Case Series

ANNALS OF MEDICINE & SURGERY

OPEN

Infiltration of nanocarbon into the trachea during thyroidectomy surgery: case series and literature review

Wu Li, MD*

Introduction: The presence of metastatic disease in the cervical lymph nodes can affect the recurrence and survival of patients with thyroid cancer. Parathyroid gland injury during surgery can result in hypoparathyroidism, particularly with total thyroidectomy. Injection of carbon nanoparticles into the thyroid will label draining lymph nodes and aid in the visualization of metastatic cervical lymph nodes during a radical operation, sparing accidental damage to the parathyroid glands. Although reported to be useful during surgery, the safety of nanocarbon particles has rarely been investigated, and adverse side effects need to be studied.

Case presentation: The author describes five patients with thyroid cancer who had carbon secretions in the trachea or mucosa after carbon nanoparticles were injected into the thyroid. A patient with carbon secretions in the trachea mucosa recovered but had progressive dyspnoea. Surgical treatment was performed, and a mass was found in the trachea mucosa. After excluding all other possibilities, the author concluded that the mass was caused by nanocarbon suspension.

Discussion: To the author's knowledge, there are no reports on nanocarbon suspension into the mucosa and no consensus has yet been reached on the precise injection site, depth, or dose for injecting carbon nanoparticles before thyroidectomy.

Conclusion: The author suggests that the most appropriate injection depth of nanocarbon suspensions should be no more than 3 mm of the thyroid gland thickness to avoid deep injection into the trachea.

Keywords: case series, nanocarbon, papillary thyroid carcinoma, surgical treatment, trachea

Introduction

Approximately 85% of all thyroid cancers are papillary thyroid carcinomas (PTC)[1,2]. PTC can be accompanied by lymph node metastasis even in its early stages[3,4], and metastasis can affect clinical outcomes[5]. Regional lymph node dissection during surgical treatment of PTC is a common treatment option[6]. Inadvertent damage to parathyroid glands during surgery can result in hypoparathyroidism. Improvements in the detection and visualization of metastatic lymph nodes can decrease damage to the parathyroid tissue and reduce the incidence of postoperative hypoparathyroidism.

Injecting nanocarbon particles into the thyroid can mark the lymphatic tissue and help visualize the lymph nodes. This leads to better differentiation of lymph nodes and facilitates more precise excision of the metastatic lymph nodes. After nanocarbon labelling of the thyroid gland lymph nodes, the parathyroid glands can be identified as unlabelled, thus reducing inadvertent damage to the parathyroid glands and the occurrence of hypoparathyroidism after the operation[5]. While this is helpful during surgery, there have been no studies on its adverse side effects. Here, we report five patients, Han Chinese, with thyroid cancer. They had carbon secretions in the trachea or mucosa following the injection of nanocarbon suspension into the thyroid. They were performed with transoral endoscopic thyroidectomy vestibular approach (TOETVA)[7] and traditional open surgery at Hunan Cancer Hospital in China. This case series has been reported in line with the SCARE criteria.

HIGHLIGHTS

- Injection of carbon nanoparticles into the thyroid will label draining lymph nodes and spare accidental damage to the parathyroid glands during thyroidectomy surgery.
- The safety and adverse effects of nanocarbon suspension in thyroid surgery have never been evaluated.
- In this report, we describe five patients with thyroid cancer who had carbon secretions in the trachea or mucosa caused by deeply nanocarbon suspension and its surgical treatment.
- We propose three possible solutions that may help avoid the same situation in the future.
- The precise injection site, depth, or dose for injecting carbon nanoparticles in the product manual should be targeted for thyroid cancer.

Department of Thyroid Surgery, Hunan Cancer Hospital &The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha, Hunan Province, China

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

**Corresponding author. Address: Department of Thyroid Surgery, Hunan Cancer Hospital &The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha 410000, Hunan Province, China. Tel.: +860 731 897 62251. E-mail: 656678786@qq.com (W. Li).*

Annals of Medicine & Surgery (2024) 86:4338–4343

Received 17 October 2023; Accepted 1 December 2023

Published online 5 February 2024

http://dx.doi.org/10.1097/MS9.0000000000001613

Case presentation

Bilateral thyroid nodules were found on a 50-year-old woman. The cytology of the thyroid nodule suggested papillary thyroid cancer. The patient was very anxious and strongly desired surgery. TOETVA surgery was performed[8] on the patient on 21 September 2020. A Nano-carbon suspension (H20073246; Chongqing LUMMY Pharmaceutical Co., Ltd.) was injected into the thyroid gland using a 1-ml skin test syringe. Unfortunately, shortness of breath occurred in the patient after the operation.

