

Relation between surgical oncologic quality indicators for papillary thyroid cancer

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Background: It remains unclear how thyroid surgical oncologic quality indicators (TSOQIs) are related to each other, and how to best interpret and apply these measures within the context of surgical quality assurance. We aimed to examine the relation between 3 TSOQIs: postoperative serum thyroglobulin level, 24-hour radioactive iodine uptake (RAIU) and metastatic lymph node ratio (MLNR).

Methods: We conducted a retrospective review of patients who underwent total thyroidectomy for treatment of papillary thyroid cancer (PTC) performed by a single high-volume thyroid surgeon at a tertiary referral centre between 2012 and 2017. To establish the strength of correlation between pairs of quality indicators and the MACIS (metastasis, age, completeness of resection, invasion and size) prognostic score, we performed tests of normality and used the Spearman correlation coefficient to determine the correlation of nonnormal data containing outliers.

Results: A total of 139 patients with PTC were included in the study. Their mean MACIS score was 5.0 (standard deviation 1.5). Fifteen patients had high-risk thyroid cancer (MACIS score > 6.99). A weak correlation was found between serum thyroglobulin level and RAIU ($r_s = 0.27, p = 0.006$) and a moderate correlation was found between serum thyroglobulin level and MLNR ($r_s = 0.40, p = 0.002$). A weak correlation between serum thyroglobulin level and MACIS score was also observed ($r_s = 0.20, p = 0.05$).

Conclusion: Based on our findings, we propose that the postoperative serum thyroglobulin level represents the quality metric that has the most clinical utility because it is measurable in all patients and also correlates with both RAIU and MLNR. With further research, surgeons seeking to evaluate the oncologic quality of thyroidectomy performed for PTC may consider applying a quality indicator to their future practice.

Contexte : On ignore encore comment les indicateurs de la qualité des soins en oncochirurgie pour la thyroïde (IQSOCT) sont interreliés et comment interpréter et appliquer le mieux possible ces mesures dans le contexte de l'assurance de la qualité en soins chirurgicaux. Nous avons voulu examiner le lien entre 3 IQSOCT : taux de thyroglobuline sérique postopératoire, absorption de l'iode radioactif (AIRA) en 24 h et taux de ganglions lymphatiques métastatiques (TGLM).

Méthodes : Nous avons procédé à une revue rétrospective des patients soumis à une thyroïdectomie totale pour le traitement d'un cancer papillaire de la thyroïde (CPT) opérés par le même chirurgien spécialiste de la thyroïde dans un centre de soins tertiaires entre 2012 et 2017. Pour établir la solidité de la corrélation entre les paires d'indicateurs de la qualité et le score pronostique MACIS (métastasis, âge, completeness of resection, invasion and size), nous avons procédé à des tests de normalité et utilisé le coefficient de corrélation de Spearman pour déterminer la corrélation des données non normales renfermant des valeurs aberrantes.

Résultats : En tout, 139 patients atteints de CPT ont été inclus dans l'étude. Leur score MACIS moyen était de 5,0 (écart-type 1,5). Quinze patients présentaient un cancer de la thyroïde à risque élevé (score MACIS > 6,99). Une faible corrélation a été observée entre le taux de thyroglobuline sérique et l'AIRA ($r_s = 0,27, p = 0,006$) et une corrélation modérée entre le taux de thyroglobuline sérique et le TGLM ($r_s = 0,40, p = 0,002$). Nous avons noté également une faible corrélation entre le taux de thyroglobuline sérique et le score MACIS ($r_s = 0,20, p = 0,05$).

Conclusion : Selon nos observations, nous estimons que le taux de thyroglobuline sérique postopératoire représente l'indicateur de qualité le plus utile au plan clinique parce qu'il est mesurable chez tous les patients et qu'il est également en corrélation avec l'AIRA et le TGLM. À mesure que la recherche s'approfondira, les chirurgiens qui souhaitent évaluer la qualité oncologique de la thyroïdectomie pour le CPT pourraient envisager d'appliquer un indicateur de qualité à leur pratique future.

