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EXTENT OF LATERAL NECK DISSECTION FOR DIFFERENTIATED THYROID CANCER: THE CONTROVERSY THEN AND NOW

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ABSTRACT

The study aims to review the literature regarding extent of lateral neck dissection for differentiated thyroid cancer by way of a systematic review. Though there is abundant data available on outcomes of lateral neck dissection in relation to differentiated thyroid cancer, including some international guidelines, there is no clear consensus which is accepted throughout the world. Apart from this, the findings of some new studies cast serious doubt on the current treatment practices, which necessitates a thorough review of all available evidence to bring out latest inferences. **Purpose:** To review the literature regarding extent of lateral neck dissection for differentiated thyroid cancer by way of a systematic review. Though there is abundant data available on outcomes of lateral neck dissection in relation to differentiated thyroid cancer, including some international guidelines, there is no clear consensus which is accepted throughout the world. Apart from this, the findings of some new studies cast serious doubt on the current treatment practices, which necessitates a thorough review of all available evidence to bring out latest inferences. **Materials and Methods:** An electronic search was conducted using the terms "PTC or thyroid neoplasms or papillary carcinoma", "neck dissection", "lateral or cervical lymphadenopathy" and "differentiated thyroid cancer" in combination with the following search strategy : **Search block Thyroid Neoplasms** - "Thyroid Neoplasms"[Mesh] OR thyroid neoplasm*[tiab] OR thyroid cancer*[tiab] OR thyroid tumor*[tiab] OR thyroid tumour*[tiab] OR thyroid carcinoma*[tiab] OR thyroid malignancy*[tiab] OR thyroid oncology*[tiab] OR dtc[tiab] OR ptc[tiab]**; Search block Neck Dissection** - "Neck Dissection"[Mesh] OR neck dissection*[tiab] OR cervical lymphadenectomy*[tiab] OR lateral lymphadenopathy*[tiab] OR cervical lymphadenopathy*[tiab]. Clinical studies were retrieved from the electronic databases of PubMed, EMBASE and SCOPUS which had been published till June 2017. These included prospective studies, randomized controlled trials, retrospective studies and smaller descriptive studies. References of the selected studies were further searched for relevant articles. Apart from this, a search was conducted over Google Scholar to obtain related articles. **Results and Conclusion:** After an exhaustive review of all available evidence, it can be stated that treatment decisions regarding extent of lateral neck dissection for differentiated thyroid cancer should be guided by presence of various risk factors discussed in this study, in addition to comprehensive preoperative evaluation of the lateral neck with physical examination, ultrasonography and FNAC. Apart from this intraoperative frozen section of central and jugular lymph nodes should be carried out when required. Future perspectives would involve exploring the role of sentinel lymph node biopsy from lateral neck.

KEYWORDS: DTC, PTC, differentiated thyroid cancer, papillary thyroid cancer, lateral neck dissection, neck dissection.

INTRODUCTION

Differentiated thyroid cancer (DTC) comprises 90% of all follicular cell-derived thyroid malignancies. Histologically, DTC can be classified into two main types – papillary thyroid carcinoma (PTC) and follicular thyroid cancer (FTC).[1] Over the last two decades, there has been a significant increase in the incidence of DTC reported from different studies throughout the world.[2-5] The 10-year overall survival rate (OS) for DTC is greater than 90%. In spite of this, local recurrence is observed in 20-30% of patients suffering from PTC because of clinically undetectable metastasis to cervical lymph nodes.[6] Cervical lymph node metastases are commonly observed in PTC, occurring primarily in central compartment (level VI) with an incidence of 20% to 90%.7-11 On the contrary, follicular thyroid cancer (FTC) exhibits haematogenous spread, such that metastasis to cervical lymph nodes is rare.[12]

One of the debatable issues with regards to differentiated thyroid cancer is the extent of neck dissection necessary for optimal oncological management of cervical nodal

metastases. The various proposed treatment modalities range from "berry picking" to a modified radical neck dissection (MRND). Apart from this, variability in management exists across different institutions. While in North America, elective lateral neck dissection for thyroid cancer is rarely performed, it is a routine protocol in many other countries.[13] The American Thyroid Association (ATA) advocates that a "therapeutic lateral neck compartmental lymph node dissection should be performed for patients with biopsy proven metastatic lateral cervical lymphadenopathy."[14] However, while the patterns of metastasis for PTC to different levels of neck are evidently predictable, there is no clear consensus on the extent of lateral neck dissection.

