Peer Review File

Peer review file: Available at http://dx.doi.org/10.21037/gs-20-273.

Comments from reviewers:
Reviewer A：

1. Abstract. Conclusion. The conclusion is poorly defined. What does it mean that the findings can provide a more accurate risk stratification assessment of DCT for better clinical treatment?

Reply: Thanks for your professional suggestions. We have modified this part. Changes shown in red front (see page 4, lines 3-5)

2. Abstract. Results. We observed a significant synergic effect between histology subtype and N stage, as well as histology subtype and M stage (RERI=48.806, AP=0.853, SI=7.656; RERI=37.889, AP=0.430, SI=1.771, respectively). Do the authors mean cancer-specific survival or all-cause survival? Please specify.

Reply: Thanks for your professional suggestions. We mean cancer-specific mortality. We have changed the statement of this part. Changes shown in red font (see page 3, line 19).

3. How do the authors think that their results can help surgeons to make safer decisions to ensure the best prognosis for patients?

Reply: Thanks for your review. Our conclusion was FTC patients with lymph node metastasis or distant metastasis may be directly classified as high-risk due to our data; Therefore, these patients may be accepted thyroidectomy or/and engrained lymph node dissection due to their higher risk.

4. Introduction. The authors state that no scoring system to date has included histology subtype, LNM, and DM. However, the 2009 ATA initial risk of stratification system and the modifications proposed in 2015 ATA Guidelines include different histologic subtypes.

Reply: Thanks for your professional suggestions. I'm sorry that maybe our description was not accurate enough. What you said was right that the 2009 ATA initial risk of stratification system and the modifications proposed in 2015 ATA Guidelines include different histologic subtypes. However, they only described the histological subtypes as high-risk risk factors separately (see the screenshot below and the literature(1)), while our study not only described the histological subtypes as high-risk risk factors, but also studied the synergic effects of the histological subtypes, lymph node metastasis and distant metastasis on the risk of DTC prognosis. We have modified our description. Changes shown in red front (see page 6, lines 4-7). I appreciate to having you

professional suggestions again.

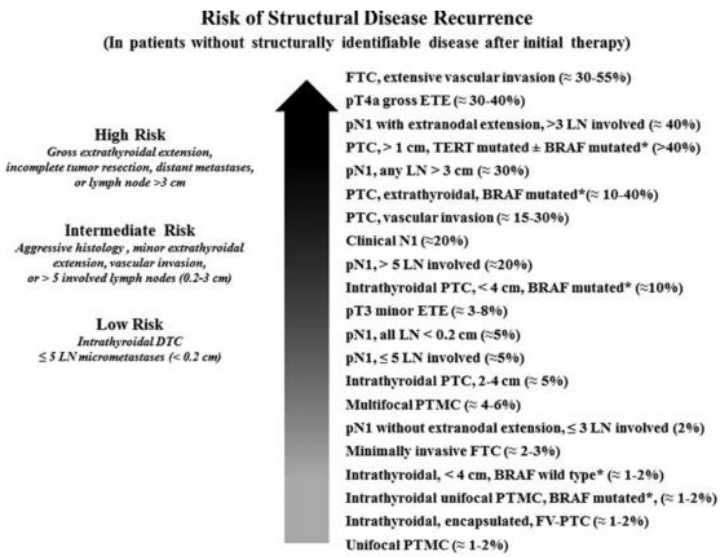

FIG. 4. Risk of structural disease recurrence in patients without structurally identifiable disease after initial therapy. The risk of structural disease recurrence associated with selected clinico-pathological features are shown as a continuum of risk with percentages (ranges, approximate values) presented to reflect our best estimates based on the published literature reviewed in the text. In the left hand column, the three-tiered risk system proposed as the Modified Initial Risk Stratification System is also presented to demonstrate how the continuum of risk estimates informed our modifications of the 2009 ATA Initial Risk System (see Recommendation 48). *While analysis of *BRAF* and/or *TERT* status is not routinely recommended for initial risk stratification, we have included these findings to assist clinicians in proper risk stratification in cases where this information is available. FTC, follicular thyroid cancer; FV, follicular variant; LN, lymph node; PTMC, papillary thyroid microcarcinoma; PTC, papillary thyroid cancer.

1. Haugen BR, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid : official journal of the American Thyroid Association*;**26**:1-133 (2016).

