

# Serum Biochemical Markers for Medullary Thyroid Carcinoma: An Update

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**Introduction:** Medullary thyroid carcinoma (MTC), a rare malignancy, requires early diagnosis for optimal patient outcomes. An important aspect of MTC diagnosis is the assessment of serum biomarkers. This review aimed to evaluate the use of serum biomarkers in the diagnosis, prognosis, and follow-up of MTC.

**Methods:** A thorough search of PubMed covering 1975 to 2022 was conducted to identify English-language articles on MTC serum biomarkers.

**Results:** The review revealed that calcitonin (Ctn) and carcinoembryonic antigen (CEA) remain the most important serum biomarkers for MTC diagnosis and management. Despite limited studies on procalcitonin (PCT), its stability and ability to exclude interference from inflammation make it a valuable potential marker of MTC. Although the positive rate of serum CA19-9 levels in MTC patients was not high, it can be used as an indicator of poor prognosis in advanced MTC. Other serum markers, including chromogranin A, gastrin-releasing peptide precursor, and neurospecific enolase, did not show any unique value in MTC diagnosis and management.

**Conclusion:** Taken together, this review emphasized the importance of serum biomarkers, particularly Ctn and CEA, in the diagnosis and management of MTC. PCT shows promise as a valuable potential marker, whereas CA19-9 can be used as a prognostic indicator of advanced MTC. Further research is needed to validate the significance of these serum biomarkers in MTC and determine the effects of confounding factors on their levels. Clinicians should consider using these markers in MTC diagnosis, prognosis, and follow-up, particularly for patients with advanced disease.

**Keywords:** medullary thyroid carcinoma, serum biochemical markers, calcitonin, carcinoembryonic antigen, procalcitonin

## Introduction

Medullary thyroid carcinoma (MTC) is a neuroendocrine neoplasm that originates from the parafollicular cells (C cells) of the thyroid gland and accounts for approximately 2% of all thyroid cancers.<sup>1,2</sup> Approximately 75% of MTCs are sporadic, with the remaining 25% inherited. C cells originate from the neuroectoderm and belong to the family of amine precursor uptake and decarboxylation cells, which secrete endocrinologically active substances, including calcitonin (Ctn), calcitonin gene-related peptide (CGRP), neuro-specific enolase (NSE), adrenocorticotrophic hormone, gastrin-related peptide (GRP), chromogranin A (CgA), and 5-hydroxytryptamine.<sup>3</sup> Furthermore, neoplastic C cells produce carcinoembryonic antigen (CEA) and carbohydrate antigen 19–9 (CA19-9).<sup>1</sup> Among these, Ctn is a highly specific and sensitive biomarker of MTC. CEA is less specific but more convenient and less expensive. Both of these biomarkers play an important role in the diagnosis, evaluation, and follow-up of MTC. In this review article, a comprehensive summary of the diagnostic and prognostic value of the common and some newly emerged serum biomarkers of MTC has been presented.

## Search Strategy

A search of PubMed using the following terms was conducted: “medullary thyroid carcinoma”[tiab] AND “calcitonin”[All fields] AND (“1975/01/01” [PDAT]: “2022/12/31” [PDAT]) AND English [lang]. The keyword calcitonin was then replaced

by other markers (carcinoembryonic antigen/procalcitonin/carbohydrate antigen 19–9/gastrin-related peptide/neuro-specific enolase/chromogranin A) separately and searched with the same search strategy. From the 2350 records returned, the most relevant articles were selected, giving priority to more recent publications. The reference lists of key papers were scanned for additional relevant articles.

## CTN

Ctn, a peptide hormone secreted by C cells, whose normal upper limit is assay-dependent, has varying normal upper limits across sex and age, with females having slightly lower levels than males and children having higher levels than adults.<sup>4</sup> The detection of serum Ctn primarily relies on various immunoassays, the most widely used of which in clinical practice are immunochemiluminometric assays. Serum Ctn stability can be affected by environmental factors, causing inaccurate outcomes. Serum Ctn levels decrease by 7%–18%, 20%–35%, and 28%–65% when stored at room temperature for >2, >6, and >12 h, respectively, and by 6%–8% and 21%–23% at 6 and 12 hours when stored at 4–8°C.<sup>5</sup>

## Diagnosis

Fine-needle aspiration (FNA) is routinely utilized to differentiate benign and malignant for nodules that are suspected to be MTC. However, its sensitivity for MTC diagnosis is only approximately 50%.<sup>6</sup> On the other hand, routine serum Ctn screening has been revealed that can detect MTC at an early stage with higher sensitivity (83.3%–100%) and specificity (95.3%–100%), outperforming FNA.<sup>6–11</sup> Nevertheless, the Ctn-positive rate in thyroid nodule screenings is extremely low (0.3%–5.9%), with only 0.1%–1.1% of Ctn-positive patients eventually diagnosed with MTC.<sup>6–11</sup>

