TRANSLATIONAL CANCER RESEARCH

Peer Review File

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Reviewer A

Comment: The authors showed the evaluation of risk factors as followed T-stage and M-stage for DTC.

The methods, results and analytical procedures are generally favorable. However. I have major comments for the authors.

M factor is recognized as one of the most powerful risk factors for DTC. In other words, patients with M1 have poor prognosis and very few patients can avoid from cancer death. Therefore, the clinical treatment for M1 patients is aimed to prolong their survival. In clinics, presence or absence of M is the prime concern and presence of M means persistent disease in spite of any treatment.

Except M factor, we have clinically used risk factors such as older age, male gender, extrathyroidal infiltration and tumor size. I am afraid that there is no role in other factors with M.

Reply: Thank you so much for your professional suggestions. Your opinion is very reasonable. Age has been shown to be an important prognostic marker in patients with DTC and is included in almost every verified risk stratification system[1]. Increasing size in DTC is associated with poorer prognosis and increasing mortality rates. Disease specific death rate is noted to be significantly higher in tumours >40 mm[2]. Extra-thyroidal extension (ETE) is a significant poor prognostic marker, with 10-year overall survival rates of 45% in patients with ETE in contrast to 91% in those with intrathyroidal tumours[3]. Risk factors associated with invasion include aggressive histological subtypes, older age and recurrent disease[4]. In general, there are some common prognostic factors that are used in most classification systems such as age, extra-thyroid extension, grade, size and distant metastasis[5]. One study demonstrates that Patients >65 years of age were found more often to develop osseous metastases and skeletal related events than those ≤50 years of age, and older age and male gender were also associated with greater mortality in these patients[6]. Regarding sex distribution in patients with cranial metastases, the ratio of well-differentiated thyroid carcinoma (WDTC) to non-WDTC cases was higher in female patients than in male patients[7]. So these clinical factors may be related to each other.

Reviewer B

Comment 1. Would change conclusion to discussion in manuscript.

Reply 1: Thanks for pointing this out. We have revised the text according to your opinion.

Changes in the text: We have changed conclusion to discussion in the manuscript. (Page 12, Line 7) "Discussion"

Comment 2. Abstract with synergistic typo.

Reply 2: Thanks for examining our manuscript so carefully. We checked the abstract part of the manuscript again

Changes in the text: We have revised the abstract according to your opinion. (Page 3, Line 16-22)

"Results: Histologic subtype, T- stage, and M- stage were found to be risk factors for cancer-specific survival and all-cause survival in multivariate analysis. The cancer-specific mortality (CSM) rates per 1,000 person-years for patients were found to be higher in FTC patients and patients with T3-T4, M1 status disease. In addition, CSM and all-cause mortality (ACM) were also associated with age, sex, race, N- stage, extension, radiation treatment, and surgical approach (all, $p < 0.001$). We also found that histologic subtype had a synergistic effect with both T and M status stage on the prognosis (RERI = 7.431, AP = 0.278, SI = 1.407; RERI = 37.889, AP = 0.430, SI = 1.771, respectively). Synergy was also noted between T- stage and M- stage (RERI = 134.125, AP = 0.537, SI = 2.168)."

Comment 3. I would recommend if making the distinction between T1-2 M1 vs others. I think the difference RR is 39 vs 32 needs to be statistically vetted.

Reply 3: Thanks for examining our manuscript so carefully. We checked the results of table 6 again and get the same results. We think it may be due to the large span of confidence interval in the results of these two subgroups, which may affect their accuracy and stability to some extent.

Comment 4. When looking at this algorithm I think it's important to determine the impact and dose of RAI and alternative therapies on the subgroups. Therefore, if patients were treated with RAI how did their outcome differ. This is clearly important as stated by you that these patients need to be treated more aggressively. Moreover, if they were treated with RAI and still had a worse outcome what do the authors suggest in that scenario.

