Author's response to reviews

Title: Prognostic factors for disease-specific survival in 108 patients with Hurthle cell thyroid carcinoma: a single-institution experience

Authors:

Rok Petric (rpetric@onko-i.si)
Barbara Gazic (bgazic@onko-i.si)
Nikola Besic (nbesic@onko-i.si)

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Author's response to reviews: see over
I am sending you herewith an original manuscript of the paper **Prognostic factors for disease-specific survival in 108 patients with Hürthle cell thyroid carcinoma: a single-institution experience** by Rok Petric, Barbara Gazic and Nikola Besic.

We are thankful to the reviewers for their most useful and beneficial comments and suggestions which undoubtedly helped a lot to improve the paper.

We accepted all the comments of the reviewers. We indicated precisely the changes we made in response to the comments and we prepared a list in which we outlined all the suggestions raised by the reviewer and our response to each of these. The changes we made in response to the comments in the text are marked with red color.

All the authors have agreed to the submission of this manuscript in its present form. The work has not been published or submitted elsewhere.

Kindly consider this paper for publication in the BMC Cancer.

Sincerely yours

Nikola Besic
The following changes were done:

1. The text was edited for English language.

BACKGROUND:

2. "More than 70% of our patients..." - this sentence does not belong in the introduction, but rather the results.
   This sentence was deleted.

3. The aim needs to be more specific. For Example" The aim of the study was to determine which factors are predictive of loco-regional recurrence and disease-specific survival in HCTC.
   
   The following text: »Our aim was to find out which factors are predictive of recurrence and disease-specific survival.« was rewritten as follows (line 65-66):

   »Another aim of the study was to determine which factors are predictive of recurrence and disease-specific survival in HCTC.«

MATERIALS AND METHODS

4. Line 73: Observation time should be "follow-up time"
   
   The text was changed as suggested by the reviewer.

5. Line 90&91: This sentence is awkwardly worded. I would suggest: Patients were categorized into two groups: less 45 years of age and 45 years of age and older.
   
   The text was changed as suggested by the reviewer.

6. Line 103-104: The criteria for disease free survival area reasonable. Please include any reference to support this or state how these criteria were determined.
   
   We added references:

7. HCTC can often present with locally advanced disease invading nearby structures in the neck. Did the authors look at locally advanced disease (i.e. invading airway or esophagus) as a variable in the analysis? Also, how were such patients treated and what was their survival?

We agree with the reviewer that these questions are very important. Namely, 16 patients had pT4 tumor and 9 patients had R2 resection. After surgical procedure a macroscopic residual tumor was present on trachea, esophagus, larynx, carotid artery, mediastinal vessels, recurrent laryngeal nerve and prevertebral fascia in 6 cases, 4, 2, 2, 2, 1 and 1 case. In one patient a tracheostomy was performed, while in another patient a recurrent tumor from trachea was resected. Our patients with locally advanced HCTC were treated with a combination of surgery, EBRT and chemotherapy as described in our text. Only two patients died of distant metastases and locoregional progression of disease after 63 and 145 months after the first therapy. That's why local infiltration in surrounding structures in the neck was not included in statistical analysis. Obviously, the current TNM classification accurately categorizes patients with HCTC.

Currently we are working on a separate paper in which we will report the treatment of 32 patients with locally advanced and/or metastatic HCTC. We believe that details of the treatment of these patients are beyond the scope of the manuscript about prognostic factors in HCTC.

We inserted the following text in the methods section (lines 126-130).

Altogether 16 patients had pT4 tumor and 9 patients had an R2 tumor resection. After surgical procedure a macroscopic residual tumor was present on trachea, esophagus, larynx, carotid artery, mediastinal vessels, recurrent laryngeal nerve and prevertebral fascia in six cases, four, two, two, two, one and one case, respectively.

8. Lines 114-117: please clarify if all patients were treated at the same center, how many has inadequate surgery + completion surgery?

The following sentence »Among surgically treated patients, 78% had primary surgery at the Institute of Oncology and 21% elsewhere (some of them had either biopsy alone or some kind of inadequate surgery elsewhere and afterwards received surgical treatment at the Institute of Oncology),« was rewritten as follows (line 113-116):

»Among surgically treated patients, 78% had primary surgery at the Institute of Oncology and 21% elsewhere (some of them had either biopsy alone or some kind of inadequate surgery). A completion thyroidectomy was performed in 20 patients.«

9. Did any patients require total laryngectomy or more radical procedures?

The following text was inserted in lines 130-132:

»None of our patients required a total laryngectomy or other radical procedures. Infiltration of trachea was surgically managed by tracheal shaving and in one case by tracheostomy.«

10. Table 1: Please define all abbreviations

The table was changed as suggested by the reviewer.
11. Please clarify what type of neck dissections patients received and which levels of the neck were addressed.