The cutoff value of basal Ctn (bCtn) is a key factor affecting the diagnostic efficiency. With a cutoff at 10 pg/mL, sensitivity was almost 100%, rarely missed MTC patients. However, the reported positive predictive value (PPV) varied widely among studies (Table 1).<sup>6–11</sup> For bCtn >100 pg/mL, nearly all studies indicated a PPV close to 100%, which

**Table 1** The Diagnostic Efficiency of the Common Biomarkers in MTC

| Indicators              | Cutoff value | Sensitivity (%) | Specificity (%) | PPV (%)   | Studies  |
|-------------------------|--------------|-----------------|-----------------|-----------|--|
| Basal Ctn (pg/mL)       | > 10         | 83.3–100        | 95.3–100        | 3.2–93.6  | Elisei et al, 2004; <sup>6</sup> Vierhapper et al, 2005; <sup>7</sup> Costante et al, 2007; <sup>8</sup> Rink et al, 2009; <sup>9</sup> Schneider et al, 2012; <sup>10</sup> Weber et al, 2022 <sup>11</sup> |
|                         | 10–20        | 87.5–100        | 95.3–99.9       | 0–3.3     | Costante et al, 2007; <sup>8</sup> Weber et al, 2022 <sup>11</sup>   |
|                         | 20–50        | 100             | 100             | 8.3–18.6  | Costante et al, 2007; <sup>8</sup> Weber et al, 2022 <sup>11</sup>   |
|                         | 50–100       | 100             | 100             | 25–68.8   | Costante et al, 2007; <sup>8</sup> Weber et al, 2022 <sup>11</sup>   |
|                         | >100         | NA              | NA              | 100       | Costante et al, 2007; <sup>8</sup> Schneider et al, 2012; <sup>10</sup> Weber et al, 2022 <sup>11</sup>  |
| Ctn-FNA (pg/mL)         | 20–40        | 90–100          | 86–100          | 62.9–100  | Kudo et al, 2007; <sup>13</sup> Massaro et al, 2009; <sup>14</sup> Diazi et al, 2013; <sup>15</sup> Trimboli et al, 2014; <sup>16</sup> Kihara et al, 2018; <sup>17</sup> Liu et al, 2021 <sup>18</sup>      |
| Ctn-FNA for LNM (pg/mL) | 23           | 100             | 100             | 100       | Boi et al, 2007; <sup>19</sup> Abraham et al, 2009; <sup>20</sup> Marques et al, 2020 <sup>21</sup>  |
| PCT (ng/mL)             | 0.2          | 91.7–100        | 97.7–100        | 91.7–100  | Trimboli et al, 2018; <sup>22</sup> Giovanella et al, 2018 <sup>23</sup>   |
|                         | 0.15         | 91.2–97.1       | 94.8            | 62.6–76.4 | Algeciras et al, 2009; <sup>24</sup> Walter et al, 2010 <sup>25</sup>  |
|                         | 0.1          | 86.4–100        | 81–100          | 31.6–100  | Giovanella et al, 2018; <sup>23</sup> Lim et al, 2016; <sup>26</sup> Kaczka et al 2012 <sup>27</sup>   |
|                         | <0.1         | 85.7–100        | 81–100          | 31.6–100  | Giovanella et al, 2018; <sup>23</sup> Lim et al, 2016; <sup>26</sup> Kaczka et al, 2012; <sup>27</sup> Kratzsch et al, 2021; <sup>28</sup> Censi et al, 2021 <sup>29</sup>                                   |

confirmed the diagnosis with almost no exception.<sup>8,10,11</sup> When bCtn was in the range of 10–100 pg/mL, PPV varied in a large range (0%–68.8%, [Table 1](#)),<sup>8–11</sup> making the diagnosis difficult. Ctn provocation test, despite enhancing stimulated Ctn levels in MTC patients and C-cell hyperplasia, failed to significantly improve PPVs for those with bCtn between 10 and 100 pg/mL.<sup>8,12</sup>

