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Original Research

Effects of Central Neck Dissection on Complications in Differentiated Thyroid Cancer

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Abstract

Objective: It is still controversial whether performing central neck dissection (CND) in addition to total thyroidectomy (TT) increases the risk of complications. In the present study, we aimed to evaluate the effect of CND on the development of complications in differentiated thyroid cancer (DTC) compared to TT.

Material and Methods: The data of 186 patients (136 females and 50 males) with a mean age of 48.73±14.78 (range, 17–82) whom were operated for DTC were evaluated retrospectively. The patients were divided into two groups; TT (Group 1) and CND±TT/Completion thyroidectomy±lateral neck dissection (Group 2).

Results: There were 117 (91 F, 26 M) patients in Group 1 and 69 (45 F, 24 M) patients in Group 2. Parathyroid auto transplantation (PA) was significantly higher in Group 2 compared to Group 1 (42% vs. 6%) (p=0.000). Total (58% vs. 21.4%, respectively; p=0.000) and transient hypoparathyroidism (52.2% vs. 20.5%, respectively; p=0.000) were significantly higher in Group 2 than in Group 1, but permanent hypoparathyroidism rates were statistically not significant (5.8% vs. 0.9%, respectively; p=0.064). In the multinomial logistic regression analysis, CND alone was determined as an independent risk factor for increased both total and transient hypoparathyroidism. The relative risk (RR) of CND for total hypoparathyroidism was 5.2 times increased (odds ratio [OR]: 0.192) (p=0.007), while the RR for transient hypoparathyroidism was 3.5 times increased (OR: 0.285) (p=0.036). According to the number of nerves at risk, CND was performed in 119 neck side and only thyroidectomy was performed in 253 neck side. Total vocal cord paralysis (VCP) rate (9 [7.6%] vs. 6 [2.4%], respectively) (p=0.017) and transient VCP rate (7 [6%] vs. 4 [1.6%], respectively) (p=0.021) in patients who underwent CND were significantly higher compared to those who underwent only thyroidectomy. In multinomial logistic regression analysis performing only CND was an independent risk factor for total VCP, and increased the total VCP RR approximately 5.34 times (OR:0.184; p=0.007).

Conclusion: Although CND can be applied without increasing the rates of permanent hypoparathyroidism and VCP compared to TT, it increases the risk of total and transient hypoparathyroidism, total, and transient VCP. Patients undergoing CND should be followed carefully in terms of transient hypoparathyroidism.

Keywords: Central neck dissection; complications, thyroid cancer.

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Introduction

Differentiated thyroid cancer (DTC) is the most common endocrine malignancy and papillary thyroid cancer (PTC) accounts for more than 85% of cases.[1,2]

Clinically positive cervical lymph node metastasis is 20–50% in DTC, and the rate of micrometastasis increases to 90% when elective central neck dissection (CND) is performed.[3]

The primary treatment of DTC is surgery, with removal of the primary tumor with non-thyroid extensions and clinically positive metastatic lymph nodes. Although the debate about the extent of surgery in DTC continues, the aim is to perform the most appropriate surgery with minimum complications.[4]

The most common lymph node metastasis in DTC is to the central region. Although there is consensus on therapeutic CND, the extent of CND and/or whether to perform prophylactic CND (pCND) is still controversial. Whether performing concomitant CND with thyroidectomy increases the risk of complications is another matter of debate.[5–7]

We aimed to evaluate the effect of CND compared to total thyroidectomy (TT) on the development of complications.

Materials and Methods

After obtaining the approval of the local ethics committee (approval no. 2981, date:08/09/2020), the data of patients who underwent primary or revision surgery for DTC between 2011 and 2017 were evaluated retrospectively. Of the 186 patients (136 women, 50 men) with a mean age of 48.73±14.78 (17–82) who met the inclusion criteria, 177 had PTC and nine had follicular thyroid cancer. Exclusion criteria were as follows: Thyroid cancers other than DTC, patients who underwent intervention in only one thyroid lobe or lodge, patients with thyroid malignancy detected in lobectomy and who underwent completion thyroidectomy, patients with only lateral compartment dissection, patients with pre-operative vocal cord paralysis (VCP), patients with pre-operative permanent hypoparathyroidism, patients with advanced locally invasive thyroid cancer, patients in whom recurrent laryngeal nerve (RLN) was intentionally resected due to tumor invasion and patients with missing data.

