

Peer Review File

Article information: <http://dx.doi.org/10.21037/gc-20-621>.

Review Comments

Comment 1: According to the results of this article (Table 3), it is still necessary to perform preoperative laryngoscopy in about 20% (486/2338=20.7%; 73/485=15.1%; 254/1205=21.1%) of patients who shows positive nomogram. There is indeed a decrease in quantity of performing this technique, which should be described in the text.

Reply1 :

Thank you very much for your kind comments. Regarding the reduction in the number of implementations of this technology. We have added descriptions of nomogram helping reduce the amount of preoperative laryngoscopy based on your suggestions.

Changes in the text :

About the decrease in quantity of performing this technique. we have modified our text as advised (see Page 14, line 316-330).

Comment 2: According to the results of Table 3, 20-25% (9/35=25.7%; 3/13=23.1%; 3/21=14.2%) of patients with preoperative VCP will show negative nomogram. About the management or prevention for these patients should be described and explained in the text.

Reply1 :

Thank you for your sincere suggestion. We have added the instruction of management or prevention for these patients with nomogram negative (below the threshold).

The sensitivity and specificity of nomogram cannot reach 100%. Preoperative tumor localization by ultrasound and intraoperative nerve monitoring (INM) are the key links in the management and prevention of nomogram negative patients. For some VCP patients without risk factors, preoperative ultrasound play an important role in reminding surgeons of the status of RLN by indicating extra thyroid infiltration. Especially for that small tumors whose anatomical location were relatively backward, that is, thyroid tumors are close to the RLN. Meanwhile, intraoperative nerve monitoring (INM) was used to localize and identify the RLN and predict vocal cord function.

Changes in the text :

About the management or prevention for these patients with negative nomogram. we have modified our text as advised (see Page 14, line 345-358)

Comment 3

3). Voice complaints are not clearly defined in this article. Hoarseness is only an overall manifestation of voice changes. Whether the roughness, Breathiness, Asthenia, etc. are included or excluded should be explained in detail. In Table 1, the hoarseness rate of VCP patients was only 5.95%, and the incidence of external cohort was only 1.31%, which is not consistent with general clinical experience, even a common cold or gastroesophageal reflux disease may cause more voice

complaints than this data. We can almost expect that when the nomogram is certainly used in clinical practice, it will show completely different results from this article.

Reply1 :

We are very appreciative of your comments and added the definition of voice symptoms based on your suggestion.

In our study, voice complaints only include hoarseness not roughness, breathiness, and asthenia. The hoarseness was complained by patients or discovered by the doctor who received it for the first time, and was finally recorded after being evaluated by experienced surgeons' assessment.

Unfortunately, in previous clinical work, we did not use voice assessment questionnaires to diagnose voice symptoms. It is very important to accurately evaluate and quantify voice quality in clinical work. At present, the voice assessment questionnaire of newly enrolled thyroid patients is mainly from the American Association of head and neck surgery (1). Second, another reason for the low proportion of hoarseness in patients with thyroid cancer is that patients with cough or hoarseness are required to delay admission almost a week to decrease the anesthesia risk. It may largely exclude hoarseness caused by cold, leading to a decrease in patients with voice symptoms. Finally, we have also noticed that the incidence of hoarseness fluctuates significantly in the records of patient complaints and mainly determined by doctors (2). We inevitably classified some patients' voice symptoms as unknown and analyzed them as an independent variable due to the retrospective

study. Although the proportion of patients with hoarseness symptoms was lower than average, hoarseness was still highly correlated with vocal cord palsy. In the nomogram, the hoarseness score is higher than the threshold value, which showed a high specificity.

Changes in the text :

About the low incidence of the hoarseness, we have modified our text as advised (see Page 6, line 135-139)

Reference :

1. Chandrasekhar SS, Randolph GW, Seidman MD, et al. Clinical practice guideline: improving voice outcomes after thyroid surgery. *Otolaryngology Head Neck Surg* 2013;148:S1-37.
2. Lee CY, Long KL, Eldridge RJ, et al. Preoperative laryngoscopy in thyroid surgery: Do patients' subjective voice complaints matter? *Surgery* 2014;156:1477-82; discussion 82-3.