No abnormalities were observed in the skin of the anterior neck. The skin of the anterior area was intact, with a flaky, hard, and relatively fixed appearance. A local wheeze from the trachea was felt, and auscultation was heard. Bilateral lymph nodes in the neck were not palpable. Except for slightly higher white blood cell counts, there were no other obvious abnormalities in laboratory examinations. A subglottic mass was observed with a laryngoscope during follow-up (Fig. 1B). Computed tomography of the neck indicated trachea stenosis (Fig. 1A). We excluded tumours in the oesophagus when no malignant tumour was found on gastroscopy (Fig. 1C-H). To solve the above problem, exploratory surgical treatment was performed on 22 February 2021, under local 0.75% lidocaine infiltration anaesthesia, combined with intravenous sedation. With the patient in the supine position, shoulder pads were used to fully expose the neck. A low-neck arc incision of ~5 cm was made. The skin and subcutaneous and platysma muscles were separated up to the level of the laryngeal knot and down to the level of the clavicle. The midline of the neck was opened and the trachea was exposed. The recurrent laryngeal nerve and the superior parathyroid glands were explored and protected. One millilitre of 2% lidocaine was then injected into

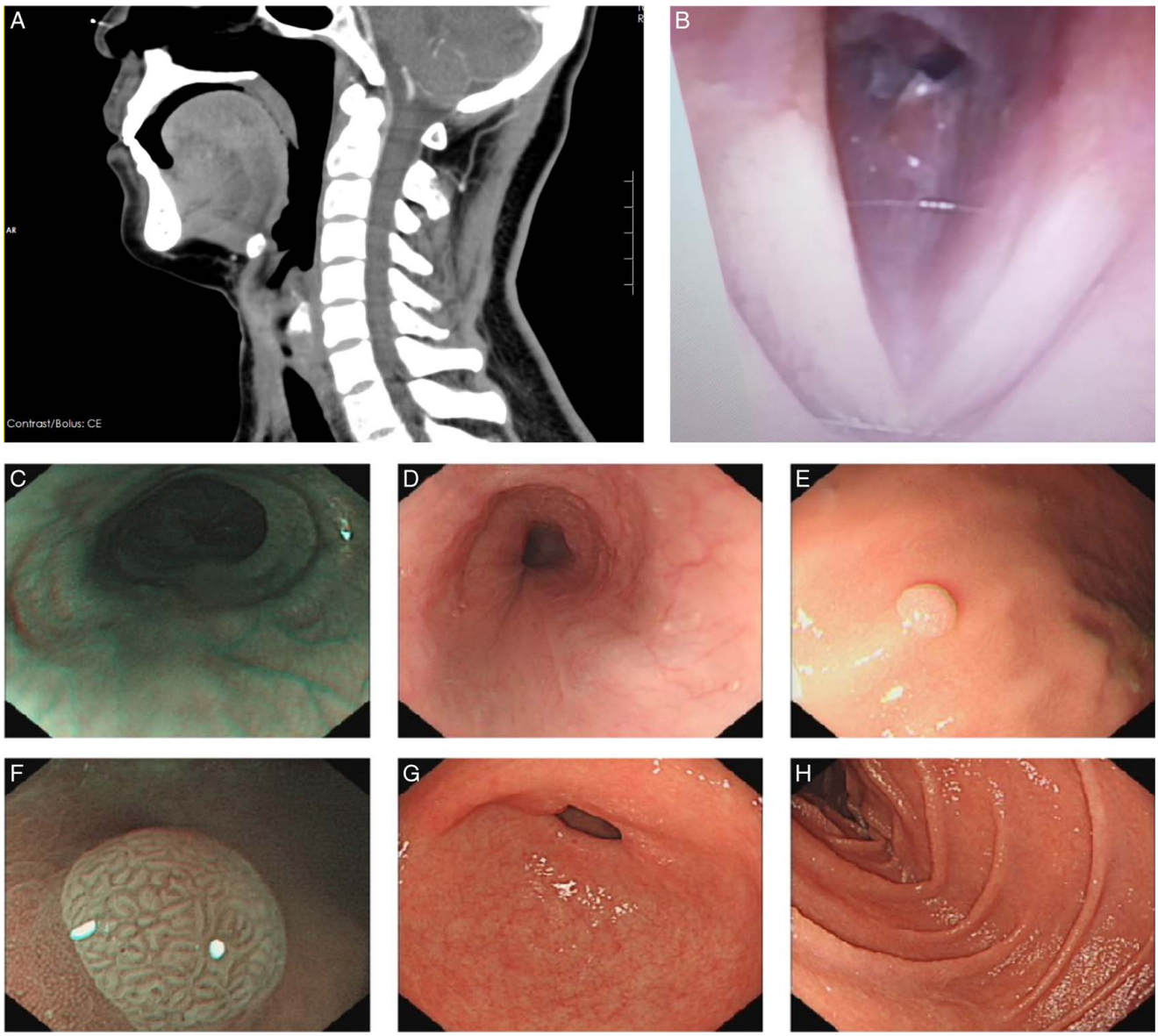

Figure 1. Preoperative neck and chest computed tomography scans indicated trachea stenosis in the cricoid cartilage plane (A). Subglottic mass can be seen under the laryngoscope (B). To exclude tumours from the oesophagus, no malignant tumour was found in the oesophagus and gastroscope (C–H).

