Cellular and Molecular Biology

C M B Association Publisher

Journal homepage: www.cellmolbiol.org

Nano Carbon Tracing-based Treatment of Breast Cancer Lymphadenectomy and Nursing Intervention of Postoperative Lymphedema

Xiaonan Li[#], Haimei Fu[#], Panpan Li, Yang Li, Wanyang Li, Fudi Zhu*

Department of Breast Surgery, Harbin Medical University Cancer Hospital, Harbin 150000, Heilongjiang Province, China

#These authors contributed equally to this work as co-first author

ARTICLE INFO

Original paper

Article history:
Received: November 02, 2021
Accepted: March 11, 2022
Published: March 31, 2022

Keywords:
carbon nanoparticles epirubicin (CNP-EPI), breast cancer, lymphadenectomy, lymphedema, nursing

ABSTRACT

To investigate the tracing and therapeutic effects of carbon nanoparticles epirubicin (CNP-EPI) on axillary lymphadenectomy for breast cancer and postoperative lymphedema nursing intervention, a total of 60 breast cancer patients in Harbin Medical University Cancer Hospital were selected for the study subjects and randomly divided into group A (n=30) and group B (n=30). They were subcutaneously injected with 1 mL of CNP-EPI 1 day before surgery and 3 days before surgery, respectively, and underwent axillary lymph node dissection. Lymphedema nursing intervention and routine care were implemented in groups A and B, respectively. After adsorption of 2 mL of 6 mg/mL epirubicin by 1 mL carbon nanoparticles, epirubicin could be slowly released with a cumulative release rate of 64.7 %. The black staining rate was 80.2 % (341/425) in group A and 57.7 % (217/376) in group B, and the difference was statistically significant ($P < 0.05$). The black staining rate in metastatic lymph nodes was 73.1 % (23/52) in group A and 65.9 % (27/41) in group B ($P > 0.05$). The incidence rate of edema at 1, 3, and 6 months after operation in group A was significantly lower than that in group B ($P < 0.05$). Carbon nanoparticles have strong adsorption properties and slow drug release ability; subcutaneous injection of CNP-EPI axillary lymph nodes around the areola 1 day before surgery has a better lymphatic tracing effect; lymphedema nursing intervention can effectively reduce the incidence of prognostic lymphedema.

DOI: http://dx.doi.org/10.14715/cmb/2022.68.3.33

Introduction

Breast cancer is a malignant tumor that occurs at the site of the ductal epithelium and terminal ductal epithelium of the breast (1). On December 15, 2020, the World Health Organization International Agency for Research on Cancer released the latest global breast cancer data, showing that there were 2.26 million new cases of breast cancer worldwide in 2020, surpassing 2.2 million cases of lung cancer for the first time and becoming the “largest cancer in the world” (2,3). In the same year, the number of new cases of female breast cancer in China was about 420,000, accounting for the first number of new cancer cases in Chinese women. Breast cancer usually presents as a malignant tumor when detected pathologically, and the presence of lymph node metastasis is often the main cause of death in patients with breast cancer. For patients with early breast cancer who have axillary lymph node metastasis but no obvious clinical manifestations, the use of sentinel lymph node biopsy can accurately diagnose benign and malignant axillary lymph nodes. If the sentinel lymph node examination results are negative, axillary lymph node dissection can be not performed. Without surgery, the incidence of postoperative lymphedema in patients with breast cancer can be significantly reduced. However, due to the skip metastasis of lymph nodes, there is still a false negative rate of about 8 % even with sentinel lymph node biopsy (4). In addition, because sentinel lymph node biopsy lacks the inherent anatomical site, and isotopes and specific detection instruments need to be used during the biopsy, the diagnostic accuracy of sentinel lymph node biopsy is still affected by factors such as operator technique and selection of diagnostic criteria, sentinel lymph node biopsy has not been widely used in China.

Axillary lymphadenectomy for breast cancer is the standard for the treatment of invasive breast cancer. However, lymph nodes tend to be insidious in adipose tissue, or accompanied by great vessels, which are not easily observed and removed (5-7). In addition, it

*Corresponding author. E-mail: zhufudi2022@yandex.com

increases the difficulty of complete removal of lymph nodes in the surgical field of blood staining. If a specific lymphatic tracer can be used to stain axillary lymph nodes to make lymph nodes easily identifiable, it can not only prevent intraoperative lymph node omission but also directly simplify the surgical procedure and save the operation time. Carbon nanoparticles (CNP) suspension have been an emerging lymph node tracer in recent years, and their carbon particles have an average diameter of around 155 nm (8,9). CNP is injected into the tissue surrounding the tumor, and nanoscale carbon particles are immediately engulfed by macrophages. Carbon particles are extruded into the lymphatic capillaries with the help of the pressure difference existing between interstitial fluid and lymph. Because carbon nanoparticles are black, so that both lymph nodes and lymphatic vessels are visualized in black and distinguished from surrounding tissues, they can produce good tracing effects on lymph nodes (10-12). CNP is widely used and has good advantages in gastric cancer, lung cancer, colorectal cancer, and thyroid cancer. In addition, carbon nanoparticles have good adsorption and release effect, after they adsorb chemotherapeutic drugs, they can not only show a good lymphatic tracing effect but also lead to degeneration and death of metastatic lymph nodes, in order to improve the prognosis of patients.

In this study, 60 patients with breast cancer admitted to Harbin Medical University Cancer Hospital were selected as the study subjects, and the prepared carbon nanoparticles epirubicin (CNP-EPI) was used as the tracer and targeted therapy drug carrier to evaluate the tracing effect of CNP-EPI injection on axillary lymph nodes of breast cancer at different periods, in order to explore the clinical efficacy of targeted chemotherapy on the metastatic lymph nodes and provide a good theoretical basis for improving the treatment of clinical breast cancer.