To understand the importance of factors predictive of recurrence after lateral neck dissection, it is imperative to discuss the landmark study by Randolph et al[15] (2012). The authors presented a review of literature with the aim of bringing out factors predictive of prognosis for PTC, in relation to specific nodal characteristics such as clinically apparent size and number, as well as presence of extranodal extension. The locoregional lymph node recurrence rates for clinically N0 patients were 2% (range 0% - 9%) versus 22% for patients who were clinically N-positive (range 10% - 42%). Also, the median risk of recurrence in N1 patients demonstrated marked variation by the number of positive nodes, < 5 nodes (4%, range 3% - 8%) versus > 5 nodes (19%, range 7% - 21%). Apart from this, the presence of extranodal extension was associated with a median risk of recurrence of 24% (range 15% - 32%) and possibly worse disease-specific survival. Similar results were reported by Conzo et al[16] (2013) who published a retrospective analysis for predictive value of nodal metastases in relation to local recurrence, in the management of differentiated thyroid cancer. With a follow-up period of 8 years, the rate of locoregional recurrence for N-positive patients was 34.7% versus 4.2% for N0 patients.

In relation to predictive factors, it would be pertinent to discuss the prognostic implications of lymph node yield in relation to neck dissection for PTC. Heaton et al[17] (2016) conducted a study involving 152 patients suffering from PTC, with an average follow-up of 69 months. The results revealed that higher lymph node yield in central and lateral neck dissection is associated with lower rates of recurrence in both central and lateral neck. This study clearly proved that "berry picking" of lymph nodes should be avoided to minimize the risk of recurrence and the need for secondary therapy with revision surgery and/or radiation. The authors recommended thorough, compartment-oriented central and lateral neck dissection when nodal surgery is to be undertaken. As an inference, it is important to take into account the optimal cut-off values of lymph node ratio (LNR) for predicting recurrence in PTC. Presenting commendable data on this topic, Lee et al[18] (2016) conducted a study involving a large cohort of 2294 patients who had undergone total thyroidectomy for PTC. The prediction probability indicated that central lymph node ratio (cLNR, level VI) of 0.4 and total LNR (tLNR, levels II-VI) of 0.5 are optimal cut-off values for precise prediction. This provides an evidence-based criteria for risk stratification.

Another important prognostic factor highlighted in a few studies is the location of primary tumour within the thyroid gland. Lee et al[19] (2015) revealed that posterosuperior lesion has a high risk of lateral and central lymph node metastasis in solitary tumours of papillary thyroid cancer. Apart from this, tumour mass size of larger than 2 cm and positive central nodal metastasis were significantly associated with lateral neck metastasis on multivariate analysis. In a similar study, Xiang et al[20] (2015) presented a review of 949 patients suffering from papillary thyroid microcarcinomas (PTMCs). PTMCs located at upper poles and middle part of middle third of thyroid gland (MPMT) exhibited high rates of lateral neck metastasis (8.6% and 8.3% respectively). Tumour size of > 0.5 cm greatly correlated with lateral neck metastasis on multivariate analysis. In relation to central neck, PTMCs located at MPMT location showed the greatest rate of central neck metastasis (CNM) among all locations (57.5%), while PTMCs located at isthmus showed the second greatest rate of CNM (44.3%). On multivariate analysis, MPMT, tumour size > 0.5 cm, young and middle age, male sex, multifocality within the affected lobe and capsular invasion were correlated with CNM.

Sugitani et al[21] (2008) presented the results of a prospective study from Japan, involving a large cohort of 361 patients with PTC. Multivariate analysis revealed specific factors for nodal recurrence in lateral cervical compartment, which could be analyzed preoperatively. For patients with no evidence of lymph node metastasis (LNM) or positive nodes only in central compartment, after evaluation by ultrasound, risk factors were identified as presence of distant metastasis ($p = 0.01$) and large primary tumour ($p = 0.03$). The authors recommended prophylactic modified radical neck dissection (MND), including lateral compartment, to reduce chances of nodal recurrence in such patients. For patients diagnosed with lateral neck lymph node metastasis preoperatively by means of ultrasound, MND was performed with central compartment neck dissection. In this group, significant risk factors for nodal recurrence were identified as age (50 years or older), large nodal metastasis (≥ 3cm), extrathyroidal invasion and higher serum thyroglobulin level (≥ 320 ng / ml). Similar suggestions were made by Ito et al[22] (2007). However, many authors (Noguchi[23] 1987, Shaha[24] 1998, Bhattacharyya[25] 2003) recommend that therapeutic lateral neck dissection should be performed only in presence of clinical or radiological evidence of disease.

There are others who recommend a staged approach to resolve the controversy. Lee et al.[26] (2014) presented their results of 185 patients with pathologically confirmed PTC and clinically node-negative lateral neck. After a median follow-up of 50-96 months, 3.2% patients developed recurrences in lateral neck at a median of 28 months after surgery. A multivariate analysis revealed that T4 disease and intraoperative diagnosis of central lymph node metastasis were independently predictive of recurrence. The study concluded that intraoperative lymph node biopsy can help identify patients at risk for recurrence and those who would benefit from lateral neck dissection. More recently, Lan et al[27] (2015) presented a meta-analysis of studies related to central lymph node metastasis as predictive factor for lateral involvement in papillary thyroid carcinoma. 21 studies were analyzed for relevant outcomes. The risk of lateral lymph node metastasis was found to be significantly higher in the central lymph node-positive group than in the negative group. Although this approach for predicting lateral neck metastasis is commendable in many ways, a possibility of skip metastasis to lateral neck cannot be ignored. This is evident from the results of a prospective trial published by Lei et al.[28] (2017). This study involved 450 PTC patients who underwent total thyroidectomy with central neck dissection combined with modified radical lateral neck dissection. The cohort was divided into two groups: with or without skip metastases. Clinicopathological parameters were analyzed by multivariate analysis. Risk factors predictive of skip metastasis to lateral neck were recognized as primary tumour location in the upper portion, primary tumour size ≤10 mm and capsular invasion. Other authors (Lim et al,[29] 2011) have emphasized on importance of lymphovascular invasion, extracapsular spread and number of positive lymph nodes dissected, as the predictive risk factors for skip metastasis.

