Nanoparticles can improve the positive rate of metastatic lymph node in thyroid cancer surgery

Xindi Su (susuniceday@163.com)  
Jinzhou Medical University

Fang Chai  
First Affiliated Hospital of Jinzhou Medical University

Benrui Lin  
First Affiliated Hospital of Jinzhou Medical University

Lu Qu  
First Affiliated Hospital of Jinzhou Medical University

Keyi Liu  
First Affiliated Hospital of Jinzhou Medical University

Jianping Huo  
First Affiliated Hospital of Jinzhou Medical University

Zhansheng Zhu  
Jinzhou Medical University

Rashid Rashid  
Jinzhou Medical University

Research

Keywords: Thyroid cancer, Carbon nanoparticles, Cervical lymph node dissection, Parathyroid gland

DOI: https://doi.org/10.21203/rs.3.rs-23046/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. 
Read Full License
Abstract

Objective.

To investigate the application of carbon nanoparticles in lymph node dissection and parathyroid gland protection during thyroid cancer surgery.

Subjects and Methods.

Retrospective analysis was performed on 282 cases of thyroid cancer surgery in our hospital from 2018 to 2019. All patients underwent total thyroidectomy and cervical central lymph node dissection. Nanocarbon was not used in the control group, but was used in the experimental group. The general situation of the patients, the number of postoperative lymph nodes and the number of metastasis were collected, and the differences between serum parathyroid hormone and blood calcium were compared before and on the 3rd and 30th day after surgery.

Results.

There was no difference in age, sex and TNM stage between the two groups (P > 0.05). The number of metastatic lymph nodes in the experimental group (9.80 ± 4.80) was different from that in the control group (6.95 ± 3.86) (P < 0.05), and the number of metastatic lymph nodes in the experimental group was different from that in the control group ($\chi^2 = 14.968$, P < 0.05). There was no difference in blood calcium and PTH between the two groups before and at 3 and 30 days after surgery (P > 0. 05).

Conclusion.

The application of carbon nanoparticles in thyroid cancer surgery can significantly increase the number of lymph nodes seized and the positive rate of metastatic lymph node removal, but the protection of parathyroid gland is not obvious.

Background

Thyroid cancer is the most common endocrine malignant tumor, and the most common pathological type is papillary thyroid cancer (PTC), accounting for more than 90% of the total thyroid cancer1-2. Surgical treatment is the main treatment of this disease3, because of its high rate of lymph node metastasis4 therefore, the routine cervical lymph node dissection in China increases the injury rate of parathyroid gland and the risk of postoperative hypocalcaemia with the expansion of surgical scope5. Studies have shown that carbon nanoparticles can darken lymph nodes and negatively develop parathyroid glands6, it is widely used in thyroid surgery, but whether carbon nanoparticles have a protective effect on
parathyroid glands is controversial\textsuperscript{10,17}. The purpose of this study was to investigate the value of carbon nanoparticles in thyroid cancer surgery and cervical central lymph node dissection.

**Subjects And Methods**

**1.1 Case data**

This study is a retrospective analysis of relevant case data from the first affiliated hospital of Jinzhou Medical University, and does not involve ethical issues. The clinical data of 282 patients who underwent surgical treatment for thyroid cancer in our department from January 2018 to June 2019 were retrospectively analyzed. Inclusion criteria were: (1) all patients underwent total thyroidectomy and underwent unilateral or bilateral cervical central lymph node dissection (2) all patients had no distant metastasis. (3) thyroid papillary carcinoma was confirmed pathologically (4) thyroid surgery was performed for the first time (5) preoperative imaging showed no lymph node metastasis in the cervical region (6) preoperative PTH and blood calcium measurements were within the normal range. Exclusion criteria were: (1) diseases associated with abnormal PTH and blood calcium; (2) history of neck surgery and radiotherapy; (3) preoperative parathyroid dysfunction; (4) metastases to other malignant tumors involving the thyroid; (5) pregnant or lactating women. Patients were randomly divided into the experimental group and the control group. The experimental group was given intraoperative carbon nanoparticles, while the control group was not. Age, sex, tumor size, tumor infiltration in capsule and surrounding muscles, TNM staging (the 8th edition of the American joint commission on cancer AJCC thyroid cancer TNM staging, 2017) and other basic information were collected. The number of lymph nodes removed and the number of metastatic lymph nodes in the two groups were counted. PTH and serum calcium values were measured preoperatively and at 3 and 30 days postoperatively. The nano carbon suspensions used in the operation were all products of Chongqing Lummy Pharmaceutical Co.Ltd.