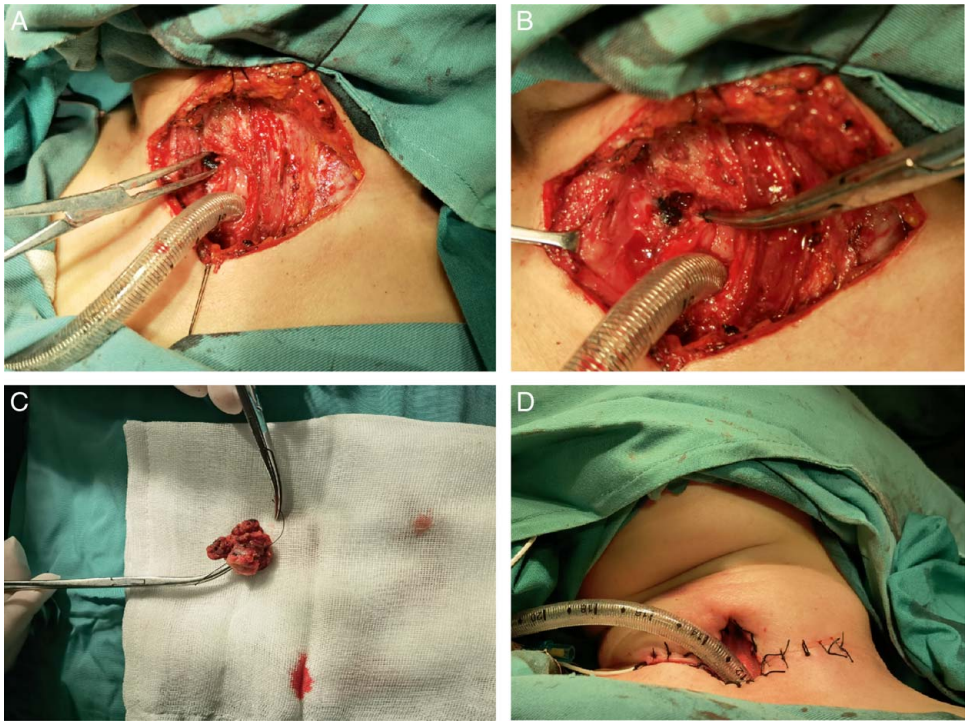

Figure 2. The total black mass was detected, which was the same colour as nanocarbon (A, B). A complete resection was performed on the mass during the rescue operation (C). A tracheostomy was performed and completed to resolve dyspnoea in this patient (D).

the trachea cavity. The third ring of the trachea front wall was opened, a trachea cannula was inserted, and general intravenous anaesthesia was administered. Continuing to explore the trachea wall, we found that the lateral wall of the trachea thickened and protruded into the trachea, forming a clear stenosis. The mass was located mainly in the right trachea, up to the cricothyroid cartilage joint, down to the fourth trachea ring, anteriorly exceeding the midline, and posterior to the tracheoesophageal groove plane. A complete resection of the mass was performed (Fig. 2C). The mass was completely black and had the same colour as nanocarbon (Fig. 2A and B). After excluding all other possibilities, we concluded that the mass was caused by nanocarbon suspension. Intraoperative frozen sections repeatedly indicated chronic inflammation, but no tumour cells were observed Fig. 3B. The skin and trachea edges were sutured for the tracheostomy. The size of the inflammatory lesion was ~2 × 1.5 cm. The upper and lower tracheas appeared unobstructed after repeated examinations. A negative pressure drainage tube was placed, and the wound was closed with no. 4 silk thread (Fig. 2D). A tracheostomy was performed on 17 May 2021, by waiting for the skin to