Another important aspect is the need for sentinel lymph node biopsy from the lateral neck. Lee et al[30] (2015) presented the results of a randomized controlled trial involving 283 patients with PTC to identify the importance of lateral neck sentinel lymph node biopsy (LSLNB). The authors concluded that LSLNB helps to identify and remove occult metastasis in lateral neck but the procedure had no effect on recurrence rates or serum thyroglobulin levels at a mean follow-up of 39 months.

THE CONTROVERSY ATTENDING LATERAL NECK DISSECTION

Though there is ambient data to support knowledge on the patterns of spread to lateral neck (Table 1) in metastatic well differentiated thyroid cancer, there is no consensus regarding the extent of lateral neck dissection necessary to achieve adequate oncologic control. The question most commonly raised in relation to this controversy is the need for clearing levels II and V within the lateral neck dissection. This is directly related to the benefits of oncologic control versus morbidity in terms of postoperative shoulder discomfort. While the proponents of selective neck dissection raise serious concerns over the collateral sequelae of shoulder syndrome[31] and relatively low incidence of positivity in levels II and V, others express more firm belief in the principles of oncological clearance which evidently outweighs any other concern, as far as prevention of recurrence is concerned.

There is no doubt that the most commonly involved levels of lateral neck, from differentiated thyroid cancer, are levels III and IV (Table 1). As such all lateral neck dissections for primary thyroid malignancy include levels III and IV as routine protocol. Metastasis to level I is rare and as a consequence, it is seldom included in neck dissection.[32-34] However, metastasis to levels II and V have been shown to be positive with a percentage usually not anticipated. Level II is further differentiated into levels IIa and IIb, the incidence of positivity for both being different. The same convention applies to level V. Carron et al[33] (2006) suggested important guidelines for a selective approach towards dissection of level II. The authors recommended the dissection of level II only when clinical or radiological evidence of disease is present. This selective approach led to most patients having pathologically confirmed metastatic disease in level II specimens (80% ipsilateral level II specimens and 71% contralateral level II specimens were positive for metastasis). This percentage yield of positive metastases were much higher than the previous studies in which level II was routinely excised (22-56%). The authors proposed intriguing guidelines for inclusion of level II in neck dissection, stating that clinically negative level II lymph nodes should be excised if there are signs of aggressive local disease, extensive contiguous level III disease or bilateral lymph node metastasis.

Table 1: Percentage incidence of lymph node positivity at various levels. R – retrospective study; P – prospective study.

Study	Study Design	Level II	Level IIa	Level IIb	Level III	Level IV	Level V	Level Va	Level Vb	No. of Patients
Sivanandan et al (2001)	R	49	72	17	65	56	29	---	---	70
Pingpank et al (2002)	R	---	43	21	76	59	28	---	---	44
Kupferman et al (2004)	R	52	---	---	57	41	21	---	---	39
Lee et al (2007)	R	60	---	---	82	75	20	---	---	46
Kupferman et al (2008)	R	57	---	---	62	62	53	---	---	70
Yanir et al (2008)	R	54	27	5	68	57	20	---	---	27
Roh et al (2008)	P	---	---	---	72	76	---	13	4	52
Lee et al (2008)	P	56	56	7	81	75	17	---	---	167
Ahn et al (2008)	R	65	58	22	80	76	15	---	---	37
Khafif et al (2008)	P	46	---	---	68	70	16	---	---	37
Farrag et al (2009)	R	65	56	9	66	50	40	0	40	53
Koo et al (2009)	R	53	51	12	72	68	16	---	---	76
Lee et al (2010)	R	63	---	---	74	82	---	---	---	70
Yuce et al (2010)	R	46	50	7	69	66	34	---	---	48
Lim et al (2010)	R	49	---	---	74	69	16	---	---	70
Vayigoglu et al (2010)	P	27	---	---	55	82	18	---	---	22
King et al (2011)	R	---	49	62	72	67	---	8	31	32
Merdad et al (2012)	R	49	---	---	67	61	29	---	---	185
Kim et al (2012)	R	---	46.7	6.7	53.3	73.3	---	20	6.7	490
Chung et al (2012)	R	30	---	---	80	78.9	12.2	---	---	90
Nam et al (2013)	P	40	---	---	46	42	10	---	---	176
Yang et al 2016)	R	45.9	---	---	62.7	55.5	12.3	---	---	220
An et al (2017)	R	17.8	---	---	31.5	36.3	1.4	---	---	138