Materials and methods

Study subjects

In this study, 60 patients with breast cancer were collected from March 2020 to August 2021 in Harbin Medical University Cancer Hospital, all of whom were female, aged 32 ~ 67 years, with an average of 46.70 ± 8.87 years. They were randomly divided into groups A and group B, with 30 cases in each group. The tumors were in the upper inner quadrant of the breast in 16 cases, in the upper outer quadrant in 35 cases, in the lower outer quadrant in 3 cases, and in the central area in 6 cases. The study was approved by the Ethics Committee of Harbin Medical University Cancer Hospital, and the informed consent form was signed by the patient or guardian.

Inclusion criteria: (i) female, aged below 70 years old; (ii) patients with invasive breast cancer; (iii) clinical examination of patients with suspected axillary lymph node metastasis, no history of axillary surgery; (iv) patients without distant metastasis; (v) patients without local chemotherapy history of breast wall; (vi) non-pregnant and non-lactating women; (vii) heart, lung, liver, and kidney tests were functional.

Exclusion criteria: (i) patients with CNP-EPI allergy; (ii) patients not willing to accept CNP-EPI suspension treatment; (iii) patients with mental illness.

Preparation of CNP-EPI at different concentrations

Group I: 1 mL nano-carbon suspension (Chongqing LUMMY Pharmaceutical Co., Ltd., China) was mixed with 1 mL of epirubicin solution (1 mg/mL, 2 mg/mL, 4 mg/mL, 6 mg/mL, 8 mg/mL), respectively, and was oscillated by vortex oscillator for 5 min. Group II: 1 mL of nano-carbon suspension was mixed with 2 mL of epirubicin solution (3 mg/mL, 6 mg/mL, 9 mg/mL, 12 mg/mL, 15 mg/mL), respectively, and the mixture was shaken by vortex oscillator for 5 min.

The above prepared multiple samples were placed in a 36℃, 120 r/min thermostatic oscillator (Changzhou Champion Instrument Manufacturing Co., Ltd., China) for 2 h to make the solution reach the adsorption equilibrium state.

Content determination and release experiment of CNP-EPI sample

The above prepared CNP-EPI samples were centrifuged at 3×10^4 r/min for 30 min by Hitachi ultra-high-speed centrifuge in Japan. The supernatants of groups I and II were diluted 250 times and 5,000 times, respectively, and then 10 μL was injected. The free concentration of epirubicin after dilution in the supernatant was detected by a 6410 liquid chromatography-tandem mass spectrometer produced by Agilent Technologies in America. The actual free mass of epirubicin was calculated as follows.

$$M_{I} = 250 \times 2 \times 1 \times 10^{-6} C \quad [1]$$
$$M_{II} = 250 \times 1.5 \times 2 \times 10^{-6} C \quad [2]$$

M_{I} represents the actual free mass of epirubicin in group I, M_{II} represents the actual free mass of epirubicin in group II, and *C* represents the free concentration of epirubicin. The adsorption rate of epirubicin is calculated as follows.

$$\text{Epirubicin adsorption rate} = (M_{Total} - M_{I} - M_{II}) / M_{Total} \times 100\% \quad [3]$$

M_{Total} represents the total quality of epirubicin.

The suspension of 1 mL CNP and 2 mL 5 mg/mL EPI was prepared according to the adsorption experiment method and then put into the dialysis bag (molecular weight was 3,500). With 100 mL of normal saline as the release medium, the dialysis bag was put into the glass bottle and the cap was tightened. Oscillating dialysis was performed on a horizontal constant temperature oscillator at 36℃ and 120 r / min. 1 mL sample was taken at 4 h, 8 h, 12 h, 16 h, 20 h, 24 h, 28 h, 32 h, 36 h, 40 h, 44 h, and 48 h, respectively, and saline at the same temperature and volume was supplemented. The release amount of epirubicin and cumulative release rate at each time point was calculated.

$$\text{Epirubicin release mass} = 100 \times 10^{-6} \times C \quad [4]$$

C means the free concentration of epirubicin.

$$\text{Adriamycin release rate} = \text{Epirubicin release mass} / \text{total epirubicin mass} \times 100\% \quad [5]$$

The cumulative release curve was drawn with time as abscissa and cumulative release rate as ordinate.

The tracing method of lymph nodes and metastatic lymph nodes

All patients received an intravenous drip of 75 mg/m^2 quintazane injection before surgery (Shandong Cisen Pharmaceutical Co., Ltd., China) and 80 mg/m^2 epirubicin hydrochloride injection (Shanghai Yaji Biological Co., Ltd., China), and 14 days as a cycle, chemotherapy 2-4 cycles. In group A, 0.25 mL nano-carbon suspension was subcutaneously injected at 4 points around the areola one day before the operation. In group B, 0.25 mL nano-carbon suspension was injected subcutaneously at 4 points around the areola 3 days before the operation. After injection, the injection site was gently pressed with a cotton swab and local massage was performed to avoid the outflow of liquid from the needle eye. Local pain, swelling, fever, and allergies were observed.

Postoperative treatment and nursing methods

After surgery, tumor node metastasis (TNM) staging, as well as histological type, regional lymph node metastasis, and pathological examination results, were performed according to the 2017 *American Joint Committee on Cancer Staging Manual* for breast cancer staging criteria (13). Adjuvant chemotherapy was performed according to the 2020 latest National Comprehensive Cancer Network (NCCN) clinical practice guidelines (14). After the end of adjuvant chemotherapy, those who underwent breast-conserving surgery underwent whole breast radiotherapy, patients with more than 4 axillary lymph node metastases underwent corresponding regional radiotherapy, and those with positive hormone receptors conducted endocrine therapy for 5 years and adjuvant molecular targeted therapy was carried out.