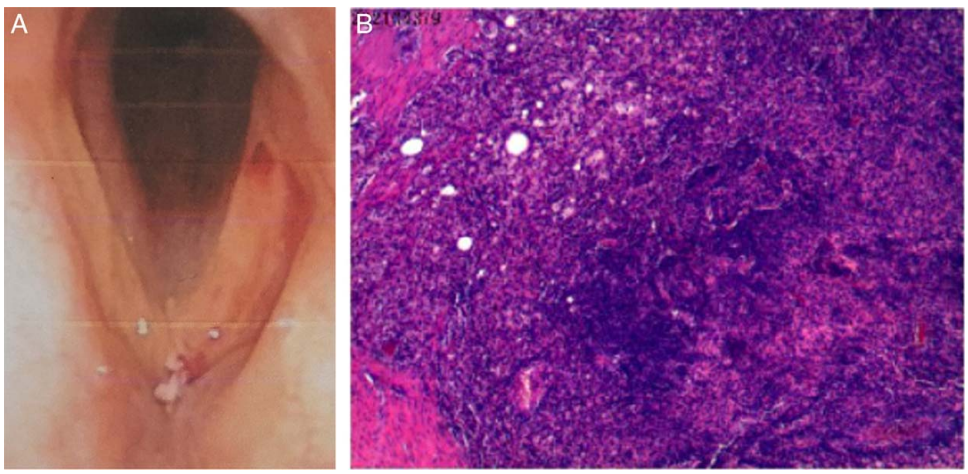

Figure 3. A subglottic mass was removed and no lesion remained after the operation (A). Inspection of paraffin tissue sections under the microscope found fibrous tissue hyperplasia with a large inflammation cell infiltration. No tumour cells were observed (B).