Lee et al (2008)[35] presented their results of a prospective study on 167 patients suffering from papillary thyroid cancer (PTC), who underwent modified radical neck dissection (MRND) between 2005 and 2007. The rates of metastasis in levels IIa and IIb were 55.5% and 6.8% respectively. The authors concluded that in the absence of clinical and radiological evidence of lymphatic metastasis, level IIb need not be incorporated in neck dissection for N1b PTC patients. Another important revelation brought about by this study was that level IIb metastasis was observed only in the presence of level IIa metastasis and chances of involvement of level IIb were significantly higher in cases with aggressive lateral cervical metastasis ($p < 0.0001$). Similar findings were reported by Koo et al[36] (2009) who published their results of 76 PTC patients who underwent therapeutic lateral neck dissection for the treatment of clinically positive lateral neck nodes between 2005 and 2008. The study concluded that level IIb dissection may be omitted if multilevel involvement including level IIa is absent. In this regard, it is pertinent to mention the well known study by Farrag et al[37] (2009), who published the results of retrospective analysis for 53 consecutive patients managed by therapeutic lateral neck dissection. The authors proposed dissection of level IIb only when level IIa is involved, based on FNA (Fine Needle Aspiration) confirmation or

when level IIb is grossly involved on intraoperative evaluation.

Exhaustive studies by Kupferman et al[32] (2004), Caron et al[33] (2006) and Sivanandan et al[34] (2001) provide descriptive data on the incidence of level V metastasis in patients with differentiated thyroid cancer. 20% to 60% of patients undergoing therapeutic neck dissection, exhibit involvement of level V. Although studies by Kupferman and Sivanandan suggest routine comprehensive neck dissection for regional metastasis, Caron et al proposed that selective neck dissection of levels III and IV in the appropriate patient is sufficient for control of regional disease. Apart from this, all three studies concluded that presence of disease at level I is rare. However, some more recent studies have presented contradictory evidence regarding level I. Eweida et al[38] (2017) conducted a prospective study on level I lymph node involvement in patients with N1b stage under neck dissection including level I. the results revealed that level I was involved in 13.9% of patients. Level I involvement exhibited significant association with number of lymph node levels affected and macroscopic extranodal invasion. The authors recommended that including level I in therapeutic neck dissection for N1b PTC patients might be recommended in selected cases of multiple level involvement and macroscopic extranodal invasion requiring sacrifice of internal jugular vein, sternocleidomastoid muscle or spinal accessory nerve.

Considerable controversy was sparked by the publication of a study by Kupferman et al[39] in 2008. Retrospective analysis was done for 70 patients who underwent thyroidectomy and neck dissection for well differentiated thyroid cancer. 53% of neck specimens were found to be positive for metastatic disease at level V, while 57% of contralateral neck dissections harbored disease at level V. Multivariate analysis revealed factors predictive of disease at level V. 33% of patients who had disease at level II, demonstrated concomitant disease at level V. In a similar trend, 38% of patients with metastases at level III ($p < .05$) or level IV ($p < .01$) demonstrated positive metastases at level V. From this data, it could be inferred that presence of disease at level II, III or IV was highly predictive of metastasis in posterior triangle. Apart from this, ipsilateral involvement of level V was associated with contralateral metastases ($p < .05$). Other factors such as age, sex, tumour size and histological classification were not found to be associated with level V metastases. The authors concluded that the high incidence of positive disease at level V, in their series, suggested routine dissection of level V lymph nodes in the setting of a comprehensive neck dissection for patients with lateral neck metastasis from well differentiated thyroid cancer. Also, patients with multifocal cancer within the thyroid gland and cervical metastases in ipsilateral jugular nodes, have a higher risk of harbouring positive metastasis at level V.

Results of the Kupferman study (2008) were positively reinforced by data presented by Merdad et al[40] (2012). The authors presented a retrospective analysis of a large cohort of patients who underwent 248 selective lateral neck dissections. Levels II, III, IV and Vb were involved in 49.3%, 76.6%, 61.6% and 29.2% of cases respectively. More than 73% of the cases exhibited involvement at multiple levels and skip lesions were detected in 9% of subjects. It is imperative to comment that this was the largest published series in the English literature describing the pattern of disease spread in PTC with metastasis to lateral neck. These results were in congruence with data presented from single-center high volume institutions (Kupferman[32] 2004, Farrag[37] 2009, Ahmadi[41] 2011), who recommended routine excision of levels II to V. Furthermore, the ATA's consensus review[42] on lateral neck dissection in differentiated thyroid cancer suggested a comprehensive neck dissection of at least the nodal levels IIa, III, IV and Vb. Similar conclusions can be drawn from recommendations of the Triological Society Best Practice Guidelines[43] published in 2010, which advocate a selective neck dissection with excision of levels IIa to Vb with or without incorporating levels IIb and Va. Khafif et al[44] (2013) proposed some new guidelines to the approach of level V for metastatic PTC. They suggested dissection of level Vb in cases with multiple positive nodes in levels II and III, positive nodes in level IV and in cases with radiological or intraoperative evidence of nodal disease at level V.