Group A implemented a nursing intervention for lymphedema (Figure 1). “Breast cancer limb lymphedema intervention” project team was established, preparation for the limb lymphedema intervention program. Medical staff built a “limb supervision” patient communication group, and were daily responsible for the hospital outside limb arm circumference measurement, supervision of patients with rehabilitation exercise, data recording, and file sorting; the upper arm circumference was correctly measured, and the management of monitoring indicators was standardized. The shoulder peak of the affected limb was connected with the olecranon, and the midpoint was taken as the measurement site. The tape was used to circle the arm. The measured circumference was the upper arm circumference of the affected limb. The method was adopted to deal with lymph pump failure and edema. Pressure therapeutic apparatus was applied at the early stage to accelerate the recovery of the lymphatic pump; manual lymph drainage technology was adopted to promote lymph reflux; scar nursing was performed to deal with lymph reflux disorder caused by scar contracture.

Group B received routine care. For example, the affected limb was raised by 10 - 15° using a soft pillow after the operation, and the soft pillow was under the affected limb (supine position). The limb was put on the chest with a bandage when getting out of bed. In addition, routine limb function exercise was carried out. Patients were instructed to exercise daily for 1 year after the operation.

Outcome measures and follow-up

After the operation, the lymph nodes were separated from the fresh samples removed by surgery and carefully examined by the professional operators. The total number of dissected lymph nodes, the number of black-stained lymph nodes, the number of metastatic lymph nodes, and the number of black-stained metastatic lymph nodes were recorded in the two groups, respectively. The time and location of distant metastases of lymph nodes were recorded; whether there was local necrosis or systemic adverse reactions to the skin by CNP-EPI suspension was observed, and the heart, liver, and kidney function were reexamined each time. The evaluation criteria for lymphedema were referred to the upper limb lymphedema functional rating scale (15). Incidence of postoperative adverse reactions was observed. The incidence of lymphedema was compared between the two groups at 1 month, 3 months, and 6 months after the operation.

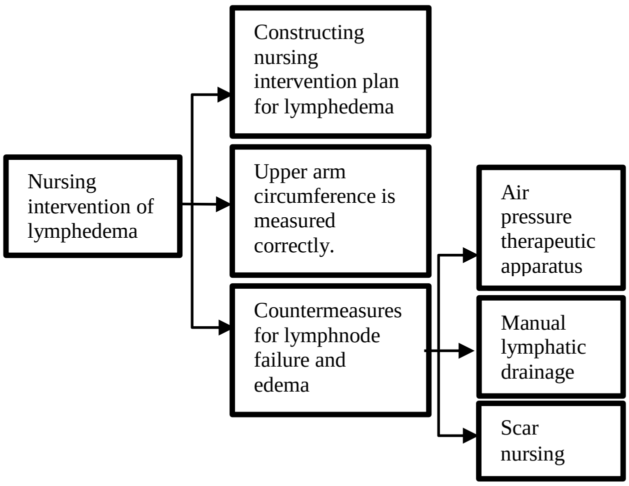

Figure 1. Implementation of nursing intervention for limb lymphedema.

Statistical methods

In this study, SPSS 22.0 was used for statistical analysis. One-way analysis of variance and least significant difference (LSD) test were used to compare the data. Measurement data were expressed as $\bar{x}\pm s$, and χ^2 test was used to analyze enumeration data. $P < 0.05$ was considered statistically significant.

Results and discussion

Adsorption results in different concentrations of epirubicin by carbon nanoparticles

Group I: adsorption rates of 1 mL carbon nanoparticles with epirubicin at 2 mg/mL, 4 mg/mL, 6 mg/mL, 8 mg/mL, and 10 mg/mL were 99.5 %, 99.3 %, 98.9 %, 94.8 %, and 93.2 %, respectively. Group II: adsorption rates of 1 mL carbon nanoparticles with epirubicin at 3 mg/mL, 6 mg/mL, 9 mg/mL, 12 mg/mL, and 15 mg/mL were 95.2 %, 89.6 %, 84.3 %, 74.2 %, and 68.7 %, respectively. As the concentration of epirubicin increased, the adsorption rate gradually decreased (Figure 2).

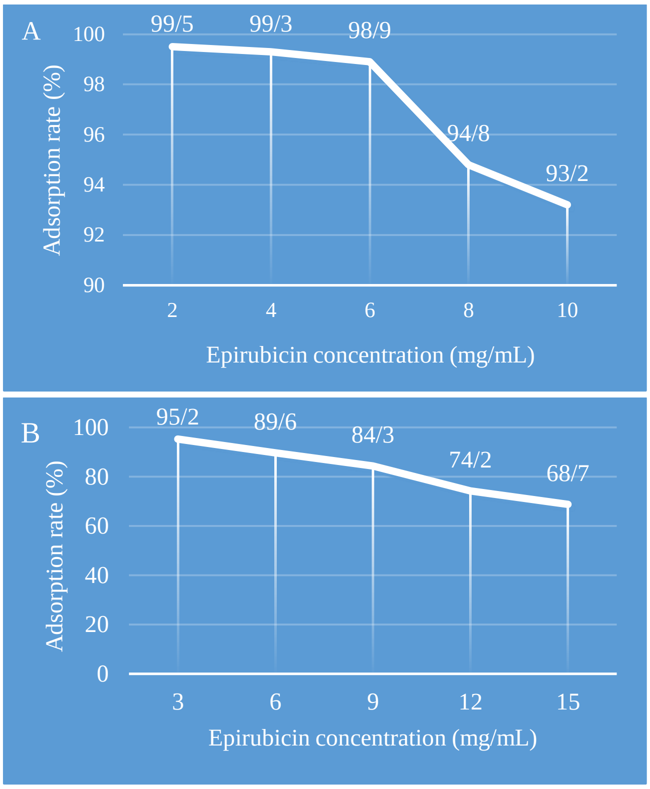

Figure 2. Adsorption rate of carbon nanoparticles for epirubicin at different concentrations.
A: group I; B: group II

The cumulative release rate of epirubicin by carbon nanoparticles

Epirubicin can be slowly released after 1 mL carbon nanoparticles adsorption of 2 mL 6 mg/mL epirubicin, without sudden release, which tends to equilibrate at about 40 h, and the cumulative release rate could reach 64.7 % (Figure 3).