In 2007, Boi et al<sup>19</sup> reported a 100% sensitivity and specificity for MTC diagnosis based on Ctn levels in FNA wash-out fluid (Ctn-FNA). Many subsequent studies, although with small patient samples, replicated high sensitivity (90%–100%) and specificity (86.7%–100%) of Ctn-FNA.<sup>13–18</sup> Its accuracy for lymph node metastasis (LNM) was even higher, with 100% sensitivity and specificity.<sup>19–21</sup> The diagnostic cutoff value remains an important factor affecting the results ([Table 1](#)). However, Ctn-FNA levels could be influenced by bCtn levels.<sup>30</sup> Accordingly, false-positive Ctn-FNA results were likely to occur in cases of C-cell hyperplasia with mildly elevated bCtn levels.<sup>14,15</sup> Thus, combining cytology and Ctn immunohistochemistry could further improve diagnostic accuracy in such situations to achieve 100% sensitivity and specificity.<sup>31,32</sup> Of note, nonsecretory MTCs, a rare subset of MTC patients with normal basal Ctn levels, accounting for approximately 0.83%–5.5% of all MTC cases, presenting a diagnostic challenge preoperatively, with definitive diagnosis primarily relying on postoperative pathology.<sup>11,33</sup>

## Tumor Burden

Preoperative serum Ctn levels can reflect the tumor burden and correlate with MTC disease extent, which are positively correlated with tumor size.<sup>34</sup> The tumor diameter is usually <1 cm with Ctn <100 pg/mL and often >2 cm when the Ctn level is >1000 pg/mL.<sup>34–38</sup> While few studies have explored the correlation between Ctn levels and LNM extent, and no definitive Ctn level has been identified for accurately indicating LNM or metastasis extent, all reports suggest a positive association between bCtn levels and LNM.

In a cohort of 300 MTC patients, Machens et al<sup>36</sup> reported no central or lateral LNM when the Ctn level was <20 pg/mL. However, when the Ctn level was >200 pg/mL, more than one-third of patients presented with central and ipsilateral lateral LNM, and the contralateral lateral LNM rate was >10% when Ctn >500 pg/mL. Similar findings were obtained by Park et al.<sup>38</sup> Furthermore, a recent multicenter study proposes an ipsilateral lateral neck dissection for patients with bCtn >240 pg/mL and a contralateral lateral neck dissection for those with bCtn >600 pg/mL.<sup>39</sup> As MTC patients with bCtn <100 pg/mL rarely have LNM in the ipsilateral lateral compartments,<sup>36,38</sup> lateral neck dissection should be carefully evaluated in these patients. To date, however, the practice of determining the extent of surgery based on the preoperative bCtn level has not been widely endorsed.<sup>40–42</sup> Nevertheless, preoperative bCtn levels have shown good predictive value for distant metastases ([Table 2](#)). Most study observed no distant metastasis in patients with Ctn levels <500 pg/mL.<sup>35,36,38</sup> It is clear that the bCtn level is closely correlated with the tumor burden. It was revealed that biochemical cure after surgery was nearly unattainable for MTC patients with preoperative Ctn was >1000 pg/mL, while 97.8% of patients with Ctn <50 pg/mL achieved it.<sup>34,43</sup> Of note, in hereditary MTC (hMTC), Ctn level is crucial for predicting tumor progression, reflecting tumor burden, and determining surgical timing. As all hMTC patients may eventually require surgical intervention, optimal timing is essential for satisfactory outcomes and minimizing complications. In MTC family members with moderate (MOD) and high (H) risk of germline RET mutations, 39%–61% and 77%–100% of patients with normal and elevated Ctn levels, respectively, were pathologically diagnosed with MTC after prophylactic thyroidectomy.<sup>44–47</sup> When the Ctn level was <30 pg/mL, the tumors were usually enclosed in the thyroid gland without LNM or distant metastasis, whereas more than one-third of patients with Ctn levels >30 pg/mL were predicted to develop LNM.<sup>44,45</sup> A recent study indicated that the prognosis for both MOD and H groups is primarily driven by tumor burden, not genetic risk outcomes.<sup>48</sup> All patients with hMTC may be biochemically cured postoperatively when preoperative Ctn does not exceed 30 pg/mL.<sup>45,49,50</sup> For members of the hMTC family with germline RET mutations at the highest class risk, the key factor in determining surgical treatment is the genetic risk class and age at diagnosis. Research has shown that 83% of the such patients who underwent prophylactic surgery under 1 year of age were pathologically diagnosed with MTC and had a significantly higher rate of biochemical cure than those who received surgery after the age of 1 year (83% vs 15%,  $p < 0.0001$ ).<sup>51</sup>