The incidence of thyroid cancer has been steadily increasing over the past several decades worldwide.^{1,2} It is projected that, by 2030, thyroid cancer will become the fourth most common cancer diagnosis in the United States, with the average annual percent increase in incidence exceeding 5% for both females and males.² This rising incidence has been attributed in part to the increased use of diagnostic imaging, with the majority of new diagnoses occurring in females.³ Concurrently, there has also been an increase in the incidence of and mortality from advanced differentiated thyroid cancer (DTC).^{4,5} Historically, about 85% of patients diagnosed with DTC undergo total thyroidectomy, and most of these patients also subsequently undergo radioactive iodine ablation. These patients also receive postoperative lifelong thyroid hormone replacement treatment with thyroid-stimulating hormone suppression.^{1,3,6,7}

Overall, disease-specific survival from DTC is very favourable, with the 5-year survival rate being greater than 98%.^{8,9} Disease-specific survival for DTC is predicted by patient age, characteristics of the primary cancer itself, the presence of metastases and the completeness of cancer resection. These clinicopathological characteristics have been included in prognostic scoring systems that predict DTC recurrence and survival, including the MACIS (metastasis, age, completeness of resection, invasion and size) prognostic scoring system.¹⁰⁻¹² The MACIS score predicts 20-year mortality risk and is a reproducible scoring system that has been found to reliably categorize patients with DTC by their risk of recurrence and death.¹³

Quality cancer care requires the coordinated efforts of multiple providers within the health care system. Different points in the cancer treatment algorithm can be subjected to measures of quality improvement. Measuring the quality of the surgical component of cancer care has traditionally centred around the volume–outcome relation. Across multiple studies, surgical complications have been found to be consistently reduced for many different types of operations when high- and low-volume thyroid surgeons are compared.¹⁴ Quantifying the quality of surgical technique itself is challenging. General approaches to the measurement of surgical quality include quantifying the nodal harvest from lymphadenectomy, evaluating the accuracy of sentinel lymph node biopsy, and assessing the adequacy of margin clearance during cancer resection. These surgical quality measures all call for ongoing close collaboration between the pathologist and the surgeon.¹⁵

For thyroid cancer operations specifically, the aim of the surgeon is removal of all normal and diseased thyroid tissue, while avoiding procedure-specific complications such as recurrent laryngeal nerve injury, hypoparathyroidism and postoperative hemorrhage. The surgeon's volume and experience have been found to predict the completeness of total thyroidectomy.^{14,16,17} Although leaving large thyroid remnants had historically been done to reduce the

risk of recurrent laryngeal nerve and parathyroid injury, those patients were also known to have poorer oncologic outcomes.¹⁶ Therefore, quality metrics that measure the volume of residual thyroid tissue and/or cancer, or the oncologic completeness of the central neck operation, may be applied to evaluate surgeon performance.

Quality indicators that relate to the oncologic quality of thyroidectomy performed for treatment of DTC have proven difficult to study owing to low disease-specific mortality rates and lengthy disease-free recurrence interval. Proposed thyroid surgical oncologic quality indicators (TSOQIs) have included preablation serum thyroglobulin level, remnant radioactive iodine uptake (RAIU) and metastatic lymph node ratio (MLNR, calculated based on pathological status of lymph nodes removed from the central neck compartment during thyroidectomy).^{18,19} Lower post-thyroidectomy unstimulated serum thyroglobulin levels, measured before radioactive iodine ablation, are associated with a smaller thyroid gland remnant and a lower risk of cancer recurrence.^{6,20-22} There is evidence that higher postoperative 24-hour RAIU is associated with greater odds of cancer recurrence.¹⁶ The MLNR on its own is not a measure of the oncologic completeness of the operation. As in colorectal cancer surgery, the nodal yield, or absolute number of lymph nodes removed at surgery, is reflective of the combined technique of the surgeon and the pathologist.^{23,24} Obtaining an adequate lymph node yield is essential for calculating the MLNR. Investigators have found that, in patients undergoing total thyroidectomy with concurrent therapeutic or prophylactic central neck lymph node dissection (CLND), the MLNR is an independent predictor of locoregional cancer recurrence when the nodal yield is 3 or higher.²⁵⁻²⁸