Reply 4: Thank you so much for your professional suggestions. The impact and dose of RAI and alternative therapies on subgroups are really important. RAI has long been known to have a role in the management of both PTC and FTC. The aim of post-operative administration of RAI, also called "ablation" was threefold: 1. to treat any remaining, unknown cancer tissue in the thyroid remnant, lymph nodes or other locations and so 2. to prevent recurrence. Furthermore, 3. the destruction of any

remaining healthy thyrocytes contributed to rendering follow-up easier by destroying non-cancerous sources of the tumor marker thyroglobulin[8]. Because thyroidectomies are performed by surgeons who vary broadly in their discipline, hospital setting, and procedural volume, different volume of thyroid remnants can be left. One study shown that in patients 40 years and older, death rates were significantly lower in patients treated with RAI than in those who did not receive RAI. This difference was not observed for younger patients[9]. However, some studies have shown that a larger thyroid residual volume is associated with a lower chance of successful remnant ablation, but it is still inconclusive whether the thyroid residual volume affects the recurrence rate and mortality[10]. However, in high radioiodine activity, the volume of thyroid remnants may not affect the outcome of RAI therapy even in patients with some high-risk factors, so the high radioiodine activities may resolve the problem caused by thyroid remnants in some cases[11]. There is likely little benefit in increasing doses of RAI in patients treated for low or intermediate-risk disease. Whether low dose is as good as no dose is a question that remains to be answered. The therapeutic ratio by which physicians utilize RAI has evolved to more fully account for its effects: to consider not just the number needed to treat, but the number needed to harm. RAI treatment is associated with increased rates of sialadenitis[12], which in turn can have a significant impact on quality of life[13]. Due to the limitations of SEER database, it is difficult for us to know the exact dose of RAI, but we adjusted for age at diagnosis, year at diagnosis, sex, race, N stage, M stage, multifocality, extrathyroidal extension, radiation, surgery. The focus of our study is synergistic effects of histologic subtype, T-stage, and M-stage. So we may study more about RAI next. About 20% of DTC patients have a locoregional recurrence and/or distant metastases[14]. Prognosis remains favourable when lesions are radioactive iodine (RAI)-avid, but unfortunately two-thirds of them become RAI-refractory, and in those patients, the 10-year survival rate drops to <10%[14], with a mean life expectancy of 3–5 years[15]. An Italian study shows that Lenvatinib is active even in a real-life RAI-refractory, progressive, metastatic unselected DTC population, including subjects older than 65 years and pretreated patients; toxicities were common but manageable[16]. The activity of lenvatinib could be improved if the drug administration started in the early phase of RAI-refractory disease[16]. The data reported for lenvatinib in RAI-refractory DTC (RAI-R DTC) are the most significant to date in this patient population, with a RECIST objective response rate above 60% and almost 80% reduction in the risk of disease progression[17]. With research an improved understanding of oncogenic pathways has allowed the development of specific targeted therapies offering promising results in many tumor types. In the case of DTC, targeted therapies act primarily on inhibition of angiogenesis and inhibition of cell proliferation/survival. Ho et al. have shown that use MAPK pathway inhibitor selumetinib can promote dedifferentiation of thyroid cancer cells to enhance uptake and retention of iodine and so renew the therapeutic efficacy of RAI in previously refractory cells[18].

Comment 5. Type and extent of surgery. Need to describe extent and also state how many had potentially R0 vs R1 resection.
Reply 5: Thank you so much for your professional suggestions. We divided the types of surgery into three categories, lobectomy, lubtotal or near-total thyroidectomy and total thyroidectomy shown in Table 1. We defined 26 Local surgical excision, 27 Removal of a partial lobe ONLY, 20 Lobectomy and/or isthmectomy, 21 Lobectomy ONLY, 22 Isthmectomy ONLY, 23 Lobectomy WITH isthmus, 30 Removal of a lobe and partial removal of the contralateral lobe as lobectomy. We can't get the information about R0 or R1 resection directly from SEER database. For patients with extrathyroidal extension (N=13673), it is difficult to achieve R0 resection. We speculate that patients undergoing lobectomy surgery are likely to reach R0 resection, otherwise doctors should have taken a more radical approach. Because of the limitation of the database, we can't obtain the exact proportion of patients with R0 or R1 resection.