The patients were divided into two groups. Group 1 consisted of patients who underwent TT or completion thyroidectomy. Group 2 consisted of patients who underwent CND±TT/CT±lateral neck dissection (LND).

All patients underwent thyroidectomy with standard intraoperative nerve monitoring (intermittent/continuous or intermittent+continuous) under general anesthesia. The thyroid lodge was exposed with the anterior approach in primary cases, from the midline, and in secondary cases, between the sternocleidomastoid muscle and the strep muscles, with a lateral approach (also called the back door approach). The primary and secondary thyroidectomy techniques were detailed in other studies.[8–12]

CND and LND have been performed in accordance with the defined standards.[13]

All patients underwent pre-operative and post-operative vocal cord examination. Periodic vocal cord examination was performed in patients who developed postoperative VCP. VCPs that improved up to 6 months were defined as transient, and those that did not improve at 6 months were defined as permanent VCPs. Post-operative hypoparathyroidism was evaluated with parathyroid hormone (PTH) measured within the first 24 h. A PTH value of <15 pg/mL in the first 24 h was defined as post-operative hypoparathyroidism.[14]

A serum calcium (Ca) value of <8 mg/dl on the post-operative 1st day was defined as biochemical hypocalcemia.[15] Permanent hypoparathyroidism was defined as a PTH value below the normal reference values and/or the need for Ca therapy at 6 months.[16] Vitamin D (vit D) value of <20 ng/mL was defined as Vit D deficiency.[17]

The effect of CND on complication rates compared to thyroidectomy was evaluated. In addition, risk factors affecting hypoparathyroidism and RLN paralysis were evaluated with multivariate analysis.

Statistical Analysis

Data were evaluated in IBM SPSS Statistics V25 program (IBM, Armonk, NY, USA). In statistical evaluation; numbers and percentages for categorical variables; and mean, standard deviation, minimum and maximum for numerical variables were given. In the comparison of the groups; differences between the ratios of categorical variables were made with the Pearson Chi-square test, and nonparametric comparisons were made with the Mann–Whitney U-test. Appropriate models were found by testing the risk factors evaluated for hypoparathyroidism and independent factors affecting VCP. Multivariate binary logistic regression was applied to test the effect of CND under adjustment for other relevant risk factors. Missing or unknown values were interpolated. A value of $p<0.05$ was accepted as significance.

Results

The types of surgery performed in both groups are given in Table 1. There were 117 (91 F, 26 M) patients in Group 1 and 69 (45 F, 24 M) patients in Group 2. There was no significant difference between the two groups in terms

Table 1. Type of intervention applied to the groups

	Group 1 *n*=117	Group 2 *n*=69
Primary surgery		
TT	113	
TT+UCND		15
TT+BCND		18
TT+BCND+LND		26
Total (Primary surgery)	113	59
Reoperative surgery		
CT	4	
CT+UCND		2
CT+BCND		2
CT+UCND+LND		2
BCND		2
BCND+LND		2
Total (Reoperative surgery)	4	10
Total (Primary+Revision surgery)	117	69

TT: Total thyroidectomy; CT: Completion thyroidectomy; UCND: Unilateral central neck dissection; BCND: Bilateral central neck dissection; LND: Lateral neck dissection.

of age, gender, pre-operative Ca, PTH, and vit D deficiency rates. Secondary intervention rate (11% vs. 5.1%, *p*=0.008), PA (42% vs. 6%, *p*=0.000), and rate of unintentionally removed parathyroid gland in the pathology specimen (37.7% vs. 9.4%, respectively; *p*=0.000) rates were significantly higher in Group 2 compared to Group 1 (Table 2).

Hypoparathyroidism

In Group 2, post-operative PTH value in the first 24 h (19.3±21 pg/mL vs. 32.5±23.3 pg/mL, respectively; *p*=0.000) and post-operative 1st day Ca value (8±0.7 mg/dl vs. 8.4±0.6 mg7dl, respectively; *p*=0.000) was lower than Group 1 (Table 2).