5. The purpose of this study is confusing, as the authors claim they want to assess whether histology subtype, LNM and DM affect DTC prognosis. Obviously this are well-known facts.

Reply: Thanks for your professional suggestions. This statement is really not exactly accurate. In addition to assessing their effects on the prognosis of DTC patients, we also want to explore whether there are synergic effects of these factors on the prognosis of DTC. We have modified our description. Changes shown in red front (see page 6, lines 15-17).

6. They should further clarify the purpose of their study and why they have chosen these three variables (histology, LNM and DM) to make synergy calculations. Why these three and no other variables? What is the starting hypothesis that the authors hoped to test in your study?

Reply: Thanks for your careful review and comments. We have taken other variables into consideration in the early design stage of the study, and we have also study the

synergic effects among a lot of other risk factors. Some risk factors have no synergic effects. We're going to do some more in-depth research on other variables.
1. A large number of studies have included variables related to TNM staging, but no one has yet studied the synergic effects of histological subtypes and variables associated with the TMN staging system.
2. The purpose of our study was to investigate the relatively important variables associated with the TMN staging system and explore whether there are synergic effects among them. We look forward to exploring the potential associations among these risk factors (additive interaction, antagonism, or no effect) to explore possible guiding significance and some clinical references for surgical treatment.
I appreciate to having you professional suggestions.

7. Methods. Section Data collection. The study included patients with DTC from January 2004 to December 2013. It is stated that follow-up was until Dec 2013. This implies that the last patients have no follow-up. Please clarify. This section should include the minimum follow-up that has been considered to include a patient in the study.

Reply: Thanks for your professional suggestions.
1. In the SEER database, follow-up time is dynamic, the database recordes whether the patient follow-up time is still at follow-up state or has ended. See attached picture below. Exactly, some patients may be followed for a short time. The last patient may have no follow -up time in December 2013, the follow-up time of the patient may be 0 or unknown.
SEER research data record description:

SURVIVAL MONTHS

NAACCR Item #: N/A
SEER*Stat Name: Survival Months
PEDSF SAS Variable Name: srvm1-srvm10
Item Length: 4

Field Description: Created using complete dates, including days, therefore may differ from survival time calculated from year and month only. For more information, see http://seer.cancer.gov/survivaltime.

Code	Description
000-9998	000-9998 months
9999	Unknown

SURVIVAL MONTHS FLAG

NAACCR Item #: N/A
SEER*Stat Name: Survival Months Flag
PEDSF SAS Variable Name: srvmflag1-srvmflag10
Item Length: 1

Field Description: Created using complete dates, including days, therefore may differ from survival time calculated from year and month only. For more information, see http://seer.cancer.gov/survivaltime.

Code	Description
0	Complete dates are available and there are 0 days of survival
1	Complete dates are available and there are more than 0 days of survival
2	Incomplete dates are available and there could be zero days of follow-up
3	Incomplete dates are available and there cannot be zero days of follow-up
9	Unknown

2. When we used SPSS statistical software for data analysis, the data with a follow-up time of unknown would be automatically eliminated by the system, which had little impact on the stability of the results. Because the follow-up time is difference, so we adjust year at diagnosis as a binary classification variable into the multivariate Cox regression analysis in our study to reduce the error.
3. We excluded the data with survival months less than or equal to 3 months, and re-analyzed the synergic effects of histological type, N stage and M stage, which was consistent with the results of our manuscript study. See the Table below:

Table Measures for estimation of synergic effect between different risk factors for the cancer-specific mortality of DTC (survival months >3months)

		Death events(%)	Total case(n)	HR (95% CI)	p value	RERI (95% CI)	AP (95% CI)	SI (95% CI)
Histology subtype and N stage								
	PTC and N0	197(0.3)	58847	ref				
	PTC and N1	296(1.7)	17405	1.637(1.420~2.175)	<0.001*	45.573(22.647~70.593)	0.662(0.761~0.875)	6.325(3.537~10.231)
	FTC and N0	59(1.3)	4410	1.612(1.285~2.159)	<0.001*			
	FTC and N1	19(13.9)	137	3.538(2.362~5.684)	<0.001*			
Histology subtype and M stage								
	PTC and M0	373(0.5)	75593	ref				
	PTC and M1	120(18.2)	659	5.937(4.754~7.286)	<0.001*	35.327(5.530~56.582)	0.326(0.109~0.524)	1.354(1.069~2.316)
	FTC and M0	38(0.9)	4410	1.480(1.035~2.113)	0.005*			
	FTC and M1	40(29.2)	137	12.763(9.559~18.976)	<0.001*			