Comment 6. Authors need to determine how FTC was described and what other tumors were identified. What was the rate of FVTC in their series and did they look at this.
Reply 6: Thank you so much for your professional suggestions. In our study, we defined 8330/3: Follicular adenocarcinoma, NOS, 8335/3: Follicular carcinoma, minimally invasive, 8332/3: Follicular adenocarcinoma trabecular,8331/3: Follicular adenocarcinoma well differentiated as FTC. And we define 8050/3: Papillary carcinoma, NOS, 8260/3: Papillary adenocarcinoma, NOS, 8340/3: Papillary carcinoma, follicular variant, 8344/3: Papillary carcinoma, columnar cell,8343/3: Papillary carcinoma, encapsulated, 8342/3: Papillary carcinoma, oxyphilic cell 8341/3: Papillary microcarcinoma as PTC. We obtained this information directly from SEER database. And there are 24864 patients with FVPTC, accounting for 30.6% of PTC.

Comment 7. Clearly other studies have shown a difference by age/sex etc. How do the authors reconcile this difference and explain how these are independent.
Reply 7: Thanks for pointing this out. Your opinion is very reasonable for that thyroid cancers are among the unique cancers where the age influences the prognosis. Patients' advanced age at diagnosis has been considered a risk factor for poor outcomes and affects patient mortality[19]. And DTC is markedly more common in women than men, and its occurrence and risk for poorer prognosis are associated with pregnancy[20]. The results of the univariate analysis of age and sex are as follows. In our study, we adjusted for age at diagnosis, year at diagnosis, sex, race, N stage, M stage, multifocality, extrathyroidal extension, radiation, surgery.

OS	CSS

Variable	HR (95% CI)	P-Value	HR (95% CI)	P-Value
Age	6.85 (6.31~7.43)	<0.001	8.47 (6.97~10.30)	<0.001
Sex	2.40 (2.24~2.57)	<0.001	3.00 (2.58~3.49)	<0.001

Comment 8. Did the authors look at LN metastasis and its impact.
Reply 8: Thank you so much for your professional suggestions. In this study, we just gave a rough description of the patients with LN metastasis (N=18628). Then we adjusted LN metastasis when study the synergic effect. In the follow-up study, we studied LN metastasis and its impact in detail.

Comment 9. When looking at distant metastasis were there locations that were more susceptible to improved outcomes vs others.
Reply 9: Thank you so much for your professional suggestions. Location of metastasis has also been shown to have a significant impact on prognosis with extra-pulmonary metastasis conferring a poorer survival[21]. Pulmonary and bone metastases are the most common sites for DTC metastasis[22]. In our study, only 1% of patients suffered distant metastasis (N=874), and the specific metastasis site is scattered. If they are also included in the study independently, there are many factors that need to be corrected, the statistical efficiency will be very poor, and the persuasiveness of the results will be poor. If necessary, we will focus on the effect of metastasis location on prognosis in later studies

Comment 10. Did total vs less than total have an impact and how many within each subgroup had poor survival.
Reply 10: Thank you so much for your professional suggestions. The results of the univariate analysis of surgery are as follows:

Variable	OS		CSS	
	HR (95% CI)	P-Value	HR (95% CI)	P-Value
Surgery				
Lobectomy	reference		reference	
Subtotal or near-total thyroidectomy	1.156 (1.056-1.267)	0.002	0.597(0.459-0.776)	<0.001
Total thyroidectomy	1.218(1.047-1.416)	0.011	1.245(0.897-1.730)	0.190

In our study, we adjusted for age at diagnosis, year at diagnosis, sex, race, N stage, M stage, multifocality, extrathyroidal extension, radiation, surgery.
The number of patients with poor outcomes in each subgroup was shown in Table 3 and we tabulated as follows:

