utilized for prediction of postoperative hypocalcaemia with variable sensitivity, specificity and accuracy.(Lombardi et al.,2004,2006) However, based on two evidence-based reviews, it was recommended that the IOPTH level within a few hours after thyroid surgery could accurately predict postoperative normocalcaemia and identify patients at-risk of developing hypocalcemia, particularly severe, symptomatic hypocalcemia.(Grodski & Serpell, 2008; Noordzij et al.,2007) It was suggested that patients could be stratified into high or low risk groups and PTH should be measured at 1-6 hrs after operation in comparison to preoperative PTH. A $<$ or $>$ 65% decline at 6 hours after operation should allow early discharge or facilitate the decision of early calcium supplement. On the other hand, a

strategy of 2 cut-off points should be considered with a high accuracy. A <50% decline within few hours after surgery allowed early discharge while a >90% decline necessitated early calcium supplement because of the accuracy in predicting normocalcaemia and hypocalcaemia respectively.(Noordzij et al.,2007) For those patients with 50-90% decline, either serial calcium monitoring or routine treatment should be considered. In the AES guideline, one single serum PTH measurement is recommended at 4 hrs after operation.(AES group, 2007) A normal PTH can predict normocalcaemia and patients can be discharged early with 7% subsequently developing mild hypocalcaemia. For patients with undetectable PTH level, oral calcium and vitamin D analogue should be administered early to avoid symptomatic hypocalcaemia. Intermediate or subnormal PTH level is a less accurate predictor of hypocalcaemia. In that case, oral calcium should commence or patients should be monitored with serial calcium levels for the need of calcium and/or vitamin D analogue.(AES group,2007) Therefore, PTH assay can now be considered as a perioperative adjunct to predict normocalcaemia or hypocalcaemia with reasonable accuracy. It can facilitate early discharge, avoid routine calcium replacement, facilitate early calcium replacement to avoid symptomatic hypocalcaemia and decrease overall cost as well as increase patients' satisfaction. However, probably in the community hospital setting where IOPTH may not be available, the least expensive alternative option for same day discharge is routine postoperative oral calcium +/- vitamin D supplementation.

3.3 Alternate energy source for intraoperative hemostasis in thyroidectomy

In addition to scalpels and ligatures, alternate energy such as electric (e.g. ligasure) and ultrasonic (e.g. harmonic scalpel (Ethicon) and Sonosurg®) have been used for cutting and hemostasis in surgery. An unique feature of thyroidectomy is that thyroid gland has one of the richest blood supplies among the organs, with numerous blood vessels and plexuses entering the parenchyma. These vessels are usually controlled with ligatures (or clamp and tie) but the ligation and division of these vessels is time consuming and so perhaps the use of these alternate energy sources may reduce the actual operating time and cost. Essentially both ligasure or harmonic scalpel were consistently shown to shorten the total operating time by approximately 15-30% but in terms of complication rates, there was no statistically difference when compared to the conventional clamp and tie technique. Similarly, a recent meta-analysis which included 7 randomized trials comparing harmonic scalpel with conventional clamp and tie technique found that there was a weighed mean reduction of operative time of 18.74 minutes (95% CI: 10.52 - 28.97 minutes, p<0.001) but there was no statistical difference in complication rates.(Cirocchi et al., 2010)

First author (year)	No. of patients	Design	Two arms	Type of surgery	Type of thyroid pathology	Conclusions
Voutilainen (2000)	36	RCT	CT vs HS	HT/TT	Benign and malignant	HS: ↓ operating time; short learning curve
Siperstein (2002)	171	RS	CT vs HS	HT/TT	Benign and malignant	HS: ↓ operative time by 30mins in HT and TT

