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RESEARCH ARTICLE
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Correlations of cancer antigen 19-9 and Carcinoembryonic antigen with histopathological and clinical features among malignant thyroid tumors

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ABSTRACT

Background: CEA and CA19-9 are important serum tumor marker for malignant tumors especially gastrointestinal tumors. This study aimed to reveal the correlations of CA19-9 and CEA titers with malignant thyroid tumors (MTTs).

Methodology: This study enrolled patients' with MTTs (n=50), and control group (n=50). Thyroid biopsies were taken from MTTs and examined histopathologically and the sera of the patients' and control groups were tested for both CEA and CA19-9, the patients' group was tested twice, preoperatively and post operatively.

Results: Papillary thyroid carcinoma (PTC) was the most common MTT [n=46, (92%)]. Neck swelling was the most frequent (89.1%) feature among PTC patients. For the patients' group, the median serum CEA results preoperatively was 1.57 (1.08-2.30) ng/ml, then it became 1.57 (0.94-2.05) ng/ml postoperatively, while the median preoperative serum CA19-9 was 12.17 (6.50-18.68) U/ml, then it became 12.24 (6.57-20.11) U/ml postoperatively; for both tumor markers, the differences between preoperative and postoperative concentrations were statistically significant (<0.05). The differences between median CEA concentrations between patients' group and control group were statistically significant (p=0.001); while for CA 19-9 were statistically non-significant (p=0.936). Histologically, 97.92% of the differentiated thyroid tumors were in stage I.

Conclusion: There is significant decline in CEA concentration postoperatively among papillary thyroid carcinoma patients, while CA 19-9 was significantly increased postoperatively. The CEA concentration is higher in MTTs than in normal population and there is non-significant difference in CA 19-9 concentrations in MTTs and in normal population.

Keywords: *Thyroid, tumors, CEA, CA 19-9, Sulaimani city*

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INTRODUCTION

Thyroid malignancies are originating from thyroid parenchymal cells. Thyroid parenchyma is consisting of two major types of cells, the follicular cells that form the thyroid follicles, and parafollicular or C-cells that are surrounding the follicles. Thyroid malignancies can arise from both thyroid cellular types; follicular cells can give rise to differentiated thyroid malignancies (DTC) and undifferentiated thyroid malignancies. The parafollicular or C-cells can give rise to medullary thyroid malignancies (1).

The differentiated thyroid malignancies are categorized into three types of carcinomas: papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC) and Hurthle cell carcinoma (HCC), while the undifferentiated thyroid malignancy progress to anaplastic thyroid cancer (ATC) which is a rare type of thyroid malignancy (1).

Thyroid carcinomas accounts for roughly 1% of all new human malignant disease (2). Of these, at least 94% are differentiated thyroid carcinomas. Another 5% are medullary thyroid carcinoma, and the remaining 1% are anaplastic thyroid carcinoma that generally derive from dedifferentiation of the differentiated carcinomas (3).

Carbohydrate antigen19-9 (CA19-9) is proved as a tumor marker for screening of malignant diseases that develops from the pancreas (4-6). The serum concentration of CA19-9 is increased in other malignant/benign conditions of the digestive tract (4), respiratory tracts (7), and in other malignancies such as prostate cancer and papillary thyroid cancer with anaplastic transformation (8-10). CA19-9 has been recorded as a recurrent tumor marker of papillary thyroid neoplasm (11). In addition, recent studies showed the presence of elevation in CA19-9 level in clinical cases of aggressive MTC (12, 13).

Carcinoembryonic antigen (CEA) is an onco-fetal glycoprotein, it is usually produced by mucosal epithelial cells. The concentration of CEA is increased in different malignancies. It is usually associated with colorectal, breast, liver, stomach, and pancreas carcinomas (14) . in addition, CEA can be found in low concentration in healthy man.

CEA is secreted from mucosal cells into the circulation and can be distributed to the mucous secretions of the stomach, small intestine and bile duct. it has been shown to be enrolled in cell adhesion that avert apoptosis (15).

Aim of the study

This study aimed to reveal the correlations of CA19-9 and CEA titers with: malignant thyroid tumors, tumor types, and clinical features of the patients; the study also compared the titers of these markers in patients with different thyroid malignancies and with others populations with non-malignant thyroid diseases or healthy people.

METHODOLOGY

Study population

This study enrolled two groups: patients' group (n=50) and control group (n=50).

Patients group

This group included patients with primary malignant thyroid tumors, then we followed them till they were undergone surgical operation, their tumor biopsies were examined histopathologically and the sera of the patients' group were tested for both CEA and CA19-9, preoperatively and post operatively.

Control group

This group enrolled three subgroups of individuals: healthy people subgroup (n=12), hypothyroidism subgroup (n=19) and hyperthyroidism subgroup (n=19). They were tested for serum CEA and CA19-9.

Inclusion criteria

For the patients' group, any person proven by confirmatory histopathological examination to have primary malignant thyroid tumor was included, while the control group was included if he/she was free of any tumor; they were either

healthy individuals or patients with hyperthyroidism or hypothyroidism.

Exclusion Criteria

Any patients that did not meet the inclusion criteria of suspected visitors, were excluded from this study.

Setting of the Study

The patients' group, hypothyroidism patients, and hyperthyroidism patients were enrolled from those consulting specialists in Smart Health Tower/ Sulaimani city, and they were investigated in the same hospital.

Duration of the Study

The study extended from November 2021 to December 2022; in this period, specimens (biopsies and sera from patients' group and sera of the control group) were collected, stored, and tested by the appropriate procedure.

Study design

This study had three different designs:

Case control study: the patients' group and control group were tested for both CEA and CA19-9, for measuring the concentration of both tumor markers in their serum.