**Table 2** The Ability of Reflecting Tumor Burden of Common Biomarkers in MTC

| Indicators   | Cutoff Value | LNM        |                 |                   | Distant metastasis (%) | Studies  |
|--------------|--------------|------------|-----------------|-------------------|------------------------|--|
|              |              | Center (%) | Lateral         |                   |                        |  |
|              |              |            | Ipsilateral (%) | Contralateral (%) |                        |  |
| bCtn (pg/mL) | 1–20         | 0–9.1      | 0               | 0                 | 0                      | Machens et al, 2010; <sup>36</sup><br>Park et al, 2020 <sup>38</sup> |
|              | 20–100       | 4.5–10.3   | 4.5–10.3        | 0                 | 0                      |  |
|              | 100–200      | 27.8–30.8  | 15.4–16.7       | 0                 | 0                      |  |
|              | 200–500      | 44.8–56.7  | 37.9–30.0       | 6.7–13.7          | 0                      |  |
|              | 500–1000     | 62.5–67.6  | 50.0–58.3       | 11.8–12.5         | 4.2–5.9                |  |
|              | 1000–2000    | 55.9–67.7  | 41.2–55.6       | 11.1–17.6         | 5.6–14.7               |  |
|              | 2000–10,000  | 54.5–100   | 63.6–74.6       | 13.6–43.6         | 4.5–15.3               |  |
|              | >10,000      | 57.1–100   | 78.6–96         | 28.6–80.0         | 28.6–72.0              |  |
| CEA (ng/mL)  | 0–10         | 33         | 20              | 22                | 0                      | Machens et al, 2007 <sup>52</sup>                                    |
|              | 10–30        | 36         | 27              | 10                | 27                     |  |
|              | 30–100       | 73         | 67              | 36                | 13                     |  |
|              | >100         | 93         | 88              | 73                | 75                     |  |
| PCT (ng/mL)  | <0.25        | 20         | 0               | 0                 | 0                      | Machens et al, 2014 <sup>53</sup>                                    |
|              | 0.25–0.5     | 8          | 8               | 0                 | 0                      |  |
|              | 0.5–1.0      | 38         | 23              | 0                 | 0                      |  |
|              | 1.0–5        | 36–39      | 25              | 4                 | 0                      |  |
|              | 5–10         | 55–91      | 73              | 36                | 18                     |  |
|              | 10–50        | 50–86      | 71              | 43                | 36                     |  |
|              | >50          | 64–100     | 91              | 36                | 36                     |  |

## Follow-Up

According to the postoperative Ctn level and imaging studies, Tuttle et al<sup>54</sup> defined the dynamic risk stratification of MTC. Studies indicate that 27%–70% of MTC patients with ER (Excellent response) exhibit a favorable prognosis with a 10-year disease-specific survival (DSS) of up to 95%–100% and a low recurrence rate of 1%–4%. Moreover, 23%–35% of MTC patients with BIR (biochemical incomplete response) showed a decreased 10-year DSS of 90%–95% and an elevated recurrence rate of 14%–37%. The prognosis was even worse for MTC patients with SIR (structural incomplete response), accounting for 7%–38% of all cases, with a mortality rate of 20%–79% within an average follow-up period of 6.2 to 12.8 years.<sup>55–59</sup> This indicates that the initial postoperative Ctn level can reflect the prognosis of the disease when no structural lesions are present.

The prognosis of patients with different Ctn levels may vary even if their postoperative Ctn is below the upper limit of the reference range. Theoretically, when the thyroid and MTC lesions are completely removed, the Ctn level should be reduced to an undetectable level (below the lower detection limit).<sup>60</sup> In a recent study involving 334 MTC patients over an 8.5-year median follow-up, the biochemical cure rate was significantly higher in the Ctn undetectable group than in the detectable control group (90.1% vs 9.2%,  $p < 0.001$ ), with no incidence of structural recurrence or death in the undetectable group.<sup>61</sup> In addition, Fanget et al<sup>62</sup> drew a similar conclusion in 127 MTC patients (recurrence rate: 3% vs 25%,  $p = 0.001$ ) after a median follow-up period of 47 months. Likewise, different Ctn levels may indicate different outcomes in patients with BIR. In a study enrolling 120 MTC patients, Ctn level  $\geq 29$  pg/mL could predict structural recurrence with 100% sensitivity, 90.5% specificity, 59.1% PPV, and 100% negative predictive value (NPV) at the assessment of response to initial therapy.<sup>56</sup> Saltiki et al,<sup>63</sup> however, suggested a Ctn level of  $>14.5$  pg/mL as a cutoff value for predicting structural recurrence. In patients with SIR, there is no consensus on whether Ctn levels can be used as a precise indicator of local and distant metastases. Pellegriti et al<sup>64</sup> and Cho et al<sup>56</sup> both observed postoperative MTC patients that higher Ctn levels ( $>150$  pg/mL) were often associated with distant metastases at the time of relapse, suggesting that this threshold could serve as an indicator of postoperative distant metastasis.<sup>1,65</sup> Further exploration of the value of different postoperative Ctn levels to predict prognosis is needed.