THE APPEARANCE OF REVIEWS

Though exhaustive studies had been presented in English literature upto 2012, addressing the controversy regarding extent of lateral neck dissection for PTC, systematic reviews were still lacking. The ATA consensus of 2012[42] was also based on a non-systematic review. In the year 2013, Eskander et al[45] presented a commendable systematic review and meta-analysis on this same topic. With the objective of analyzing the number of patients with positive involvement at a given level, 18 studies with a total of 1145 patients and 1298 neck dissections were included in our meta-analysis. Levels IIa and IIb had disease in 53.1% and 15.5% of subjects, respectively. Levels Va and Vb had positivity in 7.9% and 21.5%, respectively, but there were only three studies which could be meta-analyzed. The authors concluded that analysis of all available evidence points to the notion that a comprehensive selective neck dissection of levels IIa, IIb, III, IV and Vb should be carried out in patients with lateral neck disease from PTC. Furthermore, the study revealed that evidence for level Va is lacking, as most studies did not distinguish between levels Va and Vb. Also, the border between these two levels had been described inconsistently.

Later in 2014, Park et al[46] published a descriptive review on the subject, especially focused on the need for inclusion of levels IIb and Va. The authors suggested that in absence of suspicious lymph node metastasis at

levels II and V or multilevel aggressive neck metastasis, dissection of sublevels IIb and Va may not be required. The study emphasized on individualized optimal surgical extent of lateral neck dissection.

THE McNamara Study – swing of pendulum

Although the debate on extent of lateral neck dissection was put to rest for some time by the publication of reviews, there was never complete consensus on the issue pertaining to extent of lateral neck dissection for PTC. Most high-volume centers with the background of their own published data, continued to practice in accordance with their own institutional protocols. In what could be called a complete swing of the surgical pendulum, McNamara et al[47] published an intriguing study on this topic in 2016. The objective being to determine any probable correlation between the extent of initial dissection and the rate and pattern of neck recurrence, this large study incorporated a total of 3,664 patients with PTC treated between 1986 and 2010 at Memorial Sloan Kettering Cancer Center. This retrospective analysis revealed a total of 484 subjects to have undergone lateral neck dissection for cervical metastasis from PTC. 75% (364) of these patients underwent a comprehensive lateral neck dissection (CLND) and 25% (120) had a selective neck dissection (SND). Median duration of follow-up was 63.5 months. This exhausting analysis of such an extensive institutional database, made a revelation that would once again ignite a spark in the never-ending controversy of extent of lateral neck dissection. The results showed that for the dissected neck, the ipsilateral neck recurrence-free status was superior in the CLND patients (97.7% vs 89.4%, $p < .001$).

These revelations raise serious concerns on the issue of recurrence after different types of lateral neck dissections for PTC, a point which could not be ignored with derogatory remarks. Since patterns of recurrence form the basis for all decision making in oncosurgery, this study clearly has far-reaching implications. Concluding their results in an elegant way, the authors recommended that SND should only be done in highly selected cases with small volume disease. Results similar to the McNamara study were reported by Javid et al[48] (2016) who conducted a retrospective analysis of 241 lateral neck dissections in 191 patients. The authors brought out some astonishing facts and concluded that omitting of levels II and V during lateral neck dissection for papillary thyroid carcinoma would potentially miss level II disease in two-thirds of patients and level V disease in one-fifth of patients. Hence, formal modified radical neck dissection should be considered to avoid the morbidity of reoperative surgery.

Attention must be brought to the recent study by Xu et al[49] (2017), which reports results in contrast to the McNamara report. The objective was to bring out factors predictive of regional neck recurrence, including extent of initial neck dissection. Retrospective analysis was done on a total of 178 patients who underwent 204 neck dissections. Of these, 54% (110) had selective neck dissection (SND) and 46% (94) had comprehensive neck dissection. The mean follow-up was 6.3 years. The significant predictors of regional failure were reported to be total number of suspicious nodes on preoperative imaging ($p = 0.029$), largest positive node on initial neck dissection ($p < 0.01$) and whether patients received adjuvant radiotherapy ($p = 0.028$). For the parameter of extent of lateral neck dissection, there was no significant difference. However, it must be pointed out that the sample size in this study was relatively smaller compared to the McNamara report, which presented an extensive review of a large cohort from a major center.