Subgroup	Number
PTC and T1-T2 stage	1908
PTC and T3-T4 stage	1156
FTC and T1-T2 stage	139
FTC and T3-T4 stage	184
PTC and M0 stage	2830
PTC and M1 stage	234
FTC and M0 stage	261
FTC and M1 stage	62
T1-T2 stage and M0 stage	1988
T1-T2 stage and M1 stage	59
T3-T4 stage and M0 stage	1103
T3-T4 stage and M1 stage	237

Comment 11. Need to separate Radioactive impacts from RAI and show how treatment outcomes impacted outcomes.
Reply 11: Thanks for pointing this out. In SEER database, radiotherapy information is divided into radiation Beam, radioisotopes, radioactive implants, radiation beam+ isotopes/implants. Radiotherapy information is not strictly separated from RAI. In our study, we did not independently study the effect of radiotherapy information or RAI on prognosis, but we adjusted the radiotherapy information in our results.

Reviewer C

In the manuscript "Synergistic effects of histologic subtype, T-stage, and M-stage in the prognosis of differentiated thyroid cancer: a retrospective observational study", authors investigated the synergistic effect of clinicopathological factors, including histologic subtype, T stage, and M stage, on the prognosis of DTC. Several questions need to be answered before acceptance.

Comment 1. In line 6, the first sentence was not well described. The author should give a detailed number of how many countries increased, or the incidence of total thyroid cancer was changed from xx to xx.

Reply 1: Thank you so much for your professional suggestions. There has been a dramatic increase in thyroid cancer since the early 1990's, tripling over this time period in the United States, with similar trends seen internationally. We supplemented the manuscript according to your suggestion.

Changes in the text: We have revised the background according to your opinion. (Page 5, Line7-9)

"Several studies have confirmed the increasing incidence of differentiated thyroid cancer in the USA, Europe, Canada, Brazil, Australia and Saudi Arabia."

Comment 2. In line 9, the abbreviation of DTC should give its full name.

Reply 2: Thanks for pointing this out. We have supplemented it according to your suggestion.

Changes in the text: We have revised the abstract according to your opinion. (Page 3, Line 5) "Differentiated thyroid cancer (DTC)."

Comment 3. In line 10, data collecting was range from which year to which year should be described in the abstract.

Reply 3: Thanks for pointing this out. In our study, data from patients in the SEER database with a diagnosis of DTC from 2004 to 2013 were included.

Changes in the text: We have revised the abstract according to your opinion. (Page 3, Line 6)

"We collected data on 86,302 patients with DTC from 2004 to 2013 from the SEER database."

Comment 4. In the method of abstract, the author should give a brief description of what data was collected, such as baseline data, outcomes data (Histologic subtype, T-stage, and M- stage)

Reply 4: Thank you so much for your professional suggestions. We extracted multiple variables from the selected object of study. Demographic characteristics consisted of age at diagnosis (<55 years or ≥55 years), sex (male or female), year of diagnosis (2004-2008 or 2009-2013), and race (white, black, or other). Pathological characteristics included T- stage (T1, T2, T3, or T4), N stage (N0 or N1 stage), M stage (M0 or M1 stage), multifocality, histologic subtype (PTC or FTC), and extrathyroidal extension. Treatment characteristics included radiation therapy (none, or refused, radiation beam or radioactive implants, radioisotopes or radiation beam plus isotopes or implants) and surgery (none, lobectomy, subtotal or nearly total thyroidectomy, and total thyroidectomy).

Changes in the text: We have revised the abstract according to your opinion. (Page 3 Line 7-10)

"We extracted multiple variables from the selected object of study. Demographic characteristics consisted of age at diagnosis, sex, year of diagnosis, and race. Pathological characteristics included T- stage, N stage, M stage, multifocality, histologic subtype and extrathyroidal extension. Treatment characteristics included radiation therapy and surgery."

Comment 5. In line 17 and line 18, the full name of FTC and ACM should be presented when the abbreviation first appeared. An abbreviation list at the end of the abstract was OK.

Reply 5: Thanks for examining our manuscript so carefully. We checked the abstract part of the manuscript again and revised as you suggest.

Changes in the text: We have revised the abstract according to your opinion. (Page 2, Line 17-19)

"follicular thyroid carcinoma (FTC)"

"all-cause mortality (ACM)"

Comment 6. The authors should avoid the use of words that already in the title to increase the chance of their article being found in future searches. Please add some keywords.