Serum thyroglobulin level, 24-hour RAIU and MLNR are of interest because they are readily quantifiable during the early postoperative period and are specific for thyroid tissue and thyroid cancer, both important characteristics of surgical oncologic quality indicators. However, it remains unclear how they are related to each other, and how to best interpret and apply these measures within the context of surgical quality assurance. The primary objective of this study was to evaluate the relation between these 3 TSOQIs for papillary thyroid cancer (PTC) treated with total thyroidectomy. A secondary study objective was to evaluate the prognostic utility of these TSOQIs by assessing the strength of their correlation with the MACIS prognostic score.

METHODS

We carried out a retrospective cohort study with approval from our institutional research ethics board. Consecutive adult (age > 18 yr) patients who underwent total thyroidectomy with or without concurrent central neck compartment lymph node dissection for the treatment of DTC were evaluated. All operations were carried out over a period of 6 years (2012–2017) by a single high-volume thyroid

surgeon (S.M.W.) who performed more than 200 thyroid operations annually at a tertiary referral centre (St. Paul's Hospital, Vancouver, British Columbia, Canada). Recommendations for performance of CLND evolved over the period during which the thyroid operations were performed. Therefore, patients who underwent either therapeutic or prophylactic CLND were included. We discerned intent to perform a central nodal dissection, either prophylactic or therapeutic, through clinical and operative notes. Patients who underwent thyroidectomy with a concurrent lateral neck dissection for PTC treatment were excluded from the study population, as were those who were positive for serum thyroglobulin antibody (> 35 kIU/L), because it may interfere with the accuracy and interpretation of the measured serum thyroglobulin level. We also excluded patients who presented with distant metastatic PTC. Distant metastases cause elevation of the postoperative thyroglobulin level or 24-hour RAIU, or both, that is not related to the volume of residual central neck thyroid remnant/disease and thus confounds their use as TSOQIs.

Through retrospective chart review, we collected clinicopathological data, including the unstimulated preablation serum thyroglobulin levels collected within 6 weeks postoperatively, postoperative 24-hour RAIU and final pathological lymph node status. The threshold for detection for 24-hour RAIU at our institution is less than 0.1%. We assigned patients with RAIU of 0.1% or less a value of 0 for the purposes of statistical analysis. We calculated MACIS scores according to the Mayo Clinic published prognostic scoring system equation: MACIS score = 3.1 (if age ≤ 39 yr) or 0.08 × age (if age ≥ 40 yr), + 0.3 × tumour size (in cm), + 1 (if resection incomplete), + 1 (if locally invasive), + 3 (if distant metastases present).¹² We defined the MLNR as the total number of metastatic lymph nodes identified on final pathological examination divided by the total number of lymph nodes removed from the central neck compartment. Patients with follicular thyroid carcinoma were not included in this analysis because of their known relatively low propensity for nodal metastases.²⁹ For the purpose of this study, we calculated the MLNR for patients with PTC who underwent a central lymph node dissection and had 3 or more lymph nodes removed. For applicable portions of the analyses, only patients for whom an MLNR was calculated were included. We decided a priori that a nodal yield of 2 or less was insufficient for evaluation because lymph node positivity in these patients would lead to extreme ratios of 0.0, 0.5 or 1.0.

Statistical analysis

To establish the strength of the correlation between pairs of TSOQIs and the MACIS score, we used the Spearman test for the correlation of nonnormal data containing outliers. A correlation coefficient less than 0.20 was considered to indicate very weak correlation; 0.20–0.39, weak correlation; 0.40–0.59, moderate correlation; and 6.00 or

greater, strong correlation. Based on an α of 0.05 and a power of 80%, the smallest minimum sample size to detect very weak correlation was 194 patients. To detect moderate correlation, the minimum sample size was 47 patients. We used the Student *t* test to evaluate the difference in means between prognostic groups. A *p* value < 0.05 was chosen for the test of significance. We conducted statistical analyses using Stata software, version 15.1 (StataCorp).