While there have been opposing results published by various authors from different continents, there are a few studies which represent a balance of the two extremes. Glenn et al[50] (2015) conducted a retrospective review of 127 lateral neck dissections (LND) in 96 patients at a single institute. The authors recommend a cautious approach towards extent of lateral neck dissection, stating that LND is associated with a risk of early postoperative morbidity while long-term complications are uncommon in the hands of experienced surgeons. A comprehensive preoperative evaluation of the lateral neck is required with physical examination, ultrasonography and FNAC (fine needle aspiration cytology). In patients with suspicion of metastases, LND could be an important option but the patient should be counselled regarding potential risks and benefits.

CONCLUSION

Although there is abundant evidence available in the literature to guide treatment decisions regarding the extent of lateral neck dissection in PTC, there is no consensus towards a specific treatment protocol. Over the last two decades, commendable studies were published pertaining to this topic, some of which were impeccable in terms of their exhaustive review. Even though, time and again, guidelines were suggested by different head and neck societies throughout the world, there is no single treatment algorithm accepted across all continents. Various high-volume centers in United States have published data of high quality, which may not coincide with results from major centers in Europe and Asia. The recent publication of major studies with appreciably large cohorts and results showing significant differences for parameters analyzed, have raised serious concerns over some previously suggested guidelines, in terms of recurrence after selective lateral neck dissection. It must be emphasized that all guidelines, no matter from which head and neck society, are finally based on some basic reference studies which are considered authentic by the majority of a society or country. Thus the publication of new studies which adopt accurate research methodology and employ large test cohorts from major high-volume centers, raises doubts regarding any previous data, especially when it relates to a topic for which there has been no widely accepted consensus.

Apart from this, it is pertinent to mention that the number of prospective studies in relation to extent of lateral neck dissection for PTC is not adequate and future research efforts should be directed towards the goal of prospective study designs with large cohorts and adequate follow-up periods.

After an exhaustive review of all available evidence, it can be stated that treatment decisions regarding extent of lateral neck dissection for differentiated thyroid cancer should be guided by presence of various risk factors discussed in this study, in addition to comprehensive preoperative evaluation of the lateral neck with physical examination, ultrasonography and FNAC. Apart from this intraoperative frozen section of central and lateral lymph nodes should be carried out when required. Future perspectives would involve exploring the role of sentinel lymph node biopsy from lateral neck.

AUTHOR CONTRIBUTIONS

Author No. 1: participated in the conception and design of the manuscript, drafting of manuscript and literature search.

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CONFLICT OF INTERESTS

The author declares that there is no conflict of interests that could influence this work.

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This article does not contain any studies with human participants or animals performed by any of the authors.

REFERENCES

1. Sherman SI. Thyroid carcinoma. Lancet, 2003; 361: 501–11.
2. Haselkorn T, Bernstein L, Preston-Martin S, Cozen W, Mack WJ. Descriptive epidemiology of thyroid cancer in Los Angeles County, 1972–1995. Cancer Causes Control, 2000; 11: 163–70.
3. Hodgson NC, Button J, Solorzano CC. Thyroid cancer: is the incidence still increasing? Ann Surg Oncol, 2004; 11: 1093–7.
4. Reynolds RM, Weir J, Stockton DL, Brewster DH, Sandeep TC, Strachan MW. Changing trends in incidence and mortality of thyroid cancer in Scotland. Clin Endocrinol (Oxf), 2005; 62: 156–62.
5. Burgess JR, Tucker P. Incidence trends for papillary thyroid carcinoma and their correlation with thyroid surgery and thyroid fine-needle aspirate cytology. Thyroid, 2006; 16: 47–53.
6. Friedman M, Kelley K, Maley A. Central neck dissection. Operative Techniques in Otolaryngology -Head and Neck Surgery, 2011; 22: 169–72.
7. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association management guide-lines for adult patients with thyroid nodules and differentiated thyroid cancer. Thyroid, 2016; 26: 1–133.
8. Moo TA, McGill J, Allendorf J, Lee J, Fahey T 3rd, Zarnegar R. Impact of prophylactic central neck lymph node dissection on early recurrence in papillary thyroid carcinoma. World J Surg, 2010; 34: 1187–91.
9. Shan CX, Zhang W, Jiang DZ, Zheng XM, Liu S, Qiu M. Routine central neck dissection in differentiated thyroid carcinoma: a systematic review and meta-analysis. Laryngoscope, 2012; 122: 797–804.
10. Lang BH, Ng SH, Lau LL, Cowling BJ, Wong KP, Wan KY. A systematic review and meta-analysis of prophy-lactic central neck dissection on short-term loco-regional recurrence in papillary thyroid carcinoma after total thyroidectomy. Thyroid, 2013; 23: 1087–98.
11. Zetoune T, Keutgen X, Buitrago D, et al. Prophylactic central neck dissection and local recurrence in papillary thyroid cancer: a meta-analysis. Ann Surg Oncol, 2010; 17: 3287–93.
12. Goffredo P, Roman SA, Sosa JA. Hurthle cell carcinoma: a population-level analysis of 3311 patients. Cancer, 2013; 119: 504 –11.
13. Wada N, Duh QY, Sugino K, et al. Lymph node metastasis from 259 papillary thyroid microcarcinomas: frequency, pattern of occurrence and recurrence, and optimal strategy for neck dissection. Ann Surg, 2003; 237: 399–407.
14. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid, 2016 Jan; 26(1): 1-133.
15. Randolph GW, Duh QY, Heller KS, LiVolsi VA, Mandel SJ, Steward DL, Tufano RP, Tuttle RM; American Thyroid Association Surgical Affairs Committee's Taskforce on Thyroid Cancer Nodal Surgery. The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic

lymph nodes, as well as the presence of extranodal extension. Thyroid, 2012 Nov; 22(11): 1144-52.
16. Conzo G, Docimo G, Pasquali D, et al. Predictive value of nodal metastases on local recurrence in the management of differentiated thyroid cancer. Retrospective clinical study. BMC Surgery, 2013; 13(Suppl 2): S3.
17. Heaton CM, Chang JL, Orloff LA. Prognostic Implications of Lymph Node Yield in Central and Lateral Neck Dissections for Well-Differentiated Papillary Thyroid Carcinoma. Thyroid, 2016 Mar; 26(3): 434-40.
18. Lee SG, Ho J, Choi JB, Kim TH, Kim MJ, Ban EJ, Lee CR, Kang SW, Jeong JJ, Nam KH, Jung SG, Jo YS, Lee J, Chung WY. Optimal Cut-Off Values of Lymph Node Ratio Predicting Recurrence in Papillary Thyroid Cancer. Medicine (Baltimore), 2016 Feb; 95(5): e2692.
19. Lee DJ, Lee KH, Kim JH, Kwon KH, Yoon DY, Rho YS. Posterosuperior lesion has a high risk of lateral and central nodal metastasis in solitary papillary thyroid cancer. World J Surg, 2015 Feb; 39(2): 387-92.
20. Xiang D, Xie L, Xu Y, Li Z, Hong Y, Wang P. Papillary thyroid microcarcinomas located at the middle part of the middle third of the thyroid gland correlates with the presence of neck metastasis. Surgery, 2015 Mar; 157(3): 526-33.
21. Sugitani I, Fujimoto Y, Yamada K, Yamamoto N. Prospective outcomes of selective lymph node dissection for papillary thyroid carcinoma based on preoperative ultrasonography. World J Surg, 2008 Nov; 32(11): 2494-502.
22. Ito Y, Higashiyama T, Takamura Y, Miya A, Kobayashi K, Matsuzuka F, Kuma K, Miyauchi A. Risk factors for recurrence to the lymph node in papillary thyroid carcinoma patients without preoperatively detectable lateral node metastasis: validity of prophylactic modified radical neck dissection. World J Surg, 2007; 31: 2085–2091.
23. Noguchi S, Murakami N: The value of lymph-node dissection in patients with differentiated thyroid cancer. Surg Clin North Am, 1987; 67: 251–261.
24. Shaha AR: Management of the neck in thyroid cancer. Otolaryngol Clin North Am, 1998; 31: 823–831.
25. Bhattacharyya N: Surgical treatment of cervical nodal metastases in patients with papillary thyroid carcinoma. Arch Otolaryngol Head Neck Surg, 2003; 129: 1101–1104.
26. Lee CW, Gong G, Roh JL. Intraoperative diagnosis of central compartment lymph node metastasis predicts recurrence of patients with papillary thyroid carcinoma and clinically node-negative lateral neck and may guide extent of initial surgery. World J Surg, 2015; 39: 194–202.
27. Lan X, Sun W, Zhang H, Dong W, Wang Z, Zhang T. A Meta-analysis of Central Lymph Node Metastasis for Predicting Lateral Involvement in Papillary Thyroid Carcinoma. Otolaryngol Head Neck Surg, 2015 Nov; 153(5): 731-8.
28. Lei J, Zhong J, Jiang K, Li Z, Gong R, Zhu J. Skip lateral lymph node metastasis leaping over the central neck compartment in papillary thyroid carcinoma. Oncotarget, 2017 Apr 18; 8(16): 27022–27033.
29. Lim YC, Koo BS. Predictive factors of skip metastases to lateral neck compartment leaping central neck compartment in papillary thyroid carcinoma. Oral Oncology, 2012; 48(3): 262–265.
30. Lee SK, Lee JH, Bae SY, Kim J, Kim M, Lee HC, Jung YY, Kil WH, Kim SW, Lee JE, Nam SJ, Choe JH, Kim JH, Kim JS. Lateral neck sentinel lymph node biopsy in papillary thyroid carcinoma, is it really necessary? A randomized, controlled study. Surgery, 2015 Mar; 157(3): 518-25.
31. Kupferman ME, Patterson DM, Mandel SJ, LiVolsi V, Weber RS. Safety of modified radical neck dissection for differentiated thyroid carcinoma. Laryngoscope, 2004; 114: 403–406.
32. Kupferman ME, Patterson M, Mandel SJ, LiVolsi V, Weber RS. Patterns of lateral neck metastasis in papillary thyroid carcinoma. Arch Otolaryngol Head Neck Surg, 2004; 130: 857–860.
33. Caron NR, Tan YY, Ogilvie JB, et al. Selective modified radical neck dissection for papillary thyroid cancer — is level I, II and V dissection always necessary? World J Surg, 2006; 30: 833–840.
34. Sivanandan R, Soo KC. Pattern of cervical lymph node metastases from papillary carcinoma of the thyroid. Br J Surg, 2001; 88: 1241–1244.
35. Lee J, Sung TY, Nam KH, Chung WY, Soh EY, Park CS. Is level IIb lymph node dissection always necessary in N1b papillary thyroid carcinoma patients? World J Surg, 2008 May; 32(5): 716-21.
36. Koo BS, Yoon YH, Kim JM, Choi EC, Lim YC. Predictive factors of level IIb lymph node metastasis in patients with papillary thyroid carcinoma. Ann Surg Oncol, 2009 May; 16(5): 1344-7.
37. Farrag T, Lin F, Brownlee N, Kim M, Sheth S, Tufano RP. Is routine dissection of level II-B and V-A necessary in patients with papillary thyroid cancer undergoing lateral neck dissection for FNA-confirmed metastases in other levels. World J Surg, 2009 Aug; 33(8): 1680-3.
38. Eweida AM, Sakr MF, Hamza Y, Khalil MR, Gabr E, Koraitim T, Al-Wagih HF, Abo-Elwafa W, Ezzat Abdel-Aziz T, Diab AA, El-Sabaa B, Nabawi AS. Level I lymph node involvement in patients with N1b papillary thyroid carcinoma: a prospective study. Eur Arch Otorhinolaryngol, 2017 Apr; 274(4): 1951-1958.
39. Kupferman ME, Weinstock YE, Santillan AA, Mishra A, Roberts D, Clayman GL, Weber RS. Predictors of level V metastasis in well-differentiated thyroid cancer. Head Neck, 2008 Nov; 30(11): 1469-74.