M stage and N stage								
	M0 and N0	195(0.3)	62934	ref				
	M0 and N1	216(1.3)	17069	2.341(1.767~2.669)	<0.001*	6.832(-19.117~34.083)	0.063(-0.186~0.265)	1.047(0.631~1.366)
	M1 and N0	61(18.9)	323	10.806(7.135~14.16)	<0.001*			
	M1 and N1	99(20.9)	473	11.267(9.012~14.576)	<0.001*			

Note: Adjusted for age at diagnosis, year at diagnosis, sex,race , T stage, N stage, M stage, multifocality, extrathyroidal extension, radiation, surgery.

* represent the p value <0.05.

Abbreviations: n, number; HR, Hazard Ratios; CI, confidence interval; DTC, differentiated thyroid cancer; PTC, papillary thyroid cancer; FTC, follicular thyroid cancer; RERI, relative excess risk; AP, attributable proportion; SI, synergy index.

8. Methods. Section Data collection. Cases with missing or incomplete survival data were excluded. How many patients were excluded due to lack of data? Were there significant differences between included and excluded patients that could affect the interpretation of the results?

Reply: Thanks for your professional suggestions. Based on the SEER database data recording principle, we coded the original data from the SEER database, and a total of 13134 patients were excluded because of incomplete survival data. We performed a statistical test between the excluded datas and our study datas of the baseline information, and the test results are shown in the following table.

Characteristics	Include patients Number (%)	Excluded patients Number (%)	P
Age at diagnosis (year)			
Mean(range)	49.14 (2~105)	51.98 (3-101)	0.392
＜55 years	54785 (63.7)	7470 (56.9)	0.408
≥55 years	31247 (36.3)	5664 (43.1)	
Year of diagnosis			
2004-2008	35389 (41.1)	6174 (47.0)	0.194
2009-2013	50643 (58.9)	6960 (53.0)	
Sex			
Female	66537 (77.3)	9538 (72.6)	0.055
Male	19495 (22.7)	3596 (27.4)	
Race			
White	70568 (82.0)	10257 (80.2)	0.104
Black	5399 (6.3)	1050 (8.2)	
Other	9086 (10.6)	1487 (11.6)	

9. Methods. Section Data collection. In the abstract and introduction, the authors mention histology subtype. However, in this section they only mention the two main histological types of DTC, i.e., PTC and FTC. Have they not considered the aggressive histological variables of the PTC? Have they not taken into account the differences between, for example, minimally invasive and widely invasive follicular carcinoma? These points must be clarified, since there are histology subtypes of PTC and FTC that clearly condition the prognosis of patients.

Reply: Thanks for your careful review and comments.
1. Our research objective is to select the two main subtypes, PTC and FTC among the DTC, other subtypes are rare and highly heterogeneous.
2. We may use PSM to match baseline data between other subtypes and PTC/ FTC, and to further explore the influence of other subtypes on prognosis of DTC patients.
3. In the new guidelines for thyroid cancer, minimally invasive and widely invasive follicular carcinoma do play very important roles, and you are absolutely right that these

subtypes certainly affect the prognosis of thyroid cancer. But from the point of view of the convenience of clinical practice, we hope to make it easier for clinical physicians to control realistically which combinations of variables are at higher risk of death on the basis of considering the accuracy of mathematical statistics.

10. Methods. Section Data collection. The evaluation of radiotherapy treatments must be clarified. Most DTC patients can receive a dose of radioactive iodine. A few will receive external beam radiation. The rest of the possibilities of radiotherapy are anecdotal.

Reply: Thanks for your professional suggestions. I agree with you. Radioactive iodine is one of the most common treatments for most DTC patients. But in the SEER database, the description of the code for radiotherapy is below:

Radiation Treatment Modality--Phase I, II, III

Item Length: 2
NAACCR Item #: 1506, 1516, 1526
NAACCR Name: Phase I Radiation Treatment Modality
Phase II Radiation Treatment Modality
Phase III Radiation Treatment Modality

Radiation Treatment Modality--Phase I, II, and III are new for 2018. These data items identify the radiation modality administered during the first, second, and third phase, respectively, of radiation treatment delivered during the first course of treatment.

Radiation modality reflects whether a treatment was external beam, brachytherapy, a radioisotope as well as their major subtypes, or a combination of modalities.