First author (year)	No. of patients	Design	Two arms	Type of surgery	Type of thyroid pathology	Conclusions
Ortega (2004)	200	RCT	CT vs HS	HT/TT	Benign	HS: 15-20% reduction in operating time, less costs
Petrakis (2004)	517	RS	CT vs LS	TT	Benign	LS: ↓ operating time, less RLN injury, less blood loss, less hypocalcemia
Kiriakopoulos (2004)	80	PS	CT vs LS	TT	Benign and malignant	Similar operating time and blood loss
Kirdak (2005)	58	PS	CT vs HS	HT/TT	Benign and malignant	HS: ↓ operating time only
Cordon (2005)	60	RCT	CT vs HS	HT/TT	Benign and malignant	HS: ↓ operating time only
Franko (2006)	155	RS	CT vs LS	HT/TT	Benign and malignant	LS: ↓ operating time, less blood loss, less hypocalcemia
Lepner (2007)	403	RS	CT vs LS	HT/TT	Not specified	LS: ↓ operating time, less hypocalcemia
Sartori (2008)	150	RCT	CT vs LS/HS	HT/TT	Benign and malignant	HS: ↓ operating time, more hypocalcemia
Pons (2009)	60	RCT	CT vs LS/HS	TT	Not specified	HS: ↓ operating time, less pain and cost
Cirocchi (2010)	608	MA (7 RCTs)	CT vs HS	TT	Benign and malignant	HS: ↓ operating time, less cost but similar complication rates
Zarebczan (2011)	231	RS	HS vs LS	HT/TT	Benign and malignant	HS: ↓ operating time but complications were similar
Rahbari (2011)	90	RCT	HS vs LS	HT/TT	Benign and malignant	No difference in operating time, cost or complications

Abbreviations: RCT = randomized controlled trial; PS = prospective study; RS = retrospective study; MA = meta-analysis; CT = conventional technique; HS = harmonic scalpel; LS = ligasure; HT = hemithyroidectomy; TT = total thyroidectomy

Table 1. shows a summary of the trials and their conclusions comparing different hemostatic techniques in thyroidectomy.

4. The role of pCND in DTC

The role of pCND in DTC remains one of the most discussed surgical subjects in recent few years. To date, there is little good evidence to show that pCND improves cancer-specific survivals or reduces cancer-specific mortality in DTC.

First author /year of publication	Number of patients		Follow up duration (months)	Cancer-specific mortality		<i>p</i> -value
	CND+ group	CND- group		CND+ group	CND- group	
Tisell/ 1996	P/T - 195	199;167	156 months (median)	8.4% - 11.1%	1.6%	Not reported
Sywak/ 2006	P - 56, A	391	CND-: 70 months CND+: 25 months (median)	0%	0%	Not statistically significant
Roh/2007	P - 40, B T - 42 (26/42 with lateral neck dissection)	73	52 months (mean)	0%	0%	Not statistically significant

Abbreviations: CND-: thyroidectomy alone, CND+: thyroidectomy plus central neck dissection; P: prophylactic, T: therapeutic; A: unilateral, B: bilateral

Table 2. A literature summary of studies which specifically evaluated cancer-specific mortality between thyroidectomy alone or thyroidectomy with pCND.

To date, the strongest evidence supporting the role of pCND in DTC came from an earlier study carried out by a Swedish group. Tisell et al. evaluated 175 patients who underwent thyroidectomy with CND and compared with contemporaneous controls from other two studies of Scandinavian population conducted on patients in Norway and Finland. (Tisell et al. 1996; Kukkonen et al. 1990; Salvesen et al. 1992) They showed that patients who underwent thyroidectomy with pCND had a higher survival rate (1.6% vs. 8.4-11.1%). However, these studies were criticized for including patients with gross lymph node involvement requiring therapeutic neck dissections. (Tisell et al., 1996; Kukkonen et al., 1990; Salvesen et al., 1992)

Another important outcome parameter or survival surrogate is disease recurrence or disease-free survival.

However, it is difficult to interpret their results as there were great variations in terms of indication (therapeutic or prophylactic), extent (unilateral or bilateral) and duration of follow up among different studies. The majority of studies did not show any significant differences. Moo et al. reported a decrease in recurrence rate in patients who underwent bilateral pCND (4.4% vs 16.7% $p=0.13$). (Moo et al., 2010) Zungia et al. analyzed a cohort of 266 patients with 6.3 years mean follow up and reported the 5-year disease-free survival was comparable (88.2% vs. 85.6%; $p= 0.72$). (Zuniga et al., 2009) Interestingly, a recent meta-analysis comprising 5 retrospective comparative studies ($n=1264$) found that there was an