Cross sectional study: the serum concentration of both tumor markers tested in patients' group was correlated to clinical and demographic features.

Cohort-Prospective design: The patients' groups were tested twice, preoperatively and then postoperatively, for both CEA and CA19-9.

Carbohydrate Antigen19-9 (CA19-9) and Carcinoembryonic antigen (CEA) determinations

The electrochemiluminescence immunoassay "ECLIA" was utilized for quantitative determination of both CA19-9 and CEA in human serum using (Cobas E 411 immunoassay analyzers/Germany using CA19-9 and CEA diagnostic kits/ Roche/ Germany).

Formalin fixed-paraffin embedded block samples were used to sectioning and hematoxylin and eosin were used for staining tissue sections according to the standard procedure (16).

Statistical method for data analysis

The Statistical Package for Social Science (SPSS, Chicago, II, USA), version 26 was used for data entry and analysis. Two approaches were used: descriptive and analytic. Numerical variables were summarized using means, standard deviations (SD) for normally distributed data, while medians and interquartile ranges (IQR) for skewed variables. Mann-Whitney U test was used to compare between different groups (16-19). A P-value of ≤ 0.05 or ≤ 0.01 is considered statistically significant. In addition to the p-value, odds ratio (OR) with 95% confidence interval was used to estimate the association between MTTs and risk factors.

RESULTS:

The study showed that 70% (n=35/50) of patients with thyroid malignancies were females, while the remaining 30% (n=15/50) were males; the male to female ratio was (1:2.3) as shown in table (1). Most of the patients were in age group 31- 50 years old (n=31, 62%). The gender distribution in control group revealed 30 females (60%) and 20 males (40%). Furthermore, similar to patients' group, the age group 31- 50 years old was the most frequent age [n=22/50, (44%)]. Most of patients group were living in Sulaimani city [n=17, (34%)] followed by Hawler city [n=10, (20%)], table 1.

Housewife was the most occupation type among MTT group which was [n=29, (58%)] followed by worker employee [n=11, (22%)]. As well as, similar to patients' group, housewife was highest among control group [n=25, (50%)] followed by worker [n=14, (28%)], table 1.

The results revealed the presence of different primary malignant thyroid tumors among patients' group, these were: papillary thyroid carcinoma [n=46, (92%)], follicular thyroid carcinoma [n=1, (2%)], medullary thyroid carcinoma [n=1, (2%)], Hurthle cell carcinoma

[n=1, (2%)], and anaplastic thyroid carcinoma [n=1, (2%)]. However, the control group involved normal persons [n=12, (24%)], hyperthyroidism [n=19, (38%)] and hypothyroidism [n=19, (38%)], the confirmatory pathological description of MTTs of this study are described in the figures 1-5.

The result showed that all the MTT patients were symptomatic; among PTC patients, neck swelling was the most frequent (89.1%), also all other patients with (FTC, HCC, MTC, and ATC) had neck swelling; this is followed by dyspnea (58.7%), dysphagia (39.1%), then neck pain (37%) and changes in voice (37%).

Voice changes, neck pain, shoulder pain, and fatigue were the features manifested by FTC patient. The MTC complained from voice change, neck pain, coughing shoulder pain. Clinical features that were manifested in patient with HCC were neck pain, dyspnea, and fatigue. The clinical presentations in patient with ATC were voice change, neck pain, dyspnea, dysphagia, coughing, shoulder pain and fatigue, this is described in table 2; interestingly, none of FTC, MTC, HCC, or ATC complained from neck pain.

The median (IQR) duration between first serum specimen (preoperative serum specimen) and second serum specimen (post-operative serum specimen) was 24 (20-33) days for the PTC patients.

For PTC patients, the median (IQR) serum CEA results preoperatively was 1.57 (1.08-2.30) ng/ml, then it became 1.57 (0.94-2.05) ng/ml postoperatively, the difference between the two median titers was highly statistically significant (p=0.001).

The median (IQR) preoperative serum CA19-9 results for the PTC patients were 12.17 (6.50-18.68) U/ml, then it became 12.24 (6.57-20.11) U/ml postoperatively, and the results were also statistically significant (p=0.001), these results are described in table 4.

Preoperatively, the highest concentration of the CEA in PTC was 21.5 ng/ml and for CA19-9 was 107.0 U/ml, while the minimal CEA and CA 19-9 were 0.33 ng/ml and 1.4 U/ml respectively. While postoperatively, the highest serum CEA value was 7.5 ng/ml, whereas for CA 19-9 was 35.6 U/ml; the minimum results were 0.25 ng/ml for CEA and 1.3 U/ml for CA 19-9.

The mean (SD) duration between first serum specimen (taken preoperatively) and second serum specimen (taken post-operatively) was 26.67±8.02 day for the uncommon MTTs.

In FTC patient, the preoperative CEA titer was 1.030 ng/ml (normal range: 0-3 ng/ml) and its postoperative concentration was 1.00 ng/ml. the preoperative CA19-9 was 6.77 U/ml (normal range: 0-37 U/ml) while its postoperative serum titer was 6.140 U/ml.

In the MTC patient there was abnormally high level of preoperative serum CEA (462 ng/ml), while the preoperative serum CA19-9 was equal to 13.69 U/ml; after the surgical removal of the tumor the serum level for CEA and CA19-9 tumor markers became 47.27 ng/ml and 15.96 U/ml respectively.

Preoperative CEA serum concentration in HCC patient was 0.894 ng/ml while postoperatively it decreased to 0.697 U/ml; the CA19-9 results for the same patient preoperatively was 10.010 then it became 10.25 postoperatively.

Furthermore, the ATC was tested just once for each tumor marker (CEA=3.630 ng/ml, CA19-9=13.680 U/ml) because this anaplastic tumor was not operable, table 3.

