Peer Review File

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Reviewer A

Comment 1: Axillary LNs are not usually considered as regional LNs, but as distant metastasis. Therefore, the overall stage should be II (T4N1bM1).

Reply 1: We appreciate that the reviewer has pointed out this important issue. According to the 8th revision of the TNM staging system (1), N1b is defined as "unilateral, bilateral, or contralateral I, I, II, III, IV, V, or postpharyngeal lymph node metastasis", but axillary lymph nodes are not included in the category of cervical lymph nodes, we agree to re-defined axillary lymph node metastasis as distant metastasis—M1. After checking the surgical records and pathological reports, we confirmed that the primary tumor invaded the striated muscles, but did not invade the trachea, esophagus, and nerves, so the T stage was revised to T3b. In the end, the patient's stage was T3bN1bM1, stage II.

Reference: (1) Amin MB, Edge S, Greene F, et al. AJCC Cancer Staging Manual 8th edition. Springer International; 2017.

Changes in the text: we have modified our text as advised (see Page 7, line 114; Page 10, line 202)

Comment 2: Suppressed thyroglobulin level was under 0.04 U/ml. Please, describe the stimulated thyroglobulin level, too.

Reply 2: Thanks a lot. As suggested, the stimulated thyroglobulin level before 131 radioiodine therapy was 1.72 U/ml.

Changes in the text: we have modified our text as advised (see Page 7, line 121)

Comment 3: The patient underwent two additional surgeries because of recurrence (or persistent disease). How were those recurrences detected?

Reply 3: We are very sorry for our negligence in the presentation of this important issue. The patients followed up with regular observation due to advanced disease. During the outpatient follow-up at the 5th and 8th months after the first operation, ultrasound

detected the suspicious lymph nodes in un-operation areas, which are the unconventional region for not requiring cleaning. concerning these recur region, we especially compared it with the first preoperative image and found no abnormalities in the preoperative ultrasound and CT examination. Finally, the biopsy confirmed that lymph nodes metastasis from thyroid tumors. Therefore, the surgeon performed selective lateral dissection twice.

Changes in the text: we have modified our text as advised (see Page 7-8, line 123-131)

Comment 4: As you mentioned, IHC staining for CA 19-9 showed negative results in primary tumor and axillary metastases. Then, what is the possible reason for elevated CA 19-9 in the present case?

Reply 4: Thanks a lot. We highly value this comment. On the one hand, there was no evidence of any malignant lesions in other organs detected by ultrasound, CT, and PET/CT. On the other hand, serum CA19-9 and CA242 levels had a continuous downward trend postoperatively, despite the regional lymph nodes recurred twice, suggesting that the secreting lesions had been completely resected. Therefore, we speculate that the antigens probably originated from the DSV-PTC. We thank the reviewer for bringing this question of negative results to our attention. To exclude false-negative, the pathologist had re-stained the lesions of primary tumors and axillary metastases, but the results were still negative. Few kinds of literature have reported that there are some cases where both results of serum and immunohistochemistry were also inconsistent (2). Moreover, the pathology department in our hospital also found same phenomenon in some gastric cancers. But the exact mechanism remains unknown, which worth further exploration.

Reference: (2) Hoshi S, Yoshizawa A, Arioka H, et al. [Anaplastic thyroid carcinoma with lung metastasis producing CA 19-9 and GM-CSF]. Nihon Kokyuki Gakkai Zasshi. 2000 May;38(5):391-7. Japanese.

Nothing changes in the text.

Reviewer B

Comment 5: （Line 79 and 143）You diagnosed this case as T4aN1bM0. Which striated

muscle was invaded? If only strap muscles, T category will be T3b. Axillary lymph nodes are included in neck lymph nodes (levels I to VII). Therefore, I think ALNM is distant metastasis.

Reply 5: Thanks for your correction. We are very sorry for taking a mistake for judging the TNM staging system in the original manuscript. After checking the surgical records and pathological reports, we confirmed that the primary tumor invaded the striated muscles, but did not invade the trachea, esophagus, and nerves, so the T stage was revised to T3b. According to the 8th revision of the TNM staging system (1), N1b is defined as "unilateral, bilateral, or contralateral I, I, II, III, IV, V, or postpharyngeal lymph node metastasis" while axillary lymph nodes are not included in the category of cervical lymph nodes, we agree to re-defined axillary lymph node metastasis as distant metastasis—M1. In the end, the patient's stage was T3bN1bM1, stage II.