RESULTS

The study population consisted of 147 patients with DTC who underwent total thyroidectomy during the study period. Patient clinicopathological characteristics are summarized in Table 1. Most patients (139 [94.6%]) had PTC; 8 patients (5.4%) had follicular thyroid carcinoma. Central neck lymph node dissection was carried out with 84 total thyroidectomy procedures (57.1%). None of the patients with follicular thyroid carcinoma underwent CLND. On average, there

Table 1. Clinicopathological characteristics of patients who underwent total thyroidectomy for treatment of differentiated thyroid cancer between 2012 and 2017

Characteristic	No. (%) of patients* n = 147
Sex	
Female	107 (72.8)
Male	40 (27.2)
Age, mean ± SD, yr	47.8 ± 14.5
Age, yr	
< 40	47 (32.0)
≥ 40	100 (68.0)
Papillary carcinoma	139 (94.6)
Follicular carcinoma	8 (5.4)
Central lymph node dissection†	84 (57.1)
Time to RAIU follow-up, mean ± SD, d	95 ± 68
Time to postoperative thyroglobulin measurement, mean ± SD, d	75 ± 37
Nodal yield (n = 84)	
< 2	14 (16.7)
≥ 3	70 (83.3)
No. of nodes, mean ± SD	7.1 ± 6.6
Radioactive iodine administered postoperatively	115 (78.2)
Postoperative serum thyroglobulin level, mean ± SD, µg/L	4.3 ± 10.4
Postoperative 24-h RAIU, mean ± SD, %	2.1 ± 3.8
MLNR, mean ± SD (n = 70)	0.33 ± 0.33
MACIS prognostic score, mean ± SD	5.0 ± 1.5
MACIS prognostic score	
Group 1 (< 6.00)	118 (80.3)
Group 2 (6.00–6.99)	14 (9.5)
Group 3 (7.00–7.99)	10 (6.8)
Group 4 (≥ 8.00)	5 (3.4)

MACIS = metastasis, age, completeness of resection, invasion and size; MLNR = metastatic lymph node ratio; RAIU = radioactive iodine uptake; SD = standard deviation.
*Except where noted otherwise.
†Prophylactic dissections are included.

were 7 nodes removed by CLND. Seventy (83.3%) of the 84 patients who underwent CLND had a nodal yield of 3 or more. Radioactive iodine was administered to 115 patients (78.2%) postoperatively. Most of the cases of DTC were low risk according to the calculated MACIS prognostic score. The mean MACIS score for the entire study patient population was 5.0 (standard deviation [SD] 1.5), with 15 patients (10.2%) in the high-risk group (MACIS score > 6.99).

There were 2 positive correlations between the 3 TSOQIs evaluated that were statistically significant (Table 2 and Figure 1). Postoperative serum thyroglobulin level was weakly correlated with both MLNR and RAIU; the strongest correlation identified was between serum thyroglobulin level and MLNR. Analysis of the correlation between thyroglobulin level and MACIS score showed a very weak correlation that had a test statistic that approached significance ($p = 0.05$).

We further evaluated the relation between these 2 variables by testing the difference in means. There was no significant difference in mean thyroglobulin level between patients with an MACIS score of 5.99 or lower, and those with an MACIS score of 6.00 or higher (3.0 µg/L [SD 6.1 µg/L], 95% confidence interval [CI] 1.6–4.5 v. 3.36 µg/L [SD 4.5 µg/L], 95% CI 1.3–5.4, $p = 0.6$). Similarly, when patients were grouped into the classic 4 MACIS prognostic score groups (Table 1), no significant differences in serum thyroglobulin levels were identified.

DISCUSSION

The only significant correlations between TSOQIs identified in the present study were between serum thyroglobulin level and RAIU, and between serum thyroglobulin level and MLNR. The observed weak positive correlation between thyroglobulin level and RAIU suggests that, on a population level, these measures provide an estimate of the amount of remnant normal and/or diseased thyroid tissue remaining after total thyroidectomy. Thyroglobulin level and MLNR had a stronger correlation with each other. Given the significant positive correlation between thyroglobulin level and MLNR, if specific cut-points were established for these TSOQIs, their population risk profiles would likely be similar.