The results revealed that the median (IQR) of the CEA concentration among control group was 1.06 (0.61-1.35) ng/ml, while CEA concentration among patients' group was 1.57 (1.08-2.30) ng/ml; there was significant differences in serum levels of CEA between control and the malignant thyroid cases, (p=0.001).

On the other hand, the median (IQR) of CA19-9 concentration among control group was 11.77 (6.83-19.24) U/ml and 12.17 (6.50-18.68) U/ml for patients' group, the differences in serum titers of CA19-9 between patients' group and control group were statistically non-significant (p=0.936), table 5.

History of hypothyroidism was found in 2/50 of MTTs patients. The odds ratio regarding the

possibility of developing MTTs in hypothyroidism patients was (OR, 0.068; 95% CI, 0.003-1.668). Whereas 10/50 of MTT patients had previously hyperthyroidism, the odds ratio was (OR, 0.41; 95% CI, 0.166-1.010).

According to the AJCC (American Joint Committee in Cancer) staging system, only 2.2% of PTCs were in stage II with T3a N1a, and all remaining patients were in the first stage with different levels within this stage.

The ATC patient was in the last stage (stage IVB) with T4a N1 M0; the HCC was at stage I with T3a NX MX, the FTC in stage I with T1b N0, while MTC was in stage III with T3a N1a Mx. These results are described in table 6.

In the current study, 16/50 of MMT patients were having regional lymph node metastasis; 14/46 (30.43%) of the PTC patients had lymph node metastasize which represent the majority of patients with metastasis (n=14/16); both FTC and HCC had not metastasis. There was only one MTC case and one ATC case; both of them have lymph node metastasize, table 7.

DISCUSSION

Cancer gender disparity in incidence, disease aggressiveness, and prognosis has been observed in a variety of cancers. In the current study, the incidence of thyroid malignancies was 2.3 times more common in women than in men. Comparable findings were also observed by Jonklaas J, et al, and Rahbari R , et al. (17, 18).

One of the possible explanations for female predominance in thyroid cancer is that females are more commonly affected by thyroid diseases than males especially in terms of autoimmune diseases which are provoking pathological changes that may contribute to malignant transformation. It has been hypothesized that reproductive, menstrual and environmental factors may account for gender disparity in thyroid malignant tumor incidence (17, 18).

Sex hormones have a significant role in developing malignancy and are well documented for breast and prostate cancers. Hormone-specific nuclear receptors that control gene expression and tumor cell biology are the principle mechanism of sex hormones in cancer development (19).

The α- and β-estrogen receptors mediate the effect of estrogen and are expressed in papillary thyroid cancer. Furthermore, estrogen can dramatically increases the rate of cell proliferation in thyroid cancer cell lines compared with male sex hormones (20, 21).

The gender disparity in thyroid cancer is also specific to the histologic subtypes of thyroid cancer. This study revealed that three histological subtypes of thyroid malignancies (Medullary thyroid carcinoma, Follicular thyroid carcinoma, and Hurthle cell carcinoma) are only present in females; on the other hand, anaplastic thyroid carcinoma was present only in male.

Like the results of Ortega J, et al, and Chen AY, et al, the current study showed that differentiated thyroid cancers of follicular cell origin, especially papillary thyroid cancer, are more frequent in woman than in men (22, 23).

Previous studies concluded that individuals who are working in places with possible emission of radioactive substances are more prone to develop malignant thyroid tumors (24-26). The ionized beam stimulates follicular cells to mutate genetically and intracellular cell signaling alterations are induced which can progress to malignant transformation. On the contrary, none of the MTTs patients in the current study is working in places emitting ionizing radiation, these results clarify the contribution of many risk factors (not only ionizing radiation) in the etiology of MTTs.

There has been a steady rise in the frequency of thyroid cancer globally; particularly, the new cases of PTC has risen by 240% in the last three decades (27). This increase in MTTs have been observed in both genders and among all races and is thought to be primarily due to an increasing trend in the rate of diagnostic imaging (28, 29).

PTC is the most common endocrine cancer and is responsible for 96% of all new endocrine malignancies, and 66.8% of deaths due to endocrine cancers are caused by PTC (30). The current study showed that PTC is the most

frequent type of the primary malignant thyroid carcinoma.

While other types such as (FTC-minimally invasive) and HCC were reported as rare types of the differentiated thyroid cancer. A previous study revealed that medullary thyroid carcinoma account for 1-2% of MTTs while anaplastic thyroid carcinoma account for less than 1% (31), only one case for each of MTC-minimally invasive and ATC-Spindle cell epithelioid were reported in this study.

Previous studies reported that more than 95% of all thyroid carcinoma are diagnosed as a differentiated thyroid cancer (31), that originates from thyroid follicular cells and undergone the classification of well-differentiated thyroid cancers (32).

In line with our findings, Bonnefond, et al, showed that most frequent MTTs were PTC; followed by FTC, MTC, then the ATC which was a very rare (33).

Cooper, D.S. (34) found that the most common presenting feature in DTC was neck swelling, which is detected by the patient him/herself or by the clinician, or incidentally detected thyroid nodule on neck imaging. Our results are in line with Cooper, D.S. findings. This neck swelling in MTT patient can be due whole thyroid enlargement, only thyroid nodule, lymphadenopathy, or a combination of them.

While other symptoms were less frequent and included changes in voice, dyspnea, and dysphagia. In addition to differences in their frequencies, the symptoms were unequally manifested among different types of MTTs, for instance; voice change was the chief complaint among the patients with MTC, FTC, and ATC while 67% of PTC patients were negative for voice abnormality.