Total post-operative hypoparathyroidism (58% vs. 21.4%, respectively; *p*=0.000) and transient hypoparathyroidism (52.2%vs. 20.5%, respectively; *p*=0.000) were significantly higher in Group 2 than in Group 1 (Table 2). Although the rate of permanent hypoparathyroidism was higher in Group 2 than in Group 1, the difference was not statistically significant (5.8% vs. 0.9%, respectively; *p*=0.064) (Table 2).

In Group 2, total hypoparathyroidism was present in 10 (52.6%) of 19 patients who underwent unilateral CND

Table 2. Comparison of demographical, clinical, and biochemical features between the groups

	Group 1 (*n*=117)	Group 2 (*n*=69)	*p*
Age Mean±SD/yıl	49.6+13.4	44.95+12.6	0.189
(Min–Max)	(19–81)	(17–82)	
Gender (F/M)	91/26	45/24	0.062
Pre-operative Ca (Ort±SD mg/dl)	9.3+0.6	9.4+0.4	0.391
(Min–Max)	(8.4–10.2)	(8.2–10)	
Pre-operative PTH (Ort±SD pg/mL)	52.2+22.1	52.2+27.5	0.434
(Min–Max)	(23.1–124.4)	(21.7–127.8)	
Preoperative vit D deficiency (<20 ng/mL) n (%)	25 (%36.2)	47 (%402)	0.650
Secondary intervention n(%)	6 (5.1%)	8 (11.6%)	0.008
Parathyroid transplantation n (%)	6 (5.2%)	29 (42%)	0.000
Unintentional parathyroidectomy	11 (9.4%)	26 (37.7%)	0.000
Post-operative early Ca (Mean±SD mg/dl)	8.4+0.6	8+0.7	0.000
(Min–Max)	(5.08–10.05)	(6.2–9.9)	
Postoperative early PTH (Mean±SD pg/ml)	32.5+23.3	19.3+21	0.000
(Min–Max)	(0–102.9)	(0–108)	
Hypoparathyroidism			
Transient	24 (20.5%)	36 (52.2%)	0.000
Permanent	1 (0.9%)	4 (5.8%)	0.064
Total	25 (21.4%)	40 (58%)	0.000

Ca: Calcium; PTH: Parathyroid hormone; vit D: Vitamin D; SD: Standard deviation.

Table 3. Factors affecting the risk of total and transient hypoparathyroidism in multinomial logistic regression analysis

	Hypoparathyroidism			
	Total Hypoparathyroidism		Transient Hypoparathyroidism	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Age	1.023 (0.995–1.057)	0.099	1.017 (0.988–1.047)	0.251
Gender			0.437 (0.157–1.219)	
Male	0.400 (0.143–1.119)	0.081		0.114
Female	1,00 (reference)		1,00 (reference)	
Central neck dissection				
(–)	0.192 (0.058–0.633)	0.007	0.285 (0.088–0.924)	0.036
(+)	1,00 (reference)		1,00 (reference)	
Lateral neck dissection				
(–)	0.609 (0.178–2.086)	0.430	0.537 (0.158–1.822)	0.319
(+)	1,00 (reference)		1,00 (reference)	
Intervention type				
Primary	2.747 (0.566–13.338)	0.210	3.243 (0.623–16.878)	0.162
Secondary	1,00 (reference)		1,00 (reference)	
Parathyroid transplantation				
(–)	0.587 (0.193–1.785)	0.347	0.397 (0.134–1.178)	0.096
(+)	1,00 (reference)		1,00 (reference)	
Unintentional parathyroidectomy				
(–)	0.475 (0.160–1.412)	0.181	0.556 (0.186–1.662)	0.293
(+)	1,00 (reference)		1,00 (reference)	
Vit D deficiency				
(–)	1.191 (0.490–2.896)	0.699	0.920 (0.375–2.257)	0.856
(+)	1,00 (reference)		1,00 (reference)	

Multivariable logistic regression analyzes of risk factors for post-operative total and transient hypoparathyroidism. OR: Odds ratio; CI: Confidence interval; Vit D:Viatamin D.

(UCND) and in 30 (60%) of 50 patients who underwent bilateral CND (BCND); the difference was not significant (p=0.596). Similarly, the rate of transient hypoparathyroidism was 52.6% and 54%, and permanent hypoparathyroidism was 0% and 6%, respectively, and there was no significant difference (p=1, p=0.569, respectively).