**Table 3** Predictive Capacity of Common Biomarkers for Prognosis in MTC

| Indicators                  | Cutoff Value/<br>Stratification | 10-<br>Year<br>DSS | OS (%) |             | Recurrence<br>Rate (%) | Studies  |
|-----------------------------|---------------------------------|--------------------|--------|-------------|------------------------|--|
|                             |                                 |                    | 5-Year | 10-<br>Year |                        |  |
| Dynamic risk stratification | ER                              | 95–100             | NA     | NA          | 1–4                    | Lindsey et al, 2015; <sup>57</sup> Cho et al, 2016; <sup>56</sup> Kwon et al, 2016; <sup>57</sup> Jung et al, 2016; <sup>58</sup> Choi et al, 2018 <sup>59</sup> |
|                             | BIR                             | 90–95              | NA     | NA          | 14–37                  |  |
|                             | SIR                             | 20–79              | NA     | NA          | NA                     |  |
| Ctn-dt (year)               | 0.5                             | NA                 | 25     | 8           | NA                     | Barbet et al, 2005; <sup>66</sup> Hassan et al, 2018; <sup>67</sup> Miyachi et al, 1984 <sup>68</sup>  |
|                             | 0.5–2                           | NA                 | 92     | 37          | NA                     |  |
|                             | >2                              | NA                 | 100    | 100         | NA                     |  |
| CEA-dt (year)               | 0.5                             | NA                 | 0      | 0           | NA                     | Gawlik et al, 2010; <sup>71</sup> Laure Giraudet et al, 2008 <sup>72</sup>   |
|                             | <2                              | NA                 | 66.3   | 29.1        | NA                     |  |

**Notes:** Excellent response (ER): undetectable postoperative Ctn level, normal CEA level, and no abnormal imaging findings; biochemical incomplete response (BIR): detectable postoperative Ctn level, abnormal CEA level, and no abnormal imaging findings; and structural incomplete response (SIR): positive imaging findings.

The Ctn doubling time (Ctn-dt), which is adversely linked to the proliferation grade of MTC, is an additional critical prognostic marker for patients with postoperative Ctn abnormalities. Patients with Ctn-dt >2 years were reported to have 5- and 10-year overall survival (OS) rates of 100% (Table 3),<sup>66</sup> while those with Ctn-dt between 0.5 and 2 years had OS rates of 92% and 37% at 5 and 10 years, respectively. When Ctn-dt was <0.5 years, the 5-year and 10-year OS rates were only 25% and 8%. Similar findings were obtained by Hassan et al<sup>67</sup> and Miyachi et al.<sup>68</sup> A meta-analysis by Meijer et al<sup>69</sup> revealed that a Ctn-dt of <1 year was an indicator of poor prognosis. However, the utility of Ctn-dt in clinical practice is limited due to its time-consuming and costly nature and its inability to predict disease progression or recurrence at an early stage. A more recent study proposed using the Ctn ratio (CR, postoperative Ctn level/preoperative Ctn level) as an early indicator for predicting structural recurrence; the ratio has a recurrence rate of 41.0% and mortality rate of 4.5% (median follow-up = 3.25 years) when CR ≥ 0.15 at 3 postoperative days.<sup>70</sup>

Dynamic risk stratification is a good indicator of MTC prognosis, but the optimal time for postoperative Ctn detection and its accuracy in predicting prognosis at an early stage remain uncertain. The half-life of Ctn is the most important factor that affects its clearance time after complete tumor resection. The half-life of exogenous salmon Ctn is approximately 30 min in humans.<sup>73,74</sup> Therefore, it has been hypothesized that the serum Ctn of MTC patients can drop to normal levels within a very short time after complete resection. Faggiano et al<sup>75</sup> reported that the Ctn levels could drop to <50% of the preoperative levels 30 min after surgery in six patients who all achieved a biochemical cure. After a mean follow-up period of 14.6 months, none of these patients relapsed. Similar results were obtained in the Brauckhoff study with a median follow-up period of 21 months.<sup>76</sup> Of note, the half-life of Ctn in MTC patients can be significantly prolonged to 30 h, which is probably due to the high preoperative tumor burden and the longer time required for “calcitonin-enriched lymphatic fluid” to enter the circulatory system and be cleared after surgery. Furthermore, extremely high preoperative Ctn (>1000 pg/mL) may prolong the time to Ctn normalization to 1–2 weeks or even 8 weeks.<sup>77</sup> Therefore, it is recommended that the response to initial therapy should be performed at 2–3 months or 6–12 months after surgery.<sup>1,55–59</sup> However, whether an earlier assessment can produce an earlier and more precise indication of prognosis deserves further investigation. A study showed that 41 out of 42 patients who achieved an undetectable Ctn level 1 year after surgery had also reached an undetectable Ctn level as soon as 1 month after surgery.<sup>78</sup>