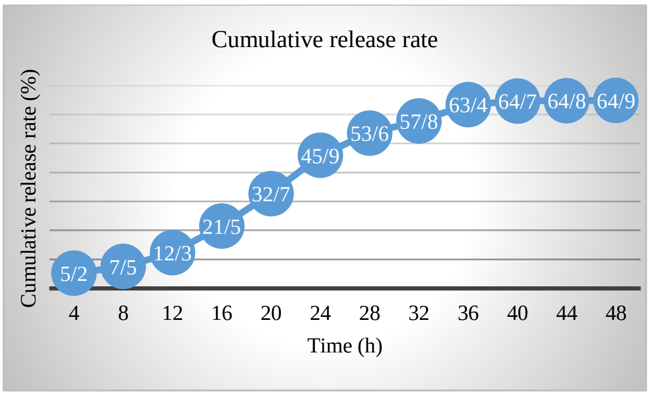

Figure 3. Cumulative release rate.

Clinicopathological features of the two groups

The tumors were in the upper inner quadrant in 16 cases, upper outer quadrant in 35 cases, lower outer quadrant in 3 cases, and the central area in 6 cases. TNM was stage I in 14 cases, stage II in 29 cases, and stage IIIA in 17 cases. There was no significant difference in tumor location, TNM staging, pathological type, etc. between the two groups (P > 0.05), indicating comparability (Table 1).

Table 1. Comparison of clinicopathological features between two groups

	Group A (n=30)	Group B (n=30)	χ^2	P
Tumor location			8.782	0.154
Upper inner quadrant	9	7		
Lower inner quadrant	0	0		
Upper outer quadrant	17	18		
Lower outer quadrant	1	2		
Central area	1	5		
TNM staging			2.561	0.573
Stage I	7	7		
Stage II	15	14		
Stage IIIA	8	9		
Pathological type			2.764	0.316
Invasive ductal carcinoma	30	29		
Breast carcinoma in situ	0	1		

Number of lymph node clearance and black staining rates

A total of 425 lymph nodes were removed in group A, with an average of 14.16 ± 4.2. A total of 376 lymph nodes were removed in group B, with an average of 12.53 ± 3.7, and the difference was not statistically significant (P > 0.05). Among the 425 lymph nodes removed in group A, 341 were black-stained, and the black staining rate was 80.2 %. Among the 376 lymph nodes cleared in group B, 217 were black-stained, with a black staining rate of 57.7 %; the difference in lymph node black staining rate between the two groups was statistically significant (P < 0.05) (Figure 4).

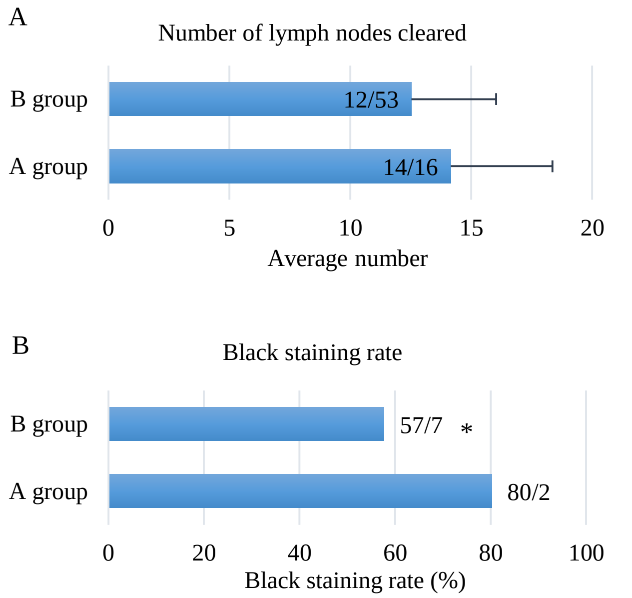

Figure 4. The number of lymph node clearance and black staining rate in the two groups. A: number of lymph nodes removed; B: black staining rate. Note: * indicates a statistically significant difference from group A (P < 0.05)

Microscopically, a large number of carbon nanoparticles could be found retained in the lymph node sinuses in the black-stained lymph nodes of patients in both groups (Figure 5).

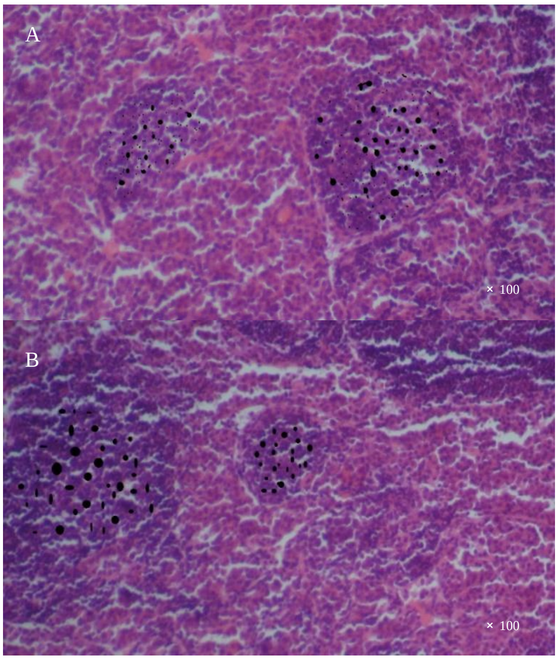

Figure 5. HE staining of carbon nanoparticles retained in lymph node sinuses in both groups (× 100). A: under the microscope, a large number of carbon nanoparticles in group A were retained in the lymph node sinus. B: under the microscope, a large number of carbon nanoparticles in group B were retained in the lymph node sinus.