The following text was inserted in lines 133 and 135:

“Levels 2-6 and levels 2-5 were removed in five and four cases, respectively.”

12. Did all patients have neck imaging pre-op? Or just thyroid imaging?

The following sentence in lines 93-95:

»In addition to chest X-ray, the diagnostic work-up also included ultrasound (US) of the neck region and determination of the serum thyroglobulin (Tg) concentration.« was changed as follows:

»In addition to chest X-ray, the diagnostic work-up also included ultrasound (US) of the thyroid gland and determination of the serum thyroglobulin (Tg) concentration.«

13. Table 1: Please separate N1a vs N1b neck disease

The table was changed as suggested by the reviewer.

14. Table 1: What is mean by disease present permanently? Please clarify.

»disease present permanently« was changed in »Initially distant metastases«

15. Line 149: Cause specific survival should be disease specific survival (keep terms consistent throughout the paper)

The text was changed as suggested by the reviewer.

16. Please clarify how survival was defined. i.e. what was day 1? Day of surgery or first day of EBRT?

Survival was defined from the day of primary treatment (Lines 154-157).

Also please clearly define overall, disease specific, and disease-free survival.

The text was changed as suggested by the reviewer (Lines 150-158).

17. Line 157-159: Please include statistical software used, if Kaplan-Meier Analysis was used, how survival curves were compared, what p value was considered significant and why this was chosen.

The text was changed as suggested by the reviewer (Lines 165-167 and lines 169-170).
RESULTS:

18. Line 163: The gender information is in table I and does not need to be repeated.

The text was changed as suggested by the reviewer.

19. Delete the mean values and keep median. No need to have both.

The text was changed as suggested by the reviewer.

20. Line 167: which levels of the neck had mets?

The following text was inserted (lines 178-179):

“Metastatic lymph nodes were found in level 2, level 3, level 4, level 5 and level 6 in three cases, five, four, one and two cases, respectively.”

21. Line 177-179: This sentence is confusing an unnecessary - delete please.

The text was changed as suggested by the reviewer.

22. Line 180-181: Why does your statistical significance chance from p<0.05 to 0.1? Please clarify.

The following text: »All factors that showed statistical correlation (p<0.1 or less) with duration of survival and factors related to treatment were included in multivariate analysis.« was changed as follows (lines 191-192):

»All factors that showed statistical correlation (p<0.05 or less) with duration of survival and factors related to treatment were included in multivariate analysis.«


The text in the Methods section was changed as suggested by the reviewer (lines 160-161). Only lymph node metastases were considered as regional recurrence.

24. Line 185-191: The wording using "risk" is confusing. Please re-word. Possibly saying "2.97 times as likely" would be easier to understand.

The text was changed as suggested by the reviewer.

25. Table 1 and 2 repeat the same information. Please combine into 1 Table.

As suggested by the reviewer Table 1 and table 4 were combined in Table 1.

DISCUSSION:

26. A paragraph discussing the limitations of the study is needed.

The following text was inserted (lines 221-225):

“The limitation of our study is that the results of treatment and survival are reported only from a single institution. Another limitation is that not all our patients were treated uniformly because during a 40-year time frame, they were treated by many surgeons and oncologists. Our study is observational and not randomized, thus it is not possible to draw conclusions about the impact of treatment on patients' survival.”
It is difficult to find patients...

The difference in treatment type is important when comparing this study to the SEER database. Please expand on this sentence and why treatment modality (especially adjuvant treatment) is particularly important in the survival of HCTC.

This is a long summary of all of the factors previously shown to be predictors of survival in HCTC. Please summarize this list and discuss how your paper differs from previous work. Emphasize that previous papers had low numbers and that your paper provides more robust data.

This was determined in Methods section (lines 91-93):

Please clarify how "residual tumor after surgery" was determined. This should be defined in the Methods section.

This can be shortened to 2-3 sentences describing the importance of the 45 year age cut off.

This wording is confusing. Please clarify.

"In patients younger than 45 years of age, the shorter disease-free survival was even 17.04 times more likely than in older patients."