The clinical features that are mostly need screening for malignancy include a neck swelling, hoarseness of voice, dysphagia, dyspnea, as well as a family history of thyroid cancer. On physical examination of the neck, firmness of the nodule, immobility, and the presence of neck lymph nodes should trigger suspicion for malignancy and need further evaluation (35).

On the other hand, anaplastic thyroid cancer can present as a rapidly enlarging neck mass and rapid occurrence of compressive symptoms of the aerodigestive tracts. Although not documented among our patients, Some patients can present with constitutional symptoms such as fever, weight loss, and anorexia (36, 37).

Elisei R, et al, recorded a case report with primary MTC with high level of both CEA and CA19-9. The CEA was 402 ng/mL (expected normal: 5.2 ng/ mL), and increased to 1447 ng/mL within 29 days (12), this elevation is due to the metastases of the MTC to other body part like liver, this finding is similar to the MTC case in the current study, in which the CEA was 462 ng/mL, but the serum level of the CEA decreased postoperatively to 47.27 ng/mL.

In addition, Elisei R, et al, reported high level of CA19-9 from 1570 (normal range: 0–39 U/mL) and elevated to >10 000 U/mL in the MTC patient; but this elevation in CA 19-9, to be attributed to MTTs, should be coupled with testing the other known causes of CA 19-9 elevation like GIT malignancies (12).

Our study showed that the CA19-9 concentration was 13.69 U/ml and it was within the normal range, furthermore, the patient with MTC that enrolled in the current study was free from any GIT malignancies and this is similar to Elisei R, et al reported case.

One possible mechanism in which the CA19-9 in the previous study was elevated is due to liver metastasis, while in the present study the primary tumor just invaded the cervical lymph node and did not spread to other body parts.

CA 19-9 could be a marker of MTC aggressiveness; Milman S, et al reported a death of MTC case and was having high serum elevation in CA 19-9 (13). Some previous studies detected CA 19-9 elevation even in the histological sections of MTC patients through performing immunohistochemistry in their study methodology (12, 13, 38, 39).

Elevation in serum CA 19-9 among HCC patients was recorded in the current study; to the best of

our knowledge, it is the only study that recorded elevation in serum level of CA19-9 among HCC. Shvero Jacob, et al revealed the presence of CEA on HCC tissue specimen using immunohistochemistry technique (40), while serum CEA in the HCC patient in the current study was within the normal range , however, this finding cannot be generalized to all HCC patients as we measured CEA in only one HCC case, consequently, a future study with an appropriate HCC sample size is needed to prove the correlation of both CEA and CA19-9 in HCC.

CEA elevations may happen in other malignancies, and in non-neoplastic conditions such as cigarette smoking, peptic ulcer disease, inflammatory bowel disease, pancreatitis, biliary obstruction, and cirrhosis; however, levels exceeding 10 ng/mL are rarely due to benign conditions (41).

The median (IQR) of both CEA and CA 19-9 among control group was 1.06 (0.61-1.35) and 11.77 (6.83-19.24) respectively, and these results were within the normal range and the control group individual was free of any kind of other primary malignant neoplasm and benign conditions that may cause elevation in the CEA and CA19-9.

CEA elevation is not uncommon among malignant colon tumors; fewer than 25 percent of patients with diseases confined to the colon have an elevated CEA level. CEA Sensitivity increases with advancing tumor stage, its concentration e is elevated in approximately 50 percent of patients with tumor metastasis to lymph nodes and in 75 percent of patients with distant metastasis (42). The highest values (above 100 ng / mL) occur in GIT malignancies associated with metastasis (43), however, poorly differentiated tumors are less likely to produce CEA (42).

Elevated serum levels of CA 19-9, occur primarily in patients with pancreatic and biliary tract cancers but also have been reported in patients with other malignancies (44). Benign conditions such as cirrhosis, cholestasis, cholangitis, and pancreatitis also result in CA 19-9 elevations (44). The antigen of tumor marker has no value in screening because its positive predictive value is less than 1 percent (45). However, the positive predictive value of CA 19-9 levels over 1,000 U/ml is 97% when it is tested in clinical situations that are consistent with pancreatic cancer (e.g., jaundice associated with a pancreatic mass). Furthermore, CA 19 9 levels above 1,000 U/ml is also associated with metastatic disease (44).

Previous study detected CEA in ATC in thyroid tissue specimen that was subjected to the anti-CEA antibody through immunohistochemical testing (46). The current study showed that serum CEA was elevated in the ATC, this result was in accordance to the findings of Ogawa, Masahiro, et al,, they revealed an increased level of CA19-9 (302.7) in the serum of a patient at the time of diagnosis with PTC, later on, CA 19-9 raised to 659.8 , the patient died due to tumor metastasis which was associated with elevation in CA 19-9 (8).

In the present study the CA19-9 was within the normal range, and the clinical investigations didn't have distant metastasis of the anaplastic neoplasm.

In this study, there was only one FTC case and both; CEA and CA19-9 were within the normal range; to the best of our knowledge, this was the first study that measured CEA and CA 19-9 in FTC patient. This result cannot be generalized as it is only one case, and a future study including larger appropriate FTC sample size should be performed for better interpretation of CEA and CA19-9 results.

Sorush, 2020, observed an increase in the mean (SD) of CEA concentration from a 1.6 ±0.6 ng/dl before radiotherapy to 2.23 ±0.69 ng/dl after radiotherapy with 30 days interval between the two readings, and the differences were statistically significant ($p<0.0005$), they supposed that radiotherapy has damaging effects on MTT cells and this caused more release of CEA from these cells to the circulation (47).

In addition, Sorush, 2020, revealed an increase in mean (SD) of CA 19-9 concentration from 9.5 ±6.32 U/dl before radiotherapy to 11.26 ±7.49 U/dl after 30 days from radiotherapy.