**1.2 surgical methods**

All patients underwent total thyroidectomy and cervical central lymph node dissection. The thyroid gland was routinely exposed. In the experimental group, 0.1ml of carbon nanoparticles was injected into the affected side at 1-2 points through a 1ml syringe. After that, the injection point was pressed with gauze to prevent nano-carbon leakage. After 10min, the lymph nodes were blackened and then the adenoidectomy was performed. During the operation, the thyroid papillary carcinoma was confirmed by rapid freezing pathology. Intraoperative attention was paid to fine dissection of thyroid capsule. The number of lymph nodes removed and the number of metastatic lymph nodes were compared between the two groups.

**1.3 statistical analysis**

The collected clinical data were statistically analyzed by SPSS 22 software. The counting data were expressed as a percentage (%), and $\chi^2$ test were performed. The measurement data is expressed by $t$ test. $P < 0.05$ was considered statistically significant.
Result

2.1 comparison of basic conditions between the two groups

There was no significant difference in age, gender, tumor size and TNM stage between the experimental group (162 cases) and the control group (120 cases) (P > .05), as shown in table 1.

2.2 Lymph node detection

The total number of lymph nodes detected in the experimental group was 1587, compared with 810 in the control group, the difference was statistically significant (P < 0.05). The detection of metastatic lymph nodes in the experimental group was significantly different from that in the control group (P < 0.05). See table 2 for details.

2.3 Postoperative changes in serum calcium and PTH

There was no significant difference in serum calcium and PTH levels between the two groups before and after 3 and 30 days, as shown in table 3.

Discuss

Papillary carcinoma of the thyroid (PTC) is the most common thyroid malignancy, with lymph node metastasis rates reported to be as high as 50-70% in patients with PTC, However, incomplete intraoperative lymph node dissection is an important factor causing postoperative recurrence in patients, and expanding the scope of dissection will increase the risk of damage to the parathyroid gland. The position of the superior parathyroid gland is relatively fixed, while the position of the inferior parathyroid gland varies greatly, Multiple lymph node metastases often require extensive dissection, which may damage the parathyroid gland or even cut it by mistake, seriously affect the prognosis and quality of life of patients, and even threaten the life of patients. Therefore, how to protect the parathyroid gland while removing lymph nodes is the key.

Carbon nanoparticles with an average diameter of 150nm can enter lymphatic vessels (with an average diameter of 500nm) rather than capillaries (with an average diameter of 30-50nm), allowing the development of lymph nodes. Since the lymphatic vessels of thyroid gland and parathyroid gland do not communicate with each other, most scholars believe that negative development of parathyroid gland has a protective effect on it, and it has been widely used in thyroid cancer surgery in recent years. The results of this study showed that there was a significant statistical difference between the experimental group and the control group in the total number of lymph nodes cleared and the positive rate of metastatic lymph nodes. Consistent with the views of Luo Wenzheng and other researchers, Considering carbon nanoparticles can help surgeons better identify lymph nodes in the central region, especially the microscopic nodes that are difficult to be distinguished by the naked eye, reduce lymph node residues, and make it easier and more accurate for
pathologists to extract lymph nodes\textsuperscript{13}. Together, the two can increase the number of lymph nodes detected, and the corresponding seizure rate of metastatic lymph nodes is also improved, which is conducive to more accurate postoperative judgment of staging and prognosis, as well as elimination of potential sources of lymph node recurrence\textsuperscript{14-15}. However, there was no statistical difference in the changes of blood calcium and PTH between the experimental group and the control group at 3 and 30 days after surgery (P > 0.05), which was consistent with the views of Liu et al\textsuperscript{16-17}; that is, the parathyroid protection is not significant. We think it may be caused by the following reasons: The recognition of parathyroid gland is closely related to the surgical experience of surgeons. Experienced physicians can completely identify the parathyroid gland by the color, texture and appearance of the parathyroid gland with the naked eye, without other development techniques to protect the parathyroid gland. In some cases, intraoperative leakage may occur due to improper handling of nanocarbons. In this case, the wound may be contaminated, making it impossible for the accessory glands to identify the nanocarbons and causing accidental injury. For small glands the dose of carbon nanoparticles should be reduced.

In conclusion, although nanocarbon does not significantly protect the parathyroid gland, it can significantly improve the number of seized lymph nodes and the positive rate of metastatic lymph node removal, facilitate accurate postoperative judgment of the stage and prognosis of patients, and reduce the recurrence rate. Therefore, nanocarbon is worth promoting for young doctors and doctors in primary hospitals. The sample size included in this study is relatively small, and there is a lack of research on longer follow-up and survival analysis of patients, so more in-depth research is needed to explore its use value.