For the multinomial logistic regression analysis, the model consisting of the factors in Table 3 was found to be suitable for both total and transient hypoparathyroidism (p=0.000 for both). Of these factors evaluated, only CND application was found to be an independent risk factor for both total and transient hypoparathyroidism. The relative risk (RR) of CND for total hypoparathyroidism was 5.2 times increased (odds ratio [OR]: 0.192) (p=0.007), while the RR for transient hypoparathyroidism was 3.5 times increased (OR: 0.285).

VCP

VCP rates were evaluated according to the number of nerves at risk. 15 VCPs (4%) developed in a total of 372 treated neck sides, of which 11 were temporary and four were permanent VCPs. All VCPs were unilateral. Six (2.4%) total VCP were seen in 253 neck sides that underwent thyroidectomy alone, and nine (7.6%) in 119 neck sides that underwent CND, which were significantly higher in the CND group (p=0.017).

The rate of transient VCP was significantly higher in those who underwent CND than in those who underwent only thyroidectomy (7 [6%] vs. 4 [1.6%]; p=0.021), there was no significant difference in terms of permanent VCP (2 [1.7%] vs. 2 [0.8%], respectively; p=0.569).

Among the models tested for VCP, the model including gender, CND, and secondary intervention was found to be

Table 4. Factors affecting the risk of total vocal cord paralysis in multinomial logistic regression analysis

	Total VCP	
	OR (95%CI)	***P***
Gender		
Male	0.766 (0.221–2.650)	0.674
Female	1,00 (reference)	
Central dissection		
(–)	0.184 (0.054–0.624)	0.007
(+)	1,00 (reference)	
Intervention type		
Primary	0.948 (0.179–5.034)	0.950
Secondary	1,00 (reference)	

Multivariable logistic regression analyzes of risk factors for postoperative total vocal cord palsy. VCP: Vocal cord paralysis; OR: Odds ratio; CI: Confidence interval.

suitable only for total VCP (p=0.030) (Table 4). In the multinomial logistic regression analysis, performing only CND was found to be an independent risk factor for total VCP (p=0.007). Performing central dissection increased the total VCP RR approximately 5.34-fold (OR: 0.184).

Apart from these, in Group 2, one patient developed chylous fistula, two patients who underwent LND developed transient paralysis of the marginal mandibular branch of the facial nerve, and three patients developed shoulder pain.

Discussion

The main complications of thyroid surgery are hypoparathyroidism and VCP, which are important factors that negatively affect the postoperative quality of life.[18,19] Although discussions about surgical treatment in DTC still continue, minimizing post-operative morbidity is one of the main factors affecting the optimal surgical extent.

Although the majority of the researchers think that CND in addition to TT increases the risk of complications compared to TT alone, there are studies reporting that it does not increase the risk of permanent complications.[7,20]

Our primary aim was to evaluate the effect of extent of surgery on complications in DTC. Hypoparathyroidism is the most common complication of thyroidectomy. In our study, the rate of total post-operative hypoparathyroidism (58% vs. 21.4%, respectively; p=0.000), and transient hypoparathyroidism (52.2% vs. 20.5%, respectively; p=0.000) was significantly higher in patients who underwent CND compared to those who underwent only thyroidectomy. The difference between the two groups in terms of the rate of permanent hypoparathyroidism was not significant (5.8% vs. 0.9%, respectively; p=0.064). In addition, performing CND was found to be an independent risk factor for both total and transient hypoparathyroidism in multinomial logistic regression analysis. CND increased the risk of total hypoparathyroidism 5.2 times (OR: 0.192) and the risk of transient hypoparathyroidism 3.5 times (OR: 0.285) compared to thyroidectomy alone.