However the current study revealed that the median (IQR) concentration of both tumor

markers were 1.57 (1.08-2.30) ng/dl for CEA and 12.17 (6.50-18.68)U/dl for CA 19-9, both tumor markers were within their normal range before surgical intervention, then CEA became 1.57 (0.94-2.05) ng/dl and CA 19-9 was 12.24 (6.57-20.11) U/dl after surgical intervention with 24 (20-33) days intervals between the two readings, the current study showed that the CEA decline and CA 19-9 slightly increased, in contrast both CEA and CA 19-9 in Sorush, 2020 were increased.

In present study, CA 19-9 was slightly elevated while Sorush, 2020, showed a significant rise in postoperative C19-9 concentration. In the contrary, the concentration of the CEA concentration was declined in the present study, while Sorush, 2020, revealed an elevation of it.

However, there is some difference in statistical tests and type of treatment between these two studies for instance, our study used the median (IQR) for the descriptive analysis while Sorush, 2020, used mean (SD) this is due to the skewness of the data, because most of the medical data were skewed (48-51), and they used ANOVA test while we use Mann-Whitney U test, on another hand we are focus on the surgical intervention while they were follow the patients after radioactive iodine therapy.

The Sorush, 2020, was using Pearson correlation to find the significance differences while this stud used spearman correlation and demonstrate a significant value ($p<0.001$) for both markers before and after treatment.

The CEA concentrations were significantly different between control group and patients' group, while CA19-9 concentrations were not differ between these two groups, these observations indicate that CEA is very useful marker in MTTs diagnosis with considering other causes that lead to elevate this tumor marker such as gastrointestinal malignancies; on the other hand, the CA 19-9 is useful for follow up the patients with PTC (47).

The current study showed that 97.92% of the DTC patients were in the stage I, this early detection may be due to early expectation of MTTs with suggestive clinical features like neck swelling then using diagnostic imaging techniques and microscopic examination of thyroid smears and biopsies, these findings are parallel to Li, Chengzhuo, et al, who found that 82.9% of DTC patients were in stage I and 14.5% were in stage II, while the remaining patients were in stage III and stage IV (52). Furthermore, in the current study, only one PTC patient was in stage II, in addition, MTC was in the third stage and the ATC at the fourth stage (52).These data may reflect the early detection and slow growth of the DTC; thus early application of diagnostic techniques play a critical role in the early detection of DTCs.

Kakudo, K1, et al, revealed that 75.1 % of their study group were having spread to regional lymph nodes (53), while the current study showed LN metastasis accounts for 30.43% of the PTC patients, this may be due to early detection of MTT due to early performing FNA for suspected cases.

Moreover, 29.17% of the DTC patients were documented positive lymph node and this observation was similar to results of Kakudo, K1, et al, and Li, Chengzhuo, et al, as both showed that 41.8 % of the DTC patients were positive lymph node metastasize (52, 53).

Both MTC and ATC patients in the current study were having positive lymph node metastasis.

CONCLUSION

Most of MTTs patients are females, in age group 31-50 years, and housewives The most common primary malignant thyroid tumor was papillary thyroid carcinoma, while FTC, HCC, MTC, and ATC are rare. neck swelling was the most frequent presentation. There is significant decline in CEA concentration postoperatively among PTC patients, while CA 19-9 was significantly increased postoperatively. The CEA concentration is higher in MTTs than in normal population; there is non-significant difference in CA 19-9 concentrations in MTTs and in normal population. Most of MTTs are in stage I and lymph node metastasis are not uncommon.