insignificant trend toward lower overall recurrence rate in the group who underwent either unilateral or bilateral pCND when compared to those who had total thyroidectomy only (2.02% vs 3.92%, odds ratio (OR) = 1.05, 95% confidence interval (CI) = 0.48 - 2.31). (Zetoune et al., 2010) Their subgroup analysis revealed no decrease in central (1.86% vs. 1.68%, OR 1.31, 95% CI = 0.44-3.91) or lateral compartment recurrence (3.73% vs. 3.79%, OR 1.21, 95% CI = 0.52 -2.75). (Zetoune et al., 2010) Therefore, based on these findings, there might be a potential benefit of lower recurrence in those who underwent either unilateral or bilateral pCND, although larger-scale prospective studies are required to confirm this.

Study design	First author / year of publication	Number of patients		Follow up (mean)	Overall recurrence		p-value
		CND+ group	CND- group		CND+ group	CND- group	
Retrospective	Gemsenjager / 2003	P - 29	88	8.1 years	3.4%	2.3%	Not mentioned
Retrospective	Wada / 2003	P - 235	155	53 months	0.4%	0.6%	Not significant
Retrospective	Sywak / 2006	P-56, A	391	CND-: 70 months CND+: 24.5 months (median)	3.6%	5.6%	Not mentioned
Retrospective	Roh / 2007	P-40, B T - 42, B	73	52 months	P - 0% T - 1.2%	4.0%	Not mentioned
Retrospective	Zungia / 2009	P-136, B	130	6.9 years	5yr DFS - 88.2%	5yr DFS - 85.6%	0.72
Retrospective	Costa / 2009	P-126, B	118	CND-: 64 months CND+: 47 months	6.3%	7.7%	0.83
Retrospective	Moo / 2010	P-45, B	36	3.1 years	4.4%	16.7%	0.13
Meta-analysis	Zetoune / 2010	P - 396, A/B	868		2.0%	3.9%	NS
Retrospective	Lang / 2011c	P - 82, A	103	26 months	3.7%	2.9%	1.0

Table 3. A literature summary of studies which evaluated recurrence rates between thyroidectomy alone or thyroidectomy with pCND.

Serum Tg level is useful in detecting persistent or recurrent DTC after thyroidectomy and RAI ablation. (Hay et al., 2002) A detectable post-surgical Tg level is associated with risk of recurrence and so it may be applied as an surrogate marker of outcome in studying prognosis of DTC. (Cooper et al., 2009; Leboulleuz et al., 2005) Sywak et al. examined 447 patients with clinically node-negative papillary thyroid carcinoma, while 56 patients underwent thyroidectomy and pCND. (Sywak et al., 2006) Though there was no significant

difference in recurrence or survival after a short median follow up (thyroidectomy plus pCND vs. thyroidectomy alone: 25 vs. 70 months), they showed that there was a significantly lower level of stimulated Tg at 6 months after RAI ablation (mean: 0.41 vs. 9.3, $p=0.02$), and higher proportion of athyroglobulinemia (72% vs. 43%; $p<0.001$). (Sywak et al., 2006) In contrast, Hughes et al. found that there was no difference in post-ablation median stimulated Tg level or rate of athyroglobulinemia between patients undergoing thyroidectomy with or without bilateral pCND. (Hughes et al., 2010) However, in their subgroup analysis of patient undergoing pCND, they demonstrated that pre-ablation Tg level was significantly higher in node positive patient these patients achieved a comparable rate of post-ablation athyroglobulinemia after a higher dose of RAI. (Hughes et al., 2010) More recently, Lang et al. retrospectively analyzed 185 patients with PTC and of these, 82 (44.3%) patients had an unilateral pCND together with a total thyroidectomy (CND+ group). (Lang et al., 2011c) They found that the CND+ group had a significantly lower median pre-ablation stimulated Tg level ($<0.5\mu\text{g/L}$ vs. $6.7\mu\text{g/L}$, $p<0.001$) and achieved a higher rate of pre-ablation athyroglobulinemia (51.2% vs. 22.3%, $p=0.024$) than those who underwent a total thyroidectomy only but these differences were not observed 6 months after ablation. They also found that pCND was the only independent factor for pre-ablation athyroglobulinemia. (Lang et al., 2011c) In their experience, most of the residual microscopic disease, presumably not removed by the initial pCND, was still able to be ablated by RAI ablation and so the group without pCND achieved similar stimulated Tg levels and similar rate of athyroglobulinemia 6 months after ablation. (Lang et al., 2011c) The authors concluded that although performing pCND in total thyroidectomy may offer a more complete initial tumor resection than total thyroidectomy alone by minimizing any residual microscopic disease, such difference becomes less noticeable 6 months after RAI ablation. (Lang et al., 2011c) The other advantage of performing pCND is the fact that the status of central lymph nodes or pN1a is better known and so more accurate staging is possible. (Lang et al., 2007b)