Tracing the effect of metastatic lymph nodes

In group A, 425 lymph nodes and 52 lymph nodes were removed, with a lymph node metastasis rate of 12.2 %; in group B, 376 lymph nodes and 41 lymph nodes were removed, with a lymph node metastasis rate of 10.9 %, and the difference was not statistically significant (P > 0.05). In group A, a total of 52 metastatic lymph nodes were removed, including 23 black-stained lymph nodes, with a black staining rate of 73.1 % in metastatic lymph nodes; in group B, a total of 41 metastatic lymph nodes were removed, including 27 black-stained lymph nodes, with a black staining rate of 65.9 % in metastatic lymph nodes; there was no significant difference in the black staining rate of metastatic lymph nodes (P > 0.05) (Figure 6).

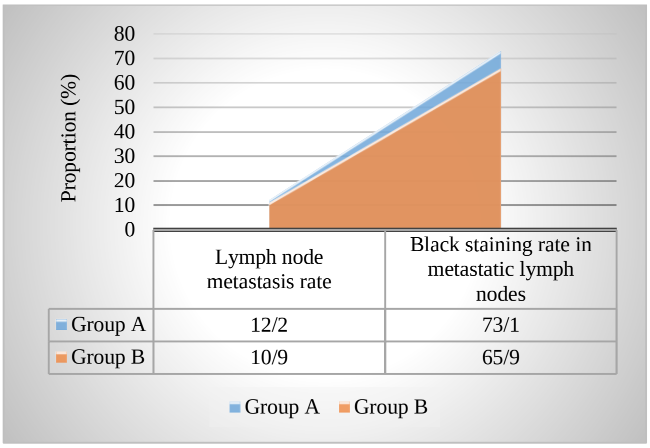

Figure 6. Lymph nodes metastasis rate and black staining rate of metastatic lymph nodes.

Microscopically, carbon nanoparticles were retained around the cancer cell mass in both groups of black-stained metastatic lymph nodes (Figure 7).

Observation of adverse reactions after local injection of CNP-EPI suspension

After local injection of CNP-EPI, patients in groups A and B showed mild swelling and pain at the injection site, which was not treated. The symptoms gradually disappeared. No allergy, necrosis, ulceration, body fever, and other adverse reactions occurred in the local skin. Postoperative examination of the resected breast cancer tissue samples revealed no necrosis or inflammatory response at the injection site.

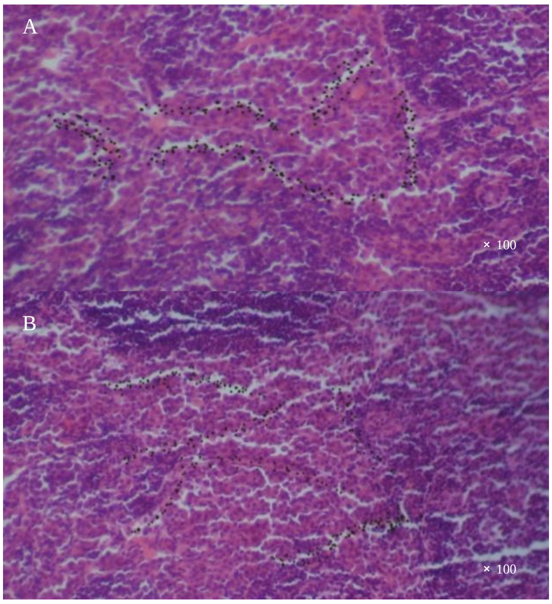

Figure 7. HE staining with nano-carbon black staining of metastatic lymph nodes in the two groups (× 100). A: under the microscope, the metastatic lymph nodes of group A were stained with carbon nanoparticles, and the carbon nanoparticles were retained among and around the cancer cells; B: under the microscope, the metastatic lymph nodes of group B were stained with carbon nanoparticles, and the carbon nanoparticles were retained among and around the cancer cells.

Comparison of nursing intervention results

At 1 month, 3 months, and 6 months after the operation, no local recurrence or distant metastasis occurred, and no significant abnormality of heart, liver, and kidney function was observed. The incidence rate of lymphedema in group A was significantly lower than that in group B at 1, 3, and 6 months after the operation, and the difference had statistical significance (P < 0.05) (Figure 8).

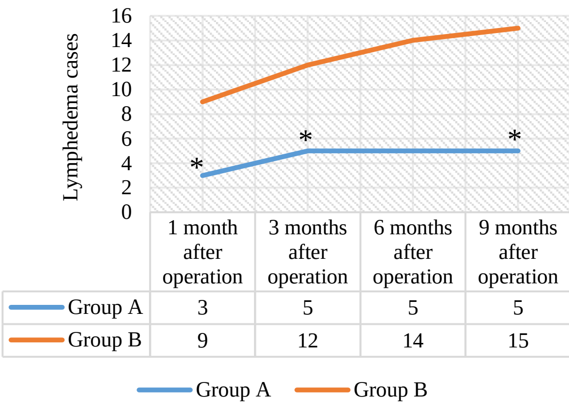

Figure 8. Comparison of nursing intervention results between the two groups. Note: * indicated statistically significant difference from group B (P < 0.05)

At present, breast cancer is one of the most common malignant tumors in the female population in China, and the confirmed cases are increasing year by year, and they gradually tend to be younger (16). Anxillary lymph node metastasis is one of the risk factors affecting the survival of breast cancer patients. Therefore, how completely removing the metastatic axillary lymph nodes is of great significance for guiding postoperative treatment and prognosis. To improve the probability of axillary lymph node dissection, carbon nanoparticles have been used as axillary lymph node tracers in breast cancer, and good tracing effect and efficacy have been achieved.