**Conclusion**

We found that the application of carbon nanoparticles in thyroid cancer surgery can significantly increase the number of detected lymph nodes and the positive rate of metastatic lymph node clearance, but the protection of parathyroid gland is not obvious. A larger sample study may be needed.

**List Of Abbreviations**

TNM: Tumor Node Metastasis

PTH: parathyroid hormone

PTC: papillary thyroid cancer

AJCC: American Joint Committee on cancer

**Declarations**

Ethics approval and consent to participate
Comrade XinDi Su Contribution to Your Edition: Nanoparticles can improve the positive rate of metastatic lymph node in thyroid cancer surgery. Confirmed by the Medical Ethics Committee of the First Affiliated Hospital of Jinzhou Medical University, the purpose of the paper, the research process, the source of the material, and the ethical matters of medical research were reviewed and passed, and the patients were informed by ethical principles. NO.KYLL202005.

After the initial audit, medical research ethical matters in line with the "Helsinki Declaration" and the Ministry of Health "involving human biomedical research ethical review method (Trial)" requirements. The medical ethics committee of our hospital will follow up the supervision of the relevant items of medical ethics research after the approval of the project.

Sign: The First Affiliated Hospital of Jinzhou Medical University Medical Ethics Committee.

Consent for publication
Not applicable

Availability of data and materials
Not applicable

Competing interests
The authors declare that they have no competing interests.

Funding
Not applicable

Authors' contributions
XinDi Su, draft, manuscript writing, study design, data collection, approval, agreement; Fang Chai, study design, draft, revise, approval, agreement; BenRui Lin, study design, revision, approval, agreement; Lu Qu, study design, revision, approval, agreement; KeYi Liu, data collection, editing of the article, approval, agreement; JianPing Huo, study, design, approval, agreement; ZhanSheng Zhu, study design, revision; Rashid, editing of the article.

Acknowledgements
We thank Huan Wang, Jia Sun for their assistance with collection of audiometric data, and perioperative patient care.

References
1. Zhao W J, Luo H, Zhou Y M, et al. Preoperative ultrasound-guided carbon nanoparticles localization for metastatic lymph nodes in papillary thyroid carcinoma during reoperation: A retrospective cohort study[J]. Medicine, 2017, 96(10):e6285.
2. Zhang X, Shen Y P, Li J G, et al. Clinical feasibility of imaging with indocyanine green combined with carbon nanoparticles for sentinel lymph node identification in papillary thyroid microcarcinoma[J]. Medicine, 2019, 98(36):e16935.

3. Yu W, Zhu L, Xu G, et al. Potential role of carbon nanoparticles in protection of parathyroid glands in patients with papillary thyroid cancer[J]. Medicine, 2016, 95(42):e5002.

4. Su A P, Wang B, Gong Y P, et al. Carbon nanoparticles facilitate lymph nodes dissection and parathyroid glands identification in reoperation of papillary thyroid cancer[J]. Medicine, 2017, 96(44):e8380.

5. Wang YH, Bhandari A, Yang F, et al. Risk factors for hypocalcemia and hypoparathyroidism following thyroidectomy: a retrospective Chinese population study[J]. Cancer management and research, 2017, 9():627-635.

6. Shi C, Tian B, Li S, et al. Enhanced identification and functional protective role of carbon nanoparticles on parathyroid in thyroid cancer surgery: A retrospective Chinese population study[J]. Medicine, 2016, 95(46):e5148.

7. Yu W, Cao X L, Xu G, et al. Potential role for carbon nanoparticles to guide central neck dissection in patients with papillary thyroid cancer[J]. Surgery, 2016, 160(3):755-761.

8. JunFeng Du, Ran An, ShiYong Li. The significance of carbon nanoparticles tracer for cervical lymph node dissection in differentiated thyroid carcinoma[J]. Chinese Journal Of Operative Procedures Of General Surgery (Electronic Edition), 2018, 12(06):20-2.

9. Yan S, Zhao W, Wang B. Preoperative injection of carbon nanoparticles is beneficial to the patients with thyroid papillary carcinoma: From a prospective study of 102 cases[J]. Medicine, 2018, 97(27):e11364.

10. ShaoNan Han. Effect of carbon nanoparticles on parathyroid function after radical thyroidectomy combined with central lymph node dissection[J]. Modern Medicine Journal of China, 2019, 21(04):70-72.