Comment 4

In discussion, the author mentioned “patients with voice complaints got 100 scores and patients with neck surgery history got almost 70 scores”. This means that once the patient complains hoarseness, the preoperative laryngoscopy will be 100% performed. This also means that there are only four parameters actually used in this article, and the result of history of neck surgery and clinical lymph node status will only be yes or no. This all means that there must be more detailed or simple

classification for this issue, and becoming the limitation of this article.

Response: Thanks for the referee's kind advice.

All available preoperative factors in the database were analyzed, and the possible related factors were given in the multivariable logistical model. The nomogram can obtain a threshold with the best sensitivity and specificity by ROC curve, rather than a simple alignment and combination of independent risk factors. Meanwhile, the nomogram can also be developed small programs or web pages to facilitate clinical decision-making.

In our database, in addition to the sound symptoms and neck surgery history confirmed by evidence-based medical evidence, eighteen patients with VCP did not have the above two factors. Among them, twelve patients had positive nomogram (positive predictive value:66.67%). In the DTCC database, seven VCP patients did not have the above two factors, and three patients got positive nomogram (positive predictive value 42.86%), showing that even without hoarseness and a history of thyroid surgery, our nomograms can still distinguish 42%-67% of VCP patients. In the total cohort, 80.03-86.65% patients without VCP negative should not undergo laryngoscope. However, only four parameters may be due to the bias of retrospective study, which made some preoperative factors lose statistical significance. We have made special mention of this in the restriction section to remind clinicians that there were 20% VCP patients showing negative nomogram.

Thank you again for your suggestions!

Changes in the text :

About the only four parameters actually used in this article, we have modified our text as advised (see Page 15, line 361-363)

Comment 5

The definition of lymphatic metastasis is not clear. N1 should be divided into N1a (central nodal metastasis) and N1b (lateral nodal metastasis). In Figure 1, a description “LNM” is supposed to mean lateral nodal metastasis, but there is no other description in the main text. If only N1b is included, how the patients with N1a are classified should be explained.

Response: We must apologize for the ambiguity caused by the abbreviation of lymph nodes metastases (LNM). In our study, preoperative lymph node metastasis was defined as central (N1a) cervical or (and) lateral cervical lymph node metastasis (N1b) detected by ultrasound.

Changes in the text :

About the definition of lymphatic metastasis is not clear. we have modified our text as advised (see Page 6, line 137-139)

Comment 6

It is easy to miss younger patients with small cancers near RLN using the linear relationship between age and tumor size. Once the preoperative VCP is not determined before surgery and bilateral postoperative VCP was developed postoperatively, the cost savings from performing laryngoscopy may not even

cover the cost of patient care, socioeconomic and litigation.

Response:

Thanks for your kind advice!

We must admit that younger patients with small cancers near RLN may exist and will be omitted because any selective preoperative laryngoscopy approach can not achieve 100% sensitivity. However, whether the magnitude of this risk omitting younger patients with small tumors remains inconclusive because subgroup analysis for younger VCP patients is currently limited.

In our database, the younger patients (< 45 yrs. old) with VCP accounted for 19.05% (16/84) (Supplementary Table) and 26.32% (5/16) patients showed negative nomogram. In the DTCC database, the younger patients (< 45 yrs. old) with VCP accounted for 47.62% (10/21) and 20.00% (2/10) patients showed negative nomogram. (Supplementary Table). And as the age decreases, the prevalence will decrease. In the pathological data, 0.15% (6/3994) younger patients had laryngeal nerve invasion. Therefore, the above situation mentioned by the reviewers may occur, but the probability may be low, especially in the case of preoperative ultrasound and intraoperative monitoring of recurrent laryngeal nerve.

Changes in the text :

About the younger patients with small cancers near RLN. we have modified our text as advised (see Page 14-15, line 347-358)