## CEA

CEA, initially known as an intercellular adhesion glycoprotein, is expressed by the neuroendocrine tissues of the gastrointestinal tract during fetal development. However, it was also found to be expressed in both normal and tumor tissues, including C cells.<sup>79,80</sup> Healthy populations typically have CEA levels ranging from 2.5 to 5 ng/mL, and a higher level in men than women.<sup>81</sup> Elevated CEA (>5 ng/mL) indicates various malignancies, including digestive tract and respiratory tumors, and can also be found in ulcerative colitis, pancreatitis, and liver cirrhosis and among heavy smokers. This suggests that CEA is not a specific tumor marker for MTC. However, previous studies reported that approximately

60%–70% of MTC patients present with elevated serum CEA levels.<sup>52,82,83</sup> While CEA is not a specific biomarker, its convenience and low test cost make it an important and commonly used serum biomarker of MTC.

Preoperative CEA levels may also reflect the tumor burden and are positively correlated with tumor size. For CEA levels of 10, 10–100, and >100 ng/mL, the sizes of the tumors were 6.5–12.5, 9.3–29.3, and 25.3–47.7 mm, respectively.<sup>36</sup> Moreover, varied elevated levels of basal CEA may be an indicator of LNM and distant metastasis. Machens et al<sup>52</sup> reported that while not statistically significant, the rate of LNM and distant metastases in the CEA normal group (n = 23) was much lower than in the CEA elevated group (n = 54) (26.1% vs 61%, p = 0.09; 8.7% vs 30%, p = 0.08) [69]. In the elevated CEA group, more than two-thirds of patients had central and ipsilateral lateral LNM when CEA was >30 ng/mL. Furthermore, when CEA was >100 ng/mL, 73% of patients had contralateral lateral cervical LNM and 75% had distant metastases.<sup>52</sup> Likewise, it was reported that LNM rate increased significantly when CEA was >30 ng/mL.<sup>84</sup> The sensitivity and specificity of this cutoff value as a predictor of lateral LNM were 75.0% and 81.6%, respectively.<sup>85</sup> All of these studies showed that CEA is a sensitive marker of tumor progression and invasion. A study involving 899 MTC patients suggested that preoperative CEA levels correlated with tumor stage, with 80.9% of stage I patients having normal CEA levels and 79.8%/97.5% of stage III/IV patients having elevated CEA levels.<sup>83</sup>

CEA is also useful for the assessment of response to initial therapy in MTC patients. However, the sensitivity of CEA to indicate prognosis is lower than that of Ctn, as only a subset of MTC have elevated serum CEA levels.<sup>56,64,86</sup> Postoperative CEA levels >5 ng/mL had a 65% sensitivity and 79% specificity for predicting recurrence, whereas postoperative CEA levels >12.66 ng/mL had up to 100% specificity to predict recurrence, but its sensitivity decreased to 57.9%.<sup>87</sup> Certain studies have considered CEA as a marker of dedifferentiation in MTC,<sup>88,89</sup> and CEA doubling time (CEA-dt) was found to be a better prognostic factor than Ctn-dt in MTC.<sup>66,69</sup> Barbet et al<sup>66</sup> reported that patients with a CEA-dt of 0.5–2 years and <0.5 years had worse OS than those with the same Ctn-dt and that the 5- and 10-year OS rates were 0% when CEA-dt was <0.5 years (Table 3). Furthermore, CEA-dt was found to be more accurate than Ctn-dt in predicting MTC disease recurrence.<sup>69</sup> However, owing to the low sensitivity of CEA, CEA-dt values could be calculated in only approximately half of the patients. Therefore, it is usually recommended to combine CEA-dt and Ctn-dt for postoperative follow-up.<sup>1,90</sup> Other studies revealed that 94% of patients had disease progression when Ctn/CEA-dt was <25 months, that their 5- and 10-year OS rates were 66.3% and 29.1%, and that the 5- and 10-year recurrence-free survival (RFS) rates were 34.9% and 13%, respectively, when Ctn/CEA-dt was <2 years.<sup>71,72</sup>

CEA can be produced in both normal and tumor tissues in humans, thereby making it difficult to assess the half-life of serum CEA in vivo. It was reported that in patients with colorectal cancer with elevated preoperative CEA levels who achieved clinical remission after surgery, the serum CEA level halved in 3–5 days after surgery; the same was observed in 3.2 days in patients with lung cancer.<sup>91,92</sup> Andrade et al<sup>78</sup> found that of 56 patients with normal CEA one year post-surgery, 63% and 97% had normal levels at one and six months postoperatively. At present, it is advised that CEA testing for response to initial therapy should be performed 2–3 months after surgery.<sup>1</sup>