Reference: (1) Amin MB, Edge S, Greene F, et al. AJCC Cancer Staging Manual 8th edition. Springer International; 2017.

Changes in the text: we have modified our text as advised (see Page 7, line 114; Page 10, line 202)

Comment 6:（Line 88）In this case, since TgAb is positive, even a low Tg level cannot indicate no recurrence of thyroid cancer. Please add a description so easy to understand.

Reply 6: Thanks a lot. We agree with your comments. When TgAb is positive, a lower Tg level cannot indicate the status of recurrence, but it is necessary to continuously observe the tendency of TgAb to assess the postoperative status (3). However, the index of Tg and TgAb still showed a continuous downward trend (Figure 4B), despite two regional recurrences during survival with disease. Therefore, we speculate that the Tg or TgAb levels may no longer be of significance in monitoring the recurrence status.

Reference: (3) Verburg FA, Luster M, Cupini C, et al. Implications of thyroglobulin antibody positivity in patients with differentiated thyroid cancer: a clinical position paper[J]. Thyroid, 2013, 3(10):1211-1225.

Changes in the text: we have modified our text as advised (see Page 8, line 136-138)

Comment 7: Because this case has recurred twice in the cervical lymph nodes, the word of `Disease free` on lines 19 and 83 is inappropriate. Please correct it. I would like to

know whether there was a change in CA19-9 and CA242 when the local recurrence occurred.

Reply 7: We appreciate that the reviewer has pointed out this important issue. The patient was followed-up with regular observation due to the advanced disease. During the outpatient follow-up at the 5th and 8th months after the first operation, ultrasound detected the suspicious lymph nodes in the unoperated areas. Concerning these recur region, we especially compared it with the preoperative image and found no abnormalities in the preoperative ultrasound and CT examination. Therefore, we believe that it is feasible to define "Disease-free" as the status of patients from the first surgery to the primary recurrence at 5th months after surgery and "Survival with disease" as the status from the primary recurrence at 5th months to the second recurrence at 8th months after surgery. Thank you again for your correction. We have modified our text based on your suggestions. Afterward, we defined “Disease-free” as the status of patients from the second recurrence at 8th months after surgery to now for no new abnormal lesions found during the two years follow-up. Also, under these two recurrences, the CA19-9 and CA242 levels remained stable within the normal range.

Changes in the text: we have modified our text as advised (see Page 3, line 48; Page 7-8, line 123-138)

Comment 8: As discussed, CA19-9 may be elevated in anaplastic thyroid carcinoma. Why did you measure CA19-9 and CA242? If you are measuring them routinely, it is recommended that you also include the positive rate of CA19-9 and CA242 for papillary thyroid carcinoma.

Reply 8: We highly value your constructive comments. Since our department major in surgical oncology, tumor markers examination is performed routinely on each patient for tumor screening and diagnosis; therefore, we unexpectedly discovered the particularity of this patient. There was no significantly elevated serum CA19-9 and CA242 levels among a total of 7000 patients with papillary thyroid carcinoma admitted in our department; yet, the number of slightly elevated levels has not been calculated. Next, as suggested, we will perform statistics and analysis on all PTC patients with serum CA19-9 and CA242. Perhaps, this will be a great discovery finding a special type of PTC. Thanks again for your excellent proposal.

Changes in the text: we have modified our text as advised (see Page 12, line 230)

Comment 9: (Line173) The sentence `early diagnosis using diagnostic modalities, such as ultrasound and CT, and timely treatment may be of significance to improve prognosis` is overstatement. This case cannot show that early diagnosis can improve prognosis. And I wonder if this case is early diagnosis because of its advanced stage.

Reply 9: Thanks for your correction. Indeed, ultrasound and CT are of great significance to "discover and diagnose" the disease, but not “early detection” in the present case for advanced stage and disease progression. As suggested, we deleted "early".

Changes in the text: we have modified our text as advised (see Page 12, line 233)