Establishing the strength of correlation between these 3 quality indicators is useful given that, unlike serum thyroglobulin level, RAIU and MLNR are not universally applicable to all patients who undergo total thyroidectomy: not all patients undergo postoperative radioactive iodine therapy or have an uptake scan, and not all patients undergo a central neck compartment lymph node dissection. The correlation between serum thyroglobulin level and MLNR is interesting in that this suggests these indicators may be markers of residual disease. Therefore, the clinician should consider the ongoing presence of micrometastatic disease and interpret the serum thyroglobulin value within the context of

Table 2. Univariate correlation between surgical quality indicators and MACIS risk score

Quality indicator	Spearman correlation coefficient	<i>p</i> value
Serum thyroglobulin level and MACIS score (<i>n</i> = 97)	0.20	0.05
Serum thyroglobulin level and 24-h RAIU (<i>n</i> = 97)	0.27	0.006
Serum thyroglobulin level and MLNR (<i>n</i> = 56)	0.41	0.002
RAIU and MLNR (<i>n</i> = 56)	0.05	0.7

MACIS = metastasis, age, completeness of resection, invasion and size; MLNR = metastatic lymph node ratio; RAIU = radioactive iodine uptake.

the extent of malignant disease. The serum thyroglobulin level should not be interpreted in isolation but, rather, within the context of extent of surgery and lymph node status. Importantly, an elevated postoperative serum thyroglobulin level may also affect the patient's eventual management. It should also be emphasized that these TSOQIs are not applicable to patients with PTC who undergo less than total or near-total thyroidectomy. Considering that the recommended extent of surgery may be limited to hemithyroidectomy for most cases of low-risk PTC, the applicability of such quality indicators will likely be limited to high-risk groups.

This study did not show a significant correlation between MACIS score and the selected TSOQIs. The very weak correlation is likely explained by the fact that some components of the MACIS score calculation, such as patient age and tumour size, are not correlated to the postoperative serum thyroglobulin level.

Our observations are limited to patients with DTC who underwent total thyroidectomy. Patients with high-risk disease usually undergo total thyroidectomy, CLND and adjuvant radioactive iodine therapy, and thus likely would be the subpopulation that would benefit most from adoption of TSOQIs. Our findings, if further validated, may be useful for surgeons who wish to monitor their overall performance and the oncologic soundness of the operations they perform in patients with PTC. Currently, serum thyroglobulin level, RAIU and MLNR would not change or guide thyroid surgical practice. However, because of the broad applicability of the preablation unstimulated serum thyroglobulin level to the high-risk DTC population and ease of postoperative measurement, this measure seems to represent the TSOQI with the most clinical utility. It also correlates with other measures of remnant normal and/or diseased thyroid tissue volume, including the presence of nodal metastases.²²

Limitations

The use of the MACIS score as a surrogate for DTC prognosis is one of the study's limitations. Other limitations include the study's retrospective nature and the relatively small sample size. The relatively short follow-up period limited our