Barczyński *et al*. reported that performing pCND with TT compared to TT-alone in primary thyroid cancer increased the rate of transient hypoparathyroidism (13.1% vs. 30.4%; p<0.001 OR 2·90, 95% C:1·92 to 4·38), and the rates of persistent hypoparathyroidism as similar (0.7% vs. 2.2%; p=0.122).[21]

In their meta-analysis of 11 studies by Wang *et al*., they found that pCND increased the risk of transient hypoparathyroidism compared to TT (RR:2.5 (95% CI: 1.95–3.25, I_2=0%), but they reported no difference in terms of long-term complications.[6]

In a meta-analysis of 17 studies by Zhao *et al*., both transient hypoparathyroidism (28.7% vs. 17.5%, OR=2.37; 95% CI: 1.89–2.96; p<0.00001) and permanent hypoparathyroidism (4.1% vs. 2.3%, OR)=1.93; 95% CI: 1.05–3.57; p=0.03) rates were found to be higher with pCND compared to TT. The overall morbidity rate was also found to be higher (OR=2.56; 95% CI: 1.75–3.74; p<0.00001).[22]

Similarly, another meta-analysis reported a higher rate of permanent hypoparathyroidism with pCND (TT: 1.55% vs. pCND: 3.45%).[5] Giordano *et al*. compared TT, TT+UCND, TT+BCND in terms of postoperative complications in the treatment of primary thyroid cancer. Transient hypoparathyroidism rate was higher in both TT+UCND (36.1%; p=0.014 [OR]: 1.477; 95%CI: 1.091–2.001) and TT+BCND (51.9%; p<0.001; OR: 2.827; 95% CI: 2.065–3.870), compared to TT (27.7%). Although the rate of permanent hypoparathyroidism was similar in TT (6.33%) and TT+UCND (7%), it was higher in TT+BCND (16.2%; p<0.001; OR: 2.860; 95% CI: 1.725–4.743).[23]

In our study, the rates of transient hypoparathyroidism were similar between patients in Group 2 who underwent UCND and BCND (52.4% vs. 54%). Although there was no statistical difference in terms of permanent hypoparathyroidism (0% vs. 6%, respectively; p=0.569), it is noteworthy that there was no permanent hypoparathyroidism in the UCND group.

Risk factors for total hypocalcemia were evaluated in recent meta-analyses and have been reported as TT (OR: 3.59), thyroid malignancy (OR:1.85), incidental parathyroidectomy

(OR: 1.58), CND (OR: 1.54), female gender (R:1.49), hypoparathyroidism (OR: 5.58), hypomagnesemia (OR: 2.85), pre-operative vit D deficiency (OR: 2.32), and modified radical neck dissection (OR: 1.57).[24]

In a meta-analysis including 115 studies, unintentional parathyroid resection (OR: 1.90), parathyroid autotransplantation (PA) (OR: 2.03), and female gender were found to be independent risk factors for transient hypoparathyroidism.[25]

In another meta-analysis of 68 studies, no factor was found to reduce permanent hypocalcemia.[26]

In our study, in the CND group, secondary intervention (11% vs. 5.1%; *p*=0.008), PA (42% vs. 6%, respectively; *P* <0.000), and rate of unintentionally removed parathyroid gland in the pathology specimen (37.7% vs. 9.4%, respectively; *P* <0.000) were significantly higher, compared to TT group. We think that the deterioration of parathyroid gland nutrition and the parathyroid glands removed between the lymph nodes in the central tissue in CND are the main factors affecting the increased PA rates. However, we think that the parathyroid glands' resemblance to enlarged lymph nodes in the central tissue and not being noticed is an important factor in the excess of parathyroid glands removed unintentionally. Although these features were included in the model in the multinomial logistic regression analysis, they were not found to be risk factors for total and transient hypoparathyroidism. However, we think that the increased rates of these features in the CND group are an important factor for CND to increase hypoparathyroidism. In addition, longer operating time in CND has a negative effect on parathyroid function secondary to hypothermal injury.[27]

In a prospective observational study evaluating patients who underwent TT+CND in primary thyroid cancer, patients who underwent unintentional parathyroidectomy had a higher rate of both postoperative hypocalcemia (64% vs. 46%; *P* <0.03) and permanent hypoparathyroidism (15% vs. 4%; *P* <0.03).[28]

Whether PA reduces permanent hypoparathyroidism is controversial. Although some studies have reported that PA reduces permanent hypoparathyroidism, other studies have reported that whether or not PA has no effect on permanent hypoparathyroidism.[29–31]

In situ preservation of the parathyroids has a critical role in preventing permanent hypoparathyroidism.[32] Preserving the vascularization of the lower parathyroids is particularly effective in reducing permanent hypoparathyroidism.[33]