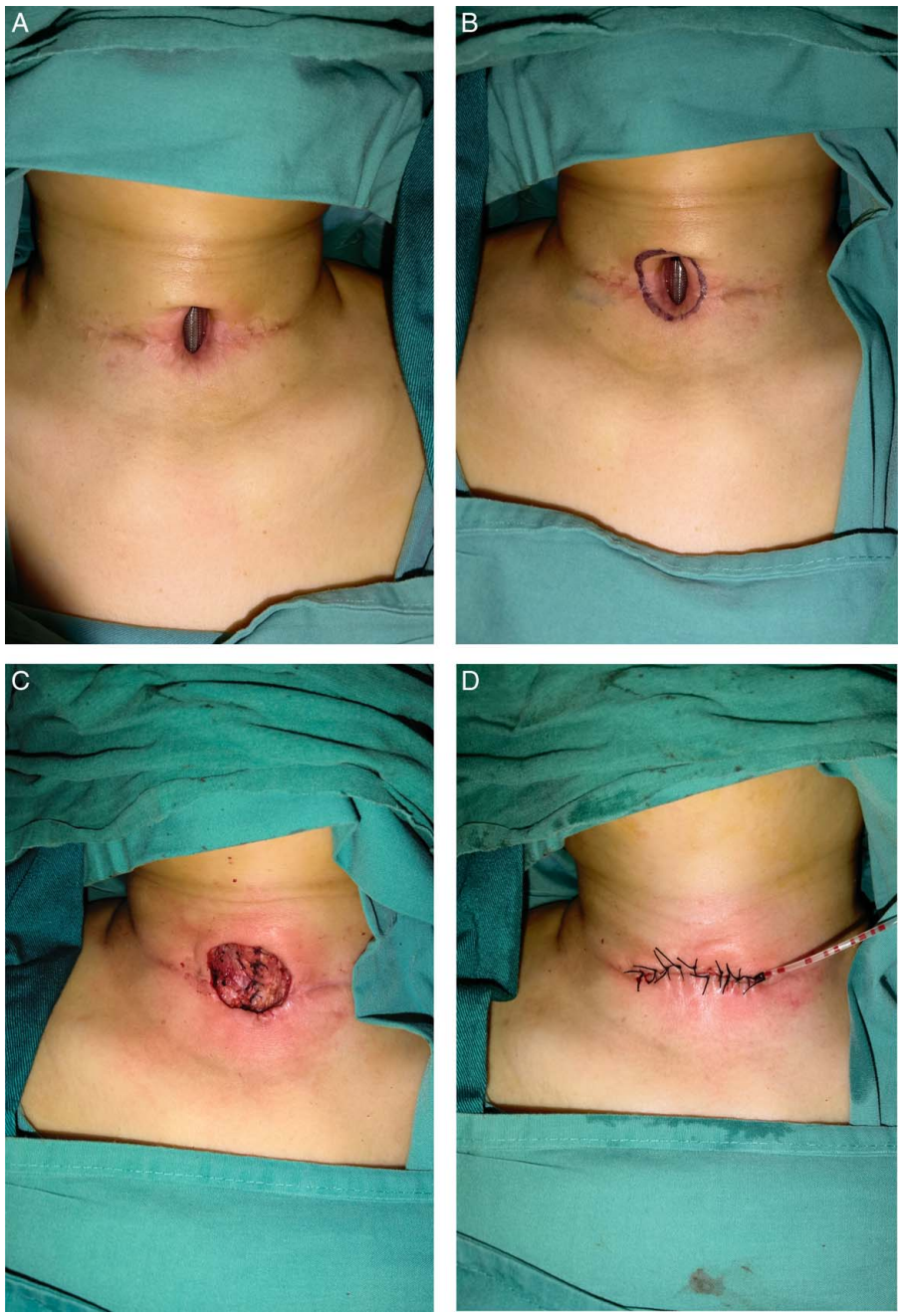

Figure 4. After the fistula was cleaned (A), methylene blue was used to design surgical incisions (B). The external port of tracheostomy was closed by a linear incision by ingenious conception and subcutaneous loosening (C, D).

loosen (Fig. 3). The fistula was cleaned and disinfected before the surgery (Fig. 4A). Methylene blue was used to design the surgical incisions(Fig. 4B). Through subcutaneous loosening, the external port of the tracheostomy was closed using a linear healing incision (Fig. 4C, D). Electronic laryngoscopy confirmed that the subglottic mass was removed, and no lesions remained postoperatively Fig. 3A. Walking long distances (> 1000 m) slowly without breathing difficulties was possible, and no other complications developed. Even in the presence of a scar, the patient was satisfied with the surgery. The patient took levothyroxine daily and was asked to exercise the neck daily (Table 1).

The other four patients who had carbon secretions in the trachea recovered without complications such as cough, fever, chest pain, or phlegm production. The four patients were under physical examination 6 months after the surgery, with good conditions and no evidence of recurrence Table 1. The work has been reported in line with the PROCESS criteria.

Discussion

More than 85% of all thyroid cancers are PTC, and lymph node metastasis can be found in up to 90% of patients at the initial

Table 1

Other 4 cases with carbon secretions in the trachea

Case	Age (year)	Occupation	Sex	Surgical method	Surgical content
1	17	Freelance	Female	TOETVA	Total thyroidectomy combined with central lymph node dissection
2	39	Business manager	Male	Traditional open surgery	Total thyroidectomy combined with central lymph node dissection
3	43	Civil servant	Male	Traditional open surgery	Right thyroidectomy combined with central lymphatic dissection
4	32	Professional technicians	Male	Traditional open surgery	Total thyroidectomy combined with regional lymph node dissection