Reply 6: Thank you so much for your professional suggestions. Your suggestion is very meaningful to us. We added keywords according to your suggestion.

Changes in the text: We have revised the keywords according to your opinion. (Page 2, Line 13-14)

"Keywords: differentiated thyroid cancer, death; synergistic effect, Histologic subtype, T- stage, M- stage, SEER"

Comment 7. In line 58, year of diagnosis is important due to the cases included was from 2004-2013, the span is long and many categories may be changed among these years.

Reply 7: Thank you so much for your professional suggestions. We agree with you very much, so in our study, we adjusted for year of diagnosis. Even though the span of our research is very long, our results are still credible.

Comment 8. In the Methods section, I think it is valuable to add a flow chart of data collection.

Reply 8: Thank you so much for your professional suggestions. Adding a flow chart of data collection is valuable in the method section.

Changes in the text: According to your suggestion, we made a flow chart of data collection as Figure 1. (Page 6, Line 14) We rearranged the number of the following figures.

"Finally, 86,032 patients were included (Figure 1)."

Comment 9. Since this paper underlines the increased risk of distant metastases in well-differentiated thyroid cancer, it would be of pivotal importance to highlight that either surgical treatment and adjuvant I-131 seem not to play a role, even in view of more restrictive indications to "aggressive therapy" coming from the literature. Moreover, it would be important that the Authors could try to explain how this lack of correlation may be consistent with the outcomes of their paper.

Reply 9: Thank you so much for your professional suggestions. Others have also described the association between decreased survival from well-differentiated thyroid cancer and male sex, increasing age, tumor stage, and distant metastasis. Distant metastases at initial diagnosis are an important prognostic factor in patients with DTC, and locoregional recurrences are significantly related to relatively poor survival in patients with DTC[23]. To minimize the overtreatment of thyroid cancer, the 2015 ATA clinical practice guidelines recommend more conservative treatment methods, including thyroid lobectomy and active surveillance in select cases, leaving room for clinical interpretation[24]. For DTC patients with intracranial metastases, neurosurgery was an independent prognostic factor of solitary intracranial metastases of DTC. Longer OS could be achieved in the patients who underwent neurosurgery than in those who did not, regardless of whether DTC metastasized to lung or bone. The decision-making of surgical treatment and adjuvant I-131 in DTC patients is complex, multifactorial, and not well understood. It requires aggregating and weighing multiple patient-related factors, including the risk of comorbidities and disease-specific factors, to provide the best recommendation.

Comment 10. In line 166, line 169, line 172, I could not find Figure 1 or Figure 2 in the manuscript.

Reply 10: Thanks for pointing this out. We rechecked the manuscript we submitted. The possible cause of the lack of figures may be the unstable network during the submission. We apologize for our negligence and we will submit the missing figures again.

Comment 11. In line 177, I could not find Figure 3 either.

Reply 11: Thanks for pointing this out. We rechecked the manuscript we submitted. The possible cause of the lack of figures may be the unstable network during the submission. We apologize for our negligence and we will submit the missing figures again.

Comment 12. In line 179, I think it should be "Discussion", not "Conclusion"

Reply 12: Thanks for pointing this out. We have revised the text according to your opinion.
Changes in the text: We have changed conclusion to discussion in the manuscript. (Page 12, Line 7) "Discussion"

Comment 13. In line 237 to line 241, I think this part should be the "Conclusion".

Reply 13: Thanks for pointing this out. We have revised the text according to your opinion.
Changes in the text: We have revised the text as you suggest. (Page 15, Line 6) "Conclusion"

Comment 14. Tables in this manuscript were well prepared, but I could not find any Figure legends or Figures in this manuscript. Please supplement these contents in the revision.

Reply 14: Thanks for pointing this out. We rechecked the manuscript we submitted. The possible cause of the lack of figures may be the unstable network during the submission. We apologize for our negligence and we will submit the missing figures again.

Reference:

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