11. Xu XF. The application of carbon nanoparticles in the lymph node biopsy of cN0 papillary thyroid carcinoma: A randomized controlled clinical trial[J]. Asian Journal of Surgery / Asian Surgical Association, 2017, 40(5):345-349.

12. Wang L, Yang D, 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[J]. OncoTargets and therapy, 2017, 10():1247-1260.

13. Liu Y, Li L, Yu J, et al. Carbon nanoparticle lymph node tracer improves the outcomes of surgical treatment in papillary thyroid cancer[J]. Cancer biomarkers: section A of Disease markers, 2018, 23(2):227-233.
14. Wang B, Du Z, Qiuc NC, et al. Application of carbon nanoparticles accelerates the rapid recovery of parathyroid function during thyroid carcinoma surgery with central lymph node dissection: A retrospective cohort study [J]. International journal of surgery (London, England), 2016, 36(Pt A): 164-169.

15. Su A, Wang B, Gong Y, et al. Risk factors of hypoparathyroidism following total thyroidectomy with central lymph node dissection [J]. Medicine, 2017, 96(39): e8162.

16. Liu X, Chang S, Jiang X, et al. Identifying Parathyroid Glands With Carbon Nanoparticle Suspension Does Not Help Protect Parathyroid Function in Thyroid Surgery: A Prospective, Randomized Control Clinical Study [J]. Surgical innovation, 2016, 23(4): 381-389.

17. Xue S, Ren P, Wang P. Short and Long-Term Potential Role of Carbon Nanoparticles in Total Thyroidectomy with Central Lymph Node Dissection [J]. Scientific reports, 2018, 8(1): 11936.

**Tables**

Table 1  basic situation analysis table of the two groups of patients
| Basic situation        | The experimental group | The control group | $\chi^2/t$ | $P$ |
|------------------------|------------------------|-------------------|------------|-----|
| Age                    | 47.24±11.72            | 51.38±12.03       | 1.672      | 0.098 |
| Male                   | 15·9.3%                | 9·7.5%            |            |     |
| Female                 | 147·90.7%              | 111·92.5%         |            |     |
| Tumor size             | 1.39±0.85              | 1.64±0.85         | 1.422      | 0.158 |
| TNM                    |                        |                   | 3.027      | 0.082 |
| Capsule infiltration   |                        |                   |            |     |
| Yes                    | 135·83.3%              | 114·95%           |            |     |
| No                     | 27·16.7%               | 6·5%              | 0.625      | 0.429 |
| Muscle infiltration    |                        |                   |            |     |
| Yes                    | 57·35.2%               | 33·27.5%          |            |     |
| No                     | 105·64.8%              | 87·72.5%          | 1.008      | 0.315 |
| Central lymph node dissection |  |                     |            |     |
| Unilateral             | 33·20.4%               | 15·12.5%          |            |     |
| bilateral              | 63·38.9%               | 69·57.5%          |            |     |
|                       | 99·61.1%               | 51·42.5%          |            |     |

Table 2  statistical table of lymph node detection in the two groups

| Group                  | Number | Total lymph node clearance | Number of metastatic lymph nodes [%] |
|------------------------|--------|-----------------------------|-------------------------------------|
| The experimental group | 162    | 9.80±4.80                   | 276·17.39                           |
| The control group      | 120    | 6.95±3.86                   | 237·29.26                           |
| $\chi^2/t$             | 3.084  | 14.968                      |
| $P$                    | 0.003  | 0.001                       |
Table 3  statistical table of changes of serum calcium and blood PTH before surgery, 3 days after surgery and 30 days after surgery

| Group                          | Before the operation | 3 days after surgery | 30 days after surgery |
|-------------------------------|----------------------|----------------------|-----------------------|
| The experimental group PTH    | 60.47±19.24          | 29.74±14.15          | 57.74±24.29           |
| The control group PTH         | 61.46±20.70          | 36.53±19.68          | 50.45±18.34           |
| t                             | 0.239                | 1.855                | 1.591                 |
| $P$                           | 0.812                | 0.068                | 0.115                 |
| Experimental group serum calcium | 2.34±0.12          | 2.20±0.16            | 2.33±0.11             |
| Control group serum calcium   | 2.31±0.14            | 2.21±0.13            | 2.29±0.14             |
| t                             | 1.136                | 0.326                | 1.597                 |
| $P$                           | 0.259                | 0.745                | 0.114                 |