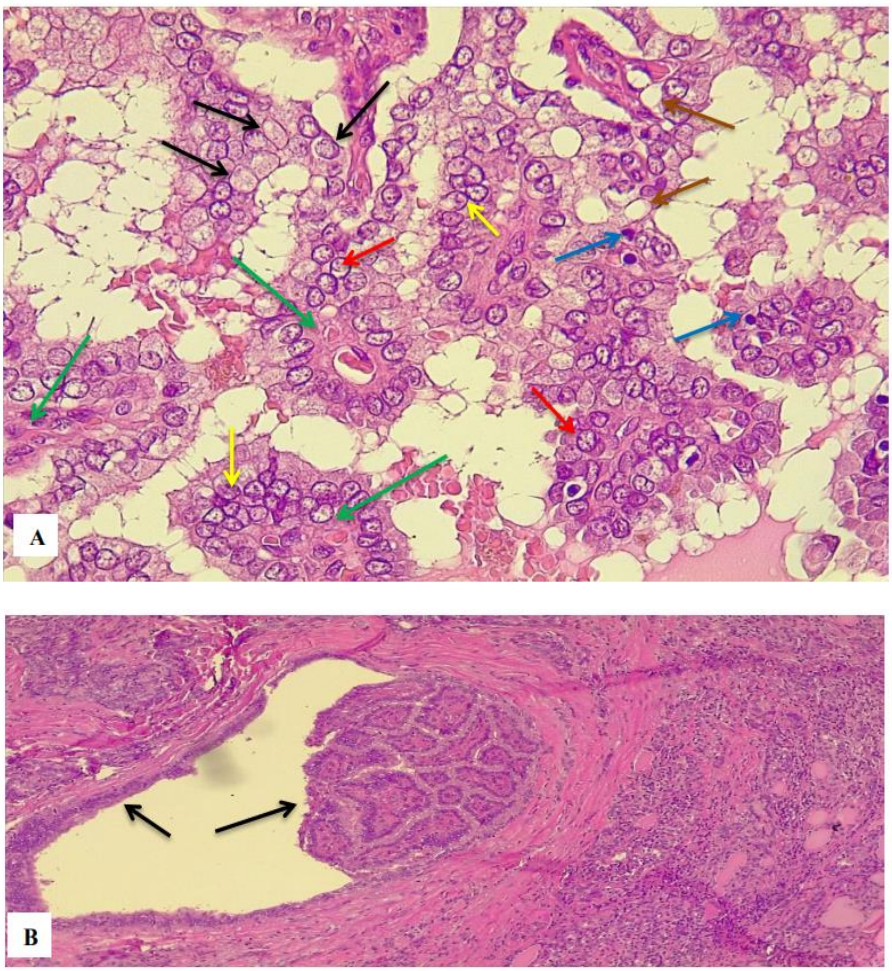
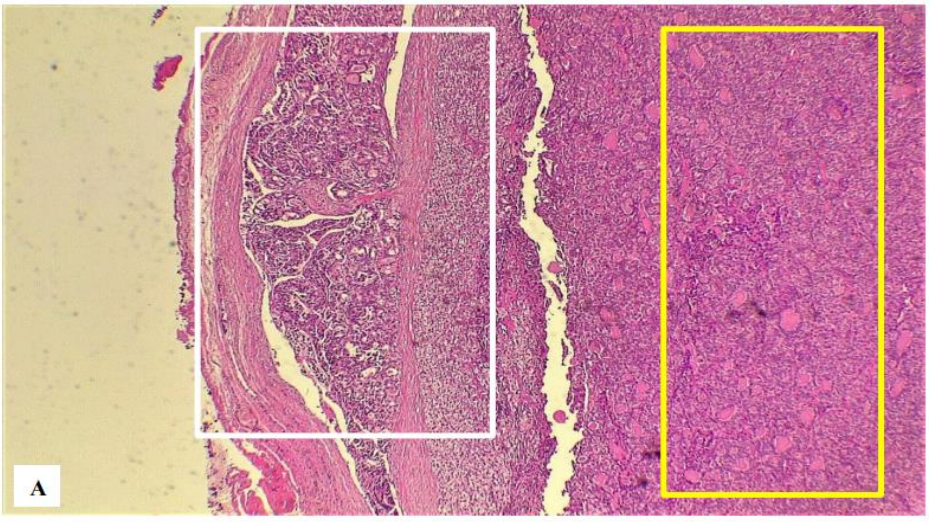


FIGURE 1: A- Photomicrograph of papillary thyroid carcinoma showing papillary architecture supported by fibro vascular core (green arrows), large nuclei (black arrows), overlapping nuclei (yellow arrows), glassy (clear) nuclei (brown arrows), nuclear grooves (red arrows) and intranuclear pseudo inclusion (blue arrows), B- Photomicrograph showing vascular invasion by the PTC (black arrows). H&E, A: 400X, B: X100.



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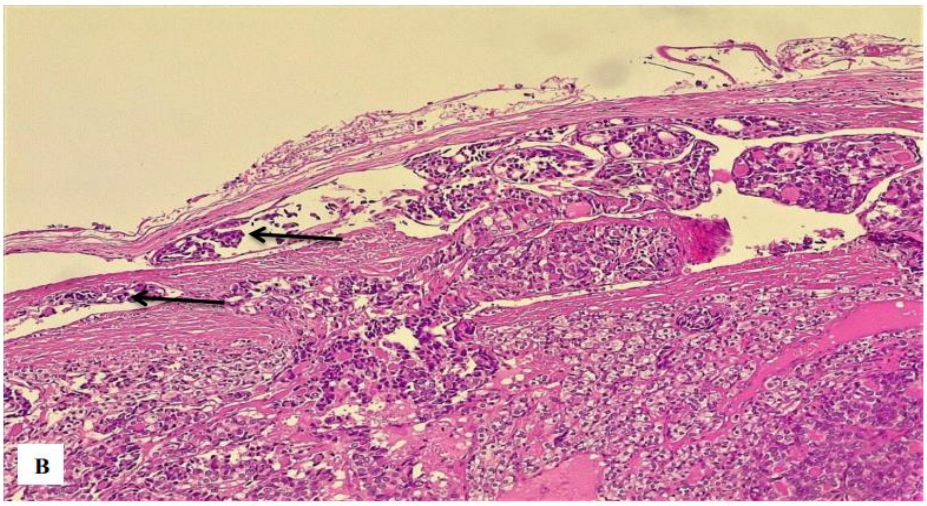


FIGURE 2: A-Photomicrograph illustrating a solid growth pattern of follicular thyroid carcinoma (yellow rectangle) with multiple micro follicles and capsular invasion (white box), B-Vascular invasion (black arrows). H&E, A&B: X100.