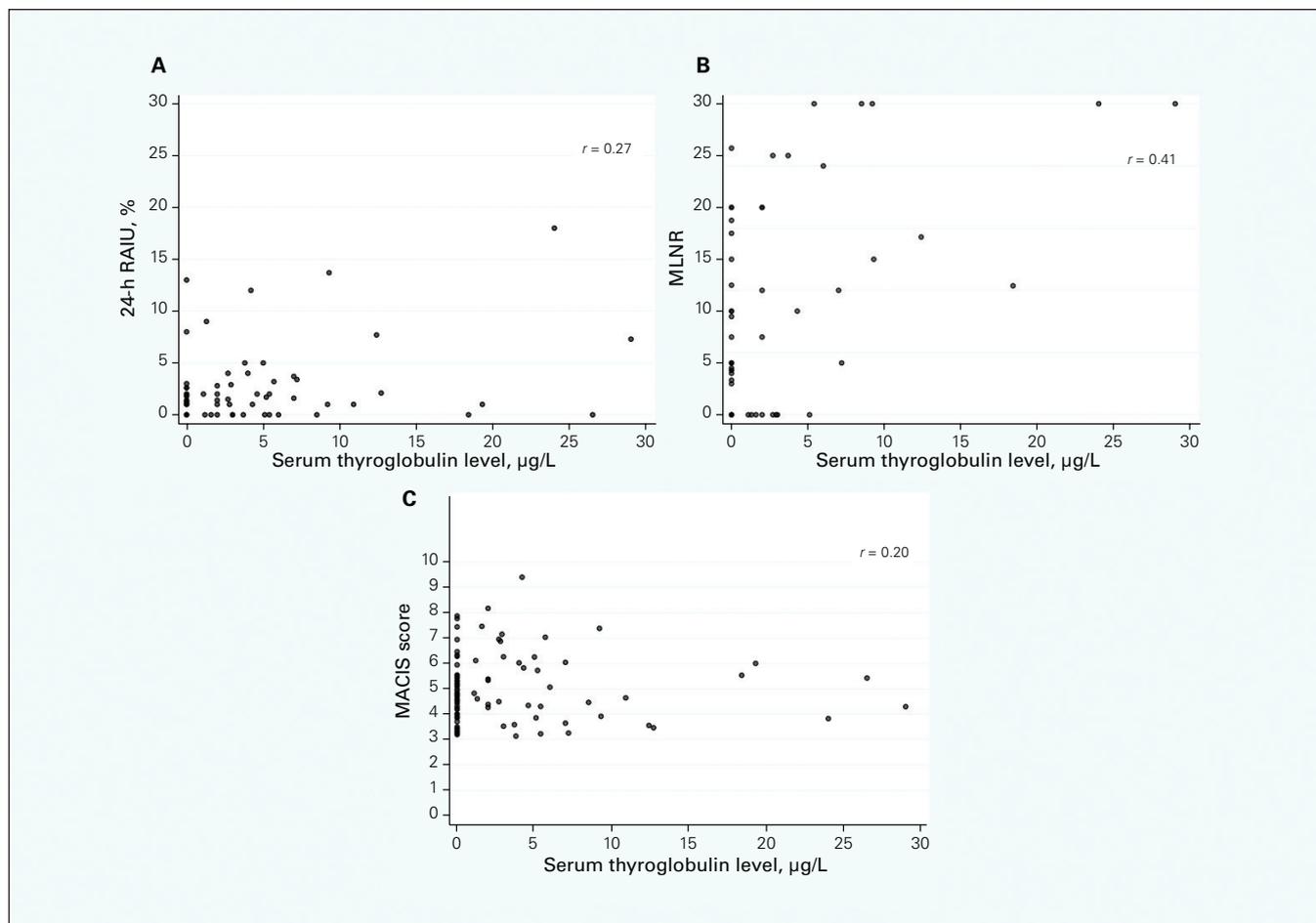


Fig. 1. Correlation between postoperative serum thyroglobulin level and (A) 24-hour radioactive iodine uptake (RAIU), (B) metastatic lymph node ratio (MLNR) and (C) MACIS (metastasis, age, completeness of resection, invasion and size) prognostic score for patients with papillary thyroid cancer who underwent total thyroidectomy with or without central neck dissection.

ability to directly evaluate the primary oncologic outcomes of recurrence and death. Considering these limitations, we investigated correlations only between the 3 TSOQIs evaluated. The correlations themselves were limited by the overall low risk of disease of the study population, which was conducted over a period during which recommendations for low-risk PTC management were evolving.⁶

CONCLUSION

The only significant correlations between TSOQIs identified were between postoperative serum thyroglobulin level and RAIU, and between postoperative serum thyroglobulin level and MLNR. Based on our findings, we propose that the postoperative serum thyroglobulin level represents the TSOQI that has the most clinical utility because it is measurable in all patients and it also correlates with both RAIU and MLNR. Future prospective investigation of TSOQIs in large, heterogeneous populations of patients with PTC treated by diverse groups of surgeons is needed. Such studies should not only assess patient and cancer

characteristics, but also consider surgeon case volumes, to better define their clinical significance. In conjunction with evolving guidelines for thyroid cancer surgery, study of TSOQIs may eventually provide thyroid surgeons with the information required to potentially improve the quality of the operations they perform.

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