40. Merdad M, Eskander A, Kroeker T, Freeman JL. Metastatic papillary thyroid cancer with lateral neck disease: pattern of spread by level. Head Neck, 2013 Oct; 35(10): 1439-42.
41. Ahmadi N, Grewal A, Davidson BJ. Patterns of cervical lymph node metastases in primary and recurrent papillary thyroid cancer. J Oncol, 2011; 2011: 735678.
42. Stack BC Jr, Ferris RL, Goldenberg D, et al. American Thyroid Association consensus review and statement regarding the anatomy, terminology, and rationale for lateral neck dissection in differentiated thyroid cancer. Thyroid, 2012; 22: 501–508.
43. Hasney CP, Amedee RG. What is the appropriate extent of lateral neck dissection in the treatment of metastatic well-differentiated thyroid carcinoma? Laryngoscope, 2010; 120: 1716–1717.
44. Khafif A, Medina JE, Robbins KT, Silver CE, Weber RS, Rinaldo A, Owen RP, Shaha AR, Ferlito A. Level V in therapeutic neck dissections for papillary thyroid carcinoma. Head Neck, 2013 Apr; 35(4): 605-7.
45. Eskander A, Merdad M, Freeman JL, Witterick IJ. Pattern of spread to the lateral neck in metastatic well-differentiated thyroid cancer: a systematic review and meta-analysis. Thyroid, 2013 May; 23(5): 583-92.
46. Park JY, Koo BS. Individualized optimal surgical extent of the lateral neck in papillary thyroid cancer with lateral cervical metastasis. Eur Arch Otorhinolaryngol, 2014 Jun; 271(6): 1355-60.
47. McNamara WF, Wang LY, Palmer FL, Nixon IJ, Shah JP, Patel SG, Ganly I. Pattern of neck recurrence after lateral neck dissection for cervical metastases in papillary thyroid cancer. Surgery, 2016 Jun; 159(6): 1565-71.
48. Javid M, Graham E, Malinowski J, Quinn CE, Carling T, Udelsman R, Callender GG. Dissection of levels II through V is required for optimal outcomes in patients with lateral neck lymph node metastasis from papillary thyroid carcinoma, 2016; 222(6): 1066–1073.
49. Xu JJ, Yu E, McMullen C, Pasternak J, Brierley J, Tsang R, Zhang H, Eskander A, Rotstein L, Sawka AM, Gilbert R, Irish J, Gullane P, Brown D, de Almeida JR, Goldstein DP. Patterns of regional recurrence in papillary thyroid cancer patients with lateral neck metastases undergoing neck dissection. J Otolaryngol Head Neck Surg, 2017 May; 46(1): 43.
50. Glenn JA, Yen TW, Fareau GG, Carr AA, Evans DB, Wang TS. Institutional experience with lateral neck dissections for thyroid cancer. Surgery, 2015 Oct; 158(4): 972-8.