

## Peer Review File

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### Reviewer A

The authors should be commended on an excellent and well-written SEER study on the importance of LND for PC. Important question and well-conducted analyses.

Reply 1: Dear reviewer, thank you for your recognition of our work.

Changes in the text: No changes.

### Reviewer B

The article submitted looks well-designed, but it comes with many biases because it relies on a foreign database for an extended period; such biases may lead the reader to misleading conclusions. We can debate the opportunity to perform a central neck dissection for parathyroid carcinoma, but often, this depends on a correct preoperative diagnosis. From the methods, it is unclear how many parathyroid carcinomas underwent a completion surgery after a post-operative diagnosis: this might be a confounder that should have been considered. Moreover, parathyroid carcinoma diagnostic criteria have changed over time, making the differential diagnosis with atypical parathyroid tumours not easily objective and sharable on a large scale.

**Dear reviewer, thanks a lot for your careful review and your valuable suggestions.**

**Comment 1:** The article submitted looks well-designed, but it comes with many biases because it relies on a foreign database for an extended period; such biases may lead the reader to misleading conclusions.

Reply 1: The incidence of PC is rare, so the time span is inevitably long to collect enough cases for analysis.

### Changes in the text:

**We have added some statements (see Page 12, line 370-373).**

This study relies on SEER database for an extended period (2004-2018), and parathyroid carcinoma diagnostic criteria have changed over time, which might confound the diagnostic results. However, we think it can be accepted that if the cases meet the diagnostic criteria at the time.

**Comment 2:** We can debate the opportunity to perform a central neck dissection for parathyroid carcinoma, but often, this depends on a correct preoperative diagnosis.

Reply 2: We agree with you very much that correct preoperative diagnosis of PC is important but difficult. And the related statement has been shown in the 1st paragraph in the introduction section (Unfortunately, diagnosing PC can be difficult, as there are no specific biomarkers or genetic signatures for this disease, making preoperative and intraoperative identification challenging.). However, it should be emphasized that one of the inclusion criteria of PC patients in this study is patients with diagnostic confirmation of positive histology (PC patients were identified by the International Classification of Diseases for Oncology, Third Edition Codes (ICD-O-3): C75.0 and site code 59 from the SEER-18 database between 2004 and 2018). Similarly, some articles published in *Front. Endocrinol* and other journals also used the code of C75.0 and the site code of 59 as a postoperative (not a preoperative) diagnostic criterion to enroll parathyroid carcinoma patients for survival analyses (1-4). Therefore, this kind of study can be regarded as a post hoc analysis research. Furthermore, this study is not a diagnostic study of parathyroid cancer or screening of preoperative molecular markers for parathyroid cancer. We only need to include patients who are finally identified as parathyroid cancer for survival analysis, so post hoc analysis is not a bad alternative research strategy in this study.

#### References

1: Zhang K, Su A, Wang X, Zhao W, He L, Wei T, Li Z, Zhu J, Chen YW. Non-Linear Correlation Between Tumor Size and Survival Outcomes for Parathyroid Carcinoma: A SEER Population-Based Cohort Study. *Front Endocrinol (Lausanne)*. 2022 Jul 1;13:882579.

2: Tao M, Luo S, Wang X, Jia M, Lu X. A Nomogram Predicting the Overall Survival and Cancer-Specific Survival in Patients with Parathyroid Cancer: A Retrospective Study. *Front Endocrinol (Lausanne)*. 2022 May 19;13:850457.

3: Ullah A, Khan J, Waheed A, Sharma N, Pryor EK, Stumpe TR, Velasquez Zarate L, Cason FD, Kumar S, Misra S, Kavuri S, Mesa H, Roper N, Foroutan S, Karki NR, Del Rivero J, Simonds WF, Karim NA. Parathyroid Carcinoma: Incidence, Survival Analysis, and Management: A Study from the SEER Database and Insights into Future Therapeutic Perspectives. *Cancers (Basel)*. 2022 Mar 10;14(6):1426.

4: Lo WM, Good ML, Nilubol N, Perrier ND, Patel DT. Tumor Size and Presence of Metastatic Disease at Diagnosis are Associated with Disease-Specific Survival in Parathyroid Carcinoma. *Ann Surg Oncol*. 2018 Sep;25(9):2535-2540.

#### Changes in the text:

We have added some statements (see Page 12, line 377-384).

And preoperative diagnosis of PC can be challenging due to its nonspecific biomarkers or genetic signature. However, it should be emphasized that one of the inclusion criteria of PC patients in this study is patients with diagnostic confirmation of positive histology. Therefore, this kind of study can be regarded as a post hoc analysis research. Furthermore, this study is not a diagnostic study, and we only need to include patients who are finally identified as parathyroid cancer for survival analysis, so post hoc analysis is not a bad alternative research strategy in this study.

**Comment 3:** From the methods, it is unclear how many parathyroid carcinomas underwent a completion surgery after a post-operative diagnosis: this might be a confounder that should have been considered.

Reply 3: We acknowledge the confounder that it is unclear how many parathyroid carcinomas underwent a completion surgery after a post-operative diagnosis. The issue can not be well addressed at present based on SEER database, because this information was not recorded. To avoid this bias to some extent, we used postoperative positive histology as the inclusion criterion (not a preoperative diagnosis). So, patients were also classified as LND (+) group even if they had a positive postoperative diagnosis and then underwent a completion surgery and LND. From this perspective, the bias can be reduced to some extent. We hope this kind of information can be added in SEER in the future for analysis. And a well-designed clinical research is required to address the issue explicitly.

**Changes in the text:**

**We have added some statements (see Page 12, line 387-393).**

Another concern is unclear how many parathyroid carcinomas underwent a completion surgery after a postoperative diagnosis. The issue can not be well addressed at present based on SEER database, because this information was not recorded. To avoid this bias to some extent, we used postoperative positive histology as the inclusion criterion. So, patients were also classified as LND (+) group even if they had a positive postoperative diagnosis and then underwent a completion surgery and LND.

**Comment 4:** Moreover, parathyroid carcinoma diagnostic criteria have changed over time, making the differential diagnosis with atypical parathyroid tumours not easily objective and sharable on a large scale.

Reply 4: We agree with you that diagnostic criteria have changed over time, but we think the diagnosis can be accepted if the cases meet the diagnostic criteria at the time. In other words, the current diagnostic criteria may also change in the future, and it is debatable to deny the present diagnosis by future diagnostic criteria.

**Changes in the text:**

**We have added some statements (see Page 12, line 372-375).**

This study relies on SEER database for an extended period (2004-2018), and parathyroid carcinoma diagnostic criteria have changed over time, which might confound the diagnostic results. However, we think it can be accepted that if the cases meet the diagnostic criteria at the time.