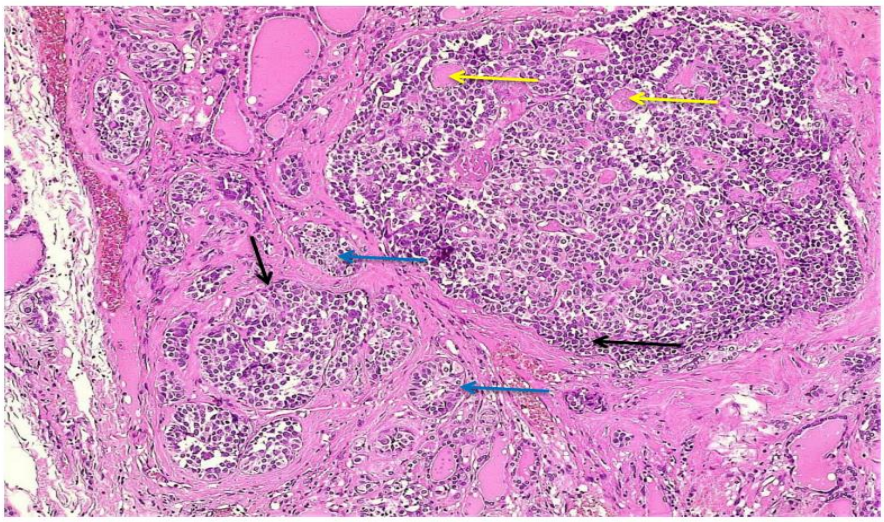
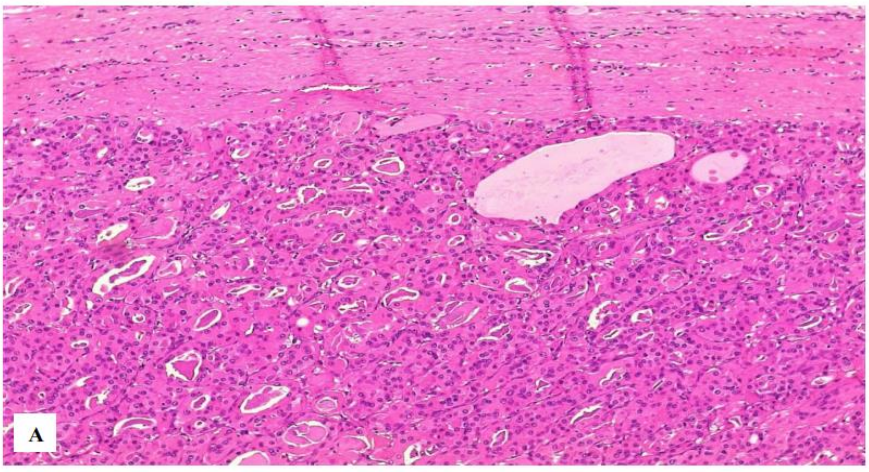


FIGURE 3: Photomicrograph of medullary thyroid carcinoma showing a solid (black arrows) and nesting (blue arrows) growth patterns of discohesive, round, polygonal, tumor cells enclosing focal amyloid deposition (yellow arrows) within a desmoplastic stroma. H&E, X100.



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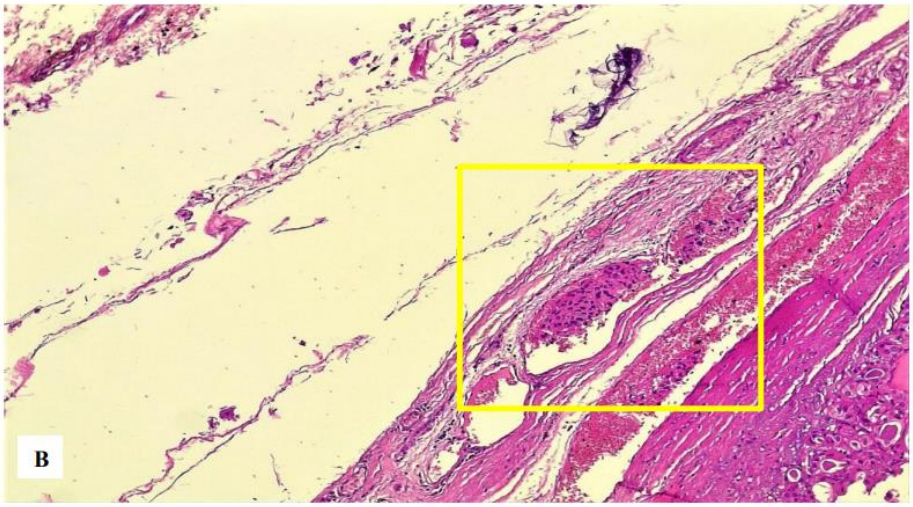

FIGURE 4: A- Photomicrograph of Hürthle cell carcinoma with large, polygonal tumor cells displaying uniform, rounded, hyperchromatic nuclei, prominent nucleoli and abundant granular cytoplasm, B- Photomicrograph showing transcapsular and vascular invasion (yellow box) by tumor cells of Hürthle cell carcinoma. H&E, A: X100, B: 40X.

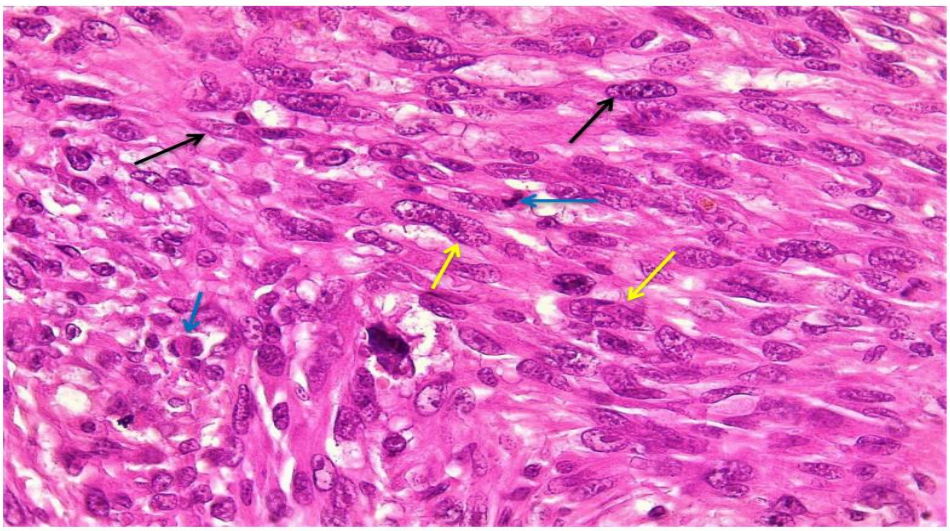

FIGURE 5: Photomicrograph of sarcomatoid anaplastic thyroid carcinoma, showing a storiform growth pattern of variable-sized, bizarre, oval to spindle-shaped tumor cells with prominent pleomorphic nuclei (black arrows) and brisk mitotic activity (blue arrows). Multinuclear giant tumor cells are also evident (yellow arrows). H&E, X400.