Code	Description
00	No radiation treatment
01	External beam, NOS
02	External beam, photons
03	External beam, protons
04	External beam, electrons
05	External beam, neutrons
06	External beam, carbon ions
07	Brachytherapy, NOS
08	Brachytherapy, intracavitary, LDR
09	Brachytherapy, intracavitary, HDR
10	Brachytherapy, Interstitial, LDR
11	Brachytherapy, Interstitial, HDR
12	Brachytherapy, electronic
13	Radioisotopes, NOS
14	Radioisotopes, Radium-232
15	Radioisotopes, Strontium-89
16	Radioisotopes, Strontium-90
99	Treatment radiation modality unknown; Unknown if radiation treatment administered

Coding Instructions

1. Assign code **13**, Radioisotopes, NOS, for Radioembolization procedures, e.g., intravascular Yttrium-90

radioactive iodine was radioisotopes, coded 13. We get the raw data of DTC patients from the SEER website, we summarized all radiation treatments of patient records, according to the SEER data descriptions of the code (see the above screenshot), radiotherapy treatments include none or refused, radiation beam or radioactive implants,

radioisotopes or radiation beam plus isotopes or implants. In our manuscript, we stated this as well (see page 7 , lines 13-15) and the sum of individual cases for each type of radiation therapy are also listed in Table 1.

11. The number of radioiodine doses received and the total cumulative activity of radioiodine are important prognostic factors that should be taken into account.

Reply: Thanks for your professional suggestions. What you say is absolutely right, but the SEER database does not record the exact radioiodine doses and the total cumulative activity of radioiodine of a patient received. This is one of the limitations of our study. We have added it into our manuscript (see page 17, lines 9-13). Several centers that working with us have taken this into account. Thanks again for your professional advice.

12. In addition, it should be clarified whether external radiation therapy received by some patients was used to treat locally advanced thyroid cancer or was used to treat distant metastases.

Reply: Thanks for your professional suggestions.
1. We carefully verified our datas, patients with distant metastases or thyroid cancer extension received external radiation therapy.
2. We performed statistical analysis between M stage and radiation therapy, results show below table, $P<0.05$, there is significant difference between Non-external radiation therapy and external radiation therapy.

variable	Non-external radiation therapy	external radiation therapy	P
M0	83806(99.1%)	1352(90.6%)	<0.001
M1	733(0.9%)	141(9.4%)	

3. It was because of this difference that we included radiotherapy as a confounding variable in Cox multivariate regression analysis to adjustment to minimize the impact it might caused.

13. Methods. Statistical analysis. Cases without data on survival duration or with incomplete follow-up duration data were eliminated from our study. What do the authors mean by “incomplete follow-up duration”?

Reply: Thanks for your professional suggestions. In SEER database, the way the datas collected meaned the survival months represented follow-up duration. If the code was blank or marked unknown, the data was incomplete follow-up duration.

14. Methods. Statistical analysis. The concepts of RERI, AP and SI are not very familiar to many clinicians and surgeons. It should be explained here what they consist of and how they are calculated.

Reply: Thanks for your generous suggestions. We have explained the concepts of RERI, AP and SI in the statistical analysis in detail. Changes shown in red font (see page 8, lines 11-20 and page 9, line 1).

15. Results. This section is very long. It should be shortened noticeably.

Reply: Thanks for your professional suggestions. We have short some unnecessary words. Changes shown in red font (see pages 9-12) .

16. Results. Table 1. This table must include the follow-up time of the patients.

Reply: Thanks for your professional suggestions. We have added survival months to Table 1. Changes shown in red font.

17. Table 2. The table heading says: Clinicopathological parameters associated with the cancer-specific survival. However, the table appears to refer to cancer-specific mortality.

Reply: Thanks for your careful suggestions. Changes would be found in the heading of Table 2.

18. Methods. Section Risk factors associated with cancer-specific survival and all-cause survival in DTC. Most of the results presented here, together with those in Tables 2 and S1, are expected and have been well reported in the literature. This section should be omitted or reduced to the minimum.

Reply: Thanks for your professional suggestions. We so sorry to make such problems. We have reduce this section to the minimum. Changes shown in red font (see page 10).

19. Methods. Section CSM and ACM rates per 1,000 person-years. The information in this section is repetitive with Tables 3 and 4. Please synthesize this information and summarize it in a single table without repeating data in text and tables.