diagnosis[3,4]. Recurrence and survival in patients with thyroid cancer are closely related to cervical lymph node metastasis. Thyroidectomy combined with regional lymph node dissection is the primary treatment for PTC. The reported incidence of permanent hypoparathyroidism after total thyroidectomy/central lymph node dissection ranges from 1.4 to 14.3%[9,10]. The incidence of hypocalcemia following hypoparathyroidism can be as high as 20.8%, which can diminish quality of life[5,10]. Carbon nanoparticles have been successfully used in gastric, colorectal, and breast cancer surgeries to identify lymph nodes[11,12]. Nanocarbon particles have also been introduced for thyroid cancer surgery[5]. Carbon nanoparticles are smaller than the lymphatic endothelial cell gap (500 nm), but larger than the capillary endothelial cell gap (30–50 nm). Carbon nanoparticles (150 nm) can enter lymphatic vessels after injection into the thyroid and become localized in lymph nodes, staining them black to make them easy to identify[13]. Because there is no lymphatic connection between the thyroid and parathyroid glands, the parathyroid glands remain unstained, while the thyroid gland lymph nodes stain black[14]. Staining with nanocarbon particles aids in the visualization and dissection of the lymph nodes and helps preserve parathyroid tissue. Their morphology and function are well recognized and preserved *in situ*, thus reducing the occurrence of hypoparathyroidism after the operation[15]. The use of carbon nanoparticles can also significantly reduce the incidence of parathyroid gland injury during a second surgery[16]. Thus, the injection of nanocarbon particles to better define lymph nodes before thyroidectomy is particularly important for the preservation of the parathyroid glands. This clinical review describes five patients with thyroid cancer. They were found to have carbon secretions in the trachea or mucosa after infusion of nanocarbon particles during TOETVA or traditional open surgery.

A complete resection of the mass was performed on the 50-year-old woman during the second surgery. The mass was completely black, with the same colour as the nanocarbon. This has three possible explanations, which are very similar to those of the previous case reported by Zhang[13]. First, the syringe needle with an injection depth of greater than 0.3 cm might have penetrated the gland, causing direct entry into the trachea through the mucosa. However, the trachea was examined endoscopically and no surgical wounds were found on the surface during the first operation. However, such pinholes are so small that they are difficult to identify. Second, the interaction between the thyroid lymphatic vessels and lymphatic capillary networks of the trachea mucosal layers may have contributed to the small amount of carbon nanoparticle leakage. Theoretically, an obvious lymphatic structure could be one cause of such a large amount of carbon nanoparticle leakage. In this case, no abnormal lymphatic structures were found during preoperative examination or intraoperative exploration. Third, inadvertent injection into a possible trachea diverticulum, thyroglossal cyst, or fistula could also cause carbon-containing secretions. However, our patient had no trachea diverticulum, thyroglossal cyst, or fistula on the preoperative neck and chest computed tomography scans. A thyroglossal cyst is located in the anterior central region of the neck; therefore, the possibility that carbon nanoparticles were injected into a thyroglossal cyst was impossible in this patient. Zhang[13] described a case of carbon secretion in the trachea caused by a nanocarbon suspension. After comparing all possibilities, we concluded that a deeply injected suspension into the trachea mucosa caused progressive dyspnoea in this case[17].

To the best of our knowledge, no allergic or toxic adverse side effects or other safety concerns have been reported with the use of nanocarbon particles. There is currently no clinical consensus on the best injection site or dosage for the injection of nanocarbons to optimize the PTC. Most reports are of four to six injection points around the tumour without injection into the tumour or blood vessels[5]. The manufacturer's manual for the nanocarbon suspension indicates that the total injection volume should range from 0.4 to 1 ml (0.1–0.3 ml per point) before surgery[5]. This amount is more than that used in our 1521 TOETVA cases and 486 traditional open surgery patients. We found that a single 0.1 ml injection is sufficient.

Nanocarbon suspensions have been reported to be safe for use in thyroid cancer surgery[11]. In addition to our experience, Zhang[13] also reported a patient with carbon secretions in the trachea caused by nanocarbon suspension. Our cases included TOETVA surgeries, and Zhang's report was from traditional open surgery.

Conclusion

Carbon nanoparticles used to delineate lymph nodes in thyroid malignancy can also lead to complications such as aggregation of these particles in the trachea mucosa. There are no reports on nanocarbon suspension into the mucosa, and no consensus has yet been reached on the precise injection site, depth, or dose for injecting carbon nanoparticles before thyroidectomy.

We propose three possible solutions that may help avoid the same situation in the future. The amount of nanocarbon injected should be 0.1 ml in the product manual for papillary thyroid carcinomas. The single injection point in the product manual should be Outer lower region without injection into the tumour or blood vessels. Finally, the length of the syringe needle to inject nanocarbon was suggested to be no more than 3 mm, which helps avoid excessive and deep injection into the trachea or mucosa.

Ethical approval

This case report did not require review by the Ethics Committee.

Consent

Written informed consent was obtained from the patient/patient guardian for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Source of funding

The study received funding from Research Project of Hunan Provincial Health Commission(202204015634), Science Popularization Special Project of Hunan Provincial Department of Science and Technology(2022ZK4148) and Hunan Cancer Hospital Research Climbing Plan (National Self cultivation Project 2020NSFC-B007).