## Procalcitonin (PCT)

PCT is a precursor peptide of calcitonin without hormonal activity. It is synthesized and secreted by C cells or other neuroendocrine cells of the lung and intestine. Typically, all PCTs produced in C cells transform into mature Ctn and circulate, rendering PCT levels undetectable in healthy individuals (<0.1 ng/mL in adults).<sup>24,93</sup> In 2003, Bihan et al<sup>94</sup> detected intact PCT in the serum of all MTC patients at a mean level 7.6 times higher than the Ctn level. Moreover, after the administration of pentagastrin, PCT levels were stimulated and elevated. Since 2023, further investigations on PCT in the diagnosis and treatment of MTC have gradually developed.

It has been suggested that the diagnostic efficiency of PCT and Ctn for MTC is similar when excluding inflammatory disruptions. A study showed that using a cutoff value of PCT > 0.1 ng/mL for the diagnosis of MTC resulted in a sensitivity of 100%, specificity of 99.9%, PPV of 77.8%, and NPV of 100%<sup>23</sup> (Table 1). A recent meta-analysis also yielded similar results.<sup>95</sup> Remarkably, PCT can improve the diagnostic efficiency in patients with mildly elevated Ctn (10–100 pg/mL).<sup>26,29,96,97</sup> In a study involving 60 such patients, all 9 patients with confirmed MTC showed PCT levels >0.1 ng/mL, whereas 46 of 51 non-MTC patients had PCT <0.1 ng/mL, resulting in a 100% NPV.<sup>96</sup> Giovanella et al<sup>97</sup> and Lim et al<sup>26</sup> also showed that the NPV of PCT in patients with mildly elevated Ctn was up to 100% and 96.3%,

respectively. Evidently, the diagnosis of MTC can be excluded when PCT is not elevated. One study showed that PPV with PCT > 0.07 ng/mL was 100% in such patients.<sup>29</sup>

Similarities between PCT and Ctn have been observed, which may indicate the tumor extent preoperatively and predict recurrence postoperatively.<sup>22,25,28,53,98</sup> Machens et al<sup>53</sup> discovered the association between PCT levels and the presence of LNM. When PCT was <0.25 ng/mL, LNM was rare, and at PCT >0.5 ng/mL, approximately 38% and 23% of patients developed central and ipsilateral lateral LNM, respectively (Table 2). Moreover, when the PCT level exceeded 1.0 ng/mL, 4% of patients developed contralateral lateral LNM, and when above 5.0 ng/mL, the rate of contralateral lateral LNM and distant metastasis were 36% and 18%, respectively. A postoperative study of 158 MTC patients (median follow-up period of 16 years) revealed significantly higher PCT level in the metastatic and minimal residual disease group compared to the cured group at the last follow-up ( $109 \pm 202$  vs  $0.511 \pm 0.800$  vs  $<0.06$  ng/mL,  $p < 0.001$ ).<sup>28</sup> Similar results were obtained in the studies of Giovanella et al<sup>98</sup> and Trimbolie et al.<sup>22</sup> Moreover, Walter et al<sup>25</sup> suggested that MTC may produce less Ctn during the process of dedifferentiation and that the PCT/Ctn ratio can be used as a predictor of recurrence or distant metastasis, with a sensitivity of 72.2% and specificity of 73.5% when the PCT/Ctn ratio is >2.4. The PCT/Ctn ratio can be measured at any time postoperatively, which is more convenient for clinical application than the Ctn/CEA-dt index. Thus, the PCT/Ctn ratio may be an effective indicator of MTC prognosis and deserves further exploration and investigation.

PCTs originating from different cells are structurally different but highly analogous and indistinguishable by current assays.<sup>28</sup> Consequently, the currently detectable serum PCT levels are susceptible to inflammation and trauma, thereby limiting their utility in the diagnosis and treatment of MTC.<sup>27</sup> However, compared with Ctn, PCT has several advantages. It is stable at room temperature, and PCT levels are highly consistent under different assays. Moreover, there is no sex-based variation in the reference values of PCR, and no false negatives due to the “hook effect” are observed.<sup>5,24,99,100</sup> As a result, PCT is expected to be a promising biomarker for diagnosing MTC by indicating tumor extent and prognosis. However, further research with larger samples is necessary to completely evaluate the utility of PCT in MTC.