Reply: Thanks for your professional suggestions. We have synthesize this information and summarize it in a single table. We also reduced the representation of data in the text. Changes shown in red font (see pages 10 and 11).

20. Methods. Section Synergic effects of histology subtype, LNM, and DM on DTC-related prognosis. This section collects the results of Tables 5, 6 and 7 (cancer-specific survival) and Tables S2, S3 and S4 (all-cause survival). The main results of the various combinations of risk factors and the different parameters studied (HR, RERI, AP and

SI) can be summarized in one or two tables. Again, repetitions between table and text should be avoided.

Reply: Thanks for your professional suggestions. We have summarized the results of Tables 5, 6 and 7 inTable 4 and the results of Tables S2, S3 and S4 in Table S2. Changes shown in Table 4 and Table S2. We have simplified the datas in the text. Changes shown in red font (see pages10-12).

21. In this section the meaning and the interpretation of the studied parameters (RERI, AP and SI) are explained on more than one occasion. This explanation should be included in the Methods section and omitted in the Results section. In this way the reader would know in advance the meaning of the calculated parameters and the length of the article would be shortened

Reply: Thanks for your professional suggestions. We have interpreted the meaning of the studied parameters (RERI, AP and SI) in the Methods section. Changes shown in red font (see pages 8 and 9). We have removed the explanation in the Result section. Changes shown in red font (see page 11, lines 15-20 and page 12, lines 1-20).

22. Results. Section Kaplan-Meier analysis of survival of DTCs. The reported effects of histology subtype and N stage on cancer-specific and overall survival is shown Figs. 1A and 1B, and is stated in the first paragraph of this section. Does this information contribute something new to what has already been reported in the previous sections?

Reply: Thanks for your professional suggestions. The survival analysis was intended to aid in the validation of the previous result (Histologic subtype was high risk factor affecting the prognosis of patients) and can be presented as a supplementary document if necessary.

23. Same concerns can be considered in relation to the information provided by Figures 2 and 3. In fact, in the discussion, the authors make no mention of the data shown in the Kaplan-Meier curves of this study.

Reply: Thanks for your professional suggestions. Similarly, the results of Figures 2 and 3 identified N stage and the M stage were high risk factors affecting the prognosis of patients. We have added the statement about the results of Kaplan-Meier analysis. Changes shown in red font (see page 14,lines 6-10).

24. Discussion is very long and can be reduced by 30-40% of its length, without losing relevant information.

Reply: Thanks for your professional suggestions. We are so sorry to bother you with such problems. We rearranged the discussion section to reduce its length. Changes shown in pages 14-17.

25. Discussion. The first two paragraphs repeat concepts from the introduction. They should be omitted.

Reply: Thanks for your professional suggestions. We have removed the first two paragraphs in the discussion section. You could find changes in manuscript in page 14.

26. Discussion. Page 15, lines 17-24. The authors comment on some aspects of the relationship between the BMI and DTC. This does not seem appropriate in this study in which the BMI of the patients has not been taken into account.

Reply: Thanks for your professional suggestions. The BMI of the patients has not been taken into account in our study, we have removed this part without losing relevant information. Changes shown in page 14.

27. Discussion. Page 16 These general comments on LNM and DM could be shortened considerably.

Reply: Thanks for your professional suggestions. We have simplified general comments on LNM and DM. . And you could find changes in pages 14-15.

28. Discussion. Page 17. Much of this page is devoted to commenting on aspects of lung and bone metastases and their influence on survival. However, the authors have not studied the different types and locations of distant metastases in their patients.

Reply: Thanks for your professional suggestions.
1. In SEER database, there were too much missing datas in the location of distant metastases, which was not convenient for statistics and analysis.
2. There were not many cases of distant metastasis in DTC patients, for the maneuverability and convenience of clinical practice, we divided distant metastases into M0 stage and M1 stage.
3. Previous studies had shown that single-lung metastasis was more common in PTC patients, and extrapulmonary metastasis was more common in FTC patients and the prognosis of PTC was better than FTC. In our study, we confirmed the prognosis of PTC was better than that of FTC from multiple perspectives. We may focus on the relationship between the different locations of distant metastases and the prognosis of different types of DTC patients.

29. Disussion. Page 17. Lines 13-24. When the authors comment on the synergic effect of histology subtype + N and histology subtype + M, they should specify whether they refer to cancer-specific survival or overall survival or both.