The adsorption mechanism of CNP-EPI is mainly physical adsorption, which absorbs the drug according to its strong adsorption capacity; then its slow-release function is used to slowly release the adsorbed therapeutic drug (17-20). Due to the strong lymphatic tropism of carbon nanoparticles, adsorbed therapeutic agents can be delivered to lymphatic vessels and lymph nodes, thus playing a role in targeted therapy. As an ideal carrier of lymphatic targeted chemotherapeutic drugs, carbon nanoparticles are widely used in targeted lymphatic chemotherapy for breast malignancies, and no adverse reactions were found in the body. Using the high degree of lymph node and lymphatic vessel tropism of CNP-EPI, it can be used as a lymph node tracer for gastric cancer, colorectal cancer, as well as breast cancer, and finally, achieve good eradication results (21). The results showed that the black staining rate was 80.2 % (341/425) in group A and 57.7 % (217/376) in group B, and the difference was statistically significant ($P <$ 0.05). CNP-EPI can stain a large number of metastatic lymph nodes, which is conducive to intraoperative operator identification of lymph nodes, and their complete removal, reducing the probability of postoperative recurrence. The black-staining effect of CNP-EPI lymph nodes injected 1 day before surgery was the most obvious, and the tracing effect was satisfactory, which was similar to the study results of Zhang et al. (2019) (22). It is speculated that the reason for this phenomenon may be that nanoscale carbon particles will be excreted from the body as lymphs circulates overtime.

Anthracyclines, as a chemotherapeutic agent, have shown good advantages in the treatment of various malignant tumors of the body, especially for lymphomas, such as gastric cancer, colorectal cancer, and breast cancer, and epirubicin and adriamycin are currently the most used (23-27). Although such drugs have obvious efficacy, they have very serious toxicity, of which the most important concern is cardiotoxicity. Compared with doxorubicin, epirubicin has less cardiotoxicity and significant efficacy. The use of epirubicin in various neoadjuvant chemotherapy combination regimens will benefit breast cancer patients differently, it is mostly used as a first-line treatment, and is currently the most popular anticancer drug in the clinical treatment of breast cancer. When epirubicin is absorbed by carbon nanoparticles, the residual cancer cells of chemotherapy can be targeted, which can not only prolong the residence time of epirubicin in lymph node cancer cells and reduce the systemic toxicity and side effects, but also stain the lymph nodes black, facilitating the operator to identify and dissect them during surgery (28). Increasing the number of completely removed lymph nodes during surgery can not only reduce the recurrence rate of postoperative patients but also improve the postoperative clinical efficacy of breast cancer patients. The results of this study showed that the adsorption rate of 1 mL nano-carbon with epirubicin gradually decreased with increasing epirubicin concentration. It may be that the adsorption capacity of carbon nanoparticles also gradually reaches the saturation state as the content is relatively stable. The results of this study verify that carbon nanoparticles do have strong adsorption properties. Based on the above results, the mixture ratio of 1 mL carbon nanoparticles with concentrations of 3 mg/mL - 9 mg/mL epirubicin was the most appropriate. In addition, the cumulative release results of epirubicin adsorbed by carbon nanoparticles in this study suggested that 1 mL carbon nanoparticles adsorbed 2 mL of epirubicin at a concentration of 6 mg/mL could slow down the release rate of epirubicin without sudden release, tended to balance at about 40 h, and the cumulative release rate could reach 64.7 %, confirming that carbon nanoparticles had the slow-release ability and providing the possibility for it to be used as targeted drug carriers. The black staining rate in metastatic lymph nodes was 73.1 % (38/52) in group A and 65.9 % (27/41) in group B. It was verified that carbon nanoparticles also had a good tracing effect on metastatic axillary lymph nodes.

Carbon nanoparticles as a tracer for axillary lymph nodes not only facilitate the detection of metastatic lymph nodes but also increase the probability of removing metastatic lymph nodes during axillary lymph node dissection, which is similar to the findings of Tian et al. (2021) (29).

Axillary lymph node injury has a certain correlation with surgical proficiency, postoperative infection, exercise, age, and other factors. When some lymphatic vessels are removed by surgery, lymphedema will occur if the retained lymph exceeds the metabolic load. In this study, when nursing intervention was used, a pneumatic pressure therapy instrument was first used to repeatedly inflate and deflate to promote lymphatic flow to improve microcirculation. Then, with the lymphatic drainage technique and scar care, pushing the retained lymph back to the normal lymph nodes and promoting lymphatic reflux can significantly reduce the incidence of prognostic lymph node edema.

Conclusions

In this study, CNP-EPI was prepared and used as a tracer and targeted therapy for axillary lymphadenectomy for breast cancer to observe the tracer effect and prognosis of lymphedema nursing effect. Finally, it was confirmed that carbon nanoparticles had strong adsorption capacity and drug slow-release performance; the mixture of 1 mL carbon nanoparticles and 2 mL epirubicin at a concentration of 6 mg/mL was more suitable; the black staining rate of axillary lymph nodes by subcutaneous injection of CNP-EPI around the areola 1 day before surgery was high, which could achieve a good lymph tracking effect; the construction of personalized lymphedema care program could effectively reduce the incidence of prognostic lymphedema. The limitation of this study is that the included sample size is small, and large sample size, the multicenter experiment is required for further in-depth exploration at a later stage. In conclusion, it provides the possibility of carbon nanoparticles as targeted drug carriers and provides a new direction for the treatment of breast cancer at the molecular level in the study.

Acknowledgments

Not applicable.

Interest conflict

The authors declare that they have no conflict of interest.

Fundings

The research is supported by: the Haiyan Science Foundation of Harbin Medical University Cancer Hospital(Youth Project) (No. JJQN 2018-19); Heilongjang Nursing Society“Weigao Angel” Nursing Research (NO. 2019510310015); Haiyan Science Foundation of Harbin Medical University Cancer Hospital (Key Project) (No. JJZD 2018-07).