TABLE 1: Descriptive statistics of both study groups regarding gender, age, residency, and occupation

Category	Patient Group=50 (%)	Control Group=50 (%)
Gender		
Male	15 (30)	20 (40)
Female	35(70)	30 (60)
Total	50 (100)	50 (100)
Age group		
11-30	9 (18)	18 (36)

31-50	31 (62)	22 (44)
51-70	7 (14)	7 (14)
71<	3 (6)	3 (6)
Total	50 (100)	50 (100)
Mean ± S.D	41.66 ± 14.07	37.28 ± 12.52
Residency		
Sulaimani	17 (34)	19 (38)
Hawler	10 (20)	6 (12)
Other	23 (46)	25 (50)
Total	50 (100)	50 (100)
Occupation		
Housewife	29 (58)	25 (50)
Worker	11 (22)	14 (28)
Other	10 (20)	11 (22)
Total	50 (100)	50 (100)

TABLE 2: Clinical features presented by the patients group

Clinical Features		**PTC=46 (%)**	**FTC=1 (%)**	**MTC=1 (%)**	**HCC=1 (%)**	**ATC=1 (%)**
Voice Change	No	63.0	0.0	0.0	100.0	0.0
	Yes	37.0	100.0	100.0	0.0	100.0
Neck Pain	No	63.0	0.0	0.0	0.0	0.0
	Yes	37.0	100.0	100.0	100.0	100.0
Dyspnea	No	41.3	100.0	100.0	0.0	0.0
	Yes	58.7	0.0	0.0	100.0	100.0
Dysphagia	No	60.9	100.0	100.0	100.0	0.0
	Yes	39.1	0.0	0.0	0.0	100.0
Coughing	No	65.2	100.0	0.0	100.0	0.0
	Yes	34.8	0.0	100.0	0.0	100.0
Shoulder Pain	No	41.3	0.0	0.0	100.0	0.0
	Yes	58.7	100.0	100.0	0.0	100.0
Fatigue	No	37.0	0.0	0.0	0.0	0.0
	Yes	63.0	100.0	100.0	100.0	100.0
Neck swelling	No	10.9	0.0	0.0	0.0	0.0
	Yes	89.1	100	100	100	100
Weakness	No	95.7	100	100	100	100
	Yes	4.3	0.0	0.0	0.0	0.0

TABLE 3: Serum levels of CEA and CA19-9 among uncommon MTTs pre-operation and post-operation

Tumor Marker	Histopathological Diagnosis				Days between first &second testing ± SD
	FTC=1	MTC=1	HCC=1	ATC=1	
CEA preoperation *	1.030	462.000	0.894	3.630	26.67±8.02
CEA postoperation*	1.000	47.270	0.697	_***	
CA19.9 preoperation**	6.770	13.690	10.010	13.680	
CA19.9 postoperation**	6.140	15.960	10.250	_***	
*CEA normal range (0-3 ng/ml), **CA19-9 normal range (0-37 U/ml), ***No available because no perform surgery.					

TABLE 4: Correlation of preoperatively tumor marker titers CEA and CA19-9 to postoperatively titers among papillary thyroid carcinomas

Operation category	CEA median (IQR)	CA19-9 median (IQR)	Days between first and second testing, median (IQR)
Pre-operation	1.57 (1.08-2.30)	12.17 (6.50-18.68)	24 (20-33)
Post-operation	1.57 (0.94-2.05)	12.24 (6.57-20.11)	
P-value*	0.001	0.001	
*Differences are significant at ≤ 0.01			

TABLE 5: Comparison between serum levels of tumor markers in patients group and control group

Markers	Patients group		Control group		P-Value*
	Median	IQR	Median	IQR	
CEA	1.57	1.08-2.30	1.06	0.61-1.35	0.001
CA 19-9	12.17	6.50-18.68	11.77	6.83-19.24	0.936
*Differences are significant at ≤ 0.01					

TABLE 6: Metastasize of The Thyroid Cancer Among Patient Group Regarding Different Histopathological Diagnosis

Thyroid cancers	**Metastasize**	**No metastasize**
	N (%)	N (%)
PTC (n=46)	14 (30.43)	32 (69.57)
FTC (n=1)	0 (0.0)	1 (100)
MTC (n=1)	1 (100)	0 (0.0)
HCC (n=1)	0 (0.0)	1 (100)
ATC (n=1)	1 (100)	0 (0.0)

TABLE 7: Pathological staging of malignant thyroid carcinomas in patients group according to American Joint Committee on Cancer, 8th edition (AJCC)

Clinical Stage	Pathological Stage*	N (%)
PTC=46		
I	pT1 N1b	1 (2.2)
	pT1a	11 (23.9)
	pT1a N0	6 (13.0)
	pT1a N1a	1 (2.2)
	pT1a N1b	1 (2.2)
	pT1b	8 (17.4)
	pT1b N0	4 (8.7)
	pT1b N1a	1 (2.2)
	pT1b N1b	3 (6.5)
	pT2	2 (4.3)
	pT2 N0	1 (2.2)
	pT2 N1b	5 (10.9)
	pT3a N1a	1 (2.2)
II	pT3a N1a	1 (2.2)
FTC=1		

I	pT1b N0	1 (100)
HCC=1		
I	pT3a NX MX	1 (100)
MTC=1		
III	pT3a N1a Mx	1 (100)
ATC=1		
IVB	gpT4a N1 M0	1 (100)

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