Reply: Thanks for your professional suggestions. We are so sorry to make such problems. We have verified the comment on the synergic effect of histology subtype +

N and histology subtype + M. Changes shown in in red font in the new manuscript (page 16, lines 10 and 12).

30. Discussion. Page 18. The authors state: “we support the use of thyroidectomy and engrained lymph node dissection for achieve better prognosis”. What is this claim based on?

Reply: Thanks for your review.
1. We have reviewed the literature (2), our statement was not accurate. Thyroidectomy and engrained lymph node dissection did not necessarily improve the prognosis of patients. We have modified this part of the statement. Changes shown in red font (see page 16, lines15-24).

2. Haddad RI, et al. NCCN Guidelines Insights: Thyroid Carcinoma, Version 2.2018. *Journal of the National Comprehensive Cancer Network : JNCCN*;**16**:1429-1440 (2018).

31. Discussion. Page 18. Postoperative radiotherapy should also be positively considered as part of the treatment. There are many doubts to support this statement with the results of this study.

Reply: Thanks for your professional suggestions. We have verified our study, the results of this study do not support the statement that postoperative radiotherapy should also be positively considered as part of the treatment. We have changed this statement of the text. You can see the changes in page 16 (see lines 15-24).

32. The lack of information on the histological subtypes of PTC and FTC is an important limitation of this analysis. Also important limitations are the absence of data on the location of metastases (lung, bone, others), as well as the chronology of distant metastases (synchronous, metachronous).

Reply: Thanks for your professional suggestions. We have added your suggestions to our manuscript. Changes shown in in red font (see page 17, lines 6-9).

33. In the discussion, some mention of the practical utility of these results is missed. What do the authors contribute as novel to the existing classifications? How could the current stratification risk systems be improved in light of their results?

Reply: Thanks for your professional suggestions. We have added related statement into our text. Changes shown in red front in page 16 (see lines 15-21). Thanks again for your review.

34. Surgeons treating patients with thyroid cancer are unaware, in most cases, of whether or not the patient has or will have MDL or DM in the immediate future. What practical use does the information provided in this report have for them?

Reply: Thanks for your professional suggestions. We can determine whether the patient has lymph nodes metastasis or distant metastasis by means of lymph node biopsy and related imaging tests. For DTC patients with signs of lymph node metastasis and distant metastasis preoperative, our findings may have some implications for them, including potential changes in surgical procedures and potential radiation therapy may be required.

Reviewer B:

This paper focus on investigating the risk factors related to the prognosis of patients with DTC and whether there is synergy effect between each two factors. It is a novel topic of the related areas but the paper needs improvement before acceptance for publication. My detailed comments are as follows:

1. Why the patients chosen in this research are diagnosed since 2004 and why was 2013 chosen as the cut-off point of year of diagnosis?

Reply: Thanks for your review. The fifth edition AJCC/UICC TNM classification (1997) was revised as the sixth edition in 2002 and further updated in 2003. The reason why we chose 2004 as the starting year was that the sixth edition of AJCC system was just updated. Although the follow-up periods for patients who were diagnosed before 2004 is longer, the information was collected based on the criteria of the older AJCC system, which could not perfectly match the new version. Thus, we didn't adopt data of patients who were diagnosed before 2004.

2. The description of survival months should be presented in Table 1.

Reply: Thanks for your professional suggestions. We have add survival months into Table 1. Changes shown in red font.

3. Page 8 Line 17-20, although this is a summary of the data, I think the author still need to briefly describe the variables mentioned above: age, year, sex, race, TNM stage, multifocality, histology type, extrathyroidal extension, radiation, and surgery.

Reply: Thanks for your professional suggestions. We have redescribed the data of variables including age, year, sex, race, TNM stage, multifocality, histology type, extrathyroidal extension, radiation, and surgery in Table 1. We also calculated the mean survival months. Changes shown in red font in Table 1.

4. Page 10 Line 15-17, is it a combination of different variables or a combination of different subgroups of the same variables? Please clearly explain this point in the manuscript.

Reply: Thanks for your review. We are so sorry to make such confusion. We have reinterpreted this point clearly. Changes shown in red font (see page11, Lines 5-8).

5. The captions of Table 3 and 4 are not appropriate. Please modify the captions of Table 3 and Table 4.

Reply: Thanks for your review. We have modified the captions of Table 3 and Table 4. And we have synthesize the information and summarize it in a single table. Changes would be found in the captions of Table 3.