References

1. Li J, Jia S, Wang Y, Zhang Y, Kong L, Cao Y, Liu Y, Zhang Y, Chen B. Long-term tracing and staining of carbon nanoparticles for axillary lymph node in patients with local advanced breast cancer treated with neoadjuvant chemotherapy. Asian J Surg. 2021 Apr 26:S1015-9584(21)00171-8. doi: 10.1016/j.asjsur.2021.03.020. Epub ahead of print. PMID: 33926797.
2. Wei N, Hou J, Chen J, Dai M, Du K, Wang S, Ni Q. Sentinel lymph node biopsy with carbon nanoparticle suspension after neoadjuvant chemotherapy for breast cancer patients. Ann R Coll Surg Engl. 2021 Nov;103(10):752-756. doi: 10.1308/rcsann.2021.0084. Epub 2021 Aug 27. PMID: 34448655.
3. Liu S, Wang H, Zhang C, Dong J, Liu S, Xu R, Tian C. In Vivo Photoacoustic Sentinel Lymph Node Imaging Using Clinically-Approved Carbon Nanoparticles. IEEE Trans Biomed Eng. 2020 Jul;67(7):2033-2042. doi: 10.1109/TBME.2019.2953743. Epub 2019 Nov 15. PMID: 31751215.
4. Yang P, Hu X, Peng S, Wang L, Yang L, Dong Y, Yang Z, Yuan L, Zhao H, He X, Bao G. Near-infrared laparoscopy with indocyanine green for axillary sentinel lymph node biopsy in early breast cancer: preliminary experience of a single unit. Gland Surg. 2021 May;10(5):1677-1686. doi: 10.21037/gs-21-223. PMID: 34164312; PMCID: PMC8184382.
5. Bhandari A, Xia E, Wang Y, Sindan N, Kc R, Guan Y, Lin YL, Wang X, Zhang X, Wang O. Impact of sentinel lymph node biopsy in newly diagnosed invasive breast cancer patients with suspicious node: a comparative accuracy survey of fine-needle aspiration biopsy versus core-needle biopsy. Am J Transl Res. 2018 Jun 15;10(6):1860-1873. PMID: 30018726; PMCID: PMC6038083.
6. Menta A, Fouad TM, Lucci A, Le-Petross H, Stauder MC, Woodward WA, Ueno NT, Lim B. Inflammatory Breast Cancer: What to Know About This Unique, Aggressive Breast Cancer. Surg Clin North Am. 2018 Aug;98(4):787-800. doi: 10.1016/j.suc.2018.03.009. Epub 2018 May 24. PMID: 30005774.