Despite all the technical developments in thyroid surgery and additional methods such as IONM, the other major complication of thyroidectomy is VCP. According to our results, the rate of both total VCP (7.6% vs. 2.4%, respectively; *p*=0.017) and transient VCP (6% vs. 1.6%, respectively; *p*=0.021) was higher in patients who underwent CND according to the number of nerves at risk, compared to those who underwent only thyroidectomy. Permanent VCP rate (1.7% vs. 0.8%, respectively; *p*=0.569) was similar. CND was an independent risk factor for total VCP, with a RR of 5.4 (OR: 0.184; 95% CI: 0.054–0.624, *p*=0.007). We believe that the higher rate of VCP in CND is associated with applying traction to the thyroid for a longer time and dissecting the entire RLN in its course in the thyroid lodge in central dissection and wider dissection due to dissection of the lymph nodes around the RLN.

The effect of central dissection on VCP is controversial. Roh *et al*. found no difference in the incidence of transient and permanent VCP in patients with primary thyroid cancer, with and without central dissection.[34]

In another study evaluating risk factors for VCP, malignancy and CND were not found to be risk factors for transient VCP.[35]

In another study, the rate of permanent VCP was higher in patients with malignancy than in patients with benign lesions (5.9% vs. 0.3%; *p*=0.029).[36]

In thyroid malignancies, pT4a tumor (OR=8.5), macroscopic extrathyroidal spread (OR=3.5), and tracheoesophageal groove involvement (OR=2.8) were found to be independent risk factors for RLN paralysis. In addition, aggressive histology and central region lymph node positivity were found to be significant risk factors in the univariant analysis.[37]

Similar to our results, Ahn *et al*. found transient VCP rates higher in TT+CND compared to TT (10% vs. 3.4%; *p*=0.029), and similar permanent VCP rates (1.4% vs. 2.7%; *p*=1).[38]

In another study, the rate of unilateral VCP in thyroid malignancies was found to be higher in those who underwent CND with thyroidectomy compared to those who underwent only thyroidectomy (4.3% vs. 9.1%, respectively; *p*=0.03). In addition, in multivariance logistic regression analysis, the highest independent risk factor for EBSLN injury combined with unilateral VCP was TT with CND (OR: 6.77; 95% CI: 1.51–30.29; *p*=0.007).[39]

In a single-center study, in which Dhillon *et al*. evaluated over 2500 RLNs, the rate of total VCP was 2.9% and the rate of permanent VCP was 0.4%, and it was found that the risk of VCP was higher in CND compared to lobectomy (adjusted ORs [aOR]=2.4, 95CI=1.0–5.9). In addition, they found that it was associated with an increase in OR parallel to the increase in T stage in patients with malignancy (ptrend<0.001). Researchers reported that the highest

risk was in patients who had CND or patients with larger tumors.[40]

In a meta-analysis by Wang *et al*., the RR for transient VCP was 1.44 (95%CI: 0.59–3.55) in patients who underwent TT+pCND compared to TT, but the rates of permanent VCP were similar (RR: 1.14, 95%CI:0.46–2.83).[6]

There are some basic limitations of this study. First, the study has a non-randomized retrospective design, and some patients were excluded because their data were missing. Second, it includes both prophylactic and central dissections. However, all cases were operated by a single surgeon, and we think that preoperative and postoperative vocal cord examinations had important positive aspects.

Conclusion

Although CND can be applied without increasing the rates of permanent hypoparathyroidism and VCP compared to TT, it is an intervention that increases the risk of total and temporary hypoparathyroidism, total, and temporary VCP. Especially for pCND, the patient's characteristics and the increased risk of complications should be taken into account in patient selection. Patients undergoing CND should be followed carefully for transient hypoparathyroidism.

Disclosures

Ethics Committee Approval: The study was approved by the Ethics Committee of Sisli Hamidiye Etfal Training and Research Hospital. (Approval no: 2981, Approval date: 08.09.2020).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – M.T.U., N.A., M.U.; Design – N.A., M.U.; Supervision – N.A., A.I., M.U.; Data collection &/or processing – M.T.U., Z.G.D., M.A.; Analysis and/or interpretation – A.I., M.U.; Literature search – M.T.U., N.A., Z.G.D., A.I., M.U.; Writing – M.T.U.; Critical review – A.I., M.U.

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