

Peer Review File

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Reviewer A

The topic is interesting and uncommon. It is remarkable that you describes both cases of malignant and benign.

a few consideration:

1: patient's age is not the same in the abstract and in the text: please clarify if you are considering the age at surgery of at follow-up, it can be confusing for the readers.

Reply 1: We have modified and clarified our text as advised

Changes in the text: Page 2, Line 23 and 26

2: There is at least another case report published in 2022 about subcutaneous implantation, please include it in your references.

Reply 2: As advised, recent papers including 2022 were included in the reference.

Changes in the text: Page 15, Line 290-300

Reviewer B

The authors present two cases of subcutaneous implantation of thyroid tissue following thyroidectomy and discuss the differential diagnosis, clinicopathological characteristics, and the possible mechanism of implantation.

In the second case follow-up length is missing.

Reply 1: We have modified our text as advised

Changes in the text: Page 6, Line 94

The criteria for distinguishing between subcutaneous implantation, thyroid remnant and ectopic thyroid need to be better stated and explained.

Reply 2: Although there is no clear criteria for distinguishing, it is described in a little more detail so that the two can be distinguished, as advised.

Changes in the text: Page 6-7, Line 112-118

More informations about first interventions are needed.

Reply 3: We included information on first interventions as advised.

Changes in the text: Page 4 and 5, Line 58 and 81

Limitations of the study have to be discussed.

Reply 4: We included limitation of our study as advised.

Changes in the text: Page 10, Line 188-193

It is important to better propose and explain which intraoperative and postoperative precautions should be implemented to avoid this problem.

Reply 5: Several precautions to avoid complications are included in the conclusion section as advised.

Changes in the text: Page 10-11, Line 200-203

Reviewer C

Authors reported their cases about the subcutaneous implantation of thyroid tissue after thyroid surgery. Although this situation is very rare in its incidence, this phenomenon is well known theory.

Reply 1: Thank you for the reviews and advices.

Reviewer D

Yongseon Kim, Juneyoung Ahn and Yong Seok Kim report on two cases of subcutaneous implantation of thyroid tissue. In the first case it was benign tissue ten years after surgery, in the other case it was poorly differentiated thyroid carcinoma nine years after surgery for nodular hyperplasia.

These cases are worth being reported but I miss some points, which need to be discussed in my opinion. For instance, the ability of thyroid tissue to implant and even gain some function has been observed in animal trials with the aim to establish thyroid “autotransplantation” and this point thyroid autotransplantation should be mentioned, in my opinion. See also doi: 10.21053/ceo.2016.01578 for an overview on this subject. Secondly, I think the consequences of thyroid tissue implantation for remote access surgery should be mentioned and discussed. See also doi: 10.1016/j.amjoto.2020.102811.

Reply 1: As you advised, We looked up the above two and mentioned them in the discussion section. We mentioned that there was no change in L-T4 therapy to relate autotransplantation to our case.

Changes in the text: Page 8-9, Line 151-158, 168-177

Have the authors considered adding a review of the previously published cases, for example as a table containing the most important findings?

Reply 2: We did not even consider creating a table for review of published cases. In the future, when more cases related to this topic accumulate, we will consider making it.

Line 2-3 : Since the authors report on two cases, I suggest changing the title into “Subcutaneous implantation of thyroid carcinoma and benign tissue after

thyroidectomy: report on two cases (and review of the current literature)”

Reply 3: As advised, we changed the title.

Changes in the text: Page 1, Line 2

Abstract, line 19: I would rather say “involving both benign and malignant thyroid tissue”.

Reply 4: We have modified our text, as advised.

Changes in the text: Page 2, Line 19

Abstract, line 30-34: I am not sure that “It is important to perform comprehensive long term postoperative evaluation and follow-up of patients who have undergone thyroid surgery to avoid missing this potential complication” would be also my conclusion. I would rather point out that surgeons should be aware of this possible long-term complication especially with the rising importance of cosmetic, extracervical accesses (TOETVA, TOVARA, axillary robotic surgery) and try to avoid seeding of both malignant and benign tissue. Please see for example: Fregoli L, Bakkar S, Papini P, Torregrossa L, Ugolini C, Rossi L, Matrone A, Elisei R, Materazzi G. First report of benign track seeding after robot-assisted transaxillary thyroid surgery. *Am J Otolaryngol*. 2021 Jan-Feb;42(1):102811. doi: 10.1016/j.amjoto.2020.102811. Epub 2020 Oct 26.

Reply 5: We have changed what we wanted to say as a conclusion as advised.

Changes in the text: Page 2, Line 32-35

Line 45: Consider including also: Kim YH, Choi IH, Lee JE, Kim Z, Han SW, Hur SM, Lee J. Late recurrence of papillary thyroid cancer from needle tract implantation after core needle biopsy: A case report. *World J Clin Cases*. 2021 Jan 6;9(1):218-223. doi: 10.12998/wjcc.v9.i1.218.

Reply 6: We have included an article for reference as advised.

Changes in the text: Page 3, Line 45

Line 52: “.” should be “.”

Reply 7: We have fixed a typo as advised.

Changes in the text: Page 4, Line 52

Line 57: what do the authors mean with “5cm bilateral goiter”? Is 5cm the size of a nodule? Wouldn't the volume in ml be more clear?

Reply 8: The size specification has been removed to avoid comprehension confusion.

Changes in the text: Page 4, Line 57

Line 94: Please see also Noussios G, Anagnostis P, Goulis DG, Lappas D, Natsis K. Ectopic thyroid tissue: anatomical, clinical, and surgical implications of a rare entity. *Eur J Endocrinol*. 2011 Sep;165(3):375-82. doi: 10.1530/EJE-11-0461. Epub 2011 Jun 29.