7. Liang Y, Zhang H, Song X, Yang Q. Metastatic heterogeneity of breast cancer: Molecular mechanism and potential therapeutic targets. Semin Cancer Biol. 2020 Feb;60:14-27. doi: 10.1016/j.semcancer.2019.08.012. Epub 2019 Aug 14. PMID: 31421262.
8. Thomas M, Kelly ED, Abraham J, Kruse M. Invasive lobular breast cancer: A review of pathogenesis, diagnosis, management, and future directions of early stage disease. Semin Oncol. 2019 Apr;46(2):121-132. doi: 10.1053/j.seminoncol.2019.03.002. Epub 2019 Jun 17. PMID: 31239068.
9. Xu X, Zhang M, Xu F, Jiang S. Wnt signaling in breast cancer: biological mechanisms, challenges and opportunities. Mol Cancer. 2020 Nov 24;19(1):165. doi: 10.1186/s12943-020-01276-5. PMID: 33234169; PMCID: PMC7686704.
10. Mittal S, Brown NJ, Holen I. The breast tumor microenvironment: role in cancer development, progression and response to therapy. Expert Rev Mol Diagn. 2018 Mar;18(3):227-243. doi: 10.1080/14737159.2018.1439382. Epub 2018 Feb 15. PMID: 29424261.
11. Mueller C, Haymond A, Davis JB, Williams A, Espina V. Protein biomarkers for subtyping breast cancer and implications for future research. Expert Rev Proteomics. 2018 Feb;15(2):131-152. doi: 10.1080/14789450.2018.1421071. Epub 2018 Jan 3. PMID: 29271260; PMCID: PMC6104835.
12. Li X, Yang J, Peng L, Sahin AA, Huo L, Ward KC, O'Regan R, Torres MA, Meisel JL. Triple-negative breast cancer has worse overall survival and cause-specific survival than non-triple-negative breast cancer. Breast Cancer Res Treat. 2017 Jan;161(2):279-287. doi: 10.1007/s10549-016-4059-6. Epub 2016 Nov 25. PMID: 27888421.
13. Weichand B, Popp R, Dziumbla S, Mora J, Strack E, Elwakeel E, Frank AC, Scholich K, Pierre S, Syed SN, Olesch C, Ringleb J, Ören B, Döring C, Savai R, Jung M, von Knethen A, Levkau B, Fleming I, Weigert A, Brüne B. S1PR1 on tumor-associated macrophages promotes lymphangiogenesis and metastasis via NLRP3/IL-1β. J Exp Med. 2017 Sep 4;214(9):2695-2713. doi: 10.1084/jem.20160392. Epub 2017 Jul 24. PMID: 28739604; PMCID: PMC5584110.
14. Etan T, Amir E, Tibau A, Yerushalmi R, Moore A, Shepshelovich D, Goldvaser H. National comprehensive cancer network recommendations for drugs without US food and drug administration approval in metastatic breast cancer: A cross-sectional study. Cancer Treat Rev. 2020 Dec;91:102113. doi: 10.1016/j.ctrv.2020.102113. Epub 2020 Oct 20. PMID: 33128993.
15. Reddy TP, Rosato RR, Li X, Moulder S, Piwnica-Worms H, Chang JC. A comprehensive overview of metaplastic breast cancer: clinical features and molecular aberrations. Breast Cancer Res. 2020 Nov 4;22(1):121. doi: 10.1186/s13058-020-01353-z. PMID: 33148288; PMCID: PMC7640663.
16. Liu N, Johnson KJ, Ma CX. Male Breast Cancer: An Updated Surveillance, Epidemiology, and End Results Data Analysis. Clin Breast Cancer. 2018 Oct;18(5):e997-e1002. doi: 10.1016/j.clbc.2018.06.013. Epub 2018 Jun 27. PMID: 30007834.
17. Huang Y, Xie P, Yang ST, Zhang X, Zeng G, Xin Q, Tang XH. Carbon nanoparticles suspension injection for the delivery of doxorubicin: Comparable efficacy and reduced toxicity. Mater Sci Eng C Mater Biol Appl. 2018 Nov 1;92:416-423. doi: 10.1016/j.msec.2018.07.012. Epub 2018 Jul 4. PMID: 30184767.
18. Xie P, Yang ST, He T, Yang S, Tang XH. Bioaccumulation and Toxicity of Carbon Nanoparticles Suspension Injection in Intravenously Exposed Mice. Int J Mol Sci. 2017 Nov 29;18(12):2562. doi: 10.3390/ijms18122562. PMID: 29186019; PMCID: PMC5751165.
19. Yin C, Wang X, Sun S. Reduction in postoperative hypoparathyroidism following carbon nanoparticle suspension injection combined with parathyroid gland vasculature preservation. J Int Med Res. 2020 Jan;48(1):300060519866606. doi: 10.1177/0300060519866606. Epub 2019 Aug 20. PMID: 31429346; PMCID: PMC7105282.
20. Wang C, Xie J, Dong X, Mei L, Zhao M, Leng Z, Hu H, Li L, Gu Z, Zhao Y. Clinically Approved Carbon Nanoparticles with Oral Administration for Intestinal Radioprotection via Protecting the Small Intestinal Crypt Stem Cells and Maintaining the Balance of Intestinal Flora. Small. 2020 Apr;16(16):e1906915. doi: 10.1002/smll.201906915. Epub 2020 Mar 18. PMID: 32187855.
21. Su AP, Wang B, Gong YP, Wu WS, Gong RX, Li ZH, Zhu JQ. Carbon nanoparticles facilitate lymph nodes dissection and parathyroid glands identification in reoperation of papillary thyroid cancer. Medicine (Baltimore). 2017 Nov;96(44):e8380. doi: 10.1097/MD.0000000000008380. PMID: 29095266; PMCID: PMC5682785.
22. Zhang D, Wang T, Dionigi G, Fu Y, Zhang J, Zhao Y, Li J, Sun H. Application of Carbon Nanoparticles in Endoscopic Thyroidectomy via Bilateral Areola Approach: Total Thyroidectomy Plus Central Lymph Node Dissection. J Laparoendosc Adv Surg Tech A. 2019 Aug;29(8):1038-1041. doi: 10.1089/lap.2019.0102. Epub 2019 Apr 1. PMID: 30939054.
23. Liu S, Wang H, Zhang C, Dong J, Liu S, Xu R, Tian C. In Vivo Photoacoustic Sentinel Lymph Node Imaging Using Clinically-Approved Carbon Nanoparticles. IEEE Trans Biomed Eng. 2020 Jul;67(7):2033-2042. doi: 10.1109/TBME.2019.2953743. Epub 2019 Nov 15. PMID: 31751215.
24. Gao Q, Xie W, Wang Q, Wei G, Yao N, Li Z, Wang Y, Lu C, Pan Y, Sun X. Novel technique to manage refractory chylous ascites with carbon nanoparticle suspension in infants. J Pediatr Surg. 2020 Apr;55(4):772-776. doi:

10.1016/j.jpedsurg.2019.09.041. Epub 2019 Oct 23. PMID: 31679773.

25. Xie P, Xin Q, Yang ST, He T, Huang Y, Zeng G, Ran M, Tang X. Skeleton labeled 13C-carbon nanoparticles for the imaging and quantification in tumor drainage lymph nodes. Int J Nanomedicine. 2017 Jul 11;12:4891-4899. doi: 10.2147/IJN.S134493. PMID: 28744123; PMCID: PMC5513824.
26. Chuntib P, Themsirimongkon S, Saipanya S, Jakmunee J. Sequential injection differential pulse voltammetric method based on screen printed carbon electrode modified with carbon nanotube/Nafion for sensitive determination of paraquat. Talanta. 2017 Aug 1;170:1-8. doi: 10.1016/j.talanta.2017.03.073. Epub 2017 Mar 30. PMID: 28501144.
27. Xu XF, Gu J. The application of carbon nanoparticles in the lymph node biopsy of cN0 papillary thyroid carcinoma: A randomized controlled clinical trial. Asian J Surg. 2017 Sep;40(5):345-349. doi: 10.1016/j.asjsur.2015.11.004. Epub 2016 Jan 15. PMID: 26783035.
28. Ge W, Li Q, Liu WJ, Zhang XQ, Fan XS, Shao LH, Tao L, Guan WX, Chen G. Carbon nanoparticle suspension could help get a more accurate nodal staging for patient with rectal cancer. Sci Rep. 2021 May 11;11(1):9933. doi: 10.1038/s41598-021-89541-5. PMID: 33976352; PMCID: PMC8113261.
29. Tian Y, Lin Y, Guo H, Hu Y, Li Y, Fan L, Zhao X, Wang D, Tan B, Zhao Q. Safety and efficacy of carbon nanoparticle suspension injection and indocyanine green tracer-guided lymph node dissection during robotic distal gastrectomy in patients with gastric cancer. Surg Endosc. 2021 Jul 12. doi: 10.1007/s00464-021-08630-8. Epub ahead of print. PMID: 34254184.