The recurrence rate in our patients was 27%, which is comparable to the reports from the literature [1,17,19,23]. Khafif et al. reported that locoregional recurrence occurred in only 4 of 42 patients (10.5%) [14]. Probable cause for their low recurrence rate is obvious difference in patient selection between our and their study group. Their patients were primarily private consultations of only two surgeons. So, HCTC was usually diagnosed at an earlier stage [14]. On the other hand, our patients had lower recurrence rate in comparison to patients from another two cancer comprehensive centers: Royal Marsden [23] and Sloan Kettering Cancer [17] center with recurrence rate of 34% and 43%, respectively. Possibly, lower recurrence rate in our patients was related to more common use of adjuvant multimodal therapy.

As a summary of previous survival studies and does not discuss your results. Please change this paragraph to compare your survival results AND WHY they may differ from other studies.

As suggested by the reviewer this paragraph was rewritten as follows (273-286):

34. Line 267-286: This is a summary of previous factors predictive of survival. This does not add new information. Please change this paragraph to discuss the importance of the factors you determined to predict survival, why these are important and how they may differ from current knowledge.

As suggested by the reviewer this paragraph (lines 288-301) was rewritten as follows:
"To our knowledge, only six reports [1, 14, 15, 17, 22, 23] were published about disease-free survival and 15 factors were found to correlate with recurrence of HCTC (Table 4). However, the majority of previous papers had a small number of patients, and only two publications [15,23] reported the results of multivariate logistic regression analysis of the disease-free interval in patients with HCTC. Our multivariate analysis showed that independent prognostic factors for disease-free survival were: gender, age of patients, regional metastases, and residual tumor after surgery. Regional metastases have already been a known independent prognostic factor from the study of Stojadinovic et al. [15]. Extrathyroidal invasion was another independent prognostic factor in their study [15]. However, in our study group, extrathyroidal invasion was a prognostic factor by univariate analysis only and was not an independent factor, while residual tumor after surgery was an independent prognostic factor. Furthermore, an old clinical observation that younger patients and females have a favorable prognosis was statistically proven by our results."

36. Line 287-293: This just repeats the results. Please discuss your findings in more detail. See #35.

As suggested by the reviewer (remark #35 and #36) this paragraph in (lines 274-293) was rewritten as follows:

“To our knowledge, only six reports [1, 14, 15, 17, 22, 23] were published about disease-free survival and 15 factors were found to correlate with recurrence of HCTC (Table 4). But majority of previous papers had low number of patients, so only two publications [15,23] reported the results of multivariate logistic regression analysis of disease-free interval in patients with HCTC. Our multivariate analysis showed that independent prognostic factors for disease-free survival were: gender, age of patients, regional metastases, and residual tumor after surgery. Regional metastases have been already known as an independent prognostic factor from a study of Stojadinovic et al. [15]. Extrathyroidal invasion was another independent prognostic factor from their study [15]. However, in our study group, extrathyroidal invasion was a prognostic factor by univariate analysis only and was not an independent factor, while residual tumor after surgery was an independent prognostic factor. Furthermore, an old clinical observation that younger patients and females have favorable prognosis was statistically proven by our results."

37. Line 297-310: The is a summary of the treatment of other papers. Please change this paragraph to discuss how treatment impacts survival, what your study showed and what the optimal treatment may be for HCTC based on available data.

As suggested by the reviewer this paragraph (lines 302-318) was rewritten as follows:

“The 10-year disease-specific survival in our patients was 88%, while it was 49%, 64%, and 73% in studies reported by Kushcayeva et al. [1], Mills et al. [23], and Stojadinovic et al. [17], respectively. It should be stressed that the survival rates represent the result of both selection bias, i.e. more advanced disease in larger tertiary centers, and the effectiveness of different treatment modalities used in patients. Fortunately, SEER [6] and our data show that nowadays majority of patients with HCTC have a favorable prognosis. Total thyroidectomy and RAI ablation of thyroid remnant tissue enable early detection of tumor recurrence. Furthermore, it is possible that such treatment affects disease-free and disease-specific survival. Furthermore, our results show also that long lasting survival can be obtained also in patients with locoregionally advanced and metastatic disease if they are treated multidisciplinary. Chemotherapy before surgical procedure may be effective in order to decrease the tumor size in HCTC [30]. Our group reported that RAI therapy may be effective in patients with metastatic HCTC [18] and that recombinant human thyrotropin-aided RAI therapy may be effective in patients with metastatic HCTC [31]. Because residual tumor after thyroid surgery is an independent prognostic factor for disease-specific as well as disease-free survival an effective locoregional therapy is mandatory. Therefore, in case of residual tumor EBRT should be used.”
38. Line 311-314: Delete this as you have a separate conclusion section

The text was deleted as suggested by the reviewer.