Reply 9: We have included an article for reference as advised

Changes in the text: Page 6, Line 100

Line 99: consider rephrasing “which accounted for only 0.14%”. You mean “of FNABs”?

Reply 10: We have modified to clarify meaning with incidence.

Changes in the text: Page 6, Line 103

Line 108: Ectopic thyroid tissue in the sternocleidomastoid muscle has been reported. See also Barrea L, Fonderico F, DI Somma C, Pugliese G, DE Alteriis G, Mascolo M, Colao A, Savastano S. Papillary thyroid carcinoma arising in ectopic thyroid tissue within sternocleidomastoid muscle: a review of current literature. *Minerva Endocrinol.* 2020 Dec;45(4):318-325. doi: 10.23736/S0391-1977.20.03167-3. Epub 2020 Aug 3. and Huang Q, Chen D, Ma Y. Bilateral papillary thyroid cancer with normal aberrant thyroid tissue. *J Surg Case Rep.* 2021 Dec 24;2021(12):rjab578. doi: 10.1093/jscr/rjab578. eCollection 2021 Dec.

Reply 11: We have modified our text base on the referenced articles.

Changes in the text: Page 7, Line 116-118

Line 126-8: “Therefore, it is crucial for patients and healthcare providers to maintain long-term follow-up to monitor for recurrences and ensure timely intervention when necessary” you mean long-term follow up after thyroidectomy for benign diagnosis? Isn't subcutaneous implantation too rare?

Reply 12: The text that long-term follow-up is necessary has been deleted and corrected.

Changes in the text: Page 7, Line 134

Line 133: doi: 10.3389/fonc.2022.896942

Reply 13: We have modified our text base on the referenced articles.

Changes in the text: Page 8, Line 139

Lines 144-6: “Panunzi et al. hypothesize that immunodeficiency caused by multiple myeloma and/or therapy-related immune suppression might contribute to implantation” : this is only one case. I wouldn't quote this example but rather mention that there are some hints that thyroid tissue can be transplanted, just like parathyroid tissue, doi: 10.21053/ceo.2016.01578.

Reply 14: Describing the mechanism of implantation and its association with transplantation is challenging for me. If Panunzi's hypothesis is not satisfactory, it may be better to omit the content.

Changes in the text: Page 9, Line 160-163

Lines 168-70: “To minimize the risk of cervical soft tissue recurrence, it is essential to implement thorough long-term postoperative evaluation for patients who have undergone thyroid surgery”. To me it seems that it is not essential to implement thorough long-term postoperative evaluation for patients who have undergone thyroid surgery for benign nodules but to avoid morcellement and cell seeding during surgery

or to recommend thorough long-term postoperative evaluation for patients, in whom benign and malignant nodules ruptured during surgery.

Reply 15: We have modified what we wanted to say as a conclusion as advised.

Changes in the text: Page 10-11, Line 200-203

Please consider also:

Dong X., Lv S., Zhang X., Li Q. Subcutaneous recurrences of thyroid cancer after conventional transcervical thyroidectomy: a case report. *Front. Surg.* 2020;7 doi: 10.3389/fsurg.2020.586106.

Koller E.A., Tourtelot J.B., Pak H.S., Cobb M.W., Moad J.C., Flynn E.A. Papillary and follicular thyroid carcinoma metastatic to the skin: a case report and review of the literature. *Thyroid.* 1998;8(11):1045–1050. doi: 10.1089/thy.1998.8.1045.

Famà F, Pino A, Cavallari V, Fadda G, Ieni A, Dionigi G. Subcutaneous implantation of oncocytic thyroid cell aggregates nine years later from thyroidectomy. A case report. *Int J Surg Case Rep.* 2022 Apr;93:106935. doi: 10.1016/j.ijscr.2022.106935. Epub 2022 Mar 10.

Takei I, Ito T, Mori T, Oda Y, Nakahara T. Subcutaneous Thyroid Tissue Implantation after Thyroidectomy: A Mimic of Benign Cutaneous Tumours. *Acta Derm Venereol.* 2023 Jan 5;103:adv00842. doi: 10.2340/actadv.v103.4407.

Hu J, Xu X, Wang S, Dong F, Zhang X, Ming J, Huang T. Case Report: Implantation of Dedifferentiated to Poorly Differentiated Thyroid Carcinoma After Endoscopic Thyroid Surgery. *Front Oncol.* 2022 May 6;12:896942. doi: 10.3389/fonc.2022.896942. eCollection 2022.

Reply 16: We have included an article for reference as advised.

Changes in the text: Page 15, Line 292-302

Reviewer E

1) the correct cytology classification of the FNAB of 2010 (line 78): negative for malignancy it is not enough. It is mandatory the reevaluation of the cytology of the fnab and the re-classification according to current guidelines

Reply 1: As advised, it was modified according to the cytology classification guideline.

Changes in the text: Page 10, Line 80

2) the final histopathological examination (line 89): poorly differentiated carcinoma or thyroid poorly differentiated carcinoma?

Reply 2: We have clearly modified to poorly differentiated thyroid carcinoma.

Changes in the text: Page 10, Line 80

3) in the Case 2, the patient underwent to a totalization thyroidectomy with the left lobectomy or not? and in case of negative response, why?

Reply 3: In the Case 2, only the mass was removed, and completion thyroidectomy with left lobectomy was not performed. Although the patient was explained the risk of recurrence, the procedure could not be performed because the patient refused because he did not want complete thyroid removal.

Changes in the text: None

4) there is a contradiction on case 2

line 84: benign follicular nodule

line 139: differentiated thyroid carcinoma

Reply 4: As you pointed out, differentiated thyroid carcinoma was modified to benign follicular nodule.

Changes in the text: Page 8, Line 146