Increased patient morbidity is one of the major concerns. Increased risk of transient hypoparathyroidism has been consistently shown in many studies. (Sywak et al., 2006; Hughes et al. 2010; Lang et al., 2011c; Palestini et al., 2008; Roh et al., 2007; Moo et al., 2010; Rosenbaum et al., 2009) The higher rate of temporary hypoparathyroidism could be explained by the higher rate of unintentional removal of parathyroid glands (i.e. unintentional parathyroidectomy) and subsequent auto-transplantation. (Sywak et al., 2006; Hughes et al., 2010; Lang et al., 2011c) Unintentional devascularization of parathyroid glands during dissection also contributes to the higher rate of temporary hypoparathyroidism. In terms of temporary recurrent laryngeal nerve injury, Palestini et al. reported a higher rate of transient recurrent laryngeal nerve injury in patients undergoing thyroidectomy plus unilateral pCND (5.4% vs. 1.4%, $p<0.05$) (Palestini et al., 2008) while other studies failed to show any statistically significant differences. (Sywak et al., 2006; Hughes et al. 2010; Lang et al., 2011; Roh et al., 2007; Sadowski et al. 2009; Rosenbaum et al., 2009) To date, no studies have shown an increase risk of permanent hypoparathyroidism or recurrent laryngeal nerve injury. A recent systematic review comprising 5 retrospective studies evaluated the morbidity of pCND and found that there was one extra case of transient hypocalcaemia for every eight pCND performed. (Chisholm et al., 2009) However, there was no increased risk of permanent hypocalcaemia, transient or permanent recurrent nerve injury. (Chisholm et al., 2009)

5. Conclusion

Despite numerous reports on the various cervical and extra-cervical endoscopic approaches, the only truly minimally invasive approach in DTC appears to be MIVAT because it is associated with a shorter skin incision, minimal tissue dissection, shortened hospital stay, less wound infection and less pain. Unlike the cervical approaches, the extra-cervical approaches appear to have similar but not better outcomes than the open or conventional thyroidectomy and randomized trials comparing these approaches with open thyroidectomy are currently lacking. However, the extra-cervical approaches remain a surgical option for patients who are motivated to remain “scarless in the neck”. The addition of da Vinci robot in endoscopic thyroidectomy (i.e. robotic-assisted thyroidectomy) may shorten operating time and increase the number of lymph nodes retrieved during thyroidectomy for DTC. Trans-oral thyroidectomy is technically feasible but remains experimental and appears to be associated with a higher rate of morbidity than the open approach. Surgical adjuncts such as IONM, IOPTH and alternate energy sources appear to be useful for surgeons to have as part of their armamentarium. Whether they actually improve surgical outcomes of patients over a standard open thyroidectomy remains to be determined by future prospective randomized studies. The role of pCND remains controversial as there is no good evidence to show that it improves long-term outcomes such as cancer-specific or disease-free survivals when compared to thyroidectomy without pCND. However, analysis of short-term markers for recurrence suggests that pCND may be associated with better short-term outcomes.

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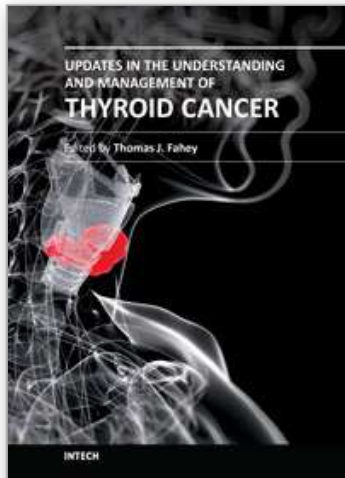
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University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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