Author contributions

W.L. contributed to collecting the clinical data, manuscript drafting and manuscript writing.

Conflicts of interest disclosure

Not applicable.

Research registration unique identifying number (UIN)

Not applicable.

Guarantor

Dr Wu Li.

Data availability statement

The manuscript is case report or case series. There is no research data.

Provenance and peer review

Not commissioned, externally peer-reviewed.

References

[1] Liu F, Yan Z, Qian Y, *et al*. Recognition of sentinel lymph nodes in patients with papillary thyroid cancer by nano-carbon and methylene blue. Pakistan J Med Sci 2017;33:1485–9.

[2] Degroot LJ, Kaplan EL, Maureen M, *et al*. Natural history, treatment, and course of papillary thyroid carcinoma. J Clin Endocrinol Metab(2) 1990;71:414–24.

[3] Podnos YD, Smith D, Wagman LD, *et al*. The implication of lymph node metastasis on survival in patients with well-differentiated thyroid cancer. Am Surg 2005;71:731–4.

[4] Zaydfudim V, Feurer ID, Griffin MR, *et al*. The impact of lymph node involvement on survival in patients with papillary and follicular thyroid carcinoma. Surgery 2008;144:1070–8.

[5] Li Y, Jian WH, Guo ZM, *et al*. A meta-analysis of carbon nanoparticles for identifying lymph nodes and protecting parathyroid glands during surgery. Otolaryngo Head Neck Surg 2015;152:1007–16.

[6] Salem FA, Bergenfelz A, Nordenstrm E, *et al*. Central lymph node dissection and permanent hypoparathyroidism after total thyroidectomy for papillary thyroid cancer: population-based study. B J Surg 2021;108: 684–90.

[7] Anuwong A, Ketwong K, Jitpratoom P, *et al*. Safety and outcomes of the transoral endoscopic thyroidectomy vestibular approach. JAMA Surg 2017;153:21–7.

[8] Liu Z, Li Z, Peng X, *et al*. Transoral endoscopic thyroidectomy vestibular approach in a patient with Class III goitre (operative steps and video). Gland Surg 2020;9:1605–13.

[9] Almquist M, Ivarsson K, Nordenstr?M E, *et al*. Mortality in patients with permanent hypoparathyroidism after total thyroidectomy: Mortality after permanent hypoparathyroidism. Br J Surg 2018;105:1313–8.

[10] Shoback DM, Bilezikian JP, Costa AG, *et al*. Presentation of hypoparathyroidism: etiologies and clinical features. J Clin Endocrinol Metab(6) 2016;101:2300.

[11] Li Z, Ao S, Bu Z, *et al*. Clinical study of harvesting lymph nodes with carbon nanoparticles in advanced gastric cancer: a prospective randomized trial. World J Surg Oncol 2016;14:88.

[12] Kai L, Chen D, Chen W, *et al*. A case–control study of using carbon nanoparticles to trace decision-making lymph nodes around inferior mesenteric artery in rectal cancer. Surg Endosc 2018;33:904–10.

[13] Zhu LB, Zhu F, Li PF. Infiltration of nanocarbon into the trachea cavity during surgical treatment of papillary thyroid carcinoma: a case report. J Int Med Res 2020;48. doi:10.1177/0300060520919251. PMID: 32314626; PMCID: PMC7175066

[14] Tian W, Jiang Y, Gao B, *et al*. Application of nano-carbon in lymph node dissection for thyroid cancer and protection of parathyroid glands. Med Sci Monitor Int Med J Exp Clin Res 2014;20:1925–30.

[15] Lun W, Dong Y, Lv JY, *et al*. Application of carbon nanoparticles in lymph node dissection and parathyroid protection during thyroid cancer surgeries: a systematic review and meta-analysis. Oncotargets Ther 2017; 10:1247–60.

[16] Chaojie Z, Shanshan L, Zhigong Z, *et al*. Evaluation of the clinical value of carbon nanoparticles as lymph node tracer in differentiated thyroid carcinoma requiring reoperation. Int J Clin Oncol 2016;21:68–74.

[17] Agha RA, Sohrabi C, Mathew G, *et al*. for the PROCESS Group. The PROCESS 2020 Guideline: Updating Consensus Preferred Reporting of Case Series in Surgery (PROCESS) Guidelines. Int J Surg 2020;84: 231–5; 60 (article in press).