## CA19-9

The glycoantigen CA19-9 is a type of Lewis A blood group-determining cluster of mucin antigens that are glycolipids expressed from or secreted on the tumor cell surface. The level of serum CA19-9 in the normal population is <37 U/mL. However, it should be noted that CA19-9 is a nonspecific tumor marker and is usually used as an indicator of pancreatic cancer. In 2011, Milman et al<sup>101</sup> reported that one patient with MTC with distant metastases had significantly elevated serum CA19-9 levels. In 2013, Elisei et al<sup>102</sup> found that liver metastatic lesions also expressed CA19-9. These findings led to the hypothesis that elevated serum CA19-9 is a marker of progression and poor prognosis in advanced MTC. It was later confirmed that positive CA19-9 expression in MTC tissue was associated with distant metastasis.<sup>103,104</sup> Furthermore, a study in 100 patients with recurrent MTC and LNM or distant metastases showed that serum CA19-9 was elevated in 16% of patients and that the distant metastasis rate and mortality were higher in the group with elevated serum CA19-9.<sup>105</sup> Similar results were found by Lorusso et al<sup>106</sup> and Alencar et al<sup>107</sup> who showed a higher mortality rate in patients with elevated CA19-9 than in those without elevated CA19-9 (60% vs 19%,  $p < 0.0001$ ). Moreover, the mortality rate was 100% in those with a CA19-9 doubling time of <1 year.<sup>106</sup> Although the rate of positive serum CA19-9 in MTC patients is low, it can be used as an indicator of poor prognosis in advanced MTC.

## Other Biomarkers

In MTC patients, the levels of certain neuroendocrine substances, such as GRP, CgA, and NSE, may be elevated. These substances may serve as potential markers of MTC. GRP is a 27-amino-acid peptide with gastrin-releasing effects, but it is not suitable for clinical testing, as its half-life is 2 min in plasma.<sup>108</sup> The gastrin-releasing peptide precursor (proGRP), the precursor to GRP, however, is stable and can reflect GRP levels. In the normal population, serum proGRP levels are typically <50 pg/mL. Elevated serum proGRP, which is a common marker for small-cell lung cancer, is also detected in some benign diseases and gastrointestinal tumors. Elevated proGRP was reported in approximately 80% of MTC patients.<sup>109,110</sup> Liang et al<sup>110</sup> showed that the diagnostic sensitivity and specificity were 53.85% and 96.98%, respectively, with a cutoff value of serum proGRP >68.3 pg/mL in MTC. Likewise, the level of proGRP in FNA wash-out fluid

(FNA-proGRP) was also a valid index with a sensitivity of 94.12% and specificity of 98.27% when FNA-proGRP was  $>22.77$  pg/mL.<sup>110</sup> Furthermore, few studies have examined the association of serum proGRP levels with tumor burden and prognosis in MTC. A study on 78 postoperative MTC patients revealed that proGRP levels were higher in the evidence of structural disease (ESD) group ( $n = 49$ ) than in the no evidence of structural disease (NESD) group (880.0 vs 74.8 pg/mL,  $p < 0.05$ ). The proGRP levels had a sensitivity of 75.9% and specificity of 97.9% for differentiating NESD from ESD using a cutoff value of 72.2 pg/mL. The sensitivity was 100%, and the specificity was 96.3% for predicting local recurrence and distant metastasis using a cutoff value of 167 pg/mL.<sup>111</sup>

CgA is a protein comprising 439 amino acids and is widely distributed in neuroendocrine cells. In the normal population, serum CgA levels are  $<100$  ng/mL. Elevated CgA levels are detected in various neuroendocrine tumors, including MTC.<sup>112</sup> It was reported that approximately 23%–50% of MTC patients, mostly advanced cases, had elevated serum CgA levels.<sup>113–117</sup> Therefore, serum CgA is not a suitable diagnostic marker and has been shown to have limited usefulness as a prognostic indicator of MTC.<sup>87,116,117</sup> Wolinski et al<sup>87</sup> found that CgA had a sensitivity of 55% and specificity of 83.8% for predicting MTC recurrence postoperatively.

In addition to CgA, NSE is a commonly used neuroendocrine tumor marker. The upper limit of normal of serum NSE is 12.5 ng/mL.<sup>118</sup> However, few studies are available on NSE in MTC. Several studies have reported that serum NSE was elevated in approximately 21%–42% of MTC patients.<sup>114,118</sup> It was also shown that when serum NSE was  $>13.95$  ng/mL, the sensitivity of predicting lateral LNM was 55.6%, and the specificity was 94.7% in MTC patients.<sup>85</sup>

## Conclusions

In clinical practice, Ctn and CEA remain the most important serum biomarkers of MTC. While few studies have been conducted on PCT, it has shown great value when excluding the interference of inflammation. No other markers have shown a more comprehensive role and unique value in the diagnosis and treatment of MTC.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

All authors have declared no